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Heart Failure and Cardiomyopathies

SERCA2A GENE TRANSFER INHIBITS PROGRESSIVE LV REMODELING IN POST MI CHRONIC HEART FAILURE

Poster Contributions
Hall C
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Session Title: Translation Approaches to Heart: Failure Therapy
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Background: Adeno-associated virus (AAV) mediated gene transfer of cardiac sarcoplasmic/endoplasmic reticulum Ca2+ ATPase pump (SERCA2a) has shown promising results in both pre-clinical and clinical studies. However, the efficacy of this therapy in heart failure of ischemic etiology remains to be validated.

Methods: An extensive anterior myocardial infarction (MI) was created in Yorkshire pigs. One month after MI, the pigs presented with increased left ventricular (LV) end-diastolic pressure, reduced LV ejection fraction and increased LV volumes. The pigs received intracoronary injection of either AAV-1.SERCA2a (n=13), or saline (Control, n=14) and hemodynamic and volumetric parameters were evaluated just prior to gene transfer and 2 months after.

Results: Although the change in ejection fraction did not differ between the groups (9.4±14.9% vs 3.1±15.4%, P=0.31), changes in end-diastolic volume index (0.4±11.0% vs 12.1±13.2%, P=0.02) and end-systolic volume index (-4.8±12.6% vs 10.9±21.7%, P=0.03) were significantly lower after SERCA2a gene transfer. Furthermore, pressure-volume loop analysis revealed significantly higher preload-recruitable stroke work in SERCA2a group 2 months after the gene transfer (44.1±14.0 mmHg vs 34.2±7.7 mmHg, P=0.04; SERCA2a vs Control, respectively). Multiple linear regression analyses using SERCA2a treatment and parameters related to the severity of HF revealed SERCA2a gene therapy as the only independent predictor of changes in both end-diastolic (R2=0.20, P=0.02) and end-systolic volume indexes (R2=0.18, P=0.03).

Conclusions: AAV-1.SERCA2a gene therapy resulted in inhibition of cardiac remodeling together with improved cardiac contractility in post MI swine chronic HF models. The efficacy of AAV-1.SERCA2a was independent of HF severity.