**THE CONUNDRUM OF MYOCARDIAL REGENERATION**

P.P. Wadowski1, M. Andreas1, C. Khazen1, T. Vukovich2, N. Khatami1,

M. De Jonge1, A. Jusic1, D. Milasinovic1, **W. Mohl**1

1Medical University of Vienna, Dept. of Cardiac Surgery, Vienna, 2Medical University of Vienna, Dept. of Laboratory Medicine, Vienna, Austria

Concepts of cardiac regeneration including cellular therapies and other interaction to recover the compromised heart remain in the early stage of clinical application. Although being controversial, recent research shows that adult cardiac muscle has potential to activate innate regenerative processes. Seminal observations showing that myocytes may re-enter the cell cycle resulting in a slow cellular turn-over, was an absolute paradigm shift. Additionally, (trans)-differentiation of resident cardiac progenitors found in cardiac niches are in discussion. With this knowledge on potential innate pathways mechanisms have to be explored how to induce and support these processes. PICSO (pressure-controlled intermittent coronary sinus occlusion), a balloon catheter intervention exposes venous endothelial and adjacent cardiac cells to cyclic strain, stretch and shear stress initiating molecular cytoprotective and regenerative processes. The same “hemodynamic” forces sculpture the heart during embryonic development. Our hypothesis “embryonic recall” postulates that recapitulation of dormant developmental processes is also able to regenerate the adult failing heart. Preclinical studies showed significant reduction in infarct size concomitant to an increase of high energy phosphates in border zones and up-regulation of vascular endothelial growth factor (VEGF), heme oxygenase 1 gene expression as well as enhanced VEGF receptor 2 protein secretions. Clinical trials revealed a survival benefit of PICSO treated patients and significant risk reduction up to 5 years follow up. Molecular analyses in heart failure patients indicate induction of the cytoprotective SAFE pathway corroborated by proliferation in cell cultures. Therefore, PICSO concept helps to resolve the conundrum of cardiac regeneration clinically beyond mainstream research concepts.