Abstracts

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Asher Kimchi, MD
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HEART FAILURE: NOVEL APPROACHES FOR DIAGNOSIS AND TREATMENT

THE WAR ON HEART FAILURE

E. Braunwald
Brigham and Women’s Hospital, Boston, MA, USA

Heart failure (HF) is a global problem with an estimated prevalence of 38 million patients worldwide, a number that is increasing with the ageing of the population. Despite some progress, the prognosis of HF is still worse than that of most cancers. Because of the seriousness of the condition, a declaration of war on HF is proposed on five fronts: 1) Efforts to treat HF by enhancing myofilament sensitivity to Ca²⁺; 2) Several abnormal Ca²⁺-handling proteins in the failing heart are candidates for gene therapy; 3) Short, non-coding RNAs—ie, microRNAs, block gene expression and protein translation. Their actions can be blocked by a new class of drugs, antagomirs, some of which have been shown to improve cardiac function in animal models of HF; 4) Cell therapy, with autologous bone marrow derived mononuclear cells, or autogenous mesenchymal cells, which can be administered as cryopreserved off the shelf products, are promising in both preclinical and early clinical HF trials; 5) Fibrosis is prominent in HF and antifibrotic drugs are promising. The approaches to the treatment of HF described, when used alone or in combination, could become important weapons in the war against HF.
Dilated cardiomyopathies (DCM) account for 10,000 deaths/year in the US; African-Americans have a 3-fold increased risk. There has been little solid information available on or the ability to make a precise genetic diagnosis in DCM. Moreover, little has been known about the prognostic or potential therapeutic advantage of genetic testing. Recent work indicates that mutations in the gene encoding the Titin protein account for up to 20% of DCM cases, with mutations in an additional 30 genes accounting for 15% of additional cases. At this point, genetic testing must be applied selectively. Several clinical factors can identify patients for whom the yield on testing will be higher, including absence of hypertension, positive family history of DCM, sudden cardiac death, elevated CK, associated muscular dystrophy, and conduction abnormalities on ECG. There are 5 – 10% of patients with DCM who have two or more likely pathogenic mutations, which may account for variance in penetrance and phenotype. High risk mutations for premature death include mutations in LMNA, DES and RBM20 genes. Truncating mutations in the Titin gene appear to account for 15% of peripartum cardiomyopathies. Presence of Titin mutations has prognostic importance. Selective testing with targeted gene panels is appropriate for patients with DCM who have increased likelihood of a pathogenic mutation. There are important therapeutic implications (ICD’s) and also potential for effective disease modifying therapy.
THE CANCER ASSOCIATED FIBROBLAST AND THE HEART FAILURE ASSOCIATED FIBROBLAST- SIMILAR PHENOTYPE, SIMILAR PATHWAYS LEADING TO POTENTIALLY SIMILAR TREATMENT

F.G. Spinale
USC School of Medicine and WJB Dorn VA, Columbia, SC, USA

While morbidity, mortality, and health care costs associated with heart failure (HF) are increasing, advancements in early diagnosis and treatment strategies have not been forthcoming. Firstly, there is a need to differentiate HF phenotypes into different disease processes, not dissimilar to what is done in cancers. Secondly, move beyond conventional thought regarding biological pathways that regulate myocardial growth and function. Thirdly, harness the insight gained from advances in biological pathways affected by chemotherapeutics that may hold relevance to HF. HF myocardial fibroblasts express transcriptional and protein markers similar to those observed in a process of mesenchymal-epithelial transformation described in cancer. These cancer associated fibroblasts (CAFs) have been shown to contribute to cancer growth and alterations in normal tissue structure/function through the release of growth factors, signaling molecules, and proteases. This laboratory and others have identified that HF associated fibroblasts (HFAFs) express a similar profile of growth factors and signaling molecules in patient and animal models. The aims: (1) Identify the phenotype classifications of clinical HF and relate these to abnormalities in fibroblast growth/function, (2) present new findings on common signaling pathways and altered expression profiles between CAFs and HFAFs, putting forward the postulate that these cell types are the same, (3) examine new translational studies of localized approaches to target HFAF and how chemotherapeutics hold a place in the treatment of HF. The imminent conclusion is that new findings in cancer research can be translated to target the transdifferentiated fibroblast in HF as a form of interstitial cancer.
The field of regenerative medicine has moved well beyond the results reported from the first decade of clinical trials of both stem cells and genes for CV disease. The early trials used almost exclusively autologous stem cells harvested from the bone marrow. There are now many new sources and types of stem cells including new international Phase III trials of allogeneic stem cells that allow use of ideal very young donors rather than older and chronically ill subjects, to genetic engineering of cardiomyocytes, and identification of resident progenitor cells in the heart that may be an important end pathway for effecting native cell regeneration from several cell types. Most of the trials in regenerative Medicine in CV Disease have targeted either chronic refractory angina or congestive heart failure, but newer trials are being conducted for peripheral vascular disease and stroke. Several of the trials are moving from Phase II to pivotal Phase III trials that is the final step for commercialization.

There has been significant progress in the use of specific genes shown to be important in the genesis and progression of cardiovascular disease, which have now moved to Phase IIB trials. The premise of using targeted genes rather than stem cells is that cells only remain in the tissues in which they are delivered for several days, and seem to exert their benefit by activating specific genes that then drive native repair. This would suggest that genes would be potentially as potent as cells alone. There are trials upcoming that will transfect a target gene into the cells to be transplanted, taking advantage of both strategies.

All data reported to date on stem cell and gene therapy have used only a single delivery of that agent. Given the proven safety of current stem cells and genes that provoke no immune response, new trials using multiple deliveries are starting. This may be one of the most important new strategies to enhance the benefit of this therapy.

The other area of significant progress in this field is in tissue engineering which is developing new ways to significantly increase cell retention when transplanted. This includes scaffolds and stents that are coated with cells or trophic agents, as well as novel agents that stimulate native repair in patients with heart failure. One other very promising application of tissue engineering is referred to as organogenesis which is the decellularization of the heart with repopulation of stem cells, including cells obtained from the patient who would be a candidate of for that organ transplant.
HEART FAILURE: NOVEL APPROACHES FOR DIAGNOSIS AND TREATMENT

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THYROID HORMONE TREATMENT OF HEART FAILURE: IS THERE A THERAPEUTIC WINDOW?
A. Martin Gerdes
New York Institute of Technology-College of Osteopathic Medicine, Old Westbury, NY, USA

In 1950, a study showed that Thyroid Hormone (TH) treatment significantly reduced cardiovascular mortality and rates of myocardial infarction in three patient groups. Rather than extend these findings, subsequent poorly designed larger clinical studies using toxic doses of TH analogs convinced the medical community that TH treatment of heart diseases was too risky, primarily due to increased risk of inducing arrhythmias. Due to a steady stream of positive new information, however, this issue has not gone away. Over the years, we have learned many things about low thyroid function and heart diseases. In many studies, low TH function has been linked to increased mortality in patients with various heart diseases. Many short term clinical studies also show improvement in cardiac patients treated with THs. A key animal study clearly demonstrated that hypothyroidism alone can eventually cause heart failure with maladaptive myocyte remodeling and impaired coronary blood flow. Other rat studies showed that low TH function promotes arrhythmias and TH treatment of myocardial infarction protects from arrhythmia induction. Cumulatively, animal studies suggest that all types of heart disease lead to low cardiac tissue T3 levels. One has to ask the question, why is there so much opposition to a drug that improves systolic/diastolic function, improves coronary blood flow, inhibits myocardial fibrosis, reverses fetal gene expression, and reduces arrhythmias? There are good reasons to be apprehensive. But, is fear of overtreatment unreasonable? Is there a safe, therapeutic window for TH treatment of heart diseases, including heart failure? Over the past few years, animal research in our lab has focused on answering the critical questions that have blocked progress to translation in this field. Results provide considerable optimism that TH treatment of heart disease can be done safely and with remarkable benefits.
BACKGROUND: While previous studies have reported a lower risk of coronary heart disease (CHD) and heart failure with moderate alcohol intake in the general population, only limited data are available on the association of moderate drinking and risk of heart failure in adults with CHD.

OBJECTIVE: We sought to test the hypothesis that light-to-moderate drinking is associated with a lower risk of heart failure in men with prevalent CHD.

METHODS: Prospective study of 2,502 participants from the Physicians’ Health Study (PHS) who completed a food frequency questionnaire between 1999 and 2002 and had prevalent CHD (prior myocardial infarction, coronary angioplasty, or bypass surgery). Information on alcohol intake and lifestyle factors was self-reported. We ascertained incident heart failure using annual questionnaires with a validation (via review of medical records) in a subsample.

RESULTS: Mean age was 71.9 years (range: 51 to 96 y) in the cohort. During a mean follow up of 8.3 years, 282 subjects developed heart failure. There was an inverse association between alcohol consumption and incidence of heart failure. When compared to never drinkers, hazard ratios (95% confidence intervals) of heart failure were 0.84 (0.60-1.19), 0.73 (0.50-1.04), 0.65 (0.46-0.91), and 0.62 (0.41-0.94) for drinkers of up to 2 drinks/week, 3-6 drinks/week, 1-2 drinks/d, and 3+ drinks/d, respectively, after adjustment for age, body mass index, smoking, exercise, prevalent atrial fibrillation, hypertension, and cancer (p trend 0.006). Exclusion of participants with less than 2 years of follow up did not alter the results (p trend 0.008).

CONCLUSION: In this cohort of US male physicians, light-to-moderate alcohol consumption was associated with a lower incidence of heart failure.
Nearly a quarter of older Medicare beneficiaries hospitalized for heart failure are readmitted within 30 days of discharge, making heart failure a leading cause of hospital readmission in older adults. Very few interventions have been shown to be consistently effective in lowering 30-day all-cause readmission in patients with heart failure. Due to financial penalties associated with higher 30-day all-cause readmission rates mandated by the Affordable Care Act hospitals are implementing interventions without proven benefit such as transition of care approaches. We examined clinical effectiveness of various heart failure medications on 30-day all-cause readmission. Findings from the Digitalis Investigation Group trial suggest that digoxin is efficacious in reducing 30-day all-cause admission in older patients with heart failure and reduced ejection fraction (HR when digoxin was compared with placebo, 0.66; 95% CI, 0.51-0.86), without any adverse effect on mortality or delayed higher readmission rates (PMID: 23490060). Finding the Alabama Heart Failure Project suggest that in real-world older hospitalized patients with heart failure with reduced ejection fraction, digoxin is effective in lowering 30-day all-cause readmission (HR for digoxin, 0.77; 95% CI, 0.63-0.95) as well as the combined end point of 30-day all-cause death or readmission (PMID: 24257326), but not in those with heart failure with preserved ejection fraction (PMID: 24067296). In contrast, discharge use of beta-blockers was not associated with 30-day all-cause readmission, though there was reduction in mortality (PMID: 25554369). Finally, discharge use of renin-angiotensin inhibitors was associated with lower 30-day all-cause readmission (HR, 0.74; 95% CI, 0.56-0.97) and 30-day all-cause mortality (HR, 0.56; 95% CI, 0.33-0.98; JACC. 2014;63:12S). If these findings can replicated in larger and more contemporary heart failure patients, ACE inhibitors and digoxin may provide inexpensive tools for lowering 30-day all-cause readmission in patients with heart failure.
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EFFECTIVENESS OF REMOTE PATIENT MONITORING AFTER DISCHARGE OF HOSPITALIZED PATIENTS WITH HEART FAILURE: THE BETTER EFFECTIVENESS AFTER TRANSITION-HEART FAILURE (BEAT-HF) RANDOMIZED CLINICAL TRIAL

M.K. Ong1,9, P.S. Romano2, S. Edgington1, A.D. Auerbach5, J.T. Black6, J.J. Escarce1,7, T.G. Ganiats4,8, S. Greenfield3, A. Kimchi6, G.C. Fonarow1
1. University of California, Los Angeles, CA, USA
2. University of California, Davis
3. University of California, Irvine
4. University of California, San Diego
5. University of California, San Francisco
6. Cedars-Sinai Medical Center
7. RAND Corporation, University of Miami
8. University of Miami
9. VA Greater Los Angeles Healthcare System

**Importance:** It remains unclear if telemonitoring approaches provide benefits for heart failure (HF) patients following hospitalization.

**Objective:** Evaluate the effectiveness of a care transition intervention using remote patient monitoring at reducing 180-day all-cause readmissions among a broad population of older adults hospitalized with HF.

**Design:** We randomized between October 2011 and September 2013 1,437 patients age 50 or older who were hospitalized and received active treatment for decompensated HF at 6 academic medical centers in California to either intervention (715 patients) or usual care (722 patients) arms of the Better Effectiveness After Transition – Heart Failure (BEAT-HF) study and followed them for 180 days.

**Intervention:** The intervention combined health coaching calls and telemonitoring. Telemonitoring used Bluetooth-enabled equipment that collected daily information about blood pressure, heart rate, symptoms, and weight; centralized registered nurses conducted telemonitoring reviews, protocolized actions, and calls.

**Main Outcomes:** The primary outcome was readmission for any cause within 180 days after discharge. Secondary outcomes were all cause readmission within 30 days, all cause mortality at 30 and 180 days, and quality of life at 30 and 180 days.

**Results:** Median age of participants was 73 years; 45.6% were female, and 22.2% were African American. The intervention and usual care groups did not differ significantly on the primary end point, which occurred in 52.2% and 50.1% of patients, respectively (adjusted hazard ratio, AHR, 1.03; 95% confidence interval [CI], 0.88–1.20; P=0.74). In secondary analyses there were no significant differences on 30 day readmission or 180 day mortality, but there was a significant difference on 180 day quality of life between the intervention and usual care groups.

**Conclusions and Relevance:** Among patients hospitalized for HF, combined health coaching and telemonitoring did not reduce 180-day readmissions. The results suggest further studies are needed to evaluate potential quality of life benefits.
HEART FAILURE: NOVEL APPROACHES FOR DIAGNOSIS AND TREATMENT

009
INDUCTION OF ENDOGENOUS T REGULATORY CELLS IS EFFECTIVE IN TREATING HEART FAILURE AND HEART FAILURE-INDUCED LUNG REMODELING
A. Chen, H. Wang, L. Hou, Y. Chen
Cardiovascular Division and Lillehei Heart Institute, University of Minnesota Medical School, Minneapolis, MN, USA

Congestive heart failure (CHF) is associated with an increase of leukocyte infiltration, pro-inflammatory cytokines and fibrosis in the heart and lung. Regulatory T cells (Tregs) suppress inflammatory responses. We postulated that expansion of Tregs attenuates CHF progression by reducing cardiac and lung inflammation in a pre-clinical CHF model. We investigated the effects of Interleukin-2 (IL-2) plus IL-2 monoclonal antibody clone JES6-1 complexes (IL2/JES6-1) on transverse aortic constriction (TAC)-induced cardiac and lung inflammation and CHF progression in mice. We demonstrated that end-stage CHF causes massive increases of lung leukocytes such as macrophages and T cells, as well as relatively mild cardiac leukocyte infiltration. Administration of IL2/JES6-1 caused a ~6-fold induction of Tregs within CD4+ T cells in the spleen, lung and heart of mice. IL2/JES6-1 treatment of mice with existing TAC-induced left ventricular (LV) failure markedly reduced lung and right ventricular (RV) weight, and improved LV ejection fraction and LV end-diastolic pressure. IL2/JES6-1 treatment significantly increased Tregs, suppressed CD4+ T-cell accumulation, dramatically attenuated leukocyte infiltration including decreasing CD45+ cells, macrophages, CD8+ T cells, and reduced pro-inflammatory cytokine expressions and fibrosis in the lung of mice. Moreover, induction of Tregs by IL2/JES6-1 treatment also significantly attenuated TAC-induced LV hypertrophy fibrosis, and dysfunction. Our data indicate that increasing Tregs attenuates lung and cardiac inflammation, RV hypertrophy and further LV dysfunction in mice with existing LV failure, as well as the development of LV hypertrophy. These data indicate that strategies to properly expand Tregs are useful in preventing LV hypertrophy and dysfunction, and in treating heart failure.
Sirtuins are emerging as key regulators of many biological functions, spanning from cell growth, metabolism to longevity. Members of the sirtuin family need NAD for their catalytic activity. The mammalian genome encodes seven sirtuin isoforms (SIRT1-SIRT7), which are localized in different subcellular compartments. Among them SIRT3 is primarily localized in mitochondria and possesses robust deacetylase activity. Increased expression of SIRT3 has been shown to be associated with increased lifespan of humans. In mitochondria SIRT3 regulates the activity of many metabolic enzymes involved in free-fatty acid oxidation, ROS production and ATP biosynthesis. Because the function of mitochondria also depends on the fusion-fission dynamics of the organelle, this study was undertaken to study the effect of SIRT3 in regulating fitness of mitochondrial population. We found that OPA1, an inner mitochondrial fusion protein is highly acetylated in hearts undergoing pathological stress, including pressure overload hypertrophy, doxorubicin-induced cardiac toxicity and diabetic cardiomyopathy. In SIRTKO hearts mitochondrial population was generally fragmented, where OPA1 was found to be acetylated. In vitro studies showed that lysine (K) acetylation reduced the GTPase activity of OPA1. SIRT3 was capable of deacetylating and preserving the enzymatic activity of OPA1. By mass-spectrometry and mutagenesis analyses we identified K926 and K931 as acetylated sites of OPA1. Furthermore, SIRT3 overexpression prevented doxorubicin-mediated mitochondrial fragmentation and myocyte cell death by deacetylating and activating OPA1. In vivo studies conducted with SIRT3 overexpressing transgenic mice showed that SIRT3 protects the heart from developing cardiac hypertrophy, fibrosis and heart failure by preserving health of mitochondrial population. In summary, our data showed that SIRT3 promotes mitochondrial function not only by regulating activity of metabolic enzymes, but also by regulating mitochondrial dynamics by targeting OPA1. Based on this and other published data I believe that SIRT3 could be a therapeutic target for the treatment of heart failure.
HEART FAILURE: NOVEL APPROACHES FOR DIAGNOSIS AND TREATMENT

011
MONTREAL COGNITIVE ASSESSMENT IS SUPERIOR TO STANDARDIZED MINI-MENTAL STATUS EXAM IN DETECTING MILD COGNITIVE IMPAIRMENT IN HEART FAILURE
K Alagiakrishnan1, D Mah1, J Dyck2, A Senthilselvan3, J Ezekowitz1
1. Department of Medicine, University of Alberta, Edmonton, Alberta, Canada,
2. Department of Pediatrics, University of Alberta, Edmonton, Alberta, Canada
3. School of Public Health, University of Alberta, Edmonton, Alberta, Canada

Aim: This study on mild cognitive impairment (MCI) in heart failure (HF), compares the utility of Montreal Cognitive Assessment (MoCA) to the Mini-Mental Status Exam (MMSE) for diagnosing MCI in a HF population.

Methods: Participants were recruited from the Alberta HEART study at the Mazankowski Alberta Heart Institute in Edmonton and St. Mary’s hospital in Camrose. This study enrolled 53 community adults with 33 HF and 20 controls aged >50 years. Participants were assessed using both the MMSE and MoCA for MCI. In all participants, depression and dementia were ruled out using the DSM IV criteria. MCI was diagnosed using the golden standard, European Consortium Criteria. Sensitivity and specificity analysis, positive and negative predictive values, likelihood ratios and kappa statistic were calculated.

Results: The mean age was 72.8 years (SD 8.4), 60.4% were females and 34% had underlying ischemic heart disease. Overall, two thirds of patients (22/33, 66%) with HF had MCI. In comparison to European Consortium Criteria, the sensitivity and specificity of MoCA were 82% and 91% in identifying individuals with MCI, and MMSE were 9% and 91%, respectively. The positive and negative predictive values for MoCA were 95% and 71%, and for MMSE were 67% and 33%, respectively. Kappa statistics showed good agreement between MoCA and consortium criteria (kappa = 0.68) and a low agreement between MMSE and consortium criteria (kappa = 0.07).

Conclusion: Cognitive dysfunction is common in patients with HF. Overall, the MoCA is a better screening tool than MMSE for MCI in HF patients.
Study is supported by Motyl Endowment Cardiac Sciences Summer Studentship Award.
OPTIMIZING EVALUATION OF PATIENTS WITH LOW TO INTERMEDIATE RISK ACUTE CHEST PAIN: WHAT IS THE RELATIVE VALUES OF STRESS MYOCARDIAL PERFUSION IMAGING WHEN INCORPORATING STRESS-ONLY IMAGING VERSUS CARDIAC COMPUTED TOMOGRAPHY

J.J. Mahmorian
Houston Methodist DeBakey Cardiology Associates, Houston, TX, USA

There remains considerable controversy regarding the relative value of stress myocardial perfusion (SPECT) versus cardiac computed tomography angiography (CTA) for evaluating patients (pts) with acute chest pain (ACP). In this regard, we recently performed a prospective randomized observational study in 598 ACP pts. who had CTA vs. SPECT assessing several important clinical metrics: length of hospital stay, test feasibility, time to diagnosis, diagnostic accuracy, radiation exposure and overall cost. Stress-only (SO) SPECT was performed in 24% pts. Pts. were followed for a median of 6.5 months with a 3.8% cardiac event rate defined as death or an acute coronary syndrome. Of 2994 patients screened, 1703 (56.9%) were not candidates for CTA due to prior cardiac disease (41%) or imaging contraindications (16%). Time to diagnosis (8.1±8.5 vs. 9.4±7.4 hours) and length of hospital stay (19.7±27.8 vs. 23.5±34.4 hours) were significantly shorter with CTA vs. SPECT (p=0.002). However, time to diagnosis (7.0±6.2 vs. 6.8±5.9 hours, p=0.20), length of stay (15.5±17.2 vs. 16.7±15.3 hours, p=0.36) and hospital costs ($4,242±$3,871 vs. $4,364±1781, p=0.86) were comparable with CTA vs. SO SPECT, respectively. SO was also superior to conventional SPECT regarding all of the above metrics and significantly reduced radiation exposure (5.5+4.4 vs. 12.5+2.7 mSv, p<0.0001). Thus, stress SPECT when optimized with SO imaging is similar to CTA in time to diagnosis, length of hospital stay, and cost with improved prognostic accuracy and less radiation exposure. Our results emphasize the importance of SO imaging particularly in low-intermediate risk ED patients who are a population likely to have a normal test result.
Advances in Cardiovascular Imaging That Will Impact Patient Care

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PET AND CT ASSESSMENT OF CORONARY FLOW PHYSIOLOGY

D.S. Berman¹, M. Motlagh¹, D. Dey¹, J.D. Friedman¹, S.W. Hayes¹, L.E.J. Thomson¹, L. Shaw², B.K. Tamarappoo³, G. Germano¹, P. Slomka¹

1. Cedars-Sinai, Los Angeles, California USA
2. Emory University, Atlanta, Georgia, USA
3. Cleveland Clinic, Cleveland, OH, USA

Assessment of fractional flow reserve (FFR) and coronary flow reserve (CFR) by invasive coronary angiography (ICA) provide physiologic assessments that complement the anatomic assessment of coronary stenosis for guiding patient management of patients with coronary artery disease (CAD). FFR provides assessment of epicardial lesion flow limitation, while CFR assesses flow across the coronary vascular tree, including the microvasculature. Discordance of 40% between these measures has been documented. Normal CFR can be seen in lesions with abnormal FFR, documenting sufficient capacity to increase flow due to increased metabolic demand, and normal FFR can be seen in lesions with abnormal CFR in the presence of microvascular dysfunction. Coronary CT angiography (CCTA) and positron emission tomography (PET) myocardial perfusion imaging (MPI) can provide multiple assessments of coronary physiology beyond coronary stenosis and perfusion defect. PET MPI, the gold standard of CFR measurement, is now routinely assessed in clinical practice. Abnormal PET CFR has shown an adverse prognosis in patients with CAD, even in the absence of demonstrable coronary plaque. As PET CFR declines, mortality increases in patients with known or suspected CAD, across the spectrum of regional perfusion defect findings. CCTA can assess coronary plaque burden and adverse plaque characteristics. Automated, reproducible quantitative assessments of these CCTA features correlate strongly with intravascular ultrasound measurements and provide incremental information over coronary stenosis alone in prediction of ischemia and in prognostic evaluation. FFR by CT (FFRct) can be assessed from a routinely acquired CCTA without requiring pharmacologic vasodilation. FFRct has been shown to correlate well with and to be a better predictor of invasive FFR than coronary stenosis. Thus, multiple assessments beyond stenosis and myocardial perfusion defects can be assessed with CCTA and PET MPI. These measurements, individually or in selected patients in combination, may be useful in guiding management of the CAD patient.
NOVEL METHODS OF ISCHEMIA EVALUATION BY COMPUTED TOMOGRAPHY

J.K. Min
Weill Cornell Medicine, Dalio Institute of Cardiovascular Imaging, New York, NY, USA

Over the last decade, the concept of measuring myocardial perfusion as a metric of ischemia has been challenged. Invasive measurements of ischemia by fractional flow reserve (FFR)—a ratio of a hyperemic pressure distal to a stenosis to the ratio before the stenosis—guide decisions of coronary revascularization in a manner that results in improved event-free survival. Given this, there has been a shift in goals from global or regional myocardial ischemia to coronary lesion-specific ischemia.

Recently, the feasibility of calculating FFR from a typically acquired coronary CT angiogram (FFR_{CT}) has been demonstrated. Three prospective multicenter trials have demonstrated high diagnostic performance of FFR_{CT} versus an invasive gold standard, with recent data revealing reduced costs with an FFR_{CT} -guided strategy versus standard of care. Importantly, these reduced costs are associated with identical outcomes from other standard of care approaches.

This talk will address issues of myocardial versus coronary lesion-specific ischemia, and will discuss the clinical outcomes data accumulated for FFR_{CT}.

(James K. Min serves as a consultant to HeartFlow, the company that commercializes FFR_{CT}).
ECHOCARDIOGRAPHIC ASSESSMENT OF LEFT VENTRICULAR DIASTOLIC FUNCTION: AN UPDATE

S.F. Nagueh Armanious
Methodist DeBakey Heart and Vascular Center, Houston, TX, USA

Left ventricular (LV) diastolic dysfunction is an important contributor to symptoms of dyspnea and reduced exercise tolerance in patients with HFrEF and in those with HFpEF. Echocardiography can be used to diagnose diastolic dysfunction, to estimate LV filling pressures and to predict clinical events in several patient populations including patients with heart failure, CAD and atrial fibrillation. Assessment is based on 2D and Doppler findings including LV EF, left atrium (LA) maximum volume index, LV wall thickness, presence or absence of valvular heart disease. Importantly, mitral inflow velocities and time intervals, tissue Doppler derived mitral annulus early diastolic velocity (e’) and peak velocity of tricuspid regurgitation (TR) jet can be used in an algorithm that can be applied to patients with depressed EF and patients with normal EF and myocardial disease. In addition, there are novel indices that include LV global longitudinal and circumferential early diastolic strain rate and LA strain. Recent studies have shown not only the diagnostic but also the prognostication potential of these indices in patients presenting with acute MI and in patients with atrial fibrillation. Aside from noninvasive hemodynamic assessment at rest, exercise stress echocardiography can provide unique insights into LV diastolic function. Thus, a diastolic stress test can be considered in patients presenting with dyspnea but who have normal LV filling pressures at rest.
ADVANCES IN CARDIOVASCULAR IMAGING THAT WILL IMPACT PATIENT CARE

016
SELECTING BETWEEN CORONARY CTA VERSUS FUNCTIONAL TESTING: DOES IT MAKE A DIFFERENCE?
R. Blankstein
Brigham and Women's Hospital, Boston, MA, USA
Harvard Medical School, Boston, MA, USA

Recent advances in both cardiac CT and functional testing techniques (e.g., exercise treadmill testing, nuclear perfusion imaging, MRI, and stress echocardiography) have improved our ability to diagnose various stages of coronary artery disease. However, among patients who require further testing, deciding on the best initial testing option is not always straightforward, and data comparing these approaches remains limited. Recently several randomized trials have compared the use of coronary CTA to various functional testing approaches. Collectively, these studies suggest that use of cardiac CT may lead to greater intensification of subsequent medical therapies as well as a small reduction in incident myocardial infarctions. However, use of cardiac CT is also associated with a higher rate of downstream invasive angiography and coronary revascularization. In order to promote efficient, cost-effective, and patient-centered care, it is imperative for clinicians and imagers to select the most appropriate test for each patient. In addition to considering local availability and expertise, the decision requires a careful consideration of both clinical factors as well as the technical strengths and limitations of each exam.
ADVANCES IN CARDIOVASCULAR IMAGING THAT WILL IMPACT PATIENT CARE

Looking Into High-Risk Plaque and DES Biology: High-Speed Integrated OCT-NIRF

J.W. Kim
Korea University Guro Hospital, Seoul, South Korea

A growing body of evidence has provided key mechanistic insight into atherosclerosis. The major goal of current cardiovascular imaging is to identify the high-risk vulnerable plaques (VP) before rupture, and many of the VP biological characteristics including inflammation, oxidative stress, and intraplaque hemorrhage are a suitable target for molecular imaging. While conventional imaging technologies allow visualization of the cardiovascular structures and assess biophysical properties, most of current imaging technologies are still limited to the evaluation of its anatomical features. To answer these unmet needs, our group has developed the fully integrated catheter system having both imaging properties of OCT and NIRF in a single fiber based on the OCT clinical platform. This highly translatable integrated OCT-NIRF imaging, as combined with a clinically approved NIRF emitting ICG, was able to simultaneously estimate both microanatomy and molecular detail in coronary plaque and DES as well. Moreover, with newly developed NIRF probe targeting specific receptor on plaque macrophages, OCT-NIRF catheter imaging system could have the potential to in vivo image macrophage subsets associated with the exposure to Hb in intraplaque hemorrhages, key feature of vulnerable plaques (VP). This novel imaging strategy could be a promising personalized approach for imaging-guided VP stabilization.
ADVANCES IN CARDIOVASCULAR IMAGING THAT WILL IMPACT PATIENT CARE

018
PET/CT-DETERMINED PERFUSION AND CORONARY FLOW IN CLINICAL ROUTINE
T.H. Schindler
Johns Hopkins University, Baltimore, MD, USA

Positron emission tomography/computed tomography (PET/CT)-determined myocardial perfusion combined with myocardial blood flow (MBF) quantification in ml/g/min has evolved from research application to clinical application in the identification and characterization of multivessel coronary artery disease (CAD) process. Adding the assessment of hyperemic MBF increase during pharmacologic vasodilation and at rest with the resulting myocardial flow reserve (MFR = MBF during stress/MBF at rest) extends the scope of conventional myocardial perfusion imaging not only to the detection of the most advanced and culprit CAD, as signified by the stress-related regional myocardial perfusion deficit, but also to the less severe or intermediate stenosis in patients with multivessel CAD. Due to the non-specific nature of the hyperemic MBF and MFR, however, the interpretation of hyperemic flow increases with PET/CT demands an appropriate interpretation in the context with microvascular function, wall motion analysis, and eventually underlying coronary morphology in CAD patients. Such diagnostic approach with cardiac PET/CT perfusion or flow measurements may emerge as pivotal tool to individualize and guide the decision-making process for coronary revascularization procedures in CAD patients in the near future that remains to be tested clinically.
ROLE OF CAC TESTING IN 2016: SHARED DECISION MAKING FOR INFORMED CHOICES

K. Nasir
1. Center for Healthcare Advancement & Outcomes, Baptist Health South Florida, Miami, FL, USA
2. Miami Cardiac & Vascular Institute (MCVI), Baptist Health South Florida, Miami FL
3. The Johns Hopkins Ciccarone Center for the Prevention of Heart Disease, Baltimore MA
4. Department of Medicine Herbert Wertheim College of Medicine & Department of Epidemiology, Robert Stempel College of Public Health, Florida International University, Miami FL, USA

The 2013 American College of Cardiology and the American Heart Association (ACC–AHA) parted the emphasis on cholesterol concentrations and target goals; instead accentuate the importance of absolute risk in guiding treatment decisions, matching of statin intensity with increasing individualized risk as well as support flexible goals for those with lower risk. Most importantly, it firmly placed the patient in driver seat to make informed choices based on their preferences, values, understanding of risk. However the guidelines considerably broadened the scope of statin candidates with more than half of adults age>40 years without established CVD are candidates for lifelong statin therapy. The dilemma of mass ‘statinization’ adding burden on an already cost-constrained healthcare system, are heightened by emerging data that suggest half of those eligible for statin therapy have a significantly lower 10-year risk than the threshold suggested by guidelines to consider them. With significant increase in population eligible for treatment, accurate identification of low-risk statin candidates who are less likely to yield meaningful benefit is critical to facilitate appropriate resource allocation and shared decision-making processes. A recent study from the Multi-ethnic of Atherosclerosis (MESA) study has demonstrated that nearly half of statin candidates had no detectable coronary artery calcium (CAC), and absence of CAC reclassified approximately half of statin therapy candidates, especially in the intermediate risk range of 5-20%, to a group that would not be considered eligible for therapy by current recommendations. Absence of CAC can afford significant value in promoting shared decision-making for flexible treatment goals in uncertain individuals deemed eligible for lifelong statins.
Computational Tomography Angiography vs. Coronary Angiography: A 3D Vessel Feature Comparison and Validation

J.A. Garcia
Orlando Health, Orlando, FL, USA

Background: Differences in vessel features between computed tomography angiograms (CTA) and coronary angiograms (CA) have not been rigorously studied, therefore we sought to validate CTA 3-dimensional (3D) vessel data against coronary angiography by forward projecting 3D-CTA based centerlines and diameters to the same view as used for standard angiograms.

Methods: We retrospectively analyzed 20 patients with both modalities. First, the features of 3D coronary tree including vessel centerlines and effective diameters were generated and exported from the CTA images. The derived 3D model was then imported into a coronary modeling software environment enabling advanced quantitative analysis, forward projection, and optimal view map generation. The validation on vessel features entailed measuring the root-mean-square (RMS) errors of centerlines and diameters between the 2D arterial tree manually identified from the angiogram and the 3D model created from CTA after this model was projected to the identical angiographic view. Offline working view selection using the CTA reconstructions versus operator selected working views were then compared in terms of vessel foreshortening.

Results: The RMS error of vessel centerlines and diameters between the 3D CTA models and 2D arteries from angiographic views were $3.42 \pm 0.92$ mm and $0.84 \pm 0.26$ mm for the left coronary arterial tree, and $3.56 \pm 1.26$ mm and $0.83 \pm 0.67$ mm for the right coronary arterial tree, respectively. When comparing the vessel foreshortening from operator selected views to optimized views predicted by 3D CTA models, vessel foreshortening could be reduced from $9.8\% \pm 6.66$ to $1.42 \pm 0.93\%$ (P=0.005).

Conclusion: The vessel features in terms of centerline and diameter created from CTA are not significantly different from those identified on CA. Use of the 3D CTA model to perform pre-procedural PCI optimal view selection may reduce vessel foreshortening for interventional working views.
With the progressing aging of the world’s population, cardiovascular disease will continue to significantly impact millions of individuals throughout the globe. This disorder remains one of five leading causes of death that are cardiac disease, cancer, chronic lower respiratory disease, stroke, and traumatic accidents. As a result, unique avenues for targeting the treatment of cardiovascular disease are desperately needed to translate knowledge of cellular mechanisms into effective clinical care. Wnt1 inducible signaling pathway protein 1 (WISP1), a matricellular protein and a downstream target of the wingless pathway Wnt1, is one such target to consider that governs cellular protection, stem cell proliferation, and tissue regeneration in multiple disorders. WISP1 has a close but complex relationship with a number of proliferative and protective pathways that include phosphoinositide 3-kinase (PI 3-K), protein kinase B (Akt), interleukins, small non-coding ribonucleic acids (RNAs), sirtuin silent mating type information regulation 2 homolog 1 (Saccharomyces cerevisiae) (SIRT1), and the mechanistic target of rapamycin (mTOR). In addition, WISP1 can influence immune based cells that can hold a fine biological control over cell death processes that involve apoptosis as well as autophagy. Further analysis and translation of these pathways may offer the necessary insight for the development of new treatments for cardiovascular disease that exceeds the efficacy of current traditional care protocols.
GENETIC BASIS OF CARDIAC DYSFUNCTION: PROTECTIVE ROLE OF ALL-TRANS RETINOIC ACID AND HISTONE DEACETYLASE INHIBITOR

K.N. Pandey, U. Subramanian, P. Kumar, I. Mani, I. Kessler, R. Raghavaraju
Department of Physiology, Tulane University Health Sciences Center, School of Medicine, New Orleans, LA, USA

In the present study, we examined the effect of genetically determined differences in the guanylyl cyclase-A/natriuretic peptide receptor-A (GC-A/NPRA) gene (Npr1) copies on the expression levels of proinflammatory mediators, matrix metalloproteinases (MMPs), and cardiac hypertrophic markers in Npr1 gene-targeted mouse models. We also determined whether stimulation of Npr1 by all-trans retinoic acid (RA) and histone deacetylase (HDAC) inhibitor, sodium butyric acid (SB) suppresses the expression of cardiac disease markers. We utilized Npr1 gene-disrupted heterozygous (Npr1+/-, 1-copy), wild-type (Npr1++/+, 2-copy), and gene-duplicated (Npr1++/++, 3-copy) mice, which were treated intraperitoneally with RA, SB, and a combination of RA/SB, hybrid drug (HB) for 2 weeks. Untreated 1-copy haplotype mice showed significantly increased blood pressure, heart weight/body weight (HW/BW) ratio, hypertrophic markers, including beta-myosin heavy chain (beta-MHC) and proto-oncogenes (c-fos and c-jun), proinflammatory mediator nuclear factor kappa B (NF-kB), and MMPs (MMP-2, MMP-9) compared with 2-copy and 3-copy mice. The heterozygous 1-copy mice treated with RA, SB or HB, exhibited significant reduction in the expression of beta-MHC, NF-kB, c-fos, c-jun, MMP-2, and MMP-9. In drug-treated animals, the activity and expression levels of HDACs were significantly reduced and histone acetyltransferase activity and expression levels were increased. The drug treatments markedly increased the fractional shortening and reduced the systolic and diastolic dysfunction of the haplotype Npr1+-/- mice hearts. The present findings demonstrate that a decreased Npr1 copy number enhances the expression of hypertrophic markers, proinflammatory mediators, and MMPs; on the contrary an increased Npr1 gene-copies as well as treatments with RA, SB, and HB repressed the cardiac disease markers and protect the heart in a Npr1 gene-dose-dependent manner.
FINDING NOVEL ANTI-FIBROTIC THERAPIES USING A DUAL-REPORTER MOUSE THAT TRACKS FIBROBLAST CELL TRANSITIONS IN VIVO AND IV VITRO

C.S. Long1, V. Martinelli2, S. Zacchigna2
1. University of Colorado, Denver, CO, USA
2. International Center for Genetic Engineering and Biotechnology, Trieste, Italy

Cardiac fibroblasts serve important roles in cardiac structure and intercellular communication and bear primary responsibility for the maintenance of the cardiac extracellular matrix. Two critical aspects of cardiac fibroblast phenotype in response to injury are well recognized. First, the transition into the myofibroblast phenotype, so named due to their expression of contractile proteins, like smooth muscle alpha-actin which contribute to wound contracture. The myofibroblast is the primary source of collagen deposition which may persist for long periods of time following resolution of injury and scar maturation. Second, the physiologic resolution of the wound healing response requires the myofibroblast to inactivate these functions and return to the quiescent basal state. It is presumed that termination occurs by apoptosis, although the regulatory mechanisms remain undefined. Thus physiologically appropriate functions of cardiac fibroblasts require profound phenotypic transitions, and termination of the activated phenotype. Studying hepatic fibrosis, David Brenner reported on a unique transgenic reagent (RFP/GFP double reporter mice) which simultaneously express the red fluorescent protein (RFP) under control of the alpha-smooth muscle actin (aSMA) promoter and the enhanced green fluorescence protein (EGFP) under the control of collagen α1 (I) promoter. We have taken advantage of these animals to study these phenotypic transitions both in vivo and in vitro targeting the heart. For the in vitro studies we have used an automated program of “counting” red, green and yellow (red+green) cells and have subjected these cells to high-throughput screening in the presence of chemical libraries and candidates found to have the most promise with this approach in vivo. We believe this represents a unique approach for defining therapeutic approaches to studying pathologic fibrosis with great potential.
Inflammation plays a monumental role in the development and progression of atherosclerosis (ATH) has been reported by many investigators. This is completely unknown whether infiltrated monocytes differentiate into various macrophage phenotypes, and their role in inflammation and atherosclerosis. We will demonstrate data on acute and chronic stages of inflammation and the type of infiltrated macrophages. Furthermore, these animals were treated with bone morphogenic protein (BMP-7) to determine their effects on macrophage phenoswitching, inflammatory cytokines and ultimately on atherosclerosis. Our data suggest that there was a decrease in arterial systolic velocity in a model of ATH following partial left carotid artery (PLCA) ligation. This decrease was associated with infiltration of monocytes and increased pro-inflammatory cytokines. Next, BMP-7 treatment inhibits plaque formation and increases arterial systolic velocity. Moreover, we found increase in M2 macrophage differentiation with significant increase in anti-inflammatory cytokine following BMP-7 treatment. We will present data on mechanistic action of BMP-7 in the protection of developed atherosclerosis.
CELLULAR AND MOLECULAR MECHANISMS OF CARDIOVASCULAR DISEASES: FROM BASIC RESEARCH TO TRANSLATIONAL MEDICINE

025
EXTRACELLULAR MATRIX TURNOVER IN VASCULAR CALCIFICATION

W. Kong
Department of Physiology and Pathophysiology, School of Basic Medical Sciences, Peking University, Beijing, P.R. China

Cumulative studies have demonstrated that extracellular matrix (ECM) turnover play a critical role during cardiovascular remodeling. Intima calcification is highly correlated with atherosclerotic plaque burden, but the underlying mechanism is poorly understood. We recently reported that cartilage oligomeric matrix protein (COMP), a component of vascular extracellular matrix, is an endogenous inhibitor of vascular smooth muscle cell calcification. Herein we further investigate whether COMP affects atherosclerotic calcification. ApoE−/−COMP−/− mice fed with chow diet for 12 months manifested more extensive atherosclerotic calcification in the innominate arteries than did ApoE−/− mice. To investigate which origins of COMP contributed to atherosclerotic calcification, bone marrow (BM) transplantation was performed between ApoE−/− and ApoE−/−COMP−/− mice. Enhanced calcification was observed in mice transplanted with COMP−/−ApoE−/− BM compared to mice transplanted with ApoE−/− BM, indicating that BM-derived COMP may play a critical role in atherosclerotic calcification. Furthermore, microarray profiling of wild type and COMP−/− macrophages revealed that COMP-deficient macrophages exerted atherogenic and osteogenic characters. Integrin β3 protein was attenuated in COMP−/− macrophages, and overexpression of integrin β3 inhibited the shift of macrophage phenotypes by COMP deficiency. Furthermore, AAV2-integrin β3 infection attenuated atherosclerotic calcification in COMP−/−ApoE−/− mice. Mechanistically, COMP bound directly to β-tail domain of integrin β3 via its C-terminus, and blocking of the COMP-integrin β3 association by β-tail domain mimicked the COMP deficiency-induced shift in macrophage phenotypes. Similar as COMP deficiency in mice, transduction of AAV2-β-tail domain enhanced atherosclerotic calcification in ApoE−/− mice. In summary, these results reveal that COMP deficiency acted via integrin β3 to drive macrophages towards the atherogenic and osteogenic phenotype and thereby aggravate atherosclerotic calcification.
Vulnerable plaques are hallmarked by more pronounced inflammation and neoangiogenesis. Although angiogenesis and lymphangiogenesis are driven by partly overlapping cues, and especially under inflammatory conditions go hand in hand, plaque lymphangiogenesis only in one single earlier report been linked to plaque stability. In this paper we show that lymph vessels are almost exclusively present in advanced atherosclerotic plaque, and that their presence is correlated with plaque inflammation. Employing a genomics-driven approach we identified a gene module highly associated with plaque lymph vessel density and we have pinpointed the most critical genes within this cluster, which were hitherto not linked to lymphangiogenesis. Loss of function studies in vitro showed an overt impact of two of four central hub genes of this module in lymph endothelial differentiation and function. Microarray analysis of lymphatic endothelial cells with silenced lead expression revealed the regulatory network of plaque lymphangiogenesis, which was seen to be enriched in the plaque lymphangiogenesis related module. Finally, blockage of this network in vivo by plaque confined silencing of one of the network members not only led to reduced lymphangiogenic response, but also to plaque expansion, suggesting that plaque lymphatics actually protect against atherosclerosis.
GENOME-WIDE IDENTIFICATION AND CHARACTERIZATION OF CARDIAC HYPERTROPHY-RELATED LONG NONCODING RNAS (CH-LNCRNAS) IN MICE

D-Z. Wang, Z-P. Wang
Boston Children's Hospital, Boston, MA, USA

Long noncoding RNAs (LncRNAs) are RNA transcripts longer than 200 nucleotides that lack protein-coding potential. Although thousands of LncRNAs have been identified, only a few have been linked to cardiac gene expression and function. In this study, we identified, from genome-scale RNA-seq data, 12 candidate LncRNAs associated with cardiac hypertrophy. The expression of these LncRNAs was altered in mouse models of cardiac hypertrophy induced by transverse aortic constriction (TAC)- or CnA transgene. To determine the function of these LncRNAs, we developed an adeno-associated virus serotype 9 (AAV9)-based functional screening in postnatal mice. An AAV9:cTNT vector, in which the cardiac troponin T (cTNT) promoter was used to direct cardiac-specific expression of target genes, was utilized to overexpress or knockdown candidate LncRNAs in mouse hearts. Postnatal day1 wild type or CnA transgenic pups were injected with AAV9 viruses and cardiac function was measured one and two months later. Thus far, we have tested 15 candidate LncRNAs for both gain- and loss-of-function studies. Among them, two LncRNAs were demonstrated regulating hypertrophy growth when knocked down. Finally, we identified the human homologues of CH-LncRNA through analyzing the conservation of the promoter regions of LncRNA genes. We showed that the expression of these human CH-LncRNA was dysregulated in human diseased hearts, suggesting the functional conservation of these LncRNAs in cardiac disease. Our study therefore demonstrated that LncRNAs are important regulator of cardiac hypertrophy and disease.
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SHORT AND LONG NON-CODING RNAs AS BIOMARKERS OF ACUTE CARDIAC CONDITIONS
Y. Devaux
Luxembourg Institute of Health, Luxembourg

The first draft of the human genome was published in 2001. However, it is only 10 years later that the ENCODE International Consortium revealed that, while more than 80% of the human genome is transcribed into RNAs, only less than 2% of these RNAs are subsequently translated into proteins. This discovery implied that the vast majority of DNA sequences within the human genome are transcribed as non-protein coding RNAs or non-coding RNAs. Multiple types of non-coding RNAs have been uncovered, with distinct biological function and cellular localization. Non-coding RNAs can be classified according to their size: microRNAs (miRNAs) are usually shorter than 25 nucleotides and long non-coding RNAs (lncRNAs) are typically longer than 200 nucleotides. The finding that both miRNAs and lncRNAs are present in the bloodstream led to the investigation of their potential as biomarkers. A plethora of studies revealed that circulating miRNAs are regulated after an acute cardiac event, and some of them reported that miRNAs might constitute a reservoir of novel cardiac biomarkers. For instance, cardiac-enriched miR-208 and miR-499 are highly up-regulated in the blood following acute myocardial infarction as a result of cardiomyocyte necrosis. MicroRNA-150 was found to predict left ventricular remodeling after acute myocardial infarction. A panel of 3 miRNAs, including miR-150, accurately discriminated patients with unstable angina pectoris from patients with non-coronary chest pain. MicroRNA-423 was identified as a biomarker of acute heart failure. Brain-enriched miR-124 predicts neurological outcome and survival after cardiac arrest. The biomarker value of lncRNAs has been only recently revealed by a few studies showing that lncRNAs are present in the blood and predict heart failure after acute myocardial infarction. Therefore, non-coding RNAs represent a novel class of potential cardiac biomarkers. Whether they can be used for personalized healthcare remains to be further investigated.
A major challenge to the development of cardiac therapeutics is the delivery of agents selectively to cardiac myocytes with little or no penetrance into other cell types. Plasmid based delivery suffers from low efficiency and requires direct injection in the myocardium; viral vectors have the drawback of pre-existing immunity or rapid development of immunity upon exposure and low efficiencies. Cell penetrating peptides (CPP) are small 6-30 amino acid peptides able to carry cargo ranging from small peptides, to proteins, DNA, siRNA, radio-isotopes, viral particles and nanoparticles across the cellular membranes resulting in internalization of the intact cargo. Our prior work utilizing a combinatorial in vitro and in vivo approach of phage display led to the identification of a 12-amino acid peptide, APWHLSSQYSRT, which we termed Cardiac Targeting Peptide (CTP), because of its ability to transduce the mouse heart tissue efficiently in vivo after an intravenous injection. Following injection, 6-carboxyfluorescein (6-CF) labeled CTP was internalized throughout normal mouse heart-tissue, as shown by co-localization of the peptide with the cytoplasmic markers actin and exclusion from laminin, a plasma membrane marker, in confocal images. Additionally, a time-course experiment using CTP labeled with a substantially larger fluorescent marker, streptavidin-AF488 (SA488) injected intravenously showed robust cardiac uptake at 30 mins without significant uptake by lungs, brain, gut, liver, spleen, adipose tissue or skeletal muscle. Some fluorescence was seen in kidney tissue at later time points, likely reflecting excretion of the peptide or the fluorescent marker. Biotinylated CTP conjugated with neutravidin-labeled fluospheres localized to the heart as determined by in vivo whole mouse live imaging. In contrast, fluospheres alone and a scrambled control peptide conjugated to fluospheres failed to localize to the heart, with the fluorescence immediately dissipating throughout the mouse body. Incubating human explanted heart tissue from patients undergoing heart transplant with CTP labeled with 6-CF showed robust transduction of cardiomyocytes, with sparing of fibrous scar tissue. The peptide localized to the cytoplasm with punctate appearance, suggesting localization to vesicular compartments without any fluorescence seen in the nucleus. This robust transduction of explanted human heart was not due to a simple increase in plasma membrane permeability, as evidenced by lack of uptake of Evans Blue dye. A scrambled control peptide and 6-CF alone showed none to minimal uptake, while 6-Arginine, a known non-tissue specific CPP showed robust cardiac uptake as well.

Hence we have identified a novel CPP that is able to target the murine heart specifically and efficiently and has the ability to carry relatively large cargo. Further studies are warranted to understand it’s mechanism of transduction as well as study its utility as a cardiac targeting agent.
DECIPHERING THE ROLE OF MITOPHAGY IN THE HEART DURING FASTING

Q. Liang
New York Institute of Technology College of Osteopathic Medicine, Old Westbury, NY, USA

Alternate-day fasting or starvation is beneficial to the heart, but the underlying mechanism remains speculative. Starvation activates general autophagy, which may contribute to the cardioprotective effect of fasting. Increased mitochondrial degradation or mitophagy is cardioprotective under certain conditions. However, it is unclear whether mitophagy is involved in fasting-induced cardioprotection. In this study, we investigated the functional significance of mitophagy in the heart during fasting. We created a novel mitophagy reporter transgenic mouse line that expresses mito-Rosella, a mitochondria-targeted dual-emission biosensor comprising a pH-stable RFP linked to a pH-sensitive GFP. These mice were subjected to fasting, and treated with vehicle or lysosomal inhibitors pepstatin A (pepA)/ E64d. Mitochondria that are being degraded in the lysosome are seen as red puncta on the overlaid confocal images. Mitophagy flux is measured as the difference in the numbers of red puncta in the presence and absence of pepA/E64d. A 24-hour fasting increased mitophagy flux in the heart by 44.2% as compared with normal feeding, which was accompanied by increased LC3-II protein levels in both cardiac tissue lysates and the mitochondrial fractions, suggesting that 24-hour fasting enhanced both autophagy and mitophagy. Surprisingly, the 48-hour starvation decreased mitophagy flux by 50.1% and 28% as compared to 24-hour fasting and normal feeding, respectively. Also, LC3-II protein levels were increased in cardiac tissue lysates but reduced in the mitochondrial fractions, suggesting that the 48-hour fasting enhanced autophagy but inhibited mitophagy, in contrast to the effects of 24-hour fasting. These results demonstrated time-dependent differential effects of fasting on cardiac autophagy and mitophagy, suggesting that mitophagy and autophagy must be regulated by different signaling pathways. Overexpression of E3 ligase Parkin, a positive regulator of mitophagy, restored mitophagy but impaired cardiac function after 48-hour fasting, suggesting that reduced mitophagy is an adaptive response essential for maintaining cardiac function during starvation.
DOES CYSTATIN SN INFLUENCE ON CYSTATIN C LEVEL IN ISCHEMIA AND PREVIOUS MYOCARDIAL INFARCTION?

N.V. Goncharova¹, G.S. Russkikh², M.M. Gevorgyan¹, N.P. Voronina², Ts.P Korolenko³, N.A. Kikhtenko¹, T.A. Korolenko¹
¹. Inst. Physiol. Fund. Med., Novosibirsk, Russia
². Inst. Biochemistry, Novosibirsk, Russia
³. Medical University, Novosibirsk, Russia

Objectives: To investigate whether patients with ischemic heart disease and previous myocardial infarction (MI) display altered serum cystatin C/cystatin SN ratio.

Background: Cystatin C, the extracellular inhibitor of cysteine proteases with protective role in vascular remodeling, was recently suggested as a candidate biomarker in CV pathology, but cystatin SN belonging to cystatin C1 superfamily, can neutralize the cystatin C inhibition of cathepsin B in circulating fluids.

Methods: 34 male patients (61.8 ± 7.3 years) with MI, treated by statins, were enrolled in a study from the Outpatient Clinic N 1 of Novosibirsk. The control group consisted of 25 healthy persons (50-65 years old). Serum CRP-hs, Cystatin C (immunoturbidimetric method), Cystatin SN (CST1) by ELISA kits (Cusabio, China) were assayed.

Results: In persons, aged 50-65, an elevation in serum cystatin SN (3.90±0.45 versus control 2.43±0.20 ng/ml, p<0.001) and increased cystatin C (1.11±0.23 mg/L, p< 0.01) was shown versus healthy persons, aged 20-40 years. Statin treatment in patients with ischemia and previous MI normalized dyslipidemia, however increased CRP-hs (p<0.001) as well as increased cystatin C level C (2.05 ± 0.21 mg/L, p < 0.001) vs the control (aged 50-65) were still noted, but serum cystatin SN level decreased.

Conclusions: Decreased cystatin SN level in patients with ischemia and MI can influence on inhibition in cystatin C/cathepsin B, followed by changes in cystatin C concentration in circulating blood.
INTERVENTIONAL CARDIOLOGY

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CLINICAL DECISION-MAKING USING FRACTIONAL FLOW RESERVE IN ACUTE CORONARY SYNDROMES

B.F. Uretsky
University of Arkansas for Medical Sciences, Little Rock, AR, USA

Background: Deferring percutaneous coronary intervention (PCI) in non-ischemic lesions by fractional flow reserve (FFR) is associated with excellent long-term prognosis in patients with stable ischemic heart disease (SIHD). While FFR is increasingly being used for clinical decision-making in acute coronary syndrome (ACS) patients with intermediate lesions, its effect on long-term prognosis has not been well established.

Methods: 206 consecutive ACS patients with 262 intermediate lesions and 370 patients with SIHD (528 lesions) in whom revascularization was deferred based on a non-ischemic FFR (>0.75) were studied. Primary outcome measure was a composite of myocardial infarction (MI) and target vessel failure (TVF) (MACE).

Results: In the entire cohort, long-term (3.4±1.6 years) MACE rate was higher in the ACS compared with the SIHD group (23% vs. 11%, p < 0.0001). After propensity score matching, (200 patients/group), MACE remained significantly higher (ACS, 25 % vs. SIHD, 12%; p<0.0001). On Cox proportional hazards analysis for MACE, ACS had HR 2.8 (95% CI 1.9-4.0; p<0.0001). In both the matched and unmatched cohorts, across all FFR categories, ACS patients had a significantly higher annualized MI/TVR rate compared with SIHD (P<0.05). ROC analysis identified an FFR cutoff (best predictive accuracy for MACE) of <0.84 for ACS (MACE 21% vs. 36%; p=0.007) and <0.81 for SIHD (MACE 17% vs. 9%; p=0.01).

Conclusion: Deferring PCI based on non-ischemic FFR in patients with initial presentation of ACS is associated with significantly worse outcomes compared with SIHD using thresholds developed for SIHD. Caution is warranted in using FFR for clinical decision-making in ACS patients using values derived from patients with SIHD and suggests the possibility of using a higher threshold (FFR >0.84) for deferral of intervention in ACS patients.
INTERVENTIONAL CARDIOLOGY

033

EXPEDITIOUS REPERFUSION IN NON-ST SEGMENT ELEVATION MYOCARDIAL INFARCTION: A SINGLE CENTER TEN YEAR EXPERIENCE

Aurora Health Care, Milwaukee, WI, USA

Background: Expeditious reperfusion in Non-ST segment elevation myocardial infarction (NSTEMI) remains controversial. Three randomized studies have shown no benefit of early intervention (EI) [defined as intervention performed within 24 hours of presentation] versus late intervention (LI) [defined as intervention performed>24 hours after presentation]. This study was conducted to determine clinical outcomes post percutaneous coronary intervention (PCI) in a large tertiary care referral center with a busy interventional practice.

Methods: A cohort of 1999 NSTEMI patients [61.5% males (n=1229), median age 66 years] was studied for survival benefit and major adverse cardiovascular events as primary endpoint after PCI. Timing of PCI was determined by the treating interventional cardiologist. Patients were divided into two groups: early intervention group (EIG: PCI within 24 hours of presentation) and late intervention group (LIG: PCI after 24 hours of presentation).

Results: Of the 1999 patients with NSTEMI, 960 (48%) patients were in the EIG compared to 1039 (52%) in the LIG. Median door to balloon time (D2BT) in EIG was markedly shorter than in LIG (5.4 hours vs. 44.6 hours). The primary outcome (a composite of death, myocardial infarction(MI), heart failure(HF) or stroke at one year) was significantly reduced in the EIG compared to LIG (19.8% Vs. 28.2%, OR 0.63, P <0.0001). The primary outcome was adjusted for multiple variables including demographic, past medical history, in-hospital medications, previous coronary procedures and extent of the coronary disease.

Conclusion: An accelerated approach toward mechanical reperfusion in patients with NSTEMI is associated with a significantly reduced composite event rate of death, MI, HF or stroke at one year. Based on this large cohort of patients, contemporary reperfusion practices in NSTEMI may need to be relooked at with bias toward early intervention.
INTERVENTIONAL CARDIOLOGY

034

EARLY ANTIPLATELET THERAPY UPGRADE IN STEMI PATIENTS TREATED WITH PRIMARY PCI

A. Lupi1, M. Lazzeri1, A. Rognoni1, C. Cavallino2, A.S. Bongo1

1. AOU Maggiore della Carità, Novara, Italy
2. S.Andrea Hospital, Vercelli, Italy

Background: Antiplatelet therapy (APT) upgrade from clopidogrel to novel P2Y12 inhibitors is common in patients with STEMI treated with primary PCI. Real-world data about this strategy, however, are limited.

Methods: From 2013 to 2014, 643 consecutive STEMI patients treated with primary PCI in the hub-and-spoke network of Novara (Italy) were enrolled in a single-centre observational registry (RENOVAMI, ClinicalTrials.gov # NCT01760382). We assessed prevalence, predictive factors and in-hospital outcomes of early (24 hours after admission) upgrade to novel APT.

Results: In the first 24 hours after admission, 449 (69.8%) patients continued on a novel APT, 118 (18.4%) upgraded from an initial clopidogrel load and 194 (30.2%) continued on clopidogrel. The novel APT was ticagrelor in the majority of patients (65.6%). The use of a drug eluting stent during primary PCI was the only independent predictive factor for the clinical decision to upgrade from clopidogrel to novel APTs (OR 2.24, 95% CI 1.44-3.48, P=0.0004). Fewer in hospital deaths were observed in upgraded patients, in comparison with those continuing on clopidogrel (Clopidogrel 9.8%, Novel APT 3.9%, Upgrade 0.8% with P<0.001 vs the first 2 groups), as well as fewer bleedings (Clopidogrel 17.0%, Novel APT 12.1%, Upgrade 7.6% with P<0.05 vs the first 2 groups). After adjustment for confounders, upgrade to novel APT was not independently correlated with in-hospital survival and bleeding rates.

Conclusion: In a real world hub-and-spoke network of STEMI patients undergoing primary PCI with contemporary APT, early upgrade from clopidogrel to novel APT did not result in increased bleedings or ischemic events.
INTERVENTIONAL CARDIOLOGY

035

BIODEGRADABLE POLYMER DRUG ELUTING STENT: EFFICACY AND SAFETY WITH SHORT REGIMEN OF ANTIPLATELET THERAPY

L. A. Iñigo-Garcia1,2, F.J Martinez-Garcia1, A. Milan-Pinilla1, A. Valle-Alberca1, L. Fernandez-Lopez1, V.V. Traverso-Castilla2, A. Delgado-Aguilar2, R. Bravo-Marques1, A. Ramirez-Moreno3, J. R Siles-Rubio1

1. Hospital Costa del Sol, Marbella, Spain
2. Clínica Santa Elena, Torremolinos, Spain
3. Hospiten, Estepona, Spain

Background: Drug eluting stents (DES) significantly reduce restenosis and target lesion revascularization. But they have introduced a new concept: late thrombosis because of the persistence of polymer, which implicates the necessity of a prolonged dual antiplatelet therapy: problems of intolerance, bleeding, need to interrupt prior to interventions, higher cost. The PLGA degrades in 8 weeks releasing CO2 and H2O only, preclinical trials using stents with this biodegradable polymer (BDP) show complete stent endothelization in 90 days.

Objectives: We assessed the hypothesis that BDP sirolimus-coated stent (Alex, Balton Ltd) could offer safety and efficacy with a short pattern of dual antiplatelet therapy, 3 months, on a long-term follow-up.

Methods and Results: We studied 159 patients underwent a PCI with only Alex DES between January 2012 and December 2013. The mean age was 68.3±9.1 years. The diagnosis at admission was unstable angina 66.66%, myocardial infarction 18.23%, stable angina 11.32% and left ventricular dysfunction 3.77%. The treated vessels were left main 8.8%, anterior descending artery 40.88%, circumflex artery 23.89% and right coronary artery 26.41%. Average follow up was 30.6 months. The primary safety end point was a composite of stent thrombosis, myocardial infarction or cardiac death. The primary efficacy end point was clinically driven target-lesion revascularization. The primary safety end point had occurred in 7 patients (4.4%): stent thrombosis in 2 patients (1.25%), myocardial infarction in 5 patients (3.1%) and cardiac death in 2 patients (1.25%). The primary efficacy end point was required in 8 patients (5.0%).

Conclusions: Our clinical outcomes show that the use of a short regimen of dual antiplatelet therapy, after the treatment with BDP sirolimus-coated stent, offers safety and efficacy on a long-term follow-up. Stents with BDP of fast degradation might represent a solution to prevent late stent thrombosis and the complications of a prolonged dual antiplatelet therapy.
INTerventional cardiology

036

systematic review of the utility of thrombus aspiration in patients with STEMI undergoing primary PCI


NY Methodist Hospital, Brooklyn, NY, USA

Background: Earlier meta-analyses of randomized clinical trials (RCT) of in ST-elevation myocardial infarction (STEMI) patients undergoing primary percutaneous coronary intervention (PPCI) with or without manual thrombus aspiration (MTA) suggested that MTA improved markers of re-perfusion without a marked effect on all-cause mortality. Following the publication of the TOTAL trial, guidelines were changed and currently recommend against routine MTA. This study sought to update previous meta-analyses investigating the efficacy and safety of MTA in PPCI after the publication of the most recent data.

Methods: Major databases were searched through November, 15 2015. We included RCTs of STEMI patients randomized to PPCI with or without MTA. The primary efficacy outcome was all-cause mortality at 1 year, and the primary safety outcome was stroke rate 30 days after intervention. Meta-regression analysis was performed for important baseline and procedural characteristics.

Results: There was no difference in late mortality between MTA and conventional PPCI (14 RCTs, 20,627 patients): RR= 0.91, (95% CI 0.81-1.03), p=0.15. There was no difference in early stroke after MTA vs. PPCI (9 RCTs, 18,756 patients): RR= 1.47, (95% CI 0.99-2.17), p=0.057. There were no differences between the groups in recurrent MI, stent thrombosis or major bleeding. There was no impact of clinical or procedural characteristics on the effect of MTA on outcomes.

Conclusion: MTA does not impact significantly the outcome of PPCI, regardless of patient or procedural characteristics.
**DOES AN UPRIGHT T WAVE IN LEAD V1 PREDICT SIGNIFICANT CORONARY ARTERY DISEASE?**

I. Suen¹, N. Sablani², M. Iskandir², B. Simmons², S. Talebi³, R. Chirurgi³, G. Fernaine², G.W. Hassen²

1. St. George's University School of Medicine, Grenada, West Indies
2. NYU Lutheran Medical Center, Brooklyn, NY, USA
3. Metropolitan Hospital Center, New York, NY, USA

**Objective:** To determine if upright T waves in lead V1 (UTW1) are associated with left anterior artery lesion (LAD).

**Background:** UTW1 have been observed as normal variant. However, tall and new UTW1 are especially concerning. Such patients are more likely to have significant coronary artery stenosis. Few studies examine the significance of UTW1 and its associations with critical stenosis in coronary arteries. Due to insufficient evidence, the use of UTW1 to predict critical stenosed vessels is limited and consequently its diagnostic utility is unclear. **Methods:** We conducted a retrospective chart review of patients who presented with symptoms of acute coronary syndrome or had positive stress test and underwent cardiac catheterization at NYU Lutheran Medical Center between 2011-2014. Pre- and post-catheterization 12-lead ECGs were reviewed. Arbitrarily, UTW1 was defined as significant if it had a positive deflection of 0.2 mV or greater. Patients with left ventricular hypertrophy, left or right bundle branch block were excluded because they are a known cause of UTW1.

**Results:** Out of 737 patients who met inclusion criteria, 122 patients had UTW1, of which 95 patients had UTW1>0.2mV. From the remaining 71 patients, 28 patients had post-catheterization resolution of UTW1, of which 20 patients with ST-elevation myocardial infarctions (STEMI) were further examined. Patients with stenosed coronary vessels had resolution of UTW1 following stent placement in the culprit artery (n=15; 75%). Of note, 8 patients with single vessel disease and anterior wall STEMI (AWMI) had resolution of UTW1 post stent placement in the LAD.

**Conclusion:** An UTW1 may signify lesions in the coronary arteries and in the appropriate clinical setting the presence of CAD should be suspected. Our study is limited by a small sample size. A large-scale study in patients undergoing cardiac catheterization might be more useful to elucidate the relationship between a UTW1 and significant CAD.
INTERVENTIONAL CARDIOLOGY

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LEFT BUNDLE BRANCH BLOCK: IS IT TIME TO RECONSIDER THE CRITERIA FOR PRIMARY PERCUTANEOUS CORONARY INTERVENTION?
J Basu, M. Mikhail, T. Realey, W. Orr
Royal Berkshire NHS Foundation Trust, Reading, UK

Background: The European Society of Cardiology includes ST-elevation and presumed new onset left bundle branch block (LBBB) as indications for immediate reperfusion therapy but LBBB may be caused by a number of alternative pathologies.

Objectives: This audit sought to ascertain the proportion of patients presenting with chest pain and LBBB who were confirmed as having acute coronary syndrome (ACS) compared to patients presenting with ST/T wave ECG changes. We also studied characteristics that might help to differentiate patients with LBBB into low and high likelihood of ACS.

Methods: We analysed data from 3103 patients presenting with chest pain. Demographics, mortality rates and co morbidity data in patients presenting with LBBB were directly compared with patients who presented with ST/T wave ECG changes.

Results: Patients with LBBB represented only 6.5% of all ACS admissions. Only 58% of these triggered primary PCI activation compared to 92% of patients admitted with ST elevation. LBBB patients were not older, were less likely to be male but had significantly higher mortality rates than patients with ST/T wave ECG changes. Several factors appear to be useful in stratifying LBBB patients into high risk of ACS including previous infarction, peripheral vascular disease, cerebrovascular disease, chronic renal failure and smoking history.

Conclusion: LBBB is only a small component of ACS admissions, is a much less accurate predictor of acute coronary occlusion, but is undoubtedly a marker of greatly increased risk of mortality. Further work is needed to identify factors that aid risk stratification of these patients.
DUAL ANTIPLATELET THERAPY AFTER CORONARY ARTERY BYPASS GRAFTING IN THE SETTING OF ACUTE CORONARY SYNDROME

M. Agarwal¹, R. Bomb², C.S. Oliphant³, R.N. Khouzam²

1. Department of Internal Medicine, University of Tennessee Health Science Center, Memphis, TN, USA
2. Division of Cardiovascular diseases, Department of Medicine, University of Tennessee Health Science Center, Memphis, TN, USA
3. Department of Pharmacy, Methodist University Hospital, Memphis, TN, USA
4. Department of Clinical Pharmacy, University of Tennessee College of Pharmacy, Memphis, TN, USA

**Objective:** To review available clinical data regarding Dual Antiplatelet therapy (DAPT) in post coronary artery bypass grafting (pCABG) patients.

**Background:** CABG is the best recommended intervention for post acute coronary syndrome (ACS) patients with severe multi-vessel coronary artery disease. Among the most common and worrisome complications in pCABG patients are recurrent ACS, venous graft thrombosis and death. Unlike post ACS medical management guidelines where DAPT use is a standard, no clear guidelines exist for pCABG patients. Hence we performed literature review to study pCABG DAPT use.

**Methods:** An extensive literature search was conducted using the terms aspirin, clopidogrel, DAPT and coronary artery bypass surgery. In addition, studies were discovered during bibliographic reviews. The studies with clear efficacy end points were included and divided into 2 groups:- significant positive results (sP) and neutral results (nR). A separate search for meta analyses was also performed.

**Results:** 12 clinical studies and 3 meta analyses were identified, and reviewed. Among 12 clinical studies, 5 sP and 7 nR were found (Table 1).

**Conclusion:** Although in the absence of contraindications, 9-12 months post operative DAPT use is reasonable, but no clear consensus exist for pCABG DAP use. Hence large, multicenter, randomized clinical trials are indicated.

**Table 1**

<table>
<thead>
<tr>
<th>Positive Result Studies</th>
<th>Outcomes</th>
<th>ASA</th>
<th>DAPT</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gurbuz et al</td>
<td>Recurrent angina</td>
<td>23 (8.6%)</td>
<td>6 (1.8%)</td>
<td>0.001</td>
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<tr>
<td></td>
<td>Death</td>
<td>22 (8.3%)</td>
<td>7 (2.2%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Kim et al</td>
<td>In hospital mortality</td>
<td>210 (1.78%)</td>
<td>31 (0.95%)</td>
<td>0.048</td>
</tr>
<tr>
<td>Gao et al</td>
<td>SVG patency at 3 months</td>
<td>198 (86%)</td>
<td>219 (92%)</td>
<td>0.043</td>
</tr>
<tr>
<td>Mannacio et al</td>
<td>Total graft occlusion</td>
<td>39 (27%)</td>
<td>22 (15%)</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>SVG occlusion</td>
<td>35 (13%)</td>
<td>19 (7.4%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Sorensen et al</td>
<td>Recurrent MI</td>
<td>25 (2.7%)</td>
<td>23 (2.4%)</td>
<td>0.78</td>
</tr>
<tr>
<td></td>
<td>Death from any cause</td>
<td>36 (3.8%)</td>
<td>14 (1.5%)</td>
<td>&lt;0.002</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Negative Result Studies</th>
<th>Outcomes</th>
<th>ASA</th>
<th>DAPT</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fox et al</td>
<td>Composite of CV death, MI, stroke</td>
<td>172 (16%)</td>
<td>147 (14%)</td>
<td>NS</td>
</tr>
<tr>
<td>Saw et al</td>
<td>Composite of 1 year death, MI, stroke</td>
<td>12%</td>
<td>14%</td>
<td>0.78</td>
</tr>
<tr>
<td>Ibrahim et al</td>
<td>Graft patency flow rate by angiography</td>
<td>50 (84%)</td>
<td>54 (93%)</td>
<td>NS</td>
</tr>
<tr>
<td>Sanon et al</td>
<td>Overall survival</td>
<td>3816 (89%)</td>
<td>861 (88%)</td>
<td>0.43</td>
</tr>
<tr>
<td>Sun et al</td>
<td>Occluded grafts assessed by CT angiography</td>
<td>11 (7.1%)</td>
<td>8 (5%)</td>
<td>0.43</td>
</tr>
<tr>
<td>Ebrahimi et al</td>
<td>Graft patency rates by angiography</td>
<td>1538 (85%)</td>
<td>878 (86%)</td>
<td>0.43</td>
</tr>
<tr>
<td>Kulik et al</td>
<td>Mean SVG intimal area per IVUS angiography (mm²)</td>
<td>4.1 ± 2.0</td>
<td>4.5 ± 2.1</td>
<td>0.44</td>
</tr>
</tbody>
</table>

ASA- Aspirin, SVG- Saphenous Vein Graft, CV- Cardiovascular, IVUS- Intravascular ultrasound, MI- Myocardial infarction, NS- non significant
INTERVENTIONAL CARDIOLOGY

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ST ELEVATED MYOCARDIAL INFARCTION AS AN EPIPHENOMENON OF NON CARDIOVASCULAR DISEASE
J.M. Telayna, J.M. Telayna (h), R.A. Costantini
Hospital Universitario Austral, Buenos Aires, Argentina

Introduction: Acute coronary syndrome in context of non cardiovascular disease (epiphenomenon) has greater mortality than ACS of primary cause. There are discrepancies in terms of reperfusion times and the procedure technique of coronary angioplasty (PTCA) in patients with ST elevated myocardial infarction (STEMI)

Objective: Compare patients with STEMI as epiphenomenon vs STEMI of primary cause to determine mortality and analyze procedure variables.

Materials and methods: From 07/2000 to 02/2016, 2602 PTCA were performed, 436 of STEMI patients. Of them, 410 belong to STEMI as primary cause (group A); and 26 to STEMI as epiphenomenon (group B).

Baseline characteristics were, group A and B respectively – n (%): age 57.9±10.8vs65.8±11.3 p<0.01; male 359(87)vs21(81)p=0.3; diabetes 74(18)vs4(15)p=0.7; smoking 291(71)vs12(46)p<0.01; CKD 9(2.2)vs6(23)p<0.01; COPD 9(2.2)vs5(19)p<0.01; prior PTCA 50(12)vs2(7)p=0.4; CABG 12(3)vs1(4)p=0.7; prior AMI 44(10)vs1(4)p=0.2; EF 55.6±15vs44.5±15.2p<0.01; anterior STEMI 178(43)vs14(54)p=0.2; non anterior STEMI 232(56)vs12(46)p=0.3; MVD 206(50)vs16(61)p=0.2; complete MVD revascularization 111(54)vs8(50)p=0.7; KKA 326(79)vs14(54)p<0.01; KKD 15(4)vs9(35)p<0.01; door to balloon time 106±58vs69±36p<0.01; IIbIIIa 71(17)vs2(8)p=0.2; TIMI 0-1 283(69)vs14(54)P=0.1; thromboaspiration 3(0.7)vs1(4)p=0.1; IABP 11(3)vs4(15)p<0.01; radial access 132(32)vs4(15)p=0.07; fluoro time 15.2±11.7vs20.2±13.9p=0.03; dye used 224.8±83.5vs238.9±89.2p=0.4; stent (mm) 37.5±25.3vs54.2±36.4p<0.01.

Results: group A and B: technical success 401(98)vs26(100)p=0.4; clinical success 386 (94)vs16 (61)p<0.01; acute thrombosis 5(1)vs0p=0.5; subacute thrombosis 4(1)vs0p=0.6; TIA/Stroke 1(0.2)vs0p=0.8; vascular access complication 6(1.5)vs0p=0.5; global mortality 14(3)vs11(42)p<0.01; intrahospital cardiovascular death 12(3)vs2(8)p=0.1; intrahospital non cardiovascular death 2(0.5)vs9(35)p<0.01.

Conclusion: Patients with STEMI as an epiphenomenon has greater mortality, minor door to balloon time, greater use of IABP and mm of stents than patients with STEMI as primary cause.
Next to beta1- and beta2-adrenoceptors, the beta3-adrenoceptors represent important regulatory sites to control cardiac function. Beta3-adrenergic receptors in the heart may protect the myocardium against adverse effects of excessive catecholamine stimulation. This may be particularly important under demanding situations, such as stress and immune system activation. A typical location of beta3-adrenergic receptors is the adipose tissue and they are involved in the regulation of lipolysis.

The aim of these studies was to verify the hypothesis that stress associated with repeated immune challenge has a negative impact on the gene expression of beta3-adrenoceptors and related regulatory factors in the adipose tissue.

Female and male Sprague-Dawley rats were intraperitoneally treated either with vehicle or lipopolysaccharide (LPS) in increasing doses for 5 days (50-200 microg/kg). Two hours after the last injection, the retroperitoneal adipose tissue and selected brain regions were collected. Concentrations of selected mRNAs were measured using real-time PCR.

Immune system activation by repeated treatment with LPS was confirmed by increased mRNA levels of interleukin-6. This immune challenge resulted in a decrease in gene expression of beta3-adrenoceptors in the adipose tissue. Adipogenic factor (peroxisome proliferator-activated receptor gamma, PPAR-gamma) gene expression was decreased after administration of LPS. As to the adipokines, both adiponectin and leptin mRNA levels decreased significantly. Treatment with LPS failed to modify expression of resistin, however mRNA levels of these adipose tissue-specific secretory factor were significantly higher in males compared to females. In contrast to adipose tissue, gene expression of beta3-adrenoceptors was unchanged in the hippocampus and prefrontal cortex. In conclusion, parallel decreases in gene expression of beta3-adrenoceptors, PPAR-gamma, leptin and adiponectin encourage further research on possible role of beta3-adrenoceptors in the adipogenesis and control of the formation of adipokines in white adipose tissue in response to immune challenge. Supported by grants of VEGA 2/0128/14 and APVV-14-0840.
GENETICS OF CARDIOVASCULAR DISEASES

VALIDATED GENETIC BIOMARKERS FOR PREDICTION OF INDIVIDUAL RISK OF MYOCARDIAL INFARCTION IN RUSSIANS
G.Z. Osmak¹,², D. Lvov³, B.V. Titov¹,², N.A. Mateeva¹,², R.M. Shakhnovich¹, T.R. Nasibullin⁴, O.E. Mustafina⁴, A.V. Favorov³,⁵, M.Ya Ruda¹, O.O. Favorova¹,²
1. Russian Cardiology Scientific and Production Center, Moscow, Russia
2. Pirogov Russian National Research Medical University, Moscow, Russia
3. Vavilov Institute of General Genetics, Russian Academy of Sciences, Moscow, Russia
4. Ufa Research Center, Russian Academy of Sciences, Ufa, Russia
5. Johns Hopkins School of Medicine, Baltimore, Maryland, United States of America

Background. Myocardial infarction (MI) remains the cause number one of death and disability worldwide. In spite of progress in cardiovascular genetics, data on genetic background of MI are still limited and need to be validated in order to be used for prediction of individual risk.

Methods and Results. In this study we found that the carriage of TGFB1 rs1982073*TT, FGB rs1800788*T, CRP rs1130864*TT was associated with MI in the discovery group of Russian descent from the Moscow region (325 patients and 185 controls). We also found several MI-associated biallelic combinations. One of them, namely IFNG rs2430561*A + PTGS1 rs3842787*T, showed nonlinear (epistatic) interaction between the genes according to our original two-component procedure that consisted of the evaluation of the Synergy Factor and the exact Fisher-like interaction numeric test. All these association data were replicated in the independent group of Russians from the Republic of Bashkortostan (220/197 samples, men only). Multiple logistic regression analysis was performed for the four identified genetic markers: three single gene variants and the epistatic pair, which was considered as an independent marker. The composite model demonstrated a rather moderate AUC of 0.66 and performed very well when applied to the independent replication sample from Bashkortostan: the two ROC curves were almost identical. Conclusions. The prognostic significance of TGFB1, FGB, CRP, and the biallelic combination of IFNG and PTGS for MI was shown. Results appeared to be very similar in the two groups of Russians from different regions of European Russia. In the future, the discovered genetic variants that replicably predict MI could be used as substantial components for the creation and implementation of prognostic tests for individual risk of MI. This work was supported by the Russian Science Foundation (project 16-14-10251).
ACUTE EFFECTS OF AIR POLLUTION ON CARDIOVASCULAR DISEASE

S-W Yang, H-R Guo
National Cheng Kung University, Tainan, Taiwan

Objectives: To evaluate the associations between air pollution and outpatient visits for cardiovascular disease (CAD) during dust storm events.

Background: Long-range transport air pollution models have suggested that air pollutants may be transported with China monsoon across oceans to influence neighbouring countries’s air quality. As air pollution increases morbidity and mortality of CAD, we conducted a study in Taipei City, where the population density is high and the air quality is affected by the basin topography and heavy traffic.

Methods: The Taiwan Environmental Protection Administration (EPA) defined a dust storm event as an episode with an average PM10 level above 100ug/m3. We obtained data on air pollutants from the five EPA monitoring stations in Taipei City. Data on daily outpatient visits for CAD (ICD-9 codes 460 to 510) from 2005 to 2010 were obtained from the National Health Insurance Research Database.

Results: We identified 229,248 CAD outpatient visits during the study period. Time series models showed that CAD outpatient visits were associated with CO (same day and with a 2-day lag), NO, NO2 (same day and with a 3-day lag) and a weekend effect. In addition, we identified 3,850 CAD cases during dust storm events. We compared 2-days average concentration changes in air pollutants before and during the events and found that O3 and PM10 were higher during the events, but CO, NO, and NO2 decreased during the events. We found that levels of O3 and SO2 were associated with CAD outpatient visits on the same day and with a 2-day lag. We also found that PM10 and PM2.5 levels were associated with CAD outpatient visits on the same day and with 1- and 2-day lags.

Conclusions: This study provides evidence supporting the effects of O3, SO2, PM10, and PM2.5 on CAD outpatient visits during dust storm events.
RELATIONSHIP BETWEEN FAMILY HISTORY OF CARDIOVASCULAR DISEASE ON CORONARY CALCIUM SCORE

S. Saberian, S. Banga, S. Mungee, K. Wattanakit
OSF St. Francis Medical Center, University of Illinois College of Medicine at Peoria, IL, USA

Background: Coronary Artery Calcium Score (CACS) on cardiac CT scan is a surrogate marker for atherosclerosis. Family history of cardiovascular disease (CVD) is associated with an increased incidence of coronary artery disease. We investigated the relationship between family history of CVD and CACS.

Methods: We identified patients who underwent cardiac CT at our institution between March 2010 and August 2014. Patients were divided into two groups. Group A included patients with prior family history of CVD, defined as history of coronary artery disease, stroke, TIA or peripheral arterial disease. Group B included patients with no prior family history of CVD. Data on demographic and co-morbidities were collected. Coronary artery calcium score (CACS) was quantified using standard methods. CACS < 300 and ≥ 300 were categorized for each group. Statistical analyses were performed using the chi-square method for categorical variables and t test for continuous variables.

Results: Of the total of 232 patients, Group A had 112 and Group B had 120 patients. There were no statistically significant differences in demographic and co-morbidities between the two groups. 27 patients in Group A and 29 patients in Group B had CACS ≥ 300 with mean CACS of 1034±713.2 and 1244.4±1415 (p-value 0.49), respectively. 85 patients in Group A and 91 patients in Group B had CACS < 300 with mean CACS of 25±54.9 and 33.7±60.3 (p-value 0.318), respectively.

Conclusions: We concluded no relationship between family history of CVD and CACS in asymptomatic patients with low risk for coronary artery disease.
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EPIDEMIOLOGY OF LOW-DOSE ASPIRIN USE FOR PRIMARY AND SECONDARY PREVENTION OF CARDIOVASCULAR DISEASE
M.E. Stuntz
Deerfield Institute, New York, NY, USA

Background and Objectives: Cardiovascular disease (CVD) is the leading cause of death in the United States. Aspirin therapy has been shown to be an effective prevention measure to reduce the risk of new or recurring cardiovascular events. The aim of this study was to provide an epidemiological analysis of the use of low-dose aspirin for primary and secondary CVD prevention from 2012–2014.

Methods: Estimates of self-reported low-dose aspirin use for primary and secondary CVD prevention were obtained from the National Health Interview Survey for the years 2012–2014. Demographics and health characteristics data were used to analyze intergroup differences for the combined time period, as well as intragroup differences from year to year.

Results: Among adults 40+ years during 2012–2014, 18.7% self-reported as taking aspirin for primary CVD prevention and 8.9% self-reported as taking aspirin for secondary CVD prevention. Adults taking aspirin for secondary CVD prevention were significantly older on average than those taking it for primary prevention (68.5 ± 11.1 vs 65.8 ± 11.2 years; p<0.0001), and consisted of a higher proportion of males (54.7% vs 44.9%; p<0.0001). The proportion of adults taking aspirin for primary CVD prevention significantly increased from 18.3% in 2012 to 19.4% in 2014 (p=0.003). The proportion of adults taking aspirin for secondary CVD prevention decreased from 9.1% in 2012 to 8.6% in 2014, though this was not statistically significant (p=0.148).

Conclusions: This study shows that over 25% of the adult population self-reports as taking low-dose aspirin for primary or secondary CVD prevention, with primary CVD prevention patients outnumbering secondary CVD prevention patients at a ratio of more than 2:1. Aspirin use for primary CVD prevention increased throughout the study period along with a concomitant decrease in aspirin use for secondary CVD prevention.
DEVELOPMENT OF A HEALTH PROMOTION MODEL GUIDED LIFESTYLE INTERVENTION PROGRAM FOR ADULTS WITH METABOLIC SYNDROME
Q. Wang, S.Y. Chair, E.M.L. Wong
The Nethersole School of Nursing, Faculty of Medicine, The Chinese University of Hong Kong

Background: Metabolic syndrome (MetS) has become a great threaten to public health because of its increasing prevalence and close relationships with other cardio-metabolic diseases. A worldwide consensus has been achieved that lifestyle modification is the primary intervention for MetS. However, previous lifestyle interventions focused in western populations, were delivered in various modalities without understanding patients’ needs, and lacked of theoretical guidance. Therefore, previous lifestyle interventions could not be directly applied in the Chinese MetS population.

Objectives: The study was to develop a feasible and culturally sensitive lifestyle intervention program (LIP) guided by the health promotion model (HPM) for Chinese adults with MetS.

Methods: A qualitative study was conducted to explore the needs of lifestyle intervention by interviewing 30 Chinese adults with MetS. Content analysis was conducted to identify the themes. The LIP was developed based on the findings of the qualitative study and updated guidelines within the framework of HPM.

Results: Patients had insufficient knowledge about MetS and were eager to adopt lifestyle modifications through education and practical lifestyle advices. Based on the findings, a 3-month LIP was developed, including a lifestyle modification booklet, one individual face-to-face pre-discharge education, and six telephone follow-ups after discharge. Knowledge enhancement and behavioral strategies were emphasized. Each component of the LIP followed the conceptual structures of HPM, namely individual characteristics and experiences, behavior-specific cognitions and affect, and behavioral outcomes. Culturally sensitive strategies, laymen language, and practical lifestyle advices were provided to ensure the acceptance of the LIP.

Conclusion: The HPM provides suitable guidance to develop lifestyle interventions for MetS population. A feasible and culturally sensitive LIP should provide knowledge enhancement and practical strategies for behavioral modifications to meet the needs of Chinese adults with MetS.
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KNOWLEDGE OF HEART DISEASE IN FEMALE AND MALE COLLEGE STUDENTS

M. Granieri, C. Bavishi, A. Koulova, J.P. Cordova, J. Tamis-Holland
Mt. Sinai St. Luke's Hospital, New York, NY, USA

Background: Educational campaigns aimed at raising awareness of heart disease (HD) in women have resulted in an improvement in women’s knowledge of HD. Less is known regarding awareness of HD in the younger generation of Americans.

Objective: To assess the knowledge of HD, among a cohort of female and male college students.

Methods: Students were invited to complete an online 42 item survey.

Results: A total of 548 students completed the survey; (mean age 21.9 +/- 6.64 years; 79.9% female; 20.1% male; 87.6% Caucasian, 2.6% Asian 4.6% black and 4.6% other). Although the majority of college students correctly identified HD as the leading cause of death in men (62% of females vs 56% of males, p=.32), less than half of all female students, and only one third of male students reported HD as the leading cause of death in women (44% vs 32%, p=0.03). Female students were more likely than male students to recognize the typical symptoms of a heart attack (86% vs 75%, p=0.005) or correctly explain the meaning of the “Red Dress” symbol (38% vs 12%, p=0.001). Most female and male students were able to identify at least 3 risk factors for developing HD (79% vs 77%, p=0.71) but few knew their own blood pressure (31% vs 26%, p=0.38) or cholesterol levels (5% vs 3% p=.49).

Conclusions: Knowledge of HD among college students is sub-optimal, with females demonstrating a greater knowledge then males. Future educational campaigns should aim to target the younger generation.
**PATTERNS OF REFERRAL AND IMMEDIATE CLINICAL IMPACT OF CORONARY ARTERY CALCIUM SCORING**

**A. Quddus, A. Smith, M. McLane, S. Agrawal, A. Sinha, D. Prutzman, J. Shirani, F. Burt**  
St. Luke’s University Health Network, Bethlehem, PA, USA

**Background:** Coronary artery calcium scoring (CACS) is gaining recognition as a risk stratifying tool in coronary atherosclerosis. We aimed to evaluate community based referral patterns for CACS and its potential immediate impact on statin therapy.

**Methods:** We retrospectively reviewed records and images of consecutive patients who underwent CACS.

**Results:** Thirty-five adults (mean age 58 years, 51% men, 94% white, 8% diabetic, 45% hypertensive, 31% smoker, 70% family history of heart disease, 69% overweight or obese) had CACS for cardiovascular risk estimation; 22 (62%) by cardiologists and 12 (37%) by primary care physicians. Overall, 25% had chest pain and negative stress test while 75% were asymptomatic. Distribution of ASCVD scores in 32 eligible patients were as follows: 46% <5%; 43% > 7.5%; 9% 5%-7.5%. CACS distribution was: 28% 0; 31% 1-100; 26% 101-300; and 14% >300. CACS of 0 was present in 40%, 33%, and 21% of those with ASCVD scores of <5%, 5%-7.5%, and >7.5%, respectively. Overall, ASCVD risk score was reclassified based on CACS in 13 of 32 patients (40%). This led to a change in management in 21/35 (60%) including initiation of statin in 17/29 (58%) not already on therapy, discontinuation of stain in 2/6 (33%) on prior therapy and in dose titration of statin in 2/6 (33%) patients. CACS of 0 was present in 10 patients with ASCVD score of 1-19 (6.2±5.5%), MESA score of 0.3-5.3 (2.4±1.4%), Framingham risk score of <1-16 (7±5.2)% and MESA arterial age <1-5 (2.6±1.5)% [p=0.02 for ASCVD vs MESA and p=0.02 for Framingham vs MESA arterial age].

**Conclusion:** In this small, retrospective study, wide heterogeneity was noted in cardiovascular risk factor profile of patients referred for CACS. Despite such differences, CACS provided important incremental information that impacted immediate cholesterol lowering medication use.
THE B12/CRP INDEX AS A SIMPLE INDICATOR OF CORONARY ARTERY DISEASE IN AN ADULT POPULATION

G.D. Spyromitros, I.D. Lagos, E.S. Papadopoulou, G.H. Katerini
Cardiology Department, Katerini, Greece

Objectives: The purpose of this study was to evaluate the utility of the vitamin B12 / C-Reactive Protein (CRP) index as a simple indicator for detecting coronary artery disease (CAD) in the general adult population.

Background: Several biomarkers to detect CAD have been investigated. The B12/CRP index has been associated with prognosis in cancer patients, but it has not been studied in patients with CAD.

Methods and results: our study comprised 89 patients (44% male, mean age 60 years) who underwent dobutamine stress echocardiography in order to detect the presence of CAD. Before the imaging test, a blood sample was drawn in order to quantify vitamin B12 and CRP serum levels. All patients in the study had a normal white blood cell count. In addition, the prevalence of traditional cardiovascular risk factors (hypertension, dyslipidemia, diabetes and smoking) was studied in relation to gender and the presence of CAD. Our analysis revealed that the B12/CRP index was higher in patients with a positive stress echocardiography exam. Notably, all women with a positive stress echocardiography exam were >50 years old. Furthermore, diabetes was prevalent in 90% of patients with a positive stress echocardiography exam, which underlines the importance of diabetes as a risk factor for CAD. Also, it was observed that the prevalence of risk factors for CAD was higher in women than in men, except for smoking (hypertension in 43% of males vs. 46% of females, dyslipidemia in 28% of males vs. 40% of females, diabetes in 28% of males vs. 32% of females and smoking in 56% of males vs. 50% of females). Notably, 90% of men with a positive stress echocardiography study were smokers, whereas the corresponding prevalence in women was 66%.

Conclusions: the B12/CRP index appears to be a useful indicator to investigate CAD in adults, in addition to the traditional cardiovascular risk factors.
PREVENTION OF CORONARY ARTERY DISEASE / RISK FACTORS FOR ATHEROTHROMBOTIC DISEASE

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PREDICTORS OF CHILDHOOD OBESITY AND ADULTHOOD BLOOD PRESSURE LEVELS

S. Singh¹, J. Kaur¹, K.K. Thumburu¹, P. Nieminen⁴, A. Chauhan¹, N. Jaiswal¹, A. Agarwal¹, M. Singh², N. Paul³, S. Sagwal³

1. ICMR Advanced Centre for Evidenced Based Child Health, Advanced Pediatric Centre, PGIMER, Chandigarh, India
2. Department of Pediatrics and ICMR Advanced Centre for Evidenced Based Child Health, Advanced Pediatric Centre, PGIMER, Chandigarh, India
3. Department of Pediatrics, Advanced Pediatric Centre, PGIMER, Chandigarh, India
4. Medical Informatics and Statistics Group, University of Oulu, Oulu, Finland

Background: Hypertension, a disease of significant public health concern, is a major cardiovascular risk factor affecting a majority of the world’s population. Many studies have shown the association between growth patterns in early life and the development of hypertension in adulthood.

Objectives: The aim of this scoping review was to examine the empirical literature that have assessed the relationship between childhood anthropometric measures and adulthood systolic (SBP) and/or diastolic blood pressure (DBP) measurements.

Methods: Electronic databases were searched from 1990 until January 2016 for studies which enrolled children and adolescents between ages 6 months to 19 years and followed them up for at least 4 years were included. The age at assessment of blood pressure was in adulthood (≥20 years). Studies from both developed and developing countries were included. Quality assessment was done using the Newcastle-Ottawa Scale.

Results: Of the 4021 studies found, sixteen studies from fourteen cohorts were included in the study. Almost all the studies that demonstrated the association between childhood BMI and adulthood SBP found a positive association, whereas most of the studies for DBP showed little or no association. Three studies showed being persistently obese from childhood to adulthood had the highest risk for having higher SBP and DBP in adulthood as compared to never being obese. Also, reverting back to a normal BMI in adulthood after being obese as a child significantly decreased the risk of having higher SBP and DBP levels. Childhood skinfold thickness, weight and waist circumference as predictors of childhood obesity also showed a positive association with adult SBP and DBP levels.

Conclusions: All the predictors of childhood obesity like BMI, weight, skinfold thickness and waist circumference positively predict adulthood blood pressure levels.

Acknowledgements: WHO, Geneva, Switzerland; ICMR, New Delhi, India
PREDICTORS AND MARKERS OF HEART FAILURE OUTCOME

GROUPING OF PATIENTS ON RELATION TO HOSPITAL READMISSION BY ACUTE HEART FAILURE

J.M. Quintana\(^1,7\), A. Anton-Ladislao\(^1,7\), S. Garcia-Gutierrez\(^1,7\), I. Lafuente\(^1,7\), M.J. Morillas\(^2\), E. Hernandez\(^3\), I. Rilo\(^4\), N. Murga\(^5\), R. Quiros\(^6,7\)

1. Unidad de Investigacion, Hospital Galdakao-Usansolo, Galdakao, Bizkaia, Spain
2. Servicio de Cardiologia, Hospital Galdakao-Usansolo, Galdakao, Bizkaia, Spain
3. Servicio de Cardiologia, Hospital Santa Marina, Bilbao, Bizkaia, Spain
4. Servicio de Cardiologia, Hospital Donostia, Donostia, Gipuzkoa, Spain
5. Servicio de Cardiologia, Hospital Universitario Basurto, Bilbao, Bizkaia, Spain
6. Servicio de Medicina Interna, Hospital Costa del Sol, Marbella, Malaga, Spain
7. Red de Investigacion en Servicios Sanitarios y Enfermedades Cronicas (REDISSEC)

Objectives: The goal of this study was to identify profiles of patients hospitalized by acute heart failure (AHF) on relation to readmissions up to one year after hospital discharge. Background: Patients readmission is considered an important quality of care problem.

Methods: Observational prospective cohort study of 6 hospitals. 448 patients diagnosed with AHF who came to the emergency services of these centers were included. Various parameters were collected on the emergency room, during admission and until discharge. Multiple correspondence analysis (MCA) and cluster analysis (CA) were performed to define types of patients.

Results: The two factors derived from the MCA (explained 82% of the total variability) were associated with patient’s severity and comorbidities, respectively. Three group of patients were identified (A, B, C) and we found statistically significant differences among them according to active variables: 96.58% of type A went to the emergency services because of decompensated chronic heart failure, 71.79% had antecedents of coronary disease and 73.50% has previous admissions. Type B included patients with new diagnosis of HF (83.06%), and is the second group with the highest number of comorbidities as COPD, diabetes or antecedents of coronary disease (p<0.0001). 11.49% of patients of type C had new diagnosis of AHF, and was the group with the highest percentage of anaemia and pulmonary hypertension (p<0.0001). Additionally, patients who were not readmitted throughout the follow up were associated with type B, while patients who were just readmitted before 30 days were associated with type C. However, patients who were readmitted before 30 days or before one year were associated with patients of type A.

Conclusions: This statistical technique create clear and different patient profiles related to the moment of readmission which may help to identify and establish different preventive or corrective measures during hospital admission to reduce readmissions.
A PREDICTIVE MODEL OF 30 DAYS DEATH IN ADMITTED PATIENTS BY ACUTE HEART FAILURE

**J.M. Quintana**\(^1,8\), A. Anton\(^1,8\), S. Garcia\(^1,8\), I. Lafuente\(^1,8\), M.J. Morillas\(^2\), E. Hernandez\(^3\), I. Rilo\(^4\), N. Murga\(^5\), R. Quiros\(^6,8\), A. Lara\(^7\)

1. Unidad de Investigacion, Hospital Galdakao-Usansolo, Spain
2. Servicio de Cardiologia, Hospital Galdakao-Usansolo
3. Servicio de Cardiologia, Hospital Santa Marina
4. Servicio de Cardiologia, Hospital Donostia
5. Servicio de Cardiologia, Hospital Universitario Basurto
6. Servicio de Medicina Interna, Hospital Costa del Sol
7. Servicio de Cardiologia, Hospital Universitario de Canarias
8. Red de Investigacion en Servicios Sanitarios y Enfermedades Cronicas (REDISSEC)

**Objectives:** Patients with a hospital admission by acute heart failure (AHF) have a high mortality rate. The goal of this study was to develop a clinical prediction rule of 30 days mortality for patients with AHF.

**Methods:** Prospective cohort study performed in 7 hospitals. Preliminary analysis of 720 admitted patients with a diagnosis of AHF seeing at the emergency department (ED). Various parameters were collected at the ED, admission, discharge, and until 30 days afterwards. Patients reported outcomes measures (PROMs) were also collected at baseline fulfilling the Minnesota (specific AHF questionnaire), the Barthel index and the EuroQol-5D questionnaires. Statistical analysis: development of the predictive models using multivariate Cox and logistic regression adjusted by hospital in a derivation and validated in the validation sample. Main outcome was death at 30 days after the ED index visit.

**Results:** The final multilevel logistic regression model included as predictors, age, COPD, cardiorespiratory arrest, cognitive impairment and complications at the episode. A risk score from 0-39 points was created and 3 severity categories, minor (0-9), moderate (10-12) and severe (13-39), were created. Mortality rates at 30 days were 3.06%, 14.79% and 36.96% (p<0.0001), respectively. AUCs of the model in the derivation and validation samples were 0.90 (0.86 – 0.94) and 0.90 (0.86 – 0.94) respectively, including the hospital, while the Hosmer- Lemeshow test p values were 0.95 and 0.67. None of the PROMs entered in the prediction models. The same risk score replicates by Cox regression. The obtained AUCs were 0.73 (0.67-0.79) and 0.73 (0.67-0.79) in the derivation and validation samples, respectively, without the hospital. The inclusion of the hospital in both models increased considerably the AUCs.

**Conclusions:** This clinical prediction rule classifies AHF patients in severity categories to better address clinical decisions. Future analysis has to clarify the role of the hospital in the prediction.
PREDICTORS AND MARKERS OF HEART FAILURE OUTCOME

CONGESTIVE HEART FAILURE CLINICS: HOW TO MAKE THEM WORK IN A COMMUNITY-BASED HOSPITAL SYSTEM

M. Kabach, O. Kreidieh, J. Larned¹, L. Tamariz², K. Raimondo¹
1. University of Miami Miller School of Medicine, Miami, Florida, USA
2. Miller School of Medicine at the University of Miami, Veterans Affairs Medical Center, Miami, Florida, USA

Background: Congestive heart failure (CHF) accounts for over $32 billion in health care costs per year. It remains a major cause of hospitalizations. Missed opportunities to treat CHF are associated with higher mortality and morbidity. CHF disease management programs have emerged as a potential solution to the CHF epidemic. The paradox remains that CHF disease management programs still cluster in tertiary hospital systems. The impact of CHF specialists and specialty teams in community health systems is less well understood. Currently there are not enough CHF-trained teams in the community setting to address this unmet health need.

Methods: We explored the impact of CHF clinics in a community-based hospital on readmission rates, mortality, and symptomatic relief. A total of 384 patients were enrolled between 2012 and 2015. Data collected included age, sex, New York Heart Association class, ejection fraction, serum creatinine and brain natriuretic peptide. Readmission and mortality rates within 30 days, 3 months, 6 months, and 1 year were compared between patients who were followed up in the CHF clinic versus those who were not.

Results: A statistically significant difference was demonstrated in readmission rates between patients who were followed up in the CHF clinic versus those who did not visit the CHF clinic for up to 1 year of follow-up.

Conclusion: CHF community hospital clinics that use a rapid and frequent follow-up format with CHF-trained teams effectively reduce rehospitalization rates up to 1 year.
PREDICTORS AND MARKERS OF HEART FAILURE OUTCOME

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EVALUATION OF IN-PATIENT CLINICAL OUTCOMES OF GUIDELINE-BASED THERAPY FOR ACUTE HEART FAILURE
K.G. Castillo, R.E. Ramboyong
The Medical City, Pasig, Philippines.

Despite evidence on guideline-based therapy for heart failure (HF), it remains a global problem, including Asia. Currently, limited reports on in-hospital clinical outcomes of guideline-based therapy among Filipinos with acute heart failure. This study was conducted to determine in-hospital clinical outcomes of patients admitted for acute heart failure who received guideline-based therapy. The study was a single-center, retrospective study design. Adult patients (> 18 years old) who were admitted at The Medical City from January to September 2105 with acute heart failure were included. In-hospital mortality from any cause, length of hospital stay, and re-hospitalization were assessed. A total of 143 patients were included. Patients were mostly female (61.5%) with mean age of 56.38 ± 16.67. The underlying co-morbidities were hypertension (75.5%), dyslipidemia (67.1%) and ischemic heart disease (65.7%). Overall, there was an increased in use of ACEI/ARB (55.2% to 79.7%), beta blocker (58.7% to 60.8%), and aldosterone antagonist (23.8% to 37.1%) on admission to discharge. The mean length of hospital stay was 6.32 ± 6.78 and majority of patients improved (98.6%). Re-hospitalization and in-hospital mortality were 2.8% and 1.4%, respectively. The use of all three pharmacologic agents was only significantly associated with length of hospital stay (p value = 0.003). Both beta blocker (p value = 0.028) and aldosterone antagonist (p value = 0.030) showed significant association with length of hospital stay. The use of ACEI/ARB alone showed no significant association with in-hospital clinical outcomes.

In conclusion, the use of all three guideline-based pharmacologic agents showed significant association with length of hospital stay. In addition, the utilization of these guideline-based pharmacologic agents was still suboptimal. Clinical benefits of guideline-based pharmacologic agents among Asians differed from western population. Therefore, more studies are recommended to further understand the response to therapy among Asians and to aid in optimizing these drugs for better outcome.
TILT TABLE TESTING TO DIAGNOSE PSEUDOSYNCOPE IN THE PEDIATRIC POPULATION

J.A. Robinson, J.K. Shivapour, C.S. Snyder
The Congenital Heart Collaborative, Rainbow Babies and Children's Hospital, Case Western Reserve University School of Medicine, Cleveland, OH, USA

Purpose: Pseudosyncope (PS) can be difficult to distinguish from true syncope. The purpose of this study is to describe the diagnostic utility of head-up tilt table (HUTT) to elicit the diagnosis of PS in the pediatric population.

Methods: A retrospective chart review from 11/12 to 7/15 of patients ≤ 23 yrs of age referred for 30-minute, 80-degree tilt with continuous monitoring of ECG and pulse ox. Blood pressure and heart rate were obtained supine, at 80-degree tilt, and q 1 minute. Pretest probability for PS was high if the patient had no response to traditional management, atypical episodes, occurrence during unusual exercise, or prolonged episode duration. Prior to and during HUTT, inductive techniques were utilized to convince patients of the likelihood of experiencing an episode during the procedure. PS was confirmed when patient had normal vital signs during their event and had reflex responses to disruptive maneuvers, including answering questions, exhibiting a startle response to a loud noise, or moving away from a sternal rub.

Results: HUTT was performed on 76 patients [median age 16 yrs (5-23); 29% male] with the majority (61%) being negative for pseudosyncope, including 45 true negatives and 1 false negative (diagnosed with pseudosyncope after HUTT). Of the 30 patients with syncope symptoms during HUTT, 21 were diagnosed with vasovagal syncope and 9 with PS [median age 16 yrs (15-21); 44% male]. PS episodes were observed immediately (<2 minutes) in 3 patients; the 6 others had late-onset symptoms. All patient with late-onset PS required induction techniques prior to the recorded episode. PS was verified by reflex response to disruptive maneuvers.

Conclusion: PS can be identified during a HUTT if inductive techniques are utilized in those patients with a high index of suspicion. Disruptive maneuvers are excellent adjunctive methods to assist with confirming the diagnosis.
Introduction: Cor-triatrium is a rare congenital cardiac anomaly in which a fibromuscular/membranous septum divides the left (sinistrum) or the right (dextrum) atria into a total of 3 chambers and hence 'triatrium'. We present a case of 60 year old lady with Cor-Triatrium Sinistrum (CTS) with concomitant CAD who underwent CABG and successful repair of CTS.

Case description: A 60-year-old Caucasian woman with h/o dyslipidemia presented with progressive dyspnea and fatigue for 1 year. Physical examination was unremarkable. 2D Echo showed an EF of 70% with moderately dilated left atrium (LA) with no valvular abnormalities. However, a diastolic gradient was present across a structurally normal Mitral Valve (MV), hence CTS was suspected. Findings of CTS were confirmed by a TEE. Right and left heart catheterization prior to surgery showed multi-vessel disease. On surgical exploration, a 3.9x3.1x0.1 cm membrane was seen just distal to the pulmonary veins in the LA with a nickel sized opening in the middle. CABG and removal of membrane were performed. Immediate postoperative period was uncomplicated and her symptoms improved.

Discussion: Cor-triatrium is a rare congenital abnormality, found in approximately 0.1-0.4% of clinically diagnosed congenital cardiac malformations. Mal-incorporation of the common pulmonary vein into the LA is the most common cause of CTS, creating two chambers that may or may not be separated by an opening. CTS is usually asymptomatic and is diagnosed in the pediatric age group, causing LA outflow obstruction mimicking mitral stenosis, or due to its association with other cardiac malformations in about 80% cases. CTS rarely remains asymptomatic till adulthood and the symptoms are based on the size of the membrane and/or the presence of fenestrations. Our patient presented at 60 years with exertional dyspnea subsequently diagnosed with CTS with concomitant CAD which is very rare, and not previously reported.
LATE COMPLICATIONS OF D-TRANSPOSITION OF THE GREAT ARTERIES S/P MUSTARD PROCEDURE

K.S. Patel, K. Ramasubbu, B. Subedi
New York Methodist Hospital, NY, USA

Introduction: D-Transposition of the great arteries (D-TGA) is a ventricular-arterial discordant lesion in which the aorta arises inappropriately from the right ventricle and the pulmonary artery arises inappropriately from the left ventricle. Complications after atrial switch Mustard procedure (ASP) include arrhythmias, right ventricular heart failure, and baffle complications. We present a female patient with a 2 week history of worsening shortness of breath, lower extremity edema, and exercise intolerance.

Case Presentation: 38 year old female with a history of D-TGA with an intact ventricular septum status post Mustard procedure around age one, supraventricular tachycardia, and heart block of unknown type with 3 pacemaker placements and extractions was admitted with cardiogenic shock. She was noted to have a regular narrow complex tachycardia at 156 beats per minutes. Our differential included sinus tachycardia and atrial tachycardia. Her echocardiogram demonstrated severe biventricular dysfunction, and severe mitral and tricuspid regurgitation. She was initially treated with intravenous furosemide, amiodarone drip, and heparin drip. However, the patient’s status declined; she was started on dobutamine and norepinephrine drips and she was intubated. Due to further hemodynamic deterioration, veno-arterial extracorporeal membrane oxygenation (VA-ECMO) for refractory cardiogenic shock was placed. The cardiogenic shock and resultant end-organ dysfunction rapidly improved, however the tachycardia remained raising suspicion for a supraventricular tachycardia. The patient subsequently underwent an electrophysiology study and ablation of multiple atrial foci with complete resolution of the tachycardia. Thereafter, the VA ECMO was able to be weaned and removed successfully.

Discussion: This case demonstrates a patient status post D-TGA repair with underlying biventricular dysfunction who presents with cardiogenic shock likely precipitated by an atrial tachycardia. This case illustrates the extraordinary utility of VA-ECMO in stabilizing a patient with cardiogenic shock, thereby allowing to address the precipitating factor with subsequent resolution of cardiogenic shock.
HEALTHY CAREGIVERS-HEALTHY CHILDREN: A PRIMARY PREVENTION PROGRAM WITH PRESCHOOL CHILDREN

R.N. Natale, S.E. Messiah, C. Chang, K. Sardinas, J. Fitzgibbons, S. Peraza
University of Miami School of Medicine, Mailman Center for Child Development, Miami, FL, USA

Background: Although cardiovascular disease is typically diagnosed in adulthood, its roots often begin in childhood. Obesity in children and adolescents associates with elevated cholesterol and elevated blood pressure and tracks from childhood to adulthood. Currently, the science needed to promote successful implementation of primary prevention practices, under naturally occurring conditions, is poorly developed. We describe here the outcomes of “Healthy Caregivers, Healthy Children (HC2)” an obesity prevention program with young children.

Methods: A randomized controlled trial was conducted with 1101 children in 24 childcare centers (n=12 intervention and 12 control). The Intervention focused on three components to support and encourage cardiovascular health: environmental changes related to food consumption and physical activity in the centers, a classroom curriculum, and family and teacher education regarding healthy role modeling behaviors. The primary outcome was the child’s body mass index (BMI), and the secondary outcomes were changes in dietary intake and physical activity at home and at the childcare centers.

Results: At 6 months post-intervention, children in the intervention centers were significantly more likely to consume fresh vegetables fruits (p.006) and vegetables (p.001) as compared to the control centers. 91% of parents who increased buying vegetables had children whose BMIs either stayed the same or improved (p=.01), and 92% of parents who increased buying fruit had children whose BMI either stayed the same or improved (p=.03).

Conclusions: The goal of this project is to develop and evaluate a multifaceted obesity prevention intervention in the early child-care setting, targeting low-income, multiethnic children. Results suggest that a preschool-based obesity prevention intervention working with parents and teachers as change-agents is effective in increasing healthy lifestyle behaviors while maintaining a healthy BMI percentile in the preschool years. These findings support efforts to implement healthy weight programs in the childcare setting as a means of primary prevention.
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APPROPRIATENESS OF AERO MEDICAL TRANSPORT FOR CARDIAC EMERGENCIES

A. Aggarwal, J. Heslop, S. Banga, S. Mungee, K. Kalvakuri
Division of Cardiology, Department of Internal Medicine, University of Illinois College of Medicine at Peoria, Illinois; OSF Saint Francis Medical Center, Peoria, Illinois, USA

Background: Air ambulance transport has been rapidly expanding and has helped improve patient outcomes by affording timely life-saving medical interventions. Significant discord exists in the acuity of the initial cardiac assessment and diagnosis requiring urgent transfer, resulting in significant economic implications and burden.

Objectives: We aimed to study the appropriateness of air transfers from other centers to our tertiary care center for cardiac emergencies.

Methodology: This is a single-center retrospective analysis over 3 year period (Jan 2012 to March 2015) of inter-facility air ambulance transfer for cardiac emergencies at OSF St. Francis Medical Center. The primary outcome assessed was the appropriateness of transfer which was decided based on medical chart review by two independent reviewers. Appropriateness for air transfers was judged based on the acuity of clinical presentation, hemodynamic stability and the need for an urgent medical intervention.

Results: 750 patients with cardiac emergencies were transported by aero-medical transport using 4 American Eurocopter EC 145 helicopters over 3 years. Mean age of patients transferred was 64±14 years, median length of stay 2 (1-48) days. Majority of transfers were from small community hospitals in rural Illinois at a mean of 61±15 road miles distance. There were 28 (3.7%) total deaths. Only 30 (4%) of the total 750 transfers were deemed to be inappropriate.

Conclusions: Aeromedical transportation provides an effective, rapid and efficient means of transfer of cardiac emergencies. This has helped to provide for an urgent and timely cardiac care in the sickest patients and thereby impacted mortality favorably.

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DECREASED DUPLICATE TESTING WITH ELECTRONIC MEDICAL RECORDS. A STUDY OF 7,400 NUCLEAR MEDICINE STRESS TESTS

A. Avezbadalov1, F. Mushtaq1, P. Hardigan2, J.J. Rozanski1, M.A. Chizner1
1. The Heart Center of Excellence, NOVA University, Fort Lauderdale, FL, USA
2. NOVA University, Fort Lauderdale, FL, USA

Objective: Duplicate testing increases health care costs and exposes patients to unnecessary harms of testing. The electronic medical record (EMR) has been widely accepted and utilized to reduce duplicate testing. Nevertheless, there are institutions that have reported an increase in repeat testing. This has been attributed to the ease of ordering and usage of electronic order sets. We sought to evaluate the difference in the number of duplicate nuclear medicine stress tests (NST) before and after the implementation of an EMR at our urban medical center.

Methods: This is a single center retrospective analysis of all NST’s performed at our institution in the period of 1 year prior to, and 1 and 2 years after the implementation of EMR. The NST’s were reviewed to assess the number of patients who underwent duplicate testing within 6 and 12 months of the index NST (Table 1).

Results:

<table>
<thead>
<tr>
<th></th>
<th>July 2011 – June 2012 (Pre-EMR)</th>
<th>July 2013 – June 2014 (EMR year 1)</th>
<th>July 2014 – June 2015 (EMR year 2)</th>
<th>P Value (for comparison of pre-EMR to both 1 and 2 years post-EMR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of NST</td>
<td>2876</td>
<td>2467</td>
<td>2103</td>
<td></td>
</tr>
<tr>
<td>Repeat NST 6 months of unique NST</td>
<td>(46) (1.6%)</td>
<td>(25) (1.2%)</td>
<td>(20) (0.9%)</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Change in duplicate testing at 6 months from 2012</td>
<td>-45.6%</td>
<td>-56.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Repeat NST 12 months of unique NST</td>
<td>(148) (5.2%)</td>
<td>(76) (3.1%)</td>
<td>(72) (3.5%)</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Change in duplicate testing at 12 months from 2012</td>
<td>-40.6%</td>
<td>-51.4%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 1

Conclusion: After the implementation of EMR, there was a significant reduction in duplicate testing of NST’s. These results were significant at both 1 and 2 years after implementing EMR. We hypothesize that electronic notifications and ease of accessibility to previous results attributed to this decrease. We found no significant difference between duplicate testing at years 1 and 2 post-EMR.
MAYO REGISTRY FOR TELEMETRY EFFICACY IN ARREST (MR TEA) STUDY: A DESCRIPTIVE ANALYSIS OF MEDICATION ADMINISTRATION DURING INPATIENT CARDIOPULMONARY ARREST RESUSCITATION

1. Mayo Clinic, Rochester, MN, USA
2. Mayo Clinic, Jacksonville, FL, USA

Introduction: Advanced cardiovascular life support guidelines exist, yet there are variations in clinical practice. Our study aims to describe the utilization of medications during resuscitation from in-hospital cardiopulmonary arrest.

Methods: A retrospective review of patients that suffered a cardiopulmonary arrest between May 2008 and June 2014 was performed. Clinical and resuscitation data, including timing and dose of medications used, were extracted from the electronic medical record and comparisons made.

Results: A total of 94 patients were included in the study. Patients were divided into different groups based on the medication combination used during resuscitation: 1. Epinephrine, 2. Epinephrine and bicarbonate, 3. Epinephrine, bicarbonate, and calcium, 4. epinephrine, bicarbonate, and epinephrine drip, and 5. epinephrine, bicarbonate, calcium, and epinephrine drip. No difference in baseline demographics or clinical data was present, apart from history of dementia and use of calcium channel blockers. The number of medications given was correlated with resuscitation duration (Spearman’s rank correlation=0.50, p<0.001). The proportion of patients that died during the arrest was 12.5% among those who received epinephrine alone, 30.0% among those who received only epinephrine and bicarbonate, and 46.7% to 57.9% among the remaining groups. Patients receiving only epinephrine had shorter resuscitation durations compared to that of the other groups (p<0.001) as well as improved survival (p=0.003).

Conclusions: Providers frequently use non-guideline medications in resuscitation efforts for in-hospital cardiopulmonary arrests. Increased duration and mortality rates were found in those resuscitations compared to epinephrine alone, likely due to the longer resuscitation duration in the former groups.
CARDIOVASCULAR QUALITY IMPROVEMENT AND OUTCOME

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CHANGES IN MANAGEMENT OF STEMI WITH MULTIVESSEL DISEASE IN A CARDIAC CATHETERIZATION LAB

J.B. Halevy, P.B. Gogo
The University of Vermont Medical Center, Burlington, VT, USA

Cardiology guidelines weigh the best available evidence to set standards of cardiac care creating a shield against claims of liability. However guidelines are only updated intermittently and can lag behind new evidence creating challenges for practicing cardiologists in deciding whether and when to change practice. In April 2012 as part of the Choosing Wisely™ campaign, the American College of Cardiology recommended questioning any intervention beyond unblocking the “culprit” artery for a myocardial infarction in hemodynamically stable patients based on non-randomized studies. The PRAMI trial (published in September 2013) and later the CvLPRIT trial (presented at European Society of Cardiology Congress in September 2014) provided randomized evidence showing improved outcomes with multivessel revascularization, resulting in withdrawal of the Choosing Wisely™ recommendation in late September 2014. In order to investigate the effect and timing of changes in practice with respect to new evidence conflicting with current guidelines, rates of multivessel versus culprit percutaneous coronary interventions at index hospitalization after STEMI activation at the University of Vermont Medical Center hospital from September 2013 to March 2015 were analyzed by calendar quarter. A significant change in practice was noted in the third quarter of 2014, prior to the withdrawal of the guideline and second trial and almost a year after the first trial, wherein patients with multivessel disease were substantially more likely to have multivessel PCI compared to previously (OR 7.60, 95% CI 1.87-30.90, p=0.0046). When the third quarter of 2014 was compared to the next 6 months, no significant change in practice was noted (OR 0.79, 95% CI 0.24-2.65, p=0.7047). In a single academic hospital catheterization lab, practice patterns lagged almost a year after substantial new high quality evidence but did change prior to changes in guidelines and publication of a second randomized trial.
CLINICAL CHARACTERISTICS, HOSPITAL MANAGEMENT PRACTICES, AND IN-HOSPITAL OUTCOMES OF PATIENTS HOSPITALIZED WITH TYPE 1 AND TYPE 2 MYOCARDIAL INFARCTION: THE WORCESTER HEART ATTACK STUDY

J. Yarzebski a; M. Tisminetzky a,b,c; E. Granillo a; R. Charan, R.P. Makam a; D.D. McManus a,b,d; D. Lessard a; J.M. Gore a,d; R. Goldberg a,b

a Department of Quantitative Health Sciences, b Meyers Primary Care Institute, Divisions of c Geriatrics and d Cardiovascular Medicine, Department of Medicine, University of Massachusetts Medical School, Worcester, MA, USA

Introduction: Extremely limited population-based data are available describing differences in the clinical and demographic characteristics, hospital management practices, and in-hospital outcomes of patients with type 1 myocardial infarction (T1MI) as compared with type 2 myocardial infarction (T2MI).

Methods: This was a community-based, observational study of 1,047 residents of the Worcester (MA) metropolitan area hospitalized with confirmed acute myocardial infarction (AMI) at all 11 central Massachusetts medical centers during 2011.

Results: T1MI was present in 75.3% (n=788) of patients hospitalized with confirmed AMI. In comparison to patients with T1MI, patients with T2MI were older, more likely to be female, and had more comorbidities previously diagnosed. A greater proportion of patients with T2MI presented to the emergency department with a major hemorrhage (6.2% vs 0.1%) and were more likely to have developed renal failure during their acute hospitalization (48.3% vs 20.2%), but less likely to have developed heart failure. Patients with T2MI were less likely to have received all 4 effective cardiac medications (88.4% vs 93.7%) and coronary revascularization procedures (6.3% vs 53.1%) and had a longer average hospital stay (10.6 days vs 4.7 days) than patients with T1MI.

Conclusions: A considerable proportion of patients hospitalized with AMI are diagnosed with T2MI. These patients present with different characteristics, may have a differential risk of various clinical complications, and are managed differently than patients with T1MI. It remains important to study the clinical profile, in-hospital management, and outcomes of patients with T2MI and to determine the best therapeutic strategies to improve their short-term outcomes.

Funding Source: National Institutes of Health (RO1 HL35434)
LIPIDS, OBESITY, METABOLIC SYNDROME AND DIABETES

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PATHOGENESIS AND THERAPY OF DIABETIC CARDIOMYOPATHY
N.S. Dhalla
St. Boniface Hospital Albrechtsen Research Centre, University of Manitoba, Winnipeg, MB, Canada

Chronic diabetes is known to be associated with the development of cardiomyopathy, metabolic derangement and cardiac dysfunction. Extensive studies in our laboratory have revealed that cardiac dysfunction due to chronic diabetes is associated with marked alterations in subcellular organelles such as myofibrils (MF), sarcoplasmic reticulum (SR) and sarcolemma (SL). These diabetes-induced changes in the heart appear to be due to the development of oxidative stress as a consequence of elevated levels of plasma glucose as well as prolonged activation of different hormonal systems and platelets. This view is based on our observations that treatment of streptozotocin-diabetic rats for 8 weeks with different antioxidants attenuated alterations in cardiac function as well as MF Ca2+-stimulated ATPase, SR Ca2+-release and Ca2+-uptake, and SL Na+-K+ ATPase activities. Furthermore, treatment of diabetic animals with sarpogrelate, an antiplatelet agent, for 8 weeks was observed to attenuate changes in the protein content of glucose transporters (GLUT 1 and GLUT 4), oxidative stress and abnormalities in cardiac function as well as alterations in various activities of MF, SR and SL. Several metabolic interventions, which prevented the occurrence of intracellular Ca2+-overload, were also observed to produce beneficial effects on the diabetes-induced abnormalities. These results suggest that elevated levels of plasma 5-HT due to platelet aggregation, in addition to metabolic derangement and oxidative stress, may play an important role in inducing defects in glucose utilization and cardiac dysfunction in chronic diabetes.
LIPIDS, OBESITY, METABOLIC SYNDROME AND DIABETES

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SEX DIFFERENCES IN THE CARDIOVASCULAR CONSEQUENCES OF DIABETES MELLITUS
N.K. Wenger
Emory University School of Medicine, Atlanta, GA, USA

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality with type 2 diabetes mellitus (DM), accounting for >75% of hospitalizations and >5% of deaths. Women have a 3-fold excess of coronary heart disease (CHD) risk compared to men, and diabetic women have a 2-fold excess fatal CHD risk compared to non-diabetic women. Myocardial infarction occurs earlier and has higher mortality in diabetic women than diabetic men. Diabetic women have a more adverse cardiovascular risk profile than their male peers, have lower revascularization rates with both PCI and CABG compared to men, and are less likely than men with DM to receive guideline-based outpatient and acute coronary syndrome therapies.

Incident heart failure is more common in diabetic women than in men. In the Framingham cohort, heart failure risk was increased 5-fold in diabetic women compared with 2-fold in diabetic men vs a nondiabetic population. Diabetic women have a higher prevalence of risk factors, including hypercholesterolemia, physical inactivity and overweight, and are counseled less about nutrition, exercise, and weight control. Diabetes increases stroke risk more in women than men, but with data on relationship between diabetes and stroke type and effect of DM duration or control on stroke incidence. Little is known about sex differences in diagnosis, symptoms, and treatment of PAD in diabetic patients, although women fare worse than men. Women with PAD and DM respond less well to exercise training than women without DM and men with and without DM; women undergoing PAD revascularization have lesser long-term survival and excess post-surgical mortality. Women with DM and heart disease have poorer control of both diseases and receive less intensive medical treatment than diabetic men, which may partly explain why CVD death has decreased among diabetic men but not women.
LIPIDS, OBESITY, METABOLIC SYNDROME AND DIABETES

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STATINS IN THE TREATMENT AND PREVENTION OF CARDIOVASCULAR DISEASES: CURRENT AND EMERGING CLINICAL AND PUBLIC HEALTH CHALLENGES
C.H. Hennekens\textsuperscript{1}, E.H. Lieberman\textsuperscript{1}; M.H. Rubenstein\textsuperscript{1}; P.R. Hebert\textsuperscript{1}; D.L. DeMets\textsuperscript{2}; M.A. Pfeffer\textsuperscript{3}
1. Charles E. Schmidt College of Medicine, Florida Atlantic University, Boca Raton, FL, USA
2. University of Wisconsin School of Medicine and Public Health, Madison, WI, USA
3. Harvard Medical School and Brigham and Women’s Hospital, Boston, MA, USA

Cardiovascular disease (CVD) is and will remain the leading avoidable cause of premature deaths in the US and is rapidly becoming so worldwide. The totality of available evidence on statins in the treatment and prevention of CVD is robust and includes over 200,000 randomized subjects from dozens of large scale trials designed a priori to test the hypothesis and their meta-analyses. In secondary and high-risk primary prevention, clinicians should more widely prescribe evidence based doses of statins as first line drugs. In low-risk primary prevention subjects previously considered ineligible, statins also have a favorable benefit to risk ratio. Statins should be adjuncts, not alternatives to therapeutic lifestyle changes of proven benefit including weight loss, physical activity, avoidance or cessation of cigarettes and diet. In addition, any decision to prescribe statins should be based on individual clinical judgments that include all the risk factors of an individual and not simply those in any risk algorithm. Further, for individuals optimally treated with a statin and the responsible clinician wishes to prescribe additional therapy, the data are far less persuasive. Ezetimibe but not nicotinic acid, omega-3 fatty acids, or fibrates have been demonstrated to add to the benefits of statins. Finally, new and novel therapies, even if eventually proven to have a favorable benefit to risk ratio, will generally be adjuncts not alternatives to statins. The utilization of guidelines as guidance for clinicians should lead to more widespread and judicious prescription of evidence based doses of statins which, in turn, will lead to even greater net clinical and public health benefits in the treatment and prevention of CVD.
Over the past 3 decades, statins have become the cornerstone of prevention and treatment of atherosclerotic cardiovascular and metabolic diseases. Albeit generally well tolerated, they can elicit a variety of muscle-associated symptoms that represent the most important reason for treatment discontinuation, switching or non-adherence. The statin-associated myopathy has been systematically underestimated by randomized controlled trials as compared with the incidence observed in clinical practice and obtained from patients’ registries. This discrepancy has several reasons among which the lack of reliable diagnostic test(s) and validated questionnaire to assess muscle symptoms are recognized as unmet needs. Therefore it is a large need to look for the cellular and molecular biomarkers to signal/diagnose muscle-related complaints.

When initiating statin therapy, attention to risk factors for statin intolerance is strongly recommended. The nocebo effect coupled with the challenges of diagnosing statin myopathy undermines drug adherence that is critical for achieving the benefits of lipid-lowering and cardiovascular risk reduction. A temporal relationship should be made between the initiation of therapy and development of symptoms to aid in diagnosis. To limit errors in the diagnosis of statin intolerance, improvements in clinician-patient communication about the side effects and benefits of statins should be attempted. The mainstay of treatment is statin cessation or statin dose reduction and evaluation of alternative causes for muscle related symptoms. Most symptoms usually resolve within 2 weeks of discontinuing therapy. The patient can be re-challenged with the same stain at a lower dose or an alternative statin. Non-statin lipid lowering therapies offer an alternative to patients who cannot tolerate statins.
Despite clinical trials of high intensity statin therapy showing 30-40% atherosclerotic cardiovascular disease (ASCVD) risk reductions, significant residual risk remains due to inadequate low density lipoprotein-cholesterol (LDL-C) lowering and/or intolerability of statin therapy. It has been less than 15 years since discovery of proprotein convertase subtilisin-like kexin type 9 (PCSK9) loss of function mutations, providing proof-of-concept for clinical development and marketing of PCSK9 monoclonal antibody (mAb) therapy for the treatment of dyslipidemia in high risk persons with ASCVD or familial hypercholesterolemia (FH). Both alirocumab and evolocumab were FDA approved in 2015 and bococizumab is currently in clinical development. Alirocumab and evolocumab provide average 60% LDL-C lowering beyond maximally tolerated statin therapy in persons with ASCVD, FH, and other high risk conditions with targets of <100 mg/dl and <70 mg/dl reached in most persons. Many patients also experience reductions in LDL-C to <25 mg/dl. PCSK9 mAb therapy also lowers levels of non-HDL-C and apoB by approximately 50% and lipoprotein(a) by approximately 30%. Neutralizing antibodies resulting in loss of efficacy are seen in <1% of subjects. Follow-up data over 11 months for evolocumab and 18 months for alirocumab show approximate 50% reductions in ASCVD event risk (compared to placebo) on top of maximally tolerated statin therapy. Recently, the National Lipid Association and the American College of Cardiology have provided guidance for considering PCSK9 mAb therapy based on whether certain LDL-C targets (e.g., <100 mg/dl or <70 mg/dl depending on risk group) or therapeutic response (e.g., >50% LDL-C lowering) has been achieved on maximally tolerated statin therapy. Results from ongoing long-term ASCVD outcomes trials will be important to further establish the role of PCSK9 mAb therapy in addressing ASCVD residual risk beyond statin therapy.
THE HIGHLY DIFFICULT LIPOPROTEIN: CONTROVERSIES AND NEW DIRECTIONS

R.S. Rosenson
Icahn School of Medicine at Mount Sinai, New York, NY, USA

Classical epidemiology has established the incremental contribution of the high density lipoprotein (HDL) cholesterol measure in the assessment of atherosclerotic cardiovascular disease risk; however, genetic epidemiology does not support a causal relationship between HDL cholesterol and future risk of myocardial infarction. Therapeutic interventions directed towards cholesterol loading of the HDL particle have been based on epidemiological studies that have established HDL cholesterol as a biomarker of atherosclerotic cardiovascular risk. However, therapeutic interventions (niacin, cholesteryl ester transfer protein inhibitors) that increase HDL cholesterol in patients treated with statins have repeatedly failed to reduce cardiovascular events. Statin therapy, particularly high-dose lipophilic statins, has been recently demonstrated to interfere with ABCA1-mediated macrophage cholesterol efflux via miR33. Unraveling the HDL puzzle will require continued technical advances in the characterization and quantification of multiple HDL subclasses, and their functional properties. Key mechanistic criteria for clinical outcomes trials with HDL-based therapies include the formation of HDL subclasses that improve the efficiency of macrophage cholesterol efflux, and compositional changes in the proteome and lipidome of the HDL particle that are associated with improved anti-oxidant and anti-inflammatory properties. These measures require validation in genetic studies and clinical trials of HDL-based therapies on the background of statins that do not diminish the efficacy of macrophage cholesterol efflux.
LIPIDS, OBESITY, METABOLIC SYNDROME AND DIABETES

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COMPREHENSIVE CARDIOVASCULAR RISK REDUCTION IN THE METABOLIC SYNDROME AND DIABETES
L.S. Sperling
Emory University School of Medicine, Atlanta, USA

Metabolic susceptibility in combination with environmental and behavioral factors have contributed to a global epidemic of non-communicable diseases with an estimated prevalence of diabetes of 380 million by 2025. Central to the pathophysiology of metabolic syndrome is visceral adiposity which leads to a clustering of vascular risk factors including a cascade of adverse processes involving upregulation of inflammatory cytokines and a prothrombotic state. Of major concern the metabolic syndrome and diabetes significantly increase the risk of vascular disease. In addition, most cardiovascular patients have evidence of abnormal glucose metabolism. Importantly, comprehensive cardiovascular risk reduction is critical for preventive strategies targeting this high risk group. Population health and disease management approaches, as well as new care models are needed as data strongly suggests that innovative integrated care will impact both quality and outcomes for those with metabolic syndrome and diabetes.
PDE5 INHIBITION IN PROTECTION OF DIABETIC HEART

Virginia Commonwealth University Richmond, VA, USA

Obesity and insulin resistance lead to impaired nitric oxide (NO) bioavailability, oxidative stress, chronic inflammation, atherosclerosis and acute coronary syndromes. Hyperglycemia is associated with increased infarct size and higher risk of congestive heart failure in patients. Phosphodiesterase 5 (PDE5) inhibitors including sildenafil, vardenafil and tadalafil protect against myocardial ischemia/reperfusion (I/R) and ischemic cardiomyopathy. Since PDE5 inhibitors increase NO production and improve endothelial dysfunction, we hypothesized that chronic treatment with the long-acting PDE5 inhibitor, tadalafil would protect the diabetic heart against I/R injury. Leptin receptor null (db/db) mice underwent treatment with tadalafil (1 mg/kg) or 10% DMSO for 28 days. The hearts were isolated and subjected to 30 min global ischemia and 60 min reperfusion. Tadalafil treatment significantly reduced fasting glucose and triglycerides. Infarct size was significantly lower in tadalafil treated mice as compared to the control. Circulating TNFalpha and IL-1beta were reduced following tadalafil treatment. Sirt1, a histone deacetylase that regulates peroxisome proliferator-activated receptor gamma coactivator-1-alpha (PGC-1alpha) which is a master regulator of mitochondrial biogenesis and co-activator of transcription factors impacting energy homeostasis. Our results showed that tadalafil treated mice had significantly higher plasma levels of NO and increased expression of myocardial Sirt1as well as PGC1alpha. Furthermore, tadalafil treatment attenuated ROS production and improved mitochondrial dysfunction as demonstrated by preservation of oxidative phosphorylation with the complex I substrate, glutamate. We conclude that chronic treatment with tadalafil protects against I/R injury in diabetic heart through mechanisms which blunt inflammation and activate NO-induced Sirt1/PGC-1alpha signaling. We conclude that tadalafil could be an attractive therapy for reducing cardiovascular risk factors while providing cardioprotective effect in diabetic patients.
INITIAL STAGES OF OBESITY ARE ASSOCIATED WITH INCREASED CARDIOVASCULAR ACTIVATION UNDER STRESS

D. Jezova¹, B. Prokopova¹,², N. Hlavacova¹

1. Institute of Experimental Endocrinology, Biomedical Research Center, Slovak Academy of Sciences, Bratislava, Slovakia
2. Department of Pharmacology and Toxicology, Faculty of Pharmacy, Comenius University, Bratislava, Slovakia

Stress and obesity are well known risk factors for cardiovascular diseases. The recognition of early markers of cardiovascular risk during the development of obesity is essential. The hypothesis tested was that under stress conditions subjects at initial stages of obesity exhibit different cardiovascular and neuroendocrine activation compared to those with normal body weight. Healthy volunteers above the upper (BMI = 26.5-35, n=17) and at the lower (BMI less than 21, n=17) limit of normal range of body weight were included. Subjects with middle-range body weight (BMI 21-26) were excluded. The subjects were exposed to a stress procedure consisting of mental (Stroop test) and physical (cold pressor test) component. Systolic and diastolic blood pressure was monitored before, during and after the stress exposure. Saliva was collected for the measurements of stress hormone concentrations and activity of alpha-amylase. Activity of this enzyme is reflecting, at least partly, the activity of the sympathetic nervous system. The same parameters were analysed in saliva collected by the subjects another day under non-stress conditions to monitor the daily rhythm. Trait and state anxiety were evaluated by Spielberger State-Trait Anxiety Inventory. Stress exposure resulted in an increase in alpha-amylase activity in both groups. Subjects with higher BMI exhibited increased activity of alpha-amylase as well as higher systolic and diastolic blood pressure compared to those with lower BMI. Volunteers with overweight were less anxious than slim individuals. Under non-stress conditions, subjects with higher BMI had higher alpha-amylase activity and lower cortisol concentrations throughout the day. Both groups showed higher state anxiety before the stress exposure than at its end. In conclusion, evaluation of stress response in subjects at initial stages of obesity revealed changes in neuroendocrine parameters suggesting a mild dysfunction of autonomic nervous system activity. Supported by VEGA 2/0057/15 and APVV-0496-12.
METFORMIN ENHANCES T0901317-REDUCED ATHEROSCLEROSIS AND INHIBITS T0901317-INDUCED HYPERTRIGLYCERIDEMIA--A NEW STRATEGY FOR ATHEROSCLEROSIS TREATMENT
C. Ma, W. Zhang, Y. Duan, Y. Chen, J. Han
College of Life Sciences, State Key Laboratory of Medicinal Chemical Biology, and Collaborative Innovation Center for Biotherapy, Nankai University, Tianjin, China

The progress on selective liver X receptor beta (LXRbeta) modulators which reduce atherosclerosis without lipogenic effect is limited. Metformin, a medicine used for diabetes treatment, activates AMPK/β to enhance energy metabolism. In this study, we determined if co-treatment of metformin with LXR ligand (T0901317) can inhibit atherosclerosis while eliminating LXR-induced hypertriglyceridemia. ApoE deficient (apoE-/-) mice were fed a high fat diet (HFD) or HFD containing T0901317 or metformin alone or both for 16 weeks. T0901317 or metformin alone inhibited lesion development of en face aorta, sinus of aortic root and other parts of aorta while the combined T0901317 and metformin further reduced lesions. Structurally, the combined T0901317 and metformin increased the content of smooth muscle cells/collagen in fibrous caps while reducing necrotic cores and mineralization within lesions suggesting increased plaque stabilization. T0901317 alone resulted in development of fatty liver, activated hepatic lipogenesis, and increased activities of aminotransferases. However, these adverse effects were eliminated by metformin. Mechanistically, co-treatment of T0901317 and metformin reduced macrophage accumulation while activated expression of ABCA1 and ABCG1 in aortic root lesion areas, and inhibited foam cell formation in vivo. In macrophages, metformin had little effect on T0901317-induced LXRalpha and LXRbeta expression or nuclear translocation. In contrast, metformin moderately inhibited T0901317-induced hepatic LXRalpha or LXRbeta expression, and selectively reduced hepatic LXRalpha, but not LXRbeta, nuclear translocation. Therefore, metformin inhibited T0901317-activated expression of lipogenic genes, such as SREBP1, ACC1 and FASN, and phosphorylation of ACC1 which substantially reduces T0901317-induced hepatic lipid accumulation. In addition, metformin inhibited LXR-induced serum total-, LDL-, VLDL-cholesterol and triglycerides levels. Taken together, our study suggests that co-treatment of metformin and T0901317 might be a new strategy for atherosclerosis treatment without lipogenesis.
MACROPHAGE DEPOSITION OF CHOLESTEROL INTO THE EXTRACELLULAR MATRIX - A PATHWAY FOR REVERSE CHOLESTEROL TRANSPORT

X. Jin¹, D. Sviridov², Y. Liu¹, B. Vaisman², L. Addadi³, A.T. Remaley², H.S. Kruth¹

1. Experimental Atherosclerosis Section, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland, USA
2. Lipoprotein Metabolism Section, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland, USA
3. Department of Structural Biology, Weizmann Institute of Science, Rehovot, Israel

Objective: To investigate the potential for mobilization of extracellular cholesterol within atherosclerotic plaques.

Background: Atherosclerotic plaques develop as a result of an imbalance between cholesterol accumulation and cholesterol removal. The macrophage plays a central role in both of these processes. How macrophages eliminate excess cholesterol has been of great interest, and is important for understanding the cholesterol accumulation process in developing atherosclerotic plaques. Our previous research has identified a novel macrophage cholesterol processing pathway, in which macrophages deposit excess cholesterol into the extracellular matrix where it can accumulate unless mobilized by HDL. Apolipoprotein A-I (ApoA-I) is the major protein component of HDL. In this study, we examined the function of ATP-binding cassette transporter A1 (ABCA1) in ApoA-I mobilization of cholesterol deposited into the extracellular matrix by cholesterol-enriched macrophages. We have also determined whether an ApoA-I mimetic peptide can mobilize macrophage deposited cholesterol.

Method: Human monocyte-derived macrophages and mouse bone marrow-derived macrophages with and without ABCA1 were cultured and cholesterol enriched. Extracellular cholesterol deposited by cholesterol-enriched macrophages was detected with a monoclonal antibody.

Results: ABCA1 causes ApoA-I and ApoA-I mimetic peptides to complex with phospholipid, a cholesterol solubilizing agent. ApoA-I and the ApoA-I mimetic peptide, 5A, mobilized cholesterol deposited by macrophages, but this depended on ABCA1 function. In contrast, ApoA-I mimetic peptide 5A pre-complexed with sphingomyelin could mobilize cholesterol deposited by macrophages deficient in ABCA1.

Conclusions: Our findings show that extracellular cholesterol deposited by macrophages can be mobilized by both ApoA-I and an ApoA-I mimetic peptide, but that mobilization depends on macrophage ABCA1. Importantly, ApoA-I mimetic peptide already complexed with phospholipid can mobilize the extracellular cholesterol even in the absence of ABCA1, suggesting that this cholesterol acceptor could have efficacy even when ABCA1 activity in atherosclerotic plaques is limited.
IMPROVEMENT IN CLINICAL OUTCOMES WITH BIVENTRICULAR VERSUS RIGHT VENTRICULAR PACING IN THE BLOCK HF STUDY

A.B. Curtis¹, S.J. Worley², E.S. Chung³, P. Li⁴, S.A. Christman⁴, M. St. John Sutton⁵

1. University at Buffalo, Buffalo, NY, USA
2. Lancaster General Health
3. Ohio Heart and Vascular, The Christ Hospital Health Network
4. Medtronic, PLC
5. Hospital of the University of Pennsylvania

Background: Sustained right ventricular (RV) apical pacing may lead to deterioration in ventricular function and an increased risk of heart failure, especially in patients with pre-existing systolic dysfunction. The randomized Biventricular versus Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block (BLOCK HF) trial demonstrated that biventricular paced patients had a reduced incidence of a composite endpoint of death, heart failure-related urgent care, and adverse left ventricular remodeling.

Objective: In a pre-specified analysis, we examined clinical outcomes, including clinical composite score, quality of life (QoL), and change in New York Heart Association (NYHA) classification.

Methods: The BLOCK HF trial randomized patients with atrioventricular block, NYHA class I-III HF, and left ventricular ejection fraction (LVEF) ≤50% to biventricular or RV pacing. NYHA classification, QoL, and clinical composite score were assessed at 6, 12, 18, and 24 months. Bayesian statistical methods were employed, with the metric of significance being a posterior probability (PP) ≥0.95.

Results: Patients with biventricular pacing showed significantly greater improvement in NYHA class at 12 months, with 19% improved, 61% unchanged, and 17% worsened, compared to 12%/62%/23% in the RV arm. QoL was significantly improved through 12 months. CCS was significantly improved at 6 months, and this improvement was sustained through 24 months.

Conclusions: For patients with atrioventricular block and systolic dysfunction, biventricular pacing not only reduces the risk of mortality/morbidity, but also leads to better clinical outcomes, including improved quality of life and heart failure status, compared to RV pacing.
Strategies for prevention of sudden cardiac death (SCD) in the setting of coronary artery disease (CAD) rely on implantable cardiac defibrillators (ICD) in a subset of patients with left ventricular ejection fractions (LVEF) <35%. Many ICDs are implanted needlessly. Moreover, many patients who suffer SCD have more preserved LVEFs. Novel strategies to improve risk stratification are needed. Given the modest odds associated with use of individual risk factors, combining multiple risk markers shows promise for more accurate predictions. Noninvasive methodologies would be ideal. Data from the Oregon Sudden Unexpected Death Study recently reported by Reiner and colleagues that were acquired from patients with CAD with no prior history of SCD showed combining selected ECG measures with LVEF improved risk prediction. In adjusted analysis, higher resting heart rate (odds ratio 2.6), QRS duration (odds ratio 1.5), and JTc (odds ratio 2.3) were independently associated with SCD during follow-up. When combined, SCD odds progressively increased with 1 (odds ratio 3.4) and 2 or more elevated markers (odds ratio 6.3). Addition of ECG markers to an adjusted model with LVEF improved net reclassification by 22.7% (p<0.0001). Recently, we used PET imaging to quantify myocardial sympathetic denervation, perfusion, and viability in patients with CAD eligible for a primary prevention ICD. The endpoint was sudden cardiac arrest (SCA) defined as arrhythmic death or appropriate ICD therapy. Volumes of total denervated (p=0.001) and viable denervated myocardium (p=0.03) predicted SCA, while hibernating and infarcted myocardium did not. Multivariate analysis identified denervated myocardium >37.6% LV, LV end-diastolic volume >98 ml/m2, creatinine >1.49 mg/dl, and no ACE-inhibition therapy as independent predictors of SCA. Absence of all four factors predicted low risk (SCA <1%/year) while two or more identified subjects at high-risk (SCA 12%/year). Noninvasively obtained markers when used in combination improve SCD risk prediction in patients with CAD.
Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) is a genetically determined cardiomyopathy which predisposes to life-threatening ventricular arrhythmias and arrhythmic cardiac arrest. The main goal of clinical management is prevention of sudden cardiac death (SCD). Treatment consists of restriction of physical exercise, antiarrhythmic drugs, catheter ablation and implantable defibrillator (ICD). Desmosomal-gene mutation carriers who practice competitive sports activity show a more severe disease phenotype and a higher risk of malignant ventricular arrhythmias. As a consequence, patients with a definite diagnosis of ARVC (and possibly even young carriers of desmosomal-gene mutations with no features of the disease) should be restricted from participation in athletic activities, with the possible exception of recreational low intensity sports. In addition, there is a strong rationale for the use of beta blockers in ARVC because of the recognized pro-arrhythmic role of adrenergic stimulation and because they lower the mechanical stress on myocytes with genetically defective desmosomes. Antiarrhythmic drugs play a significant role in decreasing number and the complexity of ventricular arrhythmias, but they do not reduce the risk of SD. The results of traditional “endocardial” catheter ablation are poor because of the high rate of ventricular tachycardia (VT) recurrence; “epicardial” VT mapping/ablation procedures is a promising approach to improve long-term success rate of catheter ablation. Implantable defibrillator (ICD) is the most effective therapy for interruption of potentially lethal arrhythmic events. Despite its life-saving potential, ICD implantation is associated with a high rate of complications and significant impact on quality of life. ICD should be reserved to selected patients after an accurate risk stratification. There is general agreement that patients with a history of cardiac arrest due to ventricular fibrillation or hemodynamically unstable VT are at high risk of SCD and needs an ICD. Indications for prophylactic ICD therapy in ARVC patients with no previous cardiac arrest or sustained VT remain a matter of debate. The decision to implant an ICD should be made on a case by case basis, by balancing the strength of the arrhythmic risk factors with the significant risk of device-related complications as well as with the impact of ICD on quality of life. Patients with no risk factors or desmosomal-gene mutation carriers with no or mild phenotypic expressions have a low arrhythmic risk and do not require an ICD.
RAISING ION CHANNEL CURRENTS TO PREVENT ARRHYTHMIAS

C. Rutledge\textsuperscript{1,2}, M. Liu\textsuperscript{1,2}, H. Liu\textsuperscript{1,2}, E.M Jeong\textsuperscript{1,2}, A. Xie\textsuperscript{1,2}, I. Efimov\textsuperscript{4}, S. Dudley\textsuperscript{1,2,3}

1. Lifespan Cardiovascular Institute, Providence, RI, USA
2. Brown University, Providence, RI, Providence, USA
3. VAMC, Providence, RI, USA
4. George Washington University, Washington, DC, USA

Introduction: Ion channel blocking drugs are used to treat arrhythmias. Nevertheless, antiarrhythmic drug use is complicated by proarrhythmic risk. We tested whether raising ion channel levels would be an alternative antiarrhythmic strategy with less proarrhythmic risk.

Methods: Myocardial infarction (MI) was induced in 12-week-old mice by coronary artery occlusion. MI mice were treated with c-Src inhibitors (PP1 or AZD0530), PP3 (an inactive analogue of PP1), or saline. Nonischemic cardiomyopathy was induced in C57BL/6 mice by hypertension after unilateral nephrectomy, deoxycorticosterone acetate (DOCA) pellet implantation, and salt water substitution. Human explanted hearts were studied using optical mapping.

Results: After MI, PP1 raised Cx43 expression by 69\% in the scar border (p = 0.048) and by 73\% in the distal ventricle (p = 0.043) compared with PP3 mice. PP1-treated mice had restored conduction velocity at the scar border (PP3: 32 cm/s, PP1: 41 cm/s, p<0.05) and lower arrhythmic inducibility (PP3: 71\%, PP1: 35\%, p<0.05) than PP3 mice. Compared to the sham mice, the ejection fraction of nonischemic cardiomyopathic mice was reduced (37.1±1.8\% vs. 49.4±3.7\%, P=0.05). Sodium current (INa) was decreased (60±10\% of sham, P=0.01). Injection of NAD+ (100 mg/kg) or mitoTEMPO (0.7 mg/kg) twice (at 24 h and 1 h before myocyte isolation) to animals restored INa. Correlating with the mouse model, failing human hearts showed a reduction in conduction velocity that improved with NAD+.

Conclusions: In summary, sodium channels and connexins are downregulated in cardiomyopathy. Strategies that raise these ion channel levels reduce arrhythmic risk without apparent proarrhythmic complications.
INNOVATIVE P-WAVE DETECTION FOR DISCRIMINATION BETWEEN VENTRICULAR AND SUPRAVENTRICULAR TACHYCARDIA IN SINGLE-CHAMBER ICDs: IS THE P-WAVE INVISIBLE DURING TACHYCARDIA?

H. Paydak
UAMS, Little Rock, AR, USA

Aims: Differentiation between supraventricular tachycardia (SVT) and ventricular tachycardia (VT) remains a substantial clinical challenge in patients with single-chamber implantable cardioverter-defibrillators (ICDs) due to absence of visible P waves. Innovative optimization of intrathoracic electrogram (EGM) configuration will facilitate P-wave detection and rhythm differentiation during tachycardia.

Methods and results: Innovative optimization of EGM configuration was originally performed to improve patient care. In this retrospective cohort study, we examined our database for records of 140 consecutive patients undergoing single-chamber ICD implantation. During the follow-ups of 61 included patients with optimized EGM configuration, 27 patients were identified to have VT and/or SVT. EGMs in the Can (generator) to superior vena cava (Can–SVC) configuration were compared with those conventionally from the Can to right ventricular coil (Can–RV coil) source in the same patients. In Can–SVC EGMs, the ratio of P/QRS amplitude was 14-fold higher (0.57±0.08 vs. 0.04±0.00, P < 0.001) compared with those in Can–RV coil EGMs during sinus rhythm. With Can–SVC configuration, the odds of atrioventricular dissociation detection in patients with VT was increased 15-fold (61.9% vs. 9.5% with Can–RV coil; odds ratio, 15.4; 95% confidence interval, 2.8 to 84.7; P < 0.0009). In patients with SVT, P-waves or retrograde P-waves were markedly more identifiable in Can–SVC configuration compared with Can–RV coil (odds ratio, 40; 95% confidence interval, 3.6 to 447.1; P < 0.0010).

Conclusion: P-wave recognition by optimizing EGM configuration provides a novel diagnostic tool for differentiation between VT and SVT in single-chamber ICDs. A potential discrimination algorithm would provide a cost-effective approach to improving the qualitative outcomes.
A reconceptualized highly networked pacemaker with anti-tachycardia pacing (hnP-ATP) capabilities to address sudden arrhythmic death is inevitable. As a stand alone device, relying on pacing therapy alone as primary therapy, such a device would provide effective treatment for the majority of expected life threatening arrhythmias at a substantially diminished cost with expected lower patient toxicities.

The consequences of removing the “shock” from a traditional transvenous implantable cardioverter defibrillator (TV-ICD) can be addressed by appropriate patient selection, further optimizing ATP therapy, using predictive algorithms, and most importantly utilizing a networked crowd sourced rescue system to replace the shock feature. Geo-location communication enhancements to the existing infrastructure can be implemented leveraging the broader network of networks and the emerging “Internet-of-Things” (IoT). This new device (hnP-ATP) would allow a better tailored, more nuanced approach making more affordable device therapy available to more individuals at risk for sudden arrhythmic death and ultimately, save more lives.
RISK STRATIFICATION IN BRUGADA SYNDROME: ICD INDICATION IN PATIENTS WITHOUT HISTORY OF CARDIAC ARREST

M. Takagi
Osaka City Graduate School of Medicine, Osaka, Japan

Background: Risk assessment in patients without previous documented VF or aborted sudden death (SCD) is not yet fully established. Indication for implantable cardioverter defibrillator (ICD) in Brugada patients without documented VF or SCD is classified as Class II or III indication.

Purpose: To evaluate the validity of the Class II indication for ICD implantation in the HRS/EHRA/APHRS Expert Consensus Statement (Consensus) with a large Japanese cohort of BrS (The Japan Idiopathic Ventricular Fibrillation Study [J-IVFS]).

Methods: A total of 213 consecutive BrS patients with ICD implanted by the JCS class II indication (mean age 53 ± 15 years, 199 males) were enrolled. Clinical outcomes during the follow-up period were compared between patients with Class IIa (n = 66) and Class IIb (n = 147) indication by the Consensus.

Results: The incidence of cardiac events (sudden cardiac death [SCD] or VF) during a mean follow-up period of 64 months was significantly higher in patients with Class IIa (n = 8 of 66, 2.2%/yr) than those with Class IIb indication (n = 4 of 147, 0.5%/yr) (p = 0.01), as determined by the Kaplan-Meier method.

Conclusions: We confirmed the validity of the Class II indication for ICD implantation in the Expert Consensus Statement. In patients without previous cardiac arrest or VF, previous syncope and spontaneous type-1 ECG might be important factors to distinguish intermediate- from low-risk patients with BrS.
One of the most significant factors affecting the quality of life in patients with congenital long QT syndrome has been their restriction from athletic participation. In 2015, the American Heart Association and American College of Cardiology released new eligibility and disqualification recommendations for competitive athletes with cardiovascular abnormalities. Recommendations for patients with channelopathies, such as long QT syndrome, were specifically addressed and significantly liberalized the eligibility of these patients to participate. Advancement in the understanding of the disease and improvements in treatment have led to this changing paradigm. Supporting these guidelines are recent studies that have shown a low risk of cardiac events during athletics. Despite the new allowances for participation, important safety precautions are recommended. The new guideline paradigm is expected to improve the quality of life for pediatric patients with long QT syndrome.
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SERUM MAGNESIUM AND MORTALITY IN THE US GENERAL POPULATION: RESULTS FROM THE NHANES I EPIDEMIOLOGIC FOLLOW-UP STUDY

X. Zhang¹, J. Xia¹, L.C. Del Gobbo², A. Hruby³, K. He³, Q. Dai³, Q. Song¹

1. Richard M. Fairbanks School of Public Health, Indiana University, Indianapolis, USA
2. Stanford University
3. Harvard T.H. Chan School of Public Health
4. School of Public Health, Indiana University, Bloomington
5. Division of Epidemiology, Vanderbilt Ingram Cancer Center; and Department of Veterans Affairs, Tennessee Valley Healthcare System, Geriatric, Research, Education and Clinical Center

Background: Whether and to what extent low serum Mg levels are associated with all-cause or cause-specific mortality in the general population is uncertain. We aimed to quantify the dose-response associations between low concentrations of serum Mg and mortality from all causes, cancer, CVD, and stroke in the US general population.

Methods: We analyzed prospective data on 14,353 participants aged 25-74 years with baseline measures of serum Mg concentrations from the National Health and Nutrition Examination Survey Epidemiologic Follow-up Study 1971-2006. We estimated the mortality hazard ratios (HRs) for participants within predefined and clinically meaningful categories of serum Mg levels, including <0.7, 0.7-0.74, 0.75-0.79, 0.8-0.9 (normal reference), 0.9-0.94, 0.95-0.99, and 1.0 mmol/L, using Cox proportional hazards models. Restricted cubic spline models were applied to examine potentially nonlinear relationships between serum Mg and mortality.

Results: During a mean follow-up of 27.6 years, 7,072 deaths occurred, 3,310 (47%) CVD deaths, 1,533 (22%) cancer deaths, and 281 (4%) stroke deaths. Twenty-one percent of all participants had low levels of serum Mg (<0.8 mmol/L) and 1.5% had extremely low serum Mg (<0.7 mmol/L). Age-adjusted all-cause mortality rates were 3845, 3491, 3471, 3400 (normal reference), 3531, 3525, and 3836 per 100,000 person-years for increasing categories of serum Mg; the HRs and 95% confidence intervals for increasing serum Mg were 1.32 (1.02-1.72), 0.93 (0.74-1.16), and 1.06 (0.96-1.18), 1.07 (0.97-1.18), 0.94 (0.77-1.13), and 0.93 (0.72-1.21), compared to the reference group (0.8-0.9 mmol/L). An L-shaped association between serum Mg concentrations and all-cause mortality was observed after adjusting for potential confounders. No statistically significant associations were observed between serum Mg and cancer, CVD, or stroke mortality.

Conclusions: Very low serum Mg levels were significantly associated with all-cause mortality in the general US population. Our findings support the hypothesis that Mg deficiency as defined by very low serum Mg may have an important influence on mortality.
NEW DIRECTIONS IN CARDIOVASCULAR SURGERY: HEART VALVE SURGERY / CORONARY REVASCULARIZATION / MECHANICAL CIRCULATORY SUPPORT / CARDIAC TRANSPLANTATION

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VALVE PROSTHESIS-PATIENT MISMATCH (VP-PM): A LONG-TERM PERSPECTIVE

D. Daneshvar, S.H. Rahimtoola
University of Southern California, Los Angeles, CA, USA

VP-PM was first described in 1978 by Rahimtoola. From that time to 2011, aortic VP-PM has received a great deal of attention but studies have come to varying conclusions especially with regard to its effect on mortality. This is because prosthetic heart valve (PHV) area [effective orifice area index (EOAi)] has been predicted rather than measured. To better assess the outcomes of VP-PM, EOAi should be measured at hospital discharge which provides information of actual PHV after insertion into the patient. It should also be measured at 6-12 months of follow-up at which time the 4 phases of physiological healing and morphological changes are complete; EOAi at this time determines the long-term impact of VP-PM on patients’ outcomes. Mild, severe and critical VP-PM should be defined as EOAi of ≥ 0.9 cm²/m², EOAi of ≤ 0.6 cm²/m² and EOAi of ≤ 0.4 cm²/m². One needs to focus especially on severe/critical degrees of VP-PM and determine if death was actually due to VP-PM and/or was VP-PM an important determinant of cardiac related cause of death by multivariate analysis?
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TRANSCATHETER AORTIC VALVE IMPLANTATION SHORTENS THE QTc INTERVAL IN PATIENTS WITH SEVERE AORTIC VALVE STENOSIS
S. Abramson, L. Zhang, P. Kowey
1. Lankenau Medical Center, Wynnewood, PA, USA
2. University of Pennsylvania, Philadelphia, PA, USA
3. Lankenau Heart Institute and the Jefferson Medical College, Philadelphia, PA, USA,

Background: In patients with severe aortic stenosis, left ventricular hypertrophy develops as a compensatory mechanism for the increase in afterload. The QTc interval has been identified as predictor of mortality in patients with left ventricular hypertrophy. The aim of this study was to determine whether the prolonged QTc interval in this patient cohort normalizes following transcatheter aortic valve implantation (TAVI).

Methods: Electronic medical records were retrieved in pts undergoing TAVI in a single center from July 2013-August 2015. Pts with permanent pacemaker prior to TAVI and those with incomplete information were excluded from analysis. Heart rate, QRS duration (QRSD), QT/QTc interval and ejection fraction (EF) were measured pre-TAVI and 1-month (mo), 2-11 mo, and ≥1 year post-TAVI.

Results: Among 170 pts (age 82±7 yrs, 54% M), TAVI performed via femoral and apical approach were 60% and 40%, respectively. EF increased 1-mo post TAVI (0.55±0.15 vs. 0.60±0.13, p < 0.001). QTc shortening occurred (469±57 ms vs. 444±34 ms, p < 0.01) at 1-year follow-up (Figure 1) despite QRS widening (102±22 ms pre- vs. 112±29 ms post, p < 0.01). Heart rate was unchanged throughout. All-cause mortality from TAVI was 0.6%.

Conclusions: The shortening of QTc interval in patients with severe aortic stenosis indicates TAVI improves both cardiac function and repolarization. Those effects may be causally related and responsible for the improved clinical outcome.
Changing Pathology of the Aorta: From Acute to Chronic Dissection

S. Peterss\textsuperscript{1,2}, A.M. Mansour\textsuperscript{1}, J.A. Ross\textsuperscript{3}, I. Vaitkeviciute\textsuperscript{4}, P. Charilaou\textsuperscript{1}, J. Dumfarth\textsuperscript{1}, M. Tranquilli\textsuperscript{1}, H. Fang\textsuperscript{5}, B.A. Ziganshin\textsuperscript{1,6}, J.A. Rizzo\textsuperscript{1,7}, A.J. Adeniran\textsuperscript{3}, J.A. Elefteriades\textsuperscript{1}

\textsuperscript{1} Aortic Institute at Yale-New Haven Hospital, Yale University School of Medicine, New Haven, CT, USA
\textsuperscript{2} Department of Cardiac Surgery, University Hospital Munich, Ludwig-Maximilians-University, Munich, Germany
\textsuperscript{3} Department of Pathology, Yale University School of Medicine, New Haven, CT, USA
\textsuperscript{4} Department of Anesthesiology, Yale University School of Medicine, New Haven, CT, USA
\textsuperscript{5} China Center for Health Development Studies, Peking University, Beijing, China
\textsuperscript{6} Department of Surgical Disease #2, Kazan State Medical University, Kazan, Russia
\textsuperscript{7} Departments of Economics and Preventive Medicine, Stony Brook University, Stony Brook, NY, USA

Background: The natural history of the progression of aortic dissections from acute to chronic is not well understood.

Objectives: The aim of the study was to evaluate the radiographic, echocardiographic and histopathologic changes from an acute to a chronic dissection, depending on time after onset of symptoms. We concentrate on typical “flap” dissection rather than variant dissections.

Methods: One hundred fifty-eight patients with diagnosed aortic dissection were analyzed by computed tomographic (CT) imaging, transesophageal echocardiography (TEE) and/or microscopic histopathology. Among these, 74 were Stanford Type A (mean age 65±13 years, 64\% male) and 84 Type B dissections (mean age 58±13 years, 64\% male).

Results: Among Type B dissections, a growth rate of 6.78 mm/year was found with a significantly higher rate within the acute and subacute stages. Thereafter, the rate of growth stabilized in the chronic phase at 1.88 mm/year. Flap thickness increased at 0.61 mm/year, showing a similar early dynamic as for diameter. Flap mobility decreased over time. No longitudinal extension or new branch involvement were noted after the initial event. Among Type A dissections, the flap showed comparable behavior. Due to the limited follow-up because of widespread early surgery in these patients, a natural growth rate could not be determined. Furthermore, no significant histologic changes were seen among Type A dissections over time, possibly related to these patients going to early surgery. However, Type B dissections showed increased fibrosis, as well as elastin fragmentation, over time as the lesion progressed from acute to chronic.

Conclusions: In the acute to chronic post-dissection transition, stabilizing after 2 months, (1) the aorta grows more rapidly early after dissection than later; (2) the flap thickens and becomes less mobile; (3) the aortic dissection did not commonly extend longitudinally or involve a new branch vessel; (4) histologically, increased wall fibrosis is noted, along with increased elastin fragmentation over time.
OUTCOMES IN NONAGENARIANS UNDERGOING TRANSAORTIC VALVE REPLACEMENT IN A SINGLE CARDIOVASCULAR CENTER

J.E. Pino, O.I. Kreidieh, M. Miller, J. Choi, L.S. Lovitz, M.E. Nores, R. Chait
University of Miami, Palm Beach Regional Campus, Atlantis, FL, USA

Background: Transcatheter aortic valve replacement (TAVR) is the standard treatment for patients with severe aortic stenosis (AS) who are inoperable. However, the evidence about its safety, efficacy and outcomes in nonagenarians is very limited.

Objective: To determine outcomes in nonagenarians with severe AS following TAVR.

Methods: A retrospective chart review of 361 patients who underwent TAVR between 04/2012 and 01/2016 in a single cardiovascular center was performed. Evaluated outcomes were: in-hospital, 30-day and 1-year mortality, post-procedure complications, hospital length of stay (LOS), and discharge placement.

Results: Forty-Four percent (160/361) of the patients were female and 28.3% (102/361) were nonagenarians and comprise the study group.

Fifty-three percent of nonagenarians were male with a mean age of 92 ±2 years. Their mean Society of Thoracic Surgeons’ Mortality risk score was 8.9± 5.3 and their mean ejection fraction was 55%. Ninety percent had New York Heart Association class III symptoms and 15% had a prior balloon aortic valvuloplasty.

Chronic kidney disease, atrial fibrillation and permanent pacemaker (PPM) were present in 13%, 47% and 25% of the nonagenarians respectively. Mean creatinine was 1.1 mg/dl and mean albumin was 3.4 mg/dl.

Femoral approach was performed in 73/102 patients. First, second and third generation Edwards Valves were placed on 35%, 26% and 23% of patients respectively.

In-hospital mortality was 3% (3/102). Thirty-day mortality was 6% (6/102) vs 7.3% (19/259--patients <90) with a p>0.05. One-year follow up was available in 49/102 nonagenarians with a mortality of 16% (8/49). PPM insertion was required in 33% (26/77). Mean LOS was 7.6 days and 47% (48/102) of nonagenarians were discharged to rehabilitation facilities due to deconditioning.

Conclusion: This single center retrospective observational study demonstrates that TAVR can be safely performed with excellent survival and minimal morbidity in a group of extremely elderly patients that are inoperable.
CONTEMPORARY UTILIZATION AND GENDER-RACIAL DISPARITIES IN CORONARY ARTERY BYPASS SURGERY IN THE UNITED STATES: ANALYSIS OF 2 MILLION PATIENTS
S.V. Patel¹, A. Rajabalan¹, P. Patel¹, A. Saggu¹, M. Patel², T. Singh¹
¹Western Reserve Health Education/NEOMED, Youngstown, OH, USA
²Christus Schumpert Highland Hospital, Shreveport, LA, USA

Objective: The aim of study to identify contemporary utilization and gender-racial disparities of coronary artery bypass graft surgery (CABG).

Background: Since the advent of CABG, that has been a tremendous progress in lowering the in-hospital mortality of CABG. However, limited data exist regarding current utilization, trends of outcomes and influence of race and gender on CABG mortality.

Methods: We have used 10 years (2003-2012) of largest all-payer inpatient data from the Nationwide Inpatient Sample with over 2 million CABG admissions. Isolated CABGs were identified using ICD-9 codes. The study cohort of 2,005,386 CABGs was analyzed using descriptive and logistic regression analysis to evaluate the utilization, In-hospital mortality trends and extent of disparities and predictors of In-hospital mortality of CABG.

Results: Over a decade (2003-2012), there has been significant steady decline of 45.8% in CABG utilizations (13.68% vs 7.42%, p<0.0001) and 34.4% in In-hospital mortality (2.12% vs 1.39%, p<0.0001). However, there has been inclination of 3% in mean length of stay (8.8 vs 9.1 days, p<0.0001) and 10.4% in mean cost of hospitalization ($35,723 vs $39,428, p<0.0001). In multivariate models, after controlling for relevant patient and hospital factors including Charlson’s score, we found that female CABG patients, irrespective of their racial/ethnic group, experienced higher In-hospital mortality rate compared to the male counterparts. Specifically, black CABG patients experienced significantly higher in-hospital mortality rates (Male 21.3%, Female 46.5% p<0.0001) compared to white male patients.

Conclusions: With the advancements in CABG procedures and the availability of quality medical care, there has been decline in In-hospital mortality and utilization of CABG. All females of different ethnic groups have significant increased risk of In-hospital mortality than males, especially black females.
ISCHEMIC PATIENTS UNDERGOING CARDIAC SURGERY HAVE SIGNIFICANT MITOCHONDRIAL COMPLEX I DYSFUNCTION

D. Schipper, C. O’Hare, R. Palsma, D. Dicken, T. Kazui, Z. Khalpey
University of Arizona College of Medicine, Department of Surgery, Tucson, AZ, USA

Background: Cardiac cells rely heavily on mitochondrial energy production through oxidative phosphorylation. Chronic ischemia may affect mitochondria and myocardial ATP formation altering cardiac function and the bioenergetic state. We present a rapid, reliable and real-time method to evaluate the differences in functional status of respiratory Complexes in mitochondrial isolates extracted from human left atrial appendages (LAA) from patients undergoing cardiac surgery.

Methods: Mitochondrial isolates were extracted from LAA in ischemic CABG patients (Group 1) (n=10) and non-ischemic control patients (Group 2) undergoing other cardiac surgery (valve repair/replacement/heart donated for transplant)(n=7). Coupling and electron transport chain assays were performed using Seahorse XFe analyzer. Oxygen consumption rates (OCR) were measured to calculate respiration states.

Results: Respiratory control rate (RCR) in Group 1 vs Group 2 was significantly decreased (5.81 ± 0.35 vs 7.51 ± 0.47, respectively)(p<0.01). Absolute respiration significantly declined in Group 1 vs Group 2 (187.8 ± 22.0 pmol O$_2$/minute/µg mitochondrial protein vs 264.2 ± 12.59, respectively)(p<0.05), but there was an insignificant difference for proton leak. Group 1 vs 2 maximal complex I/II respiration ratios were significantly different (58.9 ± 5.47 vs 90.91 ± 8.76 percent, respectively)(p<0.05). There was no significant difference in complex II/IV ratios between groups.

Conclusion: Ischemic patients have dysfunctional mitochondria at baseline highlighted by a lowered OCR. This is due to insufficient conversion of ADP into ATP due to Complex I dysfunction or loss. Maintaining or protecting Complex I activity may be a potential therapeutic strategy during cardiac surgery.
THE USE OF EXTRACORPOREAL MEMBRANE OXYGENATION FOR CARDIAC INDICATIONS: A TERTIARY CENTER EXPERIENCE

M. Rivera\textsuperscript{1}, R. Mendirichaga\textsuperscript{1}, S. Chaparro\textsuperscript{2}, M. Murman\textsuperscript{1}, V. Singh\textsuperscript{2}, R.N. Cardoso\textsuperscript{1}, G. Fernandes\textsuperscript{1}, M. Pardinas\textsuperscript{3}, S. Dickens\textsuperscript{4}, S. Krick\textsuperscript{4}

1. University of Miami Leonard M. Miller School of Medicine, Cardiovascular Division, Department of Medicine, Miami, USA
2. University of Miami Leonard M. Miller School of Medicine, Cardiovascular Division, Miami, USA
3. University of Miami Leonard M. Miller School of Medicine, Pulmonary Medicine Division, Department of Medicine, Miami, USA
4. University of Miami Leonard M. Miller School of Medicine, Pulmonary Medicine, Miami, USA

Background: Venoarterial extracorporeal membrane oxygenation is an alternative for the management of the severe decline of cardiorespiratory functions. VA-ECMO can be used adjunctively with other supportive and pharmacological measures once these have been exhausted. This review focuses on our experience with short-term mortality for patients requiring VA-ECMO for cardiac indications.

Methods: We performed a retrospective cohort analysis of patients requiring VA-ECMO at a tertiary academic medical center. Patients placed on extracorporeal cardiopulmonary support from January 2008 to June 2015 for cardiac indication were identified and included in our analysis.

Results: We identified 46 subjects with cardiac indications for VA-ECMO. Mean population age was 55.23 ± 14.44; men composed 71.7% of our population; the majority were non-Caucasians (Hispanics: 41.3% and African-Americans: 39.3%). Mean duration of ECMO was 5.1±5 days. The association of ECMO duration with 30-day mortality was not significant (p=0.48). Patient distributions by cardiac indication for VA-ECMO were: post-cardiotomy failure to wean from cardiopulmonary bypass (34.78%), post-cardiac arrest (32.6%), refractory cardiogenic shock (19.57%), bridge-to-bridge (6.52%), and massive pulmonary embolism (6.52%). Overall 30-day mortality was 71.74%. Cause of death varied by indication: cardiogenic shock, cardiac arrest and septic shock were the most frequent. VA-ECMO rescue for prolonged cardiac arrest had the worse outcomes: 30-day mortality of 93%.

Conclusion: Consensus recommendations on adequate VA-ECMO use were published by the extracorporeal life support organization in 2014. Approximately, 25% of our population was enrolled after 2014. Obstacles such as delay to ECMO initiation could account for the dire prognosis encountered in our study.
Background: Pericardial effusions are present in up to 20% of patients after heart transplantation (HT), but they usually resolve within 3 months post-transplant. Recurrence has been reported and can be due to multiple etiologies including cellular rejection, pericarditis and perforation during endomyocardial biopsy. The management of recurrent pericardial effusion is challenging due to the limited therapeutic options.

Case: A 51-year-old woman with a history of dilated cardiomyopathy due to doxorubicin treatment for breast adenocarcinoma underwent HT. She was noted to have a moderate pericardial effusion by echocardiogram (echo) 24 days post-HT. She then presented with shortness of breath and elevated jugular venous pressure and lower extremity edema. Echo showed a large pericardial effusion consistent with tamponade. She was taken for emergent pericardiocentesis. She had continued pericardial fluid accumulation so was taken for a subxiphoid window 5 days later. Pericardial fluid analysis showed transudative fluid without evidence of infection or abnormal cells. She was given corticosteroids and colchicine. Despite these interventions a follow-up echo showed a large pericardial effusion with tamponade so she underwent pericardiocentesis and a limited thoracotomy with pericardial window on post-HT day 96. The next follow-up echo on post-HT day 106 showed a large pericardial effusion with tamponade. Given the refractoriness to conventional medical and interventional procedures, the interventional cardiology team along with the cardiac surgery team decided to place a PleurX catheter in the pericardial space. Pericardial fluid was drained via the PleurX on a daily basis until the output dropped to zero. A repeat echo showed no pericardial effusion so the PleurX was removed 37 days after insertion. Follow-up echos have showed no further reaccumulation.

Conclusion: This case demonstrates the successful use of a pericardially placed PleurX catheter for prolonged drainage in a patient with a recurrent transudative pericardial effusion after heart transplant.
TRENDS IN TRANSCATHETER AORTIC VALVE REPLACEMENT (TAVR) CHARACTERISTICS AND OUTCOMES: A SINGLE CENTER EXPERIENCE

University of Minnesota Medical Center, MN, USA

Objectives: Compare temporal trends in patients undergoing TAVR at our institution.

Background: TAVR is the preferred treatment option for high-risk and inoperable patients with severe aortic stenosis.

Methods: We retrospectively analyzed data from patients undergoing TAVR between 6/2012 and 11/2015. Patients were divided into 2 groups.

Results: The mean age was 81.7 ± 9.0 (A) years versus 80.0 ± 9.5 (B) (p=0.21). STS scores trended down with a mean of 8.7 ± 4.5 (A) and 7.3 ± 4.4 (B) (p=0.03). Transfemoral (TF) access increased from 52.1% (n=73) to 77.6% (n=59) (p<0.001). Self-expandable valve use increased from 12.9% (A) to 42.1% (B) (<0.001). Moderate to severe paravalvular regurgitation was low in both groups (0.7% and 0.0%, p=NS). Stroke (5.0 vs. 1.3%) and vascular complications (7.9 vs 3.9%) were lower in B relative to A.

Conclusions: We observed an increase in TF access and self-expandable valves in 2015.

Table. Clinical Characteristics and Outcomes

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Overall (n=216)</th>
<th>2012 – 2014 (n=140)</th>
<th>2015 (n=76)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>81 ± 9.2</td>
<td>81.7 ± 9.0</td>
<td>80.0 ± 9.5</td>
<td>0.21</td>
</tr>
<tr>
<td>Male gender</td>
<td>50.5% (109)</td>
<td>50.7% (71)</td>
<td>50.0% (38)</td>
<td>0.92</td>
</tr>
<tr>
<td>STS Score</td>
<td>8.2 ± 4.5</td>
<td>8.7 ± 4.5</td>
<td>7.3 ± 4.4</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Procedural Characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transfemoral Access</td>
<td>61% (132)</td>
<td>52.1% (73)</td>
<td>77.6% (59)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Transapical / Alternate Access</td>
<td>39% (84)</td>
<td>47.9% (67)</td>
<td>22.4% (17)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Balloon-Expandable Valve</td>
<td>77% (166)</td>
<td>87.1% (122)</td>
<td>57.9% (44)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Self-Expandable Valve</td>
<td>23% (50)</td>
<td>12.9% (18)</td>
<td>42.1% (32)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Valve Size (mm)</td>
<td>25.9 ± 2.5</td>
<td>25.5 ± 2.2</td>
<td>26.8 ± 2.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>3.7% (8)</td>
<td>5.0% (7)</td>
<td>1.3% (1)</td>
<td>0.27</td>
</tr>
<tr>
<td>Vascular Complications</td>
<td>6.5% (14)</td>
<td>7.9% (11)</td>
<td>3.9% (3)</td>
<td>0.39</td>
</tr>
<tr>
<td>Paravalvular Leak (≥ moderate)</td>
<td>0.5% (1)</td>
<td>0.7% (1)</td>
<td>0.0% (0)</td>
<td>1.00</td>
</tr>
<tr>
<td>Pacemaker Placement</td>
<td>9.7% (21)</td>
<td>8.6% (12)</td>
<td>11.8% (9)</td>
<td>0.44</td>
</tr>
<tr>
<td>Length of Stay (days)</td>
<td>7.4 ± 8.5</td>
<td>7.8 ± 7.4</td>
<td>6.8 ± 10.3</td>
<td>0.43</td>
</tr>
<tr>
<td>Mortality at 30 Days</td>
<td>6.9% (15)</td>
<td>7.9% (11)</td>
<td>5.3% (4)</td>
<td>0.58</td>
</tr>
</tbody>
</table>
MARKERS OF IMPROVEMENT AFTER ECMO IMPLANTATION

A. Rifai, T. Yousuf, A. Tatooles, W. Cotts, G. Bhat
Advocate Christ Medical Center, Chicago, IL, USA

Objective: The aim of this study was to compare lactic acid and BNP levels before and after Extracorporeal Membrane Oxygenation (ECMO) placement and to evaluate these markers for predicting mortality.

Methods and Results: We retrospectively collected data on 95 patients admitted between 2005 and 2015 requiring ECMO due to profound cardiogenic shock. The indications for ECMO were as follows: post myocardial infarction (n=41), postcardiotomy (n=18), severe congestive heart failure (n=15), post left ventricular assist device (LVAD) or heart transplant (n=8), post cardiac arrest (n=6), arrhythmia (n=4), and myocarditis (n=1). The 30 day mortality rate was 47.3%. Blood lactate level and BNP were significantly elevated before ECMO placement as these patients were in a state of poor systemic perfusion. These two values decreased significantly after 48 hours of being maintained on ECMO. Lactic acid decreased from 4.2±3.6 to 1.9±1.3 (p < 0.001). BNP decreased from 1261.7±1348.1 to 950.3±1142.2 (p = 0.019). Despite this decrease the predictive value of these two markers was not significant for 30 day mortality.

Conclusion: Blood lactate measurement and BNP can be used as tools for monitoring adequate tissue perfusion during extracorporeal life support as both values decline 48 hours after ECMO implantation. However, the improvement in these two markers did not have a significant effect on short-term mortality in this study.
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CORRELATION OF DEMOGRAPHIC PROFILE AND CLINICAL RISK FACTORS WITH SYNTAX SCORE TO PREDICT SEVERITY OF CAD IN PATIENTS UNDERGOING CABG
S.P Shashidharan, S. Banga, S. Mungee, E. Mukhopadhyay
OSF St. Francis Medical Center, University of Illinois College of Medicine at Peoria, IL, USA

Background: SYNTAX Score is a validated scoring system to quantify the complexity of CAD (coronary artery disease) based on Coronary angiogram findings. There is paucity of data as to what are the demographic and clinical factors associated with high SYNTAX score.

Methods: Retrospective study of patients with no history of prior revascularization who underwent CABG for left main and/or 3-vessel disease from October 2012 to January 2014. SYNTAX score was calculated using the online tool available at http://syntaxscore.com/. Patients were divided into two groups - group A with SYNTAX score ≤ 32 and group B having score ≥33. Demographic data including age, sex, diabetes mellitus, smoking status, hypertension and differential lipid profile were collected. Statistical analysis was done using chi-square test for nominal variables and t-test for continuous variables.

Results: Of all 67 patients, there were 42 patients in Group A versus 25 patients in Group B with males being 92% vs 83%, average age 63± 10.8 years vs 67.9 ± 9.9 years. Other parameters are defined in Table 1.

Conclusions: Diabetes mellitus and smoking had positive correlation with SYNTAX score of ≥33 and complex coronary artery disease. Family h/o CAD was statistically significant in patients with SYNTAX score ≤ 32.

Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group A,N=25</th>
<th>Group B,N=42</th>
<th>p_Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension, N (N%)</td>
<td>23(92)</td>
<td>37(88.1)</td>
<td>0.613</td>
</tr>
<tr>
<td>Diabetes, N (N%)</td>
<td>4(16)</td>
<td>14(33.3)</td>
<td>0.0006</td>
</tr>
<tr>
<td>History of Smoking, N (N%)</td>
<td>5(20)</td>
<td>9(21.4)</td>
<td>0.002</td>
</tr>
<tr>
<td>Family H/o CAD, N (N%)</td>
<td>8(32)</td>
<td>4(9.5)</td>
<td>0.0203</td>
</tr>
<tr>
<td>Dyslipidemia, N ( N%)</td>
<td>23(92)</td>
<td>42(100)</td>
<td>0.062</td>
</tr>
<tr>
<td>Total cholesterol (Mean± SD) mg/dL</td>
<td>181.8±44.9</td>
<td>178.2±65.1</td>
<td>0.7905</td>
</tr>
<tr>
<td>Triglycerides (Mean± SD) mg/dL</td>
<td>148.8±80.7</td>
<td>157.4±110.5</td>
<td>0.7186</td>
</tr>
<tr>
<td>LDL(Mean± SD) mg/dL</td>
<td>110±40.2</td>
<td>101.8±59.6</td>
<td>0.2576</td>
</tr>
<tr>
<td>HDL(Mean± SD) mg/dL</td>
<td>42.4±9.2</td>
<td>43.7±16.4</td>
<td>0.6911</td>
</tr>
</tbody>
</table>
Objective: Determine the long term safety and possible feasibility of low-level laser therapy (LLLT) application to the bone marrow (BM) on patients post acute myocardial infarction (AMI).

Background: The promising field of cell-based therapy offers a complementary mode of treatment to patients post acute myocardial infarction (AMI). LLLT have been found to have a photobiostimulatory effect on various biological processes.

Methods: Patient suffers acute ST segment elevation MI and candidate to primary percutaneous coronary intervention (PPCI) were included. In the active group, LLLT was applied to the tibia bone for 100 sec non-invasively prior to PPCI, 24 and 72 hrs post-PPCI. The control group had the same protocol, but the LLLT source was powered-off. Blood samples were taken on admission and during first week post MI. Echocardiography performed 1, 20 and 270 days after PPCI post MI.

Results: Twenty four patients were enrolled. Levels of CPK accumulation (area under curve up to 5 days post AMI) were 202±75 (arbitrary units) for the laser group with significant statistical trend (P<0.09) to be lower than the value (302±53) in the placebo group indicating possible cardioprotection of the ischemic heart by laser treatment to the BM. Leukocytes count were 11200±3200 on admission and 9600±4300 at 72 hours post AMI in the active group and 12300±4300 on admission and 9400±4700 at 72 hours for the placebo group. Platelets count also showed no change during the first week post-MI. The door-to-balloon time was 59±12 min in the laser group compared with 61±9 in the control group. No adverse effects were observed in the laser treated patients.

Conclusion: Applying LLLT to the BM in order to photobiostimulate stem cells for the benefit of the infarcted heart is a safe procedure for application in humans, and offers a novel approach in cell therapy adjunctive to the PPCI.
CURRENT CONCEPTS AND FUTURE DIRECTIONS IN ISCHEMIC HEART DISEASE

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NEW IDEAS ON HYPERTENSION TREATMENT
C. Rosendorff
Icahn School of Medicine at Mount Sinai, New York, NY, USA

A new study on blood pressure targets in patients with hypertension should lead to a fundamental reassessment of the way in which we treat this condition. SPRINT evaluated a target SBP of <140 vs. <120 mm Hg and reported better outcomes in the intensive treatment arm; this was true whatever the starting BP, including values well within range usually regarded as "normal" (SBP<140 mm Hg). The question therefore arises: should we abandon the BP criteria for starting anti-hypertensive therapy, and institute therapy based solely on cardiovascular risk?
SAFETY OF THE ASSOCIATION OF RANOLAZINE AND IVABRADINE FOR ANTIANGINAL TREATMENT IN STABLE CORONARY ARTERY DISEASE

A. Lupi¹, A. Schaffer², F. Mirabelli³, A. Rognoni¹, A.S. Bongo¹
1. AOU Maggiore della Carita', 2nd Cardiology Division, Italy
2. Eastern Piedmont University, 1st Cardiology Division, Italy
3. ASL Biella, Outpatient Cardiology Service, Italy

Background: Ranolazine (RNZ) and ivabradine (IVA) are new antianginal drugs. The former selectively inhibits late sodium influx, and the latter selectively modulates heart rate blocking the sinoatrial If current. Theoretically RNZ and IVA could be added together to treat refractory angina in patients not suitable for complete revascularization, but, the experience is limited so far.

Methods: From 2011 to 2013, 285 consecutive patients with Canadian Class >2 angina or silent ischemia and coronary anatomy not suitable for complete revascularization were treated as outpatients in our Institution. Patients were grouped according the antianginal therapy (IVA Group, 75 pts; RNZ Group, 166 pts; RNZ/IVA Group, 44 pts). Clinical characteristics with QTc measurements were prospectively assessed with a median FUP of 22 months.

Results: CV risk factors were similar among groups, but pts treated with RNZ/IVA had a higher prevalence of refractory angina (IVA 28.0%, RNZ 21.0% and RNZ/IVA 54.6%, p<0.05 vs IVA and RNZ) and chronic total coronary occlusions (IVA 12.2%, RNZ 12.1%, IVA/RNZ 18.1%, p<0.05 vs IVA and RNZ). QTc increased mildly but significantly only in patients treated with RNZ (baseline 433.2 ± 38.2 vs FUP 441.8 ± 37.2 msec, p<0.05). RNZ/IVA association was not associated with significant increase of QTc (Baseline 428.7 ± 31.2 vs FUP 438.1 ± 35.5 msec, p NS) and mortality (IVA 8.0%, RNZ 7.2%, RNZ/IVA 9.1%, p=0.66), atrial fibrillation (IVA 1.3%, RNZ 0.6%, RNZ/IVA 2.2%, p=0.87) or other adverse event rates.

Conclusion: In a real world population of stable coronary artery disease, RNZ/IVA association did not increase either QTc nor mortality and other adverse event rates.
BACKGROUND: Left ventricular ejection fraction (LVEF) is an established prognostic factor for coronary artery disease.

OBJECTIVES: We applied LVEF as parameter to patients presenting with STEMI to potentially identify patients that could be discharged early.

METHODS: A total of 249 consecutive patients who underwent primary PCI for STEMI were studied retrospectively. Risk stratification of the patients was based on LVEF on LV angiography post procedure. Two groups were analyzed based on LV function as LVEF < 50% (Group A) and LVEF ≥50% (Group B) for complications, length of stay (LOS) in coronary care unit (CCU) and overall hospital LOS. Statistical analysis was performed.

RESULTS: There were 123 patients with mean age of 62.4 ± 13.9 years and 88 (71.5%) male in Group A versus 126 patients with 61.3 ± 12 years and 97(77%) male in Group B . The incidence of complications including VT/VF as seen in 11(8.9%) versus 7(5.6%); hematoma in 3(2.4%) versus 3(2.4%); use of temporary pacemaker in 3(2.4%) versus 5(4%); in Group A versus Group B respectively was statistically insignificant. Heart failure was significantly higher in Group A with 13(10.6%) patients versus 0(0%) in Group B (p-value<0.001). Similarly, Impella and IABP were significantly used in Group A with 8(6.5%) and none in Group B (p-value=0.003). There was a significant difference in the hospital LOS with 3.1 ± 2.3 days in Group A versus 2.1 ± 0.8 in Group B (p_value<0.0001). Hours of stay in the CCU was also significantly more in Group A patients with 36.54 ± 31.36 hours versus 23.97 ± 11.75 hours for Group B (p_value<0.0001).

CONCLUSIONS: We concluded that the complication rate, CCU hours and hospital length of stay were significantly lower in STEMI patients with LVEF≥ 50% on LV angiography post PCI. Early discharge can be considered as a feasible option in these patients.
CURRENT CONCEPTS AND FUTURE DIRECTIONS IN ISCHEMIC HEART DISEASE

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BETA 2 GLYCOPROTEIN I PEPTIDE PROTECTS FROM CARDIAC ISCHEMIA REPERFUSION INJURY IN MICE

G. Chen1,2, J.C. Weaver1,2,4, P. Zhang1,2,3, J. Beretov5, A. Tatsuya6, M. Qi1,2, R. Bhindi7, J.C. Qi1,2, M.C. Madigan8,9, B. Giannakopoulos1,2,10, S.A. Krilis1,2

1. Department of Infectious Diseases, Immunology and Sexual Health, St George Hospital, Sydney, Australia.
2. Department of Medicine, University of New South Wales, Sydney, Australia.
3. Department of Cardiothoracic Surgery, Tianjin Medical University General Hospital, Tianjin, China.
4. Department of Cardiology, St George Hospital, Sydney, Australia.
5. Anatomical Pathology, SEALS St George Hospital, Sydney, Australia.
6. Division of Rheumatology, Endocrinology and Nephrology, Hokkaido University Graduate School of Medicine, Sapporo, Japan.
7. Department of Cardiology, Royal North Shore Hospital, Sydney, Australia.
8. Save Sight Institute, University of Sydney and Sydney Eye Hospital, Sydney, Australia.
9. School of Optometry and Vision Science, University of New South Wales, Sydney, Australia.
10. Department of Rheumatology, St George Hospital, Sydney, Australia.

Objective: The aim of this study was to investigate the role of Beta 2 Glycoprotein I Peptide (B2GPI) and its Domain V in cardiac ischemia and reperfusion injury (IRI) using wild-type and B2GPI deficient mice.

Background: Reperfusion after a period of ischemia results in reperfusion injury (IRI), which involves activation of the inflammatory cascade. In cardiac IRI, natural antibodies (NAb) play a prominent role through binding to altered neoepitopes. Beta 2 Glycoprotein I (β2GPI) is an abundant circulating plasma protein that binds to neoepitopes on damaged cells, including anionic phospholipids through its highly conserved Domain V. Domain I of β2GPI binds circulating NAbs and may provide a link between the innate immune system, natural antibody binding and cardiac IRI.

Methods and results: An in vivo mouse coronary artery IRI model was inducted. Compared with control, treatment with Domain V prior to IRI prevented binding of endogenous β2GPI and resulted in smaller myocardial infarction size in both WT and β2GPI deficient mice. Domain V treatment in WT mice also resulted in less neutrophil infiltration, less apoptosis and improved ejection fraction at 24 h. Beta 2 deficient mice had the same infarct size as WT mice. As a result, further investigations were performed in Rag-1−/− mice. Rag-1−/− antibody deficient mice reconstituted with IgM NAbs confirmed that Domain V prevented IgM NAb induced cardiac IRI. Domain V remained equally effective when delivered at the time of reperfusion, which has therapeutic clinical relevance.

Conclusions: Based upon this study, Domain V may function as a universal inhibitor of NAb binding in the setting of cardiac IRI, which offers promise as a new therapeutic strategy in the treatment of cardiac IRI.
ASSOCIATION BETWEEN CANCER AND CORONARY HEART DISEASE - NHANES 2011-2012

P. Agasthi, D. Adedinsewo, A. Chaudhry, K. Sivakumar, A. Onwuanyi
Morehouse School of Medicine, Atlanta, GA, USA

Introduction: Recent studies suggested that the increased platelet activation, endothelial dysfunction and venous thromboembolism seen in cancer may as well contribute to the development of atherosclerosis. We conducted a study to evaluate the association between cancer and CHD in the US population.

Methods: We obtained data from the National Health and Nutrition Examination Survey (NHANES) for the most recent cycle available from CDC and examined all adults aged 20 years and older who provided cancer related information on the survey. We performed standard parametric tests of association and created a multivariable logistic regression model to evaluate the association between self reported cancer diagnosis and clinical CHD (coronary artery disease, myocardial infarction and angina). All analyses were conducted using SAS survey procedures for complex sample data and evaluated at a=0.05.

Results: Approximately 9% of the study population had been diagnosed with cancer. In unadjusted models, cancer appeared to be associated with an increased likelihood of CHD (2.19 95% CI: 1.38 - 3.48); however this association was lost after controlling for confounding factors (0.72 95% CI: 0.43 - 1.19). Limitations include small sample size of adults with cancer in our study sample and the inability to stratify by cancer type.

Conclusion: Our results did not show a significant association between cancer and CHD after adjusting for confounding factors. Limitations include the observational nature of our study and inability to assess the temporal relationship between cancer and CHD. Additional prospective studies of patients with cancer are needed to further evaluate this association.
CURRENT CONCEPTS AND FUTURE DIRECTIONS IN ISCHEMIC HEART DISEASE

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PREVALENCE OF ABDOMINAL AORTIC ANEURYSM IN VETERANS WITH MULTIVESSEL CORONARY ARTERY DISEASE
M. Dameron¹, R. Chana¹,²,³, A. Parashar¹,²,³
1. Veterans Affairs Medical Center Salem VA, USA
2. Virginia Tech Carilion SOM, Roanoke VA, USA
3. Edward Via College of Osteopathic Medicine, Blacksburg, VA, USA

Background: Coronary artery disease (CAD) and abdominal aortic aneurysms (AAA) share common risk factors. Current guidelines recommend one-time screening for AAA in males aged 65 to 75 years who have ever smoked. Emerging data indicates a greater AAA prevalence in CAD patients, even in those younger than 65 years of age.

Objectives: We conducted a retrospective study to examine the prevalence of AAA found on recent abdominal imaging in veterans with a history of 2-3 vessel CAD. To our knowledge, such a study has not been conducted in the veteran population.

Methods: The medical records of male veterans aged who had undergone revascularization for multivessel CAD were examined from a 2-year period. A total of 132 subjects had imaging data available out of 222. The data were analyzed to determine prevalence of AAA in two age groups < 65 years and > 65 years old. Univariate analysis was performed to determine the significance of various risk factors for AAA.

Results: In the 44 subjects aged <65 years, the prevalence of AAA was 13.6%, while it was 11.4% in the 88 patients aged > 65 years; univariate analysis did not find difference in prevalence of AAA between these two age groups of multivessel CAD subjects (p = 0.71). Additionally, no association was found between the degree of CAD (2 versus 3 vessel) and the presence of AAA (p = 0.67).

Conclusion: The prevalence of AAA in patients with CAD in this study was high, regardless of age or number of vessels involved. These results suggest importance of screening for AAA in a high-risk population with a history of CAD regardless of age.
CURRENT CONCEPTS AND FUTURE DIRECTIONS IN ISCHEMIC HEART DISEASE

102 RE-EVALUATING THE ROLE OF HEART SCORE IN CHEST PAIN ADMISSIONS

H.A. Lodhi¹, H. Shafiq², S. Jampana¹, M. Waqas¹, F. Hassan³, A. Shafiq⁴,⁵
¹Baptist Desoto Hospital, Southaven, MS; USA
²Aureus University, Aruba
³Fatima Jinnah Medical College, Lahore, Pakistan
⁴Saint Luke’s Mid America Heart Institute, Kansas City, MO; USA
⁵University of Missouri – Kansas City, MO, USA

Background: Optimum utilization of inpatient cardiac stress test is essential in patients who present to ER with chest pain. The HEART Score is a simple tool that can be used to identify patients with low risk chest pain, who may safely forego inpatient cardiac stress testing. Patients with low HEART Scores have been shown to have a low incidence of major adverse cardiac events (MACE) after hospital discharge, however, whether these HEART Scores correlate strongly to findings of cardiac stress testing, is not clear.

Methods: We screened patients admitted to our hospital from October 2015 to December 2015 with a diagnosis of chest pain (ICD-9 codes; 786.50, 786.51, 786.59) who had undergone cardiac stress testing. HEART Scores were calculated for these patients, to categorize them into low (HEART Scores <4) and high risk (HEART Scores ≥4) groups. Cross tabulation and Chi-square testing was conducted to determine the association between HEART Scores and stress test results.

Results: Out of 227 patients admitted with chest pain, only 15 (6.6%) had a positive stress test. Among the study group, 80% (181/227) had HEART Scores ≥ 4 and were classified as high risk. Cardiac stress tests were positive in 6% of the high risk and 9% of the low risk patients. There was no statistically significant association between HEART Scores and stress test results: \( \chi^2(1) = 0.407, p = 0.523 \).

Conclusion: In our study group, we found no noteworthy association between high and low risk chest pain based on HEART Scores and cardiac stress test results. Despite the strong association of HEART Scores to MACE demonstrated in previous studies, it may not correlate well with the results of stress testing. Further work is needed to establish this relationship to advocate the use of HEART Score as a substitute to inpatient stress testing.
THE OBESITY PARADOX ALSO OCCURS AMONG HISPANIC PUERTO RICAN PATIENTS PRESENTING WITH ACUTE CORONARY SYNDROMES

E.J. Reves-Aponte¹, A. Lopez-Candales¹, O. García-Rodríguez², M. Irizarry³, M. López³, E. García³

1. Internal Medicine, Cardiovascular Medicine Division, University of Puerto Rico Medical Sciences Campus, San Juan, Puerto Rico, USA
2. School of Health Professionals, University of Puerto Rico Medical Sciences Campus, San Juan, Puerto Rico, USA
3. Endowed Health Services Research Center, University of Puerto Rico Medical Sciences Campus, San Juan, Puerto Rico, USA

Objective: To evaluate the relationship between body mass index (BMI) and in-hospital mortality of Hispanics Puerto Rican patients with acute coronary syndrome (ACS). Background: Studies favor an association between higher BMI and lower mortality, this is part of the obesity paradox phenomenon. We evaluated this phenomenon in Hispanic, Puerto Rican, patients with ACS.

Methods: In this cross-sectional study, medical records from 3,993 patients with ACS during a 3-year period from 12 hospitals in Puerto Rico were reviewed. Study variables were: socio-demographics, comorbidities, cardiac symptoms, treatments, and inpatient complications. A p < 0.05 was considered statistically significant.

Results: Patients, mostly male, were classified by BMI as follows: 28% normal weight, 41% overweight, 20% obese, and 11% morbidly obese. Obese and morbidly obese groups were youngest; and had higher prevalence of HTN, DM II, and asthma (p < .001). Treatment for ACS [ACE inhibitors (p=.03), beta blockers (p=.23), aspirin (p=.07), plavix (p=.003), lipid lowering agents (p=.004), and enoxaparin (p=.006)], cardiac catheterization (p<.0001), and CABG (p=.008) were more often given to morbidly obese group compared to others. After adjusting by confounders, morbidly obese [OR=.41; CI 95% (0.21-0.75)], obese [OR=.59; CI 95%(0.38-0.88)], and overweight [OR=.56; CI 95%(0.40-0.78)] groups had lower in-hospital mortality compared to normal weight patients.

Conclusions: Our results are consistent with prior studies in other ethnicities regarding the occurrence of the obesity paradox in ACS. Further studies are required to identify the pathophysiological mechanism behind this phenomenon.
CURRENT CONCEPTS AND FUTURE DIRECTIONS IN ISCHEMIC HEART DISEASE

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ELEVATED TROPONINS IN A PATIENT WITHOUT MYOCARDIAL INJURY-AN INTERESTING CASE WITH MURAL THROMBUS IN THORACIC AORTA
A. Rajabalan\textsuperscript{1}, B. Bat\textsuperscript{1}, T. Bat\textsuperscript{1}, A. Elmograbhy\textsuperscript{1}, T. Jose\textsuperscript{1}, S. Patel\textsuperscript{1}, S. Lutton\textsuperscript{1}, A. Bhatti\textsuperscript{1}
\textsuperscript{1}Western Reserve Health Education/NEOMED, Youngstown, OH, USA

Introduction: Cardiac troponin is the most specific and sensitive marker of myocardial cell injury and has replaced CK-MB as gold standard. Elevated cardiac troponins indicate the presence of, but not the underlying cause for myocardial injury. Abnormal troponin values have been described in various conditions such as myocarditis, acute heart failure, pulmonary-embolism, septic shock, renal failure, cardio-toxic drugs, and also following procedures such as coronary angioplasty, electrical cardioversions and electrophysiological ablations.

Case: 85 year old African-American lady with history of asthma and COPD presented with chest pain radiating to right arm and dyspnea at rest, found to have acute elevation in cardiac troponins (13.2 from 3.7) with normal EKG, normal EF and no wall motion abnormalities on echo, with patent coronary arteries on cardiac catheterization. After ruling out ischemic causes of elevated troponins, she was evaluated with a CTA chest, which showed a 10 cm long thrombus in the descending thoracic aorta without any evidence of acute dissection or mediastinal hemorrhage, thought to be the cause for acute elevation in cardiac enzymes. Patient was managed medically and discharged home after improvement of symptoms.

Discussion: In the clinical setting, it is difficult to interpret dynamic changes of troponin in non-coronary conditions. The current treatment strategy for patients with elevated troponin and non-acute coronary syndrome is to treat the underlying cause. In our case, elevated troponins may be due to prolonged ischemia which lead to cell-membrane degradation followed by the release of myofibril-bound cytosolic complexes. To our knowledge, this is the first case to be reported with elevated troponin secondary to extensive mural thrombus in the thoracic aorta without evidence of dissection. Though a rare cause of troponinemia, clinicians should be cautious in evaluating patients presenting with a clinical picture of NSTEMI and should suspect aortic-thrombosis or mediastinal hemorrhage in atypical cases.
WHAT HAPPENS TO THE BRAIN AFTER MYOCARDIAL INFARCTION?

J.L. Mehta, X. Wang
University of Arkansas for Medical Sciences and VA Medical Center, Little Rock, AR, USA

It is assumed, but not proven, that acute myocardial infarction affects function of remote organs—such as kidneys and brain. We examined brain morphology in wild type (WT) mice subjected to left coronary artery (LCA) ligation. Coronary ligation resulted in extensive myocardial infarction (MI) and diminished cardiac contractile function. Brain morphology showed a large number of neuronal cells undergoing apoptosis (TUNEL staining and caspase-3 expression) and necrosis (cresyl violet staining) mainly in the temporal area. These changes appeared at 1 week post-MI and persisted for at least 4 weeks. Brain and cardiac tissues revealed intense inflammation (elevated IL-6 and TNF-α, and LOX-1 [a receptor for ox-LDL] expression). Plasma levels of IL-6 and TNF-α were increased over the 4 weeks, maximally at 1 week. To determine the role of LOX-1 in brain inflammation and neuronal injury following LCA occlusion, LOX-1 knockout mice were subjected to total LCA ligation; these mice showed much less increase in systemic, cardiac and brain pro-inflammatory cytokines, and much less neuronal injury than the WT mice (all P<0.05). Cardiac functional deterioration was much less in the LOX-1 KO mice than in the WT mice (P<0.05). This study shows that MI results in significant neuronal injury (apoptosis and necrosis) lasting for at least 4 weeks (equivalent to 3-5 years in humans). This study also suggests that systemic inflammation mediated by LOX-1 is a key modulator among multiple mechanisms underlying brain following MI.
NEW CONCEPTS IN THE PATHOGENESIS AND TREATMENT OF CORONARY ARTERY DISEASE

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CPG DNA REGULATION OF COAGULATION: IMPLICATIONS FOR ACUTE CORONARY ARTERY DISEASE

J.G. Filep
University of Montreal, Montreal, Quebec, Canada

**Background:** Bacteraemia is associated with increased risk of acute coronary artery disease and stroke. Bacterial DNA and mitochondrial DNA, containing unmethylated CpG dinucleotide motifs (CpG DNA) are potent inducers of immune responses during infection and tissue injury predominantly through Toll-like receptor 9 (TLR9). CpG DNA persisting in atherosclerotic plaques and blood contributes to ongoing inflammation, yet little is known about its impact on the coagulation pathway, which plays an important role in thrombus formation.

**Results:** Culture of human coronary artery cells (HCAEC) with CpG DNA evoked marked NF-κB-mediated increases in tissue factor (TF) expression at both mRNA and protein levels as well as in TF activity. Conversely, CpG DNA significantly reduced transcription, secretion and activity of tissue factor pathway inhibitor (TFPI). Inhibition of TLR9 with a telomere-derived TLR9 inhibitory oligonucleotide (iODN) or transient TLR9 knockdown with siRNA attenuated HCAEC responses to CpG DNA. In wild type mice, CpG DNA shortened the bleeding time parallel with dramatic increases in plasma thrombin-antithrombin complex and TF levels. Pre-treatment of mice with iODN or an anti-TF antibody prevented these changes, whereas depleting of circulating monocytes with clodronate resulted in a slight inhibition. Genetic deletion of TLR9 rendered mice unresponsive to CpG DNA.

**Conclusions:** Our findings demonstrate that CpG DNA through TLR9 shifts the balance of TF and TFPI towards pro-coagulant phenotype in HCAECs and activates the coagulation cascade in mice. Our study identifies TLR9 as a potential target to prevent CpG DNA-mediated activation of blood coagulation in acute coronary artery disease.

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NEW CONCEPTS IN THE PATHOGENESIS AND TREATMENT OF CORONARY ARTERY DISEASE

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TICAGRELOR AND STATIN HAVE SYNERGISTIC EFFECTS ON MYOCARDIAL PROTECTION AGAINST ISCHEMIA-REPERFUSION INJURY
Y. Ye¹, S. Nylander², Y. Birnbaum³
1. University of Texas Medical Branch, Galveston, TX, USA
2. AstraZeneca R&D, Molndal, Sweden
3. Baylor College of Medicine, Houston, TX, USA

Background: In addition to P2Y12 receptor antagonism, ticagrelor (TIC) inhibits the equilibrative-nucleoside-transporter-1 (ENT1) and thereby, adenosine cell re-uptake. Prior data show that TIC limits infarct size (IS) in non-diabetic rats and that the effect is adenosine dependent. Statins, via ecto-5’ nucleotidase activation, also increase extracellular adenosine levels and has also been shown to limit IS. Hypothesis: By inhibition of its metabolism and enhancing its production, TIC and rosuvastatin (ROS) have synergistic effects on myocardial adenosine levels, and therefore, on IS.

Methods: Male obese ZDF rats (ZDF-Leprfa/Crl) developed type-2 diabetes after feeding with Purina #5008. Rats received: water (control), TIC (150mg/kg/d), prasugrel (PRAS, 7.5mg/kg/d), ROS (5 mg/kg/d), TIC+ROS and PRAS+ROS for 3d by oral gavage. Two additional groups received, control and TIC+ROS in combination with CGS15943 (CGS, an A2A/A1 antagonist, 10 mg/kg i.p. 1h before coronary occlusion). On day 4, sixteen hours after the last dose, rats were subjected to 30min coronary artery occlusion Area at risk (AR) was assessed by blue dye and IS by TTC 24h after reperfusion.

Results: (expressed as mean±standard error): Fasting glucose levels were comparable among groups (p=0.155). Platelet aggregation was 51.2±2.1% in the control group and equally inhibited by TIC (25.1±1.6%) and PRAS (25.3±1.3%). IS (% of the AR) was significantly reduced with both ROS (31.3±1.2%) and TIC (29.5±2.6%) vs. control (52.6±1.9%), whereas PRAS had no effect (51.8±2.2%). IS was further reduced by the combination, TIC+ROS (20.8±1.8%; p<0.001 vs. control; p=0.014 vs. ROS; p=0.076 vs. TIC), whereas no additive effect was present in the PRAS+ROS combination (39.2±2.2%; p=0.139 vs. ROS alone). CGS alone had no effect on IS (52.5±2.8%), but it completely reversed the effect of TIC+ROS (51.6±2.1%).

Conclusions: Ticagrelor, but not prasugrel, augments the IS-limiting effects of rosuvastatin. The protective effect is completely reversed by adenosine receptor antagonism, suggesting an adenosine mediated effect.
NEW CONCEPTS IN THE PATHOGENESIS AND TREATMENT OF CORONARY ARTERY DISEASE

ROLE OF MICROPARTICLES IN CARDIOVASCULAR CALCIFICATION

J.D. Hutcheson, E. Aikawa

1. Center for Interdisciplinary Cardiovascular Sciences, Cardiovascular Division, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA, USA
2. Center for Excellence in Vascular Biology, Cardiovascular Division, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA, USA

Despite clinical evidence linking arterial calcification to risk of acute cardiovascular events, the mechanisms underlying mineral nucleation and growth in atherosclerotic plaques remain unknown. Finite element modeling of stress distribution within plaques indicates that subcellular microcalcifications in a plaque’s fibrous cap can promote plaque rupture. In contrast, large calcifications may stabilize the plaque, but mechanism(s) that give rise to these two morphologies are unclear. We showed that calcific mineral formation results from a series of events beginning with aggregation of calcifying vascular wall cell-derived vesicles (extracellular vesicles) and continuing through microcalcification to large macrocalcification. We developed a three-dimensional controllable collagen-hydrogel model to visualize in vitro the earliest events associated with vascular mineral deposition. Using advanced high-resolution microscopic and spectroscopic analyses of calcified human atherosclerotic plaques and three-dimensional synthetic system, we provided a crucial link between plaque collagen content and calcification morphology—the two determinants of atherosclerotic plaque stability—thus offering novel insight into the mechanisms of plaque integrity.
NEW CONCEPTS IN THE PATHOGENESIS AND TREATMENT OF CORONARY ARTERY DISEASE

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INTRAMYOCARDIAL HEMORRHAGE AFTER ACUTE MYOCARDIAL INFARCTION; PATHOGENESIS AND CLINICAL IMPLICATIONS

N. van Royen
VU University Medical Center, Amsterdam, The Netherlands

Intramyocardial hemorrhage after acute myocardial infarction was frequently observed in post-mortem studies in the era of thrombolysis treatment. Scientific interest waned after the introduction of primary percutaneous coronary intervention which was believed not to be associated with intramyocardial hemorrhage. However, using dedicated cardiac magnetic resonance, intramyocardial hemorrhage can now be visualized in patients and recently published large series of patients showed that intramyocardial hemorrhage actually occurs in up to 50% of patients with successfully PCI-treated acute myocardial infarction. Intramyocardial hemorrhage is of prognostic importance and is associated with a larger final infarct size, adverse left ventricular remodelling and a higher incidence of major adverse cardiac events. It is believed that the hemorrhage is linked to adverse remodelling via the propagation of an inflammatory response. Especially iron particles, as breakdown products of haemoglobin play a role in the sustained inflammatory response. The sequel of events leading to intramyocardial hemorrhage is not fully understood but the extravasation of erythrocytes occurs at a very early stage and is accompanied by massive destruction of the microcirculation upon reperfusion. These new insights have opened new avenues for additional treatment strategies in patients with acute myocardial infarction. Pharmaceutical protection of the endothelium, basal membrane and pericytes, or adjusting the way reperfusion is established, may prevent microvascular damage, attenuate intramyocardial hemorrhage development and prevent adverse remodelling.
NEW CONCEPTS IN THE PATHOGENESIS AND TREATMENT OF CORONARY ARTERY DISEASE

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DIFFERENCES IN META-ANALYSES RESULTS IN CARDIAC CELL-BASED REGENERATIVE THERAPIES
M. Gyongyosi
Medical University of Vienna, Vienna, Austria

Objectives. We have investigated the discordant results between several meta-analyses of clinical studies involving human cardiac cell-based therapies.

Background. Publication-based meta-analyses of clinical studies including patients with recent acute myocardial infarction (AMI) and randomized to either in placebo group, or to receive intracoronary autologous stem cells were in agreement, that this type of regenerative therapy successfully increases the global left ventricular ejection fraction (EF). The ACCRUE (Meta-Analysis of Cell-based CaRdiac stUdiEs), the recently published meta-analysis, including individual patient data (IPD) however, revealed that intracoronary administration of regenerative cells has no effect on the left ventricular performance shortly after AMI.

Methods and results. We have compared the results of all meta-analyses (n=17) published until 2015, including randomized studies with intracoronary cell therapy in recent AMI. In contrast with the IPD-based analysis, aggregate-data based meta-analyses resulted in different outcomes regarding the clinical endpoints, such as mortality or combined adverse event. All publication-based meta-analyses showed moderate but significant treatment effect (increase in EF between 2.07%-4.21%) as compared to placebo, in contrast with the ACCRUE (mean difference of EF of 0.9% between groups, not significant). In contrast with aggregate-data based meta-analyses, ACCRUE could not find any confounding factors influencing this negative results. ACCRUE revealed too, that also the patients in the placebo group with low baseline EF show more improvement at the 1-year follow-up, similar to the cell-treated patients. Comparing the different kind of meta-analyses, aggregate-data based meta-analyses have the advantage to include all published studies with large number of patients and studies, albeit the data have large heterogeneity, in contrast with the IPD-based meta-analysis.

Conclusions. Each types of meta-analyses have their role in assessment of cardiac cell-based therapies, if no sufficient amount of data of randomized patients in randomized studies exist, but the IPD-based meta-analysis should be regarded as gold-standard in meta-analytic approaches.
NEW CONCEPTS IN THE PATHOGENESIS AND TREATMENT OF CORONARY ARTERY DISEASE

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EVOLVING CELLULAR THERAPY IN CARDIOVASCULAR AND PERIPHERAL VASCULAR DISEASES

R.K. Sharma¹, R. Komatireddy², R.K. Sharma³, H.K. Reddy⁴
1. University of South Florida, Tampa Florida, USA
2. University of California, San Diego, CA, USA
3. University of Tennessee, Knoxville, TN, USA
4. St. Louis University Medical School, St. Louis, USA

Regeneration and healing of a damaged tissue is critical to survival. The regenerative potential of stem cells offers an enormous impact on clinical applications in the management of cardiovascular and peripheral vascular diseases. Atherosclerotic disease is associated with microvascular dysfunction leading to impairment of healing process. Cellular therapy addressing this dysfunction may improve the healing process in acute myocardial infarction or critical limb ischemia. Repair of damaged tissue occurs by virtue of proliferation of stem cells capable of restoring the injured tissue. The ability of stem cells to repair tissue is dependent upon the intrinsic ability of tissues to proliferate such as embryonic stem cells giving rise to virtually any type of tissue. The ability to convert adult stem cells into pluripotent cells that resemble embryonic cells, and to transplant those in the desired organ for regenerative therapy is very attractive. This has led to the exploration of innovative treatments for end stage cardiovascular diseases and critical limb ischemia for limb salvage. The race is on to find an ideal stem cell, delivery strategies, retention of stem cells in target tissue and other factors for successful homing of such cells.

There are multiple factors for success of cellular therapy such as mode of delivery, retention of stem cells in ischemic tissue, microvascular plugging, bio-distribution, homing to ischemic tissues and paracrine function of stem cells.
NEW CONCEPTS IN THE PATHOGENESIS AND TREATMENT OF CORONARY ARTERY DISEASE

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ROLE OF CD4+ T-CELLS AFTER MYOCARDIAL INFARCTION

U. Hofmann
University Clinic Halle(Saale), Germany

The role of innate immunity has been studied for long time whereas adaptive immunity quite recently came into focus in the context of myocardial disease. There is accumulating evidence that CD4+ T-cells contribute to myocardial ischemia-reperfusion injury. We showed that absence of CD4+ T-cells improves microvascular perfusion in a mouse myocardial ischemia-reperfusion model. After completion of infarction, an exaggerated or persistent inflammatory activation after myocardial infarction leads to maladaptive healing and subsequent remodeling of the left ventricle. Monocyte derived cells/ macrophages constitute the central cellular component in the innate immune response to myocardial injury. Meanwhile their role in myocardial healing is well established. CD4+Foxp3+ regulatory T cells (Treg cells) contribute to inflammation resolution. We showed that both conventional T-cells and Treg cells become activated in an experimental MI mouse model most likely due to recognition of autoantigens. Treg cells are especially recruited to the infarcted myocardium during the early healing phase. They drive the switch in macrophage polarization from a pro-inflammatory to a pro-healing phenotype. This cellular interaction especially promotes the formation of a stable scar. Experimentally, Treg cells stimulation after MI is able to improve survival and left ventricular remodeling. Therefore, the interaction of T-cells with monocyte-derived cells/ macrophages constitutes a promising field for development of future therapeutic approaches aiming at modulation of inflammation in myocardial disease.
NEW CONCEPTS IN THE PATHOGENESIS AND TREATMENT OF CORONARY ARTERY DISEASE

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RISK FACTORS FOR NON-PLATELET THROMBOXANE GENERATION

J.J. Rade¹, N. Kakouros¹, S.M. Nazarian², P.B. Stadler¹, T.J. Kickler²
1. University of Massachusetts Medical School, Worcester, MA, USA
2. Johns Hopkins School of Medicine

Background - Persistent thromboxane generation while on aspirin therapy is associated with an increased risk of cardiovascular events. The Reduction in Graft Occlusion Rates (RIGOR) study found that aspirin-insensitive TXA2 generation, indicated by elevated urine 11-dehydroTXB2 (UTXB2) 6 months after coronary artery bypass (CABG) surgery, was a potent risk factor for vein graft thrombosis and originated predominantly from non-platelet sources. Our goal was to identify risks factors for non-platelet TXA2 generation.

Methods and Results - Multivariable modeling was performed using clinical and laboratory variables obtained from 260 RIGOR subjects with verified aspirin-mediated inhibition of platelet TXA2 generation. The strongest variable associated with UTXB2 6 months after surgery, accounting for 47.2% of the modeled effect, was urine 8-isoPGF2á (U8-isoPGF2á), an arachidonic acid metabolite generated non-enzymatically by oxidative stress (standardized coefficient 0.442, P<0.001). Age, gender, race, lipid therapy, creatinine, left ventricular ejection fraction and aspirin dose were also significantly associated with UTXB2 (P<0.03), though only accounted for 4.8 to 10.2% of the modeled effect. U8-isoPGF2á correlated with risk of vein graft occlusion (OR 1.67, p=0.001) though was not independent of UTXB2. In vitro studies revealed that endothelial cells generate TXA2 in response to oxidative stress and direct exposure to 8-isoPGF2á.

Conclusions - Oxidative stress-induced formation of 8-isoPGF2á is strongly associated with non-platelet thromboxane formation and early vein graft thrombosis after CABG surgery. The endothelium is potentially an important source of oxidative stress-induced thromboxane generation. These findings suggest therapies that reduce oxidative stress could be useful in reducing cardiovascular risks associated with aspirin-insensitive thromboxane generation.
INCIDENCE OF VENTRICULAR ARRHYTHMIAS IN CYSTIC FIBROSIS PATIENTS TREATED WITH CHRONIC AZITHROMYCIN THERAPY AND OTHER QT PROLONGING DRUGS

A.K. Tripathi, M. Mohammed, L. Fitzpatrick, M. Bromstedt, D. Lakkireddy, D. Polineni
Kansas University Medical Center, Kansas City, KS, USA

Introduction: Chronic azithromycin therapy (CAT) is frequently used in the treatment of cystic fibrosis (CF) bronchiectasis and is associated with increased risk of ventricular arrhythmias (VA), especially torsade des pointes (TdP). CFTR chloride channels have been shown to prevent excessive prolongation of action potential duration and early after-depolarization, suggesting intact CFTR function may be protective against VA. CF patients may be at increased risk of VA due to aberrant CFTR function, CAT, plus other QT prolonging drugs (QTPD) often prescribed during acute treatment of CF exacerbation.

Methods: Retrospective study of CF patients admitted to KUMC during 2014. 54 out of 189 CF patients were admitted for 84 hospitalizations. We obtained telemetry data, prescription data for CAT and QTPD for 74 hospitalizations of 48 patients.

Result: The study cohort (n=48) was 52% male and mean age at hospitalization was 34 years (+/- 12). 44% of patients were taking CAT at hospitalization and 71% were exposed to >1 additional QTPD during hospitalization. In 74 available telemetry recordings, evidence of sinus tachycardia was seen in 6/48 (12.5%), PVCs were noticed in 1/48 (2.1%), NSVTs in 3/48 (6.25%) and bundle branch block pattern was noted in 3/48 patients (6.25%). Of these, 1 was found to have transient bundle branch block (not seen on successive EKG/telemetry recordings), and 2 had a chronic RBBB. SVT was noted in one patient with history of WPW syndrome. No evidence of TdP or other significant VA were noted.

Conclusion: Physicians are routinely faced with the decision to discontinue CAT when prescribing other QTPD to CF patients. Despite discontinuation of CAT, the long half-life of azithromycin still portends theoretical risk. Our data represent the largest collection of telemetry data in a CF cohort, to our knowledge. Our findings suggest that perceived risk of VA may be overestimated in the CF population.
ARRHYTHMIA I: DIAGNOSIS, DRUG THERAPY, ABLATION

115 CATHETER ABLATION RELATED CORONARY OCCLUSION AND TAMPONADE - A DOUBLE HIT

N.V.K. Pothineni¹, J. Payne¹, S. Kovelamudi¹, J. Wong¹, A. Deshmukh², H. Paydak¹
¹University of Arkansas for Medical Sciences, Little Rock, AR; USA
²Mayo Clinic, Rochester, MN, USA

Introduction: Catheter ablation (CA) is increasingly used for therapy of various arrhythmias. We present an unusual complication of coronary artery occlusion along with cardiac tamponade during CA for atrial tachycardia.

Methods: NA

Results: A 64-year old woman with h/o lymphoma was admitted with dizziness. ECG showed right atrial coronary sinus (CS) atrial tachycardia with complete heart block and ECHO showed an EF of 30%. EnSite 3-dimensional mapping confirmed CS ostium as the site of earliest activation. A cool-path Daig irrigated tip catheter was used for ablation with a power of 30-45 watts, maximum temperature of 45C for duration of 120 seconds. 14 RF applications were delivered cessation of tachycardia. Immediately post ablation, patient was hypotensive with absent motion of the LV border on fluoroscopy. ECHO showed a large pericardial effusion with tamponade requiring emergent pericardiocentesis. A coronary angiogram revealed an abrupt 100% occlusion of the right posterolateral (rPL) branch of the RCA (Fig). As the occlusion was distal, PCI was deferred. Patient did well postoperatively and underwent implantation of a BiVentricular ICD for treatment of complete heart block and non-ischemic cardiomyopathy.

Conclusions: Coronary artery occlusion is a rare complication of CA with a reported incidence of 0.2-0.5%. The PL and PDA branches of the RCA are the most commonly injured vessels during ablation adjacent to the CS. It is unclear if prior thoracic radiation is a risk factor for adverse events. Careful attention to ECG and proximity of ablation site to coronary artery anatomy is crucial.
DISTRIBUTION OF ADRENERGIC AND CHOLINERGIC NERVE FIBERS WITHIN INTRINSIC NERVES AT THE LEVEL OF THE HUMAN HEART HILUM

V. Petrakiene¹, D.H. Pauza¹, R. Benetis²

¹ Institute of Anatomy, Medical Academy, Lithuanian University of Health Sciences, Kaunas, Lithuania
² Institute of Cardiology, Medical Academy, Lithuanian University of Health Sciences, Kaunas, Lithuania

Objective: The aim of the study was to quantitatively evaluate distribution of tyrosine hydroxylase (TH) and choline acetyltransferase (ChAT) positive axons within intrinsic nerves at the level of human heart hilum (HH), since they are fundamental for determining proper treatment options for different arrhythmias.

Background: The imbalance between adrenergic (sympathetic) and cholinergic (parasympathetic) cardiac inputs initiates cardiac arrhythmias and sudden cardiac death. Although morphological pattern of epicardial ganglionated subplexuses (ENsubP) was precisely defined previously, the distribution of functionally distinct axons in human intrinsic nerves was unrevealed as yet.

Methods: Tissue samples from seven epicardial subplexuses were obtained from nine human hearts without cardiac pathology and processed for TH and ChAT immunofluorescent detection. Nerve area was measured and numbers of axons were counted using nerve microphotographs. Densities of fibers were extrapolated and compared between subplexuses.

Results: ChAT-immunoreactive (IR) fibers prevailed (>56%) in dorsal (DRA) and ventral right atrial (VRA) ENsubP nerves. TH-IR axons predominated within left (LC) and right coronary (RC) nerves (70.9% and 83.0% respectively). Despite subplexal dependence, ChAT-IR fibers preponderated in thinner nerves, while TH-IR fibers in thicker ones. Morphometry showed that: (1) LC subplexal nerves were the thickest (25737 ± 4131 μm²), the thinnest (2604 ± 213 μm²) nerves concentrated in DRA ENsubP; (2) density of ChAT-IR axons was the highest (6.8 ± 0.6/100 μm²) in ventral left atrial (VLA), the lowest (3.2 ± 0.1/100 μm²) in left dorsal (LD) nerves; (3) the highest (15.9 ± 2.1/100 μm²) density of TH-IR fibers was in LC, the lowest (4.4 ± 0.3/100 μm²) in VRA nerves.

Conclusions: (1) The principal intrinsic adrenergic neural pathways in human heart proceed via coronary ENsubP that supply both ventricles; (2) the majority of cholinergic nerve fibers access human heart through DRA and VRA ENsubP and extend toward right atrium, including the sinuatrial node region.
Comparing R2CHADS2 and CHA2DS2VASc Scores in Stroke Patients with Non-Valvular Atrial Fibrillation and Renal Failure

KUSM - Wichita, Wichita, Kansas, USA

Introduction: Atrial fibrillation (AF) is the most common rhythm disorder in hospitalized patients. CHA2DS2-VASc and R2CHADS2 are the stroke risk assessment tool scores for patients with atrial fibrillation (2). Even though renal failure is independently associated with stroke (1), it has not been included in the CHADS2-VASc risk stratification system, which is used for anticoagulation recommendation in non-valvular AF patients as endorsed by ACC/AHA. Our study retrospectively compared R2CHADS2 to CHA2DS2-VASc scores in stroke patients with a past medical history of non-valvular AF to assess differences in predicting stroke in patients with renal failure.

Methods: 171 patients admitted over two years from one hospital with a diagnosis of atrial fibrillation and strokes were reviewed. Data variables included: age, medical record number, sex, race, renal function and any previously documented CHA2DS2-VASc scores. If the CHA2DS2-VASc and R2CHADS2 scores were not documented, they were calculated based on information within the medical record. GFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration formula.

Results: The median CHA2DS2-VASc score was 6 (range 2-9) and the median R2CHA2DS2 score was 4 (range 2-8). The average GFR was 69.77 (range 6-108). A weak, but significant, correlation was found between renal function and CHA2DS2-VASc score (r = -0.263; p = 0.0005). A stronger and significant correlation was revealed between the R2CHADS2 and GFR (r = -0.70; p < 0.00001). CHA2DS2-VASc and R2CHADS2 scores also were significantly correlated (r = 0.627; p < 0.00001).

Discussion: The risk of stroke in patients with impaired renal function is high. Although CHA2DS2VASc and R2CHADS2 are significantly correlated to each other, using R2CHADS2 would be beneficial to assess stroke risk in patients with decreased renal function and non-valvular atrial fibrillation.
LEFT ATRIAL DYSSYNCHRONY AS A PREDICTOR OF POSTOPERATIVE ATRIAL FIBRILLATION IN CANCER PATIENTS

The University of Texas MD Anderson Cancer Center, Houston, TX, USA

**Background:** Based on previous reports in patients with heart failure, we hypothesized left atrial dyssynchrony (LAD) can predict new-onset postoperative atrial fibrillation (POAF) after lung lobectomy.

**Methods:** We analyzed the charts of 853 patients without history of AF who underwent lung lobectomy for primary lung cancer, sarcomas or metastasis. Among them, 151 patients (18%) developed POAF, but only 33 patients (71±1.6 years) had quality transthoracic echocardiograms (TTE) in the 3-month period prior to surgery (POAF group). Forty patients (66±1.8 years) who underwent lobectomy, had quality TTEs prior to surgery and did not develop POAF, were chosen as control group. There was no significant difference between POAF and control groups in respect to age, cardiovascular risk factors, LA size, left ventricular systolic and diastolic function. Baseline LAD was assessed with vector velocity imaging (VVI) technology by measuring time-to-peak longitudinal strain and maximum opposing wall delays (MOWD) in the mid-portion of LA walls (septal, lateral) at peak atrial contraction in standard four-chamber views of TTEs prior to surgery.

**Results:** Patients in POAF group had significantly more LAD prior to surgery compared to patients in control group (MOWD 58±34 msec vs 39±24 msec, p=0.009, respectively). Using Receiver Operating Characteristics curve analysis, we identified a MOWD cut-off value of 66 msec which can predict new onset POAF after lobectomy with 51% sensitivity and 83% specificity (area under the curve 0.68).

**Conclusions:** LAD assessment by VVI can be helpful in predicting new-onset POAF after lobectomy, thus identifying patients who might benefit from prophylactic antiarrhythmics perioperatively.
DOES OBESITY IMPACT THE RECURRENCE OF ATRIAL FIBRILLATION AFTER CRYOABLATION USING THE ARCTIC FRONT ADVANCE CATHETER?

A. Avezbadalov\textsuperscript{1}, S. Pollack\textsuperscript{2}, A.F. Osman\textsuperscript{1}

\textsuperscript{1} The Heart Center of Excellence, NOVA Southeastern University, Fort Lauderdale, FL, USA
\textsuperscript{2} St. John’s University, New York, NY, USA

Objective: The Arctic Front Advance cryoablation catheter has become widely used for the successful treatment of atrial fibrillation. Atrial fibrillation is more difficult to treat in patients with obesity due to increased pulmonary pressures and onset of heart failure. We sought to evaluate the recurrence of atrial fibrillation in the obese population after cryoablation at our urban medical center.

Methods: This is a single center retrospective analysis of all patients who were treated for paroxysmal atrial fibrillation with the Arctic Front Advance cryoablation catheter at our medical center between September 2012 and October 2014. Patients with a body mass index (BMI) greater than or equal to thirty were in the Obese group and less than thirty were in the Non-Obese group. Patients were followed for six months to monitor for recurrence of atrial fibrillation using electrocardiograms and holter monitors (Table 1). Patients who did not follow up for at least six months were excluded.

Results: (Table 1)

Conclusion: We found no significant difference between the Obese and Non-Obese groups in the recurrence of paroxysmal atrial fibrillation after successful treatment using the second generation cryoablation catheter.

Results:

<table>
<thead>
<tr>
<th>Total Number of Patients</th>
<th>Non-Obese BMI ≤ 30 (N = 54)</th>
<th>Obese BMI ≥ 30 (N = 33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients in Sinus Rhythm at 6 Months</td>
<td>43 (79.6%)</td>
<td>29 (87.9%)</td>
</tr>
<tr>
<td>Number of Patients with Recurrent Atrial Fibrillation at 6 Months</td>
<td>11 (20.4%)</td>
<td>4 (12.1%)</td>
</tr>
<tr>
<td>p value = 0.32</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 1
A 29 year old female without past medical history presented with new onset psychosis and hallucinations. She was not taking any medications and denied toxic habits. Her family history was unrevealing. On admission she was hypertensive to 170/120mmHg, tachycardic to 120 beats per minute and was complaining of palpitations. Her ECG revealed sinus tachycardia and short PR interval (85msec) without delta waves. Blood work was unremarkable and a urine toxicology test was negative. Work up for secondary causes of hypertension revealed a 3.8cm mass arising from the right adrenal gland compressing the right renal artery. Urine and plasma metanephrines were highly positive. The patient was started on phenoxybenzamine and calcium channel blockers and underwent adrenalectomy. Resection of the pheochromocytoma resulted in resolution of her symptoms. On repeat electrocardiogram post discharge the patient had a normal PR interval. Lown Ganong Levine Syndrome is characterized by a PR interval of no more than 120 msec, a normal QRS duration and paroxysmal supraventricular tachycardia without evidence of atrial fibrillation or flutter. It has been associated with endocrinopathies such as hyperthyroidism— but not pheochromocytoma—and other conditions such as chronic lung disease and glycogen storage disease. Current EP studies suggest that these patients have rather an enhanced AV nodal conduction and its diagnosis does not confer an increased risk of sudden cardiac death. After resection of the tumor PR returned to normal indicating normalization of AV conduction time and confirming the role of catecholamines in the pathogenesis of the syndrome.
VALIDATION OF AN EARLY WARNING SCORE FOR IDENTIFYING HOSPITALIZED CHILDREN AT RISK FOR CLINICAL DETERIORATION

M.C. McLellan¹; K. Gauvreau¹,²; J.A. Connor¹,²
1. Boston Children’s Hospital, Boston, MA
2. Harvard Medical School, Boston, MA

Background: Most inpatient pediatric arrests are preventable through early recognition and treatment of clinical deterioration. Children with cardiac disease have the highest arrest rates of hospitalized children. The Children’s Hospital Early Warning Score (CHEWS) was designed and implemented to identify deterioration in this high risk population. The CHEWS was then applied to all inpatients outside of the intensive care units (ICU).

Objective: This study’s objective was to validate the CHEWS in detecting clinical deterioration in cardiac and non-cardiac patients using the previously validated Brighton Pediatric Early Warning Score (PEWS) for comparison.

Methods: A retrospective cohort study reviewed all non-ICU patients at a quaternary academic pediatric hospital. CHEWS and PEWS scores were obtained on cases (n=424) and a randomly selected comparison sample (n=1024). Specificity, sensitivity and area under the receiver-operating characteristic curves (AUROC) and early warning times were calculated for both tools.

Results:

<table>
<thead>
<tr>
<th></th>
<th>CHEWS</th>
<th>PEWS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac (n=312)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUROC</td>
<td>0.917</td>
<td>0.785</td>
</tr>
<tr>
<td>Sensitivity score (≥3)</td>
<td>95.3%</td>
<td>54.7%</td>
</tr>
<tr>
<td>Specificity (≥3)</td>
<td>76.2%</td>
<td>86.3%</td>
</tr>
<tr>
<td>Median early warning time (≥3)*</td>
<td>9.25 hours</td>
<td>2.25 hours</td>
</tr>
<tr>
<td>Median early warning time (≥5)*</td>
<td>2 hours</td>
<td>0 hours</td>
</tr>
<tr>
<td>Non-cardiac (n=1136)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUROC</td>
<td>0.902</td>
<td>0.798</td>
</tr>
<tr>
<td>Sensitivity (≥3)</td>
<td>91.4%</td>
<td>73.6%</td>
</tr>
<tr>
<td>Specificity (≥3)</td>
<td>67.8%</td>
<td>73.5%</td>
</tr>
<tr>
<td>Median early warning time (≥3)*</td>
<td>11.1 hours</td>
<td>3.8 hours</td>
</tr>
<tr>
<td>Median early warning time (≥5)*</td>
<td>8.5 hours</td>
<td>35 minutes</td>
</tr>
</tbody>
</table>

Validation of CHEWS and PEWS for identifying deterioration in cardiac and non-cardiac patients (*p < 0.001).

Conclusions: CHEWS has excellent discrimination to identify clinical deterioration in hospitalized children with or without cardiac disease. CHEWS has a higher sensitivity and longer earlier warning time than PEWS.
MATERNAL EXPOSURE TO DI(2-ETHYHEXYL)PHTHALATE IMPACTS FETAL CARDIAC DEVELOPMENT

C. Wang, Y.F. Li, Y.F. Zhang, K.Y. Zhou, Y.M. Hua
Department of Pediatric Cardiovascular Disease, West China Second University Hospital, Sichuan University, Chengdu, Sichuan, China

Objective: This study aims to explore the associations between maternal occupational exposures to phthalates (a commonly used phthalate ester plasticizer,) periconceptionally and isolated congenital heart defects (CHDs) in human, and to evaluate the effects of maternal DEHP exposures on fetal cardiac development in mice.

Methods: A case control study with standardized data collection involving 761 children with isolated CHDs and 609 children without any congenital malformations was conducted. An adjusted job exposure matrix was used for maternal occupational DEHP exposure assessment. Logistic regression analysis was performed to assess the associations between maternal occupational DEHP exposures and CHDs. Totally, 75 female pregnant C57BL mice were randomized equally into 5 groups consisting the blank group, vehicle group, and three DEHP groups (0.5g/Kg, 1g/Kg and 2g/Kg). Pregnant dams in different groups received respective intervention by gavage once daily from E6.5-E14.5. HE staining was used to examine the fetal cardiac malformations. Fetal cardiac development-related genes (Nkx2.5, GATA4, TBX5, MEF2C, CHF1) mRNA and protein expression were determined by real-time quantitative PCR and WB.

Results: Maternal occupational exposures to phthalates periconceptionally are associated with perimembranous ventricular septal defect (PmVSD) (P=0.001, adjusted OR 3.7, 95%CI 1.7°C8.0), patent ductus arteriosus (PDA) (P=0.002, adjusted OR 3.8, 95%CI 1.6°C8.9), secundum atrial septal defect (s-ASD) (P=0.008, adjusted OR 3.5, 95%CI 1.4°C8.7) and pulmonary valve stenosis (PS) (P= 0.035, adjusted OR 4.2, 95%CI 1.1°C16.0). Maternal exposures to DEHP could induce various fetal cardiac malformations (including septal defects, myocardial developmental abnormalities, hypoplasia) in mice with a dose-dependent manner. The GATA4, MEF2C and CHF1 mRNA and protein expression of fetal heart were significantly down-regulated by DEHP.

Conclusions: Maternal exposures to phthalates periconceptionally increase the risk of some CHDs phenotype. Administration of DEHP can result in various fetal cardiac malformations in mice.
CONGENITAL HEART DISEASE IN INDIA

R. Bhardwaj\textsuperscript{1}, A. Kumar\textsuperscript{2}, D. Agrawal\textsuperscript{3}, B. Mohapatra\textsuperscript{4}

1. Dept. of Zoology, Inst. of Science, BHU, Varanasi, India
2. Dept. of Pediatrics, Inst. of Med Science, BHU, Varanasi, India
3. Dept. of CTVS, Inst. of Med Science, BHU, Varanasi, India
4. Dept. of Zoology, Inst. of Science, BHU, Varanasi, India

Congenital Heart Defects (CHDs) are the major cause of infant mortality and morbidity worldwide with an estimated prevalence of 9 per 1000 live births. The burden of CHD is huge in developing countries like India especially due to high birth rate. Despite of its higher prevalence and utmost clinical significance, etiology of these defects is not completely understood. Our objective is to assess the pattern and prevalence of congenital heart defects in India and to decipher underlying genetic cause by screening cardiac specific transcription factors (TFs) and functional validation of genetic variants by in silico as well as in vitro studies.

A five-year study (2011-2015), in North-central region of India revealed a prevalence of approximately 19 per 1000 individuals. VSD (33\%) was the most common, followed by ASD (19\%) and TOF (16\%). We screened 280 non-syndromic CHD cases for 12 genes NKX2-5, GATA4, BMP2, BMP4, BMP7, NODAL, CITED2, TGFB1, TGFB2, TBX20, SRF and CRELD1. Out of these genes, GATA4 and NKX2-5 were noted to be most frequently associated with CHD in this population. We identified 5 novel sequence variants (A8D, A9T, E128V, S133C and W228R) and 4 known variants (A75S, S358T, P407Q and T355S) in 20 CHD cases (7.1\%) in GATA4. Parallely, NKX2-5 as revealed 5 non-synonymous genetic variants (A61G, R95L, E131K, A148E and P247A) in 5 CHD cases (1.78\%). None of these variants were found in 200 ethnic matched controls (400 Chromosomes). These mutants also exhibited in silico and in vitro functional deficits demonstrated by western blot, immunocytochemistry and inhibition of downstream promotor (ANF/cActin) activity. The prevalence of CHDs in our cohort was high. NKX2-5 and GATA4 are also most frequently mutated genes in CHD patients in Indian population. Functional validation of mutations listed for these two genes, indicate their possible role in disease manifestation.
CLINICAL RESEARCH ON FETAL BRADYCARDIA
K.Y. Zhou, C. Wang, Y.F. Li, Y.M. Hua
Department of Pediatric Cardiovascular Disease, West China Second University Hospital, Sichuan University, Chengdu, Sichuan, China

Objective: Investigate in the prevalence, spectrum, clinical features and prognosis of fetal bradycardia, as well as the relationship between fetal bradycardia and maternal anti-SSA/Ro and anti-SSB/La.

Methods: The cases of prenatal diagnosed fetal bradycardia were enrolled and the serum level of maternal anti-SSA/Ro and anti-SSB/La and status of maternal autoimmune diseases, the prevalence, spectrum, clinical features and prognosis of fetal bradycardia were recorded and analyzed.

Results: 45 cases of fetal bradycardia were enrolled, the gestational age were 23-34 weeks (mean 28.2w). Among them, there were 21 cases of III°AVB, 16 cases of sinus bradycardia, 8 cases of irregular bradycardia (3 II°AVB, 2 LQTS and other 3 cases). 8 cases of heart rate (HR) less than 55bpm, 19 cases HR between 55-70bpm and 18 cases of HR more than 70bpm. 10 cases of fetuses were revealed companied with degrees of fetal hydrops (6 below 55bpm, 2 between 55-70bpm, and 2 more than 70bpm). Maternal autoantibodies positive (anti-SSA/Ro and anti-SSB/La) were found in 24 mother, among them, 5 systemic lupus erythematosus, 3 Sjogren's disease, 4 undifferentiated connective tissue disease and 12 without clinical symptom; and to their fetuses, there were 17 III°AVB, 5 sinus bradycardia, 2 irregular bradycardia. To the suffered fetuses, 17 cases were companied with cardiovascular malformation (12 III°AVB, 3 sinus bradycardia, 2 irregular bradycardia). In this study, there were no any cases received prenatal drug therapy. All the fetuses HR below 55bpm were terminated after prenatal diagnosis.

Conclusion: Common type of fetal bradycardia including III°AVB, sinus bradycardia and irregular bradycardia (such as the II°AVB, LQTS). The prognosis of fetal bradycardia was poor, and some types of fetal bradycardia have closely relationship to connective tissue disease, especially maternal autoantibodies positive (anti-SSA/Ro and anti-SSB/La).
COGNITIVE REQUIREMENTS FOR AUTOMATIC EXTERNAL DEFIBRILLATOR USE: ARE WE STARTING TOO YOUNG?

C.S. Snyder\(^1\), H. Hall\(^2\)

1. The Congenital Heart Collaborative, Case Western Reserve University, Cleveland OH, USA
2. Case Western Reserve University School of Medicine, Cleveland OH, USA

Background: Patient survival after experiencing out of hospital arrest is influenced by time to CPR/defibrillation. States ARE mandating CPR /automatic external defibrillators (AED) training. The purpose is to assess pediatric patients’ cognitive ability to appropriately perform CPR and utilize an AED on a human during cardiac arrest.

Methods: A search for data regarding pediatric use (<18 years) of AED’s and cognitive ability to perform similar emergent tasks was performed. Data were assimilated and discussed by pediatric electrophysiologist and psychologist. Comparisons were made between emergent duties (exit row seating on plane) and AED use with regard to cognitive and societal beliefs as to when children are prepared to perform these tasks.

Results: The psychological impact of performing CPR and appropriate use of an AED requires high levels of cognitive processing. The three cognitive decisions that a child must have to perform these tasks on a human being are: recognizing cardiac arrest, training in CPR and AED and appropriately performing CPR and utilize the AED. Studies of executive function of the developing brain reveal that younger cohorts (7-12) have single factor modeling (1 task) while older cohorts(13-15 years) have fully developed three factor model (3 tasks) consistent with higher level of executive function development.

Conclusion: The cognitive requirements necessary to appropriately perform CPR and utilize an AED on a human being includes the executive function of the brain to perform well in a three factor model, (recognize cardiac arrest, be trained in and appropriately use both CPR and AED). The group recommends that prior to teaching this necessary skill that one must be cognizant of the child’s cognitive developmental status and should wait until the child is approximately 13 years of age.
ASSOCIATIONS BETWEEN ABCB1 AND ABCG2 GENE POLYMORPHISMS OF CHILDREN AND ISOLATED SEPTAL DEFECTS IN A HAN CHINESE POPULATION

C. Wang, K.Y. Zhou, Y.F. Li, Y. Zhang, Y.M. Hua
Department of Pediatric Cardiovascular Disease, West China Second University Hospital, Sichuan University, Chengdu, Sichuan, China

Background: Substantial epidemiological data have demonstrated that several toxicants/drugs exposures periconceptionally could increase the risk of congenital heart defects (CHDs). Placental P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), encoded by the ABCB1 and ABCG2 gene in human, play an essential role in regulating fetal exposure to toxicants/drugs.

Purpose: This study aimed to explore the associations between ABCB1 and ABCG2 gene polymorphisms of children and isolated septal defects in a Han Chinese population, and to investigate the impact of these polymorphisms on expression of placental P-gp and BCRP, respectively.

Methods: An age and gender matched case-control study involving 210 pairs was conducted. Genotyping of ABCB1 and ABCG2 gene polymorphisms were conducted by sequencing. Forty-six placenta tissues and umbilical cords from healthy Han Chinese mothers with uncomplicated pregnancy were collected. Placental P-gp and BCRP mRNA and protein expression were determined by real-time quantitative PCR and western-blot.

Results: For ABCB1 gene 3435C>T polymorphism, more cases were carriers of the CC/CT genotypes (OR: 2.0, 95%CI: 1.1-3.5, P-value: 0.021). For the ABCG2 gene 34G>A polymorphism, more cases were carriers of the GA/AA genotypes (adjusted OR: 1.6, 95%CI: 1.0-2.3). There were no differences in the genotype distributions and allele frequencies of ABCG2 gene 421C>A polymorphism. The placental ABCB1 mRNA and protein expression of the TT genotype were significantly higher than that of the CC genotype. The ABCG2 mRNA and protein expression did not differ among the three genotypes of 421C>A polymorphism. For 34G>A polymorphism, the ABCG2 mRNA and protein expression of the GG genotype was significantly higher than that of the AA genotype.

Conclusions: The 3435C>T polymorphism within the ABCB1 gene and 34G>A polymorphism within the ABCG2 gene of the isolated septal defects in a Han Chinese population, presumably through regulation of placental P-gp and BCRP expression, respectively.
CORRELATION BETWEEN ECG ABNORMALITIES AND MARIJUANA USE IN THE PEDIATRIC POPULATION

J.A. Robinson, S. Somasegar, J.K. Shivapour, C.S. Snyder
The Congenital Heart Collaborative, Rainbow Babies and Children's Hospital, Case Western Reserve University School of Medicine, Cleveland, OH, USA

Purpose: The effects of marijuana on the cardiac conduction system are ill defined. The purpose is to describe the association between electrocardiogram (ECG) findings and positive drug screening (UDS) for marijuana in the pediatric population.

Methods: A retrospective chart review from 10/13 - 11/14 of patients ≤ 18 years of age that tested positive for marijuana by urine screen in the Emergency Department (ED). All ECGs performed were reviewed by two blinded pediatric cardiologists.

Results: There were 174 patients identified in the ED with a +UDS; median age 15 yrs (0-18 yrs), 42% male. ECG at time of +UDS was performed on 37 (21%). Abnormal ECG finding was identified in 16/37, of which 15 had another ECG performed on a different date. Comparisons were made between these ECGs; significant differences were noted in those patients with +UDS, including ST segment changes (4 patients), left ventricular hypertrophy (3), and one each: atrial fibrillation, QT prolongation, Mobitz type I block, and right bundle branch block.

Conclusion: Abnormal ECG findings, including serious rhythm disturbances and conduction abnormalities can be identified in pediatric patients under the influence of marijuana. An ECG should be considered on all patients with a positive urine drug screen for marijuana.
EFFECT OF FENESTRATION ON EARLY POSTOPERATIVE OUTCOME IN PATIENTS WITH DIFFERENT RISK LEVEL UNDERGOING EXTRACARDIAC FONTAN

**F. Fan, Q. Wang, Z.M. Liu, S.J. Li, T. Yi, J. Yan, F.X. Yan, X. Wang**

The Pediatric Cardiac Surgical Centre, Cardiovascular Institute and Fu Wai Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

**Objectives:** This study assessed the effect of fenestration on extracardiac Fontan patients with different risk level at the early postoperation to identify the candidates to perform the fenestration.

**Background:** Although fenestration was used to improve the postoperative course of Fontan patients, the effect of fenestration on the extracardiac Fontan seemed controversial especially at the early postoperation.

**Methods:** 183 patients having an extracardiac Fontan operation were retrospectively selected for this study. We separated the patients into low risk group (93 patients) and high risk group (90 patients) according to the risk factors recognized by the previous studies. The nonfenestrated patients compared with fenestrated patients in each group with respect to the perioperative data.

**Results:** In both groups there was no meaningful difference of preoperative and operative data between the nonfenestrated patients and fenestrated patients. The postoperative blood oxygen saturation of fenestrated patients was significantly lower in each group. In the high risk group the chest tube volume (862.0 ml vs 1426.5 ml, p=0.068) and duration (8 days vs 11.5 days, p=0.088) of fenestrated patients were lower than that of nonfenestrated patients. While there was no significant difference between the nonfenestrated patients and fenestrated patients in the low risk group about the chest tube volume and duration. The morbidity and mortality of nonfenestrated patients and fenestrated patients were similar in both groups.

**Conclusions:** Fenestration could lead a better postoperative outcomes about the chest tube volume and duration for the high risk patients. We suggested to perform fenestration for the high risk patients.
YIELD OF SPORTS PREPARTICIPATION CARDIOVASCULAR SCREENING IN MIDDLE AND HIGH SCHOOL STUDENTS

St. Luke’s University Health Network, Bethlehem, PA, USA

Background. Comprehensive initial pre-participation physical evaluation (CIPPE) is mandated for junior, middle and high schools by Pennsylvania Interscholastic Athletic Association (PIAA) primarily for reducing potential sports injuries and sudden cardiac death. Those with positive screening for cardiac disease (including findings on 12-element AHA screening questionnaire) are referred for cardiac evaluation. We aimed to evaluate the yield of pre-participation cardiac screening in this group of students.

Methods and Results. Among 3174 students from 13 schools undergoing CIPPE between 6-2015 and 2-2016, 100 (3%) [51 male, 53 white, age 14.8±2.2 years, height 166±12 cm, weight 62±17 kg] were referred for cardiac evaluation. Overall, 98 were engaged in moderate to high intensity sports. Marfanoid phenotype was present in 6 and 6 were overweight. A heart murmur was present in 58 and 1 had systemic hypertension. The following tests were performed: ECG with rhythm strip (100), echocardiogram (93), stress test (13), tilt-table test (1) and cardiac magnetic resonance (CMR) imaging (2). ECG showed minor abnormalities (likely normal variant) in 47 and no major abnormality. Echocardiogram showed 1 with bicuspid aortic valve with dilated root and another 1 with hypertrophic cardiomyopathy (both confirmed by CMR).

Conclusion. A systematic approach to screening in junior, middle and high school sports participants can lead to identification of serious, primarily unsuspected genetic cardiovascular conditions in a small minority. Appropriate screening of 1st degree relatives may enhance the general benefits of such programs.
RESOLUTION OF EARLY SECOND TRIMESTER HYDROPS FETALIS FOLLOWING TREATMENT OF FETAL TACHYCARDIA

J.A. Robinson, J.P. Strainic, J.K. Shivapour, C.S. Snyder
The Congenital Heart Collaborative, Rainbow Babies and Children's Hospital, Case Western Reserve University School of Medicine, Cleveland, OH, USA

Introduction: Hydrops fetalis is associated with risk of mortality. This is a case report of hydrops fetalis noted in a 19-week fetus due to fetal tachycardia that responded to antiarrhythmic therapy with return to normal sinus rhythm and resolution of hydrops.

Results: A 20-year-old, G1P0 woman, was referred to Pediatric Cardiology at 19 weeks gestation for concern of hydrops fetalis, after obstetric ultrasound demonstrated pleural effusion, pericardial effusion, and abdominal ascites. Fetal echocardiogram demonstrated normal cardiac anatomy with abnormal pulsatility in the umbilical vein and a fetal heart rate > 280 beats per minute. M-mode documented a long V-A interval with 1:1 conduction, consistent with a long R-P tachycardia. The mother was loaded on digoxin, then started on maintenance at 250 mcg twice daily (BID), in addition to sotalol 160 mg BID. After 3 days, when fetal tachycardia was persistent, flecainide 50 mg BID was added. No effect was achieved, despite increasing the flecainide dose to 100 mg BID. Sotalol and flecainide were discontinued and amiodarone 400 mg BID was initiated at 20 weeks gestation, with complete resolution of both the fetal tachycardia and hydrops by 22 weeks gestation. Maternal treatment with amiodarone and digoxin were continued through the pregnancy, with digoxin trough levels maintained at < 2 ng/mL. Thyroid and liver function tests were normal. The baby delivered spontaneously at 38 weeks term gestation, without complications and with a normal ECG. Maternal antiarrhythmic medications were discontinued and the baby was continued on amiodarone at 5 mg/kg/day without recurrence of his arrhythmia.

Conclusion: Persistent fetal tachycardia may lead to hydrops fetalis, which carries increased risk for intrauterine demise. Amiodarone was successfully used to terminate fetal arrhythmia, with complete resolution of hydrops fetalis.
ASSESSMENT OF ASCENDING AORTIC DIAMETER BY TRANSTHORACIC ECHOCARDIOGRAPHY: AGE AND SEX SPECIFIC REFERENCE VALUES IN ADULTS WITH AND WITHOUT SYSTEMIC HYPERTENSION

G. Kumar 1, C. Ayoub 2, P. Thapa 2, F.A. Miller 2, P.C. Spittell 2
1. Emory University School of Medicine, Atlanta, GA, USA
2. Mayo Clinic, Rochester, MN, USA

Background: Ascending aortic diameter is an important parameter in trans-thoracic echocardiography (TTE). Whilst there are published reference ranges for sinus of Valsalva, sinotubular junction and proximal ascending aorta diameter using TTE, there are no published standardized measurements for the mid ascending aorta diameter (MAAD). MAAD has therapeutic and prognostic importance in patients with aortopathies such as those associated with bicuspid aortic valve disease, hypertension and syndromes including Marfan and Loeys Dietz, where dilatation may also occur above the proximal ascending aorta. We sought to characterize MAAD reference values by age, sex and body surface area (BSA) in a large practice-based cohort.

Methods: All unique TTEs performed with documented MAAD from January 2004 to December 2009 were identified, and medical records were reviewed. Patients with bicuspid aortic valves, aortic stenosis, aortic prostheses, congenital heart disease and known aortic dilatation (>40 mm) were excluded. MAAD was obtained in a standardized manner by two-dimensional echocardiography using a leading edge to leading edge technique. Two group comparisons were performed using Student’s t test. Overall age and gender-specific relationships of the 5th and 95th percentile with BSA and MAAD were evaluated using quantile regression.

Results: 59,981 unique patients (51.1% female, median age 64.2 years) were identified. Hypertension was present in 49.3%. Females had smaller median MAAD than males (32 vs 35 mm; p<0.0001). Figure 1A and Figure 1B demonstrate the predicted 5th and 95th percentiles of MAAD in males and females respectively, as a function of age and body surface area. In subjects with a history of hypertension, there was a small but statistically significant difference in MAAD (32.4 vs 34.1 mm; p<0.0001).

Conclusion: MAAD is predominantly affected by sex, age, and body surface area, and to a lesser extent by presence of hypertension. These nomograms may serve as a useful reference for patient management.
LARGE CARDIAC HAMARTOMA: CHARACTERIZATION OF MASS AND MANAGEMENT WITH IMAGING

C. Ayoub, S.A. Luis, J. Maleszewski, P. Pellikka
Mayo Clinic, Rochester, MN, USA

Background: Advanced cardiac imaging techniques can assist in characterizing cardiac masses and directing management.

Case: An asymptomatic 14-year-old man presented with a 9 x 5 x 6 cm left ventricular mass incidentally discovered during investigation of a flow murmur. Echocardiography showed a large cavernous structure at the postero-apical left ventricle (LV) with systolic expansion and spontaneous echo contrast (Figures A and C), concerning for direct communication with the LV and possible thrombus. Despite the size of the mass, there was no obstructive physiology, and the myocardium appeared normal. Contrast echocardiography revealed late opacification of the mass relative to the LV with slow entry and low density of contrast (Figures B and D), suggesting venous connection to the mass without direct continuity with the LV cavity. Cardiac MRI (Figures E and F) showed increased signal on T1 and T2 weighted images, and rapid enhancement with gadolinium perfusion suggested a highly vascular structure. Contrast echocardiography and CMR imaging were most consistent with a benign vascular lesion, and excluded thrombus within the structure. As a result, expectant management with serial surveillance imaging was undertaken, and the patient remained asymptomatic and mass size unchanged. He died from non-cardiac cause at age 28 and autopsy demonstrated hamartoma of mature cardiac myocytes.

Conclusion: Advanced imaging techniques including contrast echocardiography and CMR provide valuable tissue characterization for assessment of cardiac masses, potentially distinguishing benign and malignant etiology and helping exclude thrombus. Accurate imaging techniques saved our patient the risks associated with unnecessary surgery or anticoagulation. The ability to accurately define size serially is essential in guiding expectant management.
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MERCELESS, METASTATIC, MALIGNANCY TO THE HEART: CASE OF PULMONARY SARCOMATOID ADENOCARCINOMA
H. Narayanasamy, T. Naqvi, S.M. Wilansky
Mayo Clinic, Arizona, USA

We describe a case of metastatic pulmonary sarcomatoid adenocarcinoma, a rare subtype with poor prognosis, causing metastatic pericardial tumor with right and left ventricular myocardial wall destruction, tamponade and death. 78 year old female with history of CKD, Hypertension presented with 1 month history of palpable painless mass in the left neck. She underwent CT imaging which showed diffuse metastasis including lung, liver, renal, peritoneal /GI Mets with partial intussusception and pericardial involvement. Even though CT reported as pericardial mass measuring about 3 cm in the apical region, given her diffuse metastasis and absence of any cardiac symptoms echocardiography was not performed. Patient developed bowel obstruction and underwent laparotomy with partial resection of small bowel. Pathology results showed wild type metastatic sarcomatoid adenocarcinoma from lung primary. To complete the tumor staging; she had MRI brain which showed solitary cerebellar metastasis and underwent brain surgery for tumor resection. Few days later she presented with dyspnea and chest pain and an echocardiogram showed 6x4cm large pericardial tumor invading the right ventricle, extending throughout the myocardial layer of the apex of the left ventricle, anterior pericardial effusion, and tamponade. In certain echo views, endocardial layer was disrupted rising the suspicion for rupture of myocardium. Given her poor prognosis she went into home hospice, and as expected she died within 1-2 days. Retrospectively, earlier echocardiography might have identified the magnitude of cardiac involvement which might have helped to determine the prognosis and avoided all the surgeries and last few days of her life in the hospital bed.

We propose that at least in selected cancers like mediastinal, lung cancer where metastatic cardiac involvement is common, baseline echocardiography should be a part of multimodality imaging for cancer staging as well as to assess cardiac function prior to treatment.
CORRELATION OF 2D AND 3D ECHOCARDIOGRAPHIC LEFT VENTRICULAR EJECTION FRACTIONS AMONG PATIENTS WITH ACUTE CORONARY SYNDROME

J. Salvanera, I. Bundalian, R. Ramboyong
The Medical City, Pasig City, Philippines

Background: Assessment of left ventricular ejection fraction provides valuable diagnostic, prognostic and therapeutic implications in patients with acute coronary syndrome. This study identified which 2D echocardiographic left ventricular ejection fraction index provides better estimate as compared to 3D echocardiography.

Methods: 54 subjects underwent 3D echocardiogram and 2D echocardiogram from July to December 2015. 2D echo left ventricular ejection fraction measurements were calculated using modified Simpsons, Quinones and Teicholz. 3D echo left ventricular ejection fractions used measurements of end-systolic and -diastolic volumes. Correlation of these methods used the following statistical tools: paired t-test, Pearsons correlation coefficient test, linear regression analysis, percentage variability and Bland-Altman plots.

Results: Paired t-tests of the mean differences between Teicholz and 3D echo showed significantly different result (p=0.0001). Linear regression graphs and Pearson correlation showed significant positive correlation with a correlation coefficient of 0.969 (p=0.0001) between modified Simpsons and 3D echo.

Conclusion: 2D echo calculation of ejection fraction using modified Simpsons compares well and has more positive correlation with 3D Echo as compared to Teicholz and modified Quinones. Modified Quinones and 3D echo also shows comparable results but with only moderate correlation. However, Teicholz showed significant difference with 3D echo but still with moderate correlation.
A CASE OF INFERIOR VENA CAVA MASS ON ECHOCARDIOGRAPHY

A. Quddus, A. Smith, M. Mchlane, S. Agrawal, A. Singh, S. Longo, J. Shirani
St. Luke’s University Health Network, Bethlehem, PA, USA

Background. Benign (leiomyoma) and malignant (renal cell, hepatocellular, leiomyosarcoma, testicular and adrenocortical carcinoma) may present as inferior vena cava masses. We present a patient with a large IVC mass and newly diagnosed metastatic small cell lung cancer.

Case. 54-year-old woman with no significant past medical history presented with two weeks of progressive cognitive decline, unsteady gait, recurrent falls and weight loss. On presentation, her blood pressure was 120/60 mmHg, heart rate 85 bpm, O2 saturation 97% on room air and respiratory rate 18 bpm. She appeared drowsy and had ataxia and dysmetria. Heart sounds were regular without murmurs. A brain MRI showed multiple infra and supra-tentorial metastatic lesions with associated obstructive hydrocephalus. CT scan of the chest, abdomen and pelvis showed widespread metastasis in the lungs, liver, right adrenal, spleen and uterus. She underwent an emergent craniotomy with resection of the posterior fossa tumor. Post-operative course was complicated by worsening somnolence and respiratory failure requiring mechanical ventilation. Echocardiography revealed a large, round (2.5 cm) sessile mass within a dilated IVC, roughly 2 cm from entrance into right atrium (figure 1A). Coronary sinus was enlarged. Due to extensive metastatic disease comfort care was initiated. Pathology of the posterior fossa mass was consistent with highly malignant (figure 1B) metastatic small cell neuroendocrine carcinoma of lung origin (thyroid transcription factor-1 positive).

Conclusion. Small cell carcinoma of lung is a highly metastatic disease that also associated with hypercoagulable state. Involvement of IVC in this disease has not been documented previously. The findings in our case are most consistent with a slow growing IVC tumor or thrombus based on focal attachment of the mass and local dilatation of the vessel.
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A GIANT LEFT ATRIAL MASS: NOT A MYXOMA
C. Gallegos, V. Singh, M. Rivera-Maza, R. Colombo, R.C. Hendel
University of Miami, Miller School of Medicine, FL, USA

Intracardiac involvement from metastatic tumors causing heart failure symptoms is a rare occurrence. We describe an unusual case of a 25-year-old man who presented with symptoms of heart failure and superior vena cava syndrome. He had a past history of right testicular cancer status post transcutal orchiectomy. Labs reported increased beta-human chorionic gonadotropin (β-hCG), alpha-fetoprotein, and lactate dehydrogenase (LDH). Chest x-ray demonstrated large, right pleural effusion, and a CT scan of the chest confirmed a mass occupying 2/3 of the right hemithorax invading the left atrium via right pulmonary veins. Transthoracic echocardiogram (TTE) a mobile left atrial mass prolapsing into the left ventricle through the mitral valve. Patient completed chemotherapy for metastatic germ cell (non-seminomatous) tumor, with significant improvement. Upon discharge, he had no further cardiac symptoms and a repeat TTE demonstrated no residual left atrial mass. In conclusion, a non-seminomatous germ cell tumor metastatic to lungs, and extending to the left atrium, is an infrequent and unique cause of heart failure presentation. TTE proved to be an excellent diagnostic and prognostic imaging tool, providing high quality images, and demonstrating the effectiveness of the chemotherapy treatment.

FIGURES
Figure 1. TTE performed on admission. A. Parasternal long axis. B. Apical four chamber views demonstrate a mobile 7.65 x 3.82 cm mass (*) in the left atrium prolapsing through the mitral valve into the left ventricle. This mass takes up >85% of the left atrium.

Figure 2. Follow-up TTE after 7 days of starting chemotherapy regimen. A. Parasternal Long axis. B. Apical four chamber views show smaller mobile 5.47 x 3.69 cm mass (*) in the left atrium no longer interfering with mitral valve function. TTE after 6 months after diagnosis demonstrating no residual mass. C. Parasternal. D. Apical four chamber view without evidence of left atrial mass.
NOVEL DIAGNOSTIC METHODS AND IMAGING TECHNIQUES

IMPACT OF DIABETES MELLITUS ON SUBCLINICAL ATHEROSCLEROSIS IN ASYMPTOMATIC INDIVIDUALS

Daejeon St. Mary's Hospital, the Catholic University of Korea, Seoul, Korea

Objectives: The purpose of this study was to investigate the impact of diabetes mellitus on the risk of subclinical atherosclerosis in asymptomatic individuals.

Background: Little is known about subclinical atherosclerosis on coronary computed tomographic angiography (CCTA) in asymptomatic individuals with diabetes mellitus.

Methods and Results: We analyzed 6,311 consecutive asymptomatic individuals aged 40 and older with no prior history of coronary artery disease (CAD) who voluntarily underwent CCTA evaluation as part of a general health examination between January 2007 and December 2011. The mean age of the study population was 54.5±7.4 years, and 4,594 (72.8%) were male. Of the study population, 1,033 (16.4%) had diabetes mellitus. After adjustment using age and gender distributions from the 2010 South Korean population census, individuals with diabetes mellitus had a significantly higher prevalence of plaque (standardized rate ratio [SRR], 1.37; 95% confidence interval [CI]: 1.17–1.60; p<0.001), non-calcified plaque (SRR, 1.71; 95% CI: 1.35–2.17; p<0.001), calcified plaque (SRR, 1.29; 95% CI: 1.09–1.53; p=0.003), mixed plaque (SRR, 1.69; 95% CI: 1.24–2.31; p=0.001), significant CAD (SRR, 2.66; 95% CI: 1.93–3.68; p<0.001), and significant CAD in the left main or proximal left anterior descending artery (SRR, 2.94; 95% CI: 1.71–5.04; p<0.001) compared with those without.

Conclusions: In asymptomatic individuals, diabetes mellitus was associated with subclinical atherosclerosis on CCTA with subsequent high risk for future cardiac events. These findings suggest the importance for control of hyperglycemia in asymptomatic individuals.
IS NON-INVASIVE MEASUREMENT OF CARDIAC OUTPUT USING ELECTRICAL CARDIOMETRY IN PATIENTS WITH AORTIC STENOSIS A RELIABLE METHOD?

P. Teefy¹, R. Bagur¹, K. Karimi-Shahri², J. Teefy², R. Sule², C. Phillips², K. Norozi²
1. Department of Medicine, Western University, London, ON, Canada
2. Department of Paediatrics, London Health Sciences Centre, Ontario, Canada

Aim: The purpose of this study is to evaluate the agreement of cardiac output (CO) measurements obtained by non-invasive Electrical Cardiometry (EC, COEC), and those derived from the “gold standard” measured by the Thermodilution (COTD) method in adults with aortic valve stenosis.

Methods: Simultaneous measurements of CO, obtained by means of COEC and COTD, were compared in twenty-one patients (16 female and 15 male) thus far, with mean ages of 74 years (SD=9) who were undergoing diagnostic right and left heart catheterization. For non-invasive measurements of COEC, which is a variation of impedance cardiography, standard surface electrodes were applied to the left side of the neck and the left side of the thorax at the level of the xiphoid process. COTD was determined during the heart catheterization.

Results: A good correlation (r = 0.65) was found between COEC and COTD (p=0.003). The bias between the two methods (COEC – COTD) was -1.1 L·min⁻¹. According to the Bland and Altman method, the upper and lower limits of agreement, defined as mean difference ± 2SD, were +0.52 L·min⁻¹ and -2.77 L·min⁻¹, respectively.

Conclusions: Although Electrical Cardiometry compared to Thermodilution in these thirty-one patients seems to underestimate the cardiac output, COEC demonstrates acceptable agreement with data derived from COTD in adults with aortic stenosis. In the first glance it seems that EC can be applied for continuous non-invasive beat-to-beat estimation of CO. Further data will be required to establish more robust analysis of data.
NOVEL DIAGNOSTIC METHODS AND IMAGING TECHNIQUES

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IMPACT OF INITIAL FUNCTIONAL EVALUATION COMPARED WITH INVASIVE ANGIOGRAPHY FOR STABLE CORONARY ARTERY DISEASE
Daejeon St. Mary's Hospital, the Catholic University of Korea, Seoul, Korea

Background: There are limited data about the clinical implications of invasive coronary angiography (CAG) or myocardial perfusion imaging (MPI) for an initial evaluation for stable coronary artery disease (CAD).

Methods: From national health insurance claims data in South Korea, patients aged 18 years or older without a known history of CAD, who underwent CAG or MPI for the diagnosis of stable CAD between 2009 and 2013, were enrolled. Patients in the hospitals, which could perform both CAG and MPI, were only evaluated. Patients were divided into CAG (n=60,525) and MPI (n=19,932) groups. The primary endpoint, defined as a composite of all-cause death and myocardial infarction, was compared between the two groups.

Results: The mean age of study participants was 60.9 years and 44,532 (55.3 %) were male. During the follow-up period (median, 2.4 years; interquartile range, 1.5–3.5), coronary revascularization was more frequently performed in the CAG group (adjusted hazard ratio [aHR] of CAG, 26.27; 95% confidence interval [CI]: 21.86–31.58; P<0.001). However, the incidence of the primary endpoint was significantly higher in the CAG group (aHR, 1.26; 95% CI: 1.16–1.36; P<0.001). The individual endpoints of all-cause death (aHR, 1.19; 95% CI: 1.09–1.29; P<0.001) and myocardial infarction (aHR, 1.81; 95% CI: 1.49–2.20; P<0.001) were also higher in the CAG group.

Conclusions: As an initial diagnostic test in patients with stable CAD, MPI is associated with better clinical outcomes than CAG.
THE EFFECT OF NEGATIVE CARDIAC NUCLEAR STRESS ON EMERGENCY-ROOM VISIT AND READMISSION FOR CHEST PAIN
S. Talebi, O. Zaher, H. Reves, O. Olatunde, F. Visco, G. Pekler
New York Medical College - Metropolitan Hospital Center, New York, NY, USA

Objectives: To determine the effect of negative nuclear stress test (NST) in the frequency of emergency department (ED) visits and hospital readmissions (HR) to rule out acute coronary syndrome (ACS).

Background: Patients with low-risk chest pain are frequently readmitted for evaluation of recurrent chest pain. A negative NST before discharge reassures the physician that the chest pain is not caused by an obstructive coronary lesion.

Method: A retrospective study using electronic charts between 2009 and 2013 was performed. We included patients who were admitted at least once to rule out ACS and had a negative NST before discharge. We compared subsequent ED visits and HR 2 years before and after the result of the NST. Patients with a positive troponin or a history of coronary artery disease were excluded.

Result: 1300 patients with NST were reviewed. 72 fulfilled the criteria for this study. Median age of participants was 61 (36-84) years and 68% (49) were women. Patients came to ED 93 times (1-5) before a negative NST and 99 times (1-7) after a negative NST (p=0.35). Patients were admitted 82 times (1-5) before a negative NST and 90 times (1-7) after a negative NST (p=0.44). Among 72 patients, 30 (42%) patients were admitted before and after a negative NST, there was 24 (33%) admissions before a negative NST and 18 (25%) admissions after a negative NST.

Conclusion: Previous result of a negative NST did not reduce either ED visits or HR to rule out ACS, although not statistically significant. It seems like clinicians are not explaining to the patients the cause of their chest pain, giving a particular diagnosis, and treating the underlying cause. Changing the management and approach to these patients might be a more effective way for reducing readmissions than stress testing alone.
NOVEL DIAGNOSTIC METHODS AND IMAGING TECHNIQUES

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MULTIMODALITY APPROACH IN PERCUTANEOUS INTERVENTION OF RENAL ARTERY FIBROMUSCULAR DYSPLASIA IN AN 80-YEAR OLD FEMALE
N. Katta, P. Velagapudi, M. Mittal, H. Agrawal, A. Kumar
University of Missouri School of Medicine, Columbia, MO, USA

We present a case of an 80-year old woman with resistant hypertension with systolic blood pressure (SBP) >200 mm Hg. Doppler ultrasound of the renal arteries showed right renal artery (RA) stenosis in mid segment with peak systolic velocity of 237 cm/sec. Magnetic resonance angiography of abdomen revealed irregular narrowing of the right mid RA suggestive of renal artery fibromuscular dysplasia (RAFMD) (Figure.1). Renal angiography showed 70% stenosis right mid RA with “string of bead appearance” characteristic of medial type of RAFMD (1) (Figure.2A). Intravascular ultrasound (IVUS) using Eagle Eye Platinum RX Digital IVUS catheter showed intermittent crescentic membranes in stenosed area characteristic of RAFMD (Figure.3B). We measured translesional systolic pressure gradient (TSPG) using a PressureWireTM AerisTM with Agile Tip 0.014” x 175cm guide-wire (Figure. 4A). The lesion was deemed functionally significant as resting TSPG was 23 mm Hg (Figure.4B). NC TREK RX 4.5 x 20mm balloon was used for balloon angioplasty. We monitored TSPG during our intervention. After 5 inflations at maximum pressure of 12 atmospheres, TSPG was reduced to less than 10 mm Hg (Figure.4C). Post procedure IVUS showed the stenosed segment reached the reference vessel diameter (Figure. 3A). Repeat Doppler ultrasound showed the peak systolic velocity decreased to 198 cm/sec, with improvement in patient’s SBP to 121 mm Hg requiring only two antihypertensive medications. Symptomatic RAFMD is rare in elderly (1). Although renal angiography or biopsy (2) is gold standard in diagnosing RAFMD, Gowda et al (3) showed superiority of IVUS by demonstrating endoluminal abnormalities when angiogram appeared normal. Despite lacking of systematic evidence, an expert consensus panel has suggested that translesional systolic and mean pressure gradients of 20mm Hg and 10mm Hg respectively, should be considered functionally significant(4). We suggest multimodality approach using IVUS, translesional pressure gradients in the percutaneous intervention of RAFMD for good results.
NOVEL DIAGNOSTIC METHODS AND IMAGING TECHNIQUES

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THE PANTYHOSE PROJECT
D.A. Bloomfield, F. Rotatori
Richmond University Medical Center, Staten Island, New York, USA

Introduction: The original EKG “electrodes” were buckets of saline in which the hands and feet were placed, thereby establishing these sites for the placement of the more modern electrodes. Consequently, recording traditional office electrocardiograms in women wearing pantyhose, stockings, or long boots requires extensive undressing, considerable time and, particularly in the elderly, often provokes annoyance and embarrassment. This study was undertaken to determine whether alternatively placing leg electrodes on each side of the abdomen, to avoid the necessity of removing clothing, altered the cardiogram’s diagnostic potential.

Method: Paired electrocardiograms, one with standard ankle electrodes and the other with the abdominal electrodes, were recorded in 108 patients with a large variety of cardiological diagnoses. The EKG frontal plane axis was statistically compared between the paired tracings. Similarly, paired cardiograms with standard electrode placement were recorded in 39 patients and compared in inspiration and expiration.

Results: The only change of any magnitude was seen in the leads I, II, III and avF, accurately represented in the frontal plane axis, which demonstrated a statistically significant difference between the leg and abdomen tracings. However, this difference had a mean value of only -4 degrees (CI between -8.81 to -3.87); which is clinically inconsequential and even lower than the difference between the inspiration and expiration EKGs (13.42 degree, CI between -17.7 and -9.05), an issue that is irrelevant to clinical diagnoses. The interpretation of the “abdominal” EKG was never different from the “leg” EKG.

Conclusion: The lower abdomen instead of the leg electrode placement does not alter the diagnostic value of the EKG and, in fact, more closely fulfills Einthoven’s criteria. Abdominal electrodes can be used to obviate the need to bare the legs of patients wearing pantyhose or stockings to an office visit and are more convenient in all patients, whether the legs are covered or not.
NOVEL DIAGNOSTIC METHODS AND IMAGING TECHNIQUES

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THE EFFICACY OF SONOGRAPHIC MEASUREMENT OF INFERIOR VENA CAVA DIAMETER AS AN ESTIMATE OF CENTRAL VENOUS PRESSURE

W. Ciozda¹, I. Kedan², R. Khandwalla², R. Zimmer², A. Kimchi²

1. David Geffen School of Medicine, University of California, Los Angeles, California, USA
2. Cedars Sinai Heart Institute, Beverly Hills, California, USA

Background: Central venous pressure is often an important parameter for the clinical evaluation of a patient. However, current measurements of central venous pressure require invasive techniques. Sonographic measurement of inferior vena cava diameter may be a reliable non-invasive estimate of central venous pressure.

Objective: Determine if ultrasound measurements of inferior vena cava diameter are clinically correlative estimates of central venous pressure or right atrial pressure.

Methods: We conducted a PubMed search to identify randomized clinical studies assessing sonographic evaluation of inferior vena cava diameter against gold standard measurements of central venous pressure and right atrial pressure.

Results: Twenty-one trials (1,340 patients) comparing inferior vena cava ultrasound measurement to central venous pressure and right atrial pressure were identified.

Conclusion: Thirteen studies showed a statistically significant positive correlation between sonographic measurement of inferior vena cava diameter and central venous pressure. Two studies showed a negative correlation and six studies were inconclusive. Given the ease and safety of imaging the inferior vena cava further research is warranted to better understand its usefulness in clinical medicine.
NOVEL DIAGNOSTIC METHODS AND IMAGING TECHNIQUES

Incidental Finding of Interventricular Membranous Septal Aneurysm in a Patient with Supraventricular Tachycardia

F. Elmi,1,2, M. Sharma,2, B. Ganguly2
1. Drexel University College of Medicine, Philadelphia, PA, USA
2. Easton Hospital, Easton, PA, USA

Introduction: Interventricular membranous septal (IVMS) aneurysm is a rare condition with no accurate incidence rate. It is known to be associated with 0.3% of congenital heart disease and 19% of ventricular septal defects. IVMS aneurysm is often asymptomatic but can be complicated with right ventricular obstruction, rupture, thromboembolism, and conduction defects. We present an incidental finding of IVMS aneurysm in a patient with supraventricular tachycardia (SVT).

Case: A 69-year-old physically active lady with history of SVT for 16 years with infrequent episodes of palpitations managed medically by metoprolol underwent echocardiography because of more frequent episodes of her symptoms. She had been refusing ablation as her episodes were infrequent. She had no history of coronary artery disease and several stress tests have been unremarkable. Echocardiography showed a new aneurysmal appearing area near the right coronary cusp consistent with a possible sinus of valsalva aneurysm. A subsequent CT angiography revealed an aneurysm measuring 2.2 X 1.5 X 1.7 cm arising from the membranous part of interventricular septum. It was extending into right ventricle with no outflow tract obstruction. The patient has remained asymptomatic since then except infrequent episodes of SVT. She has been managed with Metoprolol, aspirin and close follow up.

Conclusion: An incidental finding of IVMS aneurysm prompts evaluation for cardiac abnormalities. In the absence of complications conservative management with timely follow up along with patient education about potential complications seem to be the mainstay of management. In the absence of complications surgical resection is not indicated. In spite of the rarity of this entity there should be vigilance among clinicians and radiologists due to its potential complications.
UTILITY OF SIGNAL-AVERAGED HOLTER ELECTROCARDIOGRAM AFTER PILSICAINIDE PROVOCATION FOR RISK STRATIFICATION IN BRUGADA SYNDROME

Cardiovascular Medicine, Osaka City University Graduate School of Medicine, Osaka, Japan

Objects: To assess the utility of signal-averaged Holter ECG (S-Holter) after pilsicainide provocation (p-test) for the non-invasive risk stratification in Brugada syndrome (Br-S).

Backgrounds: Non-invasive risk stratification for ventricular fibrillation (VF) in Br-S is not fully evaluated.

Methods: We enrolled a total of 35 patients with Br-S (grouped according to histories of VF [VF]; n=10, and without VF [non-VF: including histories of syncope and asymptomatic]; n=20) and 5 controls, whom S-Holters with and without p-test were performed. We evaluated late potentials (the total filtered QRS duration [fQRS], root mean square voltage of the 40msec terminal portion of the QRS [RMS40], duration of the low amplitude electric potential component of the terminal portion [LAS40]) for 5 hours after p-test and for the same 5 hours without p-test recorded on another day in the same patients. We compared these data between the 2 groups and evaluated the utility of the S-Holter after p-test for risk stratification of VF episodes, retrospectively.

Results: The fQRS at 1 hour and LAS40 at 3 hours after p-test were significantly larger in VF group than non-VF group (fQRS; 113.9±8.9 vs 104.9±8 ms, LAS40; 45.4±5.9 vs 35.5±7.4 ms, p=0.01 and 0.01, respectively). The cut off values of these parameters were determined group as 112ms (sensitivity 80%, specificity 80%, p=0.01), and 41ms (sensitivity 90%, specificity 75%, p=0.01), respectively.

Conclusions: The fQRS at 1 hour and the LAS40 at 3 hours after p-test using S-Holter may be useful for risk stratification of VF episodes in Br-S.
THE IMPACT OF SOCIOECONOMIC HEALTH DISPARITIES IN CONGESTIVE HEART FAILURE IN OUT PATIENT MANAGEMENT A CASE SERIES RETROSPECTIVE ANALYSIS OF DIAGNOSED CASES

R. Patel¹², A. Patel³, M. Singh¹², M.D. Dao¹², B. Hussain¹², K. George¹²
1. Clinical Trial Network, Houston, TX, USA
2. Windsor University School of Medicine, St Kitts, St Kitts and Nevis
3. St George University School of Medicine, Grenada, West Indies

Objectives: To assess the direct relationship of socioeconomic factors among diagnosed cases of CHF To determine the most prevalent etiology of CHF To determine modifiable and non-modifiable risk factors.

Methodology: A retrospective review of data will be collected among patient volunteers (N=13) with Congestive Heart Failure CHF who are managed as out-patient cases on regular annual follow-up. Socioeconomic factors consisting of status of employment, source of income, highest level of education, and ongoing co-morbid health conditions such as hypertension were also collected. Primary or secondary etiology of CHF as well as Modifiable and non-modifiable health factors were also included as variables. In conclusion it was noted that participants consisted demographically of the following minorities such as African American 81 percent, Asian 5 percent, the rest of the 14 percent are Caucasians residing in Harris County, Houston, Texas who are diagnosed with CHF based on chart review. All participants are 65 years old and above, 4 Male and 9 are female, making up the total number of 13. The socioeconomic status was noted to be negligible due to the fact that 85 percent are Medicare beneficiaries while the rest have private Texas state health insurance coverage. All participants have average of greater than 80 percent of concomitant medication and PCP follow up compliance and adherence respectively. The most prevalent etiology is still hypertension and Left ventricular dilatation. Also noted among the modifiable risk factors are the following 50 percent are previous smokers; zero are previously exposed to regular alcohol use, all participants denies use of prohibited substance or drug abuse to include prescription medication abuse.
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COMPARABLE LONG-TERM PROGNOSIS AFTER THE CHANGE FROM ANGIOTENSIN-CONVERTING ENZYME INHIBITOR TO ANGIOTENSIN RECEPTOR BLOCKER IN ACUTE MYOCARDIAL INFARCTION

H.Y. Kim, S.M. Lim, K.Y. Chang, W.S. Chung, K.B. Seung
The Catholic University of Korea, Seoul, Korea

Background: Current guidelines recommend that angiotensin-converting enzyme inhibitor (ACEi) should be used as the first choice for post myocardial infarction (MI) treatment and angiotensin II receptor blocker (ARB) should be considered in patients who are intolerant to ACEi treatment. Although 2 large randomized clinical trials were published on the early 2000s, there have been a little data about head-to-head comparisons at percutaneous coronary intervention (PCI) era.

Methods: We consecutively enrolled acute myocardial infarction (AMI) patients who underwent PCI in the COREA-AMI (CardiOvascular Risk and idEntificAtion of potential high-risk population in AMI) registry including nine major university hospitals throughout South Korea from January 2004 to December 2009. The primary endpoint was the incidence rates of all-cause death and landmark analysis for 1-year post-MI survivors were performed.

Results: Of 4,748 AMI patients, 2,405 and 1,320 patients were treated with ACEi and ARB at discharge, respectively. Among 4,200 patients who were alive at 1 year stably without non-fatal MI or stroke, 799 and 795 patients have continued to take ACEi (Group A) or ARB (Group B), and 798 patients have changed from ACEi to ARB (Group C). Median follow-up duration was 43.8 months (interquartile range 29.8 to 60.5 months). Within the first year, survival in ARB group (45 death, 3.4%) was not different with ACEi group (69 death, 2.9%) (p=0.37). After 1 year from index PCI, all-cause death were 4.3% in group A, 5.8% group B (p=0.06 vs. group A), and 4.9% in group C (p=0.57 vs. group A). Overall findings were consistent in propensity matched population.

Conclusion: 1-year mortality of ARB was similar with ACEi in patients with AMI undergoing PCI. In addition, to switch from ACEi to ARB or to continue taking ARB at 1 year showed comparable long-term survival with ACEi in the stable post-MI 1-year survivors.
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THE EFFECT OF INTRAHEPATIC CHOLESTASIS OF PREGNANCY ON THE
EXPRESSION AND FUNCTIONALITY OF PLACENTAL P-GLYCOPROTEIN IN
MICE: IMPLICATIONS IN THE INDIVIDUALIZED TRANSPLACENTAL DIGOXIN
TREATMENT FOR FETAL HEART FAILURE
C. Wang, Y.M. Hua, Y. Zhang, Y.F. Li, K.Y. Zhou
Department of Pediatric Cardiology, West China Second University Hospital, Sichuan
University, Chengdu, Sichuan, China

Introduction: Placental P-glycoprotein (P-gp) plays a significant role in controlling digoxin transplacental rate. Investigations on P-gp regulation in placenta of women with different pregnant pathology are of great significance to individualized transplacental digoxin treatment for fetal heart failure (FHF). This study aimed to explore the effect of intrahepatic cholestasis of pregnancy (ICP) on the expression and functionality of placental P-gp in mice.

Methods: Pregnant dams in ICP group (n=8) and control group (n=8) received 17a-ethynylestradiol and propylene glycol by subcutaneous injection once daily from E12.5-E16.5, respectively. Maternal plasma ALT, AST, TB, DBIL, IDIL, γ-GT, LDH, ALP and TBA concentrations were detected. HE staining was applied for the observation of liver cells degeneration, necrosis and intrahepatic cholestasis. Placental Abcb1a/Abcb1b/HIF-1α mRNA and P-gp/HIF-1α protein expression were determined by real-time quantitative PCR and western-blot. Maternal plasma and fetal-unit digoxin concentrations were detected by a commercial kit assay.

Results: The ICP group showed higher levels of maternal plasma ALT, AST, TB, DBIL, IDIL, γ-GT, LDH, ALP and TBA concentrations, higher fetal still-birth/abortion rates, lower placental and fetal weights, and typical liver cells degeneration, necrosis and intrahepatic cholestasis. The placental Abcb1a mRNA and P-gp expression of ICP group were significantly increased, while digoxin transplacental rates were significantly decreased. Both placental HIF-1α mRNA and protein expression was significantly elevated in ICP group, and there was a positive correlation between Abcb1a mRNA and HIF-1α mRNA.

Conclusions: ICP could up-regulate placental P-gp expression and functionality in mice, which might be partially associated with higher expression of HIF-1α.
NEW INSIGHTS INTO PATHOGENESIS AND MANAGEMENT OF HEART FAILURE

SODIUM TANSHINONE IIA SULFONATE AND SODIUM DANSHEN SU OPEN THE PLACENTAL BARRIER THROUGH DOWN-REGULATION OF PLACENTAL P-GLYCOPROTEIN IN MICE: IMPLICATIONS IN THE TRANSPLACENTAL DIGOXIN TREATMENT FOR FETAL HEART FAILURE

C. Wang, K.Y. Zhou, Y.F. Li, Y.F. Zhang, Y.M. Hua
Department of Pediatric Cardiovascular Disease, West China Second University Hospital, Sichuan University, Chengdu, Sichuan, China

Introduction: Placental P-glycoprotein (P-gp) plays a significant role in controlling digoxin transplacental rate. Pharmacological manipulations, such as inhibition of placental P-gp would offer the advantage of enhance digoxin availability to the fetus, while minimizing drug exposure of the mother when treating fetal heart failure with digoxin.

Objective: This study aimed to determine whether sodium Tan-IIA sulfonate and sodium danshensu, the main pharmacologically active components of Danshen (a widely used traditional drug during pregnancy), could inhibit placental P-gp expression and functionality or not.

Methods: In total, 80 pregnant C57BL mice were randomly divided intro eight groups, with 10 animals in each group: blank group, vehicle group, three sodium Tan-IIA sulfonate groups (10mg/Kg, 20mg/Kg, 40mg/Kg) and three sodium danshensu groups (10mg/Kg, 20mg/Kg, 40mg/Kg). Pregnant dams in different groups received respective intervention by intraperitoneal (i.p.) injection once daily from E9.5-E15.5. Placental abcb1a/abcb1b mRNA and P-gp protein expression were determined by real-time quantitative PCR and western-blot, respectively. Maternal plasma and fetal-unit digoxin concentrations were detected by a commercial kit assay.

Results: all the placental abcb1b mRNA and P-gp expression of the sodium Tan-IIA sulfonate groups and sodium danshensu groups were significantly lower than that of vehicle group with a dose dependent manner. Compared with the vehicle group, the digoxin transplacental rate was significantly higher than that of all the sodium Tan-IIA sulfonate groups and sodium danshensu groups, while there were no differences in maternal digoxin concentrations among the different groups.

Conclusions: Both the sodium Tan-IIA sulfonate and sodium danshensu could inhibit the placental P-gp expression and its efflux functionality. These findings suggested that danshen might be considered as an adjuvant treatment to enhance drug effectiveness when treating FCHF with digoxin, while minimizing maternal drug poisoning risk.
ASSESSING THE COMPETENCY OF INTERNAL MEDICINE RESIDENTS IN ELECTROCARDIOGRAM INTERPRETATION

A. Kodra, T. Rambhatla, S. Patel, N. Coplan
Lenox Hill Hospital, New York, NY, USA

Aim: To determine if there is an increase in the ability of internal medicine residents to interpret electrocardiograms (ECG) based on level of training, number of previously interpreted ECGs, knowledge of common ECG findings, subspecialty interest and method of training.

Methods & Results: 39 residents were evaluated via a multiple-choice questionnaire on expected ECG findings in several conditions and a quiz on 13 frequently encountered ECGs, each worth 1 point. The average score on the ECG quiz was 5.2 points. Average scores by PGY level were: PGY-1: 5.6; PGY-2: 5.3; PGY-3: 4.7 (P=0.08). The average score on the multiple-choice questionnaire was 5.16 points. Average scores by PGY level were: PGY-1: 5.4; PGY-2: 5.6; PGY-3: 4.5 (P=0.38). Residents who learned to analyze ECGs from a cardiology attending, a fellow and a peer had the highest average scores, 7.0, 5.1 and 6.2 points, respectively. The residents who read <50 ECGs had an average score of 3.0 points and those who had read >300 ECGs had an average score of 6.3 points. Highest average scores (6.5 points) on the multiple-choice questionnaire and ECG quiz were among residents planning to go into Cardiology. Lowest scores were among residents interested in Heme/Onc and Pulmonary/Critical Care, 4.0 and 4.1 points, respectively (P=0.05).

Conclusion: This study echoed deficiencies in ECG interpretation which have important clinical implications. Our data suggest that standardizing training on ECG analysis, among the house staff, from the cardiology department may improve competency and is the next step in our project.
A LARGE MASS OBLITERATING THE RIGHT VENTRICLE: A TUMOR OR A THROMBUS?

S. Patnaik¹, M. Shah², S. Sharm¹, H. Seetha Rammohan³, A. Rubin¹
1. Albert Einstein Medical Center, Philadelphia, PA, USA
2. Lehigh Valley Healthcare Network, Allentown, PA, USA
3. Bassett Healthcare Network, Cooperstown, NY, USA

Introduction: Metastasis to heart is rare, though detected in ~ 9.1% in patients with known malignancies. We discuss a patient with a large cardiac mass, possibly metastatic, obliterating the right ventricle (RV).

Case report: A 69-year-old African-American woman with hypertension, diabetes, chronic kidney disease, presented with one month history of worsening episodic dyspnea, and dizziness. Two months earlier, she was diagnosed with poorly-differentiated pelvic adnexal sarcoma, associated with mature teratoma of left ovary. She underwent bilateral salpingo-oophorectomy, pelvic/paraaortic lymphnode dissection, and omentectomy. Examination revealed tachypnea (23 times/min), and bilateral pitting pedal edema. Laboratory work up was unremarkable. Chest X-ray showed homogeneous right lower lobe opacity, with multiple nodules [Fig 1]. Non-contrast CT-chest confirmed presence of innumerable scattered ground-glass pulmonary nodules, consistent with metastatic disease. Trace pericardial effusion was evident [Fig 2]. Echocardiogram demonstrated echogenic RV mass protruding into dilated right atrium with near-complete obliteration of RV cavity [Fig-3]. Tricuspid valve was not visualized. Left ventricle was normal in size and function. This mass was thought to be metastatic from her known ovarian cancer. Patient was a poor candidate for surgery/chemotherapy, and succumbed to respiratory failure.

Discussion: Non-invasive evaluation of cardiac masses include echocardiogram, cardiac CT, and MRI. Echocardiogram shows anatomical location, extent and physiological consequences of intracardiac mass by dynamic assessment during the cardiac cycle. Intracardiac mass needs to be distinguished from thrombus, which is more common. Absence of stalk, enlarged atrial chamber, low cardiac output stasis, response to thrombolytic therapy, and avascularity on contrast echocardiography favor thrombus. A giant organized thrombus can clinically mimic tumor due to immobility, close location near the wall, and poor response to thrombolysis. In difficult situations, MRI with Gadolinium is useful. Cardiac CT or MRI helps in precise anatomical delineation, characterization, and pre-operative planning of large cardiac mass. For guided biopsy of right-sided lesions, transesophageal echocardiography is preferred modality.
ASSESSMENT THE ROLE OF CORONARY CLEARANCE FRAME COUNT IN PATIENTS WITH CARDIAC SYNDROME X

E. Yildirim, U.C. Yuksel, B. Bugan, M. Celik, M. Koklu, S. Gormel, H.K. Kabul, C. Barcin

1. Gulhane Military Medical Academy, Department of Cardiology, Ankara, Turkey
2. Girne Military Hospital, Cardiology Service, Girne, North Cyprus

Background: Cardiac Syndrome X (CSX) is describing patients with typical angina pectoris with a positive stress test and normal coronary arteries on angiography. There is no simple diagnostic modality to evaluate the coronary microcirculation. Coronary clearance frame count (CCFC) is reported to be a good predictor of myocardial reperfusion achieved following primary angioplasty.

Objectives: The aim of this study was to assess the role of CCFC in patients with CSX.

Methods: Our study has a retrospective design and conducted on data acquired from a single-center. 47 patients with angina, a positive nuclear imaging test and normal coronary angiography, included to our study. The control group consisted of 47 patients who underwent angiogram for excluding coronary artery disease due to arrhythmias. CCFC was defined as the number of angiographic frames elapsed from the first frame in which the contrast medium is seen to be cleared from the ostium of the examined artery to that in which the contrast begins to be cleared from the same distal artery landmark proposed by the TIMI Group.

Results: Baseline characteristics including age, sex, and cardiovascular risk factors were similar in 2 groups. No significant differences were found between the two groups with regard to TFC-LAD, TFC-CFX and TFC-RCA. CCFC-LAD (47.10±7.84 vs 38.32±6.61), CCFC-CFX (45.54±8.58 vs 34.87±5.63) and CCFC-RCA (44.68±10.56 vs 30.99±6.04) were significantly different between two groups (p=0.001).

Conclusion: Our study demonstrated a delay in CCFC in patients with CSX. CCFC is a simple, quantitative and highly reproducible method and can be used as a marker of microvascular dysfunction in patients with CSX.
MULTI-CHAMBER CARDIAC EMBOLUS DETECTED WITH MULTI-MODAL IMAGING

V. Tavakoli, R. Grodman, J. Nfonoyim, A.R. Chaudery, V. Pandian
Richmond University Medical Center, New York, NY, USA

Massive pulmonary embolism with evidence of right atrial or ventricular thrombus is a rare phenomenon, especially, when presented in two chambers of the heart. We present a 63 year old female complaining of left leg swelling, leg pain and shortness of breath for the prior two days. Past medical history included hypertension, and recently diagnosed squamous cell cervical cancer. At the time of admission heart rate was 135/min, respiratory rate was 22/min, saturation was 87% on room air and blood pressure was 125/82 mmHg. Initial EKG showed sinus tachycardia. Portable chest x-ray did not show any acute cardio-pulmonary changes. In view of the history of cancer, leg pain and shortness of breath, pulmonary embolism was considered as a possible diagnosis. Pulmonary embolism protocol chest CT with contrast was, subsequently, performed and showed extensive bilateral pulmonary emboli as well as unexpected right ventricle and right atrium thrombosis. Vascular ultrasound of lower extremities showed acute deep venous thrombosis in left common femoral, superficial femoral, popliteal, and tibioperoneal veins. Stat echocardiography was performed before the CT results were reported and showed estimated LV ejection fraction of 60%. Mobile masses consistent with thrombosis were seen within the right ventricle and right atrium. Right ventricle was enlarged and hypokinetic. No LV wall motion abnormality was detected. Doppler suggested mild tricuspid regurgitation. Right ventricle systolic pressure was 60 mm Hg. Treatment was initiated using heparin infusion and emergent cardiac surgery consultation was placed immediately. During the cardiac surgery, the thrombi were, successfully, removed from the right atrium and right ventricle. No complication was observed in the post-operation period, vital signs remained stable and echocardiography showed clearing the cardiac chambers. The patient was discharged on full dose anticoagulation (Coumadin) to complete her cancer treatment per oncology.
CARDIOVASCULAR DISEASE IS ASSOCIATED WITH AN INCREASED RISK OF FRAILTY IN ELDERLY RESIDENTS OF A LONG-TERM CARE FACILITY

C.J. Hsieh¹, N.F. Miao²
1. National Taipei University of Nursing and Health Sciences, Taipei, Taiwan
2. Taipei Medical University, Taipei, Taiwan

Background: Due to the aging and increasingly complex nature of our patients, frailty has become a high-priority theme in cardiovascular medicine. The risk of frailty in older residents with cardiovascular disease (CVD) are unknown.

Objective: To investigate the association of different risk of frailty in elderly residents with CVD in the long-term care facility.

Methods: With a retrospective cohort design, Residents aged 65 years and older were selected. Physical functions, nutritional status, cognitive function and depressive mood were assessed using standardized evaluations. Frailty was defined using the Fried phenotype, including weight loss, grip strength, exhaustion, slowness and low physical activity. Multivariate logistic regression models were applied to assess the association of each outcome variables or scores with frailty.

Results: 164 elderly residents (median age 84.0, IQR 75.0-89.5 years), of whom 74 with CVD. 81 (49.4%) were frail. Of the frail elders, 62.2% had coexisting CVD compared with 38.9% of the non-frail. Frailty was associated with physical functions (r=-.733; p<0.001), nutritional status(r=-.692; p<0.001), cognitive function (r=-.591; p<0.001) and depressive mood (r=.668; p<0.001). Compared with non-frail, those with frailty had a lower odd of cognitive function, low IADL, and CVD (OR 5.099, 95% CI 1.208 to 21.522).

Conclusions: CVD is an independent frailty risk factor among elderly residents. As we are faced with an increased number of elderly residents with CVD and frailty, frailty assessment can help in risk stratification and decision-making, thereby improving outcomes, and preventing unnecessary harm in the most frail.
PSEUDOHYPONATREMIA CAUSED BY LIPOPROTEIN X IN OBSTRUCTIVE BILIARY CHOLESTASIS SECONDARY TO Pancreatic CANCER

K. Anouti, J. Clark, M. Maalouf, E. Gnall, T. Phiambolis, T. Shapiro
Lankenau Medical Center, Wynnewood, PA, USA

Background: Lipoprotein X (LP-X) is an abnormal lipoprotein that is frequently found in liver disease and regarded as the most sensitive and specific biochemical marker for the diagnosis of intra- and extrahepatic cholestasis. In cholestasis, bile lipoprotein, a precursor of LP-X, refluxes into the plasma and binds to albumin to form LP-X. LP-X contributes to the development of hypercholesterolemia in obstructive jaundice secondary to a failure of feedback inhibition. The presence of very high levels of LP-X has been shown to be a rare cause of pseudohyponatremia.

Case Presentation: We report the case of a 71 year old male who presented to the hospital with 2 weeks duration of abdominal pain and jaundice. CT scan of the abdomen revealed a pancreatic head tumor with diffuse biliary and ductal dilatation. Initial blood work revealed severe hyponatremia (118 mmol/L; normal range: 135-145 mmol/L), marked elevation in liver enzymes with a total bilirubin of 25.4 mg/dl, AST of 1138 U/L, and ALT of 787 U/L. He was ultimately found to have a total serum cholesterol level of 1157 mg/dL (normal range: 120-199 mg/dL) — secondary to accumulation of lipoprotein-X—causing pseudohyponatremia. The diagnosis was confirmed by measurement of serum osmolality (292 mOsm/kg H2O; normal range: 270-300 mOsm/kg H2O) and serum sodium by direct potentiometry (140 mmol/L). Following biliary stent placement and relief of the obstruction, the patient’s lipid levels markedly improved. His sodium levels also normalized as measured by indirect potentiometry.

Conclusion: This case demonstrates that extreme hypercholesterolemia from elevation of lipoprotein-X particles in cholestasis can be a rare cause of pseudohyponatremia. It highlights the importance of measuring serum sodium with direct potentiometry in the setting of extreme hypercholesterolemia prior to initiating treatment. Assays that utilize direct ion-selective electrodes are not affected by the interference of high concentrations of lipids and thus are useful in situations where such interference is suspected.
MISCELLANEOUS

156 CARDIAC TUBERCULOMA PRESENTING AS THROMBOTIC THROMBOCYTOPENIC PURPURA-HEMOLYTIC UREMIC SYNDROME

E.A. Christian, R.M. Mehta, R.N. Khouzam
University of Tennessee Health Sciences Center, Memphis, TN, USA

Objective: To review a rare case of Thrombotic Thrombocytopenic Purpura-Hemolytic Uremic Syndrome (TTP-HUS) as a sequela of tuberculosis; complicated by tuberculous endocarditis.

Background: Herein we discuss the case of a 25-year-old female who presented with complaints of confusion, fevers, night sweats, weight loss, as well as blurred vision over the course of 2 months. Of note, her father was diagnosed with active tuberculosis when the patient was 6 years old, and her own past medical history was significant for a pericardial effusion at age 9.

Method and Results: Laboratory studies were notable for pancytopenia with schistocytes, elevated lactate dehydrogenase, and an elevated serum creatinine level consistent with TTP-HUS. She subsequently underwent a 10 day course of plasmapheresis. In spite of these efforts, she had minimal clinical improvement and persistent fever. In the course of her work up, she had an echocardiogram which revealed a left atrial mass measuring in centimeters (cm) 7.0 cm x 2.8 cm x 2.6 cm. Given the patient’s history, imaging, and histopathology of the resected mass, she was treated for tuberculous endocarditis which resulted in complete clinical resolution of her symptoms.

Conclusion: TTP-HUS is a rare sequela of infective endocarditis. Even more uncommon are tuberculomas associated with tuberculosis; which are typically seen in the central nervous system of immunocompromised individuals. However, in this rare case, we encountered an immunocompetent patient who initially presented with a diagnosis of TTP-HUS, only later to unearth a large left atrial mass found to be consistent with tuberculous endocarditis.

Transthoracic echocardiogram in the parasternal long axis view demonstrating the tuberculoma in the left atrium (upward arrow).
A CASE REPORT OF CELIAC GANGLION BLOCK IN POSTURAL ORTHOSTATIC TACHYCARDIA SYNDROME

H.Y. Mistry, S.E. Hamid, A. Suleman
The Heartbeat Clinic, McKinney, Texas, USA

Background: POTS is a dysautonomia characterized by palpitations, dizziness, chest pain, dyspnea, and syncope. Median Arcuate Ligament Syndrome (MALS) is external compression of the celiac artery and possibly the celiac ganglia by median arcuate ligament. We have previously reported that 18 out of 98 POTS patients screened randomly had MALS. The response rate to laparoscopic correction of MALS is about 60%.

Objective: A case report on patients with both MALS and POTS to analyze causes and approaches to treatment.

Methods: An 18 year old male patient with POTS symptoms including chronic nausea. POTS was confirmed with tilt table testing (55bpm increase in HR at 6 min). POTS symptoms improved with Clonidine patch, Albumin/IV fluids. The patient continued to suffer from chronic nausea. Celiac artery doppler was performed to check the celiac artery velocity. Results showed high on inspiration (309 cm/sec), neutral position (450 cm/sec) and expiration (451 cm/sec). CT angiogram of abdomen showed high grade, >90% stenosis at celiac axis origin; the patient was diagnosed with MALS. He underwent laparoscopic decompression of celiac artery which showed improvement all of the patient’s symptoms. The frequency of the patient’s nausea decreased from twice a week before surgery to 4 times in 3 months after surgery. Five months post-op, he again started having nausea and early satiety. On repeating celiac artery doppler, results were high on expiration (455 cm/sec). CT angiogram of the abdomen showed >70% recurrent stenosis.

Results: The patient underwent celiac ganglion block and showed extreme improvement with nausea. Celiac doppler after ganglion block showed a velocity of 258 cm/sec on expiration.

Conclusion: Our study strongly suggests that there is an association between MALS and POTS. The improvement noted in the patient’s symptoms following celiac ganglion block can help guide alternative treatment options to redo MALS surgery.
Large Hepatic Cyst and Patent Foramen Ovale: Unusual Combination Producing Platypnea-Orthodeoxia Syndrome

B.A. Foreman¹, J Hansen²

1. Penn State Hershey Medical Center/College of Medicine, Hershey, PA, USA
2. Penn State Hershey Heart and Vascular Institute, Hershey, PA, USA

Platypnea-orthodeoxia syndrome (POS) is an infrequently encountered cause of dyspnea that is accompanied by arterial desaturations in the upright position, relieved by lying supine. Two unrelated conditions must co-exist to produce POS, most commonly a previously clinically silent patent foramen ovale (PFO). A second component, usually occurring later in life, contributes to right-to-left shunting via the inter-atrial connection, such as liver cirrhosis, pulmonary embolism, or tortuous aorta.

68-year-old-man presented with progressive dyspnea over six months. He was hypoxic with large A-a gradient: PaO2 42 mmHg with SaO2 82% on room air, no improvement with supplemental oxygen. Dyspnea occurred when standing up, accompanied by documented hypoxia, both resolving immediately with recumbency. CT chest ruled out pulmonary embolism but showed multiple large hepatic cysts causing mass effect on right atrium. Transesophageal echocardiography showed compressed right atrium and right-to-left shunt across PFO, increasing with Valsalva. Attempt at percutaneous PFO closure was unsuccessful. Percutaneous drainage of the largest hepatic cyst resulted in immediate improvement in oxygen saturation and symptoms. POS is an uncommon cause of dyspnea that requires a high index of suspicion to recognize. As symptoms occur opposite to those seen with heart failure and other cardiopulmonary conditions, patients with POS can be a medical mystery. Thorough history and exam is crucial, paying particular attention to postural changes in symptoms. Although the anatomic component is present from birth, patients typically present with POS later in life, with symptoms correlating to another cardiac or extracardiac event increasing the degree of shunting. A large hepatic cyst compressing the right atrium, accentuating right-to-left flow across the PFO, leading to platypnea and orthodeoxia is unique, with only one previous case documented.

Our case demonstrates resolution of symptoms with percutaneous drainage of liver cyst, whereas typical definitive treatment is PFO closure.
USE OF HIGH FREQUENCY PERCUSSIVE VENTILATOR AS BRIDGE TO ORGAN PROCUREMENT: LIFE GOES ON
F. Benn, A. Ashwad, I. Gulkarov, B. Fahoum, F. Khusid, M. Majumder
New York Methodist Hospital, Brooklyn NY USA

An estimated 121,000 individuals are awaiting organ transplant while there are 13,700 listed donors. Brain death donors make up the overwhelming majority of the donor pool because of the relatively preserved oxygenation. We illustrate the role of high-frequency percussive ventilation (HFPV) - volumetric diffusion respirator (VDR) as bridge to procurement for hypoxemic respiratory failure donors who have failed traditional ventilator.

A 34-year-old female was brought to our emergency department after she sustained traumatic head injury from a motor vehicle accident. She was unconscious with a Glasgow scale of 3 and saturation was 80% on 100% fraction inspired oxygen delivered by facemask. Computer tomography showed cerebral edema with midline shift and multiple skull base fractures. Her oxygenation continued to decline and her trachea was subsequently intubated and mechanically ventilated. Decompressive hemicraniotomy was performed however her neurological exam was consistent with brain death. There was worsening hypoxia and in concern for ongoing hypoxia on traditional ventilator, she was tried on VDR and in the first hour, her partial pressure of oxygen increased from 56mmhg and then to 418 mm Hg within the two hours allowing for successfully procurement.

The application of HFPV- VDR in this patient resulted in sustained but non-invasive improvement in oxygenation that could not be achieved with traditional ventilator. We were able to successfully procure two donor kidneys and transplanted to two different individuals who continue to do well. We therefore propose that using VDR in selected cases such as this can help increase the donor pool.
ASTHMA AS A RISK FACTOR OF HUMAN AND EXPERIMENTAL ABDOMINAL AORTIC ANEURYSM
C-L. Liu,1 H. Wemmelund,2 J.S. Lindholt,3 A. Daugherty,4 B.D. Levy,1 P. Libby,1 G-P. Shi1
1. Department of Medicine, Brigham and Women’s Hospital and Harvard Medical School, Boston, MA, USA
2. Department of Vascular Surgery, Viborg Regional Hospital, Viborg, Denmark
3. Elitary Research Centre of Individualized Medicine of Arterial Disease, Department of Cardiothoracic and Vascular Surgery, Odense University Hospital, Odense, Denmark
4. Saha Cardiovascular Research Center, University of Kentucky, Lexington, KY, USA

Objective: Asthma and abdominal aortic aneurysms (AAA) both involve inflammation. It remains unknown whether these diseases interact.

Approach and Results: Databases analysis from a population-based nationwide case-control study and the population-based randomized Viborg vascular screening trial demonstrated that asthma diagnosed less than one year or six months before the index date increased the risk of AAA rupture before (odds ratio OR=1.60, 2.12) and after (OR=1.51, 2.06) adjusting for AAA comorbidities. Use of bronchodilators elevated the risk of AAA rupture from ever use to within 90 days from the index date, before (OR=1.10~1.37) and after (OR=1.10~1.31) adjustment. Patients prescribed anti-asthma drugs also showed an increased risk of rupture before (OR=1.12~1.79) and after (OR=1.09~1.48) the same adjustment. Anti-asthmatic medication use associated with increased risk of AAA before (OR=1.45) or after adjustment for smoking (OR=1.45) or other risk factors (OR=1.46). In experimental mice, simultaneous production of asthma and AAA doubled abdominal aortic diameter and increased macrophage and mast cell content, arterial media smooth muscle cell (SMC) loss, cell proliferation, and angiogenesis in AAA lesions. Asthma also increased plasma IgE, reduced plasma IL5, and increased bronchioalveolar total inflammatory cell and eosinophil accumulation. Intraperitoneal administration of an anti-IgE antibody suppressed AAA lesion formation and reduced lesion inflammation, plasma IgE, and bronchioalveolar inflammation. Pre-establishment of asthma also increased AAA lesion size and lesion accumulation of macrophage, mast cell, and media SMC loss, increased plasma IgE, reduced plasma IL5, IL13, and TGF-β, and increased bronchioalveolar inflammation. Consequent production of asthma also doubled lesion size of pre-established AAA and increased lesion mast cell and T cell accumulation, media SMC loss, lesion cell proliferation and apoptosis, plasma IgE, and bronchioalveolar inflammation.

Conclusion: Recent active asthma increased risk of AAA and AAA-rupture. Airway allergic disease may have a pathological link with AAA. Production of one disease may aggravate the development and progression of the other.
Background and Objectives: Abdominal aortic aneurysm (AAA) is a degenerative disease of the aorta that mainly affects elderly population over the age of 65. Nowadays the pathways involved in its onset and progression remain unknown and angiotensin-II (Ang-II) has been widely implicated. Therefore, the potential link between CXCR6/CXCL16 axis in AAA was investigated.

Methods and Results: Apolipoprotein E-deficient mice (apoE-/-) were subjected or not to a high-fat diet and infused with Ang-II (500 ng/kg/min) for 28 days. Some of the animals were daily treated with losartan at 10 or 30 mg/kg/day. Flow cytometry and immunofluorescence were used to determine CXCL16 expression on human umbilical vein or artery endothelial cells (HUVEC and HUAEC, respectively). Parallel-plate flow chamber assay was employed to evaluate leukocyte adhesion to Ang-II (1 microM)-stimulated human endothelium. Mice subjected to a high-fat diet and infused with Ang-II showed higher incidence of AAA, increased macrophage, CD3+ lymphocyte and CXCR6+ cell infiltration and enhanced neovascularization than unchallenged animals. These effects were accompanied by increased MCP-1/CCL2, CXCL16, CXCR6 and VEGF mRNA expression within the lesion. These events were reduced when losartan was administered at 30 but not at 10 mg/kg/day. When HUVEC and HUAEC were stimulated with 1 microM Ang-II (24h), a significant increase in CXCL16 expression was detected by flow cytometry and immunofluorescence. However, neutralization of CXCL16 activity only significantly inhibited Ang-II-induced mononuclear leukocyte-HUAEC interaction by 49% without affecting their interaction with HUVEC. Ang-II-induced CXCL16 expression was found to be dependent on Nox5 expression and subsequent RhoA/p38-MAPK/NFkB activation.

Conclusion: These results suggest that the CXCR6/CXCL16 axis could constitute a new therapeutic strategy in the treatment of cardiovascular diseases associated with activation of the renin-angiotensin system (RAS).
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THE CENTRAL ROLE OF SMOOTH MUSCLE CELL MITOCHONDRIA IN THE PREVENTION OF ABDOMINAL AORTIC ANEURYSM BY LOW LEVEL LASER THERAPY

L. Gavish, R. Beeri, D. Gilon, C. Rubinstein, Y. Berlatzky, S.D. Gertz
Institute of Medical Research (IMRIC), Faculty of Medicine, The Hebrew University of Jerusalem and Hadassah University Hospital, Jerusalem, Israel

We showed, by high frequency ultrasound, that phototherapy with low-level laser (LLL), a non-thermal, near-infrared radiation, used widely for reduction of pain and acceleration of wound healing, prevents de novo formation and progression of pre-existing abdominal aortic aneurysm (AAA) in the angiotensin-II-(Ang-II)-infused apolipoprotein e-deficient (Apo-E−/−) mouse model. Correlative histomorphometric and immunohistochemical studies have shown that the protective effect of LLL in this mouse model is associated with modification of the inflammatory response and enhancement of smooth muscle cell (SMC)-driven extracellular matrix reinforcement of transmedial defects in the aortic wall, that occur near side branches, and that subtend the aneurysmal expansion. In addition, LLL was found to stimulate mitochondrial membrane potential (mitMP), suppress the expression of the pro-inflammatory cytokine, IL-1-beta, and disperse subnuclear promyelocytic leukemia protein, a cell-cycle checkpoint protein, in HaCaT human keratinocytes. In recent studies by others, Ang-II was shown to cause decay in SMC mitMP followed by reduction in generation of ATP that is of critical importance for matrix synthesis. In this presentation we will review the nature and circumstances contributory to vulnerability of SMC mitochondria and the impact of such alterations on vascular wall integrity and function. We also will present the results of our studies designed to determine whether LLL prevents Ang-II-induced suppression of SMC mitMP, whether this mechanism underlies the inhibitory effect of LLL on progression of AAA in the Apo-E−/− mouse model, and the potential relevance of these findings for targeting mechanisms of aneurysm progression in the human interventional setting.
WHAT IS THE PROGRESS WITH TREATMENTS FOR SMALL ABDOMINAL AORTIC ANEURYSMS?

J. Golledge
James Cook University and The Townsville Hospital, Townsville, Queensland, Australia

Previous trials suggest that surgical management of small abdominal aortic aneurysms (AAA; i.e. those measuring <55mm in maximum diameter) does not reduce mortality. Up to 70% of small AAAs managed conservatively continue to grow once identified and eventually require surgical treatment. Currently there are no recognised non-interventional treatments which have been shown to effectively limit AAA growth. A large number of studies have now been performed in rodent models to identify pathways which appear important in AAA pathogenesis, in particular those involved in inflammation, extracellular matrix remodelling and vascular smooth muscle cell phenotype. Translating these findings into safe and effective drugs for patients is however not proving straightforward. Some of the challenges of clinical trials designed to identify treatments for small AAAs include the small change in AAA size over follow-up, the loss of patients to surgical intervention and the frequent presence of co-morbidities in AAA patients. Recently two moderately-sized clinical trials have reported negative results illustrating some of these challenges. A further group of trials are currently on-going and expected to report over the next 1-5 years. It is hoped that these studies will identify new and safe treatment options for small AAAs.
Whole Exome Sequence for Thoracic Aortic Aneurysms

Aortic Institute at Yale-New Haven, and Department of Genetics, Yale University School of Medicine, New Haven, CT, USA

Background: Hereditary factors play an important etiologic role in thoracic aortic aneurysm and dissection (TAAD), with a number of genes proven to predispose to this condition. We initiated a clinical program for routine genetic testing of individuals for TAAD by whole exome sequencing (WES). Here we present our initial results.

Methods: The WES was performed in 102 patients (mean age 56.8 years; range 13 to 83; 70 males [68.6%]) with TAAD. The following 21-gene panel was tested by WES: ACTA2, ADAMTS10, COL1A1, COL1A2, COL3A1, COL5A1, COL5A2, ELN, FBLN4, FLNA, FBN1, FBN2, MYH11, MYLK, NOTCH1, PRKG1, SLC2A10, SMAD3, TGFBR1, TGFBR2, TGFBR3.

Results: Seventy-four patients (72.5%) had no medically important genetic alterations. Four patients (3.9%) had a deleterious mutation identified in the FBN1, COL5A1, MYLK, and FLNA genes. Twenty-two (21.6%) previously unreported suspicious variants of unknown significance were identified in 1 or more of the following genes: FBN1 (n = 5); MYH11 (n = 4); ACTA2 (n = 2); COL1A1 (n = 2); TGFBR1 (n = 2); COL3A1 (n = 1); COL5A1 (n = 1); COL5A2 (n = 1); FLNA (n = 1); NOTCH1 (n = 1); PRKG1 (n = 1); and TGFBR3 (n = 1). Identified mutations had implications for clinical management.

Conclusions: Routine genetic screening of patients with TAAD provides information that enables genetically personalized care and permits identification of novel mutations responsible for aortic pathology. Analysis of large data sets of variants of unknown significance that include associated clinical features will help define the mutational spectrum of known genes underlying this phenotype and potential identify new candidate loci.
Venous disease is a common but overlooked problem and is an important mortality and morbidity factor depending on the effected vascular territory. Both in literature and clinical practise the term chronic venous insufficiency describes a condition that affects the venous system of the lower extremities with venous hypertension and dilatation. Since varicocele or pelvic congestion syndrome is an example of chronic venous insufficiency theoretically, it is preferable to use “Dilating Venous Disease” as a general term and peripheral varicose vein or peripheral venous insufficiency, instead of chronic venous insufficiency. Vascular dilatations show a diverse clinical spectrum as in obstructive counterpart depending on the regional circulation with different clinical manifestations, and different prevalence. Coronary artery ecatsia, intracranial aneurysms, aortic aneurysms and popliteal artery aneurysms are the main vascular dilatations contributing the arterial side of vascular system, throughout the body. However clinical manifestation of dilating venous disease usually occurs in the lower part of the body, in another word, lower part of the circulatory system regarding the heart in the center. Peripheral varices of lower extremities, hemorrhoids, varicoceles, pelvic varicose veins are the vasculapathy of veins running toward heart but against gravity. Varicose remodelling of veins occure by a compex interplay of various factors including both physical forces and extracellular matrix remodelling mechanisms.
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MANAGEMENT OF VENOUS THROMBOEMBOLISM

T. Tomaru¹, T. Matsubara², E. Matsubara², S. Kodera²
1. Toho University Sakura Hospital, Sakura, Japan
2. Tokyo University Hospital, Japan

We evaluated clinical profiles of patients with deep venous thrombosis (DVT) and usefulness of anticoagulant therapy for treatment of DVT. 181 patients with symptomatic DVT and 102 with asymptomatic DVT were studied. In symptomatic DVT, 42 patients had PE and 3 of them died of PE. However, 17 died of other diseases including cancer. In asymptomatic DVT, 1 patient died of PE and 12 died of other diseases. And the patients with DVT underwent anticoagulant therapy were also evaluated. The treated patients with DVT was divided into thigh DVT (TDVT: from common iliac to popliteal vein) and calf DVT (CDVT: soleus, tibial) group. The 56 patients with TDVT and 55 with CDVT were studied. Administration of heparin followed by warfarin or oral warfarin administration was performed in the patients of warfarin group. In 9 patients, novel oral anticoagulant (NOAC) was administered. In NOAC group, 4 had TDVT, and 6 had CDVT. Venous thrombus disappeared or decreased in size in 5 patients (83.3 %) with CDVT and 3 (75 %) patients with TDVT. In warfarin group venous thrombus disappeared in 30 patients (57.7 %) with CDVT and 12 patients (24.4 %) with TDVT. In 3 patients with thrombus of mixed with green color by ultrasonic elastography, thrombus disappeared or decreased in size, however it did not change in 3 with thrombus of blue color. In patients with DVT, warfarin therapy is useful for acute thrombosis in patients with elevated D-dimer, however, chronic thrombus appeared to be resistant to anticoagulant therapy. Thigh DVT was more resistant to anticoagulant therapy than calf DVT. Poor prognosis of patients with DVT does not appear to be dependent on PE.
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DRUG ELUTING BALLOONS IN CORONARY AND PERIPHERAL INTERVENTIONS

A. Kumar¹, V. Mohan², N. Mohan³

1. Ashok Hospital, Amritsar, Punjab, India
2. Ivy Hospital, Amritsar, Punjab, India
3. Amritsar, Punjab, India

Rationale for development of Drug Eluting Balloons (DEB) derives mainly from the limitations of Drug Eluting Stents (DES). Nonstent-based local drug delivery using DEB maintains the antiproliferative properties of DES, but without its limitations. DEB may be used in torturous vessels, small vessels, long diffuse calcified lesions, or when scaffolding obstructs major side branches or in bifurcated lesions. Advantages of DEB include homogenous drug transfer to the vessel wall, rapid release of high concentrations of the drug sustained in the vessel wall no longer than a week, with little impact on long-term healing. Absence of stent avoids overdependence on antiplatelets. However DEB use is limited by acute recoil seen in postballoon angioplasty and variability of pharmacokinetics and control of dosing. Elements of DEB consists of Balloon, Antiproliferative agent and Excipient. Paclitaxel drug is primarily used due to its high lipophilic property and ability to remain in the vessel wall for nearly a week and inhibits cell division and migration. Concentration of paclitaxel on DEB is about three times higher. This is because only about 10 to 20% of the paclitaxel is transferred from the balloon surface to the vessel wall. 10% of the dose is lost during transfer through guiding catheter while 70-80% drug released at the target site is washed away in the blood stream during inflation. Excipient is a hydrophilic spacer and controls drug release rate. Iopromide, Urea, Butyry trihexyl citrate (BTHC) etc are commonly used excipients. Current guidelines recommend use of DEB for treatment of intra-stent restenosis of BMS or DES (class I,B). DEB have shown to have significantly lower rate of restenosis as compared to uncoated balloons in various DEB trials.
From balloons to stents to bypass surgery, the number of tools and differing approaches to PAD intervention are truly a myriad of philosophies, devices, and varying costs. The road to FDA approval, the burden of proof of effectiveness and safety, is relatively easy in this field compared to other arenas with the standard being balloon angioplasty, a generally accepted inferior treatment for most patients. There is a dearth of multicenter prospective trials for emerging or even current “established” interventions. Many if not most physicians do not have an idea of the cost effectiveness of the various interventions. Many health care centers similarly do not have a handle or even an influence on the tools used. Not knowing which device, tool, method, or therapy is best for SFA, iliac or below the knee interventions and which, if any, are simply too inferior to ever use, is still unknown. This lack of data suggests the latter are still being used, possibly more often than we would like to know.

The best tool for peripheral vascular interventions is………. 
NOVEL REGULATION OF VASCULAR CALCIFICATION

Y. Chen
University of Alabama at Birmingham, Birmingham, AL, USA

Vascular calcification is prevalent in patients with atherosclerosis, diabetes mellitus and end stage renal disease, which increases risk of cardiovascular events and mortality. We and others have shown increased vascular calcification in diabetic patients and animal models of diabetes. We have furthered demonstrated that increased vascular calcification was associated with elevated protein O-linked GlcNAc modification (O-GlcNAcylation) in human diabetic arteries, and in low-dose streptozotocin (STZ)-induced and Akita mutant diabetic mice. As protein O-GlcNAcylation is dynamically regulated by two enzymes, O-GlcNAc transferase (OGT) that adds O-GlcNAc onto proteins and O-GlcNAcase (OGA) that removes O-GlcNAc, we determined the effects of inhibition of OGA and OGT on vascular calcification in vascular smooth muscle cells (VSMC) in vitro and diabetic mice in vivo. Inhibition of OGA, either by a pharmacological inhibitor, Thiamet-G, or shRNA increased O-GlcNAcylation and promoted VSMC calcification. Consistently, administration of Thiamet-G to STZ-induced diabetic mice increased aortic O-GlcNAcylation and accelerated vascular calcification. In contrast, knockdown of OGT by shRNA inhibited VSMC calcification. Using a novel SMC-specific OGT deletion mice, we demonstrated that SMC-specific OGT deletion did not affect blood glucose, but significantly inhibited protein O-GlcNAcylation exclusively in SMC and inhibited vascular calcification in STZ-induced diabetic mice. At the molecular level, we found increased O-GlcNAcylation induced activation of AKT, an important upstream signal that upregulates the key osteogenic factor Runx2; which was significantly inhibited by OGT deletion. Mechanistic studies identified two new O-GlcNAcylation sites on AKT, at T430 and T479, were critical for AKT activation, Runx2 upregulation and VSMC calcification. In summary, we have demonstrated a crucial role for vascular O-GlcNAcylation in regulating diabetic vascular calcification, and identified a new mechanism of AKT O-GlcNAcylation in promoting Runx2 upregulation and VSMC calcification. Our studies have uncovered novel mechanisms linking glucose metabolism to vascular dysfunction and revealed therapeutic targets for diabetic vascular calcification.
We previously observed that the level of cholesterol and glycosphingolipids (GSL) rise and fall in tandem upon plasma exchange therapy in patients with LDL receptor negative homozygous familial hypercholesterolemia. Hence we rationalized that inhibiting GSL synthesis may be a novel approach to mitigate atherosclerosis. Feeding a high fat and cholesterol diet to apoE-/- mice and normal rabbits markedly increased atherosclerosis. Treatment with a GSL synthesis inhibitor, D-PDMP prevented atherosclerosis. Encapsulation of the GSL inhibitor within a bio-degradable polymer increased the efficacy ~10 fold due to rapid gastrointestinal absorption and slow release in mice tissues. Treatment markedly reduced arterial wall stiffness and thickness, and cardiac hypertrophy. The level of oxidized LDL, LDL, GSL and triglycerides decreased in a drug dose-dependent manner. Whereas, the level of HDL increased. Treatment also increased the expression of genes implicated in bile acid synthesis, cholesterol absorption cholesterol efflux, LDL, HDL and VLDL metabolism. Treatment also improved fractional shortening, decreased left ventricular mass and the expression of genes implicated in cardiac hypertrophy.

These findings establish that inhibiting GSL synthesis to mitigate atherosclerosis provides a novel and an alternative approach to prevent and interfere with atherosclerosis. Also biopolymer encapsulation of D-PDMP provides a superior mode of delivery compared to un-conjugated D-PDMP.

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GLYCOSAMINOGLYCANS (GAGS) IN CARDIOVASCULAR DISEASE: SEARCHING FOR THE SWEET SPOT

A. Lucas

Divisions of Cardiovascular Medicine and Rheumatology, University of Florida, Gainesville, FL, USA

The endothelial glycocalyx alters immune reactions. Among other functions, glycosaminoglycans (GAGs) in the glycocalyx bind chemokines that attract immune cell invasion. Modifying donor graft sugars can reduce complement mediated xenotransplant rejection form swine to primate. In prior work we investigated the effects of conditional deficiency of the primary heparin sulfate modifying enzyme (N-deacetylase-N-sulfotransferase-1, Ndst1<sup>-/-</sup>) in donor artery allografts demonstrated reduced vascular inflammation and plaque. We have extended this work, examining acute immune rejection in donor renal allograft transplants in Ndst1<sup>-/-</sup> mice (C57Bl/6 background), after implant into BALB/c mice with normal Ndst1 expression (Ndst1<sup>+/+</sup>). Rejection was assessed in saline treated wild type C57Bl/6 and Ndst1<sup>-/-</sup> donor allografts, with comparison to treatment with M-T7, a chemokine inhibitor that blocks chemokine/GAG interaction. Ndst1<sup>-/-</sup> donor organs treated with only saline had significantly reduced acute rejection when compared to C57Bl/6 donor organs given saline treatments. Saline treated Ndst1<sup>-/-</sup> donors had equal reductions in acute rejection when compared to M-T7 treated C57Bl/6 donors. Analysis of heparan (HS) and chondroitin sulfate (CS) disaccharide content demonstrated significant correlations with suppressed rejection. M-T7 and M-T7 point mutations were then assessed and found to have variable efficacy in reducing acute renal allograft rejection in treatment of WT and Ndst1<sup>-/-</sup> donor allografts. M-T7, E<sup>209</sup>I and M-T R<sup>171</sup>E retained anti-rejection activity while R<sup>134</sup>D was inactive. Analysis of HS GAG and disaccharide extracts again demonstrated significant correlation between altered whole organ GAG content and capacity to reduce allograft rejection. CD3+ T cell invasion in transplanted kidneys and T<sub>H</sub>17 splenocytes were reduced in Ndst1<sup>-/-</sup> grafts and with M-T7 treatment. Ndst1<sup>-/-</sup> and M-T7 treatment altered gene expression in NFκB and JAK STAT pathways. In summary, modifying donor organ GAGs and inhibition of GAG/ chemokine interactions are equally effective at inhibiting early rejection. Modifying HS content in donor organs represents a new therapeutic approach for the prevention of allograft rejection.
OXIDATIVE STRESS AND ENDOTHELIAL DYSFUNCTION

C. Chen, J. Lu, Q. Yao
Baylor College of Medicine, Houston, TX, USA

Excessive production of reactive oxygen species (ROS) and/or insufficient activity of antioxidant defense mechanisms may result in oxidative stress, which could cause the damage to DNA, lipids, proteins, and carbohydrates, and abnormal gene expression, thereby contributing to cardiovascular disease and many other inflammatory and chronic diseases. Recently, we have demonstrated that several new cardiovascular risk factors, such as antiretroviral therapy drugs, adipokines, soluble CD40L, uric acid, nitrotyrosine and chlorotyrosine significantly increased oxidative stress of endothelial cells and impaired endothelial nitric oxide synthase (eNOS) system. This impairment is involved in the reduced activity and expression of eNOS, decreased sensitivity to nitric oxide (NO) or increased degradation of NO by reaction with superoxide. Antioxidants reduce oxidative stress; therefore, they may prevent or reduce the risk of oxidative stress-related endothelial dysfunction and cardiovascular disease. Recently, we have investigated new antioxidant functions and molecular mechanisms of ginsenoside Rb1, entacapone, and dihydroxy-nitrobenzaldehyde (DHN) in the vascular system. These studies may provide a significant rationale for using new antioxidants in combination therapy with existing antioxidants such as vitamin C and vitamin E for cardiovascular disease.
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A Nanomedical Approach to the Restoration of Dysfunctional Endothelium and the Function of the Cardiovascular System
T. Malinski, S. Awad, H. Dawoud
Ohio University, Athens, OH, USA

Background: A dysfunctional endothelium is a common denominator in aging and several cardiovascular diseases: hypertension, diabetes, salt-induced hypertension and atherosclerosis. Dysfunctional endothelium is characterized by diminished concentrations of cytoprotective nitric oxide (NO) and an overproduction of cytotoxic peroxynitrite (ONOO-) and superoxide (O2-).

Methods & Results: A nanomedical approach was utilized to directly measure with nanosensors (diameter of 150-250 nm) the near real time (1 microsecond) changes of NO, O2- and ONOO-concentrations released from endothelial cells. The concentration ratio of [NO] to [ONOO-] and [O2-] was used to quantify the level of endothelial dysfunction. The studies presented here elucidate different treatments of dysfunctional endothelium which may lead to the correction/restoration of endothelial function and to hinder the rate of progression of aging and/or cardiovascular disease. [NO]/[ONOO-] ratio in normal endothelium is about 3-5 and the ratio of [NO]/[ONOO-]+[O2-] is in the range of about 1.8-2.7. In cellular and/or animal models of hypertension, diabetes or aging, the [NO]/[ONOO-]+[O2-] ratio is usually below 0.70 and can decrease dramatically to a level of 0.1 in advanced stages of disease.

There are two major sources that contribute to the generation of O2-in endothelium, uncoupled eNOS and NAD(P)H. NO is an efficient scavenger of O2- to produce ONOO-. Uncoupled eNOS accounts for about 60% of O2-, while about 40% is produced by NAD(P)H. In normal endothelium, the major source of O2- production comes from NAD(P)H, while production from eNOS is negligible. Several different treatments were used to elucidate the restoration/improvement of endothelial function: scavenging of O2- (PEG-SOD), scavenging of ONOO- (Mn(III) TM PyP), increase of eNOS coupling and the efficiency of NO production (NAD(P)H, L-arginine, sepiapterin and statins). Using these various treatments separately or in combination can restore dysfunctional endothelium by 70-95% in cellular and animal models of hypertension, diabetes and aging.
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EFFECT OF ENDOTHELIAL CELL SENESCENCE ON THE HEAT SHOCK RESPONSE AND CELLULAR FUNCTION

A.A. Knowlton, H.T. Hwang
Sacramento VA Medical Center, Mather, CA USA and University of California, Davis, CA, USA

Increasing evidence supports that replicative senescence, cessation of cell division, plays a role in the progression of the aging phenotype. With cellular senescence, cells undergo morphologic, physiologic and functional changes. We hypothesized that adult human coronary artery endothelial cells (HCAEC) would have detrimental changes with the onset of senescence including impairment of the protective heat shock response, which is critical for maintaining many cellular functions, and organelle dysfunction. Early passage (EP) and senescent (SEN) cells from the same donors were heat-shocked at 42 °C in 5% CO2 for 1 hour, and then allowed to recover for 2 hours at 37 °C. In EP HCAEC HSP90 and HSP60 levels did not change with heat shock, but the HSP72 protein was significantly elevated. This response was blunted in Sen EC. Furthermore, studies of overall cellular functions demonstrated impairment of key organelles, including the mitochondria. Aging associated cell senescence impairs endothelial cell function, contributing to vascular inflammation and dysfunction.
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Involvement of Stromal Interaction Molecule-1 in Angiotensin-II-Induced Expression of Early Growth Response Protein-1 in Vascular Smooth Muscle Cells
E.R. Simo-Cheyou, A.K. Srivastava
CRCHUM, University of Montreal, Montreal, Quebec, Canada

The early growth response protein 1 (Egr-1) is a zinc finger transcription factor that has been suggested to regulate the expression of genes linked with inflammation and cell cycle regulation. An up-regulation of Egr-1 expression has been reported in models of atherosclerosis and intimal hyperplasia. Various vasoactive peptides and growth promoting stimuli have been shown to induce the expression of Egr-1 in VSMC. Angiotensin-II (Ang-II) is a critical vasoactive peptide implicated in the pathogenesis of vascular diseases. Ang-II elevates the intracellular level of calcium through activation of store-operated calcium entry involving inositol-3-phosphate receptor (IP3R)-coupled depletion of endoplasmic reticular calcium and stromal interaction molecule 1 (STIM-1). However, an involvement of IP3R/STIM-1-induced calcium pathway in Ang-II-induced Egr-1 expression remains unexplored. Therefore in the present studies we have examined the role of Ang-II-induced calcium release in Egr-1 expression in VSMC and investigated the contribution of STIM-1 in this process. Calcium chelation with BAPTA-AM as well as pharmacological blockade of IP3R with 2-aminoethoxydiphenyl borate (2-APB) decreased Ang-II-induced calcium release measured in cells loaded with Fura-2. Consistent with this, both BAPTA-AM and 2-APB attenuated Ang-II-induced enhanced expression of Egr-1 protein and mRNA levels. Furthermore, silencing of STIM-1 via RNA interference significantly abrogated STIM-1 protein and mRNA expression and resulted in an attenuation of Ang-II-induced Egr-1 expression. Our data demonstrate that Ang-II-induced Egr-1 expression is mediated by STIM-1 and calcium release in A-10 VSMC and suggest an implication of STIM-1 in the pathogenesis of vascular proliferative diseases. (Supported by a grant from CIHR).
Endothelial cell (EC) activation and vascular inflammation occur when the endothelium is exposed to various biochemical insults such as pro-inflammatory cytokines, oxidative stress, hypertension, hyperglycemia, aging, and biomechanical stimuli such as shear stress. These insults lead to the pathogenesis of a range of disease states, including atherosclerosis, insulin resistance, and obesity. Several signaling pathways, especially nuclear factor kappa-B mediated signaling, play crucial roles in these pathophysiological processes. Recently, microRNAs (miRNAs) have emerged as important regulators of EC function by fine-tuning gene expression. We show how a specific miRNA may regulate divergent targets in EC function and vascular inflammation in response to different pathophysiologic stimuli. Recent studies in mice and human subjects highlight an important role for miR-181b as a suppressor of endothelial inflammatory responses in both acute (e.g., sepsis) and chronic vascular disease states (e.g., atherosclerosis, insulin resistance, and obesity). These studies have uncovered emerging roles for novel miRNA targets in a cell-specific manner. An understanding of the role of miRNAs in EC activation and dysfunction may provide novel therapeutic opportunities for controlling a range inflammatory disease states.
ATHEROSCLEROSIS: FROM BASIC MECHANISMS TO NOVEL OPPORTUNITIES FOR INTERVENTIONS

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IMPACT OF REACTIVE OXYGEN SPECIES ON CORONARY ARTERIAL REMODELING - A COMPARATIVE INTRAVASCULAR ULTRASOUND AND HISTOCHEMICAL ANALYSIS OF ATHEROSCLEROTIC LESIONS

M. Terashima
Toyohashi Heart Center, Toyohashi, Japan

Background: Coronary arterial remodeling, which is a response to the growth of atherosclerotic plaques, is associated with plaque vulnerability. Oxidative stress induced by reactive oxygen species (ROS) via NAD (P)H oxidase in the vasculature also plays a crucial role in the pathogenesis of atherosclerosis-based cardiovascular disease. In this study, the relationship between coronary arterial remodeling and ROS generation was examined by comparing pre-interventional intravascular ultrasound (IVUS) findings of atherosclerotic lesions to the histochemical findings of corresponding specimens obtained by directional coronary atherectomy (DCA).

Methods and Results: Pre-DCA IVUS images of 49 patients were analyzed. The remodeling index was calculated by dividing the target-lesion external elastic membrane cross-sectional area (EEM-CSA) by the reference-segment EEM-CSA. Expansive remodeling was defined as a remodeling index of greater than 1.0. ROS generation and NAD(P)H oxidase p22phox expression in DCA specimens were evaluated using the dihydroethidium staining method and immunohistochemistry as the ratio of the positive area to the total surface area in each specimen, respectively. ROS generation and p22phox expression were significantly greater in lesions with expansive remodeling than in lesions without remodeling (0.18 ± 0.12 vs 0.03 ± 0.02, p<0.0001, 0.10 ± 0.08 vs 0.04 ± 0.05, p=0.0039, respectively). Both ROS generation and p22phox expression significantly correlated with the IVUS-derived remodeling index (r=0.77, p<0.0001, r=0.53, p<0.0001, respectively).

Conclusions: Simultaneous examination with IVUS and immunohistochemistry analyses suggests that NAD(P)H oxidase-derived ROS is related to the coronary arterial remodeling process associated with plaque vulnerability.
ATHEROEOSCLEROSIS: FROM BASIC MECHANISMS TO NOVEL OPPORTUNITIES FOR INTERVENTIONS

MOLECULAR MECHANISMS OF VASCULAR DYSFUNCTION AND ATHEROSCLEROSIS REGULATED BY HEMODYNAMICS FORCES

Z-G. Jin
Aab Cardiovascular Research Institute, Department of Medicine, University of Rochester School of Medicine and Dentistry, Rochester, NY, USA

Atherosclerotic cardiovascular disease remains the leading cause of death and disability worldwide. Normally atherosclerosis tends to occur at predisposed regions exposed to proatherogenic disturbed flow, while steady laminar flow with high fluid shear stress at straight arteries is atheroprotective. We have previously shown that docking protein Grb2-associated binder 1 (Gab1) is a mechano-effector protein in response to laminar flow. The aim of this study was to determine the in vivo role of endothelial Gab1 in flow-mediated vascular remodeling and atherosclerosis and explore the underlying mechanisms. To determine the role of endothelial Gab1 in disturbed flow-induced vascular remodeling in vivo, we performed partial carotid artery ligation in Gab1 endothelium-restricted knockout (Gab1-ecKO) mice and wild-type (WT) littermates, and we observed that Gab1-ecKO mice resulted in increased intima-media thickness. To examine the role of endothelial Gab1 in atherosclerosis, we next crossed Gab1-ecKO mice with ApoE KO mice. After partial ligation, Gab1-ecKO; ApoE KO mice under high fat diet showed increased atherosclerotic lesion size compared to Gab1-WT;ApoE KO mice. Using loss- and gain-of-function studies in cultured human endothelial cells (ECs), we found that Gab1 depletion by siRNA augmented monocyte adhesion to ECs by increasing proatherogenic genes intracellular adhesion molecule-1 (ICAM1) and vascular cell adhesion molecule-1 (VCAM1) expression in response to the proinflammatory cytokine TNFα. Conversely, adenoviral overexpression of Gab1 inhibited TNFα-induced monocyte adhesion to ECs and upregulation of ICAM1 and VCAM1 in ECs. These results demonstrate that endothelial Gab1 represses disturbed flow-induced vascular remodeling and atherogenesis through inhibition of vascular inflammation. Our findings suggest that Gab1 activation might represent novel approaches for the treatment of atherosclerotic cardiovascular disease.
Vascular smooth muscle (SMC) phenotypic modulation plays an essential role in the development and progression of several major human diseases such as atherosclerosis, hypertension, restenosis after angioplasty or bypass, diabetic vascular complications, and transplantation arteriopathy, asthma, and cancer. A hallmark feature of the phenotypic modulation is the down-regulation of SMC contractile genes. Platelet-derived growth factor-BB (PDGF-BB), a well-known stimulator of SMC phenotypic modulation, down-regulates SMC genes via posttranscriptional regulation. The underlying mechanisms, however, remain largely unknown. We found that SMC gene down-regulation was caused by abnormal RNA editing of their precursor mRNAs (pre-mRNAs), which was facilitated by adenosine deaminase acting on RNA (ADAR). ADAR converts adenosines to inosines (A to I editing). PDGF-BB induced ADAR1 expression while down-regulating smooth muscle myosin heavy chain (SMMHC) and alpha- actin (α-SMA). Knockdown of ADAR1 by shRNA restored PDGF-BB-blocked SMMHC and α-SMA expression, demonstrating that ADAR1 played an essential role in SMC phenotype modulation. Animal studies showed that SMMHC and α-SMA pre-mRNA was accumulated while their mature mRNA was decreased along with the expression of ADAR1 in media SMCs initially, and neointima SMCs subsequently in balloon-injured rat carotid arteries. Of importance, knockdown or heterozygous knockout of ADAR1 dramatically inhibited injury-induced neointima formation, demonstrating a critical role of ADAR1 in vascular remodeling in vivo. ADAR1 appeared to regulate SMC proliferation through RNA editing-mediated downregulation of p27kip1. Taken together, our study unraveled a novel molecular mechanism governing SMC phenotypic modulation.
 background: Measurement of the inferior vena cava (IVC) by hand-held ultrasound (HHU) is a validated, non-invasive technique to estimate right atrial pressure at the point of care. The degree to which the presence of atrial fibrillation (AF) or atrial flutter (AFl) affects IVC measurements has not been well characterized in humans but is critical to accurate application of HHU to patient care. Objectives: We evaluated the effect of AF or AFl on maximum IVC diameter and collapsibility as assessed by HHU.

Methods: We prospectively enrolled 32 patients undergoing direct current cardioversion (DCCV) for AF or AFl. Using a HHU device (Vscan, GE Healthcare), measurements of maximum IVC diameter were obtained immediately prior to DCCV with a rhythm of AF or AFl and immediately following DCCV in normal sinus rhythm in the same patients. Results: The mean maximum IVC diameter before and after DCCV was 22.4 mm and 20.4 mm, respectively, with a mean difference of -2.0 mm (p<0.0001). 69% of patients were found to have a smaller IVC diameter when in sinus rhythm compared to when in AF or AFl. 44% of patients had a collapsible IVC when in AF or AFl, compared to 72% of patients who had a collapsible IVC when in sinus rhythm. Following DCCV to sinus rhythm, estimated right atrial pressure (low, intermediate, or high) based on maximum IVC diameter and collapsibility changed to a lower category in 44% of patients.

Conclusions: The presence of AF or AFl, as compared to normal sinus rhythm, is associated with increased maximum IVC diameter and decreased IVC collapsibility as measured by HHU. The finding of dynamic changes in IVC characteristics offers insight into the use of HHU in assessing changes in intracardiac filling pressures. Further study is indicated to evaluate the relationship of these findings to clinical outcomes.
NEW SOFTWARE BASED BEAMFORMING ALGORITHM IS SUPERIOR TO HARDWARE BASED BEAMFORMER IN ENDOCARDIAL BORDER DETECTION

R.A. Kulina\textsuperscript{1}, B. Wiley\textsuperscript{2}, S. Agarwal\textsuperscript{1}, A. Traube\textsuperscript{1}, S. Ka\textsuperscript{1}, S. Schiller\textsuperscript{1}, L. Clark\textsuperscript{1}, J. Narula\textsuperscript{1}\textsuperscript{*}, P. Sengupta\textsuperscript{1}, F. Chaudhry\textsuperscript{1}\textsuperscript{*}

1. Icahn School of Medicine at Mount Sinai, New York, NY, USA
2. National Institute of Health, Bethesda, Maryland, USA

Background: Technically limited echocardiograms can lead to non-diagnostic images that require downstream testing, increasing healthcare costs. Software-based beamforming is a signal processing technique that acquires and temporarily stores data from each probe element before analyzing it by parallel processors. This optimizes and aligns signals received by the echo transducer to improve both the spatial and contrast resolution of the image. We compare this new software algorithm with a standard, high-end hardware-based beamforming platform to evaluate endocardial borders and need for echo contrast.

Methods: Eligible participants were inpatients ≥ 18 years of age referred clinically for transthoracic echocardiograms. In addition to the routine exam, a limited study, consisting of three additional views (apical-4, apical-3 and apical-2 chamber), was performed with the new software based beamforming and standard platform. An echocardiographer blinded to the two platforms evaluated the number and quality of segments visualized using a 17-segment model. Quality of segments and endocardial borders were graded (0=not visualized, 1=incompletely visualized, 2=completely visualized). Physician reviewer reported an overall quality score for each study (0=poor, 1=adequate, 2=good) and whether contrast was needed as per ASE guidelines. Paired T-Test and Chi-squared tests were used for analysis.

Results: A total of 84 inpatients (mean age 63 +/- 16 years) were enrolled. The mean number of segments visualized in apical-4 (6.2 vs. 5.5, p<0.001), apical-3 (6.2 vs. 5.5, p<0.001), and apical-2 (6.2 vs. 5.6 p<0.001) chamber view were higher with the new versus standard platform. Average overall score for image quality was significantly better for the new platform versus standard (1.4 versus 0.9, p=<0.001). With the new platform, 23.8% were judged as requiring contrast as compared with 45.2% for the standard platform (p<0.001).

Conclusions: The new software-based beamformer identified more segments with better image quality when compared to the standard platform, decreasing the need for contrast usage.
A MIXED TREATMENT ANALYSIS COMPARING THE EFFICACIES OF IVABRADINE VERSUS BETA BLOCKERS WHEN USED AS PREMEDICATION FOR HEART RATE REDUCTION IN COMPUTED TOMOGRAPHY CORONARY ANGIOGRAPHY

S. Dayanand, J.M. Martinez
1. Univ of Central Florida, Kissimme, FL, USA
2. Einstein Medical Ctr, Philadelphia, PA, USA

Introduction: Computed Tomography Coronary Angiography (CTCA) is a non-invasive tool for the diagnosis of coronary artery disease with a high negative predictive value. To minimize coronary artery motion artifacts and optimize image quality, a HR < 65 beats per minute is required.

Hypothesis: Ivabradine is superior to beta blockers in achieving optimal heart rate when used as premedication prior to CT coronary angiography.

Methods: Studies were extracted from an electronic literature search of PubMed, MEDLINE and EMBASE. Of all relevant RCTs, 7 RCTs, including 795 patients, were identified. The main outcome of interest was the mean relative HR reduction between T0 to T2 phases of imaging after initial premedication. There were several outcomes for safety, primarily bradycardia, hypotension and other cardiac arrhythmias. A mixed-treatment comparisons analysis was then used to compare each of these agents to one another. Calculation of the probability that each treatment is best was implemented using the Bayesian Markov chain Monte Carlo method.

Results: All agents were significantly superior to placebo in achieving relative HR reduction. Ivabradine was superior to BB with an overall mean relative reduction of HR of 6.1 +/- 7.79, when compared to BB. In terms of rank probability Ivabradine had the highest rank probability of being the agent to cause maximal mean HR reduction. There were no statistically significant differences in terms of adverse events. The degree of incoherence was low for all outcomes.

Conclusion: This analysis to date is the first to compare these drugs when used in the reduction of HR prior to CTCA with different efficacy outcomes. The results of the study show that Ivabradine seems to be the most effective and safe agent when used for this purpose.
THE ROLE OF ECHOCARDIOGRAPHY IN THE MANAGEMENT OF PATIENTS UNDERGOING VENTRICULAR ASSIST DEVICE IMPLANTATION AND/OR TRANSPLANT SURGERY

T.S. Kato
Juntendo University School of Medicine, Bunkyo-ku, Tokyo, Japan

Background: Heart transplantation (HTx) is a curative treatment for patients with advanced heart failure (HF); however, since transplant opportunity is severely limited due to donor shortage, left ventricular assist device (LVAD) has evolved into a standard therapy for patients awaiting HTx. The role of echocardiography as a primary imaging modality to monitor allograft function in transplant recipients as well as to optimize LVAD settings in LVAD recipients has been expanding.

Purpose of the presentation: (1) Echocardiography for rejection diagnosis. Conventional echo parameters can detect diastolic and/or systolic dysfunction associated with acute rejection; however, these parameters are not sufficiently reliable to guide the treatment strategy in asymptomatic/clinically stable recipients. Tissue-Doppler Imaging (TDI) and 2D speckle-tracking echocardiography (2D-STE)-derived LV torsion and strain parameters are expected to detect subclinical rejection. (2) Echocardiography for LVAD management: Conventional echocardiography allow us to monitor left and right ventricular dimensions, aortic valve opening, degree of mitral regurgitation, and cardiac output through RV out flow under LVAD support, which are the essential information for optimizing LVAD settings. We can also evaluate cannula flow, position and suctioning, as well as check any thrombus by using contrast as needed. Further, we recently published the usefulness of TDI and strain parameter to predict right ventricular failure after LVAD implantation in patients who were not planned to undergo biventricular support. RAMP study is very much useful for detecting LVAD malfunction, and we present a representative case in whom RAMP study enabled us to detect LVAD thrombus.

Summary: Echocardiography is a primary imaging modality in the assessment of cardiac structure and function. It can be performed at the patient’s bedside and repeatable, and the results are immediately available. Therefore, echocardiography is an essential tool for the management of patients before and after transplantation.
COST EFFECTIVENESS OF CORONARY CT ANGIOGRAPHY IN PATIENTS WITH LOW RISK FOR CORONARY ARTERY DISEASE (CAD) AT A TERTIARY CARE CENTER

K. Kalvakuri1,2, S. Banga1, S. Singh1, W. Keattiyoat1,2, M.F. Malik1,2
1. University of Illinois College of Medicine at Peoria, Division of Cardiology, Department of Internal Medicine, Peoria, Illinois, USA
2. OSF Saint Francis Medical Center, Peoria, Illinois, USA

Background: Coronary Computed Tomography Angiogram (CCTA) has emerged as a valuable diagnostic tool in patients with low to intermediate risk for CAD. The Cost-effectiveness of using CCTA instead of invasive coronary angiography (ICA) in patients referred for CCTA for atypical chest pain and/or equivocal stress test results has not been validated.

Objectives: We sought to study the cost-effectiveness of CCTA in this low to intermediate risk population.

Methods: Retrospective chart review of patients having undergone CCTA and ICA for risk assessment for CAD using pooled data from the current electronic medical record. Patients >18 years of age having undergone CCTA with prior negative or equivocal stress tests in patients with persistent atypical chest pain in low to intermediate risk for CAD were included in the study. Student’s t test was used to test statistical significance.

Results: Of the total 88 patients, who had CCTA, 36 had normal CCTA, 34 patients had non obstructive CAD and 18 patients had significant CAD. Of the 18 patients, 13 patients had ICA and 5 patients were medically managed. Of the 13 patients who had ICA, 8 patients had significant CAD that required intervention. The total cost of an average ICA was $20,500 and the average cost of a CCTA was $2,300. The difference between the average cost of the two modalities was $18,200. For 70 patients, we saved $1,281,000 (p_value < 0.001) by not performing ICA. If we add back the cost of those who had CCTA and went on to angiography ($266,500) we still come to a net savings of $1,014,500.00.

Conclusions: CCTA is a cost-effective imaging modality for patients with low/intermediate likelihood of CAD and/or equivocal stress test. The underutilization of this investigative tool should be investigated further especially given the increased focus on achieving high quality yet cost effective care.
HYPEREMIC INSTANTANEOUS WAVE-FREE RATIO PROVIDES THE HEMODYNAMIC OUTCOME FOR MODERATE TO SEVERE CORONARY ARTERY STENOSES
Y. Kanamori, R. Aikawa
Kuwana City Medical Center, Japan

Objective: To evaluate the utility of hyperemic-iFR

Background: iFR has been established as a physiological tool for the assessment of coronary ischemia from diastolic wave-free period in stable condition without the need for hyperemic agents. It remains unclear that hyperemic-iFR (h-iFR) is available for evaluation of the ischemia. Thus, we aimed to assess the diagnostic performance of the h-iFR compared with the conventional whole-cycle Fractional Flow Reserve (FFR).

Methods: Fifty consecutive lesions, which were diagnosed to be moderate to severe stenosis by coronary angiography, were analyzed regarding the h-iFR and FFR during intravenous the intravenous administration of adenosine using a pressure wire. The h-iFR and FFR were calculated via automated algorithms.

Results: Twenty-two stenoses were positive and twenty-eight stenoses were negative. The slope of regression line in the positive group was lower than that of the negative group. The h-iFR shows a larger range in the severe stenosis group compared to the FFR group.

Conclusions: The hyperemic iFR may be a better physiological tool than the conventional cardiac full-cycle FFR in the evaluation of coronary artery ischemia.
GLOBAL LONGITUDINAL STRAIN AS A PREDICTOR OF MAJOR ADVERSE EVENTS IN ESRD PATIENTS WITH PRESERVED EJECTION FRACTION

S. Furlan, F. Abdelmalak, E. Donath, R. Chait
University of Miami, Palm Beach Regional Campus, Atlantis, FL, USA

Background: End-stage renal disease (ESRD) is associated with increased cardiovascular morbidity and mortality. 2-D speckle tracking echocardiography evaluating global longitudinal strain (GLS) is a novel way to identify left ventricular dysfunction by measuring myocardial deformation.

Objectives: Our goal was to determine if abnormal GLS predicts poor outcomes in stable ESRD patients on dialysis with a preserved EF.

Methods: We conducted a meta-analysis and searched MEDLINE, EMBASE, and Cochrane. Selected studies reported GLS and major adverse events (MAE) including cardiac deaths. The two primary outcomes were the pooled relative risk (RR) of incident MAE in normal versus abnormal GLS risk categories, as well as the pooled weighted mean difference (WMD) of GLS between those with and without MAE.

Results: Our search strategy identified three studies that met the inclusion criteria and included 242 ESRD patients on dialysis. The mean age of patients was 58.8 years old and the mean EF was 63.4%. Of the 242 patients, 62 had MAE. Our analysis revealed that those with normal GLS had a 51.9% reduction in risk of MAE compared to those with abnormal GLS (RR = 0.481; 95% CI: (0.26, 0.87); p<0.01). Additionally, those with MAE had a pooled GLS WMD of -2.35% (95% CI: (-3.36, -1.34); p<0.01) compared to those without MAE.

Conclusion: Patients with a more positive GLS value were more likely to have MAE, including cardiac death despite having a preserved EF. Thus, MAE in ESRD patients may be better detected by utilizing GLS rather than only measuring EF.
PULMONARY AND HEMODYNAMIC RESPONSES TO FRUCTOSE-1,6-DIPHOSPHATE (FDP) IN PATIENTS WITH ACUTE LUNG INJURY (ALI)

A.K. Markov, T.N. Skelton
University of Mississippi School of Medicine Department of Medicine, Jackson, MS, USA

Objective: To investigate whether FDP has a salutary effect in man as reported in animals with ALI.

Background: Experimental data indicates that treatment with FDP significantly reduces lung injury caused by α-naphthylthiourea, sepsis and endotoxemia.

Method: We used a non-randomized design in which each patient served as his own control. Treatment with IV FDP 10% 150 mg/kg Q6H for an average of 18±2.9 infusions was given to 42 consecutive patients with ALI/ARDS resulting from complications of sepsis, trauma, aspiration, near drowning, smoke inhalation, and following heart and lung transplantations. FDP treatment was discontinued after substantial improvement of oxygenation and hemodynamics.

Results: Pulmonary function before (B) and after (A) FDP treatment is given below and expressed as means±SEM, *P<0.001.

<table>
<thead>
<tr>
<th>PEEP-cmH₂O</th>
<th>O₂%</th>
<th>PaO₂ mmHg</th>
<th>PaO₂/FiO₂ Index</th>
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<tr>
<td>B</td>
<td>A</td>
<td>B</td>
<td>A</td>
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<tr>
<td>9.6</td>
<td>6.1*</td>
<td>62</td>
<td>42*</td>
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<tr>
<td>□0.7</td>
<td>□0.93</td>
<td>□3.3</td>
<td>□2.03</td>
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<tr>
<td>130</td>
<td>260*</td>
<td>□3.4</td>
<td>□8.4</td>
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<td>15.3</td>
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Pulmonary artery pressure and resistance declined following FDP treatment (P<0.001) and so did heart rate (P<0.001) while arterial pressure and cardiac output increased (P<0.001). At 45 days post treatment, 31 of the 42 patients were alive (74%).

Conclusion: As the study is non-randomized, no conclusion can be drawn on survival. The observed improvement in pulmonary function by FDP was most likely due to its known capabilities to curtail oxyradicals generation by neutrophils and suppress inflammatory cytokines expression. Hemodynamic improvement is attributed to the pharmacodynamic properties of FDP to enhance energy production from glycolysis in hypoxia.
MORTALITY OF PULMONARY EMBOLISM TREATED WITH SYSTEMIC OR INTRAPULMONARY THROMBOLYSIS: A SINGLE CENTER, 10-YEAR RETROSPECTIVE STUDY

S. Udae, J. Cholteesupachai, S. Srimahachota
Division of Cardiovascular Medicine, King Chulalongkorn Memorial Hospital, Faculty of medicine, Chulalongkorn University, Bangkok, Thailand

Background: Acute massive pulmonary embolism (PE) is a serious life-threatening condition. In patients who is contraindicated for surgical embolectomy. Medical reperfusion by systemic thrombolysis or intrapulmonary artery thrombolysis are options for treatment. However, the data are still limited.

Objective: To assess mortality and complications of patients with acute PE treated with systemic or intrapulmonary thrombolysis.

Method: A retrospective study of consecutive patients with acute PE treated with systemic thrombolysis (systemic group) or intrapulmonary thrombolysis (intraPA group) at King Chulalongkorn Memorial hospital. Demographics, hemodynamics data, complications and mortality were gathered from medical records. Chi-square and T-tests were used.

Results: Sixty five patients were included (mean age 56 years, 56.9% were diagnosed as massive PE, 52.3% were received intraPA thrombolysis). Thirty-day mortality was 26.2% in all PE combine. The 30-day mortality rate was higher in systemic group compared to intraPA group (41.9% and 11.7% in systemic and intraPA group, respectively, P= 0.006). Pre-treatment blood pressure (SBP) was 101.9+- 24.2 mmHg (97.6+-25.9 mmHg in systemic thrombolysis group, 105.3+-22.4 mmHg in intrapulmonary thrombolysis group, P= 0.21), Right ventricular systolic pressure was 41.06+-16.66 mmHg (58.4+-18.8 mmHg in systemic thrombolysis group, 55.7+-16.2 mmHg in intrapulmonary thrombolysis group, P= 0.58). Six patients (9.2%) had major bleeding, all of them were on systemic thrombolysis group.

Conclusions: Pulmonary embolism is associated with high mortality rate. The role of intrapulmonary thrombolysis in high risk PE is promising. All-cause mortality and bleeding complication is significantly lower in these group compared to the one who received systemic thrombolysis. A larger, controlled study is needed to prove the efficacy of the intrapulmonary thrombolysis in acute PE.
SHORT TERM LOW DOSE ATORVASTATIN THERAPY IMPROVES ENDOTHELIAL DYSFUNCTION IN NORMOLIPIDEMIC PATIENTS WITH PRESERVED EJECTION FRACTION HEART FAILURE

S. Yazdankhah\(^1\), S.H. Majidi\(^1\), M.H Adel\(^1\), A. Kardooni\(^1\), H. Karbalivand\(^2\), M. Maghsodi\(^1\), A. Rouhizadeh\(^1\)

1. Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Khuzestan
2. Lincoln Medical and Mental Health Center, Affiliated With Weill Cornell Medical College, Bronx, New York, USA

Heart failure with preserved ejection fraction (HFpEF) includes about half of heart failure cases that impose a heavy burden on the country’s health system. Despite wide classic medicinal prescription and use of various medical devices in HFpEF patients, we have not yet to find an evidence based therapy. Recently, endothelial dysfunction has been considered as a novel therapeutic target in patients with heart failure. The aim of this study was evaluating the effect of Statins on endothelial function of patients with HFpEF.

40 patients referred to echocardiography clinic of Imam Khomeini hospital of Ahvaz Jundishapur University of Medical Sciences were included in randomly matched clinical trial. Clinical and echocardiographic criteria for HFpEF and normal coronary angiography were found in all patients. Patients did not have indication for statin therapy and also any kind of the statins were not used before the study. Flow mediated dilatation (FMD) of brachial artery were measured in both groups. Patients were randomly assigned to placebo (20 patients) or Atorvastatin at the dose of 20 mg daily (20 patients) in addition to their current drug treatment for 2 months, after that the FMD was measured again in the patients, data were analyzed. There was a significant improvement of FMD in Atorvastatin but not in the placebo group, +41.5% and +18.25% respectively (P<0.001).

LDL level in atorvastatin group was significantly reduced after treatment, but there was no significant change in LDL level of placebo group. The change in FMD was not significantly correlated with the decrease of serum LDL in both groups. This study showed that Atorvastatin has beneficial effects on the vascular endothelial function of HFpEF without relation to lipid lowering.
ADVANCES IN HEART FAILURE, CARDIOMYOPATHIES AND PULMONARY HYPERTENSION

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A COMPARATIVE ANALYSIS OF CHRONIC HEART FAILURE IN A
PREDOMINANT AFRICAN-AMERICAN POPULATION

D. Brito¹, E. Ladron-Franco², T. Alnabelsi¹, J. Penalver¹, A. Macedo-Dias²,
H.D. Hares¹, K. Curet¹, A. Romero-Correl², B. Bozorgnia²

1. Department of Internal Medicine, Einstein Medical Center, Philadelphia, PA, USA
2. The Institute for Heart and Vascular Health, Einstein Medical Center, Philadelphia, PA, USA

Objective: To compare the efficacy of chronic heart failure management between Internal Medicine clinic (IMC) and Heart Failure clinic (HFC) in an African-American community.

Background: Heart failure (HF) results from structural or functional impairment of ventricular filling or ejection of blood. In United States 6.6 million individuals (2.8%) were diagnosed with HF by 2010. Incidence of heart failure in whites is approximately 6/1,000 person/years, while among African Americans, it is 9.1/1,000 person/years. In this observational study we would like to compare the efficacy of specialized heart failure clinics as compared to primary care management of chronic heart failure.

Methods: Retrospective observational study by chart review of 195 patients with diagnosis of HF seen in the IMC compared to HFC at Albert Einstein Medical Center Philadelphia, PA.

Results: IMC was predominantly females (57%) while HFC were males (60%). Both practices were mainly African-Americans (IM: 88%, HFC: 76.8%). In IMC, New York Heart Association (NYHA) class was not documented in 85% of subjects. 56% had ejection fraction (EF) >40% by echocardiography. HFC had mainly NYHA class II (35.8%) and III (29.5%) with an ejection fraction of <40% (64.2%). Majority of patients had non-ischemic cardiomyopathy (IMC: 74% vs HFC: 58%). Medication prescription is as follows: Beta blockers: IMC: 86%, HFC: 95%. ACEI/ARB: IMC: 79%, HFC: 84%. Hydralazine: IMC: 28%, HFC: 35.1%. Spironolactone: IMC: 11%, HFC: 31.9%. Aspirin: IMC: 70%, HFC: 70%. Statin: IMC: 66%, HFC: 67%. Diuretic: IMC 70%, HFC: 80%. ICD implant in patients with EF <35% was: IMC 40% vs HFC: 61%.

Conclusions: Specialized heart failure clinics provide better efficacy in adhering to standard of care when compared to primary care offices. Perhaps electronic medical record tools can be designed to alert clinicians of the missing therapies for patients with chronic heart failure.

Figure 1. Medication prescription for chronic heart failure between medical practices.
DOXORUBICIN-INDUCED CARDIOMYOPATHY IN CHRONIC LYMPHOCYTIC LEUKEMIA AND RICHTER'S TRANSFORMATION: DEVELOPMENT OF HEART FAILURE WITH SYSTOLIC AND DIASTOLIC DYSFUNCTION

S.H. Wan, R.L. Frye
Mayo Clinic, Rochester, MN, USA

Background: Commonly used chemotherapeutic agents for leukemia and lymphoma may result in chemotherapy-induced cardiomyopathy with features of both systolic and diastolic dysfunction.

Description: An 85-year-old man with history of chronic lymphocytic leukemia presented with worsening shortness of breath. The patient’s chronic lymphocytic leukemia one year prior had Richter’s large cell transformation with left pleural wall disease, and required two cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) and one cycle of R-CEOP (etoposide substituted for doxorubicin). He presented with six months of weight gain and dyspnea on exertion. Physical examination demonstrated bilateral pitting edema. Prior to his chemotherapy, his echocardiogram demonstrated ejection fraction of 53%. A new transthoracic echocardiogram demonstrated left ventricular enlargement with ejection fraction 30-35%, and grade 1a/4 left ventricular diastolic dysfunction with mildly elevated left ventricular filling pressures. The patient was continued on guideline directed medical therapy, including aspirin, beta blocker, and angiotensin receptor blocker. He was also initiated on furosemide for his heart failure symptoms.

Discussion: The patient’s initial manifestation of weight gain and dyspnea on exertion raised suspicion for heart failure. While he has known coronary artery disease, his history of chronic lymphocytic anemia with Richter’s transformation also raised the possibility of cardiomyopathy induced by chemotherapy. The patient has had a history of ischemic cardiomyopathy and coronary artery bypass graft, but his ejection fraction showed a marked decline from before to after chemotherapy administration. While many therapeutic agents may cause cardiomyopathy, an anthracycline agent such as doxorubicin is a particularly toxic agent that in a dose-dependent fashion may result in systolic and diastolic dysfunction.

Conclusion: Patients that develop heart failure may have cardiomyopathy secondary to chemotherapy. Anthracycline agents such as doxorubicin may lead initially to asymptomatic systolic and diastolic dysfunction, but can eventually lead to symptomatic heart failure.
Prenatal Trans-placental Digoxin Therapy for Fetal Heart Failure: A Cohort Study
K.Y. Zhou, C. Wang, Y.F. Li, Y.M. Hua
Department of Pediatric Cardiovascular Disease, West China Second University Hospital, Sichuan University, Chengdu, Sichuan, China

Objective: Study the clinical efficacy and safety of transplacental digoxin therapy for fetal heart failure.

Methods: Fetal heart failure cases, diagnosed during May 2008 to December 2014, were enrolled in this case-control study. The subjects were divided into digoxin group (Dig group) and control group (Con group). Fetal CVPS and ventricular Tei index were dynamic monitored, pregnant outcomes were observed and recorded.

Results: Fourteen cases of fetal heart failure were enrolled in Dig group, including 5 fetal SVT, 5 fetal AF, 3 fetal anemia (MA) and 1 fetal dilated cardiomyopathy (DCM). Fetal heart failure was gradually controlled in AF, SVT and MA fetuses with transplacental digoxin therapy. These cases achieved uneventful post-therapy pregnancy and full-term delivery. CVPS increased gradually, at or near the 10 points, left and right ventricular Tei index decreased gradually, closed to normal range. 10 to 55 months follow-ups have been finished, evaluation from Bayley Scale of Infant Development (BSID) revealed the normal growth and development of physique and mentality in all the enrolled children. Twelve cases of fetal heart failure cases were enrolled in Con group, including 5 AF, 4 SVT, 2 MA and 1 case of fetal cardiomyopathy. Among these cases in Con group, fetal right ventricular Tei index decreased gradually, the value is 0.48±0.05 at 20 GW and decreased to 0.38±0.04 before delivery.

Conclusions: With the alleviating of fetal heart failure, CVPS increased and ventricular Tei index decreased. CVPS and Tei index can effectively guide the prenatal transplacental digoxin therapy for fetal heart failure. Timely and effective prenatal intervention can significantly improve the prognosis of the suffered fetuses.
PATIENT PERCEPTIONS ABOUT A HOSPITAL-AT-HOME MODEL OF CARE FOR DECOMPENSATED HEART FAILURE

T. Rahman, Q. Ibrahim, H. Van Spall
1. McMaster University, Department of Medicine, Hamilton, ON, Canada
2. Population Health Research Institute, McMaster University, Hamilton, ON, Canada

Background: Small European RCTs demonstrate Hospital-at-Home (HaH) models can increase time to readmission, improve health-related quality of life, and reduce total costs in Heart Failure (HF). However, the acceptability and efficacy of HaH is unclear in North American settings.

Objectives: With a view of developing a HaH model for decompensated HF, we aimed to 1) assess whether patients presenting to the emergency department (ED) with decompensated HF find HaH an acceptable alternative to traditional hospitalization. 2) Assess patients’ perceptions regarding safety and caregiver burden associated with HaH.

Methods: Adult patients requiring admission for HF were approached in the ED of 2 large teaching hospitals in Ontario, Canada in 2016. A study nurse administered the 9-item patient questionnaire that included a 7-point Likert scale ranging from “strongly disagree” to “strongly agree”.

Results: 123 patients completed the study questionnaire. Mean age was 77 (+/- 12) years, 55% were female, and mean EF was 45 (+/-15)%. 69% lived in their own home; 14% in a caregivers/family home; and 17% in a retirement/nursing home. On average, patients had at least 2 prior hospitalizations in the preceding year. Overall, 87% of patients were either neutral to (25%) or preferred (62%) HaH over traditional hospitalization. 90% perceived HaH as comfortable, and 67% felt medical care at home could be as effective as hospital care. A vast majority of patient deemed HaH to be a safer alternative (92%), resulting in fewer complications (89%), and faster recovery time (73%) than traditional hospitalization. Patients were not concerned about delayed response time should they require urgent medical attention at home (56%). 73% indicated they or their families would not be burdened if medical staff frequently visited their homes.

Conclusions: Patients requiring admission for heart failure prefer a hospital-at-home strategy and perceive it as a safer alternative over traditional hospitalization.
A CASE OF TUBERCULOUS PERICARDITIS MIMICKING LUPUS CARDITIS

C. Panagiota¹, I. Katsa¹, J. Miles², R. Faillace¹
1. Albert Einstein College of Medicine Jacobi Medical Center, Bronx, NY, USA
2. Albert Einstein College of Medicine, Bronx, NY, USA

A 48-year-old male with no previous medical history presented with one-week history of fever and chills. Review of symptoms was unrevealing apart from a rash noted in his cheeks. The patient, a Dominican Republic native, immigrated to the US ten years ago, had not travelled recently, was not taking medications and denied any sick contacts or toxic habits. On presentation, he was febrile to 103.2 F. His exam was remarkable for an erythematous rash covering his cheeks and the bridge of nose. Heart sounds were distant but there was no jugular venous distention or pericardial rub. His laboratory workup was unremarkable. Chest x-ray showed marked cardiomegaly. An echocardiogram revealed a circumferential pericardial effusion with tamponade physiology. He underwent a pericardiocentesis with drainage of 1500ml of serosanguinous fluid. Cultures of pericardial fluid, including acid-fast smear, were negative. HIV and hepatitis C serologies were negative and Quantiferon® assay was negative for M. tuberculosis. Anti-nuclear antibody (ANA) was positive at a 1:640 titer with a speckled pattern. Nevertheless, patient met only three out of the eleven diagnostic criteria for systemic lupus erythematosus. He underwent a pericardial biopsy, which revealed a fibrinous pericardium with caseating granulomas. Acid fast bacilli were cultured from the biopsy specimen. Patient was started on four drug therapy and steroids for tuberculous pericarditis. Mycobacterium Tuberculosis is a common cause of pericarditis in the developing world yet, accounts for only 2-4% of pericarditis cases in industrialized countries. Its diagnosis can be challenging: Diagnostic tests can be falsely negative as the infection is contained to the pericardium. This case illustrates the difficulty in diagnosing TB pericarditis and the importance of maintaining a broad deferential. TB pericarditis should be strongly considered in any patient with risk factors for TB exposure who have a non-self-limited course of pericarditis.
Clinical Characteristics of Takotsubo Cardiomyopathy in Thailand

A. Ardjnaphai, J. Chaipromprasit
Division of Cardiovascular Medicine, King Chulalongkorn Memorial Hospital, Bangkok, Thailand

Background: The transient cardiac dysfunction which is proceeded by an emotional or physical trigger are termed “Takotsubo cardiomyopathy” (TTC). There are no studies about natural history, management and outcome of TTC in Thailand.

Objective: To study Clinical Characteristics of Takotsubo cardiomyopathy (TTC) and identify factors associated with mortality.

Method: We will review the medical records of all TTC patients admitted in King Chulalongkorn Memorial Hospital during 2008 – 2015. The demographic data (such as age, sex, underlying diseases etc.), TTC –inducing factors, other related - investigation results and in-hospital outcome will be collected and assessed. Chi-square and T-tests were used.

Results: Total of 29 patients were diagnosed with TTC, 25 (86%) were female. Age were ranged from 41 to 92 years (mean age 69 years). Precipitating factors were identified in most of the patients which mostly were malignancy, respiratory failure and infection, respectively. Only 8 patients had no obvious physical stressor. The most common presenting symptoms were dyspnea and chest pain. From CAG and Echo findings, only 2 had localized type of RWMA pattern, while the remaining (n = 27) were typically classic type of TCM. Nearly half (n = 13) of patients died in-hospital had significantly lower LVEF and LVEDP than patients who survived significantly.

Conclusion: The incidence of TTC patients in Thailand was much lower than incidence studied in other countries. General profile of TTC patients was indifferent; exceptionally, TTC cases in KCMH had higher in-hospital mortality upon type of physical stressors.
EMBOLIC PARADOX: WHEN TWO WRONGS MAKE A RIGHT

V. Tavakoli, R. Bindu, C. Philip, R. Grodman, D. Bloomfield
Richmond University Medical Center, Staten Island, NY, USA

We present a rare phenomenon that pulmonary embolus gets trapped in patent foramen ovale (PFO) and then, returns back to the pulmonary circulation. A 74 year old woman presented with worsening dyspnea. Examination revealed increased respiratory and pulse rate. Saturation was 91%. Ventilation-perfusion lung scan showed multiple large segmental perfusion mismatches. Lower extremities duplex scan showed deep venous thrombosis. The patient was started on anticoagulation. An initial Trans-Esophageal Echo (TTE) revealed a serpingenous mass straddling a PFO. A repeat TTE on the third day of admission revealed no evidence of intracardiac masses in either atria or ventricles. Patient offered no new symptoms between the two echo studies. In light of the vanishing atrial masses, another TEE was performed, confirming the absence of right or left atrial thrombi. A PFO was demonstrated by both color flow Doppler and microbubble contrast echo. Severe RV dilatation and hypokinesis were noted. A massive clot-burden was seen in the proximal pulmonary arteries. A CT angiography, afterward, showed central saddle pulmonary embolus (PE). The patient underwent surgical pulmonary artery thrombectomy that revealed thrombus in pulmonary arteries. The pathophysiology behind this phenomenon is based on the pressure changes in the setting of pulmonary embolism. The initial PE induced acute core pulmonale (as documented by the initial TEE), causing a right to left PFO flow. The direction of the flow caused the emboli coming from the lower extremity to get trapped through the PFO. However, the rapid pressure elevation, caused by the acute pulmonary embolism, was subsequently relieved when PE was lysed over time. Eventually, the right ventricular pressure decreased and the PFO shunt reversed to left-to-right, forcing the embolus to go back toward the pulmonary artery and causing another pulmonary embolism in the pulmonic circulation (as documented by the second TEE).
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MITRAL INTERVENTION IN CABG PATIENTS: IS LESS EVER MORE?

L.P. Perrault
Montreal Heart Institute, East, Montreal, QC, Canada

Left ventricular remodeling is an independent risk for death and heart failure in patients with ischemic mitral regurgitation (IMR). Left ventricular “reverse” remodeling is desirable and is most consistently achieved in IMR when mitral regurgitation is enduringly corrected. The literature on patients in whom the IMR grade was strictly and uniformly defined as “moderate” is limited to 4 randomized trials. These trials demonstrated that the greatest improvement in IMR grade was achieved with the addition of RA to bypass surgery versus bypass alone, and persistent IMR uncommonly progressed to severe at 1 year. Two of these trials showed a significant improvement in New York Heart Association functional class and left ventricular reverse remodeling with the addition of RA.

For the present, selecting patients for RA should first exclude those patients known not to benefit and second, as best as possible with current information, identify common baseline factors in those patients who have had enduring resolution of IMR after RA. IMR is most likely to persist after RA in patients with severe IMR who have basal dyskinesis or aneurysm and in those patients with extremely large ventricles at baseline (>70 mm mL/m2) if angina without dyspnea is the presentation, then CABG alone may be warranted. Overall condition of the patient may be an important consideration as well. Very elderly, frail patients and those with severe comorbidities (eg, chronic obstructive pulmonary disease, peripheral vascular disease, previous stroke, renal failure) may benefit from a “less is more” approach to treating CAD in the setting of moderate IMR, unless HF is problematic.

Ultimately, the goal of surgery in patients with IMR is to tailor the operation to the specific individual patient, offering the most durable result with the maximum clinical benefit at an acceptable operative risk. Identifying patients who benefit from restrictive annuloplasty in ischemic mitral regurgitation: An elusive yet essential quest! Toward a patient-tailored approach.
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VALVULAR HEART DISEASES 2016: EPIDEMIOLOGY AND IMPACT OF INTERVENTIONS

J.S. Borer, P.G. Supino
SUNY Downstate, New York, NY, USA

As valvular heart disease (VHD) has become better identified and treated, the epidemiology of VHD has been clarified. However, simultaneously, new/improved interventions have altered epidemiology. To assess the current epidemiology and impact of new interventions in 2016, we retrospectively evaluated results of the first 30 years (1983 through 2012, the last year for which complete data are available) of hospitalizations and in-hospital mortality from the New York State SPARCS (Statewide Planning and Research Cooperative System) database, including mandatory reporting from all non-Federal hospitals in the state (n=79,690,000 cases). These “real world” data reveal that, over 30 years, while total hospitalizations have decreased 16%, VHD hospitalizations have increased 36%, average age of VHD patients has increased 19.6% and valve replacements or repairs during admissions have increased 300%. Procedure increase has affected pts aged at least 65yrs (+450%) and those less than 65yrs (+190%), men (+350%) and women (+260%). During this interval in-hospital mortality has decreased 31%. Further, the 5 year results of the PARTNER trial suggest no differential impact of transcatheter valve procedures versus surgical procedures. Adjunctive pharmacologic therapy may be useful in very restricted settings, particularly if comorbid hypertension is present; otherwise drugs don’t improve outcomes and can be dangerous.

Conclusion: “real world” incidence of hospitalized VHD and of VHD interventions has risen dramatically during 30 years, is virtually linear and continuing. Despite increasing age, case fatality rates are decreasing, particularly for stenotic lesions, BUT longer term or in younger, less sick patients, or patients with MR or AR, outcomes are not yet known.
Low Gradient Severe Aortic Stenosis: Echo Features and Clinical Significance

P.A. Pellikka
Mayo Clinic, Rochester, MN, USA

Current practice guidelines define severe aortic stenosis (AS) as aortic valve (AV) area less than 1 cm² and mean AV gradient greater than 40 mmHg. Low gradient severe AS refers to the condition of mismatch between an AV area which suggests severe AS and mean gradient which is less than 40 mm Hg. Factors which can account for this discrepancy include echocardiographic measurement error, especially underestimation of the left ventricular outflow tract diameter, and small body size. Additionally, there is inherent incongruence between mean gradient and AV area; according to the Gorlin formula, AV area of .8cm² corresponds to a mean gradient of 40 mm Hg. Because gradient is a squared function of flow, a mild reduction in flow will impact gradient. Reduced ejection fraction (EF) may account for lower gradient. Stroke volume should be assessed; low flow, defined as less than 35 mL/m², is associated with increased mortality. When this is present, the potential contribution of other cardiovascular diseases such as mitral regurgitation and constrictive pericarditis to low flow should be considered. In true low flow, low gradient severe AS, concentric hypertrophy, smaller left ventricular cavity and restrictive physiology are often present. Strain imaging may reveal systolic dysfunction despite preserved EF. Compared to high gradient severe AS, the development of low output, low gradient severe AS is associated with greater increase in valvulo-arterial impedance during progression from moderate AS. Optimal timing of intervention with AV replacement is important in severe AS; obstruction often results in adverse ventricular remodeling. Valve replacement should be considered in the patient with low gradient AS if there is compelling evidence that stenosis is severe and the patient remains symptomatic despite optimal treatment of hypertension.
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Atrial Functional Mitral Regurgitation: The Left Atrium Gets Its Due Respect

B.D. Hoit
University Hospitals Case Medical Center and Case Western Reserve University. Cleveland, OH, USA

Moderate or greater mitral regurgitation (MR) is the most frequent valve disease in the United States. Competence of the mitral valve requires the temporally and spatially coordinated interaction of the mitral leaflets with the annulus, chordae tendinae, and papillary muscles; dysfunction of any of these components will affect the normal systolic coaptation of the mitral leaflets and cause mitral regurgitation; whether annular dilatation alone is sufficient for the development of MR is controversial. The mitral annulus is a thin fibrofatty ring that is bordered by variable insertions of atrial and ventricular myocardium. The nonplanarity and hyperbolic paraboloid shape of the annulus reduces mechanical stress on the leaflets and the its contraction reduces annular area and facilitates normal leaflet coaptation. Data suggest that anterior mitral leaflet musculature modulates leaflet stiffness, assists valve closure, and influences the three-dimensional geometry and function of the annulus and anterior mitral leaflet. Although functional MR has been associated with atrial fibrillation (AF), more recent data in patients referred for a first AF ablation who had both a baseline echocardiogram and one year clinical follow-up, normal LV systolic function, and at least moderate mitral regurgitation, suggest a more causal relationship; thus, maintenance of sinus rhythm resulted in greater reductions in left atrial volume and mitral annular diameter and less MR than in those whose arrhythmia recurred. While these data are provocative, they conflict with conventional dogma and should be considered hypothesis-generating. The precise mechanism of atrial functional mitral regurgitation is not clear but may be due to the effects that fibrillation-induced atrial remodeling has on atrial functions and synchrony; and annular size, geometry, and function. The prevalence of atrial functional regurgitation is unknown and its significance needs to be rigorously tested. Until then, it provides an intriguing, but untested rationale for aggressive rhythm control of AF.
OSTEOGENIC DIFFERENTIATION IS A MECHANISM FOR BIOPROSTHETIC VALVE CALCIFICATION
N.M. Rajamannan
Mayo Clinic, Rochester, MN, USA

Background: Bioprosthetic heart valve calcification is the major cause of structural valve deterioration (SVD). The mechanism of valve degeneration is unknown. This study hypothesizes that bioprosthetic valve calcification is a stem cell mediated bone differentiation process.

Method: 23 porcine valves removed from surgery were tested for SVD at and compared them to 6 control valves prior to implantation for stem cell marker and bone transcription factor for gene expression and MicroCT (Scanco). Next an in vivo model of prosthetic valve calcification by implanting normal bioprosthetic valves subcutaneously in 30 rabbits; 10 served as controls, 10 were fed 0.5% Cholesterol diet and 10 were fed 0.5% Cholesterol and were also given Atorvastatin for three months. In these 30 rabbits we measured markers of osteogenic bone differentiation.

Results: Human bioprosthetic porcine valves removed at surgery demonstrated a four-fold increase in osteogenic markers and calcium burden by MicroCT. The control valves prior to implantation had no evidence of increase bone formation.

Bioprosthetic valve tissue explanted from the rabbits fed the cholesterol diets demonstrated atherosclerosis and had evidence of cells positive for cKit, macrophage, and osteopontin expression which was attenuated in those who also received atorvastatin (p < 0.05). Control valves demonstrated a mild increase in the markers.

Conclusion: Bioprosthetic valve calcification is a mesenchymal cKit mediated osteogenic process. These experimental data are the first to demonstrate the presence of cKit and Cbfa1 gene expression in ex vivo and in vivo analysis. These findings are the first to demonstrate a biological mechanism in bioprosthetic valve calcification and have implications for future therapy of patients with bioprosthetic valves in order to slow the progression of valve calcification.
Atrial septal defect (ASD) is the second most common congenital heart disease in adults, accounting for approximately 10% of all congenital heart lesions. Moderate pulmonary arterial hypertension (PAH) is common in adults with ASDs and is independently associated with older age, female sex, and larger ASD size. In patients who develop pulmonary hypertension from their ASD, approximately 10% will progress to Eisenmenger syndrome. The hyperkinetic pulmonary blood flow in patients with ASD does not uniformly result in PAH and the mechanism that predisposes some patients to develop PAH is unknown.

Transcatheter ASD closure is safe and effective in reducing pulmonary artery systolic pressures, symptomatic improvement and positive cardiac remodeling effects. Despite early symptomatic improvement, adverse outcomes may occur in patients with elevated pulmonary vascular resistance undergoing transcatheter ASD closure. Careful haemodynamic evaluation with complete right heart catheterization should be performed on all patients. Pulmonary vascular resistance is calculated and if the patient has PAH, right heart catheterization is performed on room air and with consecutive administration of 100% oxygen, which may be followed by the addition of nitric oxide. There is however, no evidence regarding their usefulness in predicting the response of PAH to defect closure. Another simple technique is to temporarily occlude the defect and evaluate pulmonary response during occlusion. Although this technique is well known, few studies have evaluated its long-term predictive value.

Transcatheter closure in patients with secundum ASD and PAH can be successfully performed in selected subjects and is associated with good outcomes. Early improvements in are seen in patients with moderate or severe PAH undergoing transcatheter ASD closure. Continued improvement in pressures occurs in late follow-up. Despite an overall improvement in the pulmonary artery systolic pressures, many patients do not have complete normalization of pressures.

Determining operability is important in patients with ASD who present late. Although, a number of unresolved issues exist with currently available methods, a comprehensive assessment that incorporates clinical evaluation, noninvasive investigations and cardiac catheterization with calculation of flows and resistances, use of pulmonary vasodilators and test occlusion allows an appropriate management of such patients.
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AVOIDING AND SOLVING COMPLICATIONS DURING PERCUTANEOUS CLOSURE OF ASD
A. Lorber
Rambam Medical Campus, Haifa, Israel

We present 11 cases of percutaneous transcatheter occlusion of atrial septal defects (ASD's) in adults. These select cases represent an educational approach to special dilemmas, complications, and challenges which may occur during such a common procedure. The cases include:
1. Multi-fenestrated ASD
2. Balloon-assisted deployment of ASD occlude
3. Dilator-assisted deployment of ASD occlude
4. Cobra-shape disfiguration of the left-sided disc
5. ASD with deficient rim - aortic rim
6. Partial deployment in pulmonary vein
7. High (adjacent to superior vena cava) ASD
8. Large Chiari network
9. Double interatrial septum
10. Snaring a runaway occluder
11. Closure of ASD in the elderly

The interventional team is expected to be resourceful in the preparation for and performance of the procedure. Learning from others’ experience may be of benefit when coping with complex cases of ASD closure, as well as the prudent use of imaging modalities, personal experience and proper selection of equipment.
INTEGRATIONAL VALUE OF MRI IN STAGING THE SEVERITY OF AORTIC STENOSIS

M. Katayama, P.M. Panse, C.B. Kendall, J.R. Daniels, J.P. Sweeney, F.D. Fortuin, M. Belohlavek, H.P. Chaliki
Mayo Clinic, Scottsdale, AZ, USA

Background: “Paradoxical low flow low gradient severe aortic stenosis (AS)” is a new category in the ACC/AHA guidelines. The aim of this study was to test if MRI measured stroke volume has an impact on staging the severity of AS.

Methods: Thirty-eight patients with AS (mean gradient, MG ≥ 25mmHg) were prospectively enrolled and had echocardiography and cardiac MRI. Previous myocardial infarction, wall motion abnormality, non-sinus rhythms, greater than mild aortic and mitral valvular regurgitation, and left ventricular ejection fraction < 50% were excluded. Grades of AS were determined following guidelines: 1) Severe AS with high gradient (Vmax≥4m/s or mean gradient MG ≥40mmHg), 2) Severe AS with low gradient (aortic valve area (AVA) ≤1cm² with Vmax<4/m/s and MG<40mmHg), and 3) Moderate AS (AVA≥1cm², Vmax<4/m/s, MG<40mmHg). AVA was calculated using continuity equation by echocardiography and also calculated using combined modality, stroke volume (SV) by MRI with Doppler measures.

Results: Thirty-five patients were confirmed as same grade of AS by echocardiography and MRI (Table). However, 3 patients were re-classified from moderate AS to low gradient severe AS when MRI stroke volume was used. Higher stroke volume by echocardiography was observed in 2 of the 3 reclassified patients due to high left ventricular outflow tract (LVOT) velocity and consequent high time velocity integral.

Conclusion: MRI is helpful with determination of SV and staging the severity of AS, in some patients with problematic LVOT flow velocity. Larger studies are needed to confirm our study findings and further define the role of multimodality imaging.

<table>
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<tr>
<th>AVA determined by echocardiography</th>
<th>High Gradient AS (Vmax≥4m/s or MG≥40mmHg)</th>
<th>Low Gradient severe (AVA≤1) AS</th>
<th>Moderate AS</th>
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<tr>
<td>AVA determined by MRI stroke volume with Doppler measures</td>
<td>24</td>
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<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Low Gradient severe (AVA≤1) AS</td>
<td>0</td>
<td>0</td>
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Pulmonary Arterial Hypertension (PAH) increases the risk of postoperative complications in patients undergoing mitral valve surgery. With advances in the field of pharmacology and surgical techniques, risk should be decreased. In this retrospective observational study, we analyzed early postoperative outcome in patients underwent mitral valve replacement with and without preoperative PAH. We enrolled 739 patients underwent mitral valve replacement between January 2010 and June 2014. We categorized all patients in two major groups including Group 1 (With Preoperative mean PAH) and Group 2 (without preoperative mean PAH). PAH further divided into Group 2A (> 25 and <60 mmHg), Group 2B (>60 and <100 mmHg) and Group 2C (>100 mmHg) pulmonary arterial pressure. The mean age of study population was 32.3 years. On preoperative assessment PAH was present in N=445(60%) patients. According to mean Pulmonary arterial pressure N=224(50%), N=173(39%) and N=48(11%) patients were included in Group 2A, Group 2B, and Group 2C respectively. Basic characteristics were not significant in all patients. In the comparison of Group 1 vs Group 2, mean cardiopulmonary bypass and cross-clamp time was 79.37 and 54.46 minutes respectively (p>0.05). Postoperative ventilation and inotropic support time were 5.45 vs 6.88 hours and 8.9 vs 16.13 hours (p<0.001) in Group 1 and 2 respectively. Postoperative complications, intensive care unit stay and hospitalization were also significant in Group 1 and 2 (p<0.005). Overall mortality was zero in Group 1 vs 2% was in Group 2. Postoperative complications and hospitalization were increasing with the severity of preoperative PAH. Preoperative pulmonary arterial hypertension increases the risk of postoperative morbidity and mortality. PAH is an indicator for prolonged ICU and hospitalization. The severity of PAH increases the risk of the poor postoperative outcome.
Objective: To characterize resource utilization and outcomes in patients undergoing the Commando procedure.

Background: Endocarditis and degenerative calcification adversely impacts valvular function and can compromise the integrity of the intervalvular fibrous body (IFB). Once the IFB is damaged, a double valve replacement alone will not suffice. The Commando procedure involves replacement of the aortic and mitral valve with patch reconstruction of the IFB. This complex operation is performed at select institutions and few prior studies have reported associated outcomes.

Methods: Retrospective analysis of patients undergoing the Commando procedure between 2013 and 2015 at a single institution was performed. Primary endpoints examined were 30-day mortality, need for re-operation, hospital length of stay (LOS), duration of cardiopulmonary bypass (CPB), blood product utilization and postoperative organ dysfunction.

Results: A total of 14 patients were identified (mean age 56±17, 64% female). Indications for surgery were endocarditis (43%, n=6) or extensive calcification involving the IFB (57%, n=8). Concomitant procedures, including coronary artery bypass, tricuspid valve repair, Maze procedure, or myectomy were required in 36% of patients (n=5). Mean CPB time was 175±54 minutes. Mean aortic cross-clamp time was 142±43 minutes. Blood products transfused intraoperatively included red blood cells (5±4), fresh frozen plasma (4±4), platelets (3±2) and cryoprecipitate (1±1). Postoperative complications identified were heart block requiring permanent pacemaker (21%), hemodialysis (7%), cerebral ischemia (7%), and re-operation due to bleeding (14%). No patients developed respiratory failure in this series. The mean hospital LOS was 10 days. 30-day mortality was 14% (n=2).

Conclusions: The Commando procedure can be safely performed with moderate rates of morbidity and mortality in the early postoperative setting. Improvements in screening practices and earlier surgical intervention (prior to involvement of the IFB) may improve clinical outcomes.
ASYMPTOMATIC ACUTE COMPlications OF ATRIAL FIBRILLATION ABLATION USING IRRIGATED RADIOfrequency TECHNOLOGY

T. Deneké, P. Halbfaß, P. Müller, G. Szöllösi, M. Roos, J. Krug, A. Schade, A. Müller, F. Fochler, K. Nentwich
Cardiovascular Center Bad Neustadt, Germany

Complications after atrial fibrillation (AF) ablation are rare and therefore consecutive analysis of risk factors is often hard. Although, in asymptomatic patients silent cerebral events (SCE) in magnetic resonance imaging (MRI) and endoscopically detected esophageal thermal lesions (EDEL) have been documented in a much higher percentage of these patients. These asymptomatic complications may serve as surrogate indicators for the potential for severe complications (periprocedural stroke and atrio-esophageal fistula) of a specific ablation technology. We evaluated the incidence of SCE and EDEL in patients undergoing AF ablation using irrigated radiofrequency ablation technologies.

Methods: Overall 365 pts undergoing either single-tip contact-force irrigated RF ablation (N=221) or multipolar irrigated RF (nMARQ, N= 170). EDEL using post-ablation endoscopy (days 1 – 4) and SCE using diffusion-weighted brain MRI (days 1 – 3) were documented and related to procedural and patient-specific parameters. No symptomatic complications occurred in this patient cohort.

Results: 317 pts. underwent post-ablation endoscopic evaluation for EDEL and 333 post-ablation MRI to detect SCE. Overall incidence of EDEL was 17% (53) including 5% (15) esophageal ulcers and 25% (72) had SCE. In the single-tip RF ablations 13% had EDEL and 26% SCE whereas in the nMARQ ablations 21% had EDEL and 23% SCE. The incidence of EDEL was higher in patients undergoing esophageal temperature monitoring using a thermal esophagus probe with non-insulated large metal electrodes (30% versus 6% in single tip and 31% versus 6% in nMARQ ablations). The use of this specific probe was the only independent predictor of EDEL. The incidence of SCE was relevantly higher in patients ablated under continuous oral anticoagulation (37% versus 12% for single tip and 31% versus 15% for nMARQ ablations). Interrupted oral anticoagulation, persistent AF and left atrial low voltage areas were independent predictors of SCE.

Conclusions: AF ablation using irrigated RF involves a risk of asymptomatic complications to the esophagus and brain relevantly higher than symptomatic complications. The incidence of EDEL in irrigated RF is relevantly influenced by using a specific esophagus temperature probe with large non-covered metal electrodes. The incidence of SCE is modified by mode of periprocedural anticoagulation management and patient-specific factors. Reduction of asymptomatic complications may warrant beneficial effects on the most severe complications of AF ablation like periprocedural stroke and atrio-esophageal fistula.
ANTI-TROMBOTIC THERAPY FOR ATRIAL FIBRILLATION IN PATIENTS WITH CHRONIC KIDNEY DISEASE: CURRENT VIEWS

M.A. Alpert
University of Missouri, Columbia, MO, USA

Multiple randomized placebo-controlled trials have shown that in patients with non-valvular atrial fibrillation (NVAF) and intermediate to high risk of ischemic stroke (CHA2DS2Vasc score OF 1 or more in males or 2 or more in females), warfarin, with the dose adjusted to produce an INR of 2 to 3, is capable of significantly reducing cardioembolic complications including ischemic stroke. More recently, newer (novel) oral anticoagulants (NOAC’s) have been shown to reduce cardioembolic risk (including ischemic stroke) to a similar extent as warfarin and have been associated with a bleeding risk similar to or less than that of warfarin. Virtually all of these randomized controlled trials assessing the efficacy and safety of warfarin and the NOAC’s excluded patients with stage IV and stage V chronic kidney disease (CKD), including those receiving dialysis. Several small non-randomized studies have assessed the efficacy and safety of warfarin in patients with NVAF and stages IV to V CKD. The results of these studies are mixed, with some showing improvement in cardioembolic risk, some showing no effect on cardioembolic risk, and some showing higher cardioembolic risk. Many of these studies have reported excessive bleeding risk. Randomized controlled trials comparing the efficacy and safety of NOAC’s with warfarin in patients with NVAF have shown comparable cardioembolic and bleeding risks in those whose creatinine clearance was 25 to 30 ml per minute or more, but less than 50 ml per minute (essentially stage III CKD). Recommendations concerning the use of NOAC’s in patients with NVAF and a creatinine clearance less than 25 to 30 ml per minute are not evidence-based. Currently, no specific guidelines exist concerning the use of anticoagulants in patients with NVAF and stage IV to V CKD, including those receiving dialysis. Warfarin is commonly use in such patients, but justification for its use remains questionable.
ATRIAL FIBRILLATION AND SUPRAVENTRICULAR TACHYCARDIA: FROM MECHANISMS TO MANAGEMENT

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COMPlications AFTER RADIOFREQUENCY ABLATION OF ATRIAL FIBRILLATION: ATRIAL-ESOPHAGEAL AND PERICARDIOESOPHAGEAL FISTULAS

K. Seidl
Klinikum-Ingolstadt, Germany

Background: The initial experience with left atrial-esophageal fistula secondary to atrial fibrillation (AF) ablation procedures revealed a near universal mortality. A comprehensive description of the pathophysiology of atrial-esophageal fistula in the modern era and its resulting impact on morbidity and mortality is lacking in the literature.

Objective: To describe two patients who developed an atrial-esophageal and a pericardioesophageal fistula after radiofrequency ablation (RF) of AF. Both patients eventually expired. In more than 1,500 AF ablation procedures performed prior to these cases and, using the same ablation protocol, no fistulas had occurred. These cases highlight a rare but potentially life-threatening complication of an increasingly common procedure. Thus, awareness of this infrequent entity not only by cardiologists, neurologists, gastroenterologists and surgeons but also practitioners may offer the only significant potential for treatment and survival, demanding an open multidisciplinary approach.

Conclusion: Although rare, atrial-esophageal fistulas continue to remain an ominous and usually fatal complication of all AF ablation strategies. Symptoms of esophageal reflux, fever, difficulties in swallowing, shivering fits, general fatigue or neurological symptoms (seizures, stroke), and/or signs of sepsis in the first few weeks following any type of AF ablation should immediately raise suspicion about this catastrophic complication.
Wolff-Parkinson-White syndrome (WPW) is a conduction abnormality that results in sudden death due to rapid conduction down the accessory pathway during atrial fibrillation (AFib). The purpose of this study was to identify the most cost effective approach to risk assessing WPW patients.

**Methods:** A cost effectiveness analysis was performed using a decision tree model (TreeAge Pro software) comparing aVPE patients undergoing a transvenous electrophysiology study (TVEPS) vs. step wise risk assessment consisting of exercise stress test (EST), transesophageal electrophysiology study (TEEPS) and TVEPS if risk could not be determined. A TEEPS followed EST when VPE did not disappear in a single beat and TVEPS followed TEEPS when not effective inducing Afib or was risky (shortest preexcited RR interval < 250 msc). Efficacy of EST was 15% and the ability of TEEPS at inducing Afib was 88%; with 78% having no risk (published results.) Sensitivity analysis investigated the impact of changes in the efficacy assumption on the cost effectiveness results. Costs were 2009 Medicare reimbursement rates with cost of EST $ 277, TEEPS $990, and TVEPS $4035.

**Results:** The step wise approach involving EST, TEEPS and TVEPS when necessary is the most cost-effective method of identifying aVPE patients at risk with an expected cost of $2,174 compared to $4,035 for those initially undergoing TVEPS. Combining efficacy and cost data on these patients, this approach (EST- TEEPS - TVEPS) results in an average savings of $1,861 per patient. This step wise approach remained cost effective as long as TEEPS efficacy rate is > 31% on patients not screened out at EST.

**Conclusions:** This step wise approach (EST-TEEPS-TVEPS) is the most cost effective way to risk assessment of aVPE patient. This approach yields an average savings of $1,861 per patient.
The autonomic nervous system is believed to play an important role in atrial fibrillation (AF) pathophysiology. Vagal stimulation (VS) or sympathetic stimulation (SS) alone has been demonstrated to facilitate AF induction by premature beat or burst pacing. In vitro work has demonstrated that autonomic stimulation could induce triggered firing within pulmonary veins, implicating that simultaneous sympathetic and vagal nerve excitation could initiate AF. However, it remains unknown whether autonomic excitation alone is enough to initiate AF in vivo. We have examined the effects of VS, SS, or simultaneous VS+SS on spontaneous AF initiation in 8 dogs in vivo. VS was delivered to the right cervical vagus nerve and the stimulation intensity was titrated to decrease spontaneous sinus rate by 50%, which is known to facilitate AF induction when atrial premature beat or burst pacing is applied. SS was delivered to the right stellate ganglion and the intensity was adjusted to increase sinus rate by 50%. When autonomic stimulations did not trigger spontaneous AF, atrial burst pacing was applied to test AF inducibility. It was found that VS decreased heart rate from 109±8 bpm at baseline to 56±5 bpm (a reduction of 53 bpm, P<0.001). SS increased heart rate from baseline to 164±10 bpm (an increase of 55 bpm, P<0.001). SS+VS (concomitant sympathetic and vagal stimulation) resulted in a heart rate of 71±4 bpm (a reduction of 93 bpm from SS, P<0.001), confirming accentuated antagonism when both sympathetic and vagal nerves were excited. However, no spontaneous AF was triggered neither during VS, SS, nor SS + VS. When atrial burst pacing was applied, VS+SS increased AF inducibility to a similar level seen during VS alone. Thus, autonomic nerve stimulation itself cannot trigger spontaneous AF in healthy animals in vivo, though it does facilitate AF induction.
METABOLOMIC PROFILING IN RELATION TO NEW-ONSET ATRIAL FIBRILLATION IN THE COMMUNITY: THE FRAMINGHAM HEART STUDY

D. Ko
E.M. Riles
E.G. Marcos
J.W. Magnani
S.A. Lubitz
H. Lin
M.T. Long
R.B. Schnabel
D.D. McManus
P.T. Ellinor
V.S. Ramachandran
T.J. Wang
R.E. Gerszten
E.J. Benjamin
X. Yin
M. Rienstra

† Authors contributed equally to the manuscript.
* Authors contributed equally to the manuscript.

Background: Previous studies have shown several metabolic biomarkers to be associated with prevalent and incident atrial fibrillation (AF), but the results have not been replicated.

Objectives: To identify metabolite profiles associated with incident AF

Methods. We investigated metabolite profiles of 2,458 European ancestry participants from the Framingham Heart Study without AF at the index exam and followed them for 10 years for new-onset AF. Amino acids, organic acids, lipids, and other plasma metabolites were profiled by liquid chromatography-tandem mass spectrometry using fasting plasma samples. We conducted Cox proportional hazard analyses for association between metabolites and new-onset AF. We performed hypothesis generating analysis to identify novel metabolites and hypothesis testing analysis to confirm the previously reported associations between metabolites and AF.

Results. Mean age was 55.1±9.9 years, and 53% were women. Incident AF developed in 156 participants (6.3%) in 10 years of follow-up. A total of 217 metabolites were examined, consisting of 54 positively charged metabolites, 59 negatively charged metabolites, and 104 lipids. Several metabolites met the nominal level of significance (p < 0.05). However, none of the 217 metabolites met our a priori specified Bonferroni corrected level of significance in the multivariable analyses. We were unable replicate previous results demonstrating associations between metabolites that we had measured and AF.

Conclusions. In our metabolomics approach, none of the metabolites we tested were significantly associated with the risk of future AF.
TEMPORAL TRENDS IN PREVALENCE OF COMORBIDITIES IN ATRIAL FIBRILLATION PATIENTS ADMITTED WITH FIRST ISCHEMIC STROKE

S. Agrawal1, L. Garg2, N. Maheshwari1, D. Mohananey3, A. Singh1, A. Sinha1, A. Quddus1, S. Nanda1, J. Shirani1
1. St. Luke’s University Health Network, Bethlehem, PA, USA
2. William Beaumont Hospital, Royal Oak, MI
3. John H. Stroger Jr. Hospital of Cook County, Chicago, IL

Background: Atrial fibrillation (AF) increases risk of ischemic stroke (IS) five fold. We examined temporal trends in comorbidities among AF patients admitted with first IS.

Methods: Nationwide inpatient sample (NIS) database was retrospectively analyzed from 2003 to 2011.

Results: 713,409 adult AF patients were admitted with a first IS from 2003-2011. Mean age of such patients was 80±10 yrs. 41% were men and 82% were white. Number of admissions per year increased from 64,127 in 2003 to 92,399 in 2011 (p_trend<0.001) (Figure 1). Mean CHADS2 and CHADSVASc scores of these patients also increased over time (1.9±0.9 vs 2.1±0.9 and 3.6±1.2 vs 3.8±1.3 respectively in 2003 and 2011; p<0.001 for both). Prevalence of heart failure, hypertension, diabetes mellitus and peripheral vascular disease increased while proportion of females and patients aged ≥65 or ≥75 yrs decreased (p_trend<0.001 for all) (Figure 1). CHADSVASc and CHADS2 scores of <2 were present in 4.7% and 24.9% such patients. 80.7% patients with CHADS2 score <2 had a CHADSVASc score ≥2, however proportion of such patients decreased over study period (81% vs. 78.4% in 2003 and 2011 respectively, p<0.001). Higher CHADSVASc score was independently associated with higher inpatient mortality (7% vs 13.8 for scores of 0 and 7, OR 1.6 (1.4-1.8); p_trend<0.001) and increased risk for discharge to a facility other than home (28% for score of 0 vs 59.5% for score of 7, OR 1.6 (1.4-1.7); p_trend<0.001).

Conclusion: Admission rates for first IS in AF patients have increased significantly over recent years. This has been associated with increasing comorbidities despite decreasing proportions of older patients.
ATRIAL FIBRILLATION AND SUPRAVENTRICULAR TACHYCARDIA: FROM MECHANISMS TO MANAGEMENT

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COLCHICINE VERSUS PLACEBO FOR PREVENTION OF POST-PROCEDURAL ATRIAL FIBRILLATION: A SYSTEMATIC REVIEW AND META-ANALYSIS

O. Kreidieh, M. Kabach, S. El Dassouki, J. Martinez, R. Rosenstein, R. Chait
1. University of Miami Miller, Palm Beach Regional Campus, Atlantis, Florida, USA
2. Einstein Medical Center, Philadelphia, Pennsylvania, USA
3. West Palm Beach Veterans Affairs Medical Center, West Palm Beach, Florida, USA

Introduction: Inflammation has been implicated in post-cardiothoracic surgery and post-catheter ablation atrial fibrillation (AF).

Hypothesis: Colchicine, an anti-inflammatory drug, decreases the incidence of post-procedural atrial fibrillation.

Methods: We searched PUBMED, EMBASE and the Cochrane Library for randomized controlled trials comparing Colchicine to placebo for the prevention of peri-procedural AF. The primary outcomes were incidence of AF and total mortality. Secondary outcomes were stroke, total adverse events, gastrointestinal complaints, myelotoxicity, and length of stay (LOS). All endpoints were studied within 3 months of the procedure. Included articles underwent analysis via a random effects model.

Results: Of 96 retrieved entries, 7 papers from 5 studies were selected for inclusion. There was a total of 1160 patients with 806 males, and a mean age of 64.5. There were 113 recurrences of AF in 574 patients randomized to receive Colchicine and 184 recurrences in 586 patients from the placebo group (RR = 0.62 [0.48-0.8]). The finding remained significant on subgroup analysis of patients having cardiothoracic surgery and those having catheter ablation for preexisting AF. Similarly in 552 patients from 2 studies, the Colchicine treatment group had a shorter LOS (mean difference = -1.31 days [-1.86, -0.77]). There was however an increased incidence of total adverse events (52/349 vs. 29/347 HR=1.95 [1.2,3.17]), and GI side-effects (49/430 VS 20/427 HR = 2.56 [1.48,4.42]) with Colchicine therapy. Two studies reported that the incidence of death and stroke were similar amongst groups and two studies reported on myelotoxicity without events.

Conclusion: Colchicine significantly reduced post-procedural AF and in-hospital LOS in patients undergoing cardiothoracic surgery or AF ablation. The drug is also associated with an increased incidence of gastrointestinal side-effects.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Colchicine Events</th>
<th>Placebo Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deftereos 2012</td>
<td>13</td>
<td>81</td>
<td>27</td>
<td>80</td>
<td>0.48 [0.26, 0.85]</td>
</tr>
<tr>
<td>Egami 2013</td>
<td>11</td>
<td>36</td>
<td>27</td>
<td>51</td>
<td>0.58 [0.33, 1.01]</td>
</tr>
<tr>
<td>Imazio 2011</td>
<td>12</td>
<td>169</td>
<td>22</td>
<td>167</td>
<td>0.54 [0.28, 1.03]</td>
</tr>
<tr>
<td>Imazio 2014</td>
<td>61</td>
<td>180</td>
<td>75</td>
<td>180</td>
<td>0.81 [0.62, 1.06]</td>
</tr>
<tr>
<td>Sarzaeen 2014</td>
<td>16</td>
<td>108</td>
<td>33</td>
<td>108</td>
<td>0.48 [0.28, 0.83]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>574</td>
<td>586</td>
<td>100.0%</td>
<td>0.62 [0.48, 0.80]</td>
<td></td>
</tr>
</tbody>
</table>

Total events 113 184

Heterogeneity: Tau² = 0.02; Chi² = 5.51, df = 4 (P = 0.24); I² = 27%
Test for overall effect: Z = 3.71 (P = 0.0002)
GASTROINTESTINAL BLEEDING PROPHYLAXIS IN ATRIAL FIBRILLATION PATIENTS RECEIVING DABIGATRAN

T. Nantsupawat¹, S. Soonthapa¹, N. Nantsupawat², S. Klomjit², P. Tantrachoti², D. Sotello², H. Mazek², A.P. Perez-Verdia¹
1. Division of Cardiology, Department of Internal Medicine, Texas Tech University Health Sciences Center, Lubbock, TX, USA
2. Department of Internal Medicine, Texas Tech University Health Sciences Center, Lubbock, TX, USA

**Background and Aims:** Concerns have been raised regarding a significantly higher risk of gastrointestinal bleeding (GIB) with dabigatran as compared to warfarin. There is limited data on GIB prophylaxis in atrial fibrillation patients receiving dabigatran. We aim to assess whether proton pump inhibitor or H2-receptor antagonist (PPI/H2RA) treatment can lower the rate of GIB and what factors are associated with increased risk of GIB.

**Methods:** We reviewed 247 atrial fibrillation patients who used dabigatran at University Medical Center, Lubbock, Texas from October 1st 2010 to February 1st 2013. Risk factors for GIB, odds ratio (OR), and comparison of GIB between PPI/H2RA and non-PPI/H2RA groups were identified using Pearson Chi-square, Fisher’s exact test, and logistic regression.

**Results:** There were a total of 9 (3.6%) GIB events. The GIB rate was 10.9% in patients with HASBLED score >3, and 1.6% in patients with HASBLED score <3 (OR, 7.7; 95% confidence interval [CI], 1.9-31.9; P<0.01). The GIB rate was 13% in concurrent steroid use, and with 2.7% in non-steroid use group (OR, 4.87; 95% CI, 1.3-18.2; P=0.04). The GIB rate was 75% in patients with prior history of GIB within one year, and 2.5% in patients without prior history (OR, 30.25; 95% CI, 11.45-79.9; P<0.01). Patients who used PPI/H2RA had GIB rate of 11.1%, and 8.8% in patients who did not use (OR, 1.26; 95% CI, 0.30-5.22; P=1.00).

**Conclusions:** In our population a HASBLED score >3, concurrent steroid use, and prior history of GIB within one year were significant risk factors for GIB. PPI/H2RA use was not associated with lower rate of GIB in atrial fibrillation patients receiving dabigatran. Modifiable HASBLED risk factors, such as high systolic blood pressure, NSAIDs, or alcohol use should be corrected; risks and benefits should be cautiously reviewed before initiating dabigatran in high risk GIB group.
Atrial Fibrillation and Supraventricular Tachycardia: From Mechanisms to Management

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IMPACT OF CHA2DS2-VASC SCORE ON ATRIAL FIBRILLATION DETECTION IN PATIENTS WITH CRYPTOGENIC STROKE
St. Luke's University Health Network, Bethlehem, PA, USA

Introduction: Atrial fibrillation (AF) is a leading cause of ischemic stroke. Advent of insertable loop recorders has allowed detection of occult AF in patients with cryptogenic stroke. The CHA2DS2-VASc score, an indicator of progressive endothelial dysfunction, is shown to be superior to CHADS2 score in assessment of thromboembolic risk. We hypothesized that systemic causes of endothelial dysfunction are more often responsible for ischemic stroke than occult AF.

Methods: From October 2009 through September 2015, 202 loop recorders were implanted at our institution, of which 74 (37%) were inserted for detection of occult AF in patients with cryptogenic stroke (mean age 66 years, 51% women). Medtronic LINQ was implanted in 60 and Medtronic REVEAL XT in 14 patients. CHA2DS2-VASc risk score was calculated.

Results: At a mean follow up duration of 12 months, occult AF was detected in 15 patients (20%) with an average time to detection of 8 months. CHA2DS2-VASc scores were 5.13±1.84 and 4.97±1.56 in patients with and without occult AF (p>0.05). There were no statistically significant differences in congestive heart failure [20% vs. 5.1%], hypertension [66.7% vs. 67.8%], age greater than 65 years [33% vs. 22%], age greater than 75 years [47% vs. 29%], diabetes [13% vs. 32%], or vascular disease [40% vs. 59%] (p>0.05 for all) among those with and without occult AF.

Conclusion: Risk factors comprising CHA2DS2-VASc score are highly prevalent among patients with cryptogenic stroke regardless of the presence of occult AF. This finding has implications regarding optimal long term management of cryptogenic stroke.
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STATIN CANDIDATES IN “PRIMARY PREVENTION” DOUBLES WITH THE “ACC/AHA GUIDELINE ON THE TREATMENT OF BLOOD CHOLESTEROL TO REDUCE ATHEROSCLEROTIC CARDIOVASCULAR RISK”: COMPARISON OF TWO AMERICAN GUIDELINES IN TURKISH POPULATION

C. Barcin¹, F. Bayram², A. Sonmez¹, C. Gokce³, K. Gundogan²
1. Gulhane Military Medical Academy, Ankara, Turkey
2. Erciyes University, Kayseri, Turkey
3. Mustafa Kemal University, Hatay, Turkey

Objectives: In a sample representative of Turkish population, we compared “2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol” (ACC/AHA_gl) with “Adult Treatment Panel (ATP) III” guideline (ATPIII_gl) regarding statin recommendations for primary prevention.

Background: The ACC/AHA_gl differs from previous guidelines in different aspects of hyperlipidemia management.

Methods: A total of 2657 individuals (between 40 and 74; 52.8% female) without known CV disease were included. CV risk was calculated using “Global Framingham Risk Score Equations” (GFRSE) in ATPIII_gl and Pooled Cohort Risk Assessment Equations (PCRAE) (non-Hispanic Caucasians) in ACC/AHA_gl. “High risk” was defined as >=20% for “global” CV events in 10 years for GFRSE and as >=7.5% for “hard” CV events in 10 years for PCRAE.

Results: The table depicts the traditional CV risk factors. According to ATPIII_gl 27.8% (27.0% of women and 28.6% of men) of the Turkish population were candidates for statin use. This proportion rose to 53.1% (43.3% of women and 62.8% of men) using ACC/AHA_gl (p<0.001).

Conclusion: Compared to ATPIII_gl recommendations, ACC/AHA_gl increased the candidates for statins extensively. This difference was more prominent in males. Current guidelines should be interpreted cautiously in the context of efficacy, safety and cost effectiveness.
ASSESSING THE CARDIOVASCULAR HEALTH BEHAVIORS OF COLLEGE STUDENTS

M. Granieri, J.P. Cordova, A. Koulova, C. Bavishi, S. Trignano, J.E. Tamis-Holland
Mount Sinai St. Luke’s Hospital, NY, USA

Background: In 2010 the American Heart Association defined national goals to achieve ideal cardiovascular (CV) health in the United States. Studies have demonstrated poor compliance with these recommendations among American adults. Less is known regarding health behavior in the younger generation of Americans.

Objective: To assess health behaviors of college students.

Methods: Using a modified scoring system of the AHA “Life’s Simple Seven” we evaluated general health behaviors of college students through an online survey assessing CV knowledge and lifestyle. We measured 4 categories of healthy living, and each was assigned up to 2 points. We defined ideal CV health behavior as a score in the highest tertile (6-8).

Results: A total of 548 students completed the survey (mean age 21.9 +/- 6.64 years; 79.9% female; 20.1% male; 87.6% Caucasian; 2.55% Asian; 4.56% black and 4.56% other). Few students were complying with all healthy dietary guidelines, and approximately half of all students were getting adequate exercise. Close to 40% of students had an unhealthy BMI. As a result, only half of all students met the criteria for ideal CV health.

Conclusions: Future effort should focus on promoting healthier habits in the younger generation of Americans.

<table>
<thead>
<tr>
<th>Health Metric</th>
<th>N (%) Achieving Metric</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy Diet (Meeting all 3 metrics below)</td>
<td>3.0%</td>
</tr>
<tr>
<td>&lt; 36 oz. of Sugary Drinks/Week</td>
<td>80.3%</td>
</tr>
<tr>
<td>&gt; 4.5 Cups of Fruit-Vegetables/Day</td>
<td>64.9%</td>
</tr>
<tr>
<td>&gt; 2 Servings of Fish/Week</td>
<td>5.7%</td>
</tr>
<tr>
<td>Exercise &gt;75 minutes of vigorous or &gt;150 of moderate intensity/week (&gt;60 minutes/day for 18-19 year old)</td>
<td>51.9%</td>
</tr>
<tr>
<td>BMI &lt;25 (&lt;85 percentile for 18-19 year old)</td>
<td>61.8%</td>
</tr>
<tr>
<td>Not smoking</td>
<td>94.2%</td>
</tr>
<tr>
<td>Overall Score 6-8 (Ideal Health Behavior)</td>
<td>51.1%</td>
</tr>
</tbody>
</table>
HOW EFFECTIVE IS LIFESTYLE INTERVENTION IN WEIGHT MANAGEMENT AND DEPRESSION IN ADULTS WITH METABOLIC SYNDROME

Q. Wang, S.Y. Chair, E.M.L. Wong
The Nethersole School of Nursing, Faculty of Medicine, The Chinese University of Hong Kong

Background: Metabolic syndrome (MetS) is a cluster of cardiometabolic risk factors. With the global pandemic of overweight, MetS has been increasingly prevalent. Moreover, MetS has adverse impacts on physical and psychological well-being of individuals. Lifestyle intervention is regarded as the first-line intervention for MetS.

Objectives: This study examined the effectiveness of a three-month lifestyle intervention program (LIP) on weight management and depression in Chinese MetS population.

Methods: This study was a randomized control trial and recruited adults with MetS from a general hospital in Shandong, China. The control group received usual care from the hospital. In addition to usual care, the intervention group received the LIP, including an educational booklet, one session of education, and six telephone follow-ups after discharge. Body weight and depression (Depression subscale of Hospital Anxiety and Depression Scale, HADS-D) were measured at baseline (T0), one month (T1) and three months (T2). The effect of the LIP was tested by the generalized estimating equations (GEE) model.

Results: One hundred and seventy-three patients with MetS participated in the study with 86 in the intervention group and 87 in the control group. The participants had a mean body weight of 74.74 Kg (standard deviation, SD = 7.46), and a mean score of 4.22 (SD = 3.11) in HADS-D. During the 3-month study, the participants demonstrated continuous decrements in body weight and depression. Moreover, the GEE revealed significant interaction (group by time) effects on body weight and depression at both T1 and T2 (all p values < 0.05).

Conclusion: The LIP was effective in weight management and reducing depression in Chinese adults with MetS. Lifestyle interventions could be integrated in daily practice to improve the quality of care for patients with MetS.
UPDATE ON ASPIRIN IN THE PRIMARY PREVENTION OF CARDIOVASCULAR DISEASE
C.H. Hennekens
Florida Atlantic University, Boca Raton, FL, USA

Background: In secondary prevention among a wide range of patients who have survived a prior occlusive vascular event, as well as during acute myocardial infarction and acute occlusive stroke the absolute reductions far exceed the absolute risks. In primary prevention, the balance is less clear.

Methods: Meta-analyses of serious vascular events (myocardial infarction, stroke, or vascular death) and major bleeds in the primary prevention trials.

Findings: In the primary prevention trials, aspirin yielded a 12% reduction in serious vascular events (0.51% aspirin vs 0.57% control per year, p=0.0001), due mainly to a reduction of about a fifth in non-fatal myocardial infarction (0.18% vs 0.23% per year, p<0.0001). The net effect on stroke was not significant (0.20% vs 0.21% per year, p=0.4: hemorrhagic stroke 0.04% vs 0.03%, p=0.05; other stroke 0.16% vs 0.18% per year, p=0.08). Vascular mortality did not differ significantly (0.19% vs 0.19% per year, p=0.7). Aspirin increased major gastrointestinal and extracranial bleeds (0.10% vs 0.07% per year, p<0.0001), and the main risk factors for coronary disease were also risk factors for bleeding. The benefits were similar for men and women.

Interpretation: In primary prevention, the reduction in occlusive events needs to be weighed against any increase in major bleeds Specifically, the average absolute risk of subjects randomized was so low that it is not possible to get reliable estimates of the benefit to risk ratio in subjects at moderate risk. Until the results of ongoing trials are available, nobody would disagree that a non-fatal myocardial infarction or stroke is more likely to be disabling than a non-fatal bleed. Thus, at present in primary prevention, the appropriate and judicious prescription of aspirin by clinicians should be based on individual clinical judgments that weigh their absolute benefits against the absolute risks.
Background. Limited data exist on the efficacy of multifactorial lifestyle programs on impacting the progression of atherosclerosis. We examined the efficacy of a lifestyle intervention program on progression of coronary artery calcium (CAC).

Methods. We studied 235 subjects (mean age 49.7, 24.9% female), 123 randomized to the RENEW Program and 112 to standard of care. The RENEW[TM] Program consisted of 9 bi-monthly face-to-face web sessions over 16-18 weeks followed by 13 monthly check-in sessions (maintenance) over 80 weeks and included modules on responding to stress, enhancing the effects of relaxation, nourishing the immune system, physical activity, and social support. Participants also received baseline and 2-year follow-up measures of risk factors and coronary calcium measures (volume and Agatston score) from whole body computed tomography (CT); intervention group participants also received a comprehensive physician consultation regarding the CT scan results. Among 87 subjects (34 control and 43 intervention) who completed the program, we examined baseline-follow-up changes in CAC (natural log transformed) using the paired t-test within groups and Student’s t-test for comparisons between groups, with analysis of covariance for adjustment of baseline CAC scores and risk factors.

Results. Over 2 year follow-up there were CAC increases (natural log units) both in volume (0.48, p=0.001) and score (0.57, p<0.001) in the control group, but not in the intervention group (0.04, p=0.79 for volume and 0.05, p=0.72 for score) (p=0.04 for volume and p=0.01 for score changes between groups). After adjustment for baseline CAC, age, gender, and risk factors, these differences between control and intervention groups persisted (p=0.049 for volume and p=0.042 for score).

Conclusions. Our findings suggest a beneficial impact of a multifactorial behavioral program on retarding progression of atherosclerosis measured by CAC. Larger scale trials are needed to confirm findings and implications on cardiovascular outcomes.
THE EFFECT OF SELF-MONITORING OF BLOOD PRESSURE ON MEDICATION ADHERENCE AND LIFESTYLE FACTORS: SYSTEMATIC REVIEW, META-ANALYSIS AND QUALITATIVE INTERVIEWS

B.R. Fletcher, J. Hartmann-Boyce, L. Hinton, R.J. McManus
University of Oxford, Oxford, UK

Background: Self-monitoring of blood pressure (SMBP) can contribute to reduced blood pressure in people with hypertension. Potential mediators include increased medication, improved adherence, and changes in lifestyle factors. The objective of this review and associated interviews was to determine the effect of SMBP on medication adherence, medication persistence, and lifestyle factors in people with hypertension.

Methods: Electronic bibliographic databases were searched through to identify randomized controlled trials that compared SMBP to control/usual care in ambulatory hypertensive patients and reported medication or nonpharmacologic treatment adherence measures. Following this, we interviewed hypertensive patients who were engaged in self-monitoring to further investigate our findings.

Results: Twenty-eight trials with 7,021 participants fulfilled the inclusion criteria. Medication adherence was assessed in 25 trials (89%), dietary outcomes in 8 (29%), physical activity in 6 (21%), and medication persistence in 1 (4%). Blood pressure was assessed in 26 studies (93%). Pooled results of 13 studies demonstrated a small but significant overall effect on medication adherence in favor of SMBP interventions (standardized mean difference 0.21, 95% CI 0.08, 0.34), with moderate heterogeneity (I² = 43%). Where SMBP interventions had a significant effect on lifestyle factor change, the effect was unlikely to be clinically significant. Pooled results of 11 studies demonstrate a significant overall effect on diastolic blood pressure in favor of SMBP (weighted mean difference -2.02, 95% CI -2.93, -1.11), with low heterogeneity (I² = 0%). A test for subgroup differences showed no difference when studies were grouped according to whether medication adherence was significantly improved or not. Interviews with participants suggested unguided self-monitoring increased knowledge but did not alter behaviour.

Conclusions: SMBP may contribute to improvements in medication adherence in hypertensives. However, evidence for the effect of SMBP on lifestyle change and medication persistence is scarce, of poor quality, and suggests little clinically relevant benefit.
CAROTID INTIMA MEDIA THICKNESS MEASUREMENT PROMISES TO IMPROVE CARDIOVASCULAR RISK EVALUATION IN HEAD AND NECK CANCER PATIENTS

D. Jacoby1, J. Hajj1, A. Javaheri1, E. Degoma1, A. Lin1, P. Ahn1, H. Quon2

1. University of Pennsylvania, Philadelphia, PA, USA
2. Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Maryland, USA

Background: Radiation treated head and neck cancer (HNC) patients are at high risk for developing radiation vasculopathy, as evidenced by an increased stroke risk. The benefits of screening and assessing the cardiovascular risk of HNC patients using carotid intima media thickness (CIMT) ultrasound are not known.

Objective: To determine the prevalence of high cardiovascular risk in patients without known cardiovascular diseases who received radiation for HNC, determine the percentage of screened patients who had a change in clinical management as a result of an increased CIMT, and to compare this risk assessment tool on patients’ risk classification using Framingham Risk Score (FRS) and Pooled Cohort Atherosclerotic Cardiovascular disease (ASCVD) Risk Equation (recommended by AHA/ACC Guidelines on the Assessment of Cardiovascular Risk).

Methods: Retrospective medical chart review was conducted on 134 radiation treated HNC patients. The main outcome measures were cardiovascular risk (as determined by CIMT) and clinical management. Also, the FRS and the Pooled Cohort ASCVD Risk Equation were used to compare classification with CIMT.

Results: Approximately 74% of the cases were at high cardiovascular risk using CIMT technique. Approximately half of the HNC patients screened had a change in clinical management characterized by recorded initiation of aspirin and recorded initiation or increase of statin therapies. The FRS and the Pooled Cohort ASCVD Risk Equation failed to detect 40-50% of cases found to be at high risk using the CIMT technique.

Conclusion: Carotid IMT identified a much greater percentage of radiation treated HNC patients at high cardiovascular risk compared to standard cardiovascular risk calculators. By more accurately identifying the patients at high risk, this may lead to more effective prevention, and therefore a reduction in cardiovascular events.
Efficacy of a Cardiovascular Behavioral Intervention Program on Measures of Stress

A. Eisenberg¹, N.D. Wong², C. Pateo¹, J. Cecere¹, H. Eisenberg¹
1. Re-Engineering Healthcare, Tustin, California, USA
2. University of California at Irvine, Irvine, California, USA

Background. Limited data exists on the efficacy of multifactorial lifestyle programs focusing on stress management in reducing psychosocial factors of cardiovascular risk. We examined the efficacy of a lifestyle intervention program on measures of psychosocial stress.

Methods. We studied 235 subjects (mean age 49.7, 24.9% female), of which 123 were randomized to The RENEW Program[TM] and 112 received standard of care. The program consisted of 9 bi-monthly face-to-face web sessions over 16-18 weeks followed by 13 monthly check-in sessions (maintenance) over 80 weeks. The program included modules on responding to stress more effectively, enhancing the effects of relaxation, nourishing the immune system, physical activity and social support. Among 86 subjects who completed the program, we examined control and intervention group baseline-follow-up changes in Type A behavior, perception of life stress, overall psychological well-being (using the Stress Profile survey) and depression (using Becks Depression Index).

Results. Both groups showed reductions in Type A behavior: -1.82 (control, p=0.003) and -3.39 (intervention, p<0.001), perception of stress: -.72 (control, p=0.36) and -1.8 (intervention, p=0.006), and Becks depression index: -2.52 (control, p=0.01) and -4.38 (intervention, p<0.001), with increases in psychological well-being 1.20 (control, p=0.33) and 2.31 (intervention, p=0.01) that were more beneficial in the intervention group despite no significant differences between groups.

Conclusions. Our findings suggest a potentially beneficial impact of a multifactorial behavioral program emphasizing stress management for reducing psychosocial risk. Larger scale studies are needed to confirm findings and whether they may contribute to improving cardiovascular outcomes.
EFFECT OF VARIOUS CHILDHOOD ANTHROPOMETRIC MEASURES ON ADULTHOOD CAROTID INTIMA-MEDIA THICKNESS: A SYSTEMATIC REVIEW AND META-ANALYSIS


1. ICMR Advanced Centre for Evidenced Based Child Health, Advanced Pediatric Centre, PGIMER, Chandigarh, India
2. Department of Pediatrics and ICMR Advanced Centre for Evidenced Based Child Health, Advanced Pediatric Centre, PGIMER, Chandigarh, India
3. Department of Pediatrics, Advanced Pediatric Centre, PGIMER, Chandigarh, India
4. Medical Informatics and Statistics Group, University of Oulu, Oulu, Finland

Background: Various studies have examined the effect of different childhood anthropometric measures on adulthood preclinical atherosclerosis measured as carotid intima-media thickness (cIMT).

Objectives: We aimed to establish summary estimates for the relationship between childhood anthropometric measures and adulthood cIMT.

Methods: A systematic literature search was conducted to identify studies which assessed the relationship between childhood anthropometric measures and adulthood cIMT. We included studies which enrolled children and adolescents between ages 6 months to 19 years and followed them up for at least 4 years. For the meta-analysis, the effect sizes were first converted into a common effect size, standardized regression coefficients.

Results: Of the 121 studies found, twelve studies were included in the meta-analysis for the association between childhood BMI and adulthood cIMT. A 1 SD increase in adolescent BMI increased early adulthood cIMT (20-45 years) by 0.06 mm (95% CI= 0.04, 0.07) and a 1 SD increase in BMI during childhood and adolescent lead to an increase of 0.10 mm (95% CI= 0.07, 0.12) in early adulthood cIMT. A total of seven studies were included to examine the relationship between childhood and adulthood BMI on adulthood cIMT. The pooled findings showed that subjects who were overweight/obese as children and adults had significantly higher cIMT measurements than subjects who were who always had normal BMI. Also, the subjects who were overweight/obese as children but had normal BMI as adults had cIMT measurements similar to those subjects who always had normal BMI. Both childhood weight and skinfold thickness were found to have a positive relationship with adult cIMT.

Conclusion: Not only BMI but other childhood anthropometric measures have been shown to have an effect adulthood cIMT.

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DEPLETION OF THE CEREBLON GENE ENHANCES CARDIAC CONTRACTILITY, CA2+ TRANSIENT AND MITOCHONDRIAL ENERGY METABOLISM IN MICE

H.K. Kim, T.H. Ko, Y.H. Noh, S.H. Jeong, N. Kim, B.D. Rhee, K.S. Ko, J. Han
National Research Laboratory for Mitochondrial Signaling, Department of Physiology, Department of Health Sciences and Technology, BK21 Project Team, College of Medicine, Cardiovascular and Metabolic Disease Center, Inje University, Busan, Korea

Background and Purpose: Cereblon (CRBN) is an interacting protein with large-conductance calcium-activated potassium channels. A mutation of CRBN causes a mild type of mental retardation in humans. While, recent study suggested its novel function as AMPK inhibitor via direct interaction with AMPK α1 subunit. Disruption of CRBN gene enhanced hepatic AMPK activity and prevents high-fat diet induced obesity and insulin resistance in mice. The aim of study is to figure out the effect of CRBN KO in heart and its mitochondrial function.

Method and Results: Eight weeks of Control (CRBN+/+) and CRBN KO (CRBN−/−) models were examined their body weight, heart rate and heart/body ratio. In vivo cardiac functions of animals were assessed by echocardiography. To evaluate mitochondrial function of those animals, cardiac mitochondria of CRBN+/+ and CRBN−/− were isolated then examined their ATP contents and ATP production rate, ROS production rate, oxygen consumption rate and membrane potential. As results, the body weight, heart weight and heart/body ration were not significantly different between CRBN+/+ and CRBN−/− mice. Echocardiography showed enhanced cardiac contractility in CRBN−/− mice based on increased ejection fraction (%) and fractional shortening (%). CRBN KO enhance single cardiac myocyte cell contraction with intracellular Ca2+ transient. In their mitochondria, CRBN KO enhances Mitochondria Oxidative phosphorylation which lead to increase of basal ATP contents and substrate/ADP stimulated ATP production rate in CRBN−/− mice than CRBN+/+. In addition, basal H2O2 level and rotenone induced ROS production rates were significantly lower in CRBN−/− mice than CRBN+/+.

Conclusion: Our results suggested that CRBN is an important mitochondrial functional regulator which link cytosol to mitochondrial energy metabolism and Ca2+ signaling.
MITF SWITCHES FROM ACTIVATOR TO REPRESSOR OF ERBIN EXPRESSION DURING CARDIAC HYPERTROPHY

I. Rachmin1,9,10, E. Amsalem1, E. Golomb2, R. Beeri8, D. Gilon8, G. Min3, R.S.Y. Foo5, D.E. Fisher6, E. Razin1, S. Tshori7
1. Department of Biochemistry and Molecular Biology, The Institute for Medical Research Israel-Canada, Hebrew University Medical School, Jerusalem, Israel
2. Department of Pathology, Shaare Zedek Medical Center, Jerusalem, Israel
3. Department of Cancer Biology, The Scripps Research Institute, Jupiter, FL, USA
4. Sharett Institute of Oncology, Hadassah Hebrew University Medical center, Jerusalem, Israel
5. Cardiovascular Research Institute, Center of Translational Medicine, National University of Singapore, Singapore
6. Cutaneous Biology Research Center, Department of Dermatology, Massachusetts General Hospital, Harvard Medical School, Boston, USA
7. Department of Nuclear Medicine, Hadassah-Hebrew University Medical Center, Jerusalem, Israel
8. Heart Institute, Hadassah-Hebrew University Medical Center, Jerusalem, Israel
9. Department of Stem Cell and Regenerative Biology, Harvard University, Cambridge, Harvard Stem Cell Institute, Cambridge, MA, USA
10. Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA

Background: Changes in cardiac gene expression contribute to the progression of heart failure by affecting cardiomyocyte growth, function, and survival. Microphthalmia-associated transcription factor (MITF) is highly expressed in cardiomyocytes. We have previously reported that MITF-mutated mice have diminished cardiac hypertrophy in response to beta-adrenergic stimulation resulting in decreased cardiac function, and that cardiac size and function are decreased in middle aged MITF-mutated mice. Thus, MITF is required for cardiac hypertrophy but the molecular mechanisms involved are unknown.

Objective: To elucidate the molecular mechanism by which MITF regulates cardiac hypertrophy.

Methods and Results: Gene array analysis of hearts from MITF-mutated mice indicated that ErbB2 interacting protein (Erbin), which we have recently shown to be a negative modulator of pathological cardiac hypertrophy, is a candidate target gene for MITF. Here we show that Erbin expression is regulated by MITF. Under basal conditions MITF activates Erbin expression by direct binding to its promoter. However, under beta-adrenergic stimulation Erbin expression is decreased only in wild type mice, but not in MITF-mutated mice. Yeast two-hybrid screening, using MITF as bait, identified interaction with the cardiac-predominant four-and-a-half LIM domain protein 2 (FHL2), which was confirmed by co-immunoprecipitation in both mouse and human hearts. Upon beta-adrenergic stimulation, FHL2 and MITF bind Erbin promoter as a complex, and repress MITF-directed Erbin expression. Overexpression of FHL2 alone had no effect on Erbin expression, but in the presence of MITF, Erbin expression was decreased. FHL2-MITF association was also increased in biopsies from heart failure patients.

Conclusion: Our results suggest that MITF-FHL2 interaction acts as signal responsive activator/repressor of Erbin expression during cardiac hypertrophy, and this fine tuning mechanism could be an important regulator of cardiac hypertrophy.
INHIBITION OF LEPTIN RECEPTOR ABOLISHES INTRALIPID-INDUCED CARDIOPROTECTION AGAINST ISCHEMIA-REPERFUSION INJURY

N. Motayagheni, S. Phan, C. Eshraghi, M. Eghbali
UCLA, CA, USA

Objectives: We have already shown that Intralipid protects the heart. Here, we examined whether cardioprotective effect of Intralipid (ILP) against I/R injury is mediated, at least in part, through leptin receptor.

Methods: Male mice, 2-3 months old were used. Mice were anesthetized after heparinization. The heart was removed immediately and perfused with Krebs–Henseleit at 37°C for 20 min through aorta in Langendorff. The heart was then subjected to 20 minutes of global normothermic ischemia followed by 40 min reperfusion with Kreb Buffer. A catheter was directly inserted into the left ventricle (LV) to measure cardiac function. At the end of the experiments, the hearts were cut into four transverse slices and the infarct size was measured using triphenyltetrazolium chloride (TTC) staining.

Results: Adding ILP during reperfusion significantly improved cardiac function at the end of 40 min reperfusion in control group. In the presence of leptin receptor antagonist, ILP failed to protect the heart as the heart had no detectable activity at the end of 40 min reperfusion. The maximum rate of LV pressure rise (dP/dtmax) was also significantly lower in ILP+leptin receptor antagonist group (90±32 mmHg/s), compared to ILP group (2703±145 mmHg/s) or even control group (448±224 mmHg/s, p<0.01 vs. ILP and control). Consistent with much lower functional recovery in ILP-leptin receptor antagonist group, the infarct size was also significantly larger in ILP+leptin receptor antagonist group compared to ILP group.

Conclusions: Our data demonstrates for the first time that leptin receptor is involved in cardioprotection offered by ILP against I/R injury, as ILP fails to protect the heart in the presence of leptin receptor antagonist. Summary: Inhibition of leptin receptor abolishes ILP-induced cardioprotection against I/R injury.
CYP2C19 GENETIC VARIATION AND INDIVIDUALIZED CLOPIDOGREL PRESCRIPTION IN A CARDIOLOGY CLINIC

S.A. Mirabbasi1,2, K. Khalighi1,2, B. Khalighi1,3, A. Kodali1,2, Y. Wu1,2, W. Fan1,2
1. Cardiovascular Institute, Department of Medicine, Easton Hospital, Drexel University, Easton, PA, USA
2. Internal Medicine Residency, Department of Medicine, Easton Hospital, Drexel University, Easton, PA, USA
3. Temple University, School of Pharmacy, Philadelphia, PA, USA

Background: Cytochrome P2C19 enzymes play a major role in clopidogrel metabolism and may alter their enzymatic activity in patients undergoing cardiovascular procedures. Subsequently the Food and Drug administration (FDA) has recommended genetic evaluation and genotyping of patients requiring clopidogrel as part of their therapy.

Objectives: To customize clopidogrel therapy and its efficacy by utilizing CYP2C19 genotypic and phenotypic information to improve clinical outcome in patients.

Methods: 465 consecutive patients, who met the enrolment criteria and agreed to participate in this study, were followed for 2 years. The data was then reviewed by a cardiologist and reviewed with each patient, prior to any further dose adjustment or modifications.

Results: Of 465 patients, 183 were wild-type homozygotes (*1/*1), 87 were heterozygotes (*1/*2), 3 were (*1/*4), 1 was (*1/*8), 1 was (*1/*10), 35 were (*2/*17), 1 was (*8/*17), 1 was (*9/*17), 18 were homogygotes (*2/*2), 121 were (*1/*17) and 14 were (*17/*17). Distributions of variant alleles, genotypes and phenotypes were analyzed. Individual clopidogrel recommendation and a follow up plan was made. According to the current guidelines following changes have been made in the past year: 1) switching to prasugrel in Poor metabolizer genotype which improved clinical outcome; 2) Discontinuing or lowering clopidogrel doses in Rapid or Ultra rapid Metabolizer genotype to decrease bleeding risk. For those who were not on clopidogrel but carried abnormal allele(s), “clopidogrel caution” was documented. Patients have been followed up for one year. There were not any cardiac clinical symptoms, cardiac death or excessive bleeding.

Conclusions: The relatively high frequencies of both gain-of-function (18.8%) and loss-of-function (19.8%) alleles in our patients make genotyping CYP2C19 clinically relevant. None of the patients had cardiac symptoms after modification which demonstrates that improved the quality of treatment with less complications.
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A GENOME-WIDE METHYLATION ANALYSIS SHOWS DIFFERENTIALLY METHYLATED REGIONS BETWEEN FUTURE CVD CASES AND CONTROLS
O. Cottell1,2, J.V. Sorli1,3, E.M. Asensio1,3, R. Fernandez-Carrion1,3, C. Ortega-Azorin1,3, R. Barragan-Arnal1,3, I. Gonzalez-Monje3, F. Aros4, J.M. Ordovas5, D. Corella1,3
1. CiberOBN, Madrid, Spain
2. Universitat Jaume I, Castellon, Spain
3. University of Valencia, Valencia, Spain
4. University Hospital of Araba, Vitoria, Spain
5. Human Nutrition Research Center on Aging, Boston, MA, USA

Background: Epigenetic factors are emerging as important cardiovascular disease (CVD) risk factors, with the advantage that they are dynamic and can be modified. Methylation is one of the main epigenetic factors, whose specific influence is still little known in CVD events. Moreover, not only environmental factors contribute to methylation levels, but also there are genetic factors.

Objectives: 1) To undertake a pilot epigenome-wide methylation study (EWAs) on a high cardiovascular risk Mediterranean population to detect at baseline the differentially methylated loci that are associated with future cardiovascular events; and 2) To discover SNPs that are associated with differences in methylation at those loci and could be proxies of the same.

Methods: A pilot EWAS was undertaken that included 12 subjects who had developed incident CVD throughout a median of 4.8 y of follow-up and 12 controls, paired by sex, diet and follow-up time, all being participants in the PREDIMED-Valencia study. An EWAS was undertaken to analyze the data from DNA methylation at baseline using the Infinium HumanMethylation450 BeadChip. The top-ranked methylation loci were identified and the SNPs of that gene analyzed. The SNPs were associated with methylation levels and the association of the most significant SNP with CVD incidence was studied in the 1,094 PREDIMED-Valencia study participants.

Results and Conclusions: The top-ranking methylation loci was the cg21585936 island in the PPP2R2B (protein phosphatase 2 regulatory subunit B, beta) gene. At baseline, cases had higher methylation levels than controls (+8%; P=0.000006). The SNP most associated with methylation levels was the PPP2R2B-rs3844538; with variant-allele carriers having lower methylation (P<0.025). Although in the subsample, the PPP2R2B-rs3844538 minor allele was associated with lower CVD incidence (P=0.014), this protection did not reach the statistical significance in the multivariable Cox regression model for the whole population (HR: 0.63; 95%CI: 0.25-1.61), suggesting additional modulation by environmental factors.
RELATIONSHIP BETWEEN ASPRIN RESPONSE RELATED MICRORNA AND THE RISK OF CARDIOVASCULAR EVENTS IN CAD PATIENTS

J.W. Zhang¹, T.F. Liu¹, W.Y. Liang¹, X.R. Feng¹, L. Wang², P.Z. Wang², S.W. Fu³, T.A. McCaffrey³, M.L. Liu¹
¹. Department of Geriatrics, Peking University First Hospital, Beijing, China
². Department of Immunology, Basic Medical Sciences, Peking University Health Science Center, Beijing, China
³. Department of Medicine, Division of Genomic Medicine The George Washington University School of Medicine and Health Sciences, Washington DC, USA

Aims: Aspirin was widely used in the secondary prevention of cardiovascular diseases. However, individual response to aspirin varies from one patient to another. MicroRNAs (miRNAs), functioning as posttranscriptional regulators, has been reported to participate in various pathophysiological pathways. Our study tried to screen out aspirin response related miRNAs, then illustrate their correlation with cardiovascular risks in patients with coronary artery disease (CAD).

Methods: Potential aspirin response related miRNAs were screened out via miRNA sequencing, using blood samples from two groups, one consists of seventeen CAD patients who experienced cardiovascular events during regular aspirin therapy, while the other enrolled those with favorable aspirin response, and well-matched age, gender and BMI index. In order to validate our preliminary results, we enrolled CAD patients on 100 mg/d aspirin since January 2013, with medical records collected and peripheral blood samples drawn for miRNA quantitative analysis. All patients were followed up in outpatient department or by telephone calls regularly. Clinical outcomes were defined as the occurrence of cardiovascular events on aspirin treatment.

Results: Through bioinformatics analysis, 38 miRNAs differentially expressed were screened out, the ten miRNAs were chosen for further quantitative PCR analysis. High-on aspirin platelet reactivity (HAPR) was defined as AA-induced platelet aggregation - the upper quartile of our enrolled population. It was observed that miR-30c-5p was up-regulated and miR-3158-5p was down-reglated significantly in HAPR patients as compared to No-HAPR patients(P<0.05). Besides, the AUCs of miRNA 30c-5p and miRNA 3158-5p were greater than 0.7, which indicated the potential of both miRNAs in diagnosing HAPR status. What’s more, COX regression analysis showed miR-30c-5p and miR-3158-5p were significantly associated with the risk of cardiovascular events.

Conclusions: In our enrolled patients, the expression of miR-30c-5p and miR-3158-5 were correlated with aspirin responses and the risk of cardiovascular events. However, long-term and larger-scale studies are still needed.
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A GENETIC VARIANT IN THE CIRCADIAN GENE BMAL1 IS ASSOCIATED WITH HIGHER INCIDENCE OF CARDIOVASCULAR DISEASES

D. Corella1,2, J.V. Sorli1,2, F.G. Frances1,2, R. Fernandez-Carrion1,2, R. Estruch1,3, L. Parnell4, F. Aros1,5, C. Saiz2, J.M. Ordovas4, O. Coltell1,6
1. CiberOBN, Madrid, Spain
2. University of Valencia, Valencia, Spain
3. Hospital Clinic, IDIBAPS, Barcelona, Spain
4. Human Nutrition Research Center on Aging, Boston, MA, USA
5. University Hospital of Araba, Vitoria, Spain
6. Universitat Jaume I, Castellon, Spain

Background: The physiological functions of cardiovascular organs are closely related to circadian rhythm. The onset of cardiovascular diseases (CVD) such as acute coronary syndrome, atrial arrhythmia, etc exhibits diurnal oscillation suggesting that variations in clock genes may be very important in regulating these circadian rhythms and associated with CVD incidence. The Aryl hydrocarbon receptor nuclear translocator-like (ARNTL) gene, also called BMAL1, is, together with CLOCK, one of the most relevant clock genes. In mice it has been observed that BMAL1 influences critical heart functions, such as development of dilated cardiomyopathy, contractile function, as well as life span. However there are few studies that have related variations in this gene with CVD in humans. Aims: To study the association of polymorphisms in the BMAL1 gene with CVD incidence in a high-risk cardiovascular population.

Methods: We have carried out a prospective study in the PREDIMED-Valencia study participants (men and women aged 67 +/- 7 y). PREDIMED is a dietary intervention trial with Mediterranean diet (MedDiet). Participants (n=1055) were followed-up a median of approx. 5 years and incidence of CVD (including myocardial infarction, stroke and cardiovascular death were) was assessed. BMAL1 polymorphisms were determined by dense genotyping and the BMAL1-rs1982350 SNP (n=1007) was selected for associations. Multivariable Cox regression models were fitted.

Results and Conclusions: Prevalence of the BMAL1-rs1982350 was 51%GG, 39%GA and 10%AA. Carriers of the variant allele (A) had higher CVD incidence (2.7%, 5.6% and 8.2% in wild-type homozygous, heterozygous and homozygous for the variant allele, respectively; P=0.004). In the Cox model adjusted for age, sex, dietary intervention and diabetes, the HR for CVD per variant allele (additive model) was 1.56; 95%CI:1.07-2.37; P=0.023. We also found a significant association with higher risk of myocardial infarction, this being the first time that the association between this polymorphism and CVD incidence in humans has been reported.
MMP1 GENE POLYMORPHISM AND CIRCULATING MMP IN ELDERS WITH LIPEMIA AND PATIENTS WITH IHD

G.A. Paul, N.V. Goncharova, V.M. Belichenko, T.A. Korolenko
Institute of Physiology and Fundamental Medicine, Novosibirsk, Russia

Objective. We aimed to test the association between matrix metalloproteinase type 1 (MMP1) genetic polymorphisms, circulating MMP and lipemia development in young, old persons and in patients with ischemic heart disease.

Background. Polymorphism in MMP1 gene (1-bp insertion G-1607GG in the promoter sequence; rs1799750) defines existence of two alleles of gene. It was suggested that the increased formation of such enzymes is result of mutation of MMP1 gene associated with the increased risk of atherosclerosis.

Methods. DNA samples of 70 persons (<45 and >45 years with lipemia or normal lipid profile) and 15 patients with ischemic heart disease (IHD) were isolated from blood using commercial DNA Express kit (SPC Lytech, Russia). Genotyping was carried out by RT-PCR method (IQ5, BioRad). Serum MMP activity assay was made by fluorometric method against MCA-Pro-Leu-Gly~Leu-Dpa-Ala-Arg-NH2 (American Peptide Company, Inc.) as a substrate at pH 7.5 (Knight et al., 1992).

Results. In healthy persons in Novosibirsk (<45 years old, with normal serum lipids profile) the rate of MMP1 2G/2G was shown in 42.8%. In elders with lipemia MMP1 2G/2G predominated (63.6%), and MMP1 1G/2G and MMP1 1G/1G rate was equal (both 18.2%). In IHD MMP1 2G/2G also predominated (53.3%), while MMP1 1G/1G were registered in 13.3%, and MMP1 1G/2G – in 33.3%. There was a slight elevation of serum MMP activity in IHD group.

Conclusion. Elder persons with dyslipidemia and patients with IHD were characterized by increased rate in MMP1 2G/2G gene possibly related to this disease.
EVALUATION OF GENETIC PROFILES IN MEDICATION ADJUSTMENTS

A.J. Allen¹, J.M. Wetmore², M.F. Maturi Allen³, D.R. Talreja³

1. Yale Univ New Haven, CT, USA
2. CVAL, Virginia Beach, VA, USA
3. CVAL, EVMS, Norfolk, VA, USA

Background: A series of sequential high risk cardiovascular patients were followed who had noninvasive genetic testing performed using cheek swab technology. Over the next 90 days, it was ascertained what medication changes were made based on these tests.

Methods: 32 sequential patients were identified with high risk underlying cardiovascular features including prior coronary artery disease with or without previous revascularization. They underwent cheek swab genetic testing by an organization named G6 Genomics with standardized genetic testing including CYP2C19, CYP2C9, CYP2D6, CYP3A4, CYP3A5, Factor II, Factor V Leiden, MTHFR, SLCO1B1, VKORC1. Chart review was performed at 90 days on each patient to identify what independent changes were made by their clinicians in response to genomic reports produced.

Results: Of the 32 tested patients, 10 patients representing 30% of the population had ultimate changes in their medication regimens. 3 patients had changes in their lipid-specific medications, 2 patients in anti-platelet, 2 patients in anti-coagulation, 2 patients in anti-hypertensive therapy, and 1 patients in their psychoactive medications. Subsequent review at 6 months showed no patients had significant intolerance or adverse reactions as a result of these drug changes.

Conclusions: Genomic testing can help identify up to 25% of patients who may benefit from subsequent medication changes.
MICRORNA AS KEY TARGETS OF MEF2 TRANSCRIPTION FACTOR IN THE ENDOTHELIUM: ROLE IN THE PATHOGENESIS OF PULMONARY ARTERIAL HYPERTENSION

J. Kim, Y. Young
Sookmyung Women's University, Seoul, South Korea

Pulmonary arterial hypertension (PAH) is a fatal disease characterized by the vascular remodeling of the pulmonary arterioles, including formation of plexiform and concentric lesions comprised of proliferative vascular cells. Clinically, PAH leads to increased pulmonary vascular resistance resulting in right ventricular failure. The existing therapies have improved outcome but mortality remains exceedingly high. Given the high rate of mortality and limited modalities of treatment, identifying novel targets of therapy remain of utmost importance. Our recent identification of a key signaling paradigm in PAECs involving apelin, microRNAs (miRNAs) 424 and 503, and FGF2/FGFR1 demonstrate the importance of crosstalk among these molecules in maintenance of pulmonary vascular homeostasis. Here we demonstrate that the transcription factor myocyte enhancer factor 2 (MEF2) is a cis-acting factor that regulates miR-424 and miR-503 expression downstream of apelin in PAECs. MEF2 transcriptional activity was found to be significantly decreased in PAH PAECs. This is mediated by increased nuclear localization of two class IIa histone deacetylases (HDACs) in PAH PAECs, namely HDAC4 and HDAC5, which negatively regulate MEF2 function. Selective inhibition of class IIa HDACs led to restoration of MEF2 transcriptional targets, decreased PAH PAEC migration and proliferation, and amelioration of experimental pulmonary hypertension (PH) models. These studies demonstrate that restoration of endothelial MEF2 activity, achieved by selective inhibition of class IIa HDACs, is a promising therapeutic strategy in PAH.
PROCOLLAGEN TYPE I CARBOXY-TERMINAL PROPEPTIDE IS ASSOCIATED WITH BLOOD PRESSURE, CARDIAC HYPERTROPHY AND DYSFUNCTION, AND PREDICT CARDIOVASCULAR EVENTS IN HEMODIALYSIS PATIENTS

Y.O. Kim, B.M. Choi, S.J. Shin
The Catholic University, Seoul, Korea

Objective: Serum procollagen type I carboxy-terminal propeptide (PICP) is a marker of myocardial fibrosis in hypertensive heart disease. However, the clinical significance of PICP is less determined in end-stage renal disease (ESRD) patients. This study was to evaluate the association of predialysis serum PICP levels with blood pressure (BP), cardiac hypertrophy and function, and the impact of PICP levels on cardiovascular (CV) events in hemodialysis patients.

Design and Methods: Serum PICP was obtained from predialysis blood samples of 123 incidental hemodialysis patients. The patients were divided into a low PICP group (n = 61) and high PICP group (n = 62). Baseline laboratory parameters, BP pressure, echocardiographic parameters were compared between groups. The associations between serum PICP and mortality and cardiovascular (CV) events were also investigated.

Results: The high PICP group showed significant older, a lower serum albumin, higher systolic BP, higher LVMI and E/E′ and lower EF compared to the low PICP group. A direct correlation was found between serum PICP and LVMI (r=0.308, P=0.002), E/E′ (r=0.236, P = 0.009), E/A ratio (r=0.285, P=0.002). A negative correlation was found between serum PICP and EF (r=-0.289, P=0.001) and DT (r=-0.203, P=0.026). In the multivariate linear regression analysis, the serum PICP was independently positive associated with LVMI and E/E′ and negative associated with EF. In the multivariate cox regression analysis, the event-free survival rates for CV events were significantly lower in the high PICP group compared with those in the low PICP group, and the serum PICP was an independent predictor for CV events.

Conclusions: Serum PICP is significantly associated with left ventricular hypertrophy and dysfunction, and predicts CV events in incidental hemodialysis patient.
IDH2 DEFICIENCY IMPAIRS MITOCHONDRIAL FUNCTION IN ENDOTHELIAL CELLS AND ENDOTHELIUM-DEPENDENT VASOMOTOR FUNCTION

S. Jung, C. Kim
Chungnam National University, Daejeon, Korea

Mitochondrial NADP(+) -dependent isocitrate dehydrogenase (IDH2) plays an essential role protecting cells against oxidative stress-induced damage. A deficiency in IDH2 leads to mitochondrial dysfunction and the production of reactive oxygen species (ROS) in cardiomyocytes and cancer cells. However, the function of IDH2 in vascular endothelial cells is mostly unknown. In this study the effects of IDH2 deficiency on mitochondrial and vascular function were investigated in endothelial cells. IDH2 knockdown decreased the expression of mitochondrial oxidative phosphorylation (OXPHOS) complexes I, II and III, which lead to increased mitochondrial ROS (mtROS). In addition, the levels of fission and fusion proteins (Mfn-1, OPA-1, and Drp-1) were significantly altered and MnSOD expression also was decreased by IDH2 knockdown. Furthermore, knockdown of IDH2 decreased eNOS phosphorylation and nitric oxide (NO) concentration in endothelial cells. Interestingly, treatment with Mito-TEMPO, an mtROS-specific scavenger, blunted mitochondrial fission, fusion and mtROS production, and reduced the IDH2 knockdown-induced decrease in MnSOD expression, eNOS phosphorylation and NO production in endothelial cells. Endothelium-dependent vasorelaxation was impaired, and the concentration of bioavailable NO decreased in the aortic ring in IDH2 knockout mice. These findings suggest that IDH2 deficiency induces endothelial dysfunction through the induction of dynamic mitochondrial changes and impairment in vascular function.
EFFECTS OF PERIVASCULAR ADIPOSE TISSUE ON VASODILATION DIFFER BY THE SEVERITY OF METABOLIC DISORDERS

S. Kagota, S. Iwata, K. Maruyama, S. Koyanagi, K. Shinozuka
Mukogawa Women’s University, Nishinomiya, Japan

Metabolic syndrome (MetS) facilitates the development of cardiovascular disease due to atherosclerosis. We demonstrated that nitric oxide-dependent vasodilation is impaired with exposure to metabolic abnormalities in the mesenteric arteries of SHRSP.Z-Leprfa/IzmDmcr (SHRSP.ZF) rats, an animal model of MetS. In contrast, perivascular adipose tissue (PVAT), which is located outside the blood vessels, has been recently recognized as playing a role in vascular function. We have proposed that PVAT of resistant arteries of SHRSP.ZF rats helps in vasodilation regulation to compensate for impaired vasodilation observed in MetS. Therefore, we examined whether the compensatory effects of PVAT are also observed in MetS in the arteries of Otsuka Long-Evans Tokushima Fatty (OLETF) rats before type II diabetes onset. We used 20-week-old OLETF and control Long-Evans Tokushima Otsuka (LETO) rats. The body weight, waist/body length ratio, and serum lipid and glucose levels of OLETF rats were higher than those of LETO rats, but blood pressure was unchanged. Relaxations in response to nitroprusside were impaired in the isolated mesenteric arteries of OLETF rats compared with those of LETO rats, which is similar to that observed in SHRSP.ZF rats. The relaxation in the arteries enveloped by PVAT was the same in those not enveloped by PVAT in OLETF rats, which differs with that observed in SHRSP.ZF rats. These results indicate that the remarkable degree of the metabolic abnormalities, especially high blood pressure, is associated with the appearance of the compensatory effects of PVAT on vasodilation in MetS.
TRASTUZUMAB INDUCES SYSTEMIC OXIDATIVE STRESS IN AN EXPERIMENTAL BIOLOGICAL MODEL


1. Instituto Nacional de Cardiologia "Ignacio Chavez", Mexico City, Distrito Federal, Mexico
2. Instituto Nacional de Cancerologia, Mexico City, Distrito Federal, Mexico

Nearly 30% of breast cancer cases present an aggressive biology characterized by overexpression of receptor protein for human epidermal growth factor 2, ErbB2 (HER2). Treatment with Her2 directed monoclonal antibodies like Trastuzumab improves survival of these patients subgroups. Unfortunately, use of these agents induces varying grades of cardiotoxicity. Since cardiotoxicity is mediated through oxidative stress we analyzed the Trastuzumab posttreatment oxidative systemic profile in an experimental biological model.

**Methods.** 20 female Wistar rats were included in our study, with mean weight 310.25±23.51, divided in two groups: control, n=10 (with no treatment), and those treated with 4 doses of Trastuzumab (2mg/Kg qod, n=10). Two days after the 4th dose, and under anesthesia with sodium pentobarbital, serum samples were obtained to determine levels of biomolecular markers of oxidative stress: dihydro and tetrahydrobipterin (BH2, BH4), malonyl dialdehyde (MDA), endothelin-1 (ET1), bradykinin (BDK), nitric oxide (NO), 8-hydroxi-2′-deoxiguanosine, p-cresol and the total antioxidative capability.

**Results.** When compared with the group of control models, the serum of Trastuzumab treated rats had 86% decrease of CAT levels, a 3.6 times increase in MDA levels, BDK and NO had 90% and 66% decrease, each one, BH2 increased 3.98 and BH4 decreased 3 times, and finally ET1 had a 3.5 times increase.

**Conclusions.** Systemically, treatment with Trastuzumab (4 doses) induced increase of the oxidative stress, and decrease of the systemic antioxidative capability, which could represent a promoting phase for cardiac dysfunction.
TIME-DEPENDENT RELAXANT EFFECTS OF NITRIC OXIDE AND CARBON MONOXIDE INTERACTION ON ALBINO RATS AORTIC RINGS WITH SPECIAL EMPHASIS ON THE ROLES OF K+ AND CA++ CHANNELS

O.A. Al-Habib, S.S. Khalil
University of Zakho, Kurdistan Region, Iraq

The current study included time-dependent interactive relaxant effects of a combination of IC50 doses of sodium nitroprusside (NO donor) and dimanganese decacarbonyl (CO donor) and the possible roles of K+ and Ca2+ channels in norepinephrine pre-contracted from male rats using PanLab tissue bath system. Most of the relaxant effect (61.77%) induced by SNP+DMDC occurred during the first 10 minutes while in the presence of Nifedipine the relaxation rate was further enhanced to 74.15% and completed within 30 minutes. Pre-incubation of aortic rings with BaCl2 and 4-AP significantly reduced time-dependent relaxation after 30 min. This indicate that Kir and Kv channels play major roles in the process of hyperpolarization and aorta relaxation. Conversely, pre-incubation with GLIB enhanced time-dependent relaxation rate, while aortic rings treated with TEA did not show any significant change in the relaxation. Pretreatment of aortic rings with a combination of 4-AP+BaCl2, BaCl2+TEA and GLIB+BaCl2 produced highly significant reduction in time-dependent relaxation rate On the other hand, pretreatment of aortic rings with a combination of GLIB+4-AP and GLIB+TEA significantly enhanced relaxation rate whereas pre-incubation with 4-AP+AEA showed no effect on the relaxation rate induced by a mixture of SNP+DMDC. From the current study, the following novel conclusions can be complied: 1. Ca++ channel plays no role in the relaxation of aorta. 2. When using K ion channels blockers individually, both Kir and Kv channels play important roles in the process of repolarization 3. When using any two combination of K channel blockers, in addition to Kir and Kv channels, other channels such as KATP and Kca channels also participated in the process of hyperpolarization and subsequent relaxation. Key words: CO, NO, Aorta, K and Ca channel blockers, hyperpolarization, relaxation
PROTEASE-ACTIVATED RECEPTOR-2 RELAXATION OF RAT AORTAS VASODILATION IN METABOLIC SYNDROME

K. Maruyama¹, S. Kagota¹, J.J. McGuire², N. Yoshikawa¹, K. Nakamura¹, K. Shinozuka¹

1. Department of Pharmacology, School of Pharmacy and Pharmaceutical Sciences, Mukogawa Women's University, Nishinomiya, Hyogo, Japan
2. Cardiovascular Research Group, Division of BioMedical Sciences, Memorial University, St. John's, Newfoundland and Labrador, Canada

Metabolic syndrome describes the clinical condition of an individual that presents a number of cardiovascular disease risk factors, including obesity, hyperlipidemia, insulin-resistance and hypertension. Low-grade systemic inflammation is also recognized as part of metabolic syndrome. In various tissues, local cellular release of proteases like trypsin, mast cell beta-tryptase, kallikrein, and coagulation factors VIIa and Xa, can activate PAR2 (protease-activated receptor-2) to regulate production of mediators of inflammation and/or cause vasodilation. Using SHRSP.ZF-Leprfa/IzmDmcr rats (SHRSP.ZF) with metabolic syndrome, we demonstrated that PAR2-mediated nitric oxide (NO)-dependent vasodilation is sustained until 20 weeks of age (wks), but attenuated at 30 wks in aortas from SHRSP.ZF. In the current study, we examined age-related changes in the mechanism of PAR2-mediated relaxation of aortic vascular smooth muscle. Specifically, we measured protein and mRNA expression of PAR2, endothelial NO synthase (eNOS), and soluble guanylyl cyclase, PAR2 agonist-induced cGMP accumulation and aortic ring relaxations in tissues from SHRSP.ZF at 10, 20, and 30 wks. We found PAR2 mRNA and protein expression were similar in aortas of rats at 10 and 20 wks, but were less at 30 wks. eNOS content was similar in aortas of rats at all ages. In contrast, soluble guanylyl cyclase protein content in aortas of rats at 20 and 30 wks were less than in rat aortas at 10 wks. cGMP accumulation induced by PAR2-activating peptide, 2-furoyl-LIGRLO-amide, was similar in aortas of rats at 10 and 20 wks, but less in rat aortas at 30 wks. Aortic ring relaxations in response to cGMP-analog were impaired in rats at 30 wks. These results suggest that attenuation of relaxation pathway via PAR2 activation on endothelial cells, accompanying with reduced response to NO in smooth muscle cells, is involved in the impairment of PAR2-mediated vasodilation with ageing in SHRSP.ZF.
THE PROTECTIVE EFFECTS OF PARTHENOLIDE TREATMENT IN MOUSE CORTICAL MICROVASCULAR ENDOTHELIAL CELLS INVOLVED CA2+ CLEARANCE SUPPRESSION BY IMPAIRING PLASMALEMMAL CA2+ PUMP ACTIVITIES AND ER STRESS

K.L. Wong1,2,3, T.Y. Tsai4,5, S.Y. Lou5, C.W. Cheung2, Y.M. Leung6
1. Department of Anesthesiology, China Medical University & Hospital, Taichung, Taiwan
2. Department of Anesthesiology, LKS Faculty of Medicine, University of Hong Kong, Hong Kong
3. Shandong University, Qilu Hospital-Nanshan Hospital, Shandong, China
4. Cardiovascular Division, Lotung Poh-Ai Hospital, Luodong, Taiwan
5. Department of Biomedical Engineering, Chung Yuan Christian University, Chungli, Taiwan
6. Department of Physiology, China Medical University, Taichung, Taiwan.

Aims: Parthenolide has been reported to be a cardioprotectant, but not much is known of its actual mechanism. We investigated whether parthenolide affected Ca(2+) signaling in endothelial cells, key components in regulating the vascular tone.

Methods: Brain micro-vascular bEND.3 cells were from Sigma (USA). The western blots were visualized by enhanced chemiluminescence (MA, USA). Cytosolic Ca2+ in bEND was measured with Fura-2 method. Cell membrane potential (MMP) measured by MMP Assay Kit. Cell viability was measured by MTT assay. The p < 0.05 were considered significant (ANOVA).

Results: we found that a 15-h treatment with parthenolide resulted in amplified ATP-triggered Ca(2+) signal; the latter had a very slow decay rate suggesting suppression of Ca(2+) clearance. Evidence suggests parthenolide suppressed Ca(2+) clearance by inhibiting the plasmalemmal Ca(2+) pump; such suppression did not result from decreased expression of the plasmalemmal Ca(2+) pump protein. Rather, such suppression was possibly a consequence of endoplasmic reticulum (ER) stress, since salubrinal (an ER stress protector) was able to alleviate parthenolide-induced Ca(2+) clearance suppression. Conclusion: The protective effects of parthenolide treatment in bEND involved ca2+ clearance suppression by impairing plasmalemmal ca2+ pump activities and subsequently ER stress. it is important to further examine in details the perturbing effects of parthenolide on Ca(2+) homeostasis in endothelial cells

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USE OF DEEP SEDATION WITH PROPOFOL TO RELIEVE CATHETER ENTRAPMENT DUE TO SEVERE RADIAL ARTERY SPASM DURING CORONARY ANGIOGRAPHY

E.S. Roberto¹, T. Aung¹, A. Agarwal¹.²
1. Wright State University Department of Internal Medicine, Dayton, OH, USA
2. Veteran Affairs Medical Center, Dayton, OH, USA

Introduction: Trans Radial Access (TRA) is becoming increasingly favored worldwide as the preferred arterial approach site for coronary angiography. Use of TRA is supported by its advantages over the femoral artery route. Benefits include reduced instances of access site bleeding, trauma, infection, shortened hospitalization, and improvement in clinical outcomes. Potential complications have included radial artery occlusion, catheter kinking, vasospasm, hand ischemia, and even arterial perforation. Severe vasospasm leading to catheter entrapment is a rare complication with few cases reported in the literature, each case with different therapeutic methods attempted. There is no consensus approach to alleviating this complication. To date, case reports have described the use of intravenous fentanyl and midazolam, with both successful and unsuccessful outcomes. This interventional case describes severe vasospasm of the right radial artery leading to catheter entrapment, and novel resolution by deep sedation with intravenous propofol.

Case Description: A 48 year-old male with history of smoking and peripheral vascular disease underwent scheduled angiography for a newly diagnosed cardiomyopathy. Modified Allen’s Test was normal with good ulnar collateral flow noted. A 5 French radial sheath was placed into right radial artery, and antispasmodic cocktail of Verapamil, Heparin and Nitroglycerin was given. There was some difficulty upon advancing the wire through the forearm. Angiography revealed an arterial loop just after the bifurcation of brachial artery, successfully negotiated with an angled guide wire. A 5 French Jackey catheter was advanced without any difficulty up to aortic root. At that time, difficulty was noted while manipulating the catheter, as torque was not being transmitted to the catheter tip. The patient developed severe right forearm pain and the catheter was unable to be retracted. Radial artery spasm was clinically suspected. Arterial vasodilators (Verapamil, Nitroglycerin) were unsuccessful. Catheter kink was excluded as the J-wire could still be advanced inside the catheter without any difficulty. Intravenous Midazolam was given and warm compresses were applied, without improvement. Finally, intravenous propofol was administered by the anesthesiologist. Following deep sedation, the catheter was gradually withdrawn. The patient remained hemodynamically stable throughout.

Discussion: Radial artery access presents increased risk of spasm owing to increased muscular characteristics and concentration of alpha-1 adrenoreceptors. Once radial artery spasm is suspected, catheter advancement or removal should be ceased. Pain can result in further increasing vasomotor tone and vasoconstriction. Forceful manipulation can lead to radial artery transection or eversion endarterectomy. This case highlights the rare occurrence of severe radial artery spasm and catheter entrapment in the presence of an arterial loop, effectively remitted by deep sedation with intravenous propofol. Use of propofol for spasm during TRA has not been previously described in this setting for coronary angiography.
ACUTE MYOCARDIAL INFARCTION / REPERFUSION THERAPY

CORONARY REPERFUSION MANEUVER IN PRIMARY CORONARY INTERVENTION WITH RIGHT CORONARY ARTERY CULPRIT

J.M. Telayna, J.M.(h) Telayna, R.A. Costantini
Hospital Universitario Austral, Bs As, Argentina

Introduction: During acute myocardial infarction the manual thrombus aspiration has shown encouraging results by diminishing volume of residual thrombus, decreasing the likelihood of embolism, improving myocardial perfusion and cardiac mortality. However in 10% failure in crossing the lesion, 10% failure in removing all voluminous thrombus and may cause coronary dissection.

Objectives: To evaluate the clinical and angiographic results of a “low profile” coronary reperfusion maneuvering (passage of a deflated balloon into the distal bed followed by its removal) during PCI with right coronary artery (RCA) culprit.

Materials and Methods: Between 258 primary PCI where performed in pts with ST elevated myocardial infarction and initial TIMI flow 0-1, with RCA as culprit vessel in 70 pts. We excluded patients with no ST elevated myocardial infarction, acute coronary syndrome as an epiphenomenon or pts resuscitated from cardiac arrest. In the target population maneuver was performed in 40 pts (group A – PCI with maneuver) and the remaining 30 (group B) conventional PCI without maneuver. The baseline characteristics, group A and B n (%), respectively: mean age 61.8 ± 11 vs. 61.6 ± 11; male 36(90) vs 27(90); diabetic 5(13) vs 9(30); average door to balloon time 110 ± 59 vs 117 ± 49 min; radial access 15(38) vs 7(23); multiple vessel disease 19(47) vs 14(47); TIMI 2/3 after guidewire 6(15) vs 14(47) p=0.008; TIMI 2/3 flow post maneuver 23(57) vs 26(87); multiple predilation 15(37) vs 17(57), drug-eluting stents 16(40) vs 8 (27); IIb IIIa usage 5(12) vs 7(23).

Results: group A and B n(%) respectively: final TIMI III 40(100) vs 25(83) p=0.01; blush grade III 38(95) vs 25(83); cardiovascular death 1(2.5) vs 0; early coronary occlusion 2(5) vs 1(3).

Conclusions: During PCI of RCA culprit, maneuvering reperfusion showed a higher percentage of coronary flow and myocardial blush than those with conventional PCI.
CULPRIT IN A CARDIAC ARREST: RIGHT CORONARY ARTERY OR LEFT ANTERIOR DESCENDING

O.E Egbeuche, P. Agasthi, K. Sivakumar, R. Sachdeva
Section of Cardiology, Department of Medicine, Morehouse School of Medicine and Grady Memorial Hospital, Atlanta, Georgia, USA

Background: Acute myocardial ischemia/infarction (MI) is a frequent cause of cardiac arrest. We present a case of chronic right coronary artery (RCA) stenosis masking a culprit left anterior descending artery (LAD) stenosis as a cause of acute inferior wall MI leading to cardiac arrest.

Case Report: A 45-year-old man with a medical history of hyperlipidemia was brought to the emergency department (ED) after ventricular fibrillation cardiac arrest. Patient lost consciousness after running a mile and bystander cardiopulmonary resuscitation was initiated. Enroute to hospital he returned to spontaneous circulation after defibrillation. Initial electrocardiogram (EKG) revealed subtle ST-elevation in inferior leads that returned to baseline on repeat EKG. The transient inferior wall ischemia was the suspected etiology of cardiac arrest and he was taken to the catheterization laboratory. Coronary angiography revealed a long segment 99% stenosis of the RCA with TIMI-1 flow and tandem 50% stenosis in the proximal and mid LAD. Percutaneous coronary intervention (PCI) was performed in the RCA, however it behaved like a chronic occlusion instead of acute thrombotic occlusion. Echocardiogram showed inferior wall hypokinesis. Staged PCI was performed on LAD during indexed hospitalization. Two tandem stenosis were assessed for severity by fractional flow reserve (FFR). Initial FFR across tandem stenosis was 0.77 and on pullback above the mid stenosis, FFR remained same. After stent to proximal LAD stenosis, repeat FFR was 0.78 as a result of mid LAD stenosis. Bifurcation LAD, diagonal stent was performed with repeat FFR of 0.93.

Discussion: In the setting of chronic RCA stenosis, inferior wall ischemia in this patient is likely as a result of decreased flow to watershed inferior wall from tandem LAD stenosis.

Conclusions: Finding chronic stenosis in the setting of MI must prompt robust assessment of coronary arteries to identify culprit lesions.
Completeness Heart Block Following Successful Percutaneous Coronary Intervention of Left Main Stenosis

A.F. Chaudhry, P. Agasthi, D. Hirsh, R. Sachdeva
1: Section of Cardiology, Department of Medicine, Morehouse School of Medicine, Atlanta, GA, USA
2: Section of Cardiology, Department of Medicine, Emory University School of Medicine, Atlanta, GA, USA

Background: Left main coronary artery stenting is feasible in patients at high risk for coronary artery bypass surgery. Intraprocedure bradyarrhythmias are common during rotablation. We present a case of complete heart block (CHB) immediately after successful left main percutaneous coronary intervention (PCI).

Case Description: A 73 year old woman with no past medical history presented in respiratory distress requiring intubation and chest tube placement for spontaneous right pneumothorax. She also had non-ST elevation myocardial infarction with peak troponin-I, 0.64 ng/ml. Electrocardiogram showed sinus rhythm, right bundle branch block and left anterior fascicular block (Figure 1A). Systolic function was normal. After extubation and chest tube removal, she underwent coronary angiography showing 60% left main (Figure 1B) and 50% ostial right coronary artery stenosis. Surgical candidacy was poor due to centrilobar emphysema (FEV1 0.66 L). She underwent successful PCI with Impella support (Figure 1C). Rotational atherectomy of left main artery was performed prior to stent placement. At completion of angiography, patient was noted to be in CHB (Figure 1D) without ventricular escape rhythm. Transvenous pacemaker was inserted, with return to sinus rhythm with normal conduction after one hour. Subsequent electrophysiological study showed normal conduction.

Discussion: Transient bradyarrhythmia, mainly sinus bradycardia, is commonly observed in rotablation, predominantly during RCA intervention. CHB in acute coronary syndrome results from ischemia of large areas of myocardium or in the setting of pre-existing bifascicular block, as in this case. Our case is unusual in that transient CHB occurred in the final stage of the procedure after removal of hardware, which can be attributed to air embolism during flushing (not observed in this case) or ischemia of the remaining fascicle or atrio-ventricular node.

Conclusion: Transient CHB may occur during complex PCI, requiring vigilance and preparation for the unexpected.
AN OVERLOOKED UNDERRATED SYMPTOM OF ACUTE MYOCARDIAL INFARCTION IN WOMEN
A.C. Grigos, R. Seguritan, D.A. Bloomfield
Richmond University Medical Center, Staten Island, NY USA

Objective: To investigate symptom presentation, including risk factors and arrhythmias, in women diagnosed with acute myocardial infarction (AMI).

Background: Research suggests that symptom presentation differs in men and women with AMI. Women are less likely to have the chief compliant of chest pain, owing to comorbid diseases, and lack public awareness of signs and symptoms generally present in men. They are usually older, diabetic, hypertensive and possess a more diffuse, non-obstructive pattern of coronary artery disease. As a result, it is more difficult to recognize AMI, which may lead to delays in care and therefore higher overall morbidity and mortality rates. The aim of this study was to investigate the various prodromal symptoms, acute complaints, arrhythmias, and risk factors within the northern Staten Island region to quantify the presentations of AMI within the female population.

Method: This study was a retrospective analysis of 100 medical records of women with diagnosis of AMI, conducted at Richmond University Medical Center (RUMC) in 2011 and 2015. AMI was confirmed by electrocardiogram evidence of ST segment elevation, T-wave abnormalities, or changes from the last electrocardiogram in at least 2 consecutive leads. Exercise stress tests and coronary angiography confirmed AMI.

Results: Out of the 100 charts reviewed, 29 women were reported by their family to have changes in “thinking or remembering” after AMI.

Conclusions: The results indicated a high incidence of atypical presentation of women admitted and diagnosed at RUMC. A change in thinking and remembering was an unexpected symptom found after review of the more common symptoms, which could potentially suggest neurological changes post-AMI in women. More data must be collected to establish any potential relationship, and may be used to assist in diagnoses of AMI. Clinicians need to pursue a full workup and not dismiss this symptom as a result of non-cardiac cause.
ROLE OF CONTRAST ENHANCED ECHOCARDIOGRAPHY IN PROVIDING LIFE SAVING DIAGNOSIS AFTER ACUTE STEMI

J. Kiani, I. Meier, J. Jentzer, R. Daly
Mayo Clinic, Rochester, MN, USA

A 65-year-old gentleman with a 60 pack-year smoking history presented to the emergency room with persistent anterior chest discomfort of two days duration, associated with nausea, dyspnea, and orthopnea. Initial ECG showed ST elevation, Q-waves, and inverted T-waves in the inferior leads.

Coronary angiography revealed total occlusion of the distal right coronary artery (RCA) and posterior descending artery (PDA) by thrombus. Thrombectomy was performed, opening the proximal and mid-PDA. A drug-eluting stent was deployed in the mid-RCA. The distal PDA and the right posterolateral artery remained totally occluded after percutaneous coronary intervention. The final angiogram showed TIMI-II flow consistent with distal no-reflow phenomenon.

Following catheterization, the patient was admitted to the Cardiac Intensive Care Unit where he reported persistent chest pain. Repeat ECG revealed diffuse ST elevation consistent with pericarditis, which was treated with colchicine. He developed complete heart block which later converted to atrial fibrillation, prompting initiation of heparin. By hospital day three, he had recurrent chest pain and hypotension. Urgent TTE revealed an enlarging pericardial effusion with echogenic components, consistent with coagulum. Repeat TTE with micro-bubble contrast demonstrated delayed appearance of contrast in the posterolateral pericardial space confirming the diagnosis of myocardial rupture.

He was evaluated by cardiovascular surgery and taken urgently for repair. Intraoperative transesophageal echocardiogram confirmed a narrow communication from the basal inferior left ventricular wall to the pericardial space. Blood and clot were evacuated from the pericardium. No active bleeding was identified during the procedure. An epicardial patch was placed and secured with BioGlue.

In this case, high clinical suspicion and use of contrast-enhanced echocardiography led to early detection and treatment of an often fatal complication. Confirming the diagnosis prior to complete rupture allowed for off pump, low risk surgery with epicardial patch.
HYPERACUTE T-WAVES INDICATIVE OF MYOCARDIAL ISCHEMIA: AN ATYPICAL AND UNDER RECOGNIZED MUST-KNOW PATTERN ON ELECTROCARDIOGRAM

K.A. Samtani, O.M. Ali
Wright State University, Dayton, OH, USA

Introduction: This case highlights an uncommon pattern on electrocardiogram (ECG) indicative of a common and life threatening problem, myocardial ischemia. De Winter’s T-wave pattern has been described as persistent tall, prominent T-waves in precordial leads without ST segment elevation, suggestive of left anterior descending artery occlusion.

Case Report: A 54-yr-old male presented to the emergency department with acute chest pain and hyperacute, tall, prominent, T-waves on ECG. Healthcare providers recognized ECG findings as De Winter’s pattern and sent him for emergent left heart catheterization. He was found to have severe proximal/mid left anterior descending artery disease and severe proximal right coronary artery disease.

Discussion: De Winter’s T-wave pattern was first described in 2008 by R.J. de Winter et al. They highlight this ECG pattern does not consist of the typical ST segment elevations but rather hyperacute T-waves in precordial leads. This pattern was identified in 30 of 1532 (2.0%) patients with anterior myocardial infarction. In 2009 Verouden et al. described patients with acute occlusion of the proximal left anterior descending artery and absence of ST segment elevation on ECG. De Winter’s T-wave pattern was identified in 35 of 1890 (2.0%) patients who underwent primary percutaneous coronary intervention of the left anterior descending artery. The electrophysiology behind de Winter’s T-wave pattern has yet to be fully understood. It is theorized the presence of collateral circulation or anatomical variants with delays in conduction could be responsible. An alternate explanation might be myocardial ischemia leading to depletion of adenosine triphosphate and subsequent lack of activation of potassium channels in the sarcolemma. Future studies are required to understand de Winter’s T-wave pattern. It is clear this pattern should be recognized by all healthcare providers who interpret ECGs as a representation of left anterior descending artery occlusion causing myocardial ischemia requiring immediate reperfusion therapy.
HIGH-SENSITIVITY TROTONIN I (HSTNI) LEVEL IN ACUTE MYOCARDIAL INFARCTION (AMI) PATIENTS AND ITS ASSOCIATION WITH CORONARY ARTERY DISEASE (CAD) RISK FACTORS, AN INVESTIGATIVE STUDY

K.A. Floren, R.E. Ramboyong
The Medical City, Pasig City, Philippines

Introduction: CAD places a patient at risk for an acute coronary syndrome (ACS). ARCHITECT STAT hsTnI assay measures troponin I values at much lower levels and for early detection of AMI (above 15.6 pg per ml for females and 34.2 pg per ml for males). This study aims to determine the association of hsTnI level in AMI patients with CAD risk factors, the percentage increase in the level on second determination and the features of extremely high hsTnI values.

Methods: A retrospective, descriptive study done from July 2014 to June 2015. All patients were admitted in The Medical City as a case of ACS and underwent coronary angiogram. Demographics, clinical characteristics, diagnostics and treatment received were recorded. Independent samples t test and descriptive analysis were done.

RESULTS: In association with CAD risk factors, dyslipidemia has the highest mean hsTnI in both STE-ACS (1951) and NSTEMI (775) cases in females. In the males, higher mean value was observed in smokers (1293) and diabetics (2620) in both NSTEMI and STE-ACS. But results show that there is no significant difference in mean hsTnI level between NSTEMI and STE-ACS. Mean percentage increase in hsTnI from the baseline is higher in the earlier group (170x in 2-6 hours). Abnormally high hsTnI levels were observed in overweight patients, elderly women and younger men with increased number of hours (average of 36 hours) between the onset of symptoms to presentation and first determination.

Conclusion: There were no significant differences in mean hsTnI values for NSTEMI and STE-ACS related to age, diabetes, dyslipidemia, hypertension and smoking. hsTnI levels may increase up to 170x the upper limit within 6 hours. Extreme values of hsTnI is affected by the time interval from onset of symptoms to the first determination in both male and female population.
QRS COMPLEX FRAGMENTATION AS A PREDICTOR OF MYOCARDIAL SCAR IN PATIENTS WITH TRASTUZUMAB INDUCED CARDIOMYOPATHY

C.J. Hayes¹, D.J. Pytlewski², D.S. Jassal¹, C.M. Seifer¹, W.F. McIntyre¹
1. University of Manitoba, Winnipeg, MB, Canada
2. University of Saskatchewan, Saskatoon, SK, Canada

Background: Trastuzumab is a chemotherapeutic agent used in the treatment of breast cancer. It is associated with cardiac toxicity. In a series previously published from our centre, trastuzumab induced cardiac injury was shown to manifest on cardiac magnetic resonance (MR) as a subepicardial delayed enhancement in the lateral wall of the left ventricle. Fragmentation of the QRS (fQRS), defined as one or more RSR’ patterns within the QRS complex, is an electrocardiographic finding that has been shown to correlate with myocardial scar in several etiologies of cardiomyopathy.

Objective: We hypothesized that the presence of fQRS on the 12-lead ECG could predict subepicardial “scar” on MR in breast cancer patients treated with trastuzumab.

Methods: We retrospectively reviewed the charts of patients in the trastuzumab study cohort. Available 12 lead ECG’s from the study period were collected and post-processed using a 150 Hz low pass filter. ECGs were coded for the presence or absence of fQRS. The ability of fQRS to predict scar was evaluated, using MR as the gold standard.

Results: ECGs were available on 24 patients. We identified 9 as having fQRS, of which 3 had MRI evidence of scar. Conversely 15 patients did not have fQRS, of which 2 had MRI evidence of scar. The sensitivity was 60%, specificity was 68%. The PPV was 30% and the NPV 87%.

Conclusion: In this retrospective single centre series, the absence of fQRS on ECG was strongly predictive of absence of scar on cardiac MR. Presence of fQRS, however was not predictive of scar. These findings require validation in a larger, prospective series.
DETERMINANTS OF CARDIAC DYSFUNCTION AND LEFT VENTRICULAR HYPERTROPHY IN PHEOCHROMOCYTOMA

S. Agrawal¹, S. Nanda¹, S.P. Bhatt², S. Longo¹, J. Pamula³, A. Singh¹, M. Fegley¹, J. Shirani¹
1. St Luke's University Health Network, Bethlehem, PA, USA
2. University of Alabama, Birmingham, AL, USA
3. Guthrie Robert Packer Hospital, Sayre, PA, USA

Background. Pheochromocytomas (PHEO) are chromaffin cell tumors most frequently originating in adrenal medulla. Left ventricular (LV) dysfunction, similar to stress (takotsubo) cardiomyopathy has been reported in PHEO possibly related to episodic rise in circulating catecholamine concentration. The aim of this study was to identify potential predictors of LV dysfunction in histologically verified PHEO.

Methods. We reviewed demographic and clinical characteristics, as well as electrocardiographic (ECG) and echocardiographic (ECHO) findings in a series of 18 adults with histologically verified diagnosis of PHEO between 1999 and 2014 (mean age 54±19 years, 61% females).

Results. Most tumors (78%) were identified incidentally while 22% were discovered during work up for resistant hypertension or labile blood pressure. ECHO was performed in 12 patients prior to adrenalectomy and showed at least mild LV hypertrophy (LVH) in 7 (including 2 with severe LVH and dynamic LV outflow tract obstruction) and LV systolic dysfunction in the absence of epicardial coronary artery disease in 3 (LV ejection fraction 25±9%). ECG was less sensitive in identifying LVH (2/7). There was a trend in reduction of total 12-lead QRS voltage following surgical tumor removal (131±35 vs 113±20, p=0.07). QT prolongation without ventricular arrhythmia was noted in 5 patients. Age, sex, clinical characteristics, and urinary catecholamine excretion did not predict presence of cardiomyopathy while plasma nor-metanephrine was significantly higher in those with LVH (3242±1873 vs 329±372 pg/ml, p=0.02).

Conclusion. LV systolic dysfunction similar to stress (takotsubo) cardiomyopathy occurs frequently in PHEO and cannot be predicted by demographic and clinical characteristics or by random measurement of circulating or urinary concentration of catecholamines. Acute elevations of circulating catecholamines during PHEO crises may be responsible for LV dysfunction.
DIFFERENTIAL REVERSIBILITY IN HEART FAILURE DUE TO HYPOTHYROIDISM

E.S. Roberto¹, T. Aung¹, A. Agarwal¹,², R.J. Colon¹
1. Wright State University Department of Internal Medicine, Dayton, OH, USA
2. Veteran Affairs Medical Center, Dayton, OH, USA

Introduction: Dilated cardiomyopathy due to hypothyroidism is unique for its potential reversibility following hormone supplementation. Thyroid hormone profoundly affects cardiac physiology and intracellular calcium regulation. Administration of levothyroxine can restore contractile function, however the scope and extent of reversibility remains unknown. The following cases describe dilated cardiomyopathy due to hypothyroidism, with different timelines and varying degrees of reversibility. The relationship between disease timeline and reversibility deteriorating into irreversibility in dilated cardiomyopathy due to hypothyroidism has not been previously described.

Cases: A 65-year-old Caucasian male presented with new onset severe dyspnea and fatigue over three months. The patient had a history of hypothyroidism. Thyroid-stimulating hormone was markedly elevated. Following levothyroxine therapy, the dilated cardiomyopathy reversed and returned to normal within six months. Left ventricular systolic function had improved from an ejection fraction of 15% at presentation to 45% at six months. A 60-year-old Caucasian female presented minimally responsive in overt heart failure due to myxedema coma. History revealed hypothyroidism chronically uncontrolled for years prior to presentation. TSH was significantly elevated. Following prolonged hospital admission and intravenous levothyroxine therapy, the clinical status began to improve. Left ventricular function improved from an ejection fraction of 10% to 25% after six months with measurable improvement in chamber diameters.

Discussion: In conclusion, the varying degree of recovery between these two cases suggests a temporal association between uncontrolled disease and extent of reversibility. Once the underlying mechanism of heart failure was addressed, the cases displayed varying degrees of restored contractile function following thyroid hormone replacement. This may suggest that with a longer duration of uncontrolled disease and consequent cardiac structural remodelling, the possibility and extent of reversibility diminishes into irreversibility. Earlier identification and treatment of any contributing hypothyroidism in the setting of new onset dilated cardiomyopathy is essential, as reversibility may be at stake.
ELECTRO-CARDIOVERSION OF NEW ONSET ATRIAL FLUTTER LEADING TO CARDIOGENIC SHOCK

E.A. Christian, S.R. Kadire, R.N. Khouzam
University of Tennessee Health Science Center, Memphis, TN, USA

Objective: To report a unique case involving a 77-year-old male with new onset atrial flutter who experienced cardiogenic shock following successful electro-cardioversion. Background: Life-saving in urgent circumstances, electro-cardioversion can occasionally result in catastrophic consequences. Rare yet well documented complications include: cardiac arrhythmias, myocardial necrosis, thromboembolism, pulmonary edema, and cutaneous burn injuries. Less often observed is global left ventricular dysfunction following successful cardiopulmonary resuscitation. As such, atrial stunning and transient hypotension leading to clinically significant cardiac failure is highly uncommon and noteworthy.

Methods and Results: An electrocardiogram was obtained which was consistent with atrial flutter at a rate of 300 beats per minute with 2:1 atrioventricular (AV) conduction. A transthoracic echocardiogram (TTE) revealed a preserved left ventricular (LV) systolic function with an ejection fraction (EF) of 60% and normal sized atria. Next, a transesophageal echocardiogram (TEE) was performed to rule out a pre-existing thrombus. The patient was then successfully electrically cardioverted by a single 100 Joules synchronized direct current (DC) monophasic shock. Immediately thereafter, his blood pressure dropped to 70/30 mmHg followed by apneic spells. A limited bedside TTE revealed a severely depressed LV systolic function: EF 30%.

Conclusion: Global left ventricular dysfunction observed in patients with cardiac arrest status-post cardiopulmonary resuscitation is known to be related in part to defibrillation, however little is understood about the mechanism by which defibrillation can produce injury. Our case highlights this unusual phenomenon and demonstrates the importance of further research to better identify patients at risk of having clinical heart failure following cardioversion.
DILATED CARDIOMYOPATHY INDUCED BY CHRONIC STARVATION AND SELENIUM DEFICIENCY

S. Dasgupta1, A.M. Aly2
1. Dept. of Pediatrics, University of Texas Medical Branch, Galveston, Texas, USA
2. Dept. of Pediatric Cardiology, University of Texas Medical Branch, Galveston, Texas, USA

A fourteen year old male from South America was transferred to the burn unit at our institution. The patient had second-degree burns (>25% BSA) two years prior to admission. He was inappropriately managed in his home country and developed severe muscle wasting. He was severely malnourished with a weight of 19 kg [BMI 9.6 kg/m2, z score -13.1] because of poverty. Initial evaluation revealed severe cachexia and absent peripheral edema consistent with the diagnosis of marasmus. Additionally, he experienced shortness of breath with minimal physical activity. Initial labs were positive for severe hypoalbuminemia [0.2 g/dl], hypocalcaemia [3.2 mg/dl], selenium deficiency [32 ug/dl (NL 50-150 ug/L)], severe iron deficiency anemia [hemoglobin/hematocrit 6.7gm/dl/24.8%, MCV 69.3 FL] and a normal carnitine level. An initial echocardiogram (echo) showed a globular dilated left ventricle with a severely depressed systolic function [ejection fraction (EF) < 25%] consistent with congestive heart failure. At that time, he was treated with furosemide, enalapril and carvedilol. High caloric enteral nutrition was administered via a nasogastric tube with the addition of selenium [200 mcg twice daily]. He also received two blood transfusions and repeated albumin infusions within the first five days. Within one week, his cardiac function dramatically improved [EF 46%]. His selenium level, as well as other labs, normalized within two weeks. The cardiac function normalized within four weeks. His weight continued to increase, and reached 28 kg [BMI 14.1 kg/m2, z score -3.79] within three months. All cardiac medications were then discontinued and the patient’s stamina continues to improve. We report a rare case of dilated cardiomyopathy caused by severe protein energy malnutrition combined with selenium deficiency in a teenage boy.
TRIPLE TROUBLE: SINGLE CORONARY ARTERY AND CORONARY ARTERY DISEASE IN THE SETTING OF HYPERTROPHIC CARDIOMYOPATHY

S. Patnaik1, M. Shah2, S. Sharma1, N. Codolosa3, V.M. Figueredo1
1. Albert Einstein Medical Center, Philadelphia, USA
2. Lehigh Valley Health Care Network, Allentown, USA
3. Bay Area Medical Center, Florida, USA

Introduction: Isolated coronary artery anomalies (CAAs) occur in about 1.3% of patients undergoing coronary arteriography, of which single coronary artery is a potentially serious anomaly.

Case: A 49-year-old African-American male, with history of hypertension and mild congenital cognitive impairment presented with episodes of substernal discomfort radiating to the throat, lasting for 2-3 minutes each time. Examination was normal except for mild tachycardia (115 beats per minute). Initial ECG is as shown [Fig-1]. Echocardiogram revealed hyperdynamic left ventricle (LV) with ejection fraction >75%, asymmetrical LV septal hypertrophy, small LV cavity. There was systolic anterior motion of mitral valve, mild eccentric mitral regurgitation [Fig-2]. Troponin was elevated (0.29ng/mL). Coronary angiogram showed single coronary artery arising from right coronary cusp. There was 50% stenosis at the mid-left anterior descending artery and at the origin of first diagonal artery [Fig-3]. Patient was managed conservatively for noncritical CAD, and HCM (due to absence of significant resting LV cavity gradient) with aspirin, beta blockers, and high intensity statin. He was referred to adult congenital heart disease specialist.

Discussion: Single coronary artery refers to the common origin of left and right coronary arteries from a single aortic ostium. Coronary anomalies may result in myocardial ischemia due to the course in relation to aorta and pulmonary artery. Angina in HCM can occur from severe systolic narrowing of epicardial coronaries or major branches (myocardial bridges), and coronary demand-supply mismatch. Associated CAD or small vessel disease can further complicate the situation. Both HCM and single coronary artery independently increase risk of sudden cardiac death. 40% of single CAA cases are associated with congenital heart diseases such as fallot tetralogy, transposition of great arteries, persistent truncus arteriosus, and pulmonary atresia. Depending on the CAA type, management strategies include observation, coronary angioplasty with stent deployment and surgical repair (unroofing/bypass).

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LEFT VENTRICULAR OUTFLOW TRACK OBSTRUCTION AND MITRAL VALVE REGURGITATION IN A PATIENT WITH TAKOTSUBO CARDIOMYOPATHY

Y. Wu1, W.Q. Fan1, L. Chachula3, G. Costacurta1,2, R. Rohatgi1,2, F. Elmi1,2
1. Department of Medicine, Easton Hospital, Drexel University, Pennsylvania, USA
2. Easton Cardiovascular Associates, Pennsylvania, USA
3. Philadelphia College of Osteopathic Medicine, Pennsylvania, USA

Introduction: Takotsubo cardiomyopathy (TCM) can be complicated by left ventricular outflow tract (LVOT) obstruction and severe acute mitral regurgitation (MR) leading to hemodynamic instability in an otherwise benign disorder. Up to 20-25% of TCM patients develop LVOT obstruction and/or MR, it is important to recognize the clinical manifestations of these complications and adhere to specific management in order to reduce patient morbidity and mortality.

We report the clinical history, imaging, treatment strategy and clinical outcome of a patient with TCM that was complicated with severe MR and LVOT obstruction. We then discuss the pathophysiology, characteristic imaging, key clinical features and current treatment strategy for this unique patient population.

Case report: A postmenopausal woman with no clear risk factor for coronary artery disease (CAD) presented to the ED with chest pain after an episode of mental/physical stress. Physical exam revealed mitral regurgitation (MR), mild hypotension and pulmonary vascular congestion. Her troponins were mildly elevated. Cardiac catheterization excluded obstructive CAD, but revealed severe apical hypokinesia and ballooning. Diagnostic tests revealed the presence of severe acute MR and LVOT obstruction. The patient was diagnosed with Takotsubo cardiomyopathy (TCM) complicated by underlying MR and LVOT obstruction. The mechanism of her LVOT and MR was attributed to systolic anterior motion of the mitral valve (SAM), which the TEE clearly showed during workup. She was treated with beta-blocker, aspirin and ACE-I with good outcome. Nitroglycerin and inotropes were discontinued and further avoided.

Conclusion: Our case illustrated LVOT obstruction and MR associated with underlying SAM in a patient with TCM. LVOT obstruction and MR are severe complications of TCM and may result in heat failure and/or pulmonary edema. Timely and accurate identification of these complications is critical to achieve optimal clinical outcomes in patients with TCM.
PHASIC COMPRESSION OF LEFT CIRCUMFLEX CORONARY ARTERY DURING ATRIAL SYSTOLE

E.S. Roberto1, A. Agarwal1,2, T. Aung1
1. Wright State University Department of Internal Medicine, Dayton, OH, USA
2. Veteran Affairs Medical Center, Dayton, OH, USA

Introduction: Phasic coronary artery compression is a rare phenomenon. The incidence is not known as very few cases have been reported. Aside from spasm or myocardial bridging, this condition is often related to acquired changes to the anatomy of the surrounding heart chambers exerting physical pressure in conjunction with contractility. Recognizing and understanding this phenomenon is important, as treatment approach will vary widely based on etiology.

Case: 55-year-old male with multiple cardiac risk factors presented with new onset exertional dyspnea. Chest radiograph revealed bilateral pulmonary congestion, and cardiac biomarkers were normal. Electrocardiogram and echocardiography showed left atrium dilation, left ventricular ejection fraction 15-20%, with elevated filling pressures. Angiography showed non-obstructive disease. Interestingly, phasic, inside-out compression of the proximal left circumflex was noted during late ventricular diastole (Fig. 3, Video 1). Compression occurred in phase with atrial contraction. Patent flow without any compression was noted during atrial diastole. Following guideline directed medical therapy and cardiac rehabilitation, the patient’s status improved. Repeat echocardiogram one year later demonstrated left ventricular ejection fraction 40-45% with decreased atrial dilation.

Discussion: The authors describe phasic, inside-out compression of the proximal portion of left circumflex artery associated with a dilated left atrium, occurring during atrial contraction. Phasic compression of the proximal segment correlated with ballooning of the lateral and posterior regions of the atrial wall towards the atrioventricular groove in atrial systole. The circumflex artery can be seen collapsing from the interior circumference of the vessel wall. The vessel location nearest the left atrium in the atrioventricular groove most likely resulted in compression during the ballooning of a dilating wall segment. Coronary artery compression from a variety of mechanisms can ultimately lead to development of ischemia, infarction, and heart failure. Careful analysis of angiography is necessary for identifying and treating the underlying mechanism of coronary artery compression.
Introduction: In setting of newly identified cardiomyopathy, the differential diagnosis of common presentations must include uncommon causes. This consideration is critical as in cases such as catecholamine-secreting neuroendocrine tumors where inappropriate medical and surgical management may have catastrophic consequences.

Case Description: A 28-year-old man with no significant medical history other than baseline tachycardia of unclear etiology, alcohol abuse, and methamphetamine use was transferred from a referring hospital for further evaluation and management of newly identified biventricular systolic heart failure in setting of acute respiratory distress syndrome related to community acquired pneumonia. On presentation, he was intubated, tachycardic and hypertensive. Baseline laboratory tests were notable for elevated inflammatory markers and mild leukocytosis with negative urine drug screen. There were no concerning findings on the electrocardiogram. Repeat echocardiogram was notable for mild left ventricular enlargement with a phenotype of reversed apical ballooning and a calculated ejection fraction of 28%. Considering no underlying etiology was identified, further testing included a significantly elevated serum free metanephrine (1.7 nmol/L; normal <0.5 nmol/L) and a 24-hour urine metanephrine collection (3813 mcg). Subsequent CT imaging showed evidence of a right-sided pheochromocytoma (4.1 x 6.1 x 2.9 cm). The patient was started on appropriate therapy with alpha and beta blockade and ultimately underwent surgical resection. Follow-up one month later showed complete resolution of cardiac dysfunction and symptom improvement.

Discussion: It is important to entertain the possibility of catecholamine-secreting neuroendocrine tumors in young patients with cardiomyopathy of unclear origin. Prompt diagnosis and management can result in complete normalization of cardiac function.
Mitral valve prolapse (MVP) is associated with ventricular arrhythmias and sudden cardiac death (SCD). Malignant form characterized by the triad of bileaflet MVP, multifocal premature ventricular contractions (PVCs) and inferolateral T wave abnormalities was recently identified. Our study characterized patients at the MGH with MVP and SCD. ECHO lab database was searched to identify patients with MVP, while conducting an EMR search for Sudden Cardiac Death in problem lists and billing codes from 2000-2014. Patients with primary causes for ventricular arrhythmias were excluded from the study. As a result, 32 subjects with MVP and cardiac arrest were identified. Seventeen of those were excluded secondary to possible confounding etiologies, i.e. CAD, systolic dysfunction, or ruptured subvalvular apparatus. Mean age of the subjects was 64±11.3 (53% male). In 11 patients (73%) MVP affected both leaflets. Seven patients (46%) underwent mitral valve repair or replacement. Five subjects (33%) had severe, 8 (53%) had moderate and 2 (13%) had mild mitral regurgitation. Ventricular fibrillation (VF) was the first documented cardiac arrest rhythm in 85.7% of the subjects. Implantable cardiac defibrillators (ICDs) were used in all patients, 10 of whom (67%) received appropriate ICD therapies during follow-up. Even after surgical repair, 4 of 7 patients (57.1%) received appropriate ICD therapy. Prolonged QTc intervals were noted in 3 subjects, while frequent PVCs were seen in 9 of 14 subjects (64%) for whom data were available (at least one case of multifocal). Inferolateral T wave abnormalities were identified in 26.7%. Only 1 patient had an MRI with late gadolinium enhancement showing no cardiac fibrosis. In summary, the majority of subjects with MVP and SCD had bileaflet MVPs and frequent PVCs. T wave inversions were found in a minority of patients, while ventricular arrhythmias recurred following surgical mitral valve repair in the majority of the subjects.
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POST-TRANSCATHETER AORTIC VALVE REPLACEMENT (TAVR) AND AV BLOCK – PACING OUTCOMES

A. Mourad, A.F. Chu
Rhode Island Hospital, Brown University, Rhode Island, USA

Background: Transcatheter aortic valve replacement (TAVR) is an increasingly prevalent therapy in patients with severe symptomatic aortic stenosis (AS) deemed inoperable or at high risk for complications with surgical aortic valve replacement (SAVR). Atrioventricular (AV) conduction disturbances requiring permanent pacemaker (PPM) implantation may complicate TAVR. We report single-center data on 207 consecutive patients undergoing TAVR with placement of the Edward SAPIEN valve who required post-TAVR permanent pacemaker implantation for complete AV block.

Methods: A retrospective analysis of prospectively collected data includes clinical, procedural, echocardiographic, ECG and device interrogation of 207 consecutive patients who underwent TAVR procedure with placement of Edward SAPIEN valve at our institution from March 2012 to February 2016. We excluded 23 patients with prior permanent pacemaker. No patients met guideline indications for pre-TAVR permanent pacing.

Results: A total of 24 patients (13%) required post-TAVR permanent pacemaker. At 30 days post-TAVR, 7 of these patients (29.1%) required 100% ventricular pacing. The remaining 17 (70.9%) patients who received pacemakers had resolution of AV block by 30 days post-TAVR and did not require significant ventricular pacing (<1% ventricular pacing).

Conclusion: Despite 13% of post-TAVR (SAPIEN valve) patients receiving permanent pacemakers for complete AV block, 70.9% of these patients had resolution of AV block at 30 days post-TAVR and did not require ventricular pacing. This suggests a significant number of post-TAVR pacemakers may not be necessary at 30 days. Further clinical studies are required to avoid unnecessary pacemaker placement and assess possible alternative strategies including clinical observation with re-assessment of AV block 30 days post-TAVR.
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CORONARY ATHEROSCLEROSIS IN NON-CARDIAC SUDDEN UNEXPECTED DEATHS: AN AUTOPSY STUDY OF ASIAN POPULATION
Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

Objectives: To evaluate the frequency of atherosclerosis in non-cardiac-caused sudden unexpected death (SUD) in Asian population.

Background: Atherosclerosis is the most common cause of cardiac-caused SUD worldwide. The frequency of atherosclerosis in normal population was reported as 4.5%. However, the frequency of atherosclerosis in non-cardiac-caused SUD of Asian population is unclear.

Methods: The autopsy reports of out-of-hospital SUD from January 2013 to June 2014, performed at Department of Pathology, Faculty of Medicine, Ramathibodi Hospital, Bangkok, Thailand, were reviewed. The frequency of atherosclerosis in non-cardiac-caused SUD was evaluated. Basic characteristics and frequency of coronary artery atherosclerosis were also compared between cardiac-caused group and non-cardiac-caused group.

Results: A total of 371 autopsied SUD were reviewed. Among them, 125 cases died due to non-cardiac causes. Frequency of male was not different between cardiac-caused group and non-cardiac-caused group (79.3% VS 75.2%, respectively), as well as average age (52.3 years VS 50.4 years, respectively). Left anterior descending artery was the most commonly involved in both cardiac-caused and non-cardiac-caused (90.0% and 54.8%, respectively). Frequency of atherosclerosis was found more in cardiac-caused group compared to non-cardiac-caused group (52.8% VS 20.0%, respectively, p<0.01), as well as triple vessel disease (15.9% VS 2.4%, respectively, p<0.01).

Conclusions: The frequency of atherosclerosis in non-cardiac-caused SUD in Thai population was very high up to 20.0%. Atherosclerosis is an important risk factor of SUD in both cardiac-caused SUD and non-cardiac-caused SUD.
Background: Sudden cardiac arrest (SCA) accounts for 15% of all-cause mortality in US and 50% of all cardiovascular mortality in developed countries.

Objectives: Postmortem echocardiography (PME) performed at emergency department may be informative to reveal structural cardiac problems, which causes 10% of SCA.

Methods: In this preliminary case-series study, we tried to evaluate interrater reliability of PME, with which 2 emergency physicians (EP) measured diameters of left atrium (LA), left ventricle (LV), and aorta; thicknesses of posterior wall (PW) and interventricular septum (IVS); presence or absence of regional wall thinning, calcification of aortic and mitral valves and pericardial effusion. The validity was sought with the cardiologist’s measurement as a reference standard.

Results: Four mortality cases after CPR were collected. (3 male, 45-80 years old, 2 SCA, BMI 22.0–27.7 kg/m2). PME were performed by 2 EPs per each case except one case. They began within 10 minutes after death declaration with each exam taking 3-6 minutes except for one case (12 minutes). Parasternal views on either supine or left decubitus position were most helpful to identify chamber size and LV wall thickness completely, while the other parameters were evaluated incompletely (43–71%). Adequacy of the images were rated as fair by the cardiologist. Intra-class correlation coefficient for interrater reliability and validity was 0.97 (EP vs EP) and 0.95 (EP vs cardiologist), respectively. (p<.001) The mean differences (standard deviation in parenthesis) of measurement by EP and cardiologist were 0 (1), 4 (3), 1 (6), 1 (1), and 1 (4) mm for LA, LV, aorta, PW, and IVS, respectively. (n=7)

Conclusion: Reliable and valid PME could be performed by EPs. A large prospective study with close collaboration between EPs and cardiologists is needed to evaluate the feasibility and usefulness of PME to diagnose structural causes of SCA.
WEARABLE CARdioverter-DEFIBRILLATOR –WHERE ARE THE CLINICAL GUIDELINES?

M. Agarwal, V. Botta, J. Gardner, R. Khouzam
University of Tennessee Health Science Center, Memphis, Tennessee, USA

Objective: To propose a set of guidelines based on literature review on wearable cardioverter defibrillator (WCD) use for the management of patients with/or at risk for ventricular arrhythmias (VA) and/or sudden cardiac death (SCD).

Background: Implantable cardiac defibrillator (ICD) is an invasive, device based management option for patients with VA and at risk for SCD. In 2002, a non invasive alternative, WCD was FDA approved for potential use in such patient population. Since then, it has been used in a wide variety of challenging clinical settings like post myocardial infarction, post-coronary artery bypass grafting or percutaneous coronary intervention, and those with severe left ventricular dysfunction (LVD) secondary to different cardiac non-ischemic pathologies. Despite this, no clear consensus or guidelines exist to date. Although indications for intervention are continually evolving and further research is certainly warranted, this review aims at summarizing the clinical data and possible indications in a more robust manner.

Discussion: Currently extensive clinical data exist highlighting WCD indications in scenarios like post myocardial infarction (MI), awaiting heart transplantation or ICD placement, conditions requiring ICD explantation (infections, cardiac thrombi), newly diagnosed cardiomyopathies resulting in severe LVD (non-ischemic, inherited, congenital) etc. Potential hurdles for more effective use are inappropriate shocks, practical cosmetic/comfort issues, high cost and compliance. Formal clinical guidelines have yet to be presented and importantly no large-scale clinical trial has shown mortality benefit with WCD. Therefore, our detailed literature review will help build guidelines with a cohesive set of indications.

Conclusion:- WCD use should be considered in 1) early-post acute MI or early post-CABG/PCI, 2) preclusions to ICD placement, 3) ICD explantation, and 4) prolonged clinical workup of disorders (non-ischemic cardiomyopathies) predisposing high-risk VA. Adverse events, practical and financial issues need to be properly addressed. Multicenter randomized clinical trials are indicated.
COMPLICATIONS RELATED TO CARDIAC RHYTHM MANAGEMENT DEVICES (CRMD’S) THERAPY AND THEIR FINANCIAL IMPLICATION: A PROSPECTIVE SINGLE-CENTER TWO YEARS SURVEY
J.A. Fanourgiakis1,2,3, E.N. Simantirakis1, N. Maniadakis4, E.M Kanoupakis1, S.J. Chrysostomakis7, G. Kourlaba4,5, G.I. Chlouverakis7, S.E. Papadakis3, M. Vernardos1, P.E. Vardas1
1. Department of Cardiology, Heraklion University Hospital, Crete, Greece
2. Faculty of Social Sciences, Hellenic Open University, Patra, Greece
3. Department of Business Administration, Technological Educational Institute, Agios Nikolaos Crete, Greece
4. National School of Public Health, Athens, The Stavros Niarchos Foundation-Collaborative Center for Clinical Epidemiology and Outcomes Research (CLEO), Athens, Greece
5. National and Kapodistrian University of Athens, School of Medicine, Athens, Greece
6. Department of Biostatistics, Faculty of Medicine, University of Crete, Crete, Greece

Objective: The objective of this study is to estimate the complications rates relate to CRMDs implantations and moreover to estimate the additional hospital stay and cost which is associated with the management of these complications.

Background: Cardiac rhythm management devices (CRMDs) have proven their clinical effectiveness for patients with heart rhythm disorders. Little is known about safety and complication rates during implantations of these devices.

Methods: During a period of one year in total 464 consecutive recipients were subjected to CRMDs implantation and furthermore were recruited and followed up for 2 years. Finally, data were analyzed for 398 patients who completed the two years follow up, resulting in a total of 796 patient-years.

Results: From the 201 patients with initial pacemaker (PM) implantations, 6 (2.99 %) patients had seven complications (5 patients had leads dislodgement, 1 of them twice) and 1 patient developed pocket infection, while from the 117 PMs replacements 1 (0.85 %) patient developed a complication (pocket erosion). 2 patients with complication (1 with an initial PM and 1 with replacement) died before they complete the follow up from reasons unrelated to cardiac causes. There weren’t any complications neither in initial implantations (69 patients) nor in replacements (11 patients) of implantable cardioverter defibrillator (ICD). The average prolongation of the hospital stay was 7 days ranging from 1 to 35 days, resulting in 17.411 € of total additional direct hospital cost.

Conclusion: This study provides relatively low rates of complications in patients subjected to CRMDs implantation, initial or replacement, in our center compared with others studies. The additional hospitalization days and cost attributed to these complications depends on the nature of complication.
ELECTROPHYSIOLOGY: SUDDEN DEATH, ARRHYTHMIAS AND DEVICE THERAPY

PATIENTS FAVOR SHAPE OF MEDTRONIC ICD, BATTERY LIFE OFTEN MORE IMPORTANT
J. Kneller1, L. Bird2
1. Yakima Heart Center, Yakima, WA, USA
2. Kadlec Regional Medical Center, Richland, WA, USA

Introduction: ICDs differ considerably in shape, features, and battery life. Medtronic provides the only contoured ICD. Boston Scientific offers the thinnest yet widest ICD with greatest longevity. ICDs from other manufacturers represent an intermediate shape. While each may have certain advantages, little is known about the relative importance of ICD shape and longevity to ICD recipients.

Methods: 100 consecutive outpatients (male:75%; age:31-94; median:70) undergoing ICD implant (82%) or changeout (18%) were shown five ICDs: BIOTRONIK (Lumax), Boston Scientific (Teligen), Medtronic (Evera), St Jude (Ellipse & Quadra Assura). Participants were asked: "If all ICDs perform identically, which shape would you prefer?" Strength of preference (SOP) was measured from 1-10. Participants were then asked: "Is an extra year of battery life more important?"

Results: 65% expressed an ICD shape preference. Patients most preferred Medtronic (47%, SOP 36%), followed by Boston Scientific (30%, SOP 51%), St. Jude (Ellipse 21%, SOP 55%; Quadra Assura 0%), and BIOTRONIK (2%, SOP 65%). 41% of patients prioritized extra battery life over ICD shape, while others hoped to benefit from a technology advancement (64%). Among females, 10 of 19 (53%) had a shape preference (Medtronic 50%, Boston Scientific 30%, St Jude 20%). Of males surveyed, 43 of 66 (65%) had a shape preference (Medtronic 47%, Boston Scientific 30%, St Jude 21%, BIOTRONIK 2%). Most (>94%) would defer to physician judgement.

Conclusion: The majority of patients prefer the contoured Medtronic ICD. Gender differences are small. Extra battery life is of modest importance. Physician judgment is most important.
PACEMAKER COMPLICATION DOCUMENTATION AND THE EFFECT OF A CHANGE IN ANTIBIOTIC GUIDELINES

J. Basu1, L. West2, S. Firoozan2
1. Royal Berkshire Hospital, Reading, UK
2. Wycombe General Hospital, Wycombe, UK

Background: Heart Rhythm UK states that 'all implanting centres must collect data on their patients, devices and follow-up which is immediately available and facilitates audit...This is a national quality requirement and is audited by the Care Quality Commission.' Objectives: This project set out to establish if complication rates were accurately recorded and available and with regard to pacemaker complication rates, whether there had been an increase in pacemaker infection rates with the introduction of a new peri-procedure antibiotic guideline.

Methods: A search of the cardiology procedural database TOMCAT was performed to identify all pacing/pacing related procedures performed between May 2011-May 2015. As there was no way to search for specific complications other than lead revision a hand search was carried out of all letters pertaining to each of the 1281 patients.

Results: Although complications were documented they were not available on a quick search and therefore not readily accessible. Interestingly there was also a significant increase in pacemaker infection rates post antibiotic guideline changes.

Conclusions: Our results suggest that currently, we do not adhere to Heart rhythm UK recommendations regarding the documentation of pacing related complications. Our findings also suggest at least a possible role for the antibiotic guideline change in the observed increase in pacemaker infection rates. Our proposed strategy is to employ a pop up box on TOMCAT serving as a required field in any patient undergoing a pacing procedure. With regards to infection rates, switching the antibiotic regime back to the original protocol and comparing infection rates after a period of 2 years would then allow for statistical analysis to deduce if this was a contributing factor.
VENTRICULAR TACHYCARDIA STORM ON THE SAME DAY OF ICD IMPLANTATION FOR PRIMARY PREVENTION. WHAT HAPPENED?
S. Edla1, J. Chandrasekaran2, S. Neupane1, A. Shakir1
1. St John Hospital and Medical Center, Detroit, MI, USA
2. St Vincent Charity Medical Center, Cleveland, OH, USA

Background: The risk of defibrillator shock after implantable cardiac defibrillator (ICD) implantation for primary prevention is approximately 5% per year. It is very rare for a patient to have an appropriate ICD shock for a ventricular tachycardia (VT) storm on the very day of implant. We present a patient who underwent subcutaneous ICD(s-ICD) placement and had VT storm on the same day of implantation due to severe hyperkalemia.

Case: A 35 year old male with a history of nonischemic cardiomyopathy, ejection fraction of 20% and end stage renal disease on hemodialysis was admitted for elective s-ICD placement. His last dialysis was the day before procedure. All serum electrolyte levels the day of the procedure were within normal range. Patient underwent s-ICD implantation without any complications. Later that evening, the patient began complaining of dizziness. He was bradycardic with typical electrocardiogram changes for hyperkalemia. The patient subsequently developed wide complex tachycardia eventually degenerating into a VT storm. The defibrillator delivered multiple appropriate ICD shocks during this rhythm.

Decision making: Dialysis associated hyperglycemia is a well-documented but oft forgotten cause of hyperkalemia in hemodialysis patients. Given the heightened concern for possible hyperkalemia from the electrocardiogram the patient was immediately transferred to the cardiac ICU. Serum potassium level was 8.6mEq/L and glucose level was 360mg/dl. The patient underwent emergent hemodialysis with normalization of his potassium levels down to 4.4mEq/l and his glucose levels down to 140mg/dl. He improved clinically back to his baseline.

Discussion: ICD shocks are highly unusual on the day of implant. In our case, VT storm was triggered by hyperkalemia and early recognition resulted in successful resuscitation. High index of suspicion for hyperkalemia secondary to dialysis-associated hyperglycemia is warranted in hemodialysis patients. Close monitoring of electrolyte levels, especially post-implantation, may prevent serious arrhythmias.
USE OF THE NONIONIC BLOCK COPOLYMER, VEPOLOXAMER (P-188) FOR THE TREATMENT OF ADVANCED HEART FAILURE

H.N. Sabbah¹, R.C. Gupta¹, V. Sing-Gupta¹, M. Emanuele²
1. Henry Ford Hospital, Detroit, MI, USA
2. Mast Therapeutics, Inc., San Diego, CA, USA

Calcium overload occurs in cardiomyocytes (CMs) of the failing heart and contributes to cell death and progressive LV dysfunction. Vepoloxamer (VEPO), poloxamer-188, is a rheologic agent that can repair damaged cell membranes. We examined the effects of multiple acute infusions of VEPO on LV function in dogs with heart failure (HF) and tested the hypothesis that VEPO attenuates calcium overload by inhibiting unregulated calcium entry into failing CMs. 14 HF dogs were randomized to 2, 2 hrs infusions of VEPO (450 mg/kg, n=7) or saline (control, n=7) given 3 weeks (W) apart. LV ejection fraction and plasma troponin-I (TnI) were measured at baseline, at end of infusion and at 1 and 3W after each infusion. LV tissue was used to assess calcium ATPase activity (CaAA) and protein levels of phosphorylated (p) ryanodine receptors and p-sodium-calcium-exchanger-1 by Western blotting. Tissue from 7 normal (NL) dogs was used for comparisons.

Separately, freshly isolated CMs from 6 HF-Control dogs were incubated for 2 hrs with VEPO or saline and then treated with 10 µM Fura-2 AM to fluorometrically assess intracellular calcium. EF and TnI were unchanged in HF-Controls. VEPO increased EF and reduced TnI (*=p<0.05 vs. control). CaAA was reduced and p-RYR-s2808 and p-NCX-1 levels increased in HF-Controls compared to NL. VEPO normalized all calcium cycling proteins and reduced intracellular calcium concentration. In conclusion, VEPO attenuated calcium overload in CMs and normalized calcium cycling resulting in lower TnI and improved LV function. The results support the development of VEPO for treating advanced HF.
TOTAL ARTIFICIAL HEART (TAH): SURVIVAL OUTCOMES, RISK FACTORS, ADVERSE EVENTS IN INTERMACS

F. Arabia¹, I. Gregoric², V. Kasirajan³, J. D Moriguchi⁴, D. C Naftel⁵, S. L Myers⁵, J. K Kirklin⁵
1. Cedars-Sinai Medical Center, Los Angeles, CA, USA
2. University of Texas Health Science Center Houston, Houston, TX, USA
3. Virginia Commonwealth University Medical Center, Richmond, VA, USA
4. Cedars-Sinai Medical Center, Los Angeles, CA, USA
5. University of Alabama at Birmingham, Birmingham, AL, USA

Purpose: We aim to better understand the pt population with biventricular failure receiving TAH as a BTT, determine outcomes in 3 eras, effect of implanting ctr on outcomes, and adverse events related to this therapy.

Methods: Between 2006 and 2015 359 pts received TAH implants as BTT in 44 hospitals in the registry. Mean age 50 yrs, 85% males. Common primary diagnoses: 34% Dilated CM, 30% ischemic CM, and 26% other. 210 pts received a heart transplant and 114 pts died while on the device. Mean follow up 5 mths. Outcomes were analyzed with competing outcomes methods.

Results: Outcomes were separated, Era 1 (2006-09), Era 2 (2010-12), and Era 3 (2013-15); ctrs that implanted 1-5, 6-10, and =11 implants/year. Intermacs profile (IP) 1+2 accounted for 88% of pts in Era 1, 74% in Era 2, & 70% in Era 3. Competing outcome survival at 6 mths were: Era 1, 80%; Era 2, 76%; and Era 3, 67% (Era 1 vs. Era 2, p=.86; Era 1 vs Era 3, p=.24; Era 2 vs Era 3, p=.13). Ctrs that performed = 11 implants experienced survival at 85% 6 mths post implant for pts IP 1 + 2 (1-5 vs 6-10, p=.70; 1-5 vs 11+, p=.0003; 6-10 vs 11+, p=.0009). Baseline characteristic (p < 0.05) TAH vs. LVAD populations were respectively: CVP 17.3 vs. 12.9, IP1 38.7% vs 15.8%, ECMO 12.4% vs. 2.3%, ventilator 19.1% vs. 6.8%. Common AEs: bleeding 47%, resp failure 36%, renal dysf 33.7%, neuro dysf 24.9%, hepatic dysf 13.5%. Hazard function analysis revealed the following risk factors for death: older age, elevated bilirubin, lower albumin, prior history of cancer, valve surgery.

Conclusion: Centers with the largest experience have the best outcomes secondary to better pt selection, timing and mgmt. AE rates are similar when compared to those of LVAD’s.
THE BENEFITS AND RISKS OF LEFT VENTRICULAR ASSIST DEVICE IMPLANTATION; WHERE IS THE POINT OF CLINICAL EQUIPOISE?

M.R. Johnson
University of Wisconsin, Madison, WI, USA

Left ventricular assist devices (LVADs) are used to treat patients with severe heart failure, both as a bridge to transplantation and as destination therapy. However, the best time to proceed with LVAD implantation remains to be determined.

For patients implanted with an LVAD prior to August 2007, those implanted in INTERMACS Profile 1 had decreased survival versus those implanted in Profiles 2 to 7, while patients implanted in Profiles 4 to 7 had the shortest length of stay. Similarly, the most recent INTERMACS report of over 15,000 patients found device implantation at INTERMACS Level 1 or 2 to be a risk factor for mortality. This suggests that “earlier” LVAD implantation should be considered.

However, an LVAD also poses significant risks (infection, bleeding, device malfunction, stroke, and hemolysis), so implantation should be deferred until the patient truly requires it. The recent ROADMAP study may assist providers in deciding when to proceed with LVAD implantation. ROADMAP, an observational study of 200 NYHA class IIIB/IV patients not on intravenous inotropes [97 LVAD and 103 optimal medical management (OMM) patients] showed that the primary endpoint (survival on original therapy with improvement in 6 minute walk distance > 75 meters at 12 months) was achieved by 39% LVAD vs 21% OMM patients. Although in an as-treated analysis, survival was higher in LVAD than OMM patients (80 vs 63%), survival by intention to treat did not differ. Adverse events and hospitalizations, however, were higher in LVAD patients.

Thus, LVAD implantation can be considered in functionally limited, non-inotrope dependent patients to improve quality of life, but should be done only after careful informed consent of the patient and caregivers regarding the benefit/risk ratio in each case.
OPTIONS FOR REMOTE PATIENT MONITORING IN THE LVAD POPULATION
S.P. Bhavnani1,3, A. Srivastava1,3, D. Meyer2, R. Kuo1, J. Nowaczyk1, L. Wolman1, S. Baradarian1, T. Heywood1,3
1. Scripps Health, La Jolla, California, USA
2. Methodist Health System, Dallas, Texas, USA
3. Scripps Clinic and Research Institute, San Diego, California, USA

Purpose: Multiple technologies are emerging that may have roles in remote patient monitoring in the LVAD population. These include smartphone applications and wearables, nanosensors, lab-on-a-chip platforms, and miniaturized systems. We investigated the feasibility and safety of a novel ingestible nanosensor Proteus Medical to monitor medication compliance among patients with left ventricular assist devices (LVAD).

Methods: The sensor is a miniaturized circuit composed of Mg and Cu and is embedded within a medication or placebo pill. Upon ingestion, gastric acids activate the circuit producing a biogalvanic battery and a 1-2V signal. A receiver patch on the abdominal wall captures and transmits this signal to a cloud-based platform and to an iPad application. To assess the efficacy of this system, LVAD recipients meeting inclusion criteria were considered for enrollment. Study subjects ingested 4-6 sensors over a 3-day period and were continuously monitored with telemetry, defibrillator, and LVAD interrogation, and were monitored to 30 minutes post-ingestion.

Results: To date, 4 subjects have been enrolled with a combined ingestion of 18 sensors. Successful signal transmission was observed in 86% (18/21) ingestions with possible crosstalk between the LVAD and patch suspected in 3/21 ingestions. 100% positive signal detection was demonstrated after placement of the receiver patch in positions lateral or beneath the LVAD pocket. Signals were detected within 15 minutes after ingestion and no false signals were observed. No changes were evident on defibrillator or LVAD function after any ingestion.

Conclusion: This study represents an early application of emerging mobile health options that are available to the LVAD population. Clinical application for this sensor includes monitoring patients to reduce the risk of device-related complications including bleeding and thrombosis, and as a digital health strategy to improve patient safety and outcomes.
TRANSITION TO STAGE D HEART FAILURE AMONG STABLE OUTPATIENTS WITH SYSTOLIC HEART FAILURE

A.P. Kalogeropoulos, A.A. McCue, J.S. Hedley, A. Samman-Tahhan, J.B. Bjork, V.V. Georgiopoulou, J.D. Vega, A.L. Smith
Emory University, Atlanta, GA, USA

Background: Incidence rates and risk factors for transition to Stage D heart failure (HF) among patients with stable, Stage C HF with reduced ejection fraction (HFrEF) have not been described.

Methods: We evaluated 3-year transition rates to clinically determined Stage D HF, after accounting for competing mortality, in 919 outpatients (age, 62±15 years; 35.7% women; 47.3% white, 45.8% black; median ejection fraction [EF] 27.5% [20.0%-35.0%]; 47.7% with ischemic heart disease) with baseline Stage C HFrEF (EF ≤ 40%) not previously on advanced HF therapies.

Results: After a median of 3.0 years (1.7-3.2), 107 patients were deemed to have transitioned to Stage D (3-year incidence: 12.3%; annual rate: 4.5% ) and 100 died before transitioning to Stage D (3-year competing mortality: 11.6%; annual rate: 4.2%). Transition to Stage D was faster among blacks (6.4%/year vs. 2.7% in whites; P<0.001) and those with nonischemic HF (6.3%/year vs. 2.8 in ischemic; P<0.001). In adjusted models including clinical characteristics, EF, and laboratory work, additional predictors of transition were lower baseline EF and systolic blood pressure, renal and hepatic dysfunction, and lung disease.

Conclusion: Among Stage C HFrEF survivors receiving care in a referral center, approximately 5% transition to Stage D each year, with faster transition among black and nonischemic patients. Although these estimates need multi-center confirmation, our findings have implications for healthcare resources planning and allocation for these patients.
TREATING ADVANCED HEART FAILURE – THE PUMPS AND BEYOND

MYOCARDIAL RECOVERY DURING VENTRICULAR UNLOADING IN PATIENTS WITH CHRONIC CARDIOMYOPATHY: ASSESSMENT OF CARDIAC IMPROVEMENT AND WEANING FROM VENTRICULAR ASSIST DEVICES

M. Dandel
Deutsches Herzzentrum Berlin, Berlin, Germany

During ventricular assist device (VAD) support, end-stage failing hearts can recover at molecular and cellular level and occasionally also translation of these changes into functionally stable cardiac recovery allowing long-term freedom from heart failure recurrence after VAD removal is possible. Weaning from VADs is a clinical option with potential successful results for >20 years, even if cardiac recovery remains incomplete and chronic cardiomyopathy was the underlying cause for VAD implantation. Echocardiography and right heart catheterization (RHC) are paramount for assessment of relevant cardiac improvement and essential for weaning decisions. There are many useful parameters for cardiac recovery assessment and prediction of long-term weaning success, but to date there is no gold standard for recovery assessment. Nevertheless, left ventricular (LV) ejection fraction ≥45% and end-diastolic diameter ≤55mm, measured at rest during "off-pump trials", are generally accepted as basic criteria for left ventricular LVAD explantation and their stability for 2-4 weeks after maximum improvement is also accepted as an important requirement. Other off-pump echo-parameters of cardiac function (including tissue Doppler and strain imaging data) and LV geometry, as well as their pre-explant stability (between and during off-pump trials after maximum improvement) are helpful for weaning decisions. Normal and stable hemodynamics during off-pump RHC trials is necessary for weaning decisions, but not sufficiently predictive for long-term cardiac stability after VAD explantation. Off-pump CI >2.5 L/min/m² and PCWP <14 mmHg are accepted as major requirements for VAD explantation. HF history-length ≥ 5 years is one of the major risk factors for HF recurrence after VAD explantation. There are two major limitations for a potential future use of VADs as a therapeutic strategy aimed to reverse HF: first, the low probability of relevant cardiac recovery, even after additional use of drugs known to enhance reverse remodeling and second, the fact that recovery is not predictable before VAD implantation.
TREATING ADVANCED HEART FAILURE – THE PUMPS AND BEYOND

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TREATING FLUID OVERLOAD WITH FLUID; ROLE OF PERITONEAL DIALYSIS IN MANAGEMENT OF HEART FAILURE

A. Kazory
University of Florida, Gainesville, Florida, USA

Heart failure (HF) remains the most common reason for hospital admission in older patients resulting in significant burden on healthcare expenditure. The currently available therapeutic modalities for HF do not seem yet to be producing optimal results. Peritoneal dialysis (PD) represents a home-based therapeutic modality in which the gentle removal of the excess fluid (and sodium) takes place in the peritoneal cavity, hence potentially avoiding the renal adverse effects of high dose diuretics while providing continuous, predictable, and progressive decongestion. Improvement in left ventricular ejection fraction and providing a better quality of life through sustained alleviation of congestive symptoms are among proposed benefits of PD in patients with HF. Several studies of PD therapy for HF, although with small number of patients and short follow up periods, initially reported encouraging results. The findings of more recent studies that have included higher number of patients support the results of the initial reports, especially with regards to reduction in the re-hospitalization rate as well as the positive impact on left ventricular function. These findings are not only important from the standpoint of quality of life for these patients who remain free from hospitalization, but they are also of particular financial interest due to the fact that the majority of the cost of the care for HF patients is related to utilization of inpatient resources. In conclusion, based on the currently available data, PD therapy could represent a therapeutic option for patients in whom conventional and less-invasive management strategies have not been successful.
TREATING ADVANCED HEART FAILURE – THE PUMPS AND BEYOND

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ACELLULAR BIOLOGICS FOR CARDIAC REGENERATION
A. Behfar
Mayo Clinic, Rochester, MN, USA

The global drive to generate new curative therapies is fueled by a growing unmet perpetuated by the heart failure pandemic. Regenerative trials in cardiovascular disease have focused on the use of cell-based therapy in acute myocardial injury, in order to halt progression towards heart failure, or in congestive heart failure, to regenerate a deteriorating myocardium. Worldwide, large populations of patients have been treated with adult stem cell therapy with phase III trials now underway to validate the therapeutic value of cell therapy in the heart. To overcome the variability and significant cost of stem cell therapies, off the shelf technologies have been developed that are able to consistently deliver regenerative cues, avoiding the need to utilize stem cells. By creating regenerative therapies as an “off-the-shelf” product, the consistency of efficacy, cost and accessibility of this technology significantly improves. Thus, by building on the “first generation” cellular regenerative experience, the field is evolving to a new era where targeted molecular interventions can be pursued to ensure a regenerative impact following intervention.
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WHOLE HEART REGENERATION WITH HUMAN IPS CELL-DERIVED HEART PROGENITORS
B. Lin, T-Y Lu, J. Kim, M. Sullivian, K. Tobita, G. Salama, L. Yang
University of Pittsburgh, Pittsburgh, PA, USA

Objective: In US, about 50,000 people die each year due to the limited donor hearts for transplant. Thus the future treatment of heart disease requires the development of personalized therapeutic strategies, such as patient-specific cardiac tissues or whole bio-artificial hearts for transplantation.

Methods: 12 to 16-week-old C57BL6/J mice were euthanized and the ascending aorta was cannulated with a blunted 20-gauge needle to allow retrograde coronary perfusion, followed with a decellularization process with enzyme and detergent treatments. In the meanwhile, human induced pluripotent stem (iPS) cells were induced for cardiovascular differentiation using our established protocol. Approximately 10 millions human iPS cell-derived multipotential cardiovascular progenitors (MCPs) were delivered into one acellular mouse heart through the connected cannula. After 20 days culture, the engineered heart constructs showed contractions, followed with histological, electrophysiological and drug response analyses.

Results and Conclusion: In this study, we engineered human heart tissues by repopulating whole decellularized mouse hearts with human iPS cell-derived MCPs. MCPs represent the earliest heart progenitors during human cardiogenesis. The seeded MCPs differentiated in situ into CMs, smooth muscle cells (SMCs) and endothelial cells (ECs) with high efficiency, which reconstructed the decellularized mouse hearts. The recellularized mouse hearts exhibited myocardium and vessel-like structures, contracted spontaneously with a rate of 40 to 50 beats/min, exhibited intracellular Ca2+ transients (Ca2+T) and responded as expected to various drug interventions. Overall we utilized a novel patient-specific cell resource, which is the iPS cell-derived MCPs, for engineering patient-specific heart constructs that could be beneficial to future heart disease therapy.
Congestive heart failure due to systolic function is a frequent cause for hospitalization and not infrequently sudden death. Some of these patients have venous occlusion due to prior central venous access. Non traditional placement of devices has been replaced by entirely subcutaneous defibrillators. Detection and therapeutic algorithm of these devices are different from traditional trans venous implantable devices.

Elevated pressures in cardiac chambers and pulmonary venous system precede overt clinical symptoms and weight gain. Implantable device monitoring of such pressures leads to early intervention and prevention of hospitalization.

Utility of these devices in improving hospitalization and reducing mortality/morbidity is an important new development in heart failure management.
ROLE OF ECHOCARDIOGRAPHY IN EPIDEMIOLOGIC STUDIES AND CLINICAL TRIALS: AN HISTORICAL PERSPECTIVE

J.M. Gardin
Hackensack University Medical Center, Rutgers New Jersey Medical School, NJ, USA

Non-invasive transthoracic echocardiography (TTE) for assessment of subclinical and clinical heart disease – initially, left ventricular (LV) mass, geometry and function – dates from the 1980’s. In parallel, TTE successfully demonstrated in hypertensive patients reduced LV mass and improved outcomes with antihypertensive therapy. Transesophageal echocardiography (TEE) has been invaluable in intra-operative/interventional trials. Many important uses of TTE/TEE and contributions from our collaborations are summarized in Tables 1 and 2. Challenges have included poor echocardiography windows, sonographer and reader measurement variability, temporal drift, regression-to-the mean, etc. Promising newer study applications include global image telemetry, strain deformation imaging, hand-held and potentially wearable echocardiography devices.

Table 1 - Important uses of TTE and TEE in Epidemiologic Studies and Clinical Trials

| 1. Epidemiology: Characterize cardiac structure and function; identify echo prognostic parameters (e.g., in Framingham, Cornell, Helinski and CHS) |
| 2. Hypertension: Measure LV mass, systolic and diastolic function and assess treatment effects |
| 3. Valvular Disease: Assess prevalence, risk factors for development; assess prosthetic valve hemodynamics (for FDA, etc.) |
| 4. CHD/MI: Assess disease impact on LV remodeling/function; assess drug, catheter-based and surgical interventions; stress echo for ischemic vulnerability, myocardial viability, etc. |
| 5. Heart Failure: Assess LV systolic and diastolic function, LV remodeling, mitral regurgitation, and treatment effects – including reverse remodeling; assess candidates for CRT, other devices |
| 6. Toxicity: Assess effects of cancer, chemo/radiation therapy, diabetes, etc. |
| 7. Other: Diet drug valvulopathy, echo contrast agents, atrial fibrillation, TEE-guided cardioversion, interventional device (PFO and LAA closure, CRT, mitral clip, etc.) and surgical trials |

Table 2 – Selected Cohort Studies involving our Collaboration

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Echocardiography findings</th>
</tr>
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<tbody>
<tr>
<td>CHS</td>
<td>Elderly US adults: Bi-ethnic AA and C cohort</td>
<td>• Elucidated prevalence of HFrEF, HFrEF, CHD and AV disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Predictive value of LV mass, geometry and systolic function for HF, stroke and overall CVD events</td>
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<tr>
<td>CARDIA</td>
<td>Young US adults: Bi-ethnic AA and C cohort</td>
<td>• Elucidated prevalence of MV and AV disease, MVP and HCM.</td>
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<td></td>
<td></td>
<td>• Higher prevalence of LV mass in AA, associated with obesity and higher BP</td>
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<td></td>
<td></td>
<td>• Predictive value of LV systolic function for incident HF 10 years later</td>
</tr>
<tr>
<td>HF-ACTION</td>
<td>HFrEF patients (LVEF &lt; 35%)</td>
<td>• Association of LV diastolic dysfunction with exercise MVO2</td>
</tr>
<tr>
<td>Echo NoRMAL</td>
<td>International cohort collaboration: Adult populations</td>
<td>• Elucidated normal TTE values in Euro, SA, and EA populations</td>
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<td></td>
<td></td>
<td>• Demonstrated lower range of stroke volume(s) in SA</td>
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<tr>
<td>DIET DRUGS</td>
<td>Multicenter phen/fen and dexfenfluramine cessation studies</td>
<td>• Prevalence of AR= 9 - 14% (mild = 8 - 12%) versus 4% in controls; regression or no change noted 1 year later</td>
</tr>
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Abbreviations: AA = African American, AR = aortic regurgitation, AV = aortic valve, BP = blood pressure, C = Caucasian, CARDIA = Coronary Artery Risk Development in Young Adults, CHD = coronary heart disease, CHS = Cardiovascular Health Study, CIMT = carotid intima-media thickness, EA = East Asian, Echo NoRMAL = Echocardiographic Normal Ranges Meta-analysis of the Left Heart, Euro = European, HF = heart failure, HF-ACTION = Heart Failure ACTION, HFrEF = heart failure with preserved ejection fraction, HFrEF = heart failure with reduced ejection fraction, SA = South Asian
Hypertension is a major risk factor for coronary artery disease (CAD) and related morbidity. Identification of an accurate non-invasive method for diagnosis of CAD is important to plan therapeutic and interventional management in order to improve outcome. The diagnosis of CAD in hypertensive patients may represent a challenge due to certain unique characteristics. These include baseline EKG abnormalities which reduce specificity of exercise EKG. Left ventricular hypertrophy may be associated with demand ischemia in absence of obstructive CAD. Stress myocardial perfusion imaging provides good sensitivity and specificity. Some studies showed reduced specificity in patients with left ventricular hypertrophy. However, many studies demonstrated similar accuracy in patients with and without hypertension. Stress echocardiography using exercise or dobutamine was shown to have good accuracy. The technique is widely available and does not entail radiation. In addition to ischemia, left ventricular mass index predicts cardiac events. Hypertensive response during stress has been related to false positive results. A normal stress echocardiogram or radionuclide study is associated with low risk of cardiac death and myocardial infarction during intermediate and long term follow up. Coronary CT angiography is increasingly used in patients with intermediate probability of CAD and in those with equivocal stress test. The test has high negative predictive value to rule out CAD. Disadvantages include artifacts, irradiation and risk of contrast nephropathy. Obesity is a significant comorbid condition that may impair imaging quality of different techniques. Proper selection of imaging modality depends on various clinical parameters, availability and expertise of the center with each type of imaging.
Primary diseases of the heart muscle (cardiomyopathies) are often classified based on their gross morphological phenotypes and certain functional characteristics. The diagnosis is, thus, highly dependent on the findings on cardiac imaging that not only identifies the categories of the disease (hypertrophic, dilated, and restrictive) but also provides the basis for institution of specific therapeutic interventions. Even the unclassified cardiomyopathies (arrhythmogenic right ventricular cardiomyopathy and left ventricular noncompaction) are defined by their morphologic characteristics on non-invasive cardiac imaging. Echocardiography has been the most useful clinical tool for diagnosis, management and follow up of patients with cardiomyopathies. However, assessment of physiologic, and exclusion of secondary causes of cardiomyopathies may require evaluation with other advanced imaging modalities such as cardiac magnetic resonance (CMR), cardiac nuclear imaging and cardiac computed tomography. Physiologic counterparts of primary cardiomyopathies include athlete’s heart and some secondary causes of cardiomyopathy may not be distinguishable on the basis of cardiac phenotype alone. In addition, with the widespread use of genetic testing a large number of individuals are being identified in whom the primary disease has not expressed itself phenotypically. In the latter group of patients, application of sophisticated non-invasive imaging techniques (including molecular probes for assessment of subclinical metabolic abnormalities) can provide important information for understanding the clinical course of the disease. A systematic approach to cardiomyopathies, using multimodality imaging when required, ensures accurate diagnosis, institution of specific treatment and exclusion of potential alternative diagnoses that may mimic primary cardiomyopathies.
ECHOCARDIOGRAPHIC QUANTITATION OF AORTIC REGURGITATION

H. Chaliki
Mayo Clinic College of Medicine, Mayo Clinic, Scottsdale, AZ, USA

Aortic regurgitation (AR), either acute or chronic, can be due to valvular pathology or aortic root pathology or a combination. Currently, echocardiography is used in most cases to determine the etiology and severity of AR. Although, semi-quantitative methods such as color flow jet area or jet width are used for AR assessment, they are less reliable. Density of the AR regurgitation continuous wave Doppler jet signal, diastolic flow reversals in the descending thoracic aorta, size of the left ventricle when used in conjunction additional parameters such as width of the vena contracta will improve the assessment of the severity of AR. Specifically, vena contracta width of >6 mm is highly specific and sensitive for the diagnosis of severe chronic AR.

Quantitative methods such as continuity method and Proximal Isovelocity Surface Area (PISA) method are clinically more useful given their ability to more precisely determine the AR severity. Specifically, one can estimate the AR volume and effective regurgitant orifice area. When AR volume exceeds 60 mls and effective regurgitant orifice area exceeds 0.3 cm², one is considered to have severe AR based on American society of echocardiography and American college of cardiology guidelines.

Three dimensional (3D) echocardiography now make it possible to not only visualize the aortic valve anatomy better but also measure the vena contracta area and proximal isovelocity surface area without the need for geometric assumptions. Recent studies demonstrated that vena contracta area measurement using 3D color Doppler echocardiography improved quantitation of AR when compared to 2D vena contra area or conventional echo-Doppler methods when magnetic resonance imaging was used as gold standard. Further advances in 3D echocardiography will make it possible to improve the quantitation of AR even further.
MULTIMODALITY IMAGING FOR EVALUATION OF CARDIOVASCULAR DISEASE

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CURRENT STATUS OF INTRAVASCULAR IMAGING
S.K.G. Koshy, L.K. George
1. Regional One Health - University of Tennessee Health Sciences Center, Memphis TN, USA
2. University of Tennessee School of Medicine, Memphis, TN, USA

Diagnostic angiography has been the mainstay of confirmatory diagnosis of vascular atherosclerosis. Being a luminogram its ability to determine the presence and extent of atherosclerosis is limited by changes in the vessel wall that is adjacent to the atherosclerotic plaque. Moreover, the angiography does not delineate the physiological, molecular and physical characteristics of the plaque. Lack of such a data restricts physician's ability to individualize the treatment of atherosclerotic vascular disease in patients. Intravascular imaging modalities like intravascular ultrasound and Optical Coherence Tomography are currently widely used in catheterization laboratories. They provide additional data on the morphological characteristics of the vessel wall and intraluminal structures. Integrating newer technology like virtual histology and infrared spectroscopy to existing intravascular imaging platforms is a novel method that can enhance diagnostic capability of traditional intravascular imaging techniques. Hybrid use of different existing technologies and integrating novel techniques that delineate tissue characteristics would added value in vascular imaging.
THE USE OF POINT OF CARE ULTRASOUND TO GUIDE MANAGEMENT IN HEART FAILURE

I. Kedan, R. Khandwalla, R. Zimmer, K. Birkeland
Cedars Sinai Heart Institute, Beverly Hills, CA, USA

Background: Point of Care (POC) ultrasound (US) has long been used in the acute care and emergency setting for management of trauma patients. Our clinical group has applied the data acquired from POC US to assist in management of chronic heart failure (HF) patients in the ambulatory setting.

Protocol: Cardiologists selected 250 NYHA Class II-IV HF patients at high risk for hospitalization from a panel of 5500. These patients were enrolled in a clinical pharmacist run HF clinic that focused on medication safety and optimization, coordination of care, and patient education. Serial inferior vena cava measurements and serial assessment of pleural effusions were acquired with GE Vscan point of care ultrasound and were used to guide of therapeutic optimization.

Results and Discussion: 220 and 164 patients were analyzed at 6 and 12 months before and after enrollment in the program. Total inpatient hospitalization days in the 6 month cohort was 897 days pre-enrollment and 313 after enrollment \( (p < 0.001) \). Total inpatient hospitalization days in the 12 month cohort was 818 days pre-enrollment and 343 after enrollment \( (p < 0.001) \).

We have demonstrated that with the use of POC US we have been able to acquire serial anatomic measurements that results in actionable data for patient management in the ambulatory care setting. These data have allowed us to better personalize care to improve heart failure outcomes and decrease heart hospitalization.
MULTIMODALITY IMAGING FOR EVALUATION OF CARDIOVASCULAR DISEASE

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POSITIVE STRESS ECHO AND NORMAL CORONARY ARTERIES: HOW OFTEN AND WHY?
M. Prokudina¹, E. Bobrova¹, E. Shloido², I. Konstantinov¹, P. Mochalov¹
1. Almazov North-West Medical Research Center, St-Petersburg, Russia
2. City Hospital, St-Petersburg, Russia

Objective: To conduct long-term follow-up of patients with a positive result of exercise echo and the absence of significant coronary artery stenosis.

Methods: We examined 97 patients (41 men and 56 women) (63.3±8.9 years) with a positive exercise echo and the absence of significant stenosis in coronary arteries. Re-examination was carried out after 1-10 years (±6) and the patients were divided into two groups. In the first group (17 patients), the second test was again positive. 10 patients had repeated coronary angiography: 4 patients revealed significant stenosis and revascularization was performed (two with use of intravascular ultrasound). One patient presented with insignificant stenosis (less than 50%) and 3 patients had no pathology in coronary arteries. One patient was found to have cardiac X syndrome, and one more patient was found to have cardiomyopathy. In the second group (80 patients), a second test was negative. Patients were divided into two groups: patients with exercise-induced hypertension (57) and patients without development of hypertension during exercise (23 patients). The correction of antihypertensive medication before the second test was performed.

Conclusion: In 71% of patients, the false-positive test was caused by exercise-induced hypertension. With antihypertensive therapy the percentage of false-positive tests decreased to 44%. Thus, a positive stress echocardiography in a patient with exercise-induced hypertension in the absence of other high-risk signs appears to warrant expedient antihypertensive therapy follow by repeated examination.
MULTIMODALITY IMAGING FOR EVALUATION OF CARDIOVASCULAR DISEASE

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INTRAVASCULAR OPTICAL IMAGING TECHNOLOGY FOR DETECTION OF HIGH-RISK PLAQUE

H. Yoo

Hanyang University, Seoul, South Korea

Intravascular optical coherence tomography (IV-OCT) is a high-resolution imaging catheter used to visualize three-dimensional microstructure of arterial walls. Unprecedented high-resolution of IV-OCT for cardiovascular imaging enables clinicians to identify key features related to high-risk lesions inside a vessel. While gray-scale IV-OCT images allow clear visualization of the high-risk lesions, quantitative analysis requires time-consuming manual image-processing that hinders large clinical studies. To overcome this limitation, we have developed an automatic algorithm that enables robust and fast detection of lumen contour and stent struts to provide quantitative measurements of stent apposition and neointimal coverage, which are closely related to in-stent thrombosis. Additionally, we were able to measure lipid contents of lipid-rich plaque by analyzing spectral information of IV-OCT images. The algorithms would significantly improve the clinical utility of IV-OCT by providing rapid and accurate measurements regarding stent healing and plaque compositions. On the other hand, we have developed an endoscopic micro-OCT imaging catheter, which has even higher resolution up to 2 micron, to investigate cells and extracellular components associated with atherosclerosis, such as endothelium and microcalcifications. These novel imaging technologies could provide new opportunities for investigating vascular biology and stent pathobiology and for identifying high-risk plaques.
RISK STRATIFICATION AND SECONDARY PREVENTION OF CARDIOVASCULAR DISEASE

ASTHMA ASSOCIATES WITH HUMAN ABDOMINAL AORTIC ANEURYSM AND RUPTURE

C.L. Liu¹, H. Wemmelund², J. Lindholt³, B. Levy¹, P. Libby¹, G.P. Shi¹
1. Department of Medicine, Brigham and Women’s Hospital and Harvard Medical School, Boston, MA, USA
2. Department of Vascular Surgery, Viborg Regional Hospital, Viborg, Denmark
3. Department of Cardiothoracic and Vascular Surgery, Elitary Research Centre of Individualized Medicine of Arterial Disease, Odense University Hospital, Odense, Denmark

Objective: Both asthma and abdominal aortic aneurysms (AAA) involve inflammation. It remains unknown whether these diseases interact.

Methods and Results: Databases analyzed included Danish National Registry of Patients, a population-based nationwide case control study included all patients with ruptured AAA and age- and sex-matched AAA controls without rupture in Denmark from 1996 to 2012; Viborg vascular trial, subgroup study of participants from the population-based randomized Viborg vascular screening trial. Patients with asthma were categorized by hospital diagnosis, bronchodilator use, and the recorded use of other anti-asthma prescription medications. Logistic regression models were fitted to determine whether asthma associated with the risk of ruptured AAA in Danish National Registry of Patients and an independent risk of having an AAA at screening in the Viborg vascular trial. From the Danish National Registry of Patients study, asthma diagnosed <1 year or 6 months before the index date increased the risk of AAA rupture before (odds ratio [OR]=1.60–2.12) and after (OR=1.51–2.06) adjusting for AAA comorbidities. Use of bronchodilators elevated the risk of AAA rupture from ever use to within 90 days from the index date, before (OR=1.10–1.37) and after (OR=1.10–1.31) adjustment. Patients prescribed anti-asthma drugs also showed an increased risk of rupture before (OR=1.12–1.79) and after (OR=1.09–1.48) the same adjustment. In Viborg vascular trial, anti-asthmatic medication use associated with increased risk of AAA before (OR=1.45) or after adjustment for smoking (OR=1.45) or other risk factors (OR=1.46).

Conclusions: Recent active asthma increased risk of AAA and ruptured AAA. These findings document and furnish novel links between airway disease and AAA, 2 common diseases that share inflammatory aspects.
ASSOCIATION BETWEEN HIGH-DENSITY LIPOPROTEIN AND CARDIOVASCULAR DISEASE OUTCOMES

M.S. Sidhu, M. Pragani, W.E. Boden, R.P. Smith, L.H. Bopp, M.E. Rafferty
Department of Medicine, Albany Medical Center and Albany Stratton Veterans Affair Medical Center, Albany, NY, USA

Background: Epidemiologic evidence has demonstrated an inverse relationship between high-density lipoprotein cholesterol (HDL-C) and subsequent cardiovascular (CV) disease outcomes; however, pharmacologic interventions have not been shown to decrease future coronary events. We examined the association between HDL-C levels, in conjunction with other CV risk factors, and co-morbid diseases.

Methods: A retrospective chart review was performed over a 4-month period during which time 9,000 unique patients were screened. We identified 365 patients of whom 265 patients had an HDL-C ≤ 25 and 100 with HDL-C ≥ 85 mg/dL. Body mass index (BMI), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), total cholesterol, sedimentation rate, C-reactive protein and pertinent medical co-morbidities were identified in each patient. Co-morbidities identified were diabetes mellitus (DM), hyperlipidemia (HLD), hypertension (HTN), inflammatory diseases (e.g. osteoarthritis and hepatitis C), and any known history of coronary or vascular disease.

Results: This predominantly male (94.2%) cohort had an average age of 64.2 years. The average BMI among the high HDL-C, low HDL-C and low HDL-C with history of coronary artery disease (CAD) groups was 26.1, 33.27 and 32.0 kg/m2 respectively. The prevalence of type 2 DM among both groups was 9% in the high HDL-C group compared with 53.5% in the low HDL-C group. The average TG level in the high HDL-C group was 90.5 mg/dL compared with 352.2 mg/d in the low HDL-C group. Sixty patients in the high HDL-C group were shown to have HTN compared with 193 in the low HDL-C group. Ten patients in the high HDL-C group were identified to have a history of CAD compared with 81 in the low HDL-C group. Osteoarthritis was found to be prevalent in both groups, with 20 in the high HDL-C group and 25 in low HDL-C group. Hepatitis C infection was found to be more prevalent in the low HDL-C group, 12 compared with 2.

Conclusions: The higher incidence of medical co-morbidities, including type II DM, HLD, HTN, and history cardiovascular disease is associated with very low HDL-C levels. There may be a relationship between inflammatory disorders, such as hepatitis C and HDL-C levels which should be further explored in larger patient populations.
FAILING TO MEET HEART FAILURE PATIENTS’ BASIC NUTRITIONAL NEEDS—WHO’S LISTENING?

A. Kodra, J. Jacobson, R. Graham
Lenox Hill Hospital, New York, NY, USA

Aims: 1. To identify whether medical residents were following diet recommendations made by nutritionists for hospitalized malnourished heart failure patients.
2. To determine differences in readmission rates between these patients.

Methods: This study was a prospective cross-sectional observational study. Patients who were hospitalized for at least 48 hours in a telemetry cardiac unit with a diagnosis of heart failure and had an official nutrition consult for malnutrition were considered. 50 patients met these inclusion criteria. Nutritionist recommendations were extracted from patient charts. The date of diet order changes made by residents were noted. Readmissions were identified at 30 days post-discharge.

Results: 34/50 patients (68%) had diet orders that matched nutritionists’ recommendations. Of these patients, 19 had their diet changed to the suggested diet within 24 hours of the recommendation; 6 patients had their diet changed within 48 hours; 9 patients had their diet changed after 48 hours. Only 2/19 patients who had an appropriate diet ordered within 24 hours of nutritionist consultation were readmitted within 30 days. 16/31 patients who did not have the correct diet ordered within 24 hours of evaluation by a nutritionist were readmitted within 30 days.

Conclusion: Less than 1/3rd of the heart failure patients in the study had diet orders that matched recommendations from a nutritionist within 24 hours of their hospitalization. Patients who did not have a recommended diet ordered within 24 hours had higher rates of readmission. These results echo deficiencies in management of malnourished patients that may have important clinical implications.
THE RUMC INDEX: PREDICTING MORTALITY USING A COMBINED EWS AND NLR SCORING SYSTEMS

A.J. Park, X. Wang, V. Arulhasan, D.A. Bloomfield
Richmond University Medical Center, Staten Island, NY, USA

Background: The ability to accurately determine disease severity and patient mortality risk is essential to provide appropriate and timely patient care. The early warning score (EWS) and the neutrophil-to-lymphocyte ratio (NLR) are two independently proven mortality predictive scores. NLR (neutrophil % divided by lymphocyte %) has been most frequently utilized for patients with cardiac disease whereas EWS (grading the variables in the table below) has been widely used in the United Kingdom triage setting as a predictor of all-cause mortality.

Objective: To create a better mortality predictive score, the two indices were combined into a new one called the Richmond University Medical Center Index (RUMCI).

Methods: 330 medical records of patients who had expired within 30 days of admission were reviewed for the variables in the table to calculate the RUMCI by adding the scores allocated for individual variables.

Results: RUMCI ≥ 5 was able to identify 83% of the expired patients, as opposed to EWS (80%) or NLR (73%).

Conclusion: While EWS and NLR can act as an effective independent mortality predictor, the combination of the two values in RUMCI is superior.

RUMC Index Table

<table>
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<th>Variable Parameters</th>
<th>Score</th>
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<th>1</th>
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</thead>
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<tr>
<td>Respiratory Rate (bpm)</td>
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<td>9-20</td>
<td>21-30</td>
<td>31-35</td>
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<tr>
<td>SaO2 (%)</td>
<td></td>
<td>&lt; 85</td>
<td>85-89</td>
<td>90-92</td>
<td>≥ 93</td>
<td></td>
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<td>Temperature (°C)</td>
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<td>≤ 33.9</td>
<td>34-34.9</td>
<td>35-35.9</td>
<td>36-37.9</td>
<td>38-38.9</td>
<td>≥ 39</td>
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<tr>
<td>Blood Pressure (systolic)</td>
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<td>≤ 69</td>
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<td>80-99</td>
<td>100-199</td>
<td></td>
<td>≥ 200</td>
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<tr>
<td>Heart Rate (bpm)</td>
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<td>≤ 29</td>
<td>30-39</td>
<td>40-49</td>
<td>50-99</td>
<td>100-109</td>
<td>110-129</td>
<td>≥ 130</td>
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<td>Pain</td>
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<td>4.7-11.19</td>
<td>11.2-12.99</td>
<td>≥ 13</td>
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TRIAGE AFTER EXERCISE TREADMILL TEST (TEXT) STUDY: A SINGLE CENTER EXPERIENCE WITHIN AN INTEGRATED HEALTHCARE DELIVERY SYSTEM

A. Krishnaswami1, W. Ho2, W. Kwan3, C. Tsou2, O. Anaya1, S.F. Jiang4, J.J. Jang1, W. Praserthdam1

1. Division of Cardiology, Kaiser Permanente, San Jose, CA, USA
2. Division of Hospital Medicine, Kaiser Permanente, San Jose, CA, ISA
3. Division of Nuclear Medicine, Kaiser Permanente, San Jose, CA, USA
4. Division of Research, Kaiser Permanente, Oakland, CA, USA

Background: The TEXT study was designed as a quality improvement project to understand referral patterns before and after an index exercise treadmill test (ETT).

Methods: Adults at Kaiser Permanente San Jose who underwent an index ETT between 1/1/2014 and 12/31/2014 were followed till 12/31/2015. Baseline patient demographics, physician reported patient symptoms, comorbidities, medications, health care utilization, laboratory data, ETT variables, and ETT report variables were obtained thru chart review and validated algorithms based on health plan databases. The primary outcome was the receipt of further downstream noninvasive imaging without a coronary revascularization procedure. Statistical analysis was performed using logistic regression and classification and regression tree (CART) analysis.

Results: Of 1,857 patients referred for ETT, the mean age was 56.0 ± 12.5 years. We found a low risk profile at baseline demonstrated by a low number of comorbidities, adequately-controlled blood pressure, hemoglobin A1C, and cholesterol level. ETT demonstrated the average Duke treadmill score (DTS) was 7.2 ± 3.9 with a low prevalence of high risk features. Further nuclear stress imaging was performed in 9.6% of the total cohort; 2.6% underwent cardiac computed tomographic angiography. Only 2.5% underwent coronary revascularization. Significant risk-adjusted predictors for the primary outcome were DTS: Odds Ratio (OR) of 0.88 (95% CI: 0.84-0.91), and report characteristics: OR of 2.40 (95% CI: 1.74-3.29). Classification and regression tree analysis demonstrated that a 5 variable model with 8 nodes had a c-statistic of 0.76.

Conclusions: This single center study demonstrated that improvements in the referral for ETT and standardization of the reporting process are needed to maximize the utility of ETT.
RISK STRATIFICATION AND SECONDARY PREVENTION OF CARDIOVASCULAR DISEASE

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RISK OF ANXIETY DISORDERS IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION: A NATIONWIDE POPULATION-BASED COHORT STUDY
W-C. Tzeng, H-P. Feng
National Defense Medical Center, Taipei, Taiwan

Objectives: This study investigated the association between psychiatrist-diagnosed psychiatric disorders and cardiovascular prognosis after an acute myocardial infarction (MI).

Background: Most studies focusing on anxiety have used rating scales or self-report methods rather than clinical diagnostic interviews to identify anxiety following an MI. To date, no study has assessed clinical diagnosis of anxiety disorders after an acute MI in comparison with patients without MI.

Methods: Data were obtained from Taiwan’s National Health Insurance Research Database from 1997 through 2010. We identified 1,396 newly diagnosed patients with acute myocardial infarction and 13,960 age- and sex-matched non-AMI controls for comparison. The primary endpoint was the diagnosis of GAD during follow-up. The differences in demographic and clinical characteristics between both cohorts were analyzed and the risk factors for GAD were assessed using Cox proportional hazards models.

Results: During the first 2 years of follow-up, patients with MI exhibited a significantly higher risk of anxiety disorders (adjusted hazard ratio [HR] = 5.06, 95% confidence interval [CI]: 4.61–5.54) than those without MI did. The risk of anxiety disorders was higher in women and patients aged 45–64 years. Patients with post-MI anxiety had a 9.37-fold higher risk of recurrent MI than those without MI did after adjustment for age, sex, socioeconomic status, and comorbidities.

Conclusions: This nationwide population-based cohort study provides evidence that MI increases the risk of anxiety disorders during the first 2 years post-MI, and post-MI anxiety disorders are associated with a higher risk of recurrent MI. Further studies are needed to identify the bidirectional causal relationship between MI and anxiety or depressive disorders.
Acute ST elevation myocardial infarction (STEMI) is a fatal presentation of coronary artery diseases although it happens in people > 45 years old, but sometimes occurs in younger people < 40. It is estimate about 2-6 percent in young people in different countries. The mortality and morbidity, emotional stress and its economic burden of this group emphasize to search for underlying risk factors.

**Method:** 234 STEMI patients admitted to Golestan Hospital of Ahvaz, Iran. All was enrolled to two groups according to age less and higher than 40 with following criteria: typical chest pain, ECG finding compatible with ST segment elevation, new LBBB and Q wave, high level of cardiac enzymes. 34 Patients with post traumatic MI and pericarditis was excluded from study. Clinical evaluation, echocardiography and selected coronary angiography were done for all patients. All risk factors were evaluated including smoking, hypertension, diabetes, hyperlipidemia and family history.

**Results:** Male to female ratio was about 3to 1. Diabetes, hypertension and hyperlipidemia was more common among patients >40 years while smoking and positive familial history was more common in younger than 40 years. (P value <0.05) In patients > 40 STEMI was more common in LAD territory, while in younger had most often one vessel disease without specific culprit vessel but >40 years had 2 or 3 vessel disease. (p value <0.05) Many of patients <40 had normal coronary artery system with thrombus in culprit lesion.

**Conclusion:** Main risk factors of STEMI in young patients (<40 year) are smoking and positive family history. Many culprit vessels for STEMI in young age group are normal or minimal lesions.
HEARTFIT: PRELIMINARY RESULTS OF A PILOT CARDIAC OUTPATIENT SELF-MANAGEMENT PROGRAMME

J. Choy, M. Tay
Tan Tock Seng Hospital, Singapore

Objectives: This study aims to evaluate the effectiveness of a cardiac outpatient self-management group programme.

Methods: Participants were cardiac patients (n = 8; mean age = 67) recruited from a large acute-care hospital, with primary diagnosis of acute myocardial infarct. Participants attended five sessions of a lifestyle redesign programme. Modules included: Understanding Cardiac Symptoms and its Impact on Daily Activities, Application of Work Efficiency Principles, Stress Management and Sexuality. Standardised and validated self-report measures: The Self-Efficacy for Managing Chronic Disease 6-Item Scale (SEM-CD) and RAND 36-Item Health Survey 1.0 (SF-36) were administered on Session 1 and Session 5.

Results: For SF-36, there was an average increase of 15 points from 49 to 64 for Physical Functioning, an average increase of 16 points from 44 to 60 for General Health, an average increase of 29 points from 5 to 34 for Role Limitations due to Physical Health, an average increase of 13 points from 37 to 50 for Role Limitations due to Emotional Problems, an average increase of 11 points from 59 to 70 for Emotional Well-being, an average increase of 14 points from 59 to 73 for Social Functioning, an average increase of 13 points from 73 to 86 for Pain and an average increase of 10 points from 49 to 59 for Energy. For SEM-CD, there was an average increase of 1.5 points from 5.2 to 6.7.

Conclusions: Participation in HeartFit led to an improvement in quality of life and an increase in self-efficacy in management of heart disease.
DEVELOPMENT OF A HOLISTIC MODEL TO PREVENT AND REVERSE CORONARY ARTERY DISEASE: SAAOL (SCIENCE AND ART OF LIVING) SAFETY CIRCLE

B. Chhajer, V. Singh, G. Kumari
SAAOL Heart Center, New Delhi, India

Objective: To develop a simple and full proof model for heart patients which will guide them to prevent and reverse coronary artery disease.

Background: This holistic model was conceptualized at the All India Institute of Medical Sciences, where the author worked for 6 years during 1989-1995. Saaol Heart Center is an institute of Non Invasive Cardiology and has 48 branches in India, which treats heart patients with modern medicines with lifestyle changes and Enhance External Counter Pulsation.

Methods: We treated more than 100,000 heart patients in the last 20 years with aggressive risk factor intervention which would include – Yoga, walking, zero oil cooking, vegetarianism, stress management, patient education and optimum modern medical management.

Results: After 15 years and successful 100,000 patients we have developed a simple but very effective method to prevent and reverse heart disease. Patients can go for Prevention and reversal programs according to their choice. It can make the patients safe from cardiac events so we called it “SAAOL Safety Circle”. 98% of our patients have avoided heart attack and coronary artery bypass surgery.

Conclusions: This will be the best tool of patient education and guided non invasive intervention to make the world heart attack free.
DEFICIENCY OF FILAMIN A IN ENDOTHELIAL CELLS IMPAIRS LEFT VENTRICULAR REMODELING AFTER MYOCARDIAL INFARCTION

S. Bandaru¹, J. Grönros², B. Redfors¹, Ç. Çil¹, D. Pazooki¹, R. Salimi¹, E. Larsson¹, A.X. Zhou¹, E. Ömerovic¹, L.M. Akyürek¹

¹. University of Gothenburg, Sweden, 2. AstraZeneca, Mölndal, Sweden

Objectives and Background: Actin-binding protein filamin A (FLNA) regulates signal transduction important for cell locomotion, but the role of FLNA after myocardial infarction (MI) has not been explored. The main purpose of this study was to determine the impact of endothelial deletion of FLNA on post-MI remodeling of the left ventricle (LV).

Methods and Results: We found that FLNA is expressed in human and mouse endothelial cells during MI. To determine the biological significance of endothelial expression of FLNA, we used mice that are deficient for endothelial FLNA by crossbreeding adult mice expressing floxed Flna (Flnao/fl) with mice expressing Cre under the vascular endothelial-specific cadherin promoter (VECadCre+). Male Flna(o/fl) and Flna(o/fl)/VECadCre+ mice were subjected to permanent coronary artery ligation to induce MI. Flna(o/fl)/VECadCre+ mice that were deficient for endothelial FLNA exhibited larger and thinner LV with impaired cardiac function as well as elevated plasma levels of NT-proBNP and decreased secretion of VEGF-A. The number of capillary structures within the infarcted areas was reduced in Flna(o/fl)/VECadCre+ hearts. Endothelial cells silenced for Flna mRNA expression exhibited impaired tubular formation and migration, secreted less VEGF-A, and produced lower levels of phosphorylated AKT and ERK1/2 as well as active RAC1.

Conclusions: Deletion of FLNA in endothelial cells aggravated MI-induced LV dysfunction and cardiac failure as a result of defective endothelial response and increased scar formation by impaired endothelial function and signaling.
MOLECULAR CARDIOLOGY AND VASCULAR BIOLOGY, BASIC RESEARCH

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A TRANSGENIC MOUSE MODEL OF ATHEROSCLEROTIC PLAQUE CALCIFICATION
F. Romanelli¹, A.M. Corbo¹, A.Y. Savinov², J.L. Millan³, O.V. Savinova¹

1. New York Institute of Technology College of Osteopathic Medicine, Old Westbury, NY, USA
2. Sanford Research, Sioux Falls, SD, USA
3. Sanford Burnham Prebys Medical Discovery Institute, La Jolla, CA, USA

Objective: To create a model of calcified atherosclerotic plaque.

Background: Arterial calcification is associated with cardiovascular mortality independent of other risk factors. This association, however, is complex. Microcalcification is thought to promote inflammation and destabilize atherosclerotic lesions leading to plaque rupture and adverse cardiovascular events, whereas macrocalcification is associated with stable fibroatheromas. Here we designed and implemented a genetic approach to manipulate the level of plaque calcification in a mouse model. We report our initial characterization of these transgenic animals, in which TNAP – an essential enzyme that promotes biomineralization – was overexpressed in monocytes and macrophages and led to plaque calcification.

Methods: Expression of TNAP-encoding transgene (Sheen et al, 2015) was activated by the Cre recombinase driven by myeloid-specific (lyzM) gene promoter. Both the reporter (TNAP) and the driver (LyzM-cre) mice were also homozygous for a mutation in the low density lipoprotein receptor (Ldlr^Hib301). Atherosclerosis was induced in TNAP-overexpressor and control mice by feeding an atherogenic diet for 10 weeks (Paigen’s diet). Plaque area in the aortic root and plaque calcification (% of total plaque area) were measured by Oil Red O (lipids) and Alizarin Red (calcium) staining.

Results: In the absence of hypercholesterolemia, no appreciable soft tissue calcification was observed in the adult TNAP mice by full-body necropsy (n=2). During progression of atherosclerosis, plaque calcification was significantly greater in TNAP mice when compared with controls (4.85% of total plaque area in TNAP vs. 0.02% in controls, p<0.001, n=8 per group). Total plaque area in the aortic root region was not affected by calcification in this model (0.40 mm^2 in TNAP; 0.38 mm^2 in controls; p=0.75).

Conclusions: Overexpression of TNAP in macrophages can lead to plaque calcification. An animal model was developed, in which the effects of calcification on plaque stability can be studied experimentally.
Vascular complications are the major problem faced by diabetic patients. Impairment of vasorelaxation is the earliest manifestation of diabetic vascular dysfunction. Anti-hyperglycemic drugs have improved the life quality of these patients; however it still does not prevent the onset of vascular complications. Alternative therapeutic strategies are clearly needed. Studies have indicated that triiodothyronine (T3) has anti-diabetic effects. T3 is known to rapidly relax vascular smooth muscle cells (VSMCs) via mechanisms that involve nitric oxide (NO). Recently, a correlation between VASP phosphorylation at serine 239, a substrate for cGMP-dependent protein kinase (PKG), and VSMC relaxation has been demonstrated. We hypothesized that a signaling pathway through NO/cGMP/PKG/VASP is involved in T3-induced vasorelaxation. Human endothelial cells (EC) treated with 0.1uM T3 for short-time increased NO levels. Additionally, T3 stimulated VASP phosphorylation at serine 239 in human VSMCs (2.0 ± 0.2 fold of increase), which was diminished with 1uM KT5823, a selective PKG inhibitor. Rat aortas incubated with T3 showed a significant increase in PKG expression (1.8±0.1 fold of increase). Endothelium-dependent and –independent relaxation was assessed in rat aortas treated with T3 for 20 minutes. Aortas treated with T3 exhibited greater sensitivity (EC50) to acetylcholine (EC50 value: 7.80±0.07 vs. 7.10±0.05 control, p<0.0001) and sodium nitroprusside (EC50 value: 8.12±0.03 vs. 7.6±0.02, p<0.0001). T3-induced vasorelaxation independent of endothelium was partially reduced in the presence of 1uM KT5823 (EC50 value: 7.8±0.02, p<0.05). Aortas from male db/db mice, a model of type 2 diabetes, displayed decreased levels of VASP phosphorylated at serine 239 (2.7 ± 0.1 fold of decrease). Moreover, impaired relaxation response to Ach observed in db/db aortas was improved with T3 incubation. Our results suggest a novel NO/PKG/VASP molecular mechanism underlying T3-induced vascular relaxation. Strategies utilizing T3 in safe dose pose a promising approach as an adjunct therapy to treat vascular dysfunction in diabetes.
The prevalence of coronary artery disease during late pregnancy (LP) has increased over the past decade due to increased maternal age and significant changes in women’s lifestyle patterns (stress, smoking, diabetes and chronic hypertension). Clinically, myocardial infarction during LP carries a markedly worse prognosis than in non-pregnant women and is associated with significant maternal mortality. We have recently demonstrated that myocardial infarct size ~4 fold greater in LP rodent compared to non-pregnant controls. We also discovered that administration of intralipid at reperfusion resulted in ~60% reduction in infarct size of the heart in LP rat subjected to I/R injury, but the mechanism is not well understood. Here we hypothesized that intralipid protects the heart in LP by regulating the levels of specific microRNAs. The left anterior descending coronary artery was occluded in LP rats (21-22 days of pregnancy) for 45 min followed by 3 hr of reperfusion. One single bolus of PBS (control group) or 20% intralipid (intralipid group) was applied through the femoral vein 5 min before the reperfusion. The hearts of control and intralipid groups were used for microRNA microarray analysis (Ocean Ridge Biosciences). MicroRNA-microarray analysis identified miR122 as a novel micro-RNA which its expression was strikingly upregulated more than 10 fold in the heart of LP rats in intralipid group compared to control group. In cardiomyocytes subjected to hypoxia/reoxygenation injury, overexpression of miR122 resulted in reduced apoptosis, whereas knockdown of miR122 enhanced apoptosis. Our data show that the expression of Pyruvate kinase isoform M2 (PKM2) and capase-3 in the heats subjected to I/R was significantly lower in intralipid group compared to control group in LP suggesting PKM2 and caspase 3 could be two targets of miR122. In conclusion intralipid protects the heart in LP against I/R injury by reducing cardiomyocyte apoptosis via inducing miR122.
THE ACTION OF NUTRACEUTICALS ON KEY MACROPHAGE PROCESSES ASSOCIATED WITH ATHEROSCLEROSIS

T.S. Davies, H. Gallagher, J.W.E. Moss, F.B. Jaffar, W. Al-Ahmadi, F. Harris, D.P. Ramji
Cardiff University, Cardiff, UK

Objectives: To investigate the actions of nutraceuticals on key macrophage processes associated with atherosclerosis.

Background: Atherosclerosis is an inflammatory disorder of the vasculature orchestrated by the action of cytokines. Macrophages play a pivotal role in atherosclerosis and represent promising therapeutic targets. Current therapies against atherosclerosis are associated with substantial residual risk together with other issues such as adverse side effects. In addition, there have been numerous disappointments on many pharmaceutical agents identified from drug discovery programs. This has initiated interest in nutraceuticals as preventative or therapeutic agents in atherosclerosis but requires an in-depth understanding of their actions. The purpose of this study was to delineate the effects of nutraceuticals on key macrophage processes associated with atherosclerosis together with the molecular mechanisms underlying their actions.

Methods: The studies used a combination of macrophage cell lines and primary cultures. Gene expression was monitored by real time quantitative PCR and western blot analysis. The production of reactive oxygen species was determined using a kit from Abcam. Foam cell formation was monitored by uptake of fluorescently labeled modified LDL, intracellular lipid profile and cholesterol efflux. Inflammasome activation was evaluated by following the release of interleukin (IL)-1beta. Cell viability was assessed by release of lactate dehydrogenase.

Results: The studies focused on key components in olive oil and omega-6 polyunsaturated fatty acids. These attenuated the expression of key markers of inflammation induced by several proatherogenic cytokines, the uptake of modified LDL, macropinocytosis and foam cell formation in macrophages. In addition, they stimulated macrophage cholesterol efflux. A differential effect was observed for other parameters such as production of reactive oxygen species and production of IL-1beta via inflammasome activation. The mechanisms underlying such actions will be presented.

Conclusions: The studies provide novel insights into the actions of nutraceuticals on key macrophage processes associated with atherosclerosis.
HEME OXYGENASE-1 DEFICIENCY EXACERBATES ABDOMINAL AORTIC ANEURYSM

Y.C. Ho, M.L. Wu, S.F. Yet
National Health Research Institutes, Zhunan, Taiwan

Despite a protective role of the anti-oxidative and anti-inflammatory heme oxygenase-1 (HO-1) in several cardiovascular diseases has been established, the role of HO-1 in abdominal aortic aneurysm (AAA) formation remains unclear. We subjected mice deficient in apoE or deficient in both HO-1 and apoE to an angiotensin II-infused AAA model. HO-1 was barely detectable in the aorta under normal physiological conditions but markedly induced in the aortic wall after angiotensin II infusion, implicating a role in AAA. HO-1 deficiency increased AAA incidence and rupture rate, increased aortic aneurysmal area and severity, accompanied with severe elastin degradation and medial degeneration. Further analysis revealed that lack of HO-1 markedly enhanced reactive oxygen species levels, smooth muscle cell (SMC) loss, macrophage infiltration, and matrix metalloproteinase (MMP) activity in the aneurysmal aortic wall, resulting in exacerbated AAA formation. In vitro, angiotensin II induced HO-1 expressions in apoE-deficient SMCs and macrophages. Deficiency in both HO-1 and apoE rendered SMCs more susceptible to oxidant-induced cell death, and an enhanced MMP2 activity in response to angiotensin II. In primary macrophages, absence of HO-1 aggravated the responses to angiotensin II by increasing inflammatory cytokine productions and MMP9 activity. Taken together, our results demonstrate that the induction of HO-1 in the aortic wall during AAA progression might be a protective mechanism while deficiency of HO-1 exacerbates AAA via enhanced oxidative stress and inflammation. Increasing HO-1 expression in the aorta might be a promising therapeutic strategy for AAA.
PROTEOMIC PROFILING OF THE AGED MDX-4CV HEART MODEL OF DYSTROPHINOPATHY-RELATED CARDIOMYOPATHY

S. Murphy, P. Dowling, K. Ohlendieck
Maynooth University, Maynooth, Co. Kildare, Ireland

Objectives: In order to improve our general understanding of the molecular pathogenesis of muscular dystrophy-associated cardiomyopathy and to identify new marker candidates of cardiac changes in dystrophinopathy, we have carried out a comparative proteomic study of the mdx-4cv mouse model of Duchenne muscular dystrophy.

Background: Cardiomyopathy is a serious complication in X-linked muscular dystrophy, which is triggered by primary abnormalities in the dystrophin gene. The almost complete loss of the membrane cytoskeletal protein dystrophin triggers progressive muscle wasting and impaired cardiorespiratory functions.

Methods: In order to directly correlate the deficiency in dystrophin to secondary abnormalities in the dystrophic heart, this study has used label-free mass spectrometry to compare protein expression patterns in the aged mdx-4cv heart model of dystrophinopathy versus wild type heart. Bioinformatics was used to determine major changes in protein families and establish potential alterations in cardiac protein networks. Immunoblotting was employed to verify key findings from proteomic surveys.

Results: The mass spectrometric profiling of whole heart preparations has identified the reduction in the dystrophin-glycoprotein complex and a large variety of secondary changes in the dystrophic heart. Cardiac proteins with a changed abundance were shown to be involved in fiber contraction, energy metabolism, cellular signaling, the cytoskeletal network, the extracellular matrix and the stress response.

Conclusions: The proteomic findings indicate that the molecular pathogenesis of muscular dystrophy-associated cardiomyopathy is highly complex and involves alterations of energy metabolism, molecular chaperoning and ion homeostasis, as well as the maintenance of the contractile apparatus, the intracellular cytoskeleton and the extracellular matrix.
2016 UPDATE ON TREATMENT OF HYPERTENSION

W.S. Aronow
Cardiology Division, Westchester Medical Center/New York Medical College, Valhalla, NY, USA

Numerous guidelines from 2011 through 2015 except for JNC 8 recommended that the blood pressure (BP) goal should be <140/90 mm Hg in persons younger than 80 years and <150 mm Hg in persons 80 years and older. JNC 8 recommended that the BP goal should be <150/90 mm Hg in persons 60 years and older without diabetes or chronic kidney disease. The SPRINT trial randomized 9,361 persons, mean age 67.9 years (28.2% 75 years or older), with a systolic BP of 130-180 mm Hg and an increased cardiovascular risk but without diabetes, prior stroke, recent heart failure, or an ejection fraction <35% to a systolic BP target of <120 versus <140 mm Hg. At 1 year, the systolic BP was 121.4 mm Hg versus 136.2 mm Hg. Median follow-up was 3.26 years. The primary outcome of myocardial infarction, other acute coronary syndrome, stroke, heart failure, or cardiovascular death was reduced 25%, p<0.001) by the lower systolic BP. All-cause mortality was reduced 27%, p = 0.003 by the lower systolic BP. Heart failure was reduced 38%, p=0.002, by the lower systolic BP. Cardiovascular death was reduced 43%, p = 0.005, by the lower systolic BP. The primary outcome or death was reduced 22%, p <0.001, by the lower systolic BP. The lower systolic BP reduced the primary outcome 33% in persons 75 years and older and 20% in persons aged 50 to 74 years. Serious adverse events were similar in both groups. However, the lower systolic BP caused more hypotension, syncope, electrolyte abnormality, and acute kidney injury or acute renal failure. On the basis of these data, older and younger persons should be treated to a systolic BP goal of <120 mm Hg with more intensive monitoring for serious adverse events.
Nitric oxide (NO) donors are used as promising therapeutic agents for the treatment of cardiovascular diseases such as angina pectoris, myocardial infarction and congestive heart failure, however, the molecular mechanisms underlying the therapeutic activities remains poorly understood. We previously showed that nitric oxide (NO) donor, SNAP, decreased the enhanced expression of Gialpha proteins and associated functions in aortic vascular smooth muscle cells (VSMC) from spontaneously hypertensive rats (SHR). Since the enhanced expression of Gialpha proteins is implicated in the pathogenesis of hypertension, the present study was undertaken to investigate the effect of in vivo treatment of SHR with NO donor; sodium nitroprusside (SNP) on the development of high blood pressure (BP) and to explore molecular mechanisms responsible for this response. 8 week-old SHR and Wistar-Kyoto (WKY) rats were intraperitoneally injected with SNP at a concentration of 0.5mg/kg body weight twice a week for two weeks. Western blotting was used to determine the expression of various proteins. Intraperitoneal injection of SNP attenuated the high BP by about 50 mmHg; however, this treatment did not affect BP in WKY rats. In addition, increased production of superoxide anion, peroxynitrite, NAD(P)H oxidase activity, overexpression of different subunits of NAD(P)H oxidase, superoxide dismutase 1/2, Gialpha proteins, AT1 receptor, increased phosphorylation of growth factor receptors, c-Src, and ERK1/2 in aortic VSMC from SHR were attenuated to WKY levels by SNP treatment. Furthermore, the hyperproliferation of VSMC from SHR was also inhibited by SNP treatment. In conclusion, we show that in vivo treatment of SNP attenuates the high BP in SHR through the inhibition of enhanced levels of Gialpha proteins, oxidative stress, and oxidative stress-mediated signaling pathways and suggest that the new therapies targeting Gialpha proteins may be developed for the treatment of hypertension (Supported by grant from CIHR).
Hypertension continues to represent a formidable challenge to human health and to healthcare worldwide. Exciting new developments in clinical and fundamental hypertension research are poised to change how we understand and approach the clinical management of hypertension. The recently concluded Systolic Blood Pressure Intervention Trial (SPRINT), testing the effect of additionally lowering the systolic blood pressure (BP) compared to the current guidelines target (<120 mm Hg vs. <140 mm Hg), was closed earlier than planned due to demonstrating significant cardiovascular (CV) benefits and reduced all-cause mortality. Where do we go from here? (Quo Vadimus?) These results indicate the need to go both forward and back into the translational continuum that connects fundamental discoveries to the prevention and cure of hypertension: moving forward, we will need to reassess the potential impact of these findings on the current clinical treatment targets for BP, which may necessitate further clinical investigations of patients with additional existing conditions, such as diabetes, investigations across the age spectrum, or of the effects of BP measurement methodologies. The significant beneficial CV effects of lowering BP by an additional 20 mmHg indicates that we will also need to go “back-to-the-bench” to better understand the fundamental underlying biological connections between these specific CV conditions and hypertension, and to test whether these new findings could become the basis for more efficient and specific treatments for hypertension or for the prevention of specific CV conditions. Meanwhile, recent advances in fundamental research have emerged to support reported clinical associations between hypertension, immunity, arterial stiffening, and genetics. Investigational research performed in several experimental models, in which hypertension occurs spontaneously or it is induced either by aldosterone, salt, or Angiotensin II, has been elucidating cellular and molecular pathways responsible for these associations. Key regulators identified included T cells, chemokines, and redox stress. Likewise, similar experimental studies demonstrated that arterial stiffening preceded hypertension and reversing stiffening prevented hypertension in the models used. By further pursuing these pathways, we may develop new biomarkers that could signal risk of developing hypertension or new pharmacological targets for prevention and management of hypertension. Future significant benefits for the health of hypertensive and CV patients will require the continuous bench-to-bedside, as is traditional, but also the back-to-the-bench cooperation between fundamental, clinical, and implementation research to close the remaining translation gaps in hypertension.
CLINICAL IMPLICATIONS OF CURRENT RECOMMENDATIONS OF ABPM AS REQUIREMENT FOR DIAGNOSIS OF HYPERTENSION

R.C. Hermida, D.E. Ayala
University of Vigo, Vigo, Spain

On the basis of the substantial and indisputable evidence of the significantly better prognostic value of ambulatory blood pressure (BP) monitoring (ABPM) compared to office BP measurements, several international guidelines, including the most recent 2015 U.S. Preventive Services Task Force report, now propose ambulatory BP as a requirement to confirm the office diagnosis of hypertension. However, these guidelines have either ignored or only partially addressed, without binding recommendations, several highly relevant critical questions. First, consistent evidence of numerous studies substantiates the ABPM-determined asleep BP mean is an independent and stronger predictor of cardiovascular disease (CVD) risk than the awake or 24h means. Accordingly, the asleep BP mean should be the recommended gold standard to diagnose hypertension, assess CVD risk, and predict CVD event-free interval. Second, prospective outcome trials reveal significantly greater slope of CVD and stroke risk with progressively elevated BP in women compared to men as well as progressively and significantly greater differences in the risk of CVD events between men and women for awake and asleep systolic/diastolic BP means above 125/75 and 110/70 mmHg, respectively. Similarly, significant differences in CVD risk with progressively elevated BP also characterize patients with vs. without complicating co-morbidities including those diagnosed with diabetes or chronic kidney disease (CKD), and/or those having experienced past CVD events. Finally, reduction of the asleep systolic BP mean by a hypertension treatment strategy defined by ingestion of the full daily dose of at least one conventional BP-lowering medication at bedtime significantly and cost-effectively decreases CVD risk. Accordingly, bedtime treatment must be the therapeutic regimen of choice for the elderly and those with diabetes, resistant and secondary hypertension, CKD, obstructive sleep apnea, and medical history of past CVD events, among others, given their documented high prevalence of sleep-time hypertension and the associated elevated CVD risk.
Most studies support that regular exercise lowers blood pressure (BP) in hypertensive individuals by approximately 4-10 mm Hg in systolic and 3-8 mm Hg in diastolic BP regardless of age, race or gender. Recent findings also support that exercise has preventive and prognostic qualities. The age-related increase in arterial stiffness and BP are not inevitable, but a consequence of lifestyle characterized unhealthy dietary habits and physical inactivity. In prehypertensive veterans (n=2,303), the risk for developing hypertension was 66% higher (hazard ratio [HR], 1.66; 95% CI, 1.2 to 2.2) for the Low-Fit and, 72% higher (HR, 1.72; 95% CI, 1.2 to 2.3 for the Least-Fit individuals compared to the High-Fit. The exaggerated increase in BP observed in some individuals during exercise is adversely associated with end-organ damage. In our study of 790 prehypertensive individuals, exercise systolic BP at the workload of about 5 METs was the strongest predictor of left ventricular hypertrophy (LVH). Individuals who achieved a systolic BP ≤150 mm Hg had significantly greater cardiac wall thickness, left ventricular mass (LVM) index, and lower exercise capacity compared with those with systolic BP <150 mm Hg. Furthermore, the risk of LVH increased 4-fold for every 10-mm Hg incremental rise in the SBP>150 mm Hg. The exaggerated rise in BP during exercise may be modulated by fitness. Exercise BP decrease significantly in hypertensive individuals who completed 16 weeks of aerobic exercise. The exercise capacity-LVM index association was strong and inverse. The risk for LVH was 42% lower for every 1-MET increase in exercise capacity. We have also reported an inverse, independent, and graded association between exercise capacity and mortality risk in 4,631 hypertensive veterans with multiple cardiovascular risk factors. Mortality risk was 13% lower for every 1-MET increase in exercise capacity.
SYSTEMIC AND PULMONARY ARTERY HYPERTENSION: EXPENDING THERAPEUTIC OPTIONS

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TOWARDS PERSONALIZED MEDICINE FOR VASCULAR RISK REDUCTION: THE RIGHT DRUG AT THE RIGHT DOSE AT THE RIGHT TIME

D.E. Ayala, R.C. Hermida
University of Vigo, Vigo, Spain

The term “personalized medicine” is often described, using the definition adopted by the Food and Drug Administration, as providing “the right patient with the right drug at the right dose at the right time”. While current international guidelines for the diagnosis and treatment of hypertension provide detailed information on recommended blood pressure (BP)-lowering medications and their combinations for therapy according to presence/absence of complicating co-morbidities, including diabetes and chronic kidney disease (CKD), most still disregard many published clinical trials documenting reduction of asleep BP and the corresponding effects on the 24h BP pattern, i.e., increase of sleep-time relative BP decline towards the normal dipper profile, by BP-lowering medications of six different classes are greatly improved when consistently ingested at bedtime than upon awakening. The MAPEC study, first prospective randomized treatment-time investigation testing the worthiness of bedtime hypertension treatment to specifically target attenuation of asleep BP, documents, after a median follow-up of 5.6 years, hypertensive patients randomized to ingest the full daily dose of at least one BP-lowering medication at bedtime, in comparison to those randomized to ingest all prescribed hypertension medications upon awakening, displayed lower adjusted hazard ratio (HR) of total CVD events (HR=0.39 95%CI [0.29-0.51]; p<0.001) and major CVD events -- composite of CVD death, myocardial infarction, and ischemic and hemorrhagic stroke -- (HR=0.33 [0.19-0.55]; p<0.001). Bedtime hypertension treatment significantly and cost-effectively decreases CVD risk, both for individuals of the general hypertension population and patients of greater vulnerability and enhanced CVD risk, i.e., those diagnosed with CKD, diabetes, and resistant hypertension. In this regard it is noteworthy that an increasing number of international medical and scientific societies now acknowledge the clinical relevance of this specific concept of hypertension chronotherapy by recommending physicians advise their hypertensive patients ingest one or more of their prescribed BP-lowering medications at bedtime.
EXERCISE RELATED HYPERTENSION (ERH) MAY NOT BE A BENIGN PHENOMENON

Y. Charuzi, J.M. Mirocha
Cedars Sinai Medical Center, LA, USA

Blood Pressure (BP) increases with exercise. However a Systolic BP (SBP) reaching or exceeding 200mm Hg is considered pathological.

We recently observed a 78 years old male who, while walking uphill suddenly noticed loss of speech. He was diagnosed as a non-blood clot embolic stroke. The source of embolization was thought to be a calcified plaque at the origin of the left carotid artery. On a subsequent Ambulatory BP monitor he had BP of 150 correlating with the time he had his stroke. WE assumed that with a baseline HTN he probably increased his SBP further making it possible to dislodge a plaque.

Inspired by this experience we went back to our records and explored patients in who had been followed and treated for exercise related HTN. Once ERH was detected patient was placed on a low dose B blocker (BB) or baseline dose was increased. Fine titration was necessary to avoid compromise of resting BP. Every one of the patients had follow-up treadmill (FUT) to assess the efficacy of the treatment;

Results: 143 studies were done on 16 patient. M/F 11/5, age 61.8. Baseline studies 16, subsequent studies 127

Control: resting SBP 127.4, peak exercise 208.8
1 diastolic bp (DBP) . peak exercise DBP ( )

Treatment: resting SBP 123.8 peak exercise 173.1 . resting DBP ( ) ex DBP ( ) Resting control SBP vs resting FUT SBP 127.4 vs 123.8. peak SBP at control vs peak SBP in f/u was -4. Peak DBP at control vs f/u was ( )

All patients were treated with a low dose BB but at times another non BB medication had to be added for proper control.

Conclusion: ERH may be a potential risk factor for an embolic stroke. On a small group with multiple test we were able to determine that ERH t can be effectively controlled using low dose BB without compromising resting BP.
UPDATE ON EFFECT OF ISOLATED SYSTOLIC VERSUS SYSTOLIC-DIASTOLIC HYPERTENSION IN OLDER ADULTS

A. Tsimploulis¹, S. Weerakoon², A. Ahmed³
1. Georgetown University/Washington Hospital Center, USA
2. Georgetown University Hospital, Washington DC, USA
3. Veterans Affairs Medical Center, Washington DC, USA

Background: Among older adults isolated systolic hypertension (ISH) is more common than systolic-diastolic hypertension (SDH) and both appear to have similar effect on incident heart failure (HF) and all-cause mortality (Circulation. 2014; 130:A18649). However, these findings were limited by bias associated with misclassification based on inclusion of controlled hypertension in the normal blood pressure (BP) reference group.

Objective: To examine the effect of ISH and SDH on outcomes.

Methods: In Cardiovascular Health Study (CHS), of the 4927 community-dwelling older adults free of isolated diastolic hypertension (PMID: 21947466) and isolated diastolic hypertension, 1918 had ISH (systolic BP>140 and diastolic BP<90), 250 had SDH (systolic BP>140 and diastolic BP>90), and 1417 had normal BP with no anti-hypertensive medication use or no prior history of hypertension. After excluding those with baseline HF, the study cohort consisted of 1838 ISH, 240 SDH and 1417 normal-BP. Multivariable Cox regression models were used to estimate associations of ISH and SDH (vs. normal-BP) with centrally-adjudicated incident HF and all-cause mortality during 13 years of follow-up adjusting for major HF risk factors.

Results: Participants had a mean (±SD) age of 73 (±6) years, 57% were women, and 16% were African American. Unadjusted incident HF occurred in 25%, 22% and 11% of those with ISH, SDH and normal-BP, respectively. Compared to no hypertension, multivariable-adjusted hazard ratios (HR) and 95% confidence intervals (CI) for incident HF for those with ISH and SDH were 1.86 (1.51–2.30) and 1.73 (1.23–2.42), respectively. Unadjusted all-cause mortality occurred in 49%, 50% and 34% of those with ISH, SDH and normal-BP, respectively, with respective multivariable-adjusted HRs (95% CIs) of 1.22 (1.07–1.39) and 1.45 (1.16–1.80).

Conclusion: Among older adults without HF, ISH is more common than SDH; both contribute similarly to incident HF, though SDH appears to have a more pronounced effect on mortality.
SYSTEMIC AND PULMONARY ARTERY HYPERTENSION: EXPANDING THERAPEUTIC OPTIONS

GENOME-WIDE ASSOCIATION STUDY ON SALTINESS AND ASSOCIATION OF TOP-RANKING SNPS WITH BLOOD PRESSURE

D. Corella1,2, R. Fernandez-Carrion1,2, R. Barragan-Arnal1,2, A. Rodrigues-Cruz2, I. Gonzalez-Monje2, L. Quiles2, J.V. Sorli1,2, J.M. Ordovas3, O. Coltell4
1. CiberOBN, Madrid, Spain
2. University of Valencia, Valencia, Spain
3. Human Nutrition Research Center on Aging, Boston, MA, USA
4. Universitat Jaume I, Castellon, Spain

Background: The greater or lesser perception of different flavors has been associated with food consumption, obesity and cardiovascular risk, but results differ. Contributing to that is the fact that measuring taste perception through chemical laboratory tests is tedious. The preferred method is to use a genetic marker as a proxy of taste perception. However, the genes associated with taste perception, apart from bitterness, are not well known. Although some genes related with saltiness have been identified, the main genes involved in salt perception and its impact on blood pressure (BP) are mostly unknown.

Objectives: 1) To carry out a genome-wide association study (GWAs) on an elderly Mediterranean population to detect the main genes associated with saltiness perception; and 2) To study the association of top-ranking SNPs with BP in an independent sample.

Methods: 150 participants in the PREDIMED PLUS-Valencia study (elderly subjects with metabolic syndrome) were subjected to laboratory taste tests to identify their perception of bitterness, sweetness, sourness, umami and saltiness. Various concentrations were used and their perception noted on a rising scale. The highest concentration of NaCl (200mM) was used for the GWAs. Genotyping was undertaken with the Human OmniExpress Illumia array (700K). PLINK was used for association analyses. Top-ranked SNPs were genotyped in the PREDIMED-Valencia study (n=1094) and associations with BP were analyzed.

Results and Conclusions: Firstly, to check power and methodology, a GWAs for bitterness (Phenylthiocarbamide) was undertaken, as the genes associated with this are well-known. We confirmed that the top-ranking SNPs (P<10-8) were situated in the TAS2R38 gene, as expected. We then analyzed saltiness, top-ranking SNPs being rs12046966-FUBP1 (P=6.1x10-7), rs1800454-TAP2, rs2152555-GREM2 and rs12564791-NLRP3 (P=2.3x10-5). One of these newly reported genes, was significantly associated with BP (i.e. variant allele-carriers of the rs12046966-FUBP1 had significantly lower systolic BP in the PREDIMED-Valencia participants), suggesting a link.
ICD-FORUM - WEB-BASED PSYCHOSOCIAL SUPPORT FOR PATIENTS WITH IMPLANTABLE CARDIOVERTER DEFIBRILLATORS

S.M. Schulz1,2, R. Zniva1,2, O. Ritter2,3, C. Wacker4, M. Jack5, G. Groschup6, T. Deneke7, P. Pauli1,2

1. Comprehensive Heart Failure Center - Wuerzburg, University Hospital Wuerzburg, Wuerzburg, Germany
2. Department of Psychology I, University of Wuerzburg, Wuerzburg, Germany
3. Klinik für Kardiologie und Pulmologie, Medizinische Hochschule Brandenburg, Campus Klinikum Brandenburg Havel, Germany
4. Innere Abteilung, Kardiologie, Klinikum Rothenburg ob der Tauber, Germany
5. Klinik Bad Woerishofen, Deutsche Rentenversicherung Schwaben, Germany
6. Medizinische Klinik I, Abteilung Rhythmologie, Klinikum Aschaffenburg, Germany
7. Herz- und Gefaess-Klinik Bad Neustadt/Saale, Germany

Introduction: The implantable cardioverter defibrillator (ICD) has become the treatment of choice for patients at risk for potentially lethal ventricular tachycardia and fibrillation. Despite this medical success, ICD patients often suffer from anxiety (up to 87%), anxiety disorders (up to 38%) and depression (up to 30%). Routine medical care typically lacks the resources for appropriate psychosocial support. Limited mobility and low regional availability of self-help groups suggest internet-based support as an ideal supplement to traditional support models.

Methods: To investigate whether web-based support can help to prevent anxiety and depression and to improve quality of life in ICD-patients, we have developed ICD-Forum.de, a six-week internet based prevention program providing technical and medical information regarding the ICD and cognitive behavioral-therapy based self-help materials. Integrated in this program is a professionally moderated virtual self-help group. ICD-Forum.de has been evaluated on N = 119 ICD-patients in a multi-center, multi-disciplinary, half-open, part-randomized, controlled clinical trial. Demographic and medical variables and psychosocial well-being has been assessed at baseline, before and after treatment, and at 12-month follow-up in two groups (random assignment to treatment as usual [TAU] vs. TAU plus participation in ICD-Forum.de; stratification by age, sex, and ICD-indication).

Results: Comparison of data pre- to post-intervention (intent to treat analysis: ANCOVA with covariates preTx, age, sex, ICD-indication) revealed a significant improvement of psychosocial well-being (composite score of heart related anxiety, depression, quality of life) that improved further at follow up (12 months after baseline) in the intervention group as compared to the control group.

Conclusion: This is the first successful implementation of web-care for ICD-patients, resulting in a large effect on psychosocial well-being. We conclude that helping ICD-patients with low-cost web-based approaches is feasible and effective. This recommends integrating such an approach in routine care of ICD-patients.
THE SUBCUTANEOUS IMPLANTABLE CARdioverter-DEFibRILLATOR: FIRST SINGLE-CENTER EXPERIENCE WITH OTHER CARDIAC IMPLANTABLE ELECTRONIC DEVICES

J. Kuschyk, B. Rudic, S. Roeger, E. Tueluemen, V. Liebe, M. Borggrefe
University Medical Center Mannheim, DZHK (German Centre for Cardiovascular Research First Medical Department,) partner site Mannheim, Germany

Background: Subcutaneous implanta-ble cardioverter-defibrillator (S-ICD) is an implantable device for antiarrhythmic therapy with no intravascular leads.

Objective: We describe the technical feasibility of combining the S-ICD with other cardiac implantable electronic devices (CIEDs), including pacemakers with trans-venous or epicardial electrodes. We also provide the first experience of combining S-ICD with catheter-based therapies including cardiac contractility modulation (CCM) and vagus nerve stimulation (VNS).

Methods: Between 7/2011 and 11/2014 six patients received a CCM device and S-ICD, three patients with a single-chamber pacemaker using either trans-venous or epicardial pacing electrodes received S-ICD, and one patient with an implanted S-ICD received VNS. In all patients intraoperative S-ICD testing, crosstalk tests and postoperative ergo metric testing were performed.

Results: In all 10 patients device implantations were successfully performed without complications. S-ICD therapy was shown to be technically feasible with concomitant CIED. Mean follow up was nearly 17 months. S-ICD testing and crosstalk testing before and during exercise enabled device programming across a broad range of test conditions and was associated with no subsequent evidence of adverse device interaction. None of the devices required permanent inactivation or removal and no patient received an inappropriate shock.

Conclusion: In suitable patients, combining an S-ICD with CCM or pacemaker may provide an acceptable means to reduce the number of trans-vascular leads. S-ICD appeared safe with CCM over an intermediate follow up period. Additional prospective randomized controlled trials examining S-ICD in conjunction with CIEDs are warranted.
THE INCIDENCE OF TORSADES DE POINTES AFTER PROPOFOL EXPOSURE

V. Abrich¹, H. Ramakrishna², A. Mehta³, F. Mookadam¹, K. Srivathsan¹
1. Department of Cardiovascular Disease, Mayo Clinic Arizona, Phoenix, AZ, USA
2. Department of Anesthesiology, Mayo Clinic Arizona, Phoenix, AZ, USA
3. Department of Internal Medicine, University of Chicago, Chicago, IL, USA

Objective: To determine the incidence of TdP following propofol exposure.

Background: Torsades de pointes (TdP) is a rare arrhythmia associated with QT prolongation. Propofol is a general anesthetic that has proarrhythmic effects on isolated cardiac myocytes.

Methods: This retrospective study included patients treated at Mayo Clinic (Rochester, MN) from August 11, 1998, through November 20, 2015. The database was queried by using key search terms to identify patients who were exposed to propofol and developed TdP either perioperatively or during nonsurgical sedation. QT and corrected QT intervals (QTc) were obtained from electrocardiograms performed before propofol exposure and after documented TdP. T wave peak-to-end (Tp-e) intervals were measured in lead V5 or V6 and were divided by the QT interval to give the Tp-e/QT ratio; values greater than 0.28 were considered prolonged.

Results: A total of 628,784 patients received propofol. Of these patients, 21 developed TdP (12, postoperatively; 3, intraoperatively; 6, during sedation). At baseline, the QTc interval was prolonged in 17 patients; Tp-e/QT ratio was greater than 0.28 in 5 patients. After propofol exposure, the QTc increased in 12 and decreased in 9 patients. Other risk factors included QT-prolonging medications in 5 patients, potassium <3.5 mmol/L in 4 patients, magnesium <1.8 mg/dL in 2 patients, heart rate <50 beats per minute in 3 patients, and subarachnoid hemorrhage in 2 patients.

Conclusions: TdP after propofol administration was rare (1 in 30,000 patients) and was often associated with other risk factors. This study confirms the relative safety of propofol during general anesthesia.
INTRA-HIS BLOCK RARELY PROGRESS TO PACEMAKER DEPENDENCY: A CASE SERIES
L. Ragupathi, D. Johnson, B.B. Pavri
Thomas Jefferson University Hospital, Philadelphia, PA, USA

Background: It is recognized that patients with pre-existing wide QRS complex (bundle branch block) who then develop complete atrioventricular block (AVB) often progress to pacemaker (PM) dependency, and therefore dual chamber PMs are indicated. However, AVB can rarely be due to disease within the common bundle of His (intra-His block, IHB), when the conducted QRS complex remains narrow. The progression of conduction system disease and development of PM dependency in patients with narrow QRS and AVB is not known.

Methods: We retrospectively identified patients followed at our center who had documented IHB by split His-bundle signals on electrophysiologic study (EPS), or who had paroxysmal AVB with a narrow QRS on surface ECG. Clinical and PM characteristics at PM implant and at last PM follow up were evaluated.

Results: A total of 23 patients were included. Of these, 10 patients had EPS-documented IHB and 13 had PAVB with narrow QRS recorded on ECG. Of these, 19 patients presented with syncope or presyncope; 7 patients had single chamber PM implanted, and 16 patients had dual chamber PM. The mean QRS duration on the presenting ECG was 87±8ms (range=72 to 102 ms). At a median of 1.62 years (IQR 0.08-7.46) following PM implant, the median percentage of right ventricular pacing was 1% (IQR 0-83%). No patients developed PM dependency due to progression of conduction disease. There were 6 patients with >95% right ventricular pacing, but all these patients had narrow complex escape rhythms and were not PM dependent.

Conclusions: In contrast to the known development of PM dependency in patients with wide QRS complex, patients with IHB and paroxysmal AVB with narrow QRS do not typically progress to PM dependency. If confirmed with larger studies, single chamber PM may be appropriate for selected patients with IHB and paroxysmal AVB.
LONG-TERM COMPLICATIONS OF EPICARDIAL PACING WIRES ABANDONED FOLLOWING CARDIAC SURGERY

A. Singh, A. Shi, H. Vefali, S. Agrawal, A. Sinha, J. Shirani
St Lukes University Hospital, Bethlehem, PA, USA

Background: Transcutaneous epicardial pacing wires (TEPW) are used following cardiac surgery and may be left in place if difficult to remove. We aimed to review potential long-term complications of abandoned TEPWs.

Methods: We encountered a patient and identified 33 reported cases of TEPW migration (n=34, age 59±17 years, 80% men).

Results: A mean of 1.5±0.8 leads, 191±30 mm long, were abandoned for 1527±2158 days [71% right atrial (RA), 53% RV, 29% RA and RV] following coronary (59%), valve (33%), aortic (6%) or other (4%) surgery. 79% were symptomatic [38% fever, 32% skin lesions, 18% dyspnea, 15% abdominal pain, 9% cerebrovascular symptoms, 6% cough, 3% hemoptysis and 3% each chest, jaw, or pelvic pain. Anew (29%) or recurrent (27%) infection occurred in 56% [infections of TEPW (35%), skin (27%), mediastinum (18%), and native (6%) or prosthetic valve (9%)]. Other direct consequences were heart failure (15%), severe regurgitation (15%), arrhythmia (15%), hypotension (15%), and cardiac arrest (9%). Mechanical complications included native coronary or vein graft laceration (9%), compression of great vessels (3%), cardiac tamponade (6%), pleural effusion (3%), myocardial infarction (3%), or hematoma [paracardiac or pericardial (6%)]. TEPW migrated to pulmonary artery (12%), lung/bronchus (12%), mediastinum (12%), pericardial space (12%), or abdominal viscera (12%). Other destinations were RV (9%), RA (6%), aorta (9%), carotid artery (3%) and pelvis (3%). Four (12%) leads protruded out through the skin (3 chest wall, 1 jaw). Patients were either observed (18%) or underwent percutaneous (18%) or surgical (62%) removal of TEPW. Death (6%) or incomplete recovery (9%: stroke, persistent infection, prolonged hospitalization) occurred in 15%.

Conclusion: Abandoned TEPW migration can cause serious complications including incomplete recovery or death (15%). Removal of TEPWs appears justified. Periodic surveillance of remaining leads may allow early recognition of lead migration and prevention of complications.
SAFETY AND EFFICACY OF TRANSVENOUS EXTRACTION OF PACEMAKER AND CARDIOVERTER-DEFIBRILLATOR LEADS

H. Vefali, M. Durkin, A. Singh, S. Agrawal, S. Nanda, D. Traub, J. Shirani
St. Luke’s University Health Network, Bethlehem, PA, USA

Background. Increasing implantable cardiac device use has led to a proportional increase in lead related complications. Transvenous lead extraction (TLE) is commonly used to remove unwanted hardware. We present safety and efficacy of TLE at a single center. Methods/Results. Total of 78 patients (69% men; age 67±14.5 years, BMI 30.1±6.7 kg/m²) underwent TLE of pacemaker (31%) or defibrillator (69%) leads from 12-2012 to 6-2015. Leads were located in right ventricle (RV 65%), right atrium (RA 26%) and left ventricle (LV 9%) and were in situ for 2306±1543, 1634±1674, and 1692±1069 days, respectively. Indications for TLE included infection (40%), lead failure (38%), manufacturer recall (17%) and patient discomfort (5%). Patients with infected systems [38% methicillin-sensitive staphylococcus aureus] were commonly male (68%), diabetic (51%) and had chronic kidney disease (74%). TLE success rate was 97.4%. Manual traction was more often successful in RA and RV active fixation leads. Adhesion and scarring of superior vena cava (SVC) coil or SVC/RA junction were most common triggers for laser use (21%). Minor and major complications occurred in 6 and 3 patients respectively. The latter included an RA tear requiring surgical repair, a large pocket hematoma requiring evacuation and one case of jugular vein thrombosis. One patient needed snaring to recover an RV lead tip. Only 2 patients had to have their leads removed surgically including the case with RA tear.

Conclusions. TLE for infection is more likely in men with diabetes and CKD. Success rate was high (97%) and independent of TLE indication, patient age, or chronicity of the lead. Procedure time was unrelated to the chronicity of the implanted leads or the nature of fixation (active/passive) in all subsets.
Heart channelopathies are common causes of sudden death with normal cardiac anatomy. Of them, congenital long QT syndrome (LQTS) and Brugada syndrome (BrS) are two major entities.

A 48 year old woman presented with ventricular fibrillation cardiac arrest. Electrocardiogram, echocardiogram, coronary angiogram and cardiac MRI were unrevealing. Given ST elevation on telemetry precordial leads, BrS was suspected, but procainamide provocation test was negative. Subcutaneous implantable cardioverter defibrillator (S-ICD) was placed. Unfortunately, the patient had recurrent cardiac arrest four days later. The device interrogation revealed monomorphic ventricular tachycardia (mVT) and torsades de pointes, which remained undetected by S-ICD, and required external shocks. Subsequent twelve-lead EKG showed QTc of 532 msec. A dual-chamber ICD was implanted. No recurrent arrhythmias were reported at three-month follow up. Sustained mVT is common in BrS, but rare in LQTS, the trademark arrhythmia of which is torsades. In our patient, BrS is suggested by mVT and precordial ST elevation, but torsades and prolonged QTc point towards LQTS, raising the possibility of mixed phenotype channelopathy. Additionally, this case challenges the contemporary use of S-ICD as a mainstay of therapy for channelopathy in a young patient, subsequently demanding the use of conventional dual-chamber ICD to potentially pace terminate VT and prevent recurrent cardiac arrests. Despite the advances in knowledge of cardiac channelopathies and sophisticated ICDs, the clinical management is still a challenge. So, not only does the genetic enigma of channelopathies demand further research, but the optimal management of these patients warrants further study.
INAPPROPRIATE SHOCKS DUE TO CHATTERING OF THE LEADS FROM AN INVESTIGATIONAL DEVICE FOR CARDIAC CONTRACTILITY MODULATION AND A DEFIBRILLATION LEAD

T.T. Aung, A. Wase, J. Pollock
Wright State University, Dayton, OH, USA

Objectives: Cardiac contractility modulation (CCM) is an investigational adjunctive treatment to enhance ventricular contractile strength of the systolic heart failure patients. This is a case of inappropriate shock due to lead chatter between the Optimizer leads and implantable cardioverter defibrillator (ICD) defibrillation lead.

Background: Optimizer is an investigational CCM device. It sends sub-threshold electrical signals during the absolute refractory period. These non-excitatory electric signals increase the influx of calcium ions into the cardiomyocytes resulting in enhanced cardiac contractility. The manufacturer declared that CCM devices can work with any ICD system without any interaction.

Method: 72-year-old male with ischemic cardiomyopathy status-post ICD and Optimizer device underwent extraction of defibrillator lead in right ventricle. His right ventricular defibrillation lead showed high impedance and alert warning. The ICD lead was exchanged successfully. All the device parameters were within normal limit before discharge. Shortly after discharge, patient had multiple ICD shocks. Interrogation of the ICD revealed intermittent, repetitive noise which was sensed as ventricular fibrillation. The noise signals were distinct from high frequency repetitive signals as observed in electromagnetic interference. Lead fracture was unlikely as all parameters including lead impedance of the new ICD lead were normal.

Result: Under fluoroscopy, it was documented that pace sense leads were in close proximity to the ICD leads leading to intermittent chattering inside the right ventricle. The Optimizer system including all the leads was removed. There was no more noise signal detected and no more inappropriate defibrillation occurred since then.

Conclusion: The most common causes of abnormal sensing are external electromagnetic interference and lead fracture. However, we should be aware that mechanical interactions including intra-cardiac lead chattering can cause considerable interference leading to inappropriate therapies in an ICD patient, or it may potentially cause ventricular asystole in a pacemaker dependent patient.
A COMPARISON OF ACTIVE AND PASSIVE LEAD IMPLANTATION: IS OPERATING EXPERIENCE A FACTOR?

J. Basu, C. Wrigley, R. Soar, W. Orr
Royal Berkshire Hospital, Reading, UK

Background: Recent studies have shown superiority of active atrial pacemaker leads in avoiding early displacement. Despite available evidence, some clinicians fear an increased incidence of cardiac tamponade with active leads, and there are concerns about the safe usage of these leads by inexperienced operators.

Objectives: This audit sought to compare lead displacement and complication rates between atrial and ventricular leads in inexperienced (<150 implants) and experienced operators.

Methods: We analysed our local pacemaker database detailing all bradycardia device implants between 2010 and 2015. The incidence of lead displacement was categorised by site, lead-type and experience of operator. The incidence of cardiac tamponade requiring pericardiocentesis was also documented.

Results: The use of active atrial leads appeared to reduce the likelihood of displacement without increasing the risk of complication. This was not shown for ventricular leads. Atrial lead displacement was more frequently observed in cases performed by more experienced clinicians. There were no episodes of tamponade.

Conclusions: Consistent with other published data, we have not demonstrated an advantage to using active ventricular leads, but their use does facilitate stable pacing of the RV septum to protect against the development of heart failure. Increased rates of atrial lead displacement in more experienced operators likely reflects differences in allocated case complexity.
INCIDENCE AND RISK FACTORS FOR AKI PRE-CARDIAC CATHETERIZATION IN PATIENTS PRESENTING WITH STEMI

M. Ashukem¹, J. Cohen², J. Diamond², J. Badlani¹, M. Calfa³, C. Mendoza³
1. Department of Medicine University of Miami/Jackson Memorial Hospital, Miami, FL, USA
2. University of Miami School Of Medicine, Miami, FL, USA
3. Division of Cardiovascular Medicine, University of Miami/Jackson Memorial Hospital, Miami, FL, USA

Background: The incidence of Acute Kidney injury (AKI) in patients with ST-Elevation Myocardial Infarction (STEMI) is between 10-30% post-PCI. It’s a marker of both significant inpatient and long term morbidity and mortality compared to non-AKI STEMI patients. They have a higher risk of future MI, strokes, heart failure, heart failure re-admissions, risk for long term CKD and Dialysis. All the current studies have looked at incidence and risk factors of AKI post-PCI. We aim to evaluate the incidence and risk factors for AKI pre-PCI in patients with STEMI.

Methods: We retrospectively evaluated 636 patients who presented with STEMI between 2007 and 2013 in Jackson Memorial Hospital. Baseline characteristics, risk factors, echocardiographic and cardiac catheterization data were collected. AKI was defined based on AKIN network classification. i.e Cr > 0.3mg/dl from baseline - Stage 1, rise in Cr> 2x but < 3x from baseline – stage 2 and rise in Cr > 3x – stage 3.

Results: PCI was conducted in 636 patients. The incidence of AKI is 9.3%. 91.6% (55/60) with AKI stage 1, 0.03% with AKI stage 2, 0.05% with AKI stage 3. Mean age 64.3yrs vs 59.9yrs (p=0.093), Insulin dependent DM (IDDM) 21.15% vs 11.19% (p=0.035), history of CKD 8.3% vs 2.3% (p=0.016), mean EF 40.38% and 45.63% (p=0.0065) and cardiogenic shock 30% vs 14.41% (P=0.002) in the AKI and non-AKI group respectively were risk factors for development of AKI pre-PCI. Age, previous CKD and EF were independent risk factors. Gender, smoking, HTN, BMI, Hemoglobin, culprit lesion, degree of CAD in non-culprit vessel, race, were not risk factors.

Conclusion: Contrast volume and CKD though important, are not the only factors for development of AKI. Factors Pre-PCI; Age, EF, IDDM, CVD, and degree of neurohormonal activation play key roles in predisposing patients to higher risk of AKI pre and post-PCI.
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CORONARY COLLATERALS ARE NOT CARDIOPROTECTIVE IN MULTIETHNIC STEMI PATIENTS AFTER REvascularization

A. Avezbadalov, A. Jaiswal, E.N. Moustakakis, C.H. Park, A.J. Buda
New York Presbyterian Queens, Weill Cornell Medical College, New York, NY, USA

Objective: The cardioprotective role of coronary collateralization is unknown in multiethnic patients with STEMI. The aim of our study was to examine the ethnic variations in collateralization and its cardioprotective role in multiethnic patients with STEMI who underwent successful revascularization.

Methods: STEMI patients who underwent successful PCI were included. The collateral flow was graded as per the Rentrop classification and patients were categorized as having either significant collateral flow or poor/absent collateral flow to the infarct-related artery. Results: 337 patients from 5 ethnic groups: Caucasian 55%, Asian 19%, Hispanic 12%, South Asian 10%, African American 4% were included who had a TIMI flow grade (less than or equal to symbol) 1 before PCI, and TIMI III flow afterwards. 50 patients had significant collateral flow (Group A), whereas 287 patients had either poor or absent collateral flow (Group B). Ethnic, gender and age distributions and prior CAD were similar between the groups. Initial serum CPK levels were significantly lower in Group A (676 +/- 1392 ng/ml vs 1293 +/- 1987 ng/ml, P=0.03). However, peak serum CPK levels were similar between the groups. Presenting LVEF and discharge LVEF were similar between the groups. Incidence of cardiogenic shock, hemodynamic instability requiring IABP support and arrhythmias were similar between the groups.

Conclusions: This data shows no significant variability in collateralization amongst STEMI patients between ethnic groups. Contrary to prior data, the presence of prior CAD did not affect collateralization. Moreover, the presence of a well-developed collateral network does not appear to limit infarct size or early left ventricular function recovery.
THE HIGH-DEGREE ATRIOVENTRICULAR BLOCK REMAINS A SEVERE PROGNOSTIC MARKER IN THE PRIMARY PERCUTANEOUS CORONARY INTERVENTION ERA

P. Dobes
Glenfield Hospital Leicester, University Hospitals of Leicester NHS Trust, Leicester, United Kingdom

I used my research study to comment on the new study results in patients with an acute myocardial infarction (AMI) complicated by a high-degree atrioventricular block (HAVB). We collected the group of 15 patients with a transvenous temporary atrioventricular sequential cardiac pacing (TAVSCP); all patients had AMI and HAVB; cardiac output (CO)/ cardiac index (CI) was measured by thermodilution. We assessed the hemodynamic effect of TAVSCP compared to the ventricular cardiac pacing. CO/CI was measured in 7 patients. TAVSCP results: CO = 4.19 ± 0.74 L/min, CI = 2.19 ± 0.31 L/min/m2. Ventricular pacing results CO = 3.57 ± 0.91 L/min, CI = 1.86 ± 0.40 L/min/m2. TAVSCP resulted in a significantly higher CO by 17%, p < 0.0005; CI was higher by 18%, p < 0.002. HAVB results: CO = 3.40 L/min, CI = 1.76 L/min/m2. We tested one patient to detect and assess changes in sympathovagal balance caused by the loss of atrioventricular sequence because of complete heart block (CHB). We recorded the intra-cardiac ECG record of consecutive atrial potentials for 45 minutes during TAVSCP and CHB, we performed the spectral analysis of atrial heart rate variability: CHB resulted in decrease in vagal activity, Power HF component decreased from 104.0 to 10.3 ms²; Relative Power HF decreased from 63.3% to 35.3%; Ratio LF/HF increased from 0.2381 to 1.1081; Relative Power LF increased from 16.1% to 39.3%. CHB reduced the average interval between atrial potentials to 600.8 ms from 645.7 ms on TAVSCP; atrial heart rate became faster 99.86 b.p.m. from 92.92 b.p.m. Our study conclusion: TAVSCP is hemodynamically superior to the ventricular pacing. The atrial heart rate variability record suggested prompt changes in sympathovagal balance immediately after the loss of atrioventricular sequence because of CHB. These findings deserve further investigation in view of the high in-hospital mortality.
325 IMAGING DEBAKEY’S DEBACLE: AN UNUSUAL CULPRIT FOR ST ELEVATION  
A. Alsaaad, O. Odunukan  
Mayo Clinic, Jacksonville, FL, USA

Acute STEMI is associated with cardiovascular catastrophes in 1-2% of cases other than acute coronary thrombosis. Classically, treatment is emergent cardiac catheterization which can be associated with high level mortality. We present a case of an acute aortic dissection (AAD) presented as inferior STEMI without chest pain due to involvement of right coronary artery (RCA).  

A 77-year-old female smoker presented to the emergency room with three-day history of dyspnea. Electrocardiography showed inferior ST elevation. She denied chest pain but reported left arm numbness. Physical examination revealed a thin Caucasian female in moderate respiratory distress. Blood pressure was 88/55 mm Hg with a 15 mm Hg difference in pulse pressure between upper extremities. She had pectus excavatum deformity but no murmurs. Her jugular veins were not distended. Chest x-ray showed a widened superior mediastinum. An urgent bedside transthoracic echocardiogram revealed a dilated ascending aorta with a false lumen and a bicuspid aortic valve. A contrast chest CT scan demonstrated a 5 cm diameter ascending aorta with Stanford type-A AAD arising from the level of the aortic annulus with RCA arising from false lumen. Emergent surgery confirmed an ascending aortic aneurysm, AAD, aortic insufficiency, bicuspid valve and right ventricular infarct. She underwent surgical repair of the acute dissection, re-suspension of aortic valve and repair of aortic arch. Intra-operative course was however complicated by cardiac arrest with subsequent cardiorespiratory failure. She was ultimately transitioned to comfort care and passed away on Post-Operative day 4. This case illustrates the potential of acute STEMI to be a distractor when it complicates acute ascending AAD especially with involvement of RCA. Painless AAD are particularly associated with significant neurologic symptoms and have a higher mortality. Thus a high index of suspicion is needed for early diagnosis of AAD especially in the absence of classic chest pain.
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**RELATION BETWEEN THE LEVEL OF RED BLOOD CELL DISTRIBUTION AND ELECTROCARDIOGRAM CHANGES AND ECHOCARDIOGRAPHIC WALL MOTION SCORE INDEX IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION**

M. Toufan, M. Rezaazadehsaatlou, F. Akbarzadeh
1. Tuberculosis and Lung Disease Research Center, Tabriz University of Medical Sciences, Tabriz, Eastern Azerbaijan, Iran
2. Cardiovascular Research center, Tabriz University of medical sciences (TBUMS), Tabriz, Eastern Azerbaijan, Iran

**Method:**
Enrolled 100 patients with AMI. On admission RDW was measured in all participants. Electrocardiographic and echocardiographic wall motion score index and left ventricular ejection fraction in particular findings were documented by a blinded cardiologist to RDW of the patients. Possible associations between the mentioned variables and RDW were investigated.

**Result:**
Mean of RDW, WMSI, and LVEF were 13.70±0.88, 1.72±0.39, and 39.85±9.19, respectively. There was not a significant correlation between the RDW and WMSI (r=0.02, P=0.83) and RDW and LVEF (r=0.03, P=0.79) were not statistically significant. There were 56 cases with mechanical complications, including 49 cases with mitral regurgitation (MR). The mean RDW was non-significantly but in a borderline manner higher in the cases with mechanical complications (13.83% vs. 13.54%; P=0.08). Similar result was seen in comparing between the cases with and without MR (with MR: 13.86%, without MR: 13.54%; P=0.06).

**Conclusion:** The RDW might be an indicator of mechanical complications including MR in AMI patients.
SEVERE CHEST PAIN MIMICKING ACUTE CORONARY SYNDROME IN A DIABETIC PATIENT WITH MYASTHENIA GRAVIS

A. Chiriac, S.V. Pislaru, P.A. Pellikka
Mayo Clinic, Rochester, MN, USA

Objectives: To describe a case of typical angina in a patient with uncontrolled hyperglycemia, diabetes, myasthenia gravis, and normal epicardial coronary arteries on angiogram

Background: Pyridostigmine remains the cornerstone of symptomatic treatment for myasthenia gravis (MG), however, its anticholinergic side effects include abdominal muscle spasms which may be difficult to differentiate from angina in a patient with multiple coronary artery disease (CAD) risk factors.

Methods: A 75 year old man with type-1 diabetes, hypertension, dyslipidemia, CAD status post right coronary artery stenting and recently diagnosed, refractory MG was admitted for further myasthenia workup. He was started on high dose prednisone, in addition to frequent use of pyridostigmine. Several hours after the first dose of prednisone he developed hyperglycemia and severe chest pressure, associated with shortness of breath, diaphoresis and sensation of impending doom. EKG showed new ST segment elevation in aVR and ST depressions in anteroseptal and lateral leads. The pain lasted more than 30 min and did not respond to sublingual nitroglycerin. A recent evaluation at an outside institution revealed a normal EKG and negative adenosine nuclear perfusion study (MIBI). With concerns for left main disease (ST elevation in aVR) and balanced coronary ischemia (normal MIBI) the patient was sent emergently to the cardiac catheterization laboratory.

Results: Coronary angiogram revealed clear epicardial coronary arteries and myocardial bridging of the mid-distal left anterior descending artery. Microvascular disease, endothelial dysfunction and hyperglycemia-induced vasospasm were hypothesized. Serial troponins remained negative. Optimal medical management and aggressive CAD risk factor modification were emphasized. Neurology discontinued the pyridostigmine.

Conclusions: This vignette illustrates a clinical scenario with typical angina and dynamic EKG changes without obstructive epicardial coronary lesions. Endothelial dysfunction, microvascular disease, hyperglycemia-induced vasospasm and myocardial bridging may all have contributed. Pyridostigmine should be avoided in patients with chest pain and concern for anticholinergic side effects.
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ACUTE LEFT MAIN THROMBOSIS DURING EXERCISE TESTING

A. Quddus, A. Smith, A. Singh, Y. Manda, P. Puleo, J. Shirani
Department of Cardiology, St. Luke’s University Health Network, Bethlehem, PA, USA

Background. Exercise stress testing (ETT), generally considered safe, may be associated with serious adverse events including acute coronary syndrome (0.04%) and sudden death (0.01%). We present a case of acute left main coronary artery (LMCA) thrombosis during ETT.

Case. 58-year-old physically active man with hypertension and dyslipidemia presented with new onset angina. Examination: blood pressure (BP) 134/94 mmHg, heart rate (HR) regular at 54 bpm, O2 saturation 98% (room air) and respiratory rate 16 bpm; clear lungs and normal heart sounds on auscultation. ECG: normal sinus rhythm without ST-T abnormalities. Laboratory studies unremarkable with negative troponin I (3 sets). TIMI score 0. Echocardiogram showed normal left ventricle (LV) size and function without wall motion abnormality. LV global longitudinal strain was normal without segmental variation. He underwent ETT (Bruce Protocol) which was stopped prematurely (at HR 100 bpm) after 3 min 54 seconds due to recurrence of presenting chest pain and diffuse down sloping ST segment depressions in inferolateral leads followed by ST elevation in V1, V2, aVL and aVR during recovery (figure 1A). Post-stress echocardiogram revealed severe hypokinesis of anterior, anteroseptal, anterolateral, and apical walls. LV appeared dilated with reduced function. He continued to have severe chest tightness (BP 60/40; HR 60) and appeared pale with profound diaphoresis. Emergent cardiac catheterization showed total acute thrombotic occlusion of LMCA that was immediately wired and ballooned, restoring antegrade flow (figures 1B and 1C). He underwent successful emergent coronary artery bypass grafting. Postoperative (day 4) echocardiogram showed normal systolic function and mild hypokinesis of the apical septal wall.

Conclusion. To our knowledge, this is the first reported case of LMCA thrombosis following ETT. Maintenance and regular practice of appropriate emergency equipment and plans is fundamental to ensure patient safety during ETT.
Is There Any Correlation Between Platelet Indices With Extent of Coronary Artery Involvement in Ischemic Heart Diseases?

M.H. Adel¹, M. Seyedian¹, M. Jafarsalehi¹, M. Nourizadeh¹, S. Bagheri¹, M. Nourizadeh¹, P. Nabavizadeh Rafsanjani², A. Shams Akhtari²

¹. Atherosclerosis Research Center, Ahwaz Jundishapur University of Medical Sciences 2. Loghman Research Center, Shahid Beheshti Medical University, Tehran, Iran

Introduction: Ischemic heart disease (IHD) is the most common cause of death around the world. Nowadays Platelet counts (PC) and volumetric platelet indices are available routinely in most laboratories and reflect the level of mobility and production of platelets. It seems that the excessive flexibility and size of the platelets and their local activation have correlation with extent of ischemic heart disease. So our objective is the study of platelet indices in ischemic heart disease.

Materials and methods: This non-randomized prospective study was performed on 245 patients with ischemic heart disease, who underwent the coronary angiography. The patients were divided into four groups: stable angina, unstable angina, acute myocardial infarction, and control group. Platelet indices, including the platelet counts (PC), the average platelet volume (MPV), the Platelet Distribution Width (PDW) and plateletcrit (PCT) in each group with the extent of coronary disease were compared based on the Syntax Score system and observational methods.

Results: The average age of the patients was 57 years and 65% of them were male and the rest were female. A significant difference existed between indices in all three groups compared to the control that this difference was attributed to gender and the type of the coronary artery involvement. However, only in infarction group, PDW in different disease intensities was significantly different.

Conclusion: In this study, unlike many of the previous studies no relationship was found between the MPV with the extent of coronary disease.
CORRELATION BETWEEN ELECTROCARDIOGRAPHIC CHANGES AND CORONARY ANGIOGRAPHY FINDINGS IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION AND SINGLE-VESSEL DISEASE

A. Sanaani, W.S. Aronow, R. Paudel, H. Cooper
Westchester Medical Ctr/New York Medical College, Valhalla, NY, USA

Objective: To investigate the correlation of electrocardiographic (ECG) abnormalities in patients with ST-elevation myocardial infarction (STEMI) and in non-ST-elevation myocardial infarction (NSTEMI) with the location of 1-vessel obstructive (>50% occlusion) coronary artery disease (CAD).

Methods: Of 131 patients, 29 had STEMI and 102 had NSTEMI with chest pain, dyspnea, or chest pain plus dyspnea and increased cardiac troponin I (>0.04 ng/ml) with 1-vessel angiographic obstructive CAD. The 131 patients included 97 men and 34 women, mean age 64 years. An experienced electrocardiographer interpreted the location of the ECG abnormalities in a blinded study without knowing any history or angiographic findings. ECG criteria for STEMI were ST-segment elevation and pathologic Q waves. ECG ischemic abnormalities were ischemic ST-segment depression or ischemic T waves.

Results: Eleven of 11 patients (100%) with ECG anterior STEMI had left anterior descending coronary artery (LAD) obstructive CAD. Of 18 patients with inferior STEMI, 14 (78%) had right coronary artery (RCA) obstructive CAD, 3 (17%) had left circumflex coronary artery (LCX) obstructive CAD, and 1 (5%) had LAD obstructive CAD. Of 102 NSTEMI patients, 53 (52%) had definite ECG ischemic abnormalities. Of 31 patients with anterior wall definite ECG ischemic abnormalities, 30 (97%) had LAD obstructive CAD, and 1 (3%) had RCA obstructive CAD. Of 22 patients with inferior wall definite ECG ischemic abnormalities, 14 (64%) had RCA obstructive CAD, 5 (23%) had LCX obstructive CAD, and 3 (14%) had LAD obstructive CAD.

Conclusions: Only half of NSTEMI patients had ischemic ECG abnormalities. Patients with anterior wall STEMI had LAD obstructive CAD. Patients with inferior wall STEMI were likely to have RCA or LCX obstructive CAD. Patients with NSTEMI and anterior wall ischemic ECG abnormalities had LAD obstructive CAD. Only patients with 1-vessel obstructive CAD were included in the study.
TRANSCATHETER AORTIC VALVE IN VALVE REPLACEMENT: EVALUATION OF MEAN AORTIC ECHOGRAPHIC GRADIENTS

R. Radjef¹, D.D. Wang², B. Fuller³, A. Taylor⁴, J. Wyman², J. Borgi⁵, G. Paone⁵, M. Eng², A. Greenbaum², W.W. O’Neill²
1. Department of Internal Medicine, Henry Ford Hospital, Detroit, MI, USA
2. Department of Structural heart disease, Henry Ford Hospital, Detroit, MI, USA
3. Department of Cardiovascular Medicine, Henry Ford Hospital, Detroit, MI, USA
4. Department of Public Health Science, Henry Ford Hospital, Detroit, MI, USA
5. Department of Cardiac/thoracic Surgery, Henry Ford Hospital, Detroit, MI, USA

Background: Transcatheter Aortic Valve Replacement (TAVR) is performed in deteriorating surgical aortic valves (SAVR) in patients deemed high operative risk. However, there is limited data on acceptable post aortic valve (AV) gradient. This study examines the impact of TAVR in SAVR on mean AV gradient on post procedure follow ups.

Method: Between 9/2012-15, 35 patients were referred. Pre, post procedural, 1 month and 1 year follow up echocardiographic data, Brain Natriuretic Peptide (BNP) and New York Heart Association (NYHA) functional class were analyzed.

Results: 35 patients underwent TAVR in SAVR (12 Edwards Sapien, 17 XT, 5 Medtronic CoreValves, 1 Melody). Mean time interval between surgery and SAVR valve degeneration was 10 ± 2 years; 57% due to stenosis. Post procedure AV gradient (mmHg) decreased from 34.29 ± 18.29 to 16.8 ± 6.77 (p<0.001, n=25), with an increase at 1 month to 18.8 ± 8.66 (p=0.001, n=24) and 1 year to 21.91 ± 7.73 (p<0.001, n=16). BNP level decreased at 1 month follow-up (p<0.001) with a trend towards further decrease at 1 year. NYHA functional class improved from baseline III/IV to I at 1 year.

Conclusion: Despite variation in echocardiographic follow up of valve in valve mean aortic valve gradients, patients had objective sustained clinical improvement by stable BNP and NYHA classification. Given the variation in surgical valve sizes and TAVR valve sizes, larger studies will be needed to assess for acceptable mean gradients variation post TAVR in SAVR.
FIRST YEAR EXPERIENCE OF A NEW TAVR SITE: WHAT IS THE DURATION OF THE TAVR LEARNING CURVE?

G.A. Rogers, E. Kaluski, S. Sattur, F. Reitknecht, D. Sporn
Guthrie Health Systems, Sayre, PA, USA

Aim: In order to assess our initial TAVR outcomes we compared our single center first year TAVR experience to that of the USA STS registry.

Methods: We prospectively recorded and analyzed TAVR data at our center and compared it to the STS database for the same period of time.

Results: A total 41 patients underwent TAVR. Mean age 79 (58-93), 56% were male, mean STS score was 7.4 ± 3.6% (range 1.2-13.4). Devices: Sapien XT 80% and CoreValve 20%. Procedural success was 97.5%. 30-day mortality, stroke and vascular complications were 0%. Mean length of stay was 6 ± 3 days (range 3-15), 1 year mortality was 2.5%. Following TAVR 76% of patients were discharged to home with a 1 year readmission rate of 7.3%. Conclusion: With appropriate proctoring and industry guidance new centers can execute TAVR exceptionally well with a very short learning curve.

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<th>Guthrie Registry (n=41)</th>
<th>STS Registry (n=150,000)</th>
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Aortic stenosis (AS) is the most common valve disease in the elderly population and as the population of the United States ages, it is becoming increasingly prevalent. Transcatheter aortic valve replacement (TAVR) is approved in the US for the treatment of severe symptomatic AS in patients at high or prohibitive risk for surgical aortic valve replacement (SAVR). Heart team and valve clinic has become essential in evaluating patients for sAVR vs. TAVR. The availability of newer TAVR systems enhances the ability to perform TAVR on an increasing number of patients who are not optimal SAVR candidates. We compiled a database of all patients who were referred to the University of Iowa valve clinic for possible TAVR from 2011 through June 2015, and documented whether they proceeded to TAVR, SAVR, or remained on medical therapy. All patients were evaluated by the heart team for suitability for TAVR vs. sAVR. These groups were subdivided into patients evaluated before and July 2014 who were treated commercially with the Sapien valve, and after July 2014 who were treated commercially with Sapien Xt (S3) valve. We found a 9% increase in the number of patients who underwent TAVR after the introduction of the newer valve. In order to compare the procedural risk and characteristics of referred patients, the STS risk score was calculated for both cohorts, and no significant difference was found between the patient populations who underwent either TAVR or SAVR before or after the introduction of the S3 valve (7.21% ± 0.4920 vs 5.99% ± 0.6137, P = 0.1196). In conclusion, as the technology for transcatheter based valve replacement improves, we are able to offer this intervention to an even greater number of patients who previously had limited definitive treatment options for their aortic stenosis despite having similar risk scores.
EFFECT OF DAY OF PROCEDURE ON OUTCOMES OF TRANSCATHETER AORTIC VALVE IMPLANTATION IN THE UNITED STATES: ANALYSIS FROM LARGE NATIONAL REGISTRY

S.V. Patel1, P. Patel1, M. Patel2, A. Rajabalan1, A. Saggu1, T. Singh1, A. Badheka3, 1Western Reserve Health Education/NEOMED, Youngstown, OH, USA
2Christus Schumpert Highland Hospital, Shreveport, LA, USA
3The Everett Clinic, Everett, WA

Objective: There is a need to decrease cost of Transcatheter aortic valve implantations (TAVIs) without affecting clinical outcomes.

Background: With many centers being split between performing elective TAVIs on the day of admission i.e. Day 0, or on the next day of admission i.e. Day 1, we proposed to investigate if there is an economic advantage to either approach.

Methods: We performed a retrospective cohort study, using Nationwide Inpatient Sample database of 2012 and identified subjects undergoing endovascular TAVIs using the ICD-9-CM procedure code of 35.05. The cohort was divided based on the day of the TAVI i.e. Day 0 or 1. The cost of the hospitalization was the primary outcome; with in-hospital mortality and procedural complications as the secondary outcomes. We identified a total of 843 TAVIs. Propensity matched models were created.

Results: The mean age was 82 years; 54% were males and 81% were whites. The mean cost of hospitalization was $54544±963. In propensity matched dataset, TAVIs performed on Day 0 were associated with a lower cost ($51126 ± 1184 Vs $57703 ± 1508, p<0.0001) and length of stay (Mean Days, SE: 5.87 ± 0.25 Vs 7.20 ± 0.29, p<0.001) compared to Day 1. In-hospital mortality plus complication rates were relatively similar with no difference between Day 0 and 1 (31.5% Vs 34.1%, p=0.47, respectively).

Conclusions: Endovascular TAVIs performed on the same day of admission are associated with lower hospitalization costs and length of stay, and similar mortality and complication rates compared to those performed on the next day of admission.
PERCUTANEOUS CLOSURE OF A MITRAL PARAVALVULAR LEAK ANTEGRADELY WITHOUT MAKING A FEMORO-FEMORAL LOOP IN A PATIENT WITH BOTH MITRAL AND AORTIC VALVE REPLACEMENT

C. Barcin, O. Baysan, M. Celik, U.C. Yuksel, E. Yildirim, H.K. Kabul, B. Bugan
Gulhane Military Medical Academy, Ankara, Turkey

Objectives: We aimed to present a case with previous mitral and aortic valve replacement whose mitral paravalvular leak was closed percutaneously.

Background: Percutaneous closure of mitral PVL is challenging and different methods may be used in this situation.

Methods: A 73-year-old man underwent percutaneous mitral PVL closure for symptomatic heart failure. Antegrade approach was used. Following trans-septal puncture, we placed an Agilis steerable introducer in the left atrium. The defect was crossed using a 0.035-inch x260 cm Terumo floppy guide wire over a 5F multipurpose catheter (Figure 1A and B). Floppy wire was exchanged with a stiff wire (Amplatz ES) and this wire was made a loop in left ventricle for support (Figure 1C). Delivery catheter (Amplatz TorqVue2) was advanced over the stiff wire through the defect (Figure 1D). Amplatz vascular PlugIII (12mm, -AVP3) was advanced and deployed successfully (Figures E and F).

Results: Severe mitral PVL was closed almost completely using only a femoral venous access and without constructing a wire loop.

Conclusion: Making a femoro-femoral arteriovenous wire loop is the preferred method in the antegrade closure of mitral PVL. But, in case of AVR, crossing the wire through metallic valve is not recommended. Using a stiff wire which is made a loop in the left ventricle, it is possible to advance the delivery sheath without making arterio-venous femoral wire loop.

Figure 1: Angiographic views showing different steps of the procedure (Explanations are given in the text).
COMPARISON AORTIC DISSECTION DETECTION RISK SCORE AND D-DIMER IN DIAGNOSIS OF ACUTE AORTIC DISSECTION

S. Kodera, J. Kanda
Asahi General Hospital, Asahi, Chiba, Japan

**Background:** The aortic dissection detection (ADD) risk score has been proposed for detecting acute aortic dissection (AD). D-dimer alone has good diagnostic performance in AD. D-dimer alone could be better diagnostic performance than ADD risk score.

**Methods:** Patients from single center with suspected AD were retrospectively gathered from January 2012 to October 2015. The ADD risk score was calculated using retrospective blinded chart review. ADD risk score >1 was applied as cutoff. For D-dimer, a cutoff of 1µg/ml was applied.

**Results:** AD was diagnosed in 105 of 162 (64%). The sensitivity, specificity, AUC (area under curve) of ADD risk score were 86.7%, 33.3%, 0.61 respectively. The sensitivity, specificity, AUC of D-dimer were 91.4%, 33.3%, 0.81 respectively.

**Conclusion:** D-dimer was superior to ADD risk score in diagnosis of AD.
VASCULAR (PERIPHERAL AND CAROTID) AND AORTIC DISEASES

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TAKAYASU ARTERITIS PRESENTING WITH DIFFUSE AORTIC ULCERS

K. Anouti, A. Khaji, M. Maalouf, K. Hawthorne
Lankenau Medical Center, Wynnewood, PA, USA

Background: Takayasu arteritis is a chronic vasculitis of unknown etiology and poorly understood pathogenesis. It primarily affects the aorta and its primary branches. Despite the presence of multiple criteria designed to distinguish this disorder from other forms of vasculitis, the diagnosis of Takayasu arteritis remains elusive.

We present the case of a 54 year old female who presented with a syncopal episode. Her past medical history included a stroke one year prior and isolated episode of uveitis three years prior. She is a nonsmoker and has no notable family history. Extensive review of systems revealed only mild arthralgias and fatigue. Physical exam was remarkable for a loud diastolic murmur. Transthoracic echocardiogram revealed severe aortic regurgitation. Transesophageal echocardiogram found restriction of all three cusps with failure to coapt and resultant severe regurgitation. Imaging of her aorta showed diffuse thickening of all visualized segments with variable lucencies and small mobile elements. Further evaluation with a CT angiogram described calcified and noncalcified atherosclerosis along the entire course of the aorta with numerous focal outpouchings, suspicious for penetrating ulcerations. Severe stenosis of the superior mesenteric artery, celiac artery and bilateral renal arteries were noted. Workup for vasculitis was negative including ANA and ANCA. She had normal CRP and ESR. She underwent repair of the aortic root and aortic valve replacement. Surgical pathology revealed non-necrotizing giant cell arteritis, consistent with Takayasu Arteritis.

Conclusion: The diagnosis of Takayasu arteritis can often be delayed and difficult to make owing to the spectrum of presentation, extent of vessels involved and pace of disease progression. Surgical interventions should be delayed until the acute inflammatory state is treated; however assessment of disease activity can be challenging as there are no specific serological biomarkers that can reliably distinguish the active and quiescent phases.
EFFECT OF ANICOAGULANT ON DEEP VENOUS THROMBOSIS

T. Tomaru1, S. Kodera2, T. Matsubara3, E. Matsubara3, T. Kon1, J. Suzuki1, T. Tsutsumi4, T. Nakajima5
1. Toho University Sakura Medical Center, Sakura, Chiba, Japan
2. Asahi Chu-ou Hospital, Asahi, Chiba, Japan
3. Tokyo University Hospital, Tokyo, Japan
4. Eda Hospital, Yokohama, Kanagawa, Japan
5. Dokukyou University Hospital, Mibu, Tochigi, Japan

Although many studies have been done for anticoagulation on deep venous thrombosis (DVT), we do not know how to predict which patient can be effectively treated. Then, we evaluated usefulness of anticoagulant therapy for treatment of DVT.

Methods: Patients with DVT who underwent anticoagulant therapy were studied. Patients with DVT was divided into thigh DVT (TDVT: from common iliac to popliteal vein) and calf DVT (CDVT: soleus, tibial) group. The 56 patients with TDVT and 55 with CDVT were studied. DVT was diagnosed by duplex ultrasonography, and D-dimer test was done in all. Administration of heparin followed by warfarin (Vitamin K antagonist) or oral warfarin administration was performed in the patients of warfarin group.

Results: Mean age was 59.87±15.43 years old (mean±standard deviation). Prothrombin international ratio (PT-INR) was maintained more than 1.4 in most patients. Venous thrombus disappeared in 30 patients (57.7%) with CDVT and 12 patients (24.4%) with TDVT. It decreased in 4 with CDVT and in 3 with TDVT. CDVT can be dissolved more easily than TDVT. Mean D-dimer was 9.01±10 µg/ml in DVT patients in whom thrombus disappeared or decreased in size, and 4.8±3 µg/ml in patients in whom thrombus size did not change (P<0.01).

Conclusions: In patients with DVT, warfarin therapy is useful for acute thrombosis in patients with elevated D-dimer, however, chronic thrombus appeared to be resistant to anticoagulant therapy. Thigh DVT was more resistant to anticoagulant therapy than calf DVT.
PROGNOSIS OF PATIENTS WITH MILD TO MODERATE CAROTID SCLEROSIS
T. Matsubara¹, S. Kodera², E. Matsubara¹, T. Kurosu³, J. Suzuki³, T. Kon³, T. Tomaru³
1. Tokyo University Hospital, Tokyo, Japan
2. Asahi Chu-ou Hospital, Asahi, Chiba, Japan
3. Toho University Sakura Medical Center, Japan

Cardiovascular event risk has not been fully investigated in patients with moderate or slight stenosis.

Methods: Carotid sclerosis was diagnosed by carotid ultrasonography, and plaque score (PS) was calculated. We evaluated 104 patients with moderate carotid stenosis (MoCST: percent area stenosis $\geq 50\%$), 468 patients with severe carotid sclerosis (SCS: PS $\geq 10$) and compared those with 262 patients with mild carotid sclerosis (MCS: PS $< 5$). Patients with significant carotid stenosis ($\geq 50\%$ in diameter) were excluded.

Results: In 104 patients with MoCST (mean age: 70.8±7.9, mean PS: 14.8±9.0), cerebral infarction (CI) was observed in 26 patients (25.0%), peripheral artery disease (PAD) was observed in 8 (7.7%), and coronary artery disease (CAD) was observed in 39 (37.5%). In patients with SCS (mean age: 74.7±9.2, mean PS: 13.8), CI was observed in 114 patients (24.4%). PAD was observed in 32 (6.83%), and CAD was observed in 124 (26.5%). In patients with MCS (mean age: 69.5±8.6, mean PS: 3.82), CI was observed in 28 patients (10.69%) (P<0.0001 vs SCS), and CAD was observed in 24 patients (9.16%), and PAD was observed in 4 (0.85%) (P<0.0001 each vs SCS). Mean number of risk factor was 2.92±1.01 in MoCTS group, 2.56±0.99 in SCS, and 1.91±0.99 in MCS (P<0.001). In 3 year follow up, ACS developed in 8, and new CI developed in 4 in MoCST group, in 14 (2.99%) in SCS group, and in 4 (1.52%) in MCS group. All patients who developed CI had other cardiovascular disease.

Conclusions: Incidence of CAD or CI was greater in patients with SCS or MoCST than in those with MCS, however, there was no significant difference. At 3 year follow up of all patients, CI did develop more commonly in patients with SCS or MoCST than in those with MCS, but not significantly.
AGGRESSION, IRE, HOSTILITY AND CAROTID THICKNESS MEASURED IN ADOLESCENTS

V. Romero¹,², E. Silva², J. Villasmil², G. Bermudez², M. Bracho¹,², F. Madueño²

1. Instituto de Investigaciones de Enfermedades Cardiovasculares de la Universidad del Zulia, Maracaibo, Estado Zulia, Venezuela
2. Fundación Venezolana de Hipertensión Arterial, Maracaibo, Estado Zulia, Venezuela

To determine the effects of aggression, ire, hostility AAH on carotid thickness measured CTM in adolescents. This study was carried out in a random sample of schools from Maracaibo, Venezuela. The participants were 80 adolescents, males n=39 and females n=41, age-mean=14,38 years. Each one of the adolescents was asked carotid thickness measured by Echo Doppler and completed the scale of Aggression, ire and hostility Questionnaire de Buss and Perry, this scale provides a classification that put the subject in one of three categories: 1-45 points = little aggression, ire and hostility LAIH, 46-96 = moderately aggression, ire and hostility MAAH and 97-135= aggressive, ireful and Hostile AIH. The One-way ANOVA was used to study the effects of AIH on CTM. The presence of LAIH was 0% n=0, MAIH was 98,8% n=79 and AIH was 1,2% n=. The averages and standard deviation of CTM were: Average Thickness Right Carotid ATRC 0,4408±0,06016 and Average Thickness Left Carotid ATLC 0,4315±0,06996. ANOVA’s results showed a significant effect for AIH factor on CTM. For ATRC was F=1,572 p=0.081 and F =2,021 p=0.015 for ATLC. The results provide evidence for an effect AIH on carotid thickness measured, which would mean that AIH may influence the carotid thickness measured in this group that is more vulnerable to AIH due to hard changes typical of their life stage, making it vulnerable to atherosclerosis.
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PRESENCE OF AORTIC PLAQUE MAY PREDICT CORONARY ARTERY DISEASE
T. Tomaru1, S. Kodera2, E. Mastubara3, T. Matsubara3, J. Suzuki1, T. Tabata1, T. Kon1, T. Tsustumi4
1. Toho University Sakura Medical Center, Sakura, Chiba, Japan
2. Asahi Chu-ou Hospital, Asahi, Chiba, Japan
3. Tokyo University Hospital, Tokyo, Japan
4. Eda Hospital, Yokohama, Kanagawa, Japan

We evaluated association between aortic plaque and coronary artery disease (CAD).

Methods: Carotid sclerosis was diagnosed by carotid ultrasonography (US), and plaque score (PS) was calculated by summation of max thickness of each plaque. Aortic plaque was evaluated by US. We evaluated hypertension, diabetes mellitus, dyslipidemia and smoking history as risk factors for arteriosclerosis.

Results: Out of consecutive patients who underwent aortic US, 70 patients had aortic plaque and 59 patients did not. Mean age was 70.09 ± 6.30 (mean ± standard deviation) in patients with plaque (P patients) and 67.9 ± 9.16 in patients without plaque (NP patients). In P patients, 41 had CAD (58.6%), 6 had PAD and 8 had CI. In NP patients, only 6 (10.2%) had CAD, 2 had CI and none had PAD. Prevalence of CAD was higher in P patients than that in NP patients (P<0.01). Mean PS was 9.11 ± 4.0 in P patients and 3.49 ± 7.18 in NP patients (P<0.001). Mean number of risk factor was 2.79 ± 0.80 in P plaque and 1.52 ± 0.82 in NP patients (P<0.001). In 46 patients with abdominal aortic aneurysm (AAA), mean PS was 10.2 ± 6.0. In AAA group, CAD was observed in 12 (26%) patients and CI was observed in 6 (13%) patients. CAVI was 11.8 ± 1.66 in P patients, 10.3 ± 1.0 in AAA, and 9.1 ± 1.22 in NP patients (P<0.001 vs AAA, or Plaque).

Conclusions: Aortic plaque is more closely associated with CAD than AAA, and presence of both aortic and carotid plaque may have sensitivity of more than 95% for diagnosis of CAD.
ELECTROCAUTERY INDUCED ATRIAL FIBRILLATION - WHAT IS THE MECHANISM?

N.V.K. Pothineni¹, J. Payne¹, S. Kovelamudi¹, A. Shanbhag¹, P. Gurram¹, A. Deshmukh², H. Paydak¹

¹University of Arkansas for Medical Sciences, Little Rock, AR; USA
²Mayo Clinic, Rochester, MN, USA

Introduction: Electrocautery (EC) is known to cause electromagnetic interference. We report a rare case of EC induced atrial fibrillation (AF).

Methods: NA

Results: A 63 year old man with a dual chamber pacemaker for Mobitz type II 2nd-degree AV block was referred for a BiV ICD upgrade for non-ischemic cardiomyopathy and left bundle branch block (EF 30%). He had a Boston Scientific pacemaker (Altrua 60TM pacing system - Boston Scientific, Inc.) implanted 4 years ago. The right atrial lead was a 1288TC (Tendril™ STS Lead - St. Jude Medical, Inc) lead. A CS catheter was inserted to guide LV lead position. During exposure of the pacemaker pocket, EC was used for hemostasis. During the second application of EC, patient went into AF. Review of CS electrograms was suggestive of EC induced AF (Figure). As AF persisted even after EC was stopped and there was a concern for right atrial lead malfunction, we proceeded with direct current cardioversion with restoration of atrial paced rhythm. Interrogation of the right atrial lead did not show evidence of insulation breach (Impedance 360Ω). Rest of the procedure was uncomplicated and successful.

Conclusions: Previous cases of EC induced VT and VF have been reported. To the best of our knowledge, this is the first reported case of EC induced AF. Myocardial stimulation with direct application of EC on the pulse generator, connector or the lead is the most likely cause. Minimal power settings, distant grounding patch placement and immediate access to external cardioverters-defibrillators are crucial to manage EC induced arrhythmias.
ATRIAL FIBRILLATION AND SUPRAVENTRICULAR ARRHYTHMIA

LOW ENERGY CARDIOVERSION FOR ATRIAL FLUTTER
V.O. Obi, N. Isber, D. Bloomfield, M. Arulhasan
Richmond University Medical Center, Staten Island, New York NY, USA

Atrial flutter can be electrically cardioverted with small energy levels less than 50J, decreasing the risk of skin burns. In our series, successful return to sinus rhythm was achieved in 65% with energy levels averaging 21J. In order to avoid the need for repeated shocks, we studied comorbidities to determine which patients were no more likely to require a high energy level.

Method. 44 patients with atrial flutter underwent cardioversion initially at low energy levels below 50 J. If the procedure was unsuccessful, a shock of great energy was utilized. In all patients, comorbidities of hypertension, hyperlipidemia, diabetes, coronary artery disease, congestive heart failure, prior pacemaker insertion together with age, sex and weight were recorded. The patients were separated into a low energy group (below 50J) and a high-energy group (above 50J) and compared using a two-sided t-test with 95% confidence interval statistical analysis.

Results. Females showed a high requirement of energy (p=0.018) but there was no significant differences in regard to age and weight. Coronary artery disease showed a relationship to low energy (p= 0.0046) as it did congestive heart failure (p=0.033). The other comorbidities showed no difference between the requirement of low or high energy levels for successful cardioversion.

Conclusion. Effective low energy cardioversion, though important in reducing the mild side effects such as burns and muscle fatigue, failed to convert one third of the patients. The inability to predict which patients would require higher energy leads to the recommendation that all cases of atrial flutter should be cardioverted initially at energy levels higher than 50J.
ATRIAL FIBRILLATION AND SUPRAVENTRICULAR ARRHYTHMIA

NEW-ONSET ATRIAL FIBRILLATION ASSOCIATED WITH CYCLOPHOSPHAMIDE-INDUCED CARDIOTOXICITY: CASE REPORT
A.C. Guta, A.M. Daraban, A. Burducea, D. Bartos
Bucharest Emergency Clinical Hospital- Foreasca, Romania

Introduction: Chemotherapy-induced cardiac dysfunction has become an important cause of heart failure and mortality in neoplastic patients. The relationship between arrhythmias and chemotherapy has not been well established, however atrial fibrillation has been reported as a high-dose cyclophosphamide therapy side-effect. We report a case of acute heart failure in a patient with cyclophosphamide-induced cardiac toxicity and new-onset atrial fibrillation.

Case presentation: A 65-year-old Caucasian woman, diagnosed 9 years ago with invasive mammary carcinoma, underwent surgery, radiotherapy and polychemotherapy. She presented with a 2-months history of increasing dyspnea and fatigability. On admission to hospital ECG demonstrated atrial fibrillation at a rate of 96 bpm. Blood tests revealed a raised proBNP at 2398 pg/ml and the estimated GFR was 28ml/min/1.73m2. Echocardiography showed generally impaired biventricular systolic function with a left ventricular ejection fraction of 30%. Cyclophosphamide-induced cardiotoxicity was suspected and she was given treatment for congestive heart failure. Pharmacological cardioversion with amiodarone succeeded and her symptoms ameliorated. She was discharged on the seventh day with a left ventricular ejection fraction of 45% and normal right ventricular function.

Conclusions: Drug-induced cardiotoxicity should be taken into consideration when using cyclophosphamide therapy. The impact of new-onset atrial fibrillation in the setting of cardiac dysfunction can be dramatic, and aggressive therapy to restore sinus rhythm may have lasting benefit.
ATRIAL FIBRILLATION AND SUPRAVENTRICULAR ARRHYTHMIA

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EFFECT OF DABIGATRAN ON PLATELET REACTIVITY-A PROOF OF CONCEPT STUDY
S.R. Devabhaktuni1, A. Annapureddy2, A. Namazi1, A. Malik1, L. Dizon3, C. Miranda4, A. Gururaj1, C. Ahsan1
1. University of Nevada School of Medicine, Las Vegas, NV, USA
2. Griffin hospital, Derby, CT, USA
3. UMC, Las Vegas, NV, USA
4. NHVC, Las Vegas, NV, USA

Background: Dabigatran is a new oral anticoagulant, a direct thrombin inhibitor approved for use in non-valvular atrial fibrillation and pulmonary embolism management. It was associated with statistically non-significant increase in risk of MI in several trials. Previous study showed that thrombin receptor- activated peptide (TRAP) mediated platelet aggregation is less with both dabigatran and warfarin, but there was less inhibition of platelet aggregation by dabigatran compared to warfarin. To our knowledge no study has reported the effect of dabigatran and warfarin on platelet reactivity unit (PRU) values assessed by point of care VerifyNow P2Y12 test.

Objective: We hypothesized that the trend towards increased MI events in patients receiving Dabigatran could be due to an increase in platelet reactivity as measured by the VerifyNow P2Y12 test.

Methods: This is a proof of concept study. We enrolled 40 patients who have been on dabigatran or warfarin for at least 6 months into one of the two study arms: Dabigatran arm or Warfarin arm. Platelet reactivity was measured by Accriva’s VerifyNow device and the PRU values were recorded. Analysis was done using Student t-test.

Results: The mean PRU value in Dabigatran group was 222.4 with SD of 35.19. The mean PRU value in Coumadin group was 235.25 with SD of 34.49. T value was 1.498. Two-tailed P value was 0.25 with 95 CI ranging from -35.47 to 9.77.

Conclusion: Platelet reactivity assessed by VerifyNow did not differ in the two groups. These findings do not explain the observed trend in increased events of MI in the large clinical trials with dabigatran.
ATRIAL FIBRILLATION AND SUPRAVENTRICULAR ARRHYTHMIA

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INTRACARDIAC THROMBUS IN A WARFARIN RESISTANT PATIENT

F. Khan, B.C. Berger
Abington Jefferson Health, Abington, PA, USA

Introduction: Warfarin has been the drug of choice for prophylaxis of thromboembolic events in atrial fibrillation and post-valvular surgeries. Its resistance is not an unknown phenomenon. We report a case of increscent intracardiac thrombus in a patient with warfarin resistance leading to recurrent thromboembolic events.

Case Report: Our case is of a 75-year-old African-American female with history of paroxysmal atrial fibrillation (PAF) for which she was on warfarin. She underwent replacement of mitral valve (MV) with a bioprosthetic valve for mitral regurgitation. Given the history of PAF, left atrial appendage was over-sewn. Two- and three-months postoperatively she had two episodes of CVA, respectively despite adequate anticoagulation. Transesophageal echocardiogram (TEE) during the latter episode showed a thrombus on the MV ring (Fig. 1). Four-month post-surgery she had a new splenic infarct and warfarin was continued. She returned at six-months postoperatively with recurrent splenic infarct. TEE showed enlarged thrombus on the MV (Fig. 2). She was considered warfarin resistant. She was not a candidate for novel anticoagulation (NOAC) because of the prosthetic valve, so enoxaparin was chosen.

Conclusion: There is no data to support genetic testing to guide warfarin dosing in African-American patients. Alternative anticoagulation should be considered in such patients.
ARRHYTHMIAS: DIAGNOSIS AND TREATMENT

THE EFFECT OF FLECAINIDE AND RANOLAZINE ON CALCIUM TRANSIENTS IN RAT CARDIOMYOCYTES

S. Chawla, A. Alvarez-Laviada, K. Macleod
Myocardial Function Unit, Imperial University, Hammersmith. UK, University of Southampton, Southampton; UK

Background: Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a genetic condition that results in an increased propensity for arrhythmias. It is derived from mutations in either the ryanodine receptors (RYR2) or calsequestrin, both of which are involved in intracellular calcium handling in cardiac myocytes. Currently, CPVT is generally managed by beta-blockers, although flecainide, an established class 1c anti-arrhythmic, and has recently been demonstrated as having significant clinical benefit for CPVT due to its peak Ina blocking properties. Ranolazine, an anti-anginal, has also gained prominence due to its late Ina blocking properties, and therefore potentially represents a greater role in managing arrhythmias in failing hearts.

Aims: Our study aimed to determine the effect of flecainide and ranolazine on calcium transients in healthy and failing rat cardiomyocytes.

Method: Ventricular myocytes were isolated from healthy and 16-week MI rats. Wide-field epi-fluorescence microscopy was used to image waves, and Ca2+ transients were recorded using Fluo-4 AM loaded cells. Cardiomyocytes were infused with 5µM of flecainide or 10µM ranolazine, and paced at 0.5 Hz. 20 mM caffeine spritz was used to assess SR Ca content.

Results: Both flecainide and ranolazine infusion in healthy cardiomyocytes showed no significant change in calcium transient height (0.41 ± 0.06 vs. 0.26 ± 0.06, p= 0.13, and 0.57 ± 0.14 vs. 0.2 ± 0.1, p= 0.22). Ranolazine infusion in failing cells also resulted in no significant reduction in transient height (0.45 ± 0.03 vs. 0.07 ± 0.03, p=0.25). However flecainide led to a significant transient height reduction in the failing cardiomyocytes (0.65 ± 0.12 vs. 0.17 ± 0.02, p<0.5).

Conclusion: Ranolazine exposure had no significant effect in reducing calcium transients in both healthy and failing cardiomyocytes. Flecainide however seemed to have a significant effect on cells isolated from failing cardiomyocytes, which indicates a greater role for it in such situations.
ARRHYTHMIAS: DIAGNOSIS AND TREATMENT

Efficacy of Class IC Versus Class III Antiarrhythmics After Cryoablation Using the Arctic Front Advance Catheter

A. Avezbadalov¹, S. Pollack², A.F. Osman¹

¹. The Heart Center of Excellence, NOVA Southeastern University, Fort Lauderdale, FL, USA
². St. John’s University, New York, NY, USA

Objective: The second-generation cryoablation balloon is very effective in treating atrial fibrillation. Treating with antiarrhythmics post-ablation has shown favorable results in preventing recurrent atrial fibrillation. We sought to evaluate if any of the two classes of antiarrhythmics had better success of preventing recurrent atrial fibrillation after cryoablation.

Methods: This is a single center retrospective analysis of all patients with paroxysmal atrial fibrillation who underwent cryoablation using the Arctic Front Advance catheter at our medical center between September 2012 and October 2014. All patients received either a Class IC or Class III antiarrhythmic and followed for six months for any documented episodes of atrial fibrillation (Table 1). Amiodarone was separated into an independent group to be compared against the remaining two groups. Any patient who did not follow up for a minimum of six months was excluded.

Results: When Amiodarone was separated into an independent group, no statistical significance was found between the three groups (p value = 0.97).

Conclusion: We found no significant difference between using Class IC or Class III antiarrhythmic agents for the prevention of recurrent atrial fibrillation after successful cryoablation. There was no statistically significant difference when Amiodarone was compared to the Class IC and rest of Class III antiarrhythmic medications.

Results:

<table>
<thead>
<tr>
<th>Total Number of Patients</th>
<th>Class IC (N = 29)</th>
<th>Class III (N = 71)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 100</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Flecainide (18)</td>
<td>Amiodarone (53)</td>
</tr>
<tr>
<td></td>
<td>Propafenone (11)</td>
<td>Sotalol (14)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dronederoone (4)</td>
</tr>
<tr>
<td>Number of Patients in Sinus Rhythm at 6 Months</td>
<td>24 (82.8%)</td>
<td>58 (81.9%)</td>
</tr>
<tr>
<td>Number of Patients with Recurrent Atrial Fibrillation at 6 Months</td>
<td>5 (17.2%)</td>
<td>13 (18.3%)</td>
</tr>
</tbody>
</table>

p value = 0.89

Table 1
ELECTROCARDIOGRAPHIC BRUGADA PATTERN UNMASKED BY CORONARY VASOSPASM IN A COCAINE USER

Y. Manda, S. Nanda, A. Singh, S. Agrawal, W. Samuel Towne, J. Shirani
St. Luke’s University Health Network, Bethlehem, PA, USA

Background: Brugada pattern on electrocardiogram (ECG) has been reported in those using cocaine and also in patients with coronary vasospasm (CV). The co-existence of all three conditions has been rarely reported.

Case: A 40-year old woman with history of hypertension, asthma and cocaine use presented with 3 hours of intermittent chest pain radiating to left shoulder associated with nausea. ECG on arrival showed sinus rhythm with nonspecific ST-T changes and i-STAT troponin was 0.37 ng/dL (normal <0.04). She developed recurrent chest pain and repeat ECG revealed ST-segment elevation in leads V1 and V2 (Panel A). Emergent coronary angiography showed sequential, long-segment, critical yet smooth narrowing of the dominant right coronary artery (Panel B). This was complicated by ventricular fibrillation that was successfully defibrillated using a single biphasic shock at 200J. Administration of multiple doses of intracoronary nitroglycerin (total 800 mg) resulted in resolution of CV and ST-segment elevation (Panels C-D). ECG changes were felt to be a result of unmasking of the Brugada pattern by CV triggered by cocaine use. Patient was treated with long acting calcium channel blockers and remained asymptomatic at 1 year of follow up while abstaining from cocaine.

Conclusion: We have previously shown ischemia-induced Brugada phenocopy in obstructive CAD. This case demonstrates Brugada ECG pattern unmasked by CV following cocaine use.
ARRHYTHMIAS: DIAGNOSIS AND TREATMENT

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WIDE COMPLEX TACHYCARDIA WITH PROPafenONE USE - EXPLAIN IT TO MY HEART
S. Neupane¹, S. Edla¹, A. Shakir¹
¹. St John Hospital and Medical Center, Detroit, MI, USA

Case Presentation: A 72-year-old female was evaluated for symptomatic palpitations and subsequently diagnosed with paroxysmal atrial fibrillation. Her other cardiac history included non-obstructive coronary artery disease with normal left ventricular function. She was started on propafenone 150 mg three times (TID) a day along with metoprolol 25 mg TID. She was prescribed mobile cardiac outpatient telemetry (MCOT) for documentation of arrhythmia control. On day 23 of MCOT, a wide complex tachycardia was reported but the MCOT company could not reach her. EMS was contacted immediately the prescribing physician. The patient was found unconscious on the floor at her home. She was defibrillated and transferred to the hospital. She had another episode of wide complex tachycardia in the emergency room, which too required defibrillation. She was aggressively treated with sodium bicarbonate for presumed diagnosis of propafenone toxicity.

Decision-Making: The differential diagnoses of wide complex tachycardia in this case were ventricular tachycardia and atrial flutter with 1:1 conduction which may be seen with the use of class IC antiarrhythmic agents. She underwent Electrophysiology study, which showed no inducible sustained ventricular tachycardia. However, she was found to have inducible typical isthmus dependent flutter which was successfully ablated. Therefore her wide complex tachycardia was likely atrial flutter with 1:1 conduction due to propafenone toxicity despite being on a concomitant av-blocking agent. She was found to have decreased CYP2D6 activity upon further investigation.

Conclusion: Propafenone is frequently used in the management of atrial fibrillation and metabolized primarily by CYP2D6 isoenzyme. Approximately 6% of Caucasians are naturally deficient in CYP2D6 activity predisposing them to its toxicity. Our patient had the enzyme deficiency leading to proarrhythmic effects even with very low dose of the drug despite being on concomitant AV blocking agent.
IVABRADINE’S POTENT EFFECT ON THE AV NODE: A CASE OF 2ND DEGREE HEART BLOCK

**B. Louka**, V. Abrich, B. Yeneneh, K. Srivathsan
Mayo Clinic- Arizona, USA

*Background:* Ivabradine is a medication that blocks the funny channel in the SA node leading to a reduction in heart rate without affecting blood pressure. This makes it attractive for the management of inappropriate sinus tachycardia. It is known to cause sinus bradycardia or occasionally 1st degree heart block. We present a case in which Ivabradine contributed to the development of 2nd degree Wenckebach AV block.

*Case:* A 39-year-old female with a history of recurrent supraventricular tachycardia (SVT) had undergone an ablation of the slow pathway of the AV node for AV nodal reentrant tachycardia and an atrial focus in the crista terminalis. At that time she was also found to have sinus node dysfunction and a dual-chamber pacemaker was placed. She later developed severe tricuspid regurgitation, leading to removal of the right ventricular lead with placement of a coronary sinus lead in the anterior interventricular vein. The lead was turned off shortly after due to the development of diaphragmatic stimulation. A month later, she presented with recurrent symptoms and was diagnosed with inappropriate sinus tachycardia following another EP study. She was then started on Ivabradine 5 mg daily which effectively led to a reduction in heart rate. The following day, she developed Wenckebach 2nd degree AV block with episodes of 2:1 conduction causing a ventricular rate of 32 beats a minute. A new right ventricular lead was placed and a pacemaker interrogation 24 hours later revealed 19% atrial pacing, 35% ventricular pacing, and a heart rate of 60-70 beats per minute.

*Conclusion:* This case demonstrates the potential for Ivabradine to cause 2nd degree Wenckebach AV block, which has not been previously described. Ivabradine should therefore be used with caution in patients who have had a previous ablation in the region of the compact AV node.
ARRHYTHMIAS: DIAGNOSIS AND TREATMENT

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BRUGADA PATTERN ELECTROCARDIOGRAPHIC CHANGES IN A PATIENT WITH LITHIUM TOXICITY AND FEVER

N. Mehta, A. Kanthala, M. Schinlever
Rochester Regional Health, Unity Hospital, Rochester, NY, USA

Introduction: Lithium toxicity (levels > 1.2 mmol/L) can cause electrocardiographic (ECG) changes by affecting sodium channels on cardiac myocytes. We present a case of Lithium toxicity with subsequent aspiration pneumonitis, found to have Brugada pattern changes on ECG.

Case Summary: A 54 year old female presented with confusion, insomnia, agitation, and restlessness since 24 hours. Her medical history was significant for bipolar disorder and depression, and home medications included Lithium, Amitriptyline, Quetiapine, and Zolpidem. She reported noncompliance with medications and blood work on admission showed an elevated lithium level (3.0 mmol/L). Shortly after presentation, she vomited, became febrile (39.2°C) and severely hypoxic secondary to aspiration pneumonitis.

We obtained an ECG that showed normal sinus rhythm (NSR) with prolonged QTc of 509 msec. Repeat ECG 12 hours later showed change in rhythm to junctional escape at 57/min with premature bigeminy complexes and a classical Brugada pattern - J point elevation with coved ST segment and TWI in V1 and V2 (Image). She was treated for lithium toxicity with fluid resuscitation and symptomatically managed for her aspiration pneumonitis. The next day her lithium levels normalized (1.2 mmol/L) and so did her ECG changes. On day 3 she was discharged to primary care follow up.

Discussion: Lithium toxicity has been associated with T wave flattening, bradycardia, and QTc prolongation, but not with the Brugada pattern and junctional escape rhythm as seen in our patient. The presence of moderate grade fever complicates the picture, as pyrogens are known for bizarre ECG changes such as ST segment elevations and rarely even Brugada like patterns. First glance abnormal rhythm and ST segment changes draw providers towards common disease entities like myocardial infarction and fatal arrhythmias. Being familiar with transient ECG changes in the setting of medication toxicity and pyrogens may help avoid premature conclusions.
USE OF MECHANICAL CIRCULATORY SUPPORT IN OCTOGENARIANS FOR PERCUTANEOUS CORONARY INTERVENTIONS

St Luke's University Health Network, Bethlehem, PA, USA

Background: Mechanical circulatory support (MCS) is commonly used in the setting of high-risk percutaneous coronary intervention (PCI). However, the effectiveness, safety, and trends of use of this modality in highly vulnerable octogenarians have not been well studied.

Methods: Using the Nationwide Inpatient Sample (NIS) database, we estimated the rates and trends of MCS devices for PCI in octogenarians and their inpatient mortality rates.

Results: From 2003-2011 a total of 812,338 patients age >80 years underwent PCI of which 17,790 (2.2%) were performed with the support of MCS and the mean age increased from 83.7±3.4 to 84.5±3.8 years between 2003 and 2011 (p<0.001). 50.6% were male and 84.4% were white. 53.3% were admitted with a primary diagnosis of STEMI, and 26.8% with NSTEMI. 51.6% had cardiogenic shock. Intra-aortic balloon pump (IABP) was used in 96.1%; a peripheral ventricular assist device (PVAD) was employed in 3.9%. The proportion of MCS supported PCI in octogenarians increased from 1.5% in 2003 to 3.6% in 2011 (odds ratio (OR) 1.055, p<0.001). 9.7% of the PCIs among octogenarians in which MCS was employed over the study period were elective; there was no significant change in the proportion of such admissions over the study period (p=0.46). The in-hospital mortality rate among octogenarians with MCS use during PCI was 35.5%, with a downward trend for in-hospital mortality over the years of study (OR 0.96; p<0.001). In subgroup analysis, the mortality rates were 42% for STEMI patients, 28.5% for NSTEMI patients, and 48.7% for patients with cardiogenic shock, each of these subgroups exhibited a significant trend for decrease in in-hospital mortality over the study period (p<0.001 for all).

Conclusion: Mechanical support devices are increasingly employed in high-risk PCI in octogenarians, and there is a downward trend in mortality in recent years.
LACK OF POST LVAD IMPLANTATION WEIGHT LOSS IS ASSOCIATED WITH VOLUME OVERLOAD DURING INTERMEDIATE FOLLOW UP

Albany Medical Center, Albany, NY, USA

Background: We investigated the association between early (5 months) post LVAD implantation weight changes and volume status during subsequent follow-up visits, up to 24 months.

Methods: 359 individual consecutive follow-up patient-visits in 19 Heartmate-II recipients were included in the analysis. Patients were separated into groups based on the maximum weight loss, as compared to pre-LVAD weight, achieved during the first 5 months post LVAD implantation: group I with 0-5% weight loss, group II with 5-10%, group III with >10%.

Results: There were no significant between group differences in demographic parameters, etiology of cardiomyopathy, and prevalence of diabetes, hypertension, or pre-LVAD use of inotropic agents. Heartmate II speed, power, and pulsatility index were similar as well. Rates of reported dyspnea and/or rales during follow-up visits were not associated with post-LVAD weight loss. Despite of significantly increased use of post-LVAD diuretics, edema was observed more frequently in patients with minimal or no weight loss post-LVAD (group I, Table). The differences in rates of edema were significant at 5, 12 and 24 months (Table).

Conclusion: Weight change observed early post LVAD implantation may help to identify patients at risk for future fluid retention and signs of right-side ventricular failure.

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THE HIBERNATING LIMA: A CASE REPORT DESCRIBING IMPROVEMENT IN LEFT INTERNAL MAMMARY ARTERY GRAFT FLOW AFTER PROGRESSION OF NATIVE VESSEL CORONARY ARTERY DISEASE

S. Desai, B. Louka, F.D. Fortuin
Mayo Clinic Arizona, Department of Cardiovascular Disease, Scottsdale, AZ, USA

Background: The utility of the Internal Mammary Artery as a bypass conduit has been studied in surgical laboratories for more than seventy years. Furthermore, occlusion of the Left Internal Mammary Artery (LIMA) following bypass grafting to a moderately diseased vessel has also been well studied. The hemodynamic effects of competitive flow between involved vessels have long been debated as a mechanism of graft failure. We present a unique case of dynamic LIMA patency when there is progression of coronary disease in a non-Left Anterior Descending (LAD) vessel.

Case: We present a 91 year old male who is 14 years status post coronary artery bypass grafting for multi-vessel coronary artery disease. The LIMA was grafted to the ramus intermediate along with two vein grafts going to a diagonal branch and posterior descending artery. Three years after his bypass surgery, the patient underwent coronary angiography revealing an atretic LIMA graft with a patent ramus intermediate vessel. Eleven years later, the patient again presented with angina and was taken for left heart catheterization. During this instance, LIMA injection revealed a widely patent graft, however, an entirely occluded ramus intermediate vessel.

Discussion: When studying patients with a LIMA bypass graft to the LAD, Nasu et al found that a smaller degree of stenosis in the LAD correlated with less LIMA flow volume. With that said, we suspect that the atretic LIMA in our patient was recruited once the patient had progression of coronary disease in his native ramus intermediate vessel. Although re-establishing flow in the LIMA when there is worsening of native vessel coronary disease has been reported previously, it is not well described in non-LAD vessels. This case highlights the dynamic patency of the LIMA as a bypass conduit, even when grafted to non-LAD vessels.

Figure 1 A) Left main injection 3 years after CABG revealing patent Ramus Intermediate (arrow). B) Atretic LIMA graft (arrow). C) Angiogram 14 years after CABG revealing occluded Ramus Intermediate (arrow). D) Widely patent LIMA graft (arrow).
THROMBOSIS IN THE HEARTWARE PUMP: CLINICAL PRESENTATION AND MANAGEMENT DECISIONS

M.B. Jayanna, C. Inampudi, R. Kafa, J.L. Franzwa, V. Cotarlan, J.K. Bhama, K. Light-McGroary
University of Iowa Carver College of Medicine, Iowa City, IA, USA

Background and Objectives: Continuous flow Left ventricular assist devices (CF-LVAD) are being increasingly used for the management of End-stage Heart failure. Increased durability of the devices has heightened the awareness of complications like gastrointestinal bleeding and VAD thrombosis. We describe the use of Computed Tomographic Angiography (CTA) to diagnose pump thrombus in an asymptomatic patient with normal Plasma Free Hemoglobin (PFHb) and Lactate Dehydrogenase (LDH) but with abnormal pump parameters.

Case: 66 year Caucasian male who is a nursing home resident with history of Coronary artery disease (CAD), Stage D Heart Failure S/p LVAD- HeartWare, Chronic kidney disease-stage 3, Diabetes Mellitus-Type 2, admitted for evaluation and management of low flow alarms of one-day duration. Plasma free hemoglobin and LDH on admission were within normal range. Patient was fluid resuscitated with no improvement in pump flows. Transthoracic echocardiography (TTE) showed poor Left ventricular function and abnormal RAMP study. CTA showed partially obstructive thrombus in the proximal portion of LVAD outflow cannula. Anticoagulation with Heparin was pursued until therapeutic International Normalized Ratio (INR) of 2.5-3.5. Additionally, Aggrenox was added and Aspirin was continued with normalization of pump parameters prior to discharge.

Conclusion: LVAD Pump thrombosis carries substantial morbidity and mortality. Despite excellent sensitivity and specificity of elevated LDH and PFHb for diagnosis of pump thrombosis some patient-associated factors or location of the thrombus within the VAD may affect the test results. Nevertheless, both our case and published evidence to date support that no single test can reliably exclude diagnosis of VAD thrombosis. While echocardiography provided a clear indication that the VAD was not functioning normally, we propose that addition of gated cardiac CT in select cases is a valuable tool in the early diagnosis of pump thrombosis when the index of suspicion is high.
A 17 year old male consulted a neurologist due to recurrent episodes of syncope with prodrome of blurring, palpitations and light headedness, usually occurring after exertion. Neurologic examination was unremarkable. Magnetic Resonance Imaging (MRI) of the brain revealed contrast enhancing lesions in the right thalamus and hypothalamus and non-enhancing fairly defined lesions in the left thalamus and left centrum semiovale. The working diagnosis was stroke in the young, further investigation including a referral to a cardiologist was done. Physical examination revealed normal heart rate, regular rhythm, soft S1 and a low frequency diastolic sound of the same intensity heard both at the mitral and tricuspid areas with a grade 3/6 holosystolic murmur at the apex radiating to the axilla. Two dimensional transthoracic echocardiography revealed ectopic densities in the left atrium, right atrium and right ventricle probably a triple chamber myxoma. He was referred to thoracic cardiovascular surgery and was scheduled for triple chamber cardiac myxoma excision. Pre-operative transesophageal echocardiogram confirmed the presence of three masses, with each mass, located in the right atrium, left atrium and right ventricle probably a triple chamber myxoma. He tolerated the procedure well and was stable postoperatively. Multiple myxoma are present in less than 5% with bi-atrial myxomas occurring in 2.5% of cases. Literature search revealed only one reported case of triple chamber myxoma and 1 case of sporadic myxoma involving all chambers.
MEDIASTINAL HEMATOMA CAUSING SYNCOPE: AN EXTRA-PERICARDIAL CULPRIT FOR TAMPOANDE

S.M. Dhannoon1, A.A. Alsaad2
1. University of Central Florida, Orlando, Florida, USA
2. Mayo Clinic, Jacksonville, Florida, USA

Cardiac tamponade is commonly caused by fluid collection between the visceral and the parietal pericardium. However, extra-pericardial causes may contribute to the pathogenesis of this disease. We are reporting a patient with severe aortic valve stenosis who developed anterior mediastinal hematoma after mechanical aortic valve replacement. The hematoma formation in the anterior mediastinum was complicated by cardiac tamponade physiology. A 40-year-old male with a history of severe aortic valve stenosis had a mechanical valve replacement with no immediate post-operative complications and was discharged on warfarin treatment. Ten days after discharge the patient presented with an episode of syncope with cardiogenic features. He also had progressive shortness of breath, tiredness, and lower extremities edema since the surgery. Initial workup revealed supra-therapeutic INR of 8.9 and azotemia. Chest-X-ray revealed mild increase in cardiac silhouette. Bedside echocardiography identified a fluid collection below the mid-sternal area and revealed diastolic collapse of right ventricle. Computerized tomography of the chest with no contrast revealed a new retrosternal fluid collection measuring 6cm X 10cm X 13cm pushing the right ventricle; findings are suggestive of anterior mediastinal hematoma that is compromising the cardiac function and causing tamponade physiology. Patient was treated with fresh frozen plasma and prothrombin concentrate complex. He was taken to surgery. Hematoma was evacuated successfully. The culprit was the internal mammary artery which was repaired successfully with no complications.

Conclusion:
- Mass effect caused by fluid accumulation, hematoma or tumors in the mediastinum may be an uncommon culprit for cardiac tamponade.
- Close and strict monitoring of the international normalized ration is always recommended in patients with recent valve replacement to prevent hematoma formation in the mediastinum.
INTRAOPERATIVE GRAFT VERIFICATION IN CORONARY SURGERY: WHY, WHEN AND HOW SHOULD WE VERIFY CORONARY ARTERY BYPASS GRAFTS

G. Di Giammarco, D. Marinelli, M. Foschi, M. Di Mauro, M. Di Natale
University "G.D'Annunzio", Chieti, Italy

The incidence of perioperative graft failure has been estimated to range from 5% to 11%. Early graft failure is related to technical error during anastomosis construction. The use of intraoperative graft verification procedures is able to reduce the number of failures and improve both the patient and graft outcome as reported on many papers in the literature. Transit-Time Flow Measurement (TTFM) is a fast, easy to use and well reputed method to check the flow of coronary artery bypass grafts the main limitation being the low positive predictive value that may lead to a high number of undue anastomotic revisions. We started to use TTFM in 1995 and from 2009 we added high resolution imaging to TTFM with the aim to improve the predictive power of this technology. Our policy had been since the beginning to verify all the coronary grafts, either in isolated and after combined Coronary Artery Bypass Grafting (CABG) procedures. On the practical point of view we usually measure sequentially the graft flow with a different protocol according to the surgical strategy adopted, if on- or off-pump. In ON-pump procedures we measure after aortic cross-clamp removal and after protamine administered; in OFF-pump CABG we check the conduit immediately after anastomosis completed and after protamine administered. Using both methods we noticed an improvement of diagnostic accuracy of the procedure that came close to 100%. On the basis of our experience we developed a flow chart with the aim to provide a easy and fast tool to check conduits, coronary anastomoses and to predict the fate of the grafts according to distal runoff. A low MGF (<<15ml/min) with an high PI (>>3) and very low %BF (=0) represents the picture of anastomotical error; a low MGF (<15 ml/min), high PI (>>3) and very high %BF (>>3%) is the picture of a conduit grafted downward a not critical native stenosis. A MGF >15 ml/min, PI <3, %BF (>0<3) is the picture of a well functioning graft. Intraoperative Dobutamine Test (20mcg/Kg in a single bolus injection) may help to check the competitive flow reversal and to assess the fate of the graft at a late follow-up. In conclusion, the method a valid help to accomplish a reliable intraoperative graft verification in coronary surgery proving the correctness of the surgical technique.
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EVIDENCE FOR BENEFITS FOR CHRONIC TOTAL OCCLUSION INTERVENTIONS IN 2016
R. Sachdeva
Morehouse School of Medicine, Grady Memorial Hospital, Atlanta, GA, USA

Chronic total occlusion (CTO) is present in 15-30% of patients undergoing coronary angiography. CTOs are the most technically challenging lesions to vascularize by percutaneous approach, hence their presence has a major influence on the decision and referral for coronary artery bypass grafting. Complete functional revascularization of ischemic myocardium has better outcomes than incomplete. CTO percutaneous intervention (PCI) attempt rates have not changed in past five years. When one faces with patients with a CTO for whom surgery appears high risk, CTO PCI of viable myocardium can only be expected if ischemia is present and to improve the function of hibernating myocardium, if its continuing dysfunction is causing symptoms. Physicians are reluctant to refer for CTO PCI, because of perceived notion that well collateralized CTO is a benign condition and CTO PCI has inherent high risk. There are several recent advances in procedural success, safety with a considerable body of evidence supporting a survival benefit following successful revascularization. CTO PCI does improve ischemia and left ventricular dysfunction and quality of life and prognosis.
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PREVENTION OF ACUTE MI BY AGGRESSIVE APPROACH TO TREAT UNSTABLE ANGINA

Y. Ueda
Osaka National Hospital, Osaka, Japan

Although the incidence of in-hospital death from acute myocardial infarction (MI) is about 5%, about 40% of the patients who suffer acute MI die before hospitalization. Indeed, 6,000 of 69,000 hospitalized acute MI patients die and 34,000 acute MI patients die before hospitalization every year in Japan. Therefore, the prevention of acute MI is very important. Acute MI is known to occur within a day after coronary plaque disruption in a half of the patients, while it takes days to weeks in the rest half. A half of the hospitalized acute MI patients are known to have experienced chest pain days to weeks before the onset of MI. This symptom of unstable angina is often disregarded by the patients because it is often a mild chest pain or heartburn of short duration. If we can treat all of those unstable angina patients, we can prevent them from suffering MI and we can reduce the number of MI patients into half. This effect can be translated into the medical cost reduction of 70,000,000,000 yen per year. All we have to do to achieve this aim is to make those unstable angina patients go to hospital and to diagnose and treat them properly. In order to make them go to hospital, “STOP MI campaign” is now under preparation by The Japanese Circulation Society. Although it may take a long time to eliminate the occurrence of MI from this world, we can and we should make it half immediately.
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U. Thadani
OU Medical Center and VA Medical Center, Cardiovascular Section, Oklahoma City, Oklahoma, USA

Currently many treatment options, including medicines, and revascularization procedures are available to treat patients with stable angina pectoris. All patients with angina pectoris due to underlying CAD should be treated with a low dose aspirin and a high dose, potent statin, if tolerated, to reduce the occurrence of adverse clinical outcomes (sudden ischemic death, myocardial infarction, unstable angina). In addition an initial trial of antianginal drugs for the relief of angina is indicated as there is no evidence that revascularization is superior to medical therapy. The initial choice of a drug class or combination therapy can be made by taking into consideration patient’s baseline heart rate, blood pressure, and left ventricular (LV) function and any comorbidities. Because none of the antianginal drugs have been shown to improve survival, and if there are no issues with heart rate or blood pressure, or LV function, one can use either a beta-blocker (BB) or a long acting nitrate or a calcium channel blocker (CCB) or ranolazine as the first step, in addition to sublingual nitroglycerin as initial therapy. If the clinical response is inadequate, one can either substitute or add another class of drug to better control symptoms. When the LV systolic function is impaired an initial choice would be a BB, and nitrates rather than a CCB. Patients with low blood pressure and or low heart rates are good candidates for ranolazine or trimetazidine as these agents do not have any significant effects on heart rate or blood pressure or LV function. Hypertensive patients with angina need a better control of blood pressure and use of a beta-blocker or a CCB or the combination of two. Patients with significant COPD or asthma, should be treated with a CCB or a nitrate or ranolazine or ivabradine or trimetazidine and not a BB. Triple therapy may not always be more effective than dual antianginal treatment. Patients who do not respond to medical treatment need to be considered for coronary artery revascularization.
Antiplatelet therapy is critical for patients with acute coronary syndromes, those undergoing coronary stenting, and especially for patients with both indications. Aspirin continues to be the backbone of antiplatelet strategies in cardiovascular secondary prevention. The concept of dual antiplatelet therapy – that is, aspirin plus an adenosine diphosphate receptor antagonist – has been a major advance in secondary prevention. Specifically, dual antiplatelet therapy is indicated for a year after an acute coronary syndrome. The most recent data support use of dual antiplatelet therapy even beyond a year in high risk patients with a history of prior myocardial infarction, assuming that they are at low bleeding risk. In patients without acute coronary syndromes who have received stents, the optimal duration of dual antiplatelet therapy remains a controversial point. Studies are ongoing to determine if second generation drug eluting stents may require a shorter mandated duration of dual antiplatelet therapy. Beyond the controversies of duration of dual antiplatelet therapy, physicians remain uncertain about which patients benefit most from intensification of the antiplatelet regimen, either with oral or intravenous agents. The major challenge remains balancing reductions in ischemic events with increases in bleeding. No antiplatelet agent has yet succeeded in uncoupling anti-thrombotic benefit from bleeding hazards. Perhaps no area is as challenging in this regard as the management of patients with acute coronary syndromes and atrial fibrillation. Major randomized clinical trials are underway to determine the best combinations and durations of antiplatelet and anticoagulant therapies in this cohort of patients.
THE ROLE OF HEMODYNAMIC SUPPORT IN THE MANAGEMENT OF AMI WITH SHOCK

G.W. Vetrovec
VCU Medical Center Richmond, Virginia USA

Outcomes for Acute Myocardial Infarction (AMI) have improved significantly with acute Percutaneous Coronary Intervention (PCI). However, the incidence of associated cardiogenic shock (CS) has increased and remains a major cause of death. Factors associated with improved outcomes in AMI/CS include urgent PCI and complete revascularization. Given the continued risk of AMI/CS despite complete and rapid revascularization, an additional opportunity is effective hemodynamic support to provide safety during revascularization, to support coronary and systemic perfusion while limiting myocardial oxygen consumption with left ventricular (LV) unloading. IV inotropes, increase blood pressure, but they also increase afterload leading to higher myocardial wall stress and oxygen consumption. Mechanical support devices include the Intra Aortic Balloon Pump (IABP) not a true pump that minimally increases cardiac output. IABP use has failed to show improved survival in AMI/CS. Another device, Extra Corporeal Membrane Oxygenation (ECMO) effectively improves oxygenation when needed but does not unload the Left Ventricle (LV) and thus does not reduce myocardial oxygen requirements. The Impella temporary pump system provides optimal mechanical support in AMI/CS. The Impella Hemodynamic pump effectively increases mean arterial pressure, cardiac output and coronary flow while reducing LV filling pressures due to ventricular unloading. Impella support stabilizes cardiac hemodynamics while reducing myocardial oxygen consumption. The clinical experience of Impella 2.5 in AMI/CS in the USPella Registry demonstrated that early (before PCI) insertion of the Impella in the setting of AMI/CS was associated with improved survival. The pre PCI implant group had a hospital survival of 65.1% compared to 40.7% survival for the late support (post PCI) patients (p=0.003).

Summary: In AMI/CS, appropriately selected mechanical support using Impella provides effective hemodynamic stability with LV unloading potentially limiting myocardial damage, while providing safety and time for optimal revascularization.
DELIRIUM IN THE INTENSIVE CARE UNIT: MORE THAN A NUISANCE

G.W. Barsness
Mayo Clinic, Rochester, MN, USA

Background: Regardless of the underlying condition and comorbidities, along with pain and agitation, delirium is a common condition with major impact on the care and outcome of patients requiring intensive care unit (ICU) hospitalization. Sixty to eighty percent of ICU patients will develop delirium during their hospitalization with resultant complication and prolongation of ICU stay. Indeed, the more severe and prolonged the delirium, the more potential impact on outcome, including increased cost, morbidity and mortality.

Results: A primary step in delirium management involves awareness and recognition, an essential, although often neglected, component of ICU care. Key features of delirium include fluctuating disturbances in consciousness and cognition that develop over a short period of time. Several tools are available to assist in delirium assessment, including Confusion Assessment Method (CAM-ICU) and Intensive Care Delirium Screening Checklist (ICDSC). Once recognized, delirium management strategies include addressing reversible contributing conditions (toxic, respiratory, infectious or metabolic), along with delirium-specific non-pharmacologic and pharmacologic interventions. Recent studies have suggested the additional benefit of aggressive early mobilization protocols in reducing the incidence and lessening the duration of ICU delirium and associated adverse outcome.

Conclusions: Delirium is a frequent and costly condition in hospitalized patients that not only complicates and prolongs ICU care, but has a major adverse impact on short and long-term outcome. Growing awareness of the importance of early recognition and management of delirium necessitates a routine and systematic care process that integrates established assessment tools and management strategies to optimize ICU patient outcome.
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UPDATE ON CONTRAST REMOVAL FROM CORONARY SINUS DURING CORONARY ANGIOGRAPHY OR INTERVENTION FOR PREVENTION OF CONTRAST INDUCED NEPHROPATHY

M.R. Movahed
CareMore, Tucson, Arizona, University of Arizona College of Medicine, USA

Contrast usage during coronary angiography or intervention in patients with renal disease is associated with substantial risk of contrast induced nephropathy that can lead to higher mortality, longer hospital stay and substantial cost. It is well known that the amount of contrast used during coronary intervention correlates with contrast-induced nephropathy. Coronary veins drain into the coronary sinus before entering the right atrium. Anatomically, it should be possible to remove most of the contrast from coronary sinus during coronary intervention by using a catheter that can remove blood mixed with contrast from the coronary sinus during contrast injection. We were first to report that we could successfully remove approximately 50% of contrast from coronary sinus in a swine model using commercially available coronary sinus catheters during coronary angiography. Earlier human studies confirmed safety of contrast removal from coronary sinus. In study of contrast removal in 4 patients, authors were able to remove contrast media effectively (44%+/-8%) as assessed by fluoroscopy and dilution of blood. Many devices are in development for this purpose. In a recent human study, contrast removal from coronary sinus was associated with better renal function post contrast exposure and appears to be a promising method for prevention of contrast induced nephropathy in the near future.
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TRANSULNAR INTERVENTIONS
E. Kaluski, M. Singh, S. Sattur
Guthrie Health System, PA, USA

The use of transradial access for diagnostic and therapeutic interventions has dramatically increased in the recent years and has become the preferred approach for coronary angiography and intervention. The ulnar artery is similar in diameter however is somewhat deeper than the radial artery and adjacent to the ulnar nerve. Although transulnar approach can serve as an alternative strategy it is infrequently taught and rarely (<1%) used. We performed a detailed search and identified all key studies in which the transulnar approach was used (n=3,512). The procedural success of transulnar approach (68-96%) is slightly inferior to the transradial approach in certain centers. The equipment and medications used, safety, efficacy and type of complications observed are similar to transradial interventions. The patient-centered, astute and versatile and interventional cardiologist should master transulnar interventions to better serve is patients. Dedication education and tools (like ultrasound) may further enhance the success rate and popularity of the transulnar approach.
Chronic kidney disease (CKD) is associated with an elevated risk for developing cardiovascular disease, and ischemic heart disease (IHD) is a major reason for this increased risk. Reasons for a high prevalence of ischemic heart disease include traditional risk factors but also involve CKD related factors including increase in inflammatory mediators and vascular calcification that is associated with secondary hyperparathyroidism of renal origin. Data on therapeutic interventions to minimize cardiovascular events related to IHD in patients with CKD is lacking, primarily due to exclusion of patients with CKD from major cardiovascular trials. ISCHEMIA-CKD is the first major cardiovascular trial specifically examining the optimal management of stable IHD in patients with advanced CKD. Data from this and hopefully more trials will help in guiding clinicians who care for this high risk population in the management of IHD to improve clinical outcomes.
Assays for cardiac troponin have become increasingly sensitive, and are now able to detect very low concentrations of circulating cardiac troponin in a substantial proportion of stable patients who are not suspected of having myocardial infarction. These low levels of cardiac troponin are frequently well within the range of what is considered normal and are associated with a significant increase in the risk of major cardiovascular events, including heart failure, myocardial infarction, and death in patients with and without established cardiovascular disease. The strength and consistency of these associations, and the fact that adding cardiac troponin to traditional risk factors improves the accuracy of existing cardiovascular risk prediction algorithms, raises the possibility of using cardiac troponin for therapeutic decision-making in ambulatory populations. However, a specific intervention that can mitigate troponin-associated risk has not been identified. Thus, the therapeutic implications of troponin elevations for individual patients remain unclear. Ongoing research seeks to better understand the underlying cause of troponin release in these patients and to identify therapeutic interventions that can effectively mitigate troponin-associated cardiovascular risk. The development of high-sensitivity assays for cardiac troponin offers the opportunity to gain insight into the causes and consequences of chronic myocardial injury, and may, in the future, help guide therapy directed at improving the outcomes of ambulatory patients at high risk for cardiovascular events.
Cardiopulmonary exercise testing (CPX) is a diagnostic tool used to detect serial changes in exercise capacity, and it is of particular benefit for patients with chronic heart failure to assess peak oxygen uptake (peak VO2) and minute ventilation/carbon dioxide production (VE/VCO2) slope. In addition, it provides an integrative approach to assessing cardiac function, gas exchange, and muscular physiology. We have shown the impact of predictor of poor prognosis on exercise oscillatory ventilation during CPX, heart rate recovery, and combination peak VO2 and late gadolinium enhancement on cardiovascular magnetic resonance in patients with dilated cardiomyopathy (DCM).

On the other hand, pulmonary hypertension (PH) is defined by pulmonary arterial pressure (PAP); it is characterized by right heart failure in its advantage stages. In the previous study, in order to reach the predefined treatment goals, combination treatment, including endothelin receptor antagonists (ERAs) and phosphodiesterase-5 (PDE5) inhibitor, eventually became necessary in almost half of the patients. Thus, the use of combination treatment may yield acceptable results in the majority of patients with PAH. Peak VO2 has been shown to be predictive of survival in PH, with 3 studies providing cutoff values of 10.4 ml/min/kg, 11.5 ml/min/kg, and 13.2 ml/min/kg below which mortality is increased. Current guideline shows peak VO2 has been suggested as a goal of therapy, with >15 ml/min/kg indicating better prognosis. According to this guideline, our treatment strategy performed sequential combination therapy in PAH. These results showed at baseline and after 3, 6 and 12 months after PAH-specific treatment, mean peak VO2 was 11.8, 13.2, 13.8, and 13.2 mL/kg/min and mean VE/VCO2 slope was 58, 49, 45 and 48 mm Hg, respectively. These investigations indicate variables obtained from CPX: (1) reflect varying degrees of PH severity; (2) positively respond to several pharmacologic and surgical interventions; and (3) may provide prognostic value.
MECHANISMS CONTRIBUTING TO HEART FAILURE DEVELOPMENT AND PROGRESSION

CARDIOVASCULAR EFFECTS OF CARFILZOMIB, A NEW PROTEASOME INHIBITOR, ON CORONARY ARTERY RESISTANCE, VASCULAR TONE AND VASCULAR REACTIVITY

T.M. Scarabelli
The University of Alabama at Birmingham, Birmingham, AL, USA

Background: Carfilzomib (CFZ) is a proteasome inhibitor which was recently approved in the United States as a single agent for the treatment of patients with relapsed and refractory Multiple Myeloma (MM). Chemically it is a tetrapeptide epoxyketone and an analog of epoxomicin. A recent cross-trial analysis examining the safety profile of single agent carfilzomib in patients with relapsed and refractory MM reported an incidence of aggregated cardiac-failure events (including congestive heart failure, pulmonary edema, and decreased ejection fraction) of 7.2%. Of note, the use of CFZ is not contraindicated in patients with recent myocardial infarction/unstable angina who had been excluded in phase II safety trials.

Aim of study: To investigate whether CFZ can exert \textit{in vitro} effects on vascular tone and reactivity, as well as endothelial function.

Methods and Results: CFZ-mediated cardiovascular toxicity and potential pathophysiological mechanisms were assessed in an isolated experimental model of rabbit thoracic aortic-strips. In a first set of experiments, we evaluated the effect of single injections of CFZ on the basal tone of isolated aortic strips (n= 6) placed in 10 ml organ bath at 37°C containing Krebs-Henseleit solution. Vasoconstriction, as documented by an overall increase in tension of 0.5 g, was observed with increasing concentrations of CFZ (from 1 \times 10^{-9} to 10^{-7} \text{mol/L}; p:0.041). In a second set of experiments, the effect of three different spasmogenic agents [potassium chloride (KCl) (n= 6), noradrenaline (NA) (n= 6), and angiotensin II (A) (n= 6)] on naive aortic strips (group 1) was compared to that on aortic strips pretreated for 60 minutes with CFZ at a concentration of 15 nmol/L (group 2). Pretreatment with CFZ resulted in amplified vasoconstriction (2.4±0.4 g vs 2.1±0.3 g for KCl administration; 2.5±0.3 g vs 2.0±0.2 g for NA; 2.6±0.2 g vs 2.0±0.2 g for A; all p<0.005) and impaired vasodilation following administration of nitroglycerin (NTG) on the plateau of contraction induced by each spasmogenic agent (100% vs 82% for KCl; 100% vs 67% for NA and 100% vs 51% for A; all p<0.05). In a third and final set of experiments, aortic strips treated with CFZ exhibited impaired relaxation, as compared to naive strips (100% versus 40% in tension reduction; p:0.028), following administration of acetylcholine (Ach), an endothelium-dependent vasodilating agent, on the plateau of NA contraction.

Conclusions: Our findings showed that CFZ exerts significant \textit{in vitro} effects on vascular tone and reactivity. CFZ increased the resting vasoconstricting tone and amplified the spasmogenic effect of different agents. Moreover, preincubation with CFZ decreased the anti-spasmogenic activity of NTG and reduced by over 50% the vasodilating effect of Ach, suggesting that CFZ can impair vasodilation by inducing endothelial dysfunction. Further studies are therefore warranted to better elucidate the vascular effects of CFZ, above all in the coronary vasculature, in order to establish its clinical safety in patients with known CAD and prior history of coronary spasm.
Concurrent worldwide increases in the aging population and prevalence of heart failure (HF) are accompanied by a parallel increase in the elderly (age ≥ 65 years) with two leading causes of HF, hypertension (HTN) and myocardial infarction (MI). Aging results in progressive cardiovascular remodeling with an “aging phenotype” that negatively impacts disease expression and response to therapy. Aging-related changes contribute to adverse cardiac remodeling with HF and preserved ejection fraction (HFpEF) and result in increased risk for HTN which exacerbates HFpEF, and MI which leads to HF with reduced EF (HFrEF). The remodeling involves changes in structure, physiological and pathophysiological pathways and responses to stress/injury. Optimal healing is critical for a favorable outcome and defective post-MI healing with aging contributes to adverse remodeling with poor outcome. The cardiac extracellular matrix (ECM) is critical for maintaining cardiac shape/function and progression of HF due to MI and HTN involves adverse ECM remodeling with disruption of the ECM network and dysregulation of ECM homeostasis and metabolism resulting in shape deformation and dysfunction. While better post-MI therapies improve survival, therapy for optimizing post-MI healing is needed to further improve outcome. While early reperfusion reduces MI size, delayed reperfusion results in reperfusion damage, impaired healing and adverse remodeling and progression to HF in the elderly. Therapy for the young may not be optimal for the old. Several recommended post-MI therapies can impact early and late phases of healing in positive or negative directions. Preclinical studies suggest that pathways during early and late phases can be targeted for optimizing post-infarct healing and the march to HF. Progressive remodeling and progression to HFpEF or HFrEF are persistent problems in older patients and have important therapeutic implications. Studies suggest that in the elderly, novel pathways can be targeted for optimizing therapy in HFrEF post-MI and HFpEF post-HTN.
DOXORUBICIN PROVOKES MALADAPTIVE AUTOPHAGY AND NECROTIC CELL DEATH OF CARDIAC MYOCYTES BY DISRUPTING MITOCHONDRIAL RESPIRATION CHAIN COMPLEX IV

R. Dhingra, H. Gang, V. Margulets, L.A. Kirshenbaum
Institute of Cardiovascular Sciences, St. Boniface Hospital Albrechtsen Research Centre, Department of Physiology, Faculty of Health Sciences, College of Medicine, University of Manitoba, Winnipeg, Manitoba, Canada

Doxorubicin is known for its cardiotoxic effects and inducing cardiac failure, however, the underlying mechanisms remain cryptic. Earlier we established the inducible death protein, Bcl-2-like Nineteen-Kilodalton-Interacting-Protein 3 (Bnip3) to be crucial for disrupting mitochondrial function and inducing cell death of cardiac myocytes. Whether Bnip3 underlies cardiotoxic effects of doxorubicin toxicity is unknown. Herein we demonstrate a novel signaling pathway that functionally links activation and preferential mitochondrial targeting of Bnip3 to the cardiotoxic properties of doxorubicin. Perturbations to mitochondria were observed in cardiac myocytes treated with doxorubicin. Impaired mitochondrial function was accompanied by an accumulated increase in autophagosomes and necrosis demonstrated by increase release of LDH, cTnT and loss of nuclear High Mobility Group Protein 1 (HMGB1) immunoreactivity. Notably, mitochondrial associated Bnip3 in cells treated with doxorubicin formed strong protein interactions with Cytochrome c oxidase subunit1 (COX1) of respiratory chain. This displaced uncoupling protein 3 (UCP3) from COX1 resulting in increased ROS production, decline in maximal and reserved respiration capacity and cell viability. Interestingly, inhibition of autophagy with 3-methyl adenine (3-MA), or Atg7 knock-down suppressed doxorubicin induced necrotic cell death. Importantly genetic inhibition of Bnip3 preserved UCP3-COX complexes, mitochondrial respiratory integrity and abrogated doxorubicin induced necrotic cell death. Moreover, Bnip3-/- mice were resistant to doxorubicin cardiotoxicity displaying normal mitochondrial morphology, cardiac function and survival rates comparable to wild type vehicle treated litter mates. In this report, we demonstrate that doxorubicin provokes maladaptive autophagy resulting in necrotic cell death of ventricular myocytes by a mechanism that involves mitochondria dysfunction induced by the Bcl-2 death protein Bnip3.
MECHANISMS CONTRIBUTING TO HEART FAILURE DEVELOPMENT AND PROGRESSION

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DIABETES AND HEART FAILURE: AN INFLAMMATORY PERSPECTIVE

M. White
Montreal Heart Institute and Universite de Montreal, Montreal, Quebec, Canada

Diabetes is associated with an increased risk for developing heart failure (HF). Similarly HF is associated with an increase prevalence of diabetes which intensifies with the disease severity. HF is characterized by a broad increase in pro-inflammatory markers. In fact markers for neuro-humoral activation, extra-cellular matrix turnover, pro-inflammation such as hs CRP, interleukins, osteopontin, ST2, galactine-3, and pro-oxidative markers such as TBARS are markedly elevated even in ambulatory patients with reduced as well as in those with preserved ejection fraction. Scientific evidences have shown that a pro-inflammatory milieu at the vascular, myocardial and systemic levels contributes to the physiopathology of HF and diabetes. At the vascular level, inflammation contributes to coronary atherosclerosis, endothelial and micro-vascular dysfunction. Local myocardial inflammation likely play a significant role on cardiac remodeling and fibrosis, early pathological processes in heart failure with preserved EF. Systemically, inflammation impaired oxygenation at the pulmonary and peripheral levels and as such contribute to symptoms and disease progression in HF. In addition to the increase in various markers it appears that the neutrophil, neutrophil-derived microparticles, and neutrophils extra-cellular traps (NETs) are likely to play a significant role in this disease condition. Further investigations are ongoing in order to better understand the behavior and role of these markers in HF and diabetes.
Heart failure is a leading cause of morbidity and mortality worldwide. Clinical studies have shown that heart failure is associated with insulin resistance, which affects myocardial energy supply and blood perfusion. As one of the important targets of insulin action, the heart has been reported to have abnormal energy metabolism and develop myocardial insulin resistance independent of systemic insulin resistance during ischemic heart failure. Given the importance of myocardial insulin signaling in the protection against ischemia-induced myocardial injury and subsequent cardiac dysfunction and remodeling, myocardial insulin resistance and its association with post-ischemic heart failure are inadequately investigated. Our previous study has shown that myocardial insulin resistance occurs before systemic insulin resistance and contributes to the development of post-ischemic heart failure. The impaired myocardial insulin action is partly mediated by overproduction of pro-inflammatory cytokine TNF-alpha induced by myocardial infarction. Recently we found that atrial natriuretic peptide (ANP), a cardiogenic hormone which increased significantly during heart failure, suppressed systemic insulin sensitivity. On the other hand, post-myocardial ischemia and resultant impaired myocardial insulin signaling induced systemic insulin resistance via increasing ANP production in heart failure. These findings suggest that myocardial insulin signaling plays an important role in the protection of ischemic heart against heart failure.
HEMODYNAMIC ADAPTATION TO EXERCISE IN HYPERTROPHIC CARDIOMYOPATHY
Q. Ciampi, C. Viola, B. Villari
Fatebenefratelli Hospital, Bevenento, Italy

Exercise stress test is a useful tool for symptom evaluation in patients with hypertrophic cardiomyopathy (HCM). Current guidelines for HCM assign exercise testing a class IIa recommendation for the assessment of functional capacity and response to therapy. Latent obstruction in HCM is an important pathophysiologic entity and may cause heart failure symptoms. The recent ESC guidelines assign class of recommendation IB to exercise stress echocardiography in symptomatic patients without a resting LVOT to detect provokable exercise-induced LVOT obstruction and mitral regurgitation. Myocardial ischemia has been clearly demonstrated in HCM patients, and it is a major risk factor for sudden cardiac death. Coronary microvascular dysfunction, caused by different mechanisms such as structural abnormalities of small vessels, inadequate capillary density, fibrosis, myocyte disarray, and increased left ventricular end-diastolic pressure may provoke diffuse impairment of coronary flow reserve, thus representing a substrate for recurrent ischemia. In the expert consensus of the European Association of Cardiovascular Imaging, the assessment of myocardial ischemia was an important topic in HCM but the best way for its evaluation remains unclear. Increased at-rest flow velocity and decreased vasodilator peak flow velocity concur to blunt CFVR in HCM, mirroring coronary microvascular dysfunction unrelated to presence and extent of left ventricular hypertrophy. Thus, CFVR assessment by transthoracic Doppler represents an attractive additional biomarker for identifying patients with HCM at increased risk. Recently, our study demonstrated that SE imaging ischemia-related criteria (CFVR reduction and NWMA) were the best predictors for risk stratification purposes: the authors suggested a multifactorial approach to SE, considering clinical signs and the presence of ischemic-related signs, in addition to the standard, recommended evaluation of the stress-induced LVOT gradient.
MECHANISMS CONTRIBUTING TO HEART FAILURE DEVELOPMENT AND PROGRESSION

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PREVENTION OF LV DIASTOLIC DYSFUNCTION AND ATRIOMEGALY IN THE AGING POPULATION

H.K. Reddy¹, R. Komatireddy²
1. Heart and Vascular Institute of Southern Missouri, USA
2. University of California, San Diego, CA, USA

Prevalence of diastolic congestive heart failure (DCHF) and atriomegaly have become increasingly common with aging US population. Above the age of 65, LV diastolic dysfunction accounts for 50% of patients with heart failure. Since, no specific treatment is available for DCHF, there has been growing morbidity and mortality in this population. Pathophysiology of DCHF is poorly understood. Excess and altered interstitial collagen have been implicated in some of these patients. Associated risk factors for DCHF include aging, genetic predisposition, longstanding hypertension, obesity, inactivity, increased serum insulin and creatinine levels. It has been reported that increased peripheral vascular stiffening might contribute to the pathophysiology of DCHF. In the elderly population with DCHF, the common echocardiographic findings include, LVDD, atriomegaly and pulmonary hypertension. Prevention of LVDD and DCHF may be possible with early interventional steps to control obesity-deconditioning, hypertension, diabetes, inactivity and sleep apnea. Management of patients with DCHF is often complicated and unsatisfactory. Symptomatic therapy with diuretics, rate control with betablockers and calcium channel blockers have been recommended. Long term treatment with ACE inhibitors and/or angiotensin receptor blockers and aldosterone antagonists appear to have some modest benefit in these patients.
MECHANISMS CONTRIBUTING TO HEART FAILURE DEVELOPMENT AND PROGRESSION

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CAN GDF-15 BE USED AS A BIOMARKER IN DILATED CARDIOMYOPATHY

N. Nair
Texas Tech HSC, Lubbock, TX, USA

Growth and Differentiation Factor-15 (GDF-15) has been found to play an important role in fibrosis, inflammation and ventricular remodeling. The role of GDF-15 in regulation of cardiac remodeling in idiopathic dilated cardiomyopathy (DCM) is less well-defined. A review of existing literature on the utility of GDF-15 in diagnosis and prognosis is presented here. GDF-15 is upregulated along with brain natriuretic peptide (BNP) in the setting of increasing wall stress. GDF-15 also correlates well with other biomarkers such as soluble ST2 in this sub population. A moderate association is also noted with functional capacity as well as echocardiographic indices (left ventricular ejection fraction and Left ventricular internal dimension). Other interesting associations of GDF-15 included varying degrees of association with different serum matrix metalloproteinases (TIMP, MMP2, MMP3, and MMP9). GDF-15 is elevated in many disease conditions including sepsis. Hence it is unlikely to be useful as a solo biomarker in specific diagnosis. GDF-15 could prove useful when used along with BNP or as part of a panel of biomarkers.
MECHANISMS CONTRIBUTING TO HEART FAILURE DEVELOPMENT AND PROGRESSION

CLINICAL UNDERSTANDING OF INFLAMMATION, INDUCING THROMBOGENESIS, RESPIRATORY IMPAIRMENT, MYOCARDIAL CELL APOPTOSIS AND REMODELLING, ANAEMIA AND RENAL DYSFUNCTION IN PATIENTS WITH PULMONARY AND COINCIDENT CARDIAC DYSPNEA

I. Angomachalelis, S. Tryfon, G. Kyriazis, N. Angomachalelis
Aristotle University of Thessaloniki, School of Medicine, Department of Clinical Pulmonology, Heart-Lung Section, "G. Papanicolaou" General Hospital, Thessaloniki, Macedonia, Greece

Purpose: The study aims to investigate understanding of clinical pathophysiology of primary inflammation in pulmonary and coincident cardiovascular dyspnea patients (Pts).


Results: Resulted abnormal values of serum Biomarkers, echocardiographic and Doppler indices, PFTs, ABGs and Blood tests presented significant correlations as follows: CRP with A) D-dimers B) PCO₂ C) NT-ProBNP D) EF E) LVID. Furthermore, A) D-dimers with A1) RVSP, correlated to LAD and LVID, A2) RVSP correlated with P (A-a)O₂ and –FVC and –TLC, A3) PCO₂. B) PCO₂ with NT-ProBNP, FEV₁ and Na, correlated with left ventricular E-Wave. C) NT-ProBNP with EF, PCO₂ and C1) Tr-I, C2) ASH, C3) Hb, C4) Urea and Creatinine, C5) Pleural NT-ProBNP. However, C1) Tr-I correlated with left ventricular E/A ratio, MMP-2, EPO, - FVC and –TLC, -Na and Creatinine. C2) ASH with EF, Urea and Creatinine. C3) Hb with Pleural NT-ProBNP, TLC and PCT, correlated with MMP-2, Tr-I, EPO and PCO₂. D) EF with FVC and Tr-I. E) LVID with LAD, RVSP, RVID, Creatinine and Urea.

Conclusions: 1. Reported abnormal results and significant correlations arise originally from an inflammatory process, expressed by CRP levels, introducing various pathways of clinical pathophysiology, correlated with D-dimers, PCO₂, NT-ProBNP, EF and LVID. 2. All indices lead either to thrombogenesis and/or pulmonary, myocardial and renal dysfunction, followed by disarrangement of haemopoiesis and infective complications. 3. Inflammatory Thrombogenesis also seems developing on the grounds of cardiovascular apoptosis and remodelling. 4. Molecular and interstitial disarray phenomena, combined with pulmonary and renal impairment, further worsen haemopoietic disorders and late infection, all possibly creating a dynamic early-late inflammation-infection pathophysiology, carrying on Thrombogenesis, pulmonary and cardio-renal dyspnea.
RISK OF INCIDENT CARDIOVASCULAR DISEASE ACCORDING TO THE METABOLIC HEALTH AND OBESITY STATES


1 Garcia-Orcoyen Hospital, Navarra Health Service - Osasunbidea. Spain
3 University of Navarra Clinic, Pamplona. Spain
4 IdiSNA - Health Research Institute of Navarra
5 University of Navarra, Pamplona. Spain
6 Centre of Biomedical Research in Pathophysiology of Obesity and Nutrition (CIBERObn), Carlos III, Madrid. Spain

Objectives: To assess the risk of cardiovascular disease (CVD) according to the metabolic health and obesity states. The TyG index and the ATP-III components of the metabolic syndrome were used to define these states.

Background: Mortality from CVD has decreased in recent decades, attributed to reductions in cholesterol levels, blood pressure or smoking prevalence. However, these decreases were offset by rises in obesity and diabetes. Some obese individuals may be at low risk of metabolic related complications, while normal-weight individuals are not "healthy".

Methods and Results: A total of 5003 patients free of CVD participants were followed up during 9.1 ±4.3 years. A Cox proportional HR was used to estimate the risk of incident CVD across the metabolic health and obesity states. The HR for metabolically unhealthy non-obese and obese was 1.49 (95% CI: 1.08-2.07) and 1.89 (95% CI: 1.24-2.89), respectively, according to the TyG index criteria for metabolic health. When using the ATP-III criteria for classification, the HR was 1.38 (95% CI: 1.07-1.77) and 1.40 (95% CI: 0.94-2.10), respectively.

Conclusions: Metabolically unhealthy individuals exhibited a greater risk of CVD than metabolically healthy obese and non-obese. The TyG index may be a useful candidate marker to define the metabolic health status.

Table 1. Risk of incident CVD according to the metabolic health and obesity states

<table>
<thead>
<tr>
<th>Metabolic health and obesity states based on TyG indexa</th>
<th>MHNO</th>
<th>MHO</th>
<th>MUNO</th>
<th>MUO</th>
<th>p for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>3289</td>
<td>673</td>
<td>632</td>
<td>409</td>
<td></td>
</tr>
<tr>
<td>Number of incident cases of CVD</td>
<td>241</td>
<td>50</td>
<td>102</td>
<td>71</td>
<td></td>
</tr>
<tr>
<td>Incidence (%)</td>
<td>7.32</td>
<td>7.43</td>
<td>16.14</td>
<td>17.36</td>
<td></td>
</tr>
<tr>
<td>Person-years</td>
<td>30809.9</td>
<td>5669.9</td>
<td>5533.7</td>
<td>3329.9</td>
<td></td>
</tr>
<tr>
<td>Incidence/1000 person-years</td>
<td>7.82</td>
<td>8.81</td>
<td>18.43</td>
<td>21.32</td>
<td></td>
</tr>
<tr>
<td>Multivariate adjusted model b</td>
<td>1 (ref)</td>
<td>0.89</td>
<td>(0.59-1.33)</td>
<td>1.49</td>
<td>(1.08-2.07)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Metabolic health and obesity states based on ATP-III criteriaa</th>
<th>MHNO</th>
<th>MHO</th>
<th>MUNO</th>
<th>MUO</th>
<th>p for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>3189</td>
<td>626</td>
<td>732</td>
<td>456</td>
<td></td>
</tr>
<tr>
<td>Number of incident cases of CVD b</td>
<td>222</td>
<td>53</td>
<td>121</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td>Incidence (%)</td>
<td>6.96</td>
<td>8.47</td>
<td>16.53</td>
<td>14.91</td>
<td></td>
</tr>
<tr>
<td>Person-years</td>
<td>30010.2</td>
<td>5385.1</td>
<td>6333.4</td>
<td>3614.8</td>
<td></td>
</tr>
<tr>
<td>Incidence/1000 person-years b</td>
<td>7.39</td>
<td>9.84</td>
<td>19.10</td>
<td>18.81</td>
<td></td>
</tr>
<tr>
<td>Multivariate adjusted model b</td>
<td>1 (ref)</td>
<td>1.07</td>
<td>(0.72-1.61)</td>
<td>1.38</td>
<td>(1.07-1.77)</td>
</tr>
</tbody>
</table>

a MHNO: metabolically healthy non-obese, MHO: metabolically healthy obese, MUNO: metabolically unhealthy non-obese, MUO: metabolically unhealthy obese. b Adjusted for age, sex, BMI, cigarette smoking, daily alcohol intake, lifestyle pattern, hypertension, type 2 diabetes, antiaggregation therapy, HDL-C, LDL-C and TG.
Background: Atherosclerosis is a major cause of cardiovascular disease. Activated T cells and dendritic cells (DCs) are co-localized in the atherosclerotic plaques in association with plaque rupture. Oxidized forms of low-density lipoprotein (oxLDL) can promote inflammation and are accumulated in foam cells. Statin, HMG-CoA reductase inhibitor has anti-inflammatory properties in addition to lower LDL levels. Objectives: We study the effects of statins (atorvastatin and simvastatin) on human DC maturation and T cell proliferation.

Methods and Results: Human peripheral blood monocytes were differentiated to DCs and stimulated with oxLDL. Naive T cells were co-cultured with pretreated DCs. The effects of statin were tested on DCs and T cells. Atorvastatin and simvastatin suppressed the DC maturation showing lower expression of CD80, CD83 and CD86, and limited their production of TNF-alpha, IL-1beta and IL-6. Statin-treated DCs inhibited Th1 and/or Th17 polarization by down-regulation of transcriptional factors T-bet, ROR gamma t expression, while induced T regulatory cells with IL-10 production. The oxLDL-induced phosphorylation of Akt, and miRNA let7c were also repressed. Experiments on T cells derived from carotid atherosclerotic plaques showed the similar results.

Conclusions: We demonstrate that statins repress human dendritic cell maturation induced by oxLDL and limit the consequent T cell activation. Further, statin promotes the anti-inflammatory cell response and induction of T regulatory cells. Our finding shows a novel beneficial effect of statins, especially associated with chronic inflammation and plaque rupture-prone lesions.
RENAL ARTERY DENERVATION IN KAZAKHSTAN: IMPACT OF ETHNICITY AND AGE

A.A. Mussayev 1,2, M.A. Aripov 1, S.A. Alimbayev 1, M.A. Temirkulov 1, E.B. Otarbaev 1, A.Y. Goncharov 1, G.K. Zhusupova 2, Y.V. Pya 1

1 National Research Cardiac Surgery Center, Astana, Kazakhstan
2 Astana Medical University, Astana, Kazakhstan

Objective: To explore the impact of age and ethnicity on blood pressure (BP) reduction after renal artery denervation.

Background: The prevalence of hypertension in Kazakhstan is up to 70% in adults aged 50-75 years and the majority of patients are not adequately controlled. Treatment with renal artery denervation could represent a useful therapeutic option for this subset of patients and has not been previously studied in Kazakh patients.

Methods and Results: We performed renal artery denervation on 63 patients with resistant hypertension with Symplicity catheter (Medtronic, Inc.). Ambulatory and office blood pressure was measured at baseline and month 12 and post-hoc subgroup analyses were performed based on age and ethnicity. There was a decrease of 36±22 mmHg in systolic office BP and a decrease in 22±14 mmHg in diastolic office BP from baseline to 12 months in all patients (N=63, p<0.001). Similar reductions in BP were observed from baseline to 12 months for every age group (<45 years, 45-59 years, 60+) and also for ethnic Kazakh and European subgroups (Table).

Conclusions: Our observations from this Kazakhstani cohort are consistent with other non-controlled studies and this treatment modality deserves further research.

Table. Office blood pressure changes after renal artery denervation impact of age and ethnicity

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Office systolic blood pressure mean (SD)</th>
<th>Office diastolic blood pressure mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline 12 months</td>
<td>Baseline 12 months</td>
</tr>
<tr>
<td>Overall (n=63)</td>
<td>186 (21) 150 (13)</td>
<td>111 (14) 87 (8)</td>
</tr>
<tr>
<td>Age &lt;45 (n=11)</td>
<td>185 (20) 155 (14)</td>
<td>111 (16) 88 (7)</td>
</tr>
<tr>
<td>Age 45-59 (n=30)</td>
<td>187 (23) 151 (13)</td>
<td>111 (14) 89 (9)</td>
</tr>
<tr>
<td>Age 60+ (n=17)</td>
<td>186 (18) 146 (10)</td>
<td>110 (13) 88 (8)</td>
</tr>
<tr>
<td>European (n=19)</td>
<td>184 (19) 151 (10)</td>
<td>108 (13) 88 (8)</td>
</tr>
<tr>
<td>Kazakh (n=39)</td>
<td>187 (21) 150 (14)</td>
<td>111 (14) 89 (8)</td>
</tr>
</tbody>
</table>
THE CARDIOVASCULAR PRESENTATIONS AND OUTCOMES OF DIABETIC PATIENTS ADMITTED TO THE HEART HOSPITAL OVER 2 DECADES: INSIGHT FROM A HIGH-INCOME DEVELOPING COUNTRY

A.A. El-Menyar1,2, J. Al Suwaidi3, H. Al-Thani4, H. AlBinali3, R. Singh3
1. Clinical Research, Hamad General Hospital, Doha, Qatar
2. Clinical Medicine, Weill Cornell Medical College, Doha, Qatar
3. Heart Hospital, Hamad Medical Corporation, Doha, Qatar
4. Vascular Surgery, Hamad General Hospital, Doha, Qatar

A retrospective analysis of a prospectively collected data was conducted (1991-2012) including all diabetic patients admitted to the Heart Hospital (HH) in Qatar.

Results: Out of the 48,803 cardiovascular diseases (CVD) admissions, 19500 patients were diabetic (40%). Among diabetics, ST-elevation myocardial infarction (STEMI) (47.5%) was the frequent presentation, followed by unstable angina (28%), non-STEMI (24%), congestive heart failure (CHF, 23%), dysrhythmia (8.9%), PAD (0.6%) and cerebrovascular accident (0.4%). STEMI occurred at an earlier age (55±11) compared with NSTEMI (59±11) and CHF (63±10). PCI increased significantly from 3% in 1991 to 26% in 2012. On admission, aspirin, beta-blockers (BB) and ACEI use increased from 59% to 92%, 10% to 71% and 30% to 56%, respectively. At discharge, the use of statins increased significantly, from 4% to 78% across the study period. A total of 1112 CVD patients died with an annual mortality rate of 1 in 10,000 people. The overall trend of DM-related mortality decreased over the time. Diabetic Asian patients died 9 years earlier than diabetic Arabs (52.7±8 vs.61.5±11). Multivariate regression analysis revealed that predictors of age –adjusted mortality in diabetics were lack of BB use (OR 4.35; 95% CI:0.20 – 0.27), lack of ACEI use (OR 3.58; 95% CI:0.23 –0.32), myocardial infarction (OR 3.20; 95% CI:2.77 – 3.68), lack of aspirin use (OR 2.56; 95% CI:0.34 –0.45), and CHF (OR 1.75; 95% CI:1.50 –2.04).

Conclusions: the admission rate of diabetic patients in the HH is increasing; however, the mortality rate is decreasing. STEMI is the most common CVD presentation in young diabetic patients. The lack of evidence-based CVD medications in diabetic patients is associated with a 4 times increase in the mortality in the HH. More efficient primary and secondary prevention strategies are required in diabetic patients.
CENTRAL OBESITY: AN INDEPENDENT ROLE OR SYNERGISTIC EFFECT TO METABOLIC SYNDROME ON LEFT VENTRICULAR FUNCTION (SYSTOLIC VS DIASTOLIC)?

F.F. Salim, S.W. Bakhour, Z.A. Ashour, D.R. Elremisy
Kasr Alainy Hospital. Cardiology Department, Cairo University, Egypt

Background: The metabolic syndrome (MS) has been shown to affect the left ventricle (LV). Whether the impact of central obesity (CO) on LV function is independent of the MS is uncertain.

Objective: To assess the impact of CO with or without MS diagnosis on LV systolic and diastolic function.

Methods: Cross-sectional study of 100 patients (56 women) with CO defined as a waist circumference (WC) >102 cm in men, >88 cm in women. MS was defined by the presence of ≥ 3 ATP-NCEP-III criteria. All patients were subjected to conventional echocardiography.

Results: MS was diagnosed in only 57 patients. The left atrial (LA) dimension, septal wall thickness (SWT) and posterior wall thickness (PWT) were significantly higher (p= 0.033, p=0.001, and p= 0.003) in MS compared to non-MS patients. Mitral flow E/A ratio was significantly lower in MS compared to non-MS patients (p = 0.006). There was no significant difference in ejection fraction (EF) and fraction shortening (FS) (p= 0.444 and p=0.856 respectively) between MS and non-MS patients. The independent predictors for SWT and PWT were WC (B=0.004, p=0.004 and B = 0.005, p=0.001 respectively) and SBP (B=0.003, p=0.000 and B=0.003, p=0.003 respectively), for LA dimension was WC (B = 0.013, p=0.000) and for mitral E/A ratio was age (B = -0.014, p= 0.000) and after multivariable adjustment for age SBP was the independent predictor (B = -0.006, p= 0.000).

Conclusion: CO in the presence of MS has a greater synergistic impact than CO alone on LV diastolic function mainly. WC and SBP had a significant impact on LV wall thicknesses while SBP alone had a significant impact on LV diastolic function independent of the other components of the MS.
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PEROXIREDOXIN1 PROTECTS MACROPHAGES FROM IMPAIRED LIPOPHAGIC FLUX BY OXIDATIVE STRESS IN ATHEROSCLEROSIS
G.T Oh, S.-J Jeong, S Kim
Ewha Womans University, Seoul, South Korea

Oxidative stress activates autophagy and contributes to the atherogenesis via lipophagic flux, a form of lipid removal by autophagy. However, it has not been studied whether the endogenous anti-oxidant enzymes are involved in lipophagic flux. We demonstrated that anti-oxidant Peroxiredoxin1 (Prdx1) restored autophagic flux impaired by oxidative stress. Prdx1 was more highly-expressed than other anti-oxidant enzymes in macrophages in murine and human atherosclerotic plaque. Consistent with this observation, ApoE/-/- mice transplanted with bone marrow (BM) cells from Prdx1/-/-ApoE/-/- mice had accelerated plaque formation upon high fat diet compared to ApoE/-/- BM transplanted recipients. We revealed that Prdx1-deficient macrophages had higher intracellular cholesterol mass and lower cholesterol efflux compared to wild-type controls. Prdx-1 deficiency also inhibits maintenance of lipophagic flux in macrophages. This perturbation in cholesterol homeostasis was due to impaired lipophagic cholesterol hydrolysis by excessive oxidative stress, resulting in the inhibition of free cholesterol formation and reduction of LXRalpha activity. Notably, impairment of both lipophagic flux and cholesterol efflux was restored by the 2-Cys Prdx mimics ebselen and gliotoxin. This study reveals that Prdx1 is crucial to regulating lipophagic flux and maintaining macrophage cholesterol homeostasis against oxidative stress. We suggest that Prdx1-dependent control of oxidative stress may provide a strategy for treating atherosclerosis and autophagy related human diseases.
HYPOLIPIDEMIC EFFECT OF MANNAN IN ACUTE LIPEMIA IN MICE INDUCED BY LIPASE INHIBITOR POLOXAMER 407

N.V. Goncharova¹, M.V. Khrapova¹, A.P. Lykov², E. Korolenko³, Z. Nescakova⁴, T.A. Korolenko¹

1. Inst. Physiol. Fund. Med., Novosibirsk, Russia
3. West University, Vancouver, Canada

Objectives: Mannan, belonging to immunomodulators of polysaccharide origin, was shown to stimulate macrophages in vivo via mannose receptor and can be used for stimulation and effective removing of circulating atherogenic lipoproteins.

Background: Wall yeast polysaccharide water-insoluble zymosan was shown to decrease atherogenic serum lipids in lipemia. Beta-Glucan and mannan are the main components of zymosan, however mannan hypolipidemic effect has not been studied precisely. The aim: to evaluate effect of immunomodulator mannan in murine model of lipemia induced by lipase inhibitor poloxamer 407 (P-407).

Methods and Results: Mannan C. albicans serotype A (Institute of Chemistry, SAN, Bratislava, Slovakia) was used in a dose 50 mg/kg (5-times) or 100 mg/kg (twice) before acute lipemia in CBA/Lac mice induced by the single administration of P-407 (300 mg/kg). In vitro mannan (50 mcg/ml) was shown to stimulate the proliferative potential (p<0.05) and NO production (p<0.05) of murine peritoneal macrophages, similar to beta-glucan. Preliminary administration of mannan significantly (p<0.001) reduced atherogenic LDL fraction, as well as total cholesterol and triglyceride concentrations (more significant in the dose of 50 mg/kg). In liver tissue total triglycerides level decreased in mannan pretreated group of mice with lipemia. Serum chitotriosidase activity increased in mice with lipemia and mannan administration as a result of macrophage stimulation.

Conclusion: The results obtained indicate significant protective activity of mannan and imply its potential study and application as hypolipidemic compound. It was concluded that mannan seems to be perspective hypolipidemic drug among other polysaccharide immunomodulators (like â-glucan).
EFFECT OF STATINS ON HIGH SENSITIVITY C-REACTIVE PROTEIN LEVELS IN SYSTEMIC LUPUS ERYTHEMATOSUS – A META-ANALYSIS

P. Tantrachoti¹, S. Klomjit¹, A. Karukote², P. Chariyawong¹, J. Teerakanok¹, K. Nugent¹

¹ Department of Internal Medicine, Texas Tech University Health Sciences Center, Lubbock, TX, USA
² Mahidol University, Bangkok, Thailand

Introduction: Patients with systemic lupus erythematosus (SLE) are at increased risk of cardiovascular complications mainly from generalized, chronic inflammation. Hydroxymethylglutaryl-coA reductase inhibitors or statins can exert strong anti-inflammatory reaction. We conducted a meta-analysis with the hypothesis that statin therapy can decrease cardiovascular complications by using the reduction of high sensitivity C-reactive protein (hsCRP) as a surrogate outcome.

Methods: Literature search in MEDLINE and EMBASE from inception to May 2015 was conducted by two independent authors. Eligibility criteria included: 1) RCTs, 2) comparing statins with placebo in patients with SLE, 3) have hsCRP as one of study endpoints, and 4) English literatures. The outcome was mean differences of hsCRP between statin-treated group and placebo group.

Results: Out of 83 studies retrieved, four RCTs (198 statin-treated and 175 placebo-treated patients) were included in the meta-analysis. The pooled weighted mean difference of hsCRP between statins and placebo groups was -0.08 mg/l (95% CI – 0.29 to 0.12). The heterogeneity among included studies was insignificant (Chi² = 1.22, I² = 0%, p = 0.75).

Conclusion: The routine use of statins to prevent cardiac complications in systemic lupus erythematosus is not indicated. However, due to limited data, more RCTs are needed before any definite conclusion can be made.
A STUDY OF THE CONFOUNDING RELATIONSHIP OF FOOD, ALCOHOL, COFFEE AND CIGARETTE CONSUMPTION ON SUBSEQUENT BLOOD PRESSURE READINGS IN AMERICAN POPULATION

R.U. Mian
The Wright Center for Graduate Medical Education, Scranton, PA, USA

Introduction: Blood pressure readings can be impacted by daily habits. The relationship of food, alcohol, and coffee and cigarette consumption on subsequent blood pressure readings is unclear.

Methods: Data from the 2007-2008 National Health and Nutritional Examination Survey (NHANES) were used. Participants included individuals who responded to blood pressure related standard questionnaire and had systolic blood pressure (SBP) measured subsequently. Questionnaire included inquiry into consumption of food, alcohol, coffee and cigarettes within 30 minutes period prior to blood pressure measurement (N=7,146). Procedures for blood pressure measurement were standardized for NHANES; values were mm Hg. Multinomial regression analyses examined relationship of food, alcohol, coffee and cigarette consumption on blood pressure measurement. Further models were adopted to analyze relationship across gender, age, as well as categorical blood pressure readings.

Results: Unadjusted analyses revealed that food intake in the proceeding 30 minutes was associated with elevated risk of increased blood pressure measurement (OR=1.18, P <0.01), while alcohol consumption and cigarette smoking were associated with reduced risk (OR=0.09, P=0.01)(OR=0.53, P<0.01). Subset analysis revealed that this relationship was more at higher levels of SBPs than lower. The relationship for coffee intake was not statistically significant (OR=0.72 P=0.19). Similar relationship was seen in our model for categorical blood pressure readings. In adjusted analyses for gender and age, significant relationship persisted in all models for cigarette use.

Conclusion: Blood pressure readings may be confounded by food, alcohol, and smoking cigarettes prior to measurements.

<table>
<thead>
<tr>
<th>Continuous Blood pressure</th>
<th>Categorical blood pressure</th>
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<tbody>
<tr>
<td>Unadjusted Model</td>
<td>Unadjusted Model</td>
</tr>
<tr>
<td>OR (95%CI)</td>
<td>P value</td>
</tr>
<tr>
<td>Food</td>
<td>1.18 (1.06-1.29)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>0.09 (0.02-0.53)</td>
</tr>
<tr>
<td>Coffee</td>
<td>0.72 (0.44-1.18)</td>
</tr>
<tr>
<td>Cigarettes</td>
<td>0.53 (0.40-0.71)</td>
</tr>
</tbody>
</table>

1 adjusted model for age
2 adjusted model for gender
3 adjusted model for age and gender

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Chronobiology is a branch of biomedical sciences devoted to the study of biological rhythms. Individual circadian rhythms may play a role in some personal characteristics, defined as ‘chronotype’ (Horne & Ostberg, 1976). A person's chronotype indicates how a person may perform at different times of day. Some people (‘larks’) find themselves most alert earlier in the day, and will go to bed early. ‘Owls’ may be most alert at night and prefer to go to bed late. A growing body of research indicates that chronotype, and sometimes gender, may be associated with a series of unfavourable conditions, such as metabolic disorders and body composition. Among a wide series of activities, the circadian clock also regulates energy homeostasis, and its disruption may contribute to many human diseases. Sleep duration also represents crucial point for a healthy life. Living "against the clock" may be accompanied by unhealthy habits, eg, reduced physical activity and wrong dietary habits, so favouring the onset of metabolic disorders. In particular, evening subjects (‘owls’) are most interested, starting with the younger generations. Eveningness tendency –more often when associated with female gender– may present many unfavorable aspects. Although chronotype is a characteristic of a person in a certain point of one’s lifetime and it slowly changes with age, it is evident that our society is transforming into a technologic society populated by forced and unforced ‘owls’, characterized by an evening/night use/abuse of devices, i.e., laptop, pc, tablet, smartphone, equipped with light-emitting diodes (LED) with a short wavelength (blue range).
EDUCATION AND MORTALITY: IS A COLLEGE DEGREE UNIVERSALLY PROTECTIVE?
A.L. Klatsky1,2, H.N. Tran2
1. Kaiser Permanente Division of Research, Oakland, CA, USA
2. Kaiser Permanente Oakland Medical Center, Oakland, CA, USA

Purpose: To study risk of death in relation to educational attainment in 273,843 persons.

Background: Low socio-economic status (SES) has been associated with increased incidence of many medical conditions and connected to racial and ethnic health disparities. Interacting factors include lifestyle, environmental exposures, and health care quality. Using education as a marker of SES, we studied its apparent impact on long-term mortality in a large multiethnic population.

Methods: Logistic regression with 8 covariates; the education referent was persons with no college.

Results: With average follow-up of >30 years, there were 103,218 deaths. Odds ratios (OR) and 95% confidence intervals for death were 0.84 (0.81-0.85) for persons with some college and 0.65 (0.63-0.67) for college graduates (GRAD). For male GRAD the OR was 0.61; for female GRAD it was 0.71. For White, Black, and Asian GRAD the ORs were 0.65, 0.64, and 0.73 respectively. The p value for each of these estimates was <0.001. GRAD had lower risk (p < 0.01) in strata of specific Asian ethnicity (Chinese, Japanese, Filipino, South Asian), smoking habit, interval to death, and BMI, except for persons >60 years old at baseline (OR = 0.90 [0.80-1.01, p = 0.07]). For selected death causes (cardiovascular, non-cardiovascular, coronary, cancer, respiratory, liver disease, accidents/violence) GRAD ORs ranged from 0.46 (liver) to 0.74 (cancer) with all p values < 0.001.

Conclusion: College graduates across gender, race, and smoking strata have substantially lower risk of all-cause mortality and of death from multiple diagnostic groups.
CARDIOVASCULAR DISEASE RISK ASSESSMENT AND PREVENTION: ALL YOU NEED TO KNOW

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SECONDARY PREVENTION OF CARDIOVASCULAR EVENTS
S. Mora
Brigham and Women’s Hospital, Harvard Medical School, Boston, MA, USA

Cardiovascular risk among individuals with manifest cardiovascular disease remains high and has been termed “residual risk”. Results from a meta-analysis of statin trials involving 90,056 individuals found that the rate of a major vascular event occurring during 5 years of follow-up among statin-treated patients was 21.7% (1 in 5) for individuals with prior cardiovascular disease. Results from contemporary trials and registries of patients with optimally treated cardiovascular disease also indicate a high rate of residual vascular events. The mechanisms underlying this residual risk are uncertain. This presentation will discuss residual risk determinants, including lipid-related residual risk, inflammatory-related residual risk, and other clinical determinants of residual risk. Furthermore, while it is commonly believed that the risk factors responsible for vascular events among statin-treated patients are the same as those for patients not taking statins, new data suggest there may be differences. Recognition of these factors is important for more effective tailoring of risk reduction strategies to match the individual level of risk and for development of new therapeutic targets.
Biomarkers of the Future: Metabolomic Predictors of Cardiometabolic Disease

S. Cheng
Brigham and Women’s Hospital, Boston, MA, USA and Framingham Heart Study, Framingham, MA, USA

By providing information on the diversity of small molecule metabolites in biological systems, current era metabolomics now offer the potential to comprehensively integrate data on both the intrinsic and extrinsic exposures that contribute to complex diseases such as cardiovascular disease (CVD). Targeted metabolomics methods have already been used to identify novel molecular markers of CVD risk, including branched chain amino acids, select unsaturated lipid species, and trimethyl-N-oxide. Early studies have also discovered metabolite correlates of cardiometabolic traits in addition to intriguing links between dietary intake, patterns of gut microbial activity, and CVD risk. As metabolomics technologies continue to develop, the scope and throughput with which small molecule profiling can be performed is increasing – and prospects for further discovery are rapidly growing. Current challenges facing the field include: bioinformatics approaches needed to handle high-throughput untargeted metabolomics data, strategies for identifying the biochemical structure and functional role of novel metabolites, and methods for determining the true clinical relevance of metabolites observed in association with CVD outcomes. Progress made in addressing these challenges will allow metabolomics approaches the potent to substantially transform diagnostics and therapeutics in cardiovascular medicine.
INTEGRATIVE MEDICINE APPROACHES TO PREVENTING HEART DISEASE
S. Malik
University of California, Irvine, Orange, CA, USA

Integrative Medicine approaches to preventing heart disease include an emphasis on lifestyle management, genetic polymorphisms and micronutrient repletion, as well as mind-body therapies. Functional medicine emphasizes personalized therapies based on genetic polymorphisms and biomarker assessment. These therapies can include specific nutritional strategies as well as supplementing certain micronutrients above the dietary reference intake. Finally, holistic mind-body therapies such as yoga, meditation, and tai chi have increasing evidence for improved outcomes. These approaches can be combined with conventional therapies to achieve optimal risk factor levels and lower cardiovascular events.
We are seeing more patients with cardiac illness and resultant morbidities despite the recent advances in Medicine. Advanced imaging-revascularization techniques address patients with significant coronary artery disease (CAD) but several groups remain undertreated. There are a significant proportion of our patients having debilitating symptoms without occlusive CAD. On the other end of the spectrum we encounter patients on maximal medications who not candidates for revascularization. Advancing age and numerous comorbidities oftentimes increases risk of iatrogenic complications. Increasingly, people are turning to alternative medicine with over a third of US adults using these therapies in 2007. Majority of our patient population have unhealthy and sedentary lifestyles. Ideally, health care providers should allocate ample time with patient and family to evaluate social, lifestyle and psychological issues. Identifying personal interests, passion, habits and life goals plays a major role in developing an individualized holistic prescription according to patient preferences. By implementing holistic health concepts in our University and VA cardiology practice, we are increasing the reach, effectiveness and scope of care. We work with qualified providers in the fields of Naturopathy, Yoga, diet based therapies, meditation, mindfulness- based stress reduction and weight control, exercise physiologists and tele-monitored cardiac rehabilitation. We emphasize understanding what motivates and engages the mind, personal interests and priorities, of each patient. In conjunction with family we explore tailored diet, exercise and lifestyle plans that are realistically achievable and sustainable for the individual. We recognize that majority of people will find it challenging to initiate and sustain these lifestyle changes. We continually realign prescription with patients’ changing medical and social circumstances. Our success is based on instilling trust, positive attitude, confidence and purpose. Increasingly patients recognize holistic health as their true nature and as the freedom to better engage in all their life pursuits.
CARDIOVASCULAR DISEASE RISK ASSESSMENT AND PREVENTION: ALL YOU NEED TO KNOW

A CURRENT UPDATE ON INFLUENZA AND CARDIOVASCULAR DISEASES

M. Madjid
University of Texas Health Science Center at Houston, Houston, TX

Much emphasis has been placed so far on the role of chronic risk factors leading to development and progression of atherosclerosis over years, however new studies show an important role for triggers of acute coronary syndromes (ACS). ACS triggers can cause a quick transition of stable plaques into unstable plaques which are the culprit pathology for ACS. Influenza has been established as a clinically relevant, yet preventable trigger for ACS. In over 35,000 autopsies over 8 years, we showed that each and every influenza epidemic is associated with a sharp rise in cardiovascular death. In apo-E knockout hypercholesterolemic mice, we have shown that influenza infection can cause a marked increase in inflammatory cells in atherosclerotic plaques leading to focal inflammation in synergy with profound systemic inflammation. Multiple retrospective, prospective, and ultimately clinical trial studies in various patient groups showed that influenza vaccination is associated with a significant reduction in risk of myocardial infarction, sudden cardiac arrest, stroke, and hospitalization for cardiac causes. Based on these, American Heart Association and American College of Cardiology secondary prevention guidelines recommend influenza vaccination for all patients with cardiovascular disease (CVD). Unfortunately, the vaccine usage in patients with CVD remains less than 65% in US, and is even lower in most other countries. Efforts are needed to increase vaccination rate in cardiac patients. Moreover, in retrospective studies we have found that treatment of influenza with neuraminidase-inhibitor medications is associated with a decreased risk of developing stroke or transient ischemic events as well as cardiovascular events in high risk subjects. These studies suggest an important role for influenza in pathogenesis of acute cardiovascular events and call for multi-disciplinary efforts to improve vaccination rates in high risk subjects and also to consider anti-influenza agents for preventing cardiovascular events after influenza infection.
COCOA FLAVANOLS FOR PREVENTION OF DIABETES

L. Wang
Brigham and Women’s Hospital, Harvard Medical School, Boston, MA, USA

Recent research has demonstrated multiple health benefits of cocoa products, which are mainly attributed to the high content of flavonoids, particularly flavanols. A large body of evidence indicates that dietary intake of cocoa and flavanol-rich chocolate (as dark chocolate) may reduce the morbidity and mortality of cardiovascular disease (CVD) and related cardiometabolic disorders including type 2 diabetes (T2D). Experimental studies show beneficial effects of cocoa flavanols on glucose and insulin metabolism. Prospective cohort studies found a reduced risk of T2D with greater intake of flavanols. Meta-analyses of cohort studies and small-scale, short-term trials that assessed the effects of cocoa, chocolate, or flavanol intake on CVD risk factors reported that flavanols from cocoa may improve glucose homeostasis, insulin sensitivity, and beta-cell function. We recently conducted an updated meta-analysis of randomized, controlled trials (RCTs) published from January 1965 to December 2015 and found similar results. Pooled data from a total of 19 RCTs showed that the weighted mean differences (WMD) and 95% confidence intervals (95% CI) of glycemic biomarkers comparing active cocoa flavanol supplement with placebo were -2.33 uIU/mL (95% CI: -3.47, -1.19) for fasting insulin, -0.93 (95% CI: -1.31, -0.55) for homeostatic model assessment of insulin resistance (HOMA-IR), 0.03 (95% CI: 0.01, 0.05) for quantitative insulin sensitivity check index (QUICKI), and 2.54 (95% CI: 0.63, 4.44) for insulin sensitivity index (ISI). Although accumulating evidence suggests a clinically important effect of cocoa flavanols on reducing T2D risk and improving glycemic measures, along with other biological benefits, existing data from clinic trials are limited by the small sample size, short duration, cross-over design, a wide range of flavanol doses, and method of intervention. There is need for large-scale, long-term RCTs that directly evaluate the effects of cocoa flavanols on T2D risk and other related chronic disease outcomes.
Chronic obstructive pulmonary disease (COPD) is commonly associated with cardiovascular disease (CVD) since they are both linked with shared factors such as age and smoking history; however, in clinical practice, these two diseases are treated separately. COPD and CVD are among the most prevalent diseases and account for significant morbidity and mortality in the US and globally. About 85.6 million Americans are living with some form of cardiovascular disease or the after-effects of stroke. The prevalence of COPD in the adult US population is about 15 million (14%).

Despite this frequent association, pulmonologists and cardiologists in both clinical and research settings often underestimate the importance of a correct diagnosis and severity stratification of the two combined conditions. Spirometry, in particular, is largely under prescribed. Missed diagnosis and severity stratification combined with an incomplete knowledge of adverse drug events lead to under treatment of patients with both COPD and CVD. Moreover, pulmonologists do not typically do appropriate CVD risk assessment in their COPD patients; the use of global risk scores such as the ASCVD Pooled Cohort Risk Calculator can be applied to determine their 10-year and lifetime risk of CVD and who may benefit from appropriate preventive therapies (e.g., statins) for the prevention of CVD. We have previously demonstrated a strong association of global risk scores with severity of COPD and that their use improves risk stratification of patients with COPD. Thus, use of appropriate CVD risk assessment in patients with COPD is important for identifying who may need appropriate CVD preventive therapies and for predicting the long term survival of COPD patients.
Data comparing the hemodynamic performance of stented pericardial and porcine aortic valves are conflicting. We performed a systematic review and meta-analysis comparing the early hemodynamic parameters of stented pericardial and porcine valves in patients undergoing isolated aortic valve replacement. Medline, EMBASE and Web of Science were queried for English language original publications from 2000 to 2013. Studies comparing porcine (PoV) and pericardial (PeV) with regard to their hemodynamic parameters were included in this review. Continuous data were pooled using the mean difference (MD) or the standardized mean difference (SMD). A random-effect inverse weighted analysis was conducted; a P-value <0.05 is considered statistically significant. Results are presented with 95% confidence intervals. Thirteen studies (1265 PeV patients and 871 PoV patients) were included in this analysis. The pooled transvalvular mean gradient was lower for PeV [MD -4.6 (-6.45 to -2.77) mmHg; P<0.01]. Limiting this analysis to small valves (19 and 21 mm; eight studies; 714 patients) revealed that the PeV gradients were significantly lower [MD -4.5 (-5.7 to -3.2); P=0.001]. The corresponding effective orifice area of PeV was significantly larger than PoV [SMD 0.42 (0.15–0.69); P < 0.01]. A sensitivity analysis comprising only randomized controlled trials did not significantly alter results. When compared with porcine valves, stented pericardial aortic valves have lower mean transvalvular gradients early after implant. Even pericardial valves in smaller sizes (19 and 21 mm) have a better hemodynamic profile when compared with their counterparts.
Objective: Compare clinical characteristics and outcomes of transcatheter aortic valve replacement (TAVR) patients ≥85 versus <85 years.

Background: Mean age of patients undergoing TAVR based on data from the Society of Thoracic Surgeons (STS)/American College of Cardiology TAVR Registry is 84 years. The number of patients ≥85 undergoing TAVR is projected to rise, however, this cohort remains understudied.

Methods: We retrospectively analyzed data from patients undergoing TAVR between 6/2012 and 11/2015. Patients were divided in 2 groups: Group A included patients ≥85 (n=97, 88.9 +/- 3.0) and Group B <85 (n=119, 75.0 +/- 7.4).

Results: Group A had higher STS score than B (9.3% vs 7.3%, p=0.001). 30-day mortality was 8.2% and 5.9% (p=0.50) and rate of major stroke was 6.2% and 1.7% (p=0.14), respectively. Permanent pacemaker implantation was 13.4% in A and 6.7% in B (p=0.10). Vascular complications were 9.3% and 4.2% (p=0.17), respectively. The incidence of paravalvular leak, moderate or severe, was low in both groups (1% vs 0%, p=0.45). The length of stay was 6.5 +/- 5.9 in A and 8.2 +/- 10.2 days in B (p=0.17).

Conclusion: In a single center experience, TAVR outcomes in patients ≥85 are similar to those <85 despite higher STS score.
ASSOCIATION BETWEEN SERUM OSTEOPONTIN LEVELS AND CALCIFIC AORTIC STENOSIS: A META-ANALYSIS

1. Morehouse School of Medicine, Atlanta, GA, USA
2. University of Miami, Miller School of Medicine, Miami, FL, USA

Background: Osteopontin (OP) is a multifunctional glycophosphoprotein known to regulate bone remodeling via stimulation and differentiation of osteoclast cells. OP is involved in cell mediated inflammation and biomineralization of ectopic and dystrophic sites. The association between OP and calcific aortic stenosis (CAS) remains unclear. We conducted a meta-analysis to evaluate the relationship between serum OP levels and CAS.

Methods: We searched MEDLINE, CINAHL and COCHRANE databases for studies reporting serum OP levels in the patients with CAS and healthy controls. We calculated the weighted standardized mean difference (SMD) in serum OP levels between the CAS and control groups.

Results: Our search strategy yielded 41 articles and we included 4 studies enrolling 294 participants. The median age of the CAS group was 76 yrs. (IQR 76-77) vs 63 yrs. (IQR 61-65) in the control group. The median female percentage and serum calcium level in the CAS group were 48% (IQR 44-53) and 9.2 mg/dl (IQR 9.2-9.25) vs 46% (IQR 39-49) and 9.3 mg/dl (IQR 9.25-9.30) in the control group. The unweighted median serum OP levels in the CAS group were 64.34 ng/ml (IQR 63.42-211.34) compared to 30.31 ng/ml (IQR 29.08-117.67) in the control group. The SMD of serum OP level was 4.25 (95% CI 0.81-7.78) P=0.01 comparing those in the CAS group and control group.

Conclusion: An elevated serum OP level is significantly associated with the presence of CAS. OP may potentially be used as a novel biomarker of CAS in asymptomatic patients.
PERATRIAL DEVICE CLOSURE OF DIFFERENT LOCATIONS OF MITRAL PARAVALVULAR LEAKS USING A PROBE-ASSISTED DELIVERY SYSTEM

L. Hongxin, G. Wenbin, H-Z. Zhang, F. Liang, G. Zhang
1. Department of Cardiovascular Surgery, Shandong Provincial Hospital Affiliated to Shandong University
2. Echocardiography Lab, Shandong Provincial Hospital Affiliated to Shandong University, China

Background: The transcatheter closure of mitral paravalvular leak (MPVL) includes transseptal, transaortic and transapical approaches. Each of them is only suitable for some specific locations of the MPVLs. The challenges come from transseptal puncture, accessing the MPVL site, and the absence of dedicated delivery systems. We introduce a peratrial technique for device closure of different locations of MPVLs using a probe-assisted delivery system under three-dimensional transesophageal echocardiography (3D TEE).

Methods: After general anesthesia, a 4.0 cm parasternal incision was made in the fourth right interspaces. A pursestring suture was placed on the right atrium. The interatrial septum was punctured and dilated, followed by a guidewire passing through the septum. A specially designed J-shaped bendable hollow probe was advanced over the wire into the left atrium. The steerable hollow probe was adjusted to cross the MPVL and introduced a stiff guidewire through the channel of the probe into the left ventricle (LV). An 8F short delivery sheath was advanced over the wire through the MPVL into the LV. A proper sized muscular septal occluder was then selected and deployed. In two patients with a crescent-shaped MPVL, two guidewires were sent to the LV. Two devices were positioned to close the MPVL and the residual regurgitation.

Results: TEE revealed complete occlusion of the MPVL in 5 of 6 patients, with no residual leak and a good function of the prosthetic valve after a follow-up of 3 months to 2 years. Mild residual paravalvular regurgitation occurred in an early patient with a crescent-shaped MPVL. All patients’ symptoms improved by at least 1 NYHA functional class.

Conclusions: The probe-assisted delivery system can access and close MPVLs at different locations through a right minithoracotomy approach. This technique has the advantages of easy transseptal puncture, easy accessing the MPVL, and no exposure to radiation.
DO FASCICULAR BLOCKS CAUSE MITRAL REGURGITATION?

E. Obasare¹, E. Melendres¹, V. Bhalla¹, M.B. West², S. Mainigi¹, G.S. Pressman¹, V.M. Figueredo¹
1. Einstein Medical Center, Philadelphia, PA, USA
2. San Juan Regional Medical Center, Farmington, NM, USA

Objective/Background: The anterior fascicle of the left bundle branch supplies the anterolateral papillary muscle while the posterior fascicle supplies the posteromedial papillary muscle. We therefore sought to see whether fascicular blocks (FB) may contribute to mitral regurgitation (MR).

Methods: This was an observational study of 300 consecutive patients with right bundle branch block (RBBB) and either left anterior fascicle block (LAFB), left posterior fascicle (LPFB), or no FB. Patients were selected with background RBBB because isolated LPFB is rare. 284 patients had 2D echocardiography within 3 months of the EKG.

Results: Ninety-five patients had LAFB, 90 patients had LPFB, and 99 had no FB. Presence of MR was significantly higher among patients with FB (table). Comparing LAFB with LPFB there was no significant difference in presence of MR. Among patients with MR, 75% were trace/mild in those with FB vs 83% with no FB; there was no significant difference in the severity of MR between groups. On multivariate analysis (adjusted for age, sex, race, ejection fraction, wall motion abnormality [WMA], acute MI, coronary arterial disease, atrial fibrillation/flutter) FB remained a significant predictor of MR (p=0.04, OR 1.68, 95% CI [1.02-2.78]).

Conclusion: Fascicular block is associated with an increased prevalence of MR.
VALVULAR HEART DISEASE MECHANISMS AND TREATMENT OPTIONS

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AORTIC VALVE REPLACEMENT IN SINGLE CORONARY ARTERY
A. Sinha1, R. Kumar2, J. Shirani1
1St. Lukes’ University Health Network, Bethlehem, PA, USA
2Howard University Hospital, Washington DC,

Background. Isolated single coronary artery (SCA) is a rare congenital heart defect (incidence <0.05%). Surgical and transcatheter aortic valve replacement (SAVR and TAVR, respectively) in patients with SCA may present technical challenges.

Methods/results. We identified 22 reported cases of SAVR (n=15) or TAVR (n=7) in adults with SCA between 1995-2016 (age 72±12 years, 50% women, presenting complaints: 3 angina, 2 dizziness/syncope, 9 dyspnea). Valves were predominantly tricuspid (65%) and stenotic (91%). All patients with bicuspid valves (n=7), obstructive coronary artery disease (n=3), interarterial course of anomalous coronary artery (n=2) and less than severe stenosis (n=2) underwent SAVR. Coronary angiography (100%), echocardiography (100%), cardiac computed tomography (68%) and cardiac magnetic resonance imaging (5%) were used as diagnostic modalities. Most (86%) cases could be classified based on most recent classification1 (LCC=7; IA=1, IB=2, 1B=1); (RCC=15; IIA=2, IIB=1, IIB=3, IIB=3, IID=1, IID=1). Single coronary ostium was located in right coronary cusp in 6 and in left coronary cusp in 1 out of 7 SCA patients who underwent TAVR (classification: IIB=2, IIB=3, 1B=1). The valves used in TAVR were: 3 Edward Sapiens, 2 Medtronic Core valve, 1 Lotus valve; sizes 23 -29 mm (transfemoral approach in 3). Distance from aortic annulus to coronary ostium was 12-15.4 mm. Aortic valve replacement was successful in 21 and associated with complication (coronary compression) in 1(5%).

Conclusion. SAVR and TAVR are feasible and associated with excellent outcomes in carefully selected patients with various forms of SCA. 1 Shirani J., Roberts WC. JACC 1993; 21:137.
SPONTANEOUS LEFT ATRIAL DISSECTION CAUSED BY MITRAL VALVE ENDOCARDITIS

H. Vefali, M. Durkin, A. Singh, S. Agrawal, S. Longo, M. Averbach, J. Shirani
St. Luke's University Health Network, Bethlehem, PA, USA

Background. Non-traumatic, non-iatrogenic spontaneous left atrial dissection (SLAD) is rarely reported in association with mitral annular calcification, aortic dissection, myocardial infarction or amyloidosis. We report a case of an SLAD in a patient with mitral valve endocarditis.

Case. A 66 year old man with stage IV melanoma on chemotherapy (tafinlar and mekinist) presented with persistent fever and retinal hemorrhage, and group B streptococcal bacteremia. Transthoracic echocardiogram (TTE) was abnormal and a transesophageal (TEE) study revealed SLAD involving the posterior wall of the atrium (figure 1A) and significant regurgitation into the dissection cavity (false lumen). This was further verified by cardiac magnetic resonance (CMR) imaging (figure 1B). No cardiac metastatic lesions were identified by CMR. Patient received antibiotics with complete symptomatic recovery and negative blood cultures but was denied surgery due to advanced cancer. Six months later he was admitted with Staphylococcus lugdunensis bacteremia, osteomyelitis of spine and septic emboli to the brain. Repeat TEE showed marked increase in valvular vegetation burden and no change in SLAD (figure 1C). Medical therapy resulted in complete symptomatic recovery and patient has remained symptom-free despite lack of surgical intervention for 2 years. Repeat TTE showed fibrosis/calcification of mitral annulus, leaflet and dissected atrial wall.

Literature Review. Only 2 prior cases of SLAD associated with endocarditis (both mitral, fatal and caused by methicillin-sensitive Staphylococcus aureus) have been reported.

Conclusion. We present a unique case of SLAD caused by group B streptococcal mitral valve endocarditis that has been stable for >2 years despite medical therapy alone.

* Dissection cavity. LV=left ventricle. Arrow=vegetation
MASSIVE THROMBOSIS OF STRUCTURALLY NORMAL MITRAL VALVE IN PRIMARY ANTI-PHOSPHOLIPID ANTIBODY SYNDROME

St. Luke’s University Health Network, Bethlehem, PA, USA.

Background: Primary antiphospholipid antibody syndrome (PAPS) is frequently associated with small non-inflammatory lesions including non-bacterial, thrombotic vegetations. Few cases of large, hemodynamically significant valvular thrombi have been documented. We present the largest reported valvular thrombus on an otherwise structurally normal mitral valve in a 43 year old man with undiagnosed PAPS.

Case report: Patient presented with sudden onset of dysarthria and expressive aphasia. CT and MRI of the brain confirmed right frontal lobe infarcts and CTA was consistent with embolic obstruction of second division of middle cerebral artery. Transthoracic echocardiogram revealed a large mass on anterior mitral leaflet of mitral valve. Two and three-dimensional transesophageal echocardiogram confirmed presence of a large (37x24 mm), multilobulated, echogenic, highly mobile mass on atrial aspect of anterior mitral leaflet (figures 1A and 1B) that prevented leaflet coaptation and caused moderate regurgitation. IgG anti-cardiolipin antibody was elevated [116 Units/ml (normal <10)] and lupus anticoagulant profile was highly abnormal [dilute Russel viper venom test time (97.4 s, normal <55.1), PTT-LA time (107.8 s, normal <50), hexagonal phase neutralization time (51.7 s, normal <8s), dilute PT time (96.1 s, normal <55), PTT-LA mix time (99.5 s, normal <50.0), dPT confirm ratio (1.67, normal <1.2) dRVVT confirm ratio (2.5, normal <1.4) and DRVVT mixing time (82.7 s, normal <45.4)]. ANA antibodies were negative. Patient underwent mitral valve replacement due to the massive size of the thrombus. All blood and specimen cultures were negative for infective endocarditis and resected mass (figure 1C) was consistent with layered thrombus of different ages (figure 1D).

Conclusion: Massive valvular thrombosis of otherwise structurally normal native valves may be the presenting feature of PAPS and should be included in the differential diagnosis of large valvular lesions in the adult.
VALVULAR HEART DISEASE MECHANISMS AND TREATMENT OPTIONS

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A TALE OF TWO OUTCOMES: PSEUDOANEURYSM OF THE MITRAL-AORTIC INTERVALVULAR FIBROSA; A RARE AND DANGEROUS CONDITION

K.A. Samtani1, R.J. Bohinc2, V.S. Tivakaran3, J.B. Gibson2
1. Wright State University, Dayton, OH, USA
2. Kettering Medical Center, Dayton, OH, USA
3. VA Medical Center, Dayton, OH, USA

The mitral-aortic intervalvular fibrosa is a relatively avascular structure which lies between the anterior leaflet of the mitral valve and left coronary or noncoronary aortic cusp, alongside the left ventricular outflow tract. Pseudoaneurysm of this structure is a rare and potentially fatal abnormality. Although some patients with this abnormality are asymptomatic, more commonly it is associated with infection, or injury related to aortic valve surgery. Other associations include congenital disease, inflammatory conditions, or procedure based trauma.

Review of literature identifies two comprehensive review articles detailing reports of pseudoaneurysm of the mitral-aortic intervalvular fibrosa (P-MAIVF). In the first by Sudhakar S et al, published in 2010 by the American Society of Echocardiography, 88 cases were identified in English-language articles published from 1966-December 2009. The second by Sahan E et al, published in 2015 by Herz, identified a total of 166 cases in articles published from 1960-March 2014. Since March 2014, three additional cases have been discussed in the available English-language reports per our review. We report an additional two cases. Though primary investigation is generally with transthoracic echocardiography, transesophageal echocardiography is more diagnostically specific. Cardiac computed tomography and magnetic resonance imaging can be further helpful in surgical evaluation. Rupture of the pseudoaneurysm into the pericardium may be fatal and hence when pseudoaneurysm is diagnosed, surgical treatment should be recommended to all patients even if they are asymptomatic. Several complications may arise in patients with P-MAIVF which may include rupture, fistula formation, compression, thrombosis, infection, and heart failure. In conclusion, further studies are required in order to earlier identify and effectively treat patients with P-MAIVF. For now, we encourage physicians to be watchful for P-MAIVF and its complications in those patients with higher risk such as those with infection (endocarditis), and trauma related to aortic valve surgery.
HEART FAILURE: NOVEL RISK FACTORS, PREDICTORS, NEW TREATMENT OPTIONS AND OUTCOME

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NO DIFFERENCE IN SODIUM REMOVAL WITH ULTRAFILTRATION THERAPY VERSUS CONVENTIONAL DIURETIC THERAPY IN PATIENTS WITH ACUTE HEART FAILURE

A. Koratala, S.I. Qadri, A. Kazory
Division of Nephrology, Hypertension, and Renal Transplantation, University of Florida, Gainesville, Florida, USA

Introduction: There has been a renewed interest in the use of ultrafiltration therapy as an efficient method of decongestion for patients with acute decompensated heart failure (ADHF). Enhanced sodium removal has been proposed as an advantage of ultrafiltration over conventional diuretic-based treatment, and a key mechanism underlying the sustainability of its beneficial effects. There is a paucity of evidence regarding the impact of ultrafiltration as it relates to sodium balance in this setting.

Methods: We utilized data on the urine and ultrafiltrate sodium concentration, extracted from a pilot randomized controlled trial on 16 patients with ADHF, treated with ultrafiltration or diuretics. These findings were applied to the data from the Ultrafiltration in Decompensated Heart Failure with Cardiorenal Syndrome (CARRESS-HF) study. The 4-day urine and ultrafiltrate volumes of 188 patients were included. The daily and total fluid and sodium removal were calculated for both modalities and the differences were then compared using unpaired t-test.

Results: The urine sodium concentration was 85 mmol/L in patients receiving medical therapy and 26 mmol/L in the ultrafiltration group. The ultrafiltrate sodium concentration was 138 mmol/L. Although urine output was consistently lower in the ultrafiltration arm, the total extracted fluid volume was similar for both groups at 4 days (12.25 L of urine for medical treatment vs. 5.1 L of urine and 7.2 L of ultrafiltrate for ultrafiltration, p= 0.68). The total sodium removal was 1127 mmol (mean 282±95 mmol/day) for ultrafiltration (urine and ultrafiltrate) and 1041 mmol (mean 260±25 mmol/day) for medical therapy (p=0.68).

Conclusion: Compared to conventional diuretic-based medical treatment, ultrafiltration therapy did not result in significantly greater sodium removal in patients with ADHF despite comparable fluid removal and higher concentration of sodium in the ultrafiltrate. Reduced urinary sodium concentration in patients treated with ultrafiltration is the primary reason for its reduced efficacy.
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EFFICACY AND SURVIVAL IN PATIENTS WITH CARDIAC CONTRACTILITY MODULATION: LONG-TERM SINGLE CENTER EXPERIENCE IN 81 PATIENTS

J. Kuschyk¹, S. Roeger¹, B. Rudic¹, K. Stach¹, C. Weiss¹, T. Papavassiliu¹, B. Rousso³, D. Burkhoff⁴, M. Borggrefe¹

1. University Medical Centre, I. Medical Department, Mannheim, Germany
2. University Medical Centre, Institute for Medical Statistics, Mannheim, Germany
3. IMPULSE Dynamics, Orangeburg, NY, USA
4. Columbia University, Cardiology, NY, USA

Aims: To analyze long-term efficacy and survival in patients with chronic heart failure treated with cardiac contractility modulation.

Methods: 81 patients implanted with a CCM device between 2004 and 2012 were included in this retrospective analysis. Changes in NYHA class, ejection fraction (EF), Minnesota Living with Heart Failure Questionnaire, NT-proBNP and peak VO2 were analyzed during a mean follow up of 34.2 ± 28 months (6–123 months). Observed mortality rate was compared with that predicted by the MAGGIC Score.

Results: Patients were 61 ± 12 years old with EF 23 ± 7%. Heart failure was due to ischemic (n= 48, 59.3%) or idiopathic dilated (n=33, 40.7%) cardiomyopathy. EF increased from 23.1±7.9 to 29.4±8.6% (p < 0.05), mean NT-proBNP decreased from 4395 ± 3818 to 2762 ± 3490 ng/l (p < 0.05) and mean peak VO2 increased from 13.9 ± 3.3 to 14.6 ± 3.5 ml/kg/min (p= 0.1). The overall clinical responder rate (at least 1 class improvement of NYHA within 6 months or last follow-up) was 74.1%. 21 (25.9%) patients died during follow up, 11 (52.4%) due to cardiac conditions and 10 (47.6%) due to non-cardiac conditions. Mortality rates at 1 and 3 years were 5.2% and 29.5% compared to mortality rates estimated from the MAGGIC risk score of 18.4% (p < 0.001) and 40% (p = ns), respectively. Log-Rank analysis of all events through 3 years of follow-up, however, was significantly less than predicted (p= 0.022).

Conclusions: CCM therapy improved quality of life, exercise capacity, NYHA class, EF and NT-proBNP levels during long-term follow up. Mortality rates appeared to be lower than estimated from the MAGGIC score.
ULTRAFILTRATION VS PHARMACOLOGICAL DIURESIS IN HEART FAILURE: A META-ANALYSIS

N. Agrawal, A. Jain, A. Kazory
University of Florida, Gainesville, FL, USA

Introduction: The role of ultrafiltration (UF) in acute decompensated heart failure (ADHF) has been a topic of debate and discussion. Multiple randomized control trials (RCT) have been done to compare UF versus pharmacological diuresis in this setting. Since the results of these studies have provided conflicting evidence, we performed a meta-analysis to consolidate the evidence.

Methods: Systematic review of PUBMED and COCHRANE database was performed for RCTs comparing UF with pharmacological diuresis in ADHF. We then performed a meta-analysis to explore the impact on weight change, rehospitalisation and mortality. Mantel-Haenszel odds ratio (OR) was calculated for dichotomous data and weighted mean difference (WMD) was calculated for continuous data.

Results: 7 RCTs with a total of 771 patients were included in our analysis. Weight loss was significantly higher in the UF group with WMD of 1.35 (95% CI 0.49-2.21, p<0.01). UF group also had lower heart failure rehospitalisation rate, OR 0.60 (95% CI 0.37-0.98, p=0.04). There was no difference in mortality between the two groups, OR 1.03 (95% CI 0.68-1.57, p=0.89).

Conclusion: As compared to pharmacological diuresis, the use of UF is able to achieve more weight loss and also improve heart failure rehospitalisation in ADHF patients, without any significant change in mortality.
Objective: To determine the efficacy and economic benefit of creating and implementing a clinical care pathway for heart failure to reduce variation and improve quality of care as measured by Milliman’s Index.

Background: A Milliman’s Index \( \frac{\text{Observed average length of stay (ALOS)}}{\text{Expected ALOS}} \) was calculated for all inpatient heart failure patients (Using Medicare Diagnosis-Related Group (MS-DRG) numbers: 291, 292 and 293) for admissions at an Academic Medical Center in 2015. A Milliman’s Index greater than 1.0 represents opportunity for improvement.

Method: Retrospective analysis of data was used to identify variation in care, followed by prospective trial on heart failure patients admitted with a heart failure MS-DRGs. Potential variables identified were: substandard initial Furosemide dosing the day of admission; low average daily Furosemide dosing; poor standing and daily weight compliance. Data was tracked and analyzed using analysis software linked to the hospital electronic medical records. Findings were shared weekly with the multidisciplinary project steering team, which included representation from hospitalist medicine, cardiology and nursing.

Results: 474 admitted heart failure patients were studied. Patients’ mean age and standard deviation was 64.03 ± 15.75 years. Average first Furosemide dose administered to patients increased by 26% from 28.2 mg to 35.5 mg after implementation of the care pathway. Daily weight monitoring increased by approximately 10%. Average daily Furosemide dose ordered on patients by the physicians on the floor increased by 159% from an average of 30.1 mg to 78.2 mg. Consequently, the Milliman’s Index decreased by 32% from 1.244 to 0.840.

Conclusion: Implementation of a standardized care pathway reduces clinical variation, enhances coordination of care, and most importantly, improves clinical outcomes for patients with heart failure.
HEART FAILURE: NOVEL RISK FACTORS, PREDICTORS, NEW TREATMENT OPTIONS AND OUTCOME

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RACIAL DIFFERENCES IN CLINICAL CHARACTERISTICS OF HEART FAILURE WITH PRESERVED EJECTION FRACTION

Y.R. Patel1,2,3, K.E. Kurgansky1, T.F. Imran1,2,3, A.R. Orkaby1,2,3, K. Cho1, D.R. Gagnon1, Y. Ho1, J.M. Gaziano1,2,3, L. Djousse1,2,3, J. Joseph1,2,3
1. Boston VA Healthcare System, Boston, MA, USA
2. Brigham and Women’s Hospital, Boston, MA, USA
3: Harvard Medical School, Boston, MA, USA

Background: Studies suggest that African-American patients have a higher prevalence of heart failure with preserved ejection fraction (HFpEF) than white patients. However, studies describing the clinical characteristics of HFpEF are drawn from predominantly white cohorts.

Objective: To examine clinical characteristics of white and African-American veterans diagnosed with HFpEF.

Methods and Results: We identified all patients diagnosed with heart failure (HF) between 2002 and 2014 from the national Veterans Affairs database. All recorded values of ejection fraction (EF) were extracted using a Natural Language Processing tool. HFpEF was defined as: EF≥50% with the presence of signs, symptoms, and HF specific treatment. Amongst 91,139 HFpEF patients, 14% were African-American and 96% were men. African-American patients were younger, had higher blood pressure and heart rate, were more likely to have hypertension, type 2 diabetes, chronic kidney and liver disease, and cerebrovascular disease, and were more likely to be prescribed renin-angiotensin antagonists, beta blockers, and calcium channel blockers at the time of HFpEF diagnosis (Table 1).

Conclusion: Our results describe the characteristics of veterans with HFpEF and suggest that African-American patients have a higher prevalence of comorbidities that may be potential targets for the prevention and treatment of HFpEF in African-Americans.

Table 1. Racial differences in baseline characteristics around the time of diagnosis of heart failure with preserved ejection fraction in a large national veterans affairs database

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>White (N=78,604)</th>
<th>African-American (N=12,535)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>73.3 (11.0)</td>
<td>68.3 (12.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Males (%)</td>
<td>96.6</td>
<td>95.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Body Mass Index (BMI)</td>
<td>32.2 (8.1)</td>
<td>32.3 (8.6)</td>
<td>0.5141</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>136.3 (22.9)</td>
<td>145.2 (26.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>72.2 (12.7)</td>
<td>78.3 (15.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Heart Rate</td>
<td>76.95 (16.9)</td>
<td>78.95 (16.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>EF (%), median (range)</td>
<td>60 (50-100)</td>
<td>60 (50-95)</td>
<td>0.003</td>
</tr>
<tr>
<td>Hypertension</td>
<td>90.4</td>
<td>94.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>73.1</td>
<td>64.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Type 2 Diabetes</td>
<td>58.2</td>
<td>65.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>31.4</td>
<td>14.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>52.9</td>
<td>38.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>28.2</td>
<td>41.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td>6.5</td>
<td>7.3</td>
<td>0.0011</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>54.4</td>
<td>46.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Stroke/TIA</td>
<td>6.2</td>
<td>7.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Serum sodium</td>
<td>138.5 (4.1)</td>
<td>139.3 (3.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>1.4 (0.8)</td>
<td>1.8 (1.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ACE or ARB prescription</td>
<td>55.3</td>
<td>61.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Beta blockers prescription</td>
<td>58.2</td>
<td>60.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Calcium channel blockers prescription</td>
<td>32.5</td>
<td>46.6</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Values reported are mean (SD) for continuous variables.
HEART FAILURE: NOVEL RISK FACTORS, PREDICTORS, NEW TREATMENT OPTIONS AND OUTCOME

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RISK FACTORS ASSOCIATED WITH DIAGNOSTIC DISCREPANCY FOR LEFT VENTRICULAR HYPERTROPHY BETWEEN ELECTROCARDIOGRAPHY AND ECHOCARDIOGRAPHY
M. Pareek¹, S.S. Petersen¹, L.R. Pedersen¹, M.L. Nielsen¹, S.Z. Diederichsen¹, M. Leosdottir², P.M. Nilsson³, A.C.P. Diederichsen⁴, M.H. Olsen¹
1. Cardiovascular and Metabolic Preventive Clinic, Department of Endocrinology, Centre for Individualized Medicine in Arterial Diseases (CIMA), Odense University Hospital, Odense, Denmark
2. Department of Cardiology, Skane University Hospital, Malmo, Sweden
3. Department of Clinical Sciences, Lund University, Skane University Hospital, Malmo, Sweden
4. Department of Cardiology, Odense University Hospital, Odense, Denmark

Background and objective: ECG is recommended for assessment of left ventricular hypertrophy (LVH) in asymptomatic adults with hypertension or diabetes. The sensitivity of echocardiography to detect LVH is greater than that for ECG, but the latter is simple, inexpensive, and has high specificity. The objective of this study was to investigate the influence of cardiovascular risk factors, including fasting plasma glucose (FPG), on the association between electrocardiographic and echocardiographic LVH in an elderly population.

Materials and methods: Study subjects were derived from the Malmo Preventive Project Re-Examination Study, a population-based cohort study, conducted 2002-2006. Cross-sectional associations between electrocardiographic and echocardiographic LVH, defining LVH according to the Sokolow-Lyon voltage combination, Cornell voltage-duration product, or left ventricular mass index (LVMI) were tested. Differences between standardized LVMI and Sokolow-Lyon voltage combination or Cornell voltage-duration product (absolute value/cut-off value for LVH) were used as outcome variables in order to identify explanatory variables associated with diagnostic discrepancies between ECG and echocardiography.

Results: Of the 1455 subjects included, 75% did not display any signs of LVH, 7% had LVH defined by ECG only, 12% had LVH defined by echocardiography only, and 6% had LVH on both ECG and echocardiography. Older subjects and those with higher blood pressure were more likely to have a relatively greater LVMI on echocardiography than that predicted on ECG (odds ratio: 1.95 per 10 years (95% confidence interval (CI): 1.53-2.47) and odds ratio: 1.15 per 10 mmHg (95% CI: 1.08-1.23), respectively, p<0.0001 for both). In addition, discrepancy was also seen in subjects receiving antihypertensive medication (odds ratio: 1.36 (95% CI: 1.04-1.79), p=0.03), but FPG did not independently influence discrepancy between ECG and echocardiography.

Conclusion: Age, blood pressure, and use of antihypertensive medication were associated with a greater risk of non-consistency between LVH determined by ECG and echocardiography.
HEART FAILURE: NOVEL RISK FACTORS, PREDICTORS, NEW TREATMENT OPTIONS AND OUTCOME

ECHOCARDIOGRAPHIC PREDICTORS OF HEART FAILURE IN HYPERTENSIVE CARDIOMYOPATHY

A. Bhullar, M. Bhullar, M. Singh, K. Muhyieddeen, B. Khatri, R. Ferdman, A. Najafi, C. Katikireddy
UCSF Fresno Medical Education Program, Fresno, CA, USA

Objective: To determine the echocardiographic (Echo) predictors of heart failure (HF) in hypertensive cardiomyopathy (HTN-CM).

Background: In hypertensive cardiomyopathy (HTN-CM), Echocardiographic (Echo) predictors of heart failure (HF) are not well studied. We sought to evaluate the atrial, ventricular, valvular and vascular (aortic) morphologic and functional predictors of HF in HTN-CM.

Methods: From Echo laboratory, we identified 280 consecutive cases of HTN-CM and 62 controls with a history of hypertension and no cardiomyopathy (HTN-No CM). We examined them for a history of HF, clinical, EKG and Echo variables including but not limited to left ventricular (LV) mass, LV geometry, LV EF, diastolic function and mitral annular systolic velocity (S'), a surrogate of myocardial systolic function. HTN-CM with HF was compared with the group without HF and controls.

Results: In HTN-CM, 66 %, 28 % and 6 % had concentric hypertrophy, concentric remodeling and eccentric hypertrophy respectively. Females were 57%; Mean age was 56 ± 14 years. 39% had HF among which 82% had HF with preserved EF (EF >50%). On bivariate analysis, a significant difference was noted in 2 out of 14 Echo variables (LV diastolic dysfunction and S’) and 4 clinical parameters (CAD, renal dysfunction, tobacco and methamphetamine abuse). Of note, no difference was observed in LV phenotype, mass and EF between HTN-CM with and without HF groups. On multivariate analysis, LV advanced (moderate to severe grade) diastolic dysfunction (OR: 2.36; CI: 1.13-4.93; p=0.02) and impaired S’ (≤6cm/sec, OR: 1.79; CI: 1.30-3.30; p=0.01) were the only independent Echo predictors of HF (figure).

Conclusion: LV functional (advanced diastolic dysfunction and impaired S’) but not the morphologic parameters (CM phenotype, LV mass) are the independent Echo predictors of HF in HTN-CM.
THE EFFECT OF MATERNAL OBESITY ON THE EXPRESSION AND FUNCTIONALITY OF PLACENTAL P-GLYCOPROTEIN: IMPLICATIONS IN THE INDIVIDUALIZED TRANSPLACENTAL DIGOXIN TREATMENT FOR FETAL HEART FAILURE

C. Wang, K.Y. Zhou, H.Y. Li, Y.F. Li, Y. Zhang, Y.M. Hua
Department of Pediatric Cardiology, West China Second University Hospital, Sichuan University, Chengdu, Sichuan, China

Introduction: Placental P-glycoprotein (P-gp) plays a significant role in controlling digoxin transplacental rate. Investigations on P-gp regulation in placenta of women with different pregnant pathology are of great significance to the individualized transplacental digoxin treatment for fetal heart failure (FHF). This study aimed to explore the effect of maternal obesity on the expression and functionality of placental P-gp both in human and in mice.

Methods: Placenta tissues from obese and lean women were collected. Female C57BL mice were fed with either a normal chow diet or a high-fat diet for 12 weeks before mating and throughout pregnancy. Maternal plasma glucose, HDL-C, LDL-C, TC, TGs, insulin, IL-1β, IL-6 and TNF-α concentrations was detected. Placental ABCB1/abc1a/abc1b/IL-1β/IL-6/TNF-α mRNA and P-gp/IL-1β/IL-6/TNF-α protein expression were determined by real-time quantitative PCR and western-blots, respectively. Maternal plasma and fetal-unit digoxin concentrations were detected by a commercial kit assay.

Results: Both ABCB1 gene mRNA and protein expression of obesity group was significantly lower than that of control group in human. The high-fat dietary intervention resulted in an overweight phenotype, a significant increased Lee’s index, higher levels of plasma glucose, HDL-C, LDL-C, insulin and TGs, increased peri-renal and peri-reproductive gland adipose tissue weight and larger size of adipose cell. Compared with control group at the same gestational day (E12.5, E15.5, E17.5), placental Abcb1a mRNA and P-gp expression of obese group were significantly decreased in mice, while digoxin transplacental rates were significantly increased. Higher maternal plasma IL-1β/TNF-α concentrations and placental IL-1β/TNF-α expression were observed in obesity groups in comparison with control group at the same gestational age.

Conclusions: Maternal obesity could inhibit placental P-gp expression and its functionality both in human and in mice, which might be resulted from a heightened inflammatory response.
UTILITY OF THE LACE INDEX AT THE BEDSIDE IN PREDICTING 30-DAY READMISSION OR DEATH IN PATIENTS HOSPITALIZED WITH HEART FAILURE

P. Yazdan-Ashoori¹, S. Lee², Q. Ibrahim², H.G.C. Van Spall¹,²
1. McMaster University, Hamilton, Canada
2. Population Health Research Institute, Hamilton, Canada

Background: The LACE index threshold of 10 predicts readmission or death in general medical patients in administrative databases. We assessed whether LACE, computed at the bedside without adjustment for clinical variables, can predict 30-day clinical outcomes in patients hospitalized for heart failure (HF).

Methods: We used logistic regression with LACE index as the continuous predictor and 30-day readmissions and 30-day readmission or death as outcomes. We determined an optimal LACE threshold for predicting risk, using logistic regression and the closest-to-(0,1) criterion for dichotomized LACE scores. We assessed model discrimination with c statistic and 95% CI.

Results: Of 378 patients, a majority (91%) had LACE scores >10 making this an impractical threshold for risk prediction. Each increment in LACE score increased the odds of 30-day readmissions (OR 1.13, 95% CI 1.02-1.24) and 30-day readmissions or death (OR 1.11, 95% CI 1.01-1.22). C statistics for 30-day readmissions (0.59, 95% CI 0.52-0.65) and 30-day readmission or death (0.57, 95% CI 0.51-0.64), were comparable to the Centers for Medicare/Medicaid Services endorsed readmission risk score for these outcomes (P=0.598 and P=0.225, respectively). LACE ≥13 predicted 30-day readmissions (OR 1.92, 95% CI 1.18–3.13) and 30-day readmission or death (OR 1.60, 95% CI 1.00–2.54), and met the closest-to-(0,1) criterion for optimal threshold.

Conclusions: The LACE index calculated at the bedside predicts 30-day clinical outcomes in hospitalized HF patients with discrimination that is modest, but comparable to more complex risk prediction models. While there is a continuum of risk, a threshold of ≥13 is optimal to identify high-risk patients.
HEART FAILURE: NOVEL RISK FACTORS, PREDICTORS, NEW TREATMENT OPTIONS AND OUTCOME

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MIXED TREATMENT ANALYSIS OF TOLVAPTAN, ULTRAFILTRATION AND LOOP DIURETICS IN THE MANAGEMENT OF ACUTE CONGESTIVE HEART FAILURE

S. Dayanand¹, J.M. Martinez², R. Chait³
1. Univ of Central Florida, Kissimme, FL, USA
2. Einstein Medical Ctr, Philadelphia, PA, USA
3. Univ of Miami/JFK Medical Ctr Palm Beach Regional GME Consortium, Atlantis, FL, USA

Introduction: Tolvaptan a V2 receptor antagonist has been used to treat volume overload in patients with heart failure (HF). Hypothesis: To compare the efficacy of Tolvaptan to furosemide and ultrafiltration when used in the management of volume overload in HF.

Methods: Studies were extracted from an electronic literature search of PubMed, MEDLINE and EMBASE. Of all relevant RCTs, 9 RCTs, including 5278 patients were identified. The main outcome of interest to assess effectiveness in the treatment of volume overload was the mean relative reduction of body weight from baseline. There were several other outcomes of interest including relative increase in urine output and change in dyspnea scores. Outcomes for safety, primarily serious adverse events, adverse events causing discontinuation of drug, hypotension, change in baseline mean creatinine values and incidence of cardiac arrhythmias were also compared. A mixed-treatment comparisons analysis was used to compare each of these drugs to one another. Calculation of the probability that each treatment is best was implemented using the Bayesian Markov chain Monte Carlo method.

Results: Ultrafiltration had a 78% probability of being the best agent to cause significant reduction in body weight, it was also noted to be associated with the highest rank probability of causing deterioration of renal function. Tolvaptan had a 73% probability of being the second best agent to cause reduction in mean body weight. Tolvaptan showed a relative decrease of 0.72 kg (-0.21; 1.71) of the mean body weight when compared to furosemide. Tolvaptan was associated with the highest rank probability of 61% in causing any adverse events, followed by ultrafiltration and Loop diuretics.

Conclusion: The results of the study show that Tolvaptan has a comparable efficacy to that of furosemide and ultrafiltration, when used in the management of volume overload in HF but is associated with a higher risk of adverse events.
IMPLICATION OF MIR-1 AND MIR-144 IN INTRALIPID-INDUCED CARDIOPROTECTION AGAINST ISCHEMIA/REPERFUSION INJURY

N. Motayagheni, S. Sharma, J. Li, M. Eghbali
UCLA, Los Angeles, CA, USA

Objective: The objective of this study is to investigate the role of miRNA-1 (miR-1) and MiR-144 in intralipid-induced cardioprotection against ischemia/reperfusion (I/R) injury.

Background: We have recently reported that intralipid protects the heart against ischemia/reperfusion injury in male rodents. Intralipid reduced the infarct size in in-vivo model of I/R injury by ~70% and significantly increased heart functional recovery after an ischemic insult in isolated Langendorff perfused hearts. However, the underlying molecular mechanisms involved in cardioprotection offered by intralipid are not well understood. MicroRNA (miRNA) has been implicated as a regulatory molecule in many cardiovascular diseases, including myocardial I/R injury.

Methods and Results: The left coronary artery was occluded for 30 minutes followed by 3 hr of reperfusion in male rats. One single IV bolus of PBS (CTRL) or intralipid (20%, 5ml/kg body weight) was administered 5 min before reperfusion. Total RNA enriched in miRNAs was extracted only from the LV of the in-vivo hearts using miRVana RNA extraction kit. P<0.05 was considered statistically significant. Values are expressed as mean± SE. Our data shows that the expression of miR-1 was significantly upregulated in the hearts subjected to in-vivo I/R injury which received one bolus of intralipid compared to control hearts (2.23±0.46 in intralipid group vs. 1.25±0.2 in CTRL, p<0.05). Expression of miR-144 was also upregulated in intralipid group compared to control in hearts subjected to I/R injury (1.67±0.2 in intralipid group vs. 0.87±0.07 in CTRL, p<0.05). Our data suggests that intralipid may exert its cardioprotective action by up-regulating miR-1 and MiR-144 in the heart.

Conclusions: Intralipid protects the heart against I/R injury at least in part by inducing miR-1 and miR-144.
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REVERSAL OF XYLAZINE-INDUCED BRADYCARDIA WITH INTRALIPID
N. Motayagheni, M. Eghbali
UCLA, Los Angeles, CA, USA

Objectives: Sudden cardiac arrest accounts for 300,000 to 400,000 deaths annually in United States both in men and women. Cardiac arrest could be due to abnormally slow heart rate known as bradycardia. Bradycardia is a catastrophic event which is associated with significant mortality and morbidity.

Background: We have previously shown that Intralipid protects the heart against ischemia/reperfusion injury as well as Bupivacaine induced cardiotoxicity. Here we examined whether intralipid can protects the heart against bradycardia.

Method: Wild type female mice C57/Bl6 (2-4 month old) were anesthetized by isoflurane after heparinization. The heart was removed immediately and placed in cold Krebs–Henseleit buffer. The aorta was cannulated and the isolated heart (Langendorff) was perfused with Krebs–Henseleit at 37°C for 15 min for stabilization. Xylazine (100–300 mg) was directly applied to the heart surface for 1-2 min until bradycardia was achieved. The heart was then perfused with either Krebs-Henseleit (KH) solution (control group), or 1% ILP (intralipid group). Hemodynamic parameters and heart rates were recorded with a catheter directly inserted into left ventricle.

Results: The heart rates at the baseline before inducing bradycardia was 224±7 beats/min and the left ventricular pressures was 64±4 mmHg. Administration of Xylazine decreased the heart rate significantly to 81±9 beats/min and left ventricular pressure to 5±2 mmHg (p<0.001). Perfusion of the heart with intralipid rapidly restored the heart rate to 209±30 and left ventricular pressure to 59±4 which were not significantly different than their values before inducing bradycardia at the baseline. In the hearts that received Krebs–Henseleit after bradycardia, the heart rate (81±10 beats/min) and left ventricular pressure (20±8 mmHg) were significantly lower than intralipid group. In conclusion Intralipid has the ability to rapidly reverse bradycardia in female mice.
HIGH SALT DIET DURING GESTATION ALTERS SALT SENSITIVITY OF THE CARDIOVASCULAR SYSTEM IN OFFSPRING

S. Kagota, K. Maruyama, K. Shinozuka
Mukogawa Women’s University, Nishinomiya, Japan

The fetal environment—the mother’s body—has important effects on the offspring's cardiovascular system. Previously, we demonstrated that offspring of spontaneously hypertensive rats (SHR) fed a high-salt diet during gestation and lactation have lower blood pressure and left ventricular systolic and diastolic function, compared with offspring of SHR fed a control diet. It is unclear, however, whether the high salt intake affects cardiac function in offspring more during gestation or during lactation. In this study, we investigate the influence on cardiac function of a maternal high salt diet during gestation only, compared to the effects of high salt intake during both gestation and lactation. Some SHR were fed a high salt (6% NaCl) diet during gestation and lactation (HH-dam), some were fed a high salt diet during gestation and a control (0.3% NaCl) diet during lactation (HN-dam), and some were fed a control diet during both gestation and lactation (NN-dam). After weaning at 4 weeks of age, the offspring were fed either the control or the high salt diet for 8 weeks. Systolic blood pressure and heart rate of the offspring were measured using a photoplethysmographic tail-cuff system without heating, and ventricular weight was determined as an index of hypertrophy in 12-week-old offspring. Offspring of HH-dams and HN-dams had lower blood pressure and heart rate compared with offspring of NN-dams. Blood pressure and heart weight of offspring of NN-dams were increased by a postnatal salt diet, but those of offspring of HH-dams and HN-dams were not altered. In contrast, there was no significant difference in heart rate among all offspring. These results suggest that a maternal high salt intake, especially during gestation, is a predisposing factor for disturbance of salt sensitivity of the cardiovascular system in offspring.
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STUDY OF THERAPEUTIC AND CARDIOPROTECTIVE EFFECT OF CURCUMIN ON ISOPROTERENOL-INDUCED MYOCARDIAL INJURY IN RATS
M.S. Oliveira¹, L. Zangi², K.M. Mata¹, V. Blefari¹, S.G. Ramos¹
1. University of Sao Paulo, Ribeirao Preto, SP, Brazil
2. Icahn School of Medicine at Mount Sinai Hosp, New York, NY, USA

Curcumin (diferuloylmethane), a principal member of the Curcuma species, is find to suppress TGF-beta activity and for his well-known anti-inflammatory and anti-oxidant activities.

Objectives: Hence we wanted to test the cardioprotective (pretreatment) and therapeutic (posttreatment) potential effects of curcumin (CUR) in isoproterenol (ISO)-induced myocardial injury.

Methods: We compared between 6 groups designed as: Control, DMSO, ISO, CUR, CUR+ISO and ISO+CUR for lipid peroxidation, biochemical parameters and histopathological findings in isoproterenol (ISO)-induced myocardial injury in Wistar rats. In this study Curcumin (200mg/kg) was administered using Alzet Mini-pumps for 15 days along with ISO (85 mg/kg, SC, at 24 hr interval) on 1st day (Group ISO+CUR) or 14th day (Group CUR+ISO) in rats. For immunohistochemistry we used antibody 3-nitrotyrosine (3-NT). We measured the activities of creatine kinase-muscle, brain (CK-MB), malondialdehyde (MDA), glutathione (GSH) and Superoxide dismutase (SOD). For histopathological examination measuring collagen deposition, picro-sirius red staining was used. In addition to our in vivo work, we tested the role of curcumin to induce survival in a primary culture of one-day-old neonatal rat cardiac myocytes. For this we culture cells with ISO (10microM) for 48 hours and stimulated them with curcumin (4 microM) for 2 hours and stain for apoptosis marker, TUNEL.

Results: Our results suggest that curcumin pretreatment decreased the nitrotyrosine levels (marker of formation of peroxynitrite) (P<0.001) and a tendency towards reduction in the GSH values, but this reduction was not observed in the posttreatment group (ISO + CUR). Cardiac tissue collagen concentration increased in ISO administered group and decreased after curcumin pretreatment and posttreatment groups (P<0.001). The ISO-CUR treated groups showed a statistically significant decrease in TUNEL staining (P< 0.001) when compared to ISO only administration group.

Conclusion: Our preliminary data suggests that within a narrow dose range curcumin could reduces isoproterenol-induced cardiomyocyte death, lipid peroxidation and collagen deposition.
REGULATION OF REDOX-HOMEOSTASIS BY METABOLIC DRUG ELTACIN IN THERAPY OF AGING PATIENTS WITH ISCHEMIC HEART DISEASE

E.V. Kalinina1, R.M. Zaslavskaya2, Y.R. Nartsissov3
1. People’s Friendship University of Russia, Moscow, Russia
2. Hospital 60, Moscow, Russia
3. Research Institute of Cytochemistry and Molecular Pharmacology, Moscow, Russia

Objectives: Intracellular reduction-oxidation imbalance, called oxidative stress, can subsequently contribute to the development and/or progression of cardiovascular diseases such as atherosclerosis, ischemia-reperfusion injury, chronic ischemic heart disease. The aim of this investigation was to determine the effect of metabolic drug eltacin contained amino acids (glutamate, cysteine, glycine) on cellular redox homeostasis state in old patients with ischemic heart disease.

Methods: The use of eltacin (220 mg x 3 times per day) in addition with traditional therapy (β-adrenoblockers, aspirin, Ca-antagonists, nitrates, diuretics) of aging patients (69 ± 2.7 years old) with ischemic heart disease, angina pectoris functional class II-III was estimated. Before and 21 days after the therapy ECG-monitoring, EchoCG data were examined. Activities of antioxidant enzymes, reduced (GSH) and oxidized (GSSG) glutathione maintenance in erythrocytes, malonyl dialdehyde (MDA) level in plasma have been tested.

Results: The use of eltacin in therapy of patients resulted in an increase of glutathione (GSH) maintenance, GSH/GSSG ratio and activity of GSH-related enzymes (glutathione peroxidase, glutathione transferase) as well as glutaredoxin and thioredoxin, Cu,Zn-superoxide dismutase, catalase in erythrocytes up to control values depressed until the treatment. The increase of antioxidant state of erythrocytes was accompanied by the decrease of lipid peroxidation and depression of ROS production. Extent of the development of antioxidant response was time-related and correlated with positive alteration of patient states: a rise of exercise tolerance, reduction of myocardial power consumption, antiarrhythmic effect.

Conclusions: It may be concluded that eltacin has ability to reduce oxidative stress by improving cellular redox state that give it perspective for the use in therapy of ischemic heart disease.
EXPRESSION OF OPIOID RECEPTORS DELTA AND KAPPA IN THE HUMAN TISSUE OF DIABETIC'S PATIENTS

M. Ismail1,2, A. Rungatscher1, M.A. Gebrie1, G.B. Luciani1, I. Cristobo2, S. Notararigo2, C. Chen-Scarabelli2, T. Scarabelli2, G. Faggian1
1. University of Verona, Italy
2. University of Alabama at Birmingham, USA

Background: Opioid receptors include four major subtypes, i.e. mu (MOR), delta (DOR), kappa (KOR), and nociceptin receptor (NOR), all of which G protein-coupled receptors. Prior studies carried out both in animal models and the human hearts have shown that opioid receptor activation induces cardioprotection. Although it is well known that diabetic patients (DMPs) undergoing on-pump cardiac surgery (OPCS) have higher morbidity and mortality than non-diabetic patients (NDMPs), the molecular mechanisms responsible for the reported worse outcomes remain unknown.

Objectives: The present study investigated the expression levels of DOR and KOR in the right atrium of DMPs and NDMPs undergoing OPCS.

Methods: A total of 20 sequential biopsy specimens were obtained from the right atrium of 10 DMPs and 10 NDMPs before cardiopulmonary bypass. The expression levels of DOR and KOR RNA and protein were evaluated by Real-Time (RT) PCR, as well as Western Blotting (WB) and immunohistochemistry, respectively.

Results: By RT-PCR and WB analysis, DOR and KOR RNAs and proteins were detected in all samples from DMPs and NDMPs. Cytosolic and perinuclear expression of DOR and KOR proteins was detected by immunohistochemistry in 55+/−6% of cardiac cells from DMPs and in 53+/−8% of myocytes from NDMPs (p: >0.05). Colocalization of DOR and KOR proteins was seen in the vast majority of cardiac cells (87+/−11% in DMPs and 82+/−8% in NDMPs; p: >0.05).

Conclusion: The expression levels of DOR and KOR proteins assessed prior to cardioplegic arrest in patients undergoing OPCS was not found to be different between DMPs and NDMPs. Further experiments are warranted to verify whether cardioplegic arrest can induce differently DOR and KOR RNAs and proteins in NDMPs vs DMPs and, if so, whether this change in expression can affect myocytes survival in either patient population.
Cardiomyocytes (CMs) generated from human induced pluripotent stem cells (hiPSCs) are increasingly used in disease modeling and drug evaluation. However, they are typically a heterogeneous mix of ventricular-, atrial- and nodal-like cells based on action potentials (APs) and gene expression. This heterogeneity and the paucity of methods for high-throughput functional phenotyping hinder the full exploitation of their potential. Therefore, to develop a method for rapid, subtype-specific phenotyping of hiPSC-CMs with respect to AP morphology and single-cell arrhythmias, we used cardiac lineage-specific promoters to drive the expression of a voltage-sensitive fluorescent protein, enabling subtype-specific optical AP recordings. In a patient-specific hiPSC model of long-QT syndrome type 1, AP prolongation and frequent early afterdepolarizations were evident in mutant ventricular- and atrial-like, but not in nodal-like hiPSC-CMs compared to their isogenic controls, consistent with the expression of the disease-causing gene. Furthermore, we demonstrate the feasibility of sequentially probing a cell over several days to investigate genetic rescue of the disease phenotype and to discern CM subtype-specific drug effects. Taken together, by combining a genetically-encoded membrane voltage sensor with promoters that drive expression in the major subtypes of hiPSC-CMs, we developed a convenient system for disease modeling and drug evaluation in the relevant cell type that has the potential to advance the emerging utility of hiPSCs in cardiovascular medicine.
LOW SERUM HIGH DENSITY LIPOPROTEIN CHOLESTEROL LEVEL AND LOW BODY MASS INDEX ARE ASSOCIATED WITH CONTRAST-INDUCED ACUTE KIDNEY INJURY IN PATIENTS UNDERGOING PRIMARY PERCUTANEOUS CORONARY INTERVENTION FOR MYOCARDIAL INFARCTION
B.M. Choi, Y.O. Kim, H.W. Kim
The Catholic University, Seoul, Korea

Background: Contrast-induced acute kidney injury (CI-AKI) after primary percutaneous coronary intervention (PCI) is associated with significantly increased morbidity and mortality in patients with myocardial infarction (MI). Previous studies have shown that the most important risk factor for developing CI-AKI is pre-existing renal insufficiency. Older age, anemia, contrast volume, peri-procedural hemodynamic instability, diabetes mellitus, and acute hyperglycemia are also associated with CI-AKI. The aim of this study was to identify additional risk factors for CI-AKI in patients with MI undergoing primary PCI.

Methods: This study included 433 MI patients treated with emergency primary PCI. Baseline characteristics and clinical outcomes were compared between the groups of patients with and without CI-AKI and logistic regression analysis was performed to identify independent risk factors for CI-AKI.

Results: Serum high density lipoprotein (HDL) cholesterol level (odds ratio [OR] 0.950, 95% confidence interval [CI] 0.907–0.995; p = 0.031) and body mass index (BMI) (OR 0.794, 95% CI 0.664–0.951; p = 0.012) were found to be risk factors for development of CI-AKI in addition to pre-procedural estimated glomerular filtration rate (eGFR) (OR 0.951 95% CI 0.928–0.975; p < 0.001), and pre-procedural plasma glucose level > 154 mg/dL (OR 6.270, 95% CI 1.623–24.228; p = 0.008) on multivariate analysis.

Conclusion: In addition to decreased pre-procedural eGFR, and increased pre-procedural plasma glucose level, low serum HDL cholesterol level and lower BMI are associated with an increased risk of CI-AKI.
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DEFINITIVE ACUTE STENT THROMBOSIS IN A PATIENT WITH NON-ST ELEVATION MYOCARDIAL INFARCTION
S. Zamin, G. Wilson, K. Suarez, K. Slicker
Baylor Scott & White Health/Texas A&M College of Medicine, TX, USA

Background: With incidence below 1%, acute stent thrombosis is an uncommon complication of percutaneous coronary intervention (PCI), and can occur despite the use of drug-eluting stents (DES) and dual anti-platelet therapy (DAPT).

Case: An 87-year-old lady with history of coronary artery disease and PCI presented with sudden onset chest discomfort, nausea, and dyspnea. Her electrocardiogram showed normal sinus rhythm without dynamic ST segment changes, but troponin levels increased to 0.30 after 6 hours. Treatment started with Heparin drip, Aspirin, Metoprolol, and Atorvastatin. She subsequently went for angiography revealing 95% stenosis of the proximal right coronary artery (RCA) as well as 90% in-stent restenosis of the posterior descending artery (PDA). Successful PCI was achieved with DES to the proximal RCA and balloon angioplasty to the PDA. She was then started on Aspirin and Plavix.

Clinical decision: Shortly after returning to the floor, she became diaphoretic and described sudden, severe back pain, with a blood pressure of 70/40 mmHg and a junctional bradycardic heart rhythm. Atropine was followed by a dopamine infusion. Electrocardiogram revealed elevation of the ST segment in leads III and aVF. A repeat angiogram revealed that the proximal RCA was entirely occluded, consistent with acute stent thrombosis. During revascularization, she went into asystole and return of spontaneous circulation was attained after 5 minutes. Repeat PCI was successful, but a temporary pacemaker was placed for junctional bradycardia and she required hemodynamic support with inotropes. Plavix was replaced with Brilinta. She was placed in the ICU, where over a 2 day period, the inotropes were tapered. Patient was later discharged home.

Conclusion: While rare, stent thrombosis can occur in the setting of appropriate therapy with DES and DAPT, and early detection is critical given high risk of mortality. This case demonstrates the importance of recognition and intervention of acute stent thrombosis.

Figure 1. Initial angiogram of RCA
Figure 2. Initial angiogram post PCI
Figure 3. Repeat angiogram stent thrombosis
Figure 4. Repeat angiogram post PCI
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WELLENS’ SYNDROME REVISED

S. Oo¹, K. Khalighi², C. May¹, T.T. Aung

1. Easton Hospital, Easton, PA, USA
2. Easton Hospital Easton, PA, Drexel University, School of Medicine, Easton Cardiovascular Associates, Easton, PA, USA

Objective: Wellens’ syndrome is characterized by the state of impending myocardial infarction even with optimal medical treatment. Our patient presented with type A Wellens’ sign before the stent was placed and type B Wellens’ sign after drug eluting stent placement. Resolution of the characteristic electrocardiogram (EKG) changes was the routine result of appropriate coronary intervention. However, our patient still had abnormal EKG even after the intervention.

Background: Wellens’ syndrome is a condition in which characteristic Biphasic T waves in V2, V3 (25%) or deep and symmetrical T inversions in V2, V3 (75%) with history of angina chest pain, normal or minimally elevated cardiac enzyme levels. All patients with Wellens’ syndrome must undergo coronary intervention. Stress test is contraindicated since it can lead to sudden cardiac death.

Method: A 52-year man with no significant past medical history presented with chest pain. His cardiac enzymes were normal. EKG showed biphasic T waves in V2 and V3, consistent with type A Wellens’ sign. He underwent urgent coronary angiography, which revealed 99% occlusion in proximal left anterior descending artery (LAD) which was intervened with a drug eluting stent.

Result: His chest pain was resolved after intervention. However, post-procedure EKG still present Wellens’ type B changes. Reperfusion of the ischemic myocardium was a possible explanation. Ongoing research should evaluate the prognosis of patients with persistent abnormal EKG changes even after the appropriate intervention.

Conclusion: Wellens’ syndrome is characterized by T wave changes in EKG with or without chest pain. This syndrome represents a pre-infarction stage of coronary artery disease involving proximal LAD, which can subsequently lead to extensive anterior myocardial infarct and even death without coronary artery revascularization. Therefore, it is crucial for clinicians to recognize EKG features of Wellens’ syndrome in order to take appropriate therapy to reducing mortality and morbidity form impending myocardial infarction.
DIFFUSE MULTIVESSEL CORONARY ARTERY SPASM (CAS) INDUCED BY GUIDEWIRE INSERTION LEADING TO CARDIAC ARREST: A CASE REPORT

B.T. Yeneneh, B. Louka, E. Yang, D. Fortuin
Mayo Clinic, Arizona, USA

Introduction: Coronary artery spasm (CAS) during PCI is well described, although multivessel involvement rarely occurs. Diffuse CAS solely following guidewire insertion is a very rare phenomenon, comprising about 1%. To our knowledge, diffuse, multivessel CAS induced by guidewire insertion leading to cardiac arrest has not been reported.

Case Report: JL, a 74 years old man, presented to the catheterization laboratory due to abnormal stress echocardiogram. Using right radial approach, angiography of the right and left coronary systems showed 50% lesions in the proximal LAD and proximal RCA. Given the abnormal stress test, decision was made to assess fractional flow reserve (FFR) across these lesions, starting with the LAD. A 0.014” St Jude PressureWire was inserted crossing the lesion in proximal LAD. Following this, the patient suddenly developed bradycardia and hypotension that quickly progressed to PEA arrest. Standard CPR protocol was initiated. Angiography showed diffuse multivessel coronary spasm, with total occlusion of LAD and near-total occlusion of left circumflex. 400 mcg of nitroglycerin was administered into the left main coronary artery. Adding inotropic and vasopressor support, spontaneous circulation was restored. Repeat angiography revealed complete restoration of the above multivessel CAS suggesting resolution. The procedure was completed and patient was admitted to the ICU for continued care.

Conclusion: CAS induced solely by guidewire insertion is a very rare phenomenon, comprising about 1% in a study of 906 patients undergoing intracoronary Doppler flow measurement using 0.014” or 0.018” Doppler FloWire. Two cases have reported diffuse right coronary artery spasm induced by guidewire insertion, with those patients’ being mainly asymptomatic. CAS during coronary angiography usually responds well to intracoronary injection of nitrated and calcium channel blockers. Prompt recognition and immediate treatment of diffuse multivessel CAS is crucial to avoid a potential hemodynamic catastrophe that could result in severe debility or even death.
ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION AND FACTORS ASSOCIATED WITH STENT CHOICE

J.D. Nunez Breton, J.C. Duque Ballesteros, C.A. Gomez, C. Rueda Rios, J.P. Zambrano, C.E. Mendoza, A. Ferreira
Jackson Memorial Hospital, Miami, FL, USA

Objective: This study aims to identify predictors of stent choice during primary percutaneous coronary intervention (PCI).

Background: Although drug eluting stents (DES) are associated with reduced risk for repeat revascularization compared to bare-metal stent (BMS) in the setting of ST-Segment elevation myocardial infarction (STEMI), BMS are still used for a large number of patients. In addition to concerns regarding the ability to comply with long term dual antiplatelet therapy, other factors may influence stent choice.

Methods and results: We performed a retrospective review of all 561 STEMI patients treated with primary PCI from January 2009 to December 2013 in a large safety-net hospital. Groups were divided according to type of stent. Population included Latinos (56%), Caucasians (24%) and Blacks (19%). Sixty-six percent (n=342) received a BMS. Patients were predominantly males (79.4%), of whom (68.3%) received BMS, compared to (58.5%) of the female patients who received BMS (p=0.05). Mean age for subjects who received DES was 60.9 (±10) years-old compared to 59.0 (±12) in the BMS group (p=0.07). No difference was found in terms of traditional risk factors including: hypertension, diabetes mellitus, hyperlipidemia, tobacco use, history of stroke or coronary artery disease. No difference with cocaine use. Oral anticoagulants predicted the use of BMS (31.6% versus 1.7%, p=0.02), no association with other home medication was found. The BMS use trended higher in altered mental status (9.2% versus 2.3% p=0.26) and ventricular tachycardia/fibrillation prior to procedure (11.9% versus 5.1%, p=0.57). Although higher initial troponin level was found in patients with DES use (p=0.049), there was no correlation with the number of obstructed vessels.

Conclusions: Factors associated with BMS use were home anticoagulation, male gender and initial troponin level. More patients with initial altered mental status and ventricular arrhythmia were observed in the BMS group. No association with cocaine use was found.
METHYLENEDIOXYMETHAMPHETAMINE (MDMA) INDUCED SPONTANEOUS CORONARY ARTERY DISSECTION

F. Benn, A. Afzal, B. Subedi, M. Majumder,
New York Methodist Hospital, Weill Cornell Affiliate, Brooklyn, NY, USA

Spontaneous coronary artery dissection (SCAD) is an uncommon but important cause of sudden cardiac death (SCD) with a predilection for females during pregnancy and post partum period. The syndrome has also been described in the setting of inflammatory, connective tissue disorders and hyperadrenergic states. We report the case of a female who presented with chest pain and ST segment elevations and found to have angiographic evidence of SCAD.

A 27 year-old female with no significant medical history presented with complaints of left chest pain starting 6 hours prior. She reported using 'Molly' the night prior to admission and had no family history of premature coronary artery disease (CAD) or SCD. Workup revealed a normal hemogram and chemistry panel, negative urine pregnancy test and chest radiography was clear of infiltrates with normal mediastinum. EKG showed diffuse ST elevations most prominent in the lateral leads, with normal troponin I and mildly elevated CKMB to 4.7. Subsequent EKGs showed similar pattern but repeat cardiac biomarker 4 hours later showed marked elevation in CKMB and troponin I to 125.7 and 7.65 respectively. She was urgently taken for a left heart catheterization which revealed dissection of the proximal left anterior descending coronary artery with apical akinesis and bare metal stent was successfully deployed.

The mechanism of SCAD leading to acute coronary syndrome and SCD is thought to be from compressive ischemia that results from an intramural hematoma after dissection of the coronary artery. Patient presenting with this syndrome typically lack traditional CAD risk factors and may present with a myriad of symptoms making it difficult to recognize thus a high degree of suspicion and detailed history may help identify the syndrome. Management is still debatable but when suspected, prompt intervention often with percutaneous angiography and stenting is generally employed to prevent potentially fatal consequences.

Figure 1. Cranial fluoroscopic view showing dissection

Figure 2. Post stent placement in proximal LAD
ECTATIC CORONARY VESSELS WITH MULTIPLE GIANT ANEURYSMS

K. Tan, F. Kho, I. Syed
Khoo Teck Puat Hospital, Singapore

Background: Coronary ectasias are rare, but coronary aneurysms are even rarer.
Method: We describe an elderly patient with such coronary anomalies, presenting to us with acute coronary syndrome. To the best of our knowledge, this is the first case describing triple vessel ectasias with coexisting multiple giant aneurysms in an elderly individual.

Abbreviations: LAD – left anterior descending artery; LCx – left circumflex artery

Results and conclusions: A 75-year-old Indian man, with a history of heavy smoking, presented with a four-day history of chest pain. His ECG on arrival showed anterior hyperacute T-wave with elevated troponins. A coronary angiography was immediately performed on him.

On angiography, his three epicardial coronary arteries were ectatic with aneurysmal segments in the LAD (10mm) and LCx (50mm). The mid-LAD was not visualised after the aneurysmal segment, representing the culprit occlusion. The LCx beyond the mid-segment giant aneurysm was also not well visualized, likely due to a silent thrombosis (Figure 2). No percutaneous intervention was attempted due to high thrombus burden in the aneurysmal segment. Transthoracic echocardiography showed segmental wall abnormalities in the anterior and lateral walls. The mid-LCX giant aneurysm was captured in the atrioventricular groove beside the coronary sinus. He was started on subcutaneous enoxaparin.

The patient was asymptomatic following anticoagulation. Relook invasive and computed tomography coronary angiography was not performed due to patient’s financial constraints. He was started on long term oral anticoagulation and discharged with subsequent follow up in India.
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DECADe LONG TRENDs (2001-2011) IN THE USE OF EVIDENCE BASED MEDICAL THERAPIES AT THE TIME OF HOSPITAL DISCHARGE FOR PATIENTS SURVIVING ACUTE MYOCARDIAL INFARCTION: A POPULATION BASED PERSPECTIVE

R.P. Makam¹, N. Erskine¹, D.D. McManus², D. Lessard¹, J.M. Gore², J. Yarzebski¹, R.J. Goldberg¹

1. Department of Quantitative Health Sciences University of Massachusetts Medical School Worcester, MA, USA
2. Department of Medicine University of Massachusetts Medical School Worcester, MA USA

Background: Optimization of medical therapy during discharge planning is vital for improving patient outcomes after hospitalization for acute myocardial infarction (AMI). However, limited information is available about recent trends in the prescribing of evidence-based medical therapies in these patients, especially from a population-based perspective. We describe decade-long trends in the discharge prescribing of aspirin, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, beta-blockers, and statins in hospital survivors of AMI.

Methods: The study population consisted of 5,253 patients who were discharged from all 11 hospitals in central Massachusetts after an AMI in 6 biennial periods between 2001 and 2011. Combination medical therapy (CMT) was defined as the prescription of all 4 cardiac medications at the time of hospital discharge.

Results: The average age of this population was 69.2 years and 57.7% were men. Significant increases were observed in the use of CMT, from 25.6% in 2001 to 48.7% in 2011, with increases noted for the individual cardiac medications examined. Subgroup analysis also showed improvement in discharge prescriptions for P2Y12 inhibitors in patients who underwent a percutaneous coronary intervention (PCI). Presence of a DNR order, prior co-morbidities, hospitalization for NSTEMI, and failure to undergo cardiac catheterization or a PCI were associated with underuse of CMT.

Conclusions: Our study demonstrates encouraging trends in the prescribing of evidence-based medications at the time of hospital discharge for AMI. However, certain patient subgroups continue to be at risk for underuse of CMT, suggesting the need for strategies to enhance compliance with current practice guidelines.
LIPIDS, OBESITY, METABOLIC SYNDROME AND DIABETES

DIABETES AND ISCHEMIC HEART DISEASE DEATH IN PEOPLE AGE 25-54: A MULTIPLE-CAUSE-OF-DEATH ANALYSIS BASED ON OVER 400 000 DEATHS FROM 1990 TO 2008 IN NEW YORK CITY

A.M. Quinones1, I. Lobach1, G.A. Maduro2, N.R. Smilowitz1, H.R. Reynolds1
1. NYU Langone Medical Center, New York, NY, USA
2. Department of Health and Mental Hygiene, New York, NY, USA

Background: Over the past decade, ischemic heart disease (IHD) mortality trends have been less favorable among adults age 25-54 than age ≥55 years.

Hypothesis: Disorders associated with IHD such as diabetes, chronic inflammatory and infectious diseases, and cocaine use are important contributors to premature IHD mortality.

Methods: Multiple-cause-of-death analysis was performed using the New York City (NYC) Vital Statistics database. Frequencies of selected contributing causes on death records with IHD as the underlying cause for decedents age ≥25 were assessed (n = 418,151; 1990-2008). Concurrent Telephone risk-factor surveys (NYC Community Health Survey, Centers for Disease Control Behavioral Risk Factor Survey in New York State) were analyzed.

Results: In sum, a pre-specified contributing cause was identified on 13.6% of death certificates for IHD decedents age 25-54. Diabetes was reported more frequently for younger IHD decedents (15% of females and 10% of males age 25-54 vs 6% of both sexes age ≥55). In contrast, concurrent diabetes prevalence in New York State was 3.4% for those age 25-54 and 13.6% for those age >55 (P < 0.0001). Systemic lupus erythematosus, human immunodeficiency virus, and cocaine were also more likely to contribute to IHD death among younger than older people.

Conclusions: Diabetes may be a potent risk factor for IHD death in young people, particularly young women, in whom it was reported on IHD death records at a rate 5X higher than local prevalence. The high frequency of reporting of studied contributing causes in younger IHD decedents may provide a focus for further IHD mortality-reduction efforts in younger adults.
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SERUM MAGNESIUM AND IMPAIRED FASTING GLUCOSE IN NON-DIABETIC ADULTS

L.C. Del Gobbo¹, X. Zhang², L. Wang³, H.D. Sesso³, J.E. Manson³, A. Pradhan³, Y. Song²

1. Department of Medicine, Division of Cardiovascular Medicine, Stanford University, Stanford, CA, USA
2. Department of Epidemiology, Richard M. Fairbanks School of Public Health, Indiana University, Indianapolis, IN, USA
3. Division of Preventive Medicine, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA, USA
4. Division of Cardiovascular Medicine, VA Boston Healthcare System, Boston, MA, USA

Background: Epidemiological evidence on the link between Magnesium (Mg) and fasting glucose has been mixed.

Objectives: This study investigated whether and to what extent blood levels of Mg were independently associated with fasting glucose levels in nondiabetic adults.

Methods: We conducted a cross-sectional study among 890 participants aged 51-87 years from the Clinical Translational Science Center (CTSC) subcohort of the VITamin D and OmegA-3 TriaL. Participants were free of self-reported diabetes mellitus, cardiovascular disease, and cancer and had fasting glucose <126 mg/dl. We used linear regression to compare fasting glucose levels across five categories of serum Mg levels at 0.54-0.75, 0.76-0.83, 0.83-0.88, 0.89-0.95, and 0.96-1.04 mmol/L. Logistic regression and restricted cubic spline regression was used to explore both linear and nonlinear associations of serum Mg with prevalent impaired fasting glucose (defined as fasting glucose in the range of 100-126 mg/dl). Multivariable models adjusted for age, sex, race/ethnicity, body mass index, smoking, parental history of ischemic heart disease, physical activity, alcohol consumption, history of hypertension, and renal function (eGFR).

Results: Of 890 nondiabetic participants, serum Mg levels were 0.85(±0.06) mmol/L and 181(20.3%) had impaired fasting glucose levels. Serum Mg was inversely associated with fasting glucose levels (94.5, 94.2, 93.1, and 91.3 mg/dL across increasing serum Mg categories, P for linear trend=0.05). The odds of impaired fasting glucose was higher in the lower categories of serum Mg; the ORs and 95% confidence intervals (CIs) for increasing categories of serum Mg were 1.65 (0.84-3.25), 1.67 (1.02-2.76), and 1.00 (referent), 1.14 (0.61-2.13), and 0.75 (0.33-1.69) (P for linear trend = 0.02). The trends remained similar in sensitivity analyses after excluding 370 participants with abnormal renal function or currently using antihypertensive medications.

Conclusions: Among non-diabetic individuals, serum Mg was inversely correlated with fasting glucose levels and presence of impaired fasting glucose.
ASSOCIATION BETWEEN THE RS11614913 POLYMORPHISM IN THE HSA-MIR-196A2 AND OBESITY-RELATED PARAMETERS

O. Coltell\textsuperscript{1,2}, D. Corella\textsuperscript{1,3}, R. Barragan-Arnal\textsuperscript{1,3}, E.M. Asensio\textsuperscript{1,3}, R. Fernandez-Carrion\textsuperscript{1,3}, O. Portoles\textsuperscript{1,3}, E. Ferriz\textsuperscript{1,3}, J.I. Gonzalez\textsuperscript{1,3}, J.M. Ordovas\textsuperscript{4}, J.V. Sorli\textsuperscript{1,3}

1. CiberOBN, Madrid, Spain
2. Universitat Jaume I, Castellon, Spain
3. University of Valencia, Valencia, Spain
4. Human Nutrition Research Center, Boston, USA

\textit{Background:} MicroRNAs (miRs) are small noncoding, single-stranded RNA molecules, that form base-pairs with target messenger RNA, leading to negative regulation of their translational stability and efficiency. They are involved in almost all cellular processes. Single nucleotide polymorphisms (SNPs) occurring in the miRNA gene region may have effects on the function of miRNAs through altering miRNAs expression, binding and/or maturation. Although there are several studies analyzing the effects of miRs polymorphisms on obesity-related phenotypes, there has been a lack of consistency in the results. In a previous study, consisting of a GWAS of 2,300 variants in miRNA-encoding sequences and their associations with some cardiometabolic traits, the SNP rs11614913(C>T), in the hsa-miR-196a2 was the one most associated with waist to hip ratio. In animal studies this miR-196a2 has been shown to be primarily involved in the regulation of inflammation.

\textit{Aims:} Our aim was to study whether the SNP rs11614913(C>T) in hsa-miR-196a2 is also associated with anthropometric parameters in a high cardiovascular risk Mediterranean population.

\textit{Methods:} We analyzed PREDIMED-Valencia participants (n=1,094; aged 67+/-7 y) at baseline. Anthropometric measurements were taken by direct measurement. We analyzed the rs11614913-SNP with a high-density array. Multivariable regression models were fitted.

\textit{Results and Conclusions:} Prevalence of miR-196a2-SNP genotypes was 36% CC; 48% CT and 15% TT. Variant allele carriers tended to have higher waist circumference in the whole population (102+/-12 cm; 103+/-12 cm and 104+/-12 cm; P=0.087). This association was higher and reached the statistical significance in women (P=0.028). Also in women, we found a significant association of this SNP with waist-to-height ratio, which was greater in variant-allele carriers (P=0.015). No association was found with BMI. In conclusion, this study has replicated the previously described association between the miR-196a2-rs11614913 SNP and waist measurement, mainly in women, so providing further evidence of the involvement of this miR in abdominal obesity.
Objectives: Mannan, belonging to immunomodulators of polysaccharide origin, was shown to stimulate macrophages in vivo via mannose receptor and can be used for stimulation and effective removing of atherogenic lipoproteins from circulation.

Background: Wall yeast polysaccharide water-insoluble zymosan was shown to decrease atherogenic serum lipids in lipemia. Beta-Glucan and mannan are the main components of zymosan, however mannan hypolipidemic effect has not been studied precisely. The aim: to evaluate effect of immunomodulator mannan in murine model of lipemia induced by lipase inhibitor poloxamer 407 (P-407).

Methods and Results. Polysaccharide mannan C. albicans serotype A (Institute of Chemistry, SAN, Bratislava, Slovakia) was used in a dose 50 mg/kg (5-times) or 100 mg/kg (twice) before acute lipemia in CBA/Lac mice induced by the single administration of P-407 (300 mg/kg). In vitro mannan (50 μg/ml) was shown to stimulate the proliferation (0.79 optical units vs 0.54 optical units, mannan-stimulated and basal respectively, p < 0.05) and NO production (22.3 μM/ml vs 16.2 μM/ml, mannan-stimulated and basal respectively, p < 0.05) of murine peritoneal macrophages, similar to beta-glucan. Preliminary administration of mannan significantly reduced atherogenic LDL fraction, as well as total cholesterol and triglyceride concentrations (more significant in the dose of 50 mg/kg). In liver tissue total triglycerides level decreased in P-407-induced lipemia model as well as in mannan pretreated group of mice with lipemia. Serum chitotriosidase activity increased in mice with lipemia and mannan administration as a result of macrophage stimulation.

Conclusion: The results indicate significant protective activity of mannan and imply its potential study and application as hypolipidemic compound. It was concluded that mannan seems to be perspective hypolipidemic drug among other polysaccharide immunomodulators (like â-glucan).
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THE OBESITY PARADOX DECODED: BMI AFFECTS CO-MORBIDITIES BUT NOT OUTCOMES IN ISCHEMIC STROKE
J.A. Pieper, M. Ashamalla, D. Sedhom, N. Yager, M. Torosoff
Albany Medical College, Albany, NY, USA

Background: We investigated an association between the following variables and their effect on mortality: CAD, PVD, HTN, dyslipidemia, evidence of atherosclerosis by echocardiography, end stage renal disease [ESRD], diabetes, and BMI.

Materials and Methods: We performed retrospective chart review in 996 consecutive patients treated for ischemic stroke at a single tertiary medical center. Patients were divided according to BMI groups according to the National Institute of Health. This study was approved by the institutional IRB.

Results: Despite the similar prevalence of morbid obesity in both sexes (52% female, 48% males), there were significantly more females with BMI <25 (63.2% with 0-18.5 and 58.4% with 18.5-24.9 kg/m2, p<0.05), and more males with BMI>25 (60.82% with 25-30 and 59.2% with 30-35 kg/m2, p<0.05). CAD was associated with normal (HR 10.4, CI 1.3-82.3, p=0.03) or increased weight (HR 7.92, CI 1.0-62.5, p=0.049); ESRD was less likely in overweight patients (HR 0.11, CI .014-0.775, p=0.03), and diabetes correlated with morbid obesity (HR 11.3, CI 2.2-58.4, p=0.004). When adjusted for comorbidities, PVD (HR 3.5, CI 1.6-7.9, p=0.002), ESRD (HR 3.6, CI 1.5-8.5, p=0.005), evidence of atherosclerosis by echocardiography (HR 1.64, CI 1.1-2.5, p=0.02), but not BMI, were associated with increased mortality.

Conclusion: In patients with ischemic stroke, BMI appears to be a marker for specific comorbidities, but does not independently portend improved or worsened prognosis.
HYPERTENSION

LIFE-STYLE CHARACTERISTICS AND CARDIOVASCULAR DISEASES IN TOUR MANAGERS
Y-C Tseng, F-Y Lan, H-R Guo
Chang Jung Christian University, National Cheng Kung University Hospital, Taiwan

Objectives: To assess the prevalence of high-risk life-style characteristics for cardiovascular diseases (CAD) in tour managers and revaluate whether they have a higher risk of CAD. Background: Tourism is rapidly developing worldwide, and many workers engaged themselves in this growing industry. Because of frequent travel, tour managers might have higher prevalence of various life-style characteristics that are risk factors for CAD such drinking, smoking, and lack of sleep. However, data on the health conditions of this working population are limited.

Methods: We recruited tour managers and office staff in tour agencies in Taiwan and sent anonymous questionnaires to the participants to collect data. Life-style characteristics, medical history, and recent symptoms were compared between these two groups.

Results: A total of 390 workers, including 152 tour managers and 238 office staff participated in this study. We found tour managers had significantly higher prevalence of drinking (p < 0.01) but slept less (5.8 ± 1.3 versus 6.9 ± 1.2 hours during a typical work day, p < 0.001). They also have a higher proportion of smokers with marginal statistical significance (20.8% versus 12.8%, p = 0.06). In addition, tour managers had a significant higher prevalence of hypertension (odds ratio [OR]: 2.3, 95% confidence interval [CI]: 1.2-4.4) and a higher prevalence of palpitation at the time of survey with marginal statistical significance (OR: 3.2, 95%CI: 0.8-13.1).

Conclusions: We observed higher prevalence of hypertension and palpitation in tour managers compared to office staff. Intervention measures should be introduced to prevent and control CAD in this occupation.
HYPERTENSION

CFC NATIONAL SURVEY ON HYPERTENSION TREATMENT
on behalf of the CFC National Hypertension Board, Italy

Background: Guidelines for hypertension (HT) management recommend association therapy since the beginning of pharmacologic treatment in most hypertensive patients.

Methods: The Italian Council for Cardiology Practice is carrying out a national online survey (www.cfccardiologia.it) with a simple multiple answer 10 item questionnaire for cardiologists, internists or general practitioners involved in the daily care of hypertensive patients. The questionnaire focused on the physicians’ awareness of the disease stage, their strategies to deal with the disease and their propensity to use triple antihypertensive drug associations and in general polypill therapies.

Results: 67.3% respondents are working in hospital, 11.5% in the territory, 9.6% in private clinics. 36.5% are specialists.

- 75% monotherapy used in stage 1, 4.1% in stage 2.
- 85% choose therapy according to the presence of multiple cardiovascular risk factors.
- 35.4% use the association CCB / ACEI as first association therapy.
- 80.8% introduce more than 3 drugs in patients with stage 3.
- 76.6% use 24 h ABPM to monitor the response to therapy.
- 62.5% increase the number of drugs used in the absence of arterial pressure control.
- 70.8% consider triple therapy to normalise BP value.
- 50% through hard find to use the association therapy [preconceived].
- 45% are interested to use polypill with: antihypertensive – antilipidemic - antithrombotic agents for the future.

Conclusions: The preliminary data of the CFC survey on the daily life use in clinical practice of association therapy for blood pressure control show that association therapy and triple therapy are widely considered to obtain pressure control in stage 2 and 3 hypertension pts and 24h ABM is used in monitoring the response to therapy. However, preconceived associations are still considered in 50% of doctors as difficult to prescribe.
HYPERTENSION

EFFECT OF OLMESARTAN ALONE, AND IN COMBINATION WITH AZELNIDIPINE IN THE CONTROL OF HYPERTENSION AND PLASMA B-TYPE NATRIURETIC PEPTIDE LEVELS

Kanazawa University, Kanazawa, Japan

Background: Data regarding the efficacy of combination therapy in hypertension (HT) are inadequate. Herein, we evaluated the effect of olmesartan taken alone, or in combination with azelnidipine on blood pressure (BP) control and plasma B-type natriuretic peptide (BNP) and pentraxin-3 (PTX-3) levels.

Methods: This prospective study included 19 patients with essential HT (9 males; mean age, 63.8 years). All patients initially received olmesartan (10 to 20 mg). Azelnidipine (16 mg) was added when blood pressure (BP) failed to normalize with 20 mg of olmesartan within 12 weeks. Systolic and diastolic BP, plasma BNP, and PTX-3 were measured at baseline and at 28 weeks.

Results: At 28 weeks, 8 patients each were receiving 10 mg and 20 mg of olmesartan, and 3 required addition of azelnidipine. Target BP was achieved in 18 (94.7%) patients. There was a significant reduction in mean systolic (154.8 to 123.5 mmHg, p < 0.001) and diastolic BP (87.9 to 75.2 mmHg, p < 0.001) compared to the baseline values. While plasma BNP levels decreased significantly compared to baseline values (58.6 to 45.2, p = 0.03, no significant change was demonstrated in PTX-3 levels (1.90 to 1.79, p = 0.30).

Conclusions: A treatment strategy of olmesartan alone, or in combination with azelnidipine resulted in normalizing BP, as well as plasma BNP level, suggesting its effectiveness in lowering BP and improving cardiac function.
THE RELATIONSHIP BETWEEN BLOOD PRESSURE VARIABILITY AND 10-YEAR CARDIOVASCULAR RISK

M. Celik, U.C. Yuksel, E. Yildirim, E. Gursoy, M. Koklu, S. Yasar, S. Gormel, B. Bugan, C. Barcin
Gulhane Military Medical Academy, Ankara, Turkey

Objectives: The aim of this study is to retrospectively analyze the impact of 24-hour blood pressure variability (BPV) on the development of future cardiovascular disease determined by The Pooled Cohort Risk Assessment Equations 10-year risk calculator.

Background: Blood pressure (BP) values alone may not fully explain the destructive effects of high BP. Although the adverse effects of hypertension are largely dependent on mean BP values, recent attention has focused on the possible role of BPV in the pathogenesis of hypertensive complications.

Methods: We retrospectively analyzed 250 adult patients, who had 24 h ambulatory blood pressure monitoring (ABPM). We defined mean blood pressure values, standard deviation (SD), and coefficient of variation (CV) of blood pressure on the basis of the recorded 24 h ABPM values as an indicator for variability in BP. The CV and SD of SBP over 24h were the primary parameters investigated in our study. The Pooled Cohort Risk Assessment Equations 10-year risk score was calculated as indicated by the ACC/AHA 2013 guideline on the assessment of cardiovascular risk and patients were grouped according to their risk profile; group 1 was consisted of patients with lower risk score (<7.5), and group 2 was consisted of those with higher risk score (≥7.5).

Results: Our analysis showed that mean systolic BP (SBP) value was higher in patients with higher risk score compared to those with lower risk scores. Parameters showing the BPV such as SD and CV of mean blood pressures were also significantly higher in in patients with elevated 10-year risk score compared to others. Our data revealed that that each 1% increase in CV of SBP could lead to a 1.258 fold increase in 10-year risk.

Conclusions: Our study showed that independently from baseline SBP, increased CV of SBP was associated with increased cardiovascular risk, as assessed by The Pooled Cohort Risk Assessment Equations 10-year risk calculator.
Background and Objectives: Valvular heart diseases (VHDs), of which the mitral valve is frequently implicated, are collectively responsible for more than 20,000 annual deaths in the United States. The economic burden on the public health system due to VHDs is estimated in the billions of dollars. The aim of this study was to assess the number of mitral valve disease hospitalizations and surgical procedures in the United States during the period 2010–2013.

Methods: The National Inpatient Sample (NIS) is the largest publicly available all-payer inpatient healthcare database in the United States. Patients diagnosed with mitral valve disease were identified using the International Classification of Diseases 9th revision (ICD-9) codes 394.0–394.2, 394.9, 396.0–396.3, 396.8, and 396.9. ICD-9 procedure codes 35.12, 35.23, 35.24, and 35.97 were used to identify surgeries to repair or replace the mitral valve.

Results: There were 871,290 mitral valve disease hospitalizations in 2013, a decrease from 882,485 in 2010. However, the mitral valve disease proportion of total hospitalizations increased from 2.26% in 2010 to 2.45% in 2013. Among adults 65 years and older, the mitral valve disease proportion of total hospitalizations increased each year from 2010 (4.64%) to 2013 (5.03%). Mitral valve surgical procedures, including transcatheter mitral valve repair (TMVR), open repair, tissue graft, and synthetic replacement, increased from 2010 (34,570 procedures) to 2013 (38,030 procedures). The proportion of mitral valve disease hospitalized patients that underwent a procedure increased during this time period, from 3.87% in 2010 to 4.32% in 2013.

Conclusions: This study reveals that mitral valve disease is a growing public health problem in the United States, particularly among older adults. Hospitalizations for mitral valve disease increased relative to the overall number of hospitalizations, and an increasing proportion of these patients underwent surgical procedures to repair or replace the valve.
**Valvular Heart Disease**

**Recent Trends in Prevalence, Microbiology, Treatment, and Outcome of Infective Endocarditis in End-Stage Renal Disease**


1. St Luke's University Health Network, Bethlehem, PA, USA
2. Vanderbilt University, Nashville, TN, USA
3. John H. Stroger Jr. Hospital of Cook County, Chicago, IL, USA

**Background:** Infective endocarditis (IE) may complicate clinical course in end-stage renal disease (ESRD) patients, however data from large studies are lacking. This study examined contemporary trends of hospitalization rates, microbiology, and outcomes of IE in patients with ESRD.

**Methods:** We queried the Nationwide Inpatient Sample database for years 2006 through 2011 to identify ESRD patients admitted with a primary diagnosis of IE.

**Results:** A total of 44,822 IE hospitalizations in ESRD patients were identified with a significant increase in annual rates of admission during the study period (Table). Mean age was 59±15 years, and patients were predominantly male (53%) and white (44%). Staphylococcal, Enterococcal, fungal, and GNB IE increased while rates of Streptococcal IE remained unchanged (Table). In-hospital mortality declined from 19.4% in 2006 to 15.8% in 2011 (relative change -18.6%; p <0.001). Rates of valve surgery did not change significantly during the study period (7.7% in 2006 and 7.6% in 2011; p = 0.58). Enterococcal (p=0.02) and fungal (p<0.001) IE were more likely whereas Staphylococcal aureus and gram negative (p<0.001 for both) IE were less likely to need valve surgery.

**Conclusion:** Clinical profile, microbiology and treatment of IE in ESRD patients have changed significantly in recent years.

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of admissions</th>
<th>IE per 1000 U.S. ESRD patients</th>
<th>In-hospital Mortality (%)</th>
<th>Valve replacement surgery per 1000 IE admissions</th>
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<tr>
<td></td>
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<td></td>
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</tr>
</tbody>
</table>

Relative Δ: +52.9% **<0.001** +27.4% **<0.001** -18.6% **<0.001** 0% NS +16% NS +29% NS +35% +6% +150%

Staph aureus=Staphylococcus aureus, GNB=gram negative bacteria
UNUSUAL COMPLICATION FROM A RARE ENDOCARDITIS: AORTA-RIGHT VENTRICLE FISTULA AND MITRAL VALVE PERFORATION

F. Khan, M. Garrido, E. Kostacos, V. Mallavarapu
Abington Jefferson Health, Abington, PA, USA

Introduction: Salmonella endocarditis, although rare, carries a high overall mortality rate. Perivalvular abscess is more commonly seen when aortic valve is involved. Fistulas are extremely rare. Salmonella tends to involve the prosthetic valves in the elderly.

Case Report: We report a case of a 64-year-old male who presented with chest pain and dyspnea. He had a history of a failed bioprosthetic aortic valve (AV) followed by mechanical AV replacement. His initial workup revealed negative cardiac enzymes and normal white cell count. Chest x-ray showed pulmonary congestion. A month prior to current presentation, he was treated for Salmonella sepsis. His blood cultures grew Salmonella on current admission. A transthoracic echocardiogram (TTE) showed severe aortic regurgitation (AR), and appearance of an ascending aorta - right ventricular fistula (Image 1). A transesophageal echocardiogram (TEE) was performed which showed aortic root abscess, fistulous communication between the aorta and right ventricle, and mitral valve perforation (Image 2). These findings were confirmed in the operating room.

Conclusion: Surgical interventions have promising outcomes in patients with prosthetic valve complications. TEE plays a crucial role in assessing the anatomy of AV lesions and dictating the post-operative success.
INTERCOMMISSURAL DISTANCE AS THE LONE ANNULOPLASTY RING SIZING STRATEGY MAY NOT PREVENT SAM
S. Edla, E. Maiodna, S. Neupane, H. Rosman
St John Hospital and Medical Center, Detroit, MI, USA

Introduction: Systolic anterior motion (SAM) is a rare but major complication of mitral valve repair (MVr). Selecting the right ring size can be challenging given the plethora of sizing strategies available. Despite a low incidence of 2-5% of all MVr cases, SAM developing as a result of inadequate sizing can be potentially life-threatening. We report a case of SAM following MVr with a CarboMedics AnnuloFlex ring (Sorin-CarloMedics, Austin, USA) causing significant left ventricular outflow tract (LVOT) obstruction and precipitating in cardiogenic shock.

Case: A 67-year-old male with history of coronary artery disease presenting with exertional dyspnea had an elective cardiac catheterization which revealed significant three-vessel coronary disease. Transthoracic echocardiogram showed moderate mitral regurgitation (MR) with an ejection fraction (EF) of 55%. Hence, the patient was scheduled for coronary artery bypass graft along with MVr. After sizing the mitral valve geometry using the manufacturer-recommended intercommissural distance, MVr was performed with a CardioMedics AnnuloFlex ring. Postoperative TEE confirmed a well-seated ring with trivial MR. Around 18 hours post-procedure, the patient developed worsening hypotension. Stat TEE showed severe MR and a new SAM of the anterior mitral leaflet causing severe LVOT obstruction with a peak gradient of 103 mmHg and EF of 35%. Patient immediately underwent emergent mitral valve replacement. Postoperative TEE showed no MR and an EF of 60%. Patient remained critical but stable over the next 24 hours. However, he gradually developed multi-organ dysfunction and eventually expired 48 hours later.

Discussion: Despite the critical importance of accurate ring size selection in MVr, the sizing strategies are fairly arbitrary and dependent on manufacturers’ recommendations. Many commercial rings use the intercommisural distance as the primary selection strategy even though no significant literature exists supporting one strategy over the other. Cases such as ours indicate a need for stronger scientific justification of sizing strategies.
STABILIZED RATE OF AORTIC VALVE SURGERY PERFORMED IN THE UNITED STATES IN RECENT YEARS WITH MARKEDLY LOWER RATE PERFORMED IN WOMEN

M.R. Movahed¹,², M. Hashemzadeh²,⁴, M. Hashemzadeh³
1. CareMore, Tucson, Arizona, USA
2. University of Arizona College of Medicine,
3. Long Beach VA Health Care System,
4. PIMA College

Background: Aortic valve surgery have been performed increasingly in high risk patients. The goal of this study was to evaluate this trend in based on gender in the United States.

Method: The Nationwide Inpatient Sample (NIS) database was utilized to calculate the age-adjusted utilization rate for aortic valve surgery from 1988 to 2007 in the United State using ICD-9 coding for aortic valve surgery.

Results: A total population of 504371 type 2 DM patients underwent PCI between 1988-2006 were available for our study over the age of 40. We found that age adjusted rate of aortic valve surgery gradually increased from 1988 until 2000 and stabilized thereafter with persistently higher rate for men (For men age adjusted rate in 1988 was 13.3 per 100,000 vs. 23.8 in year 2000 and 22.1 in the year 2007 per 100,000. For women, age adjusted rate in 1988 was 6.07 per 100,000 vs. 10.1 in year 2000 and 9.3 in the year 2007 per 100,000)

Conclusion: Aortic valve surgery utilization has stabilized in recent years in both gender in the United State. However, this rate is has been persistently more than double in men. The cause of this higher utilization in male is not known.
Serotonin is a modulator of coronary vasomotor tone produced by carcinoid tumors. Carcinoid heart disease (CHD) with tricuspid and pulmonic insufficiency is a late complication of carcinoid syndrome. Left-sided valvular disease in CHD is seen in less than 10% of all cases. A 22-year-old male with a history of asthma presented with two months of fevers, cough and abdominal pain. Five months earlier he was hospitalized with left upper lobe pneumonia and a new murmur, echocardiography showed insignificant mitral leaflet thickening and aortic valve fibrinous strands. On re-admission, lung consolidation remained. CT chest showed a left bronchus mass, biopsies revealed a carcinoid tumor and excision was scheduled. At surgery, as the tumor was manipulated transient ST-segment elevations were observed on the rhythm monitor and confirmed by 12-lead electrocardiography. Troponin-I was elevated, coronary angiography was normal. Left ventricular end-diastolic pressure was elevated at 19 mmHg. Putting the puzzle together- asthma, mitral and aortic valve abnormalities, ST-segment elevation with normal coronary anatomy, the diagnosis of left-sided carcinoid heart disease was established. Intraoperative myocardial ischemia is associated with increased morbidity and mortality. In our case, ST-elevation was likely due to carcinoid tumor manipulation causing release of serotonin resulting in coronary vasospasm. This case is also unique given the mitral and aortic valve abnormalities, whereas CHD typically affects the right-sided valves. Left-sided valve involvement is usually secondary to a primary bronchial carcinoid, as in our patient, right-to-left shunting that circumvents the lungs or severe carcinoid syndrome that saturates the monoamine oxidase in the liver and lungs. Another interesting but rarely discussed factor is the left bronchial venous drainage system which provides a direct route to the left atrium, bypassing monoamine oxidase present in the lungs.
NATIVE VALVE EMPHYSEMATOUS ENTEROCOCCAL ENDOCARDITIS

St. Luke’s University Health Network, Bethlehem, PA, USA

Background: Infective endocarditis (IE) caused by gas forming organisms is extremely rare. Emphysematous endocarditis from Finegoldia magna, Citrobacter, Clostridium and gas producing strains of E coli has been reported but enterococcal emphysematous IE has never been described. We present infective endocarditis of a native (non myxomatous) mitral valve with gas forming enterococcus fecalis.

Case report: 82-year old man with hypertension, obesity, obstructive sleep apnea and chronic kidney disease presents with fever and rapidly progressing shortness of breath. He was found to be in atrial fibrillation (AF) with rapid ventricular rates. Two-dimensional transthoracic echocardiography demonstrated severe mitral regurgitation (MR). Subsequent two and three dimensional transesophageal echocardiogram revealed a large highly mobile vegetation (9.6 x 6.9mm) on the atrial surface of the anterior mitral leaflet with aneurysmal destruction of the lateral scallop leading to severe MR (figures 1A, 1B and 1C). Given the severity of MR, congestive heart failure and ensuing atrial fibrillation the patient underwent mitral valve replacement with a bioprosthetic valve. The resected valvular specimen showed gram-positive cocci (figure 1D) aggregated at the endocardial surface surrounded by macrophages and Langhans giant cells along with interstitial gas consistent with pneumotosis (figure 1E and 1F). Interestingly his blood cultures remained negative. Genomic sequencing revealed the organism to be enterococcus fecalis. Enterococcus is an anaerobic gram-positive cocci that can infrequently produce gas using a heme dependent catalase. This case is unique as this is the first reported case of culture negative emphysematous enterococcal endocarditis.

Conclusion: Emphysematous IE is a rare but serious infection that can be caused by Enterococcus fecalis. It should be included in the differential diagnosis of valvular vegetations in patients with a rapidly progressing clinical course especially if immunocompromised.