Transplantation of Autologous Bone Marrow: Mononuclear Cells Does Not Alter Arrhythmia Threshold in Adult Swine With Chronic Myocardial Ischemia

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Background: Bone marrow-derived mononuclear cells (BM-MNCs) can give rise to endothelial progenitor cells and localized transplantation of BM-MNCs in ischemic myocardium may augment neovascularization. However, not much is known of the arrhythmogenic potential of BM-MNCs after intramyocardial transplantation. Objective: Evaluate the threshold for ventricular arrhythmia induction with conventional electrophysiology study (EPS) with programmed stimulation in swine with chronic ischemic myocardial ischemia treated with autologous BM-MNCs. Methods: Adult Yucatan swine underwent left circumflex (LCX) aortic interruption. At 4 weeks, animals were randomized to receive either BM-MNCs (n=8) or DMEM culture medium as control (n=8). Bone marrow (30-50ml) was aspirated from sternum and if necessary, iliac crest. Mononuclear cells were isolated using density gradient centrifugation. Catheter-based (Boston Scientific Stiletto™) intramyocardial injections were performed with combined fluoroscopic and intracardiac electroanatomic (ACE) guidance. The treatment group received a total of 1 x 10^6 BM-MNCs at 10 sites, 5 ischemic (LCX) and 5 in non-ischemic (LAD) region. Four weeks after cell treatment, global wall motion index score (GWMIS) was evaluated by dobutamine stress echocardiography. Subsequently, electrophysiologic study was performed with right ventricle stimulation at apex and outflow tract, using a basic cycle length of 500 and 400msec and 1-3 extrastimuli. Results: No difference was found in total number of cases with inducible arrhythmias in BM-MNC and control groups: 3 of 8 animals (38%) in BM-MNC group (2 polymorphic VT and 1 VF) and 3 out of 8 animals (38%) in control group (1 monomorphic VT and 2VF). There was also no difference in global wall motion (GWMIS=1.03 in BM-MNCs; 1.17 in sham, p=0.38) and there was no correlation between GWMIS and ventricular arrhythmia induction (1:29 for induced pigs; 1:10 for non induced pigs). Conclusion: Transplantation of autologous BM-MNCs into ischemic myocardium did not alter the threshold for ventricular arrhythmia. Left ventricular dysfunction was not related to arrhythmia inducibility.

Monocyte Chemoattractant Protein-1 Induced Monocyte Infiltration and Angiogenesis Does Not Result in Atherogenesis or Improved Function in Chronically Infarcted Myocardium

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Monocyte chemoattractant protein 1 (MCP-1) stimulates invasion of monocytes into ischemic tissue with concomitant adhesion to endothelial cells. This process has been shown to be involved in the induction of atherogenesis, i.e., the development of function arterioles resulting in improvement of perfusion in contrast to angiogenesis without changes in blood flow. The effects of MCP-1 on atherogenesis and arteriogenesis and changes of left ventricular function were tested in infarcted rat hearts. Anesthetized rats were subjected to open-chest ligation of the left coronary artery with subsequent myocardial infarction. After six weeks, animals were randomized to receive either MCP-1 (3iu in 0.15ml NaCl, group 1, n=9) or saline (0.15ml, group 2, n=9), which was injected after thoracotomy into the myocardium at the infarct border zones. Transthoracic echocardiography was performed for assessment of left ventricular diameters and cardiac function (ejection fraction, EF) at baseline, six weeks after myocardial infarction, and four weeks after MCP-1 or saline injection, by use of a 12 MHz pediatric transducer. For microscopic analysis, tissue was stained by Elastica-van-Gieson and von-Willebrand factor for blood vessels and endothelial cells, respectively. In a subset of animals, hearts were excised 24 hours after MCP-1 (n=9) or saline (n=9) administration for assessment of monocyte infiltration by staining of the CD-31 antigen. EF decreased from 60.3% to 25.5% in group 1 (p<0.005) and from 58.2% to 26.4% in group 2 (p<0.005) after coronary occlusion, without further changes four weeks after treatment (EF 26.3% in group 1, EF 25.6% in group 2). At the injection site, 39±10 endothelial cells were found in group 1 versus 285±14 in group 2 (p<0.005). Monocyte infiltration was shown in MCP-1 treated animals but not in saline treated animals. There were 19±2 arteriolar structures in group 1 versus 16±1 in group 2, p<0.05. A single intramyocardial injection of MCP-1 into the infarct border zone induced neo-angiogenesis and monocyte infiltration. MCP-1 injection did not result in atherogenesis or functional improvement of chronically infarcted myocardium in this experimental rat model.

Preoperative QRS Widening and Ventricular Dysrhythmia Predict Adverse Outcomes Following Left Ventricular Reconstruction for Ischemic Cardiomyopathy

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Objective: Interventions that target the cardiac conduction system such as AICD placement and biventricular pacing improve symptoms and survival in patients with congestive heart failure. However, the role of the conduction system in outcome after surgical ventricular reconstruction is undefined. We reviewed our experience with left ventricular reconstruction (LVR) in patients with ischemic cardiomyopathy to determine the effect of preoperative conduction abnormalities on outcome after surgery. Methods: LVR was performed in 223 pts (80% male, mean age 62±10 yrs, 66% NYHA Class III/IV) between 1997 and 8/02. Mean pre-operative EF was 26±9%. QRS duration was 122±32msec and an AICD was present in 15%. Time related outcomes considered were: 1) survival, 2) freedom from composite event (transplant, revascularization, LVAD) and 3) freedom for heart failure. Mean follow-up is 1.5±1.1 yrs. Results: Survival at 30 days, 1yr and 3 yrs was 96%, 92% and 88% respectively. Patients who had an AICD preoperatively had a higher early mortality (p=0.002). Freedom from readmission for heart failure was 89%, 95%, and 61% at 30 days, 1 yr, and 3 yrs. Patients with a prolonged preoperative QRS had more frequent rehospitalizations (p=0.006).

Conclusion: Surgical left ventricular reconstruction in heart failure patients with ischemic cardiomyopathy yields an encouraging medium term survival and freedom from hospitalization for heart failure. Preoperative predisposition to lethal ventricular arrhythmia requiring an AICD was a strong predictor of mortality. This deserves closer examination. Left ventricular dysynchrony (prolonged QRS) was a strong predictor of residual or recurrent heart failure and further underscores the importance of ongoing investigations of cardiac resynchronization therapy as an adjunctive treatment to surgery for heart failure in this group of at risk patients.