Evaluation of the Porcine Ameroid Constrictor Model of Chronic Myocardial Ischemia for Therapeutic Angiogenesis Studies

Peter W. Radke, Amanda Heinl-Green, Oliver M. Frass, Mark Post, Duncan M. Geddes, Eric W. Altom, Imperial College London, London, United Kingdom

Background: The porcine model of chronic myocardial ischemia is widely used for preclinical testing of angiogenic genes and proteins. Important characteristics of this model lie in the context of ischemia occlusion on the presence of myocardial ischemia as well as the relation between morphological, functional, and hemodynamic measurements. However, they have not been described in detail.

Methods: We performed a systematic analysis of six study animals undergoing concomitant coronary artery constriction (LCX). In addition to a comprehensive evaluation including echocardiography, coronary angiography and myocardial blood flow measurements at rest and stress conditions. By solving a set of algebraic equations (TIMS-rf in LCX or collateral flow Rentrop class >1) another 29% (27/94) of study animals with myocardial ischemia under pharmacological stress conditions could be identified. Echocardiographic parameters of regional and global myocardial function were not associated with myocardial blood flow or the level of ischemia. There was, however, a strong correlation between fractional shortening and the left atrial pressure as a surrogate for cardiac preload (R=0.36, p<0.005). There was no relation between the extent of coronary collateralisation as assessed by angiography and left ventricular systolic function. Whereas aortocoronary bypass grafts were associated with myocardial ischemia.

Conclusion: Occlusion of the aortalized instrumented coronary artery is not a pre-requisite for successfully establishing the pathophysiology of chronic myocardial ischemia. The above defined angiographic criteria are useful in identifying animals with appropriate ischemia, despite incomplete LCX occlusion. The left atrial pressure as a surrogate of cardiac preload serves as a valuable predictor of regional myocardial function.

Diabetes, Hyperglycemia, GIK, and Cardioprotection: Do ATP-Regulated Potassium Channels Play a Role?

John F. Leibel Jr., John O. Krotkiewski, Lynda M. Ludwig, Paul G. Pegg, David C. Warfield, Judy R. Kersten, Medical College of Wisconsin, Milwaukee, WI, Marquette University, Milwaukee, WI

Background: islets are protected, whereas, hyperglycemia is occlusive during myocardial ischemia and reperfusion injury. Diabetes and hyperglycemia attenuate, but insulin activates ATP-regulated potassium (KATP) channels. We tested the hypothesis that blockade of KATP channels with tolbutamide or cycloheximide before ischemia abolishes reductions of myocardial infarct size produced by GIK on reperfusion.

Methods: The temporal dependence of cardioprotection was investigated in barbiturate-anesthetized dogs (n=7 in each group) randomly assigned to receive GIK (25% dextrose; 50 U insulin/L; 80 mU/kg min KCl infused at 1.5 ml/kg/hr) starting 75 minutes before coronary artery occlusion or five minutes before reperfusion. The role of KATP channels in the cardioprotective effects of GIK were evaluated in dogs pretreated with glyburide (0.1 mg/kg iv). The effect of GIK was further investigated by increasing blood glucose concentration to 100, 300, or 600 mg/dL (intravenous dextrose) or in diabetic dogs (3 weeks after alloxan-streptozotocin)

Results: There were no differences in area at risk (AAR) or collateral blood flow among groups. Myocardial infarct size (percentage ischemia of left anterior descending coronary artery) was 25±2% of the AAR in control dogs. GIK significantly (P<0.05) decreased infarct size when administered at reperfusion independent of blood glucose concentration (13±2 and 12±2%: 100 and 600 mg/dL, respectively). The protective effects of GIK upon reperfusion were abolished in diabetic animals (25±3%), animals receiving glyburide (30±2%), and in those subjected to hyperglycemia before ischemia (27±4%, 600 mg/dL). GIK did not protect against infarction when administered before ischemia (31±3, 27±2 and 35±3% during blood glucose concentrations of 100, 300, and 600 mg/dL, respectively).

Conclusion: The protective effects of GIK and the increased susceptibility to ischemia and reperfusion injury are associated with diabetes and glyburide. The protective effects of GIK and the increased susceptibility to ischemia and reperfusion injury are abolished in diabetic animals. This strongly suggests that the protective effects of GIK and the increased susceptibility to ischemia and reperfusion injury are mediated through KATP channels.

A New Model of Coronary Microthrombosis in Rats and the Protective Effect of a New Thrombin Inhibitor

Qizhaojing Shi, Jinping Ge, Liangying Chen, Qiyong Zheng, Yukui Luo, Chuan Liang, Shuangjie Li, Hao Zhu Chen, Huiyan Song, Wei Mo, Duan Ma, Zhongshan Hospital of Fudan University, Shanghai, People’s Republic of China, Fudan University, Shanghai, People’s Republic of China

Background: and Objective: Miniature myocardial infarction after interventional treatment is not uncommon in the clinic. The aim of this study was to develop a new model of minor myocardial infarction based on endothelial damage and thrombotic occlusion in coronary artery, leading to small myocardial infarcts in rats. Moreover, the protective effect of h-RGD-Hinudin, a thrombin inhibitor, was investigated in this model. METHODS: Forty-eight male Sprague-Dawley rats were used in the present study. Rats were anesthetized with sodium pentobarbital and ketamine, and 200 μg of sodium laurate was injected into the coronary artery. The thrombotic induction and consequent endothelial damage were examined by histopathological analyses and electron microscopy. To determine the protective effects of h-RGD-Hinudin, 1.5 mg/kg was administered intravenously 5 minutes after the injection of sodium laurate; the control group was injected saline instead. RESULTS: Three hours after the injection of sodium laurate, microscopic examination of the heart revealed thrombus formation at the site of injection (n=9) and Carstairs Stain sections (n=8) revealed that microthrombi containing fibrin strands obstructed the perforating arteries in the myocardium. Under a transmission electron microscope (n=5), endothelial cells appeared exfoliated and the vascular lumen was obstructed by a thrombus composed of degranulated platelets, fibrin, leukocytes, and erythrocytes. Multiple