



Reversal of Cardiac Dysfunction After Long-Term Expression of SERCA2a by Gene Transfer in a Pre-Clinical Model of Heart Failure

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Objectives The aim of this study was to examine the effects of sarcoplasmic reticulum Ca²⁺ ATPase (SERCA2a) gene transfer in a swine heart failure (HF) model. **Background** Reduced expression and activity of SERCA2a have been documented in HF. Prior studies have reported the beneficial effects of short-term SERCA2a overexpression in rodent models. However, the effects of long-term expression of SERCA2a in pre-clinical large animal models are not known. **Methods** Yorkshire-Landrace pigs were used (n = 16) to create volume overload by percutaneously severing chordae tendinae of the mitral apparatus with a bioptome to induce mitral regurgitation. At 2 months, pigs underwent intracoronary delivery of either recombinant adeno-associated virus type 1 (rAAV1) carrying SERCA2a under a cytomegalovirus promoter (rAAV1.SERCA2a) (n = 10; group 1) or saline (n = 6; group 2). **Results** At 2 months, study animals were found to be in a compensated state of volume-overload HF (increased left ventricular internal diastolic and systolic diameters [LVIDD and LVIDs]). At 4 months, gene transfer resulted in: 1) positive left ventricular (LV) inotropic effects (adjusted peak left ventricular pressure rate of rise (dP/dt)_{max/P}, 21.2 ± 3.2 s⁻¹ group 1 vs. 15.5 ± 3.0 s⁻¹ group 2; p < 0.01); 2) improvement in LV remodeling (% change in LVIDs -3.0 ± 10% vs. +15 ± 11%, respectively; p < 0.01). At follow-up, brain natriuretic peptide levels remained stable in group 1 after gene transfer, in contrast to rising levels in group 2. Further, cardiac SERCA2a expression was significantly decreased in group 2 whereas in group 1 it was restored to normal levels. There was no histopathological evidence of acute myocardial inflammation or necrosis. **Conclusions** Using a large-animal, volume-overload model of HF, we report that long-term overexpression of SERCA2a by in vivo rAAV1-mediated intracoronary gene transfer preserved systolic function, potentially prevented diastolic dysfunction, and improved ventricular remodeling.

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