A Specific Anti-ICAM Antibody Prevents Neutrophil Mediated Injury in the Postischemic Heart

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It has been hypothesized that PMN-mediated reperfusion (R) injury is triggered by increased expression of intracellular adhesion molecule 1 (ICAM-1), on the surface of the coronary endothelium following ischemia and reperfusion which in turn triggers CD18-mediated adhesion of circulating neutrophils (PMN) and subsequent postischemic inflammation. In order to evaluate the role of ICAM in the pathogenesis of postischemic injury, experiments were performed in an isolated rat heart model perfused with isolated PMNs and plasma. The efficacy of a specific monoclonal antibody (MAb) against ICAM, IA-29 (Upjohn), was studied in hearts subjected to 20 min of global ischemia and 60 min of reperfusion. The hearts were then explanted and perfused with Evan’s blue and triphenyl tetrazolium chloride dyes to define the coronary distribution and regions of myocardial necrosis. Sections of myocardium from the area at risk were assayed for myeloperoxidase (MPO) content, an index of neutrophil infiltration. No hemodynamic or adverse effects were noted in the CY 1503 treated group. Infarct size, expressed as a percent of the area at risk was reduced by 68% in CY 1503 treated dogs (p = 0.007). MPO content in the ischemic Cx territory was also markedly reduced in the CY 1503 group (p = 0.02).

We conclude that inhibition of neutrophil-endothelial cell adhesion by CY 1503 reduces infarct size well beyond thrombolytic-mediated reperfusion, and is a highly attractive strategy for future clinical investigation.

Collateral Flow Influences the Myocardial Collagen Content Early After Acute Myocardial Infarction

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Collateral flow, even when developed after acute myocardial infarction (AMI), prevents the progressive left ventricular dilation and remodeling after AMI, independent of infarct size reduction. The mechanisms underlying this situation are unknown. The purpose of this study was to examine the hypothesis that collateral flow influences the collagen volume fraction in the necrotic area. We studied ten mongrel dogs with AMI. The dogs were sacrificed five days later. The hearts were arrested in diastole, perfused fixed, and sliced. Sections from each slice were taken from the center of the infarct zone, and stained with hematoxylin and eosin or picrosirius red. Collagen analysis was performed using polarized light microscopy. Using a random sampling morphometric technique, the relative density of collagen, was calculated. To confirm the results from morphometry fresh transmural myocardial tissue samples were also taken from the center of the infarct zone, and processed for measurement of hydroxiproline content (µg/g dry tissue weight). Myocardial blood flow was measured with 125I- labeled microspheres (10 µm). Collagen deposition was analyzed in relation to baseline variables including the anatomic area at risk, necrosis, collateral blood flow and hemodynamic determinants of myocardial metabolic demand (heart rate, blood pressure, rate pressure product). Stepwise multivariate regression analysis showed that only collateral blood flow contributed to the model predicting an increase in myocardial collagen content (R² = 0.89 p = 0.01. In conclusion, we found that after a myocardial infarction a rich collateral flow to the necrotic area is associated with an increase in the collagen content. This is probably one of the reasons why after AMI, collateral flow has a positive influence on ventricular remodeling, independent of infarct size reduction.