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Arterial spin labeling CMR quantifies increased perfusion in hearts of mice treated with cardioprotective, AAV9-mediated EcSOD gene therapy prior to myocardial infarction

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Introduction

Experimental myocardial infarction (MI), direct gene transfer with adeno-associated viral (AAV) vectors and CMR in mice are powerful tools for studying the roles of individual genes in MI and post-MI left ventricular (LV) remodeling. Arterial spin labeling (ASL) enables the quantification of myocardial perfusion (MP) by CMR, but is sensitive to variable heart rates and irregular respiration, prohibiting accurate measurement early after MI. We developed a cardio-respiratory gated (CRG) ASL method that is insensitive to these factors to measure MP in mice.

Purpose

The objective of this study was to test the hypotheses that AAV9-mediated overexpression of extracellular superoxide dismutase (EcSOD) from the cardiac Troponin-T (cTnT) promoter would increase capillary density and protect the heart against myocardial infarction (MI). Furthermore, we tested the hypothesis that an improved method of ASL could quantitate the elevation in MP resulting from increased capillary density.

Methods

CRG-ASL was developed on a 7 T MR system and employed to measure MP both before and 4 wks after gene therapy. AAV vectors were cross-packaged into AAV9 capsids expressing EcSOD or eGFP from the cTnT promoter (AcTnTEcSOD or AcTnTeGFP), and were injected IV into 4-5 week-old C57Bl/6 mice (3×10^{11} vp/mouse). Four weeks after injection, MI was induced by a 30 min coronary occlusion. Infarct size and area at risk (A@R) were measured 24 h later by TTC and Phthalo blue staining, respectively. Capillary density was measured 4 wks post injection in remote myocardium immunostained for CD31.

Results

MP as measured by CRG-ASL increased by 30% from 4.3 + 0.5 before to 5.6 + 0.3 ml/g-min at 4 wks post AcTnTEcSOD injection ($P < 0.05$), then dropped to 2.4 + 0.6 ml/g-min in the infarct zone 24 h post-MI. A single IV injection of AcTnTEcSOD provided uniform EcSOD overexpression throughout the myocardium (Panel A). Infarct size (as % A@R, Panel B) was reduced by 45% in EcSOD mice (33.9 + 6.3, mean + SEM, n = 4) compared to eGFP mice (61.3 + 3.8, n = 4, $P < 0.05$). Capillary density was 23.6% higher in EcSOD mice (5446 + 368/mm^2) compared to eGFP mice (4405 + 271/mm^2, $P < 0.05$), Figure 1.

Conclusion

CRG-ASL quantifies the increase in MP resulting from cardioprotective gene therapy with EcSOD. Transcriptional targeting with the cTnT promoter in combination with the high-efficiency AAV9 capsid provides cardioprotective

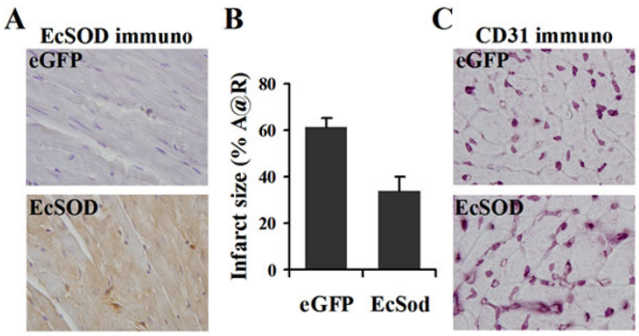

Figure 1

gene therapy from a single IV injection. AAV9-mediated overexpression of EcSOD from the cTnT promoter significantly increases capillary density, improves myocardial perfusion and reduces infarct size in the murine heart.