**DANTROLENE, A RYANODINE RECEPTOR STABILIZER, REDUCES ATRIAL FIBRILLATION IN HEART FAILURE**

C. Nofi1, K. Zhang2, Y.-D. Tang2, Y. Li1, A. Migirov1, K. Ojamaa1, A. Gerdes1, **Y. Zhang**1

1New York Institute of Technology College of Osteopathic Medicine, Old Westbury, NY, USA

2Fuwai Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

**Background**: Heart failure (HF) is associated with an increased risk of atrial fibrillation (AF). Cardiac ryanodine receptor (RyR2) dysfunction and diastolic Ca2+ leak have been linked to arrhythmogenesis not only in inherited arrhythmia syndromes but also in acquired forms of heart disease including HF and AF. Thus, stabilizing RyR2 may exert therapeutic effects in these conditions. In this study, we aimed to investigate the effects of stabilizing RyR2 with chronic dantrolene treatment on HF development and AF inducibility in a myocardial infarction (MI) induced HF model in rats.

**Methods and Results**: MI was induced in adult Sprague-Dawley rats by ligation of the left anterior descending coronary artery. Two weeks following MI surgery, rats with large MI (≥40%) were randomly assigned into MI-vehicle (n=14) and MI-dantrolene (10mg/kg/d, n=13) groups. Sham-surgery rats (n=7) served as controls. Compared to vehicle-treated MI group, 4-week dantrolene treatment significantly improved cardiac function with increased left ventricle (LV) fractional shortening (19.48±3.61% vs. 15.43±2.65%, *P*<0.01), decreased LV end-diastolic pressure (12.58±8.52mmHg vs. 21.91±7.25mmHg, *P*<0.01), left atrial diameter (4.97±0.75mm vs. 6.09±1.53mm p<0.05) and fibrosis content (6.42±0.78% vs. 9.76±2.25%, *P*<0.001). Dantrolene significantly decreased AF inducibility (69% in MI-vehicle vs. 23% in MI-dantrolene group, *P*<0.05). Dantrolene treatment was associated with reduced phosphorylation of RyR2, and favorably altered gene expression involving ion channels, sympathetic signaling, oxidative stress, and inflammatory markers.

**Conclusions:** Chronic dantrolene treatment attenuated LV dysfunction and reduced AF inducibility, which were associated with decreased phosphorylation of RyR2 and restoration of many adverse changes in gene expression. Stabilizing RyR2 with dantrolene is a promising novel treatment in AF and HF.