IGF-1 protects myocardium from reperfusion injury by preventing cellular infiltration


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Abstract

Introduction: Ischemia-reperfusion (IR) injury can cause cardiac dysfunction after myocardial infarction and coronary artery disease. During ischemia, if prolonged, the injured myocardium undergoes irreversible tissue injury and at risk myocytes are primed for apoptosis. While reperfusion is necessary to save myocardium, it may accelerate apoptosis of remaining viable surrounding cardiac myocytes by recruitment and accumulation of inflammatory cells in the tissue.

Methods: After 30 minutes ex-vivo ischemia, LAD/TIMI and LAD mouse hearts were reperfused with modified Kreb's solution in the presence or absence of IGF-1 (10 ng/ml) or TNF-α (250 ng/ml) and perfused at a flow rate of 3ml/min for 1h. Following reperfusion and stabilization in the perfusion system, a second series of experiments were reperfused with bone marrow derived PMN and lymphocytes in the presence or absence of TNF-α or IGF-1. Using Image Pro-Plus software, the extent of myocardial injury and peri-vascular infiltration on the H&E stained slides were analyzed.

Results: IR with modified Kreb's for 1 hr increased the interstitial spaces and number of necrotic myocytes in each random field relative to freshly excised hearts. Vascular endothelial integrity was preserved in 90% of random fields. TNF-α increases the interstitial spaces and necrotic cells in each random field. Vascular injury and peri-vascular infiltration were reduced with IGF-1 in the presence of TNF-α. Coordination with this protective effect of IGF-1 is noted in the determination of cardiac myocyte mitochondrial DNA/nuclear DNA (mtDNA/nDNA) ratios. It has been reported that a higher ratio may reflect "healthy" cells and it may be a predictor of myocardial injury and protection. The determination of mtDNA/nDNA was a more sensitive marker and predictor of myocardial injury and protection than CPK. This will allow for further study of possible mitochondrial-dependant mechanisms that may generate reperfusion injury.

Conclusion: We conclude that IGF-1 can protect ischemic myocardium from further reperfusion injury by direct action on the integrity of vascular endothelium and myocardium and subsequent reduction in inflammatory-cell infiltration.

Specific Aims

- To identify the mechanism of reperfusion injury in a model of ex vivo global cardiac ischemia and markers of injury that more closely represent the possible pathologic mechanism.
- To test an intervention, reperfusion with IGF-1, to prevent further injury after ischemia.

Methods & Materials

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- Systolic/Diastolic Pressure tracings indicate higher cardiac performance in IGF-1 reperfused hearts when compared to control or TNF-α treated hearts.

Results

- Representative H&E images of ischemia-reperfused (IR) murine hearts. Images are of control, ischemia without reperfusion and ischemia with IGF-1 reperfusion. This protective effect of IGF-1 correlated to a determination of cardiac myocyte mitochondrial DNA/nuclear DNA (mtDNA/nDNA) ratios. It has been reported that a higher ratio may reflect "healthy" cells and it may be a predictor of myocardial injury and protection. The determination of mtDNA/nDNA was a more sensitive marker and predictor of myocardial injury and protection than CPK. This will allow for further study of possible mitochondrial-dependant mechanisms that may generate reperfusion injury.

Conclusions

- IGF-1 protects myocardium against the reperfusion-associated injury as determined with performance, histology and CPK release.
- This protective effect of IGF-1 correlated to a determination of mtDNA/nDNA.
- The determination of mtDNA/nDNA was a more sensitive marker and predictor of myocardial injury and protection than CPK. This will allow for further study of possible mitochondrial-dependant mechanisms that may generate reperfusion injury.

References