Transmyocardial revascularization ameliorates ischemia by attenuating paradoxical catecholamine-induced vasoconstriction

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Background. **The mechanism by which transmyocardial revascularization (TMR) offers clinical benefit is controversial. We hypothesized that TMR ameliorates ischemia by reversing paradoxical catecholamine-induced vasoconstriction.**

Methods and Results. **Chronic ischemic cardiomyopathy was created in 11 dogs by placing ameroid constrictors on the proximal coronary arteries and their major branches. Six weeks later, 35 channels were created percutaneously in the left circumflex artery region, with the left anterior descending artery region serving as control. At rest, wall thickening and myocardial blood flow did not change in the treated region, whereas they deteriorated in the control bed. Contractile and myocardial blood flow reserve increased in the treated region but deteriorated in the control region. There was diminished iodine 123 metaiodobenzylguanidine uptake and a significant reduction in noradrenergic nerves in the treated region compared with the control region, with a corresponding reduction in tissue tyrosine hydroxylase activity.**

Conclusions. **We conclude that the absence of a catecholamine-induced reduction in MBF reserve and contractile reserve in the TMR-treated region with associated evidence of neuronal injury indicates that the relief of exercise-induced ischemia after TMR most likely results from reversal of paradoxical catecholamine-induced vasoconstriction. These findings may have implications in selecting patients who would benefit from TMR. (J Nucl Cardiol 2007;14:207-14.)**

Key Words: Cardiomyopathy • ischemia • lasers • revascularization

Several hypotheses have been put forth to explain angina relief,[1-9] improved exercise tolerance, and better quality of life[8,10-13] after transmyocardial laser revascularization (TMR). These range from increased myocardial blood flow (MBF) from the left ventricular (LV) cavity via laser-induced channels[14-16] and angiogenesis[17-21] to pain relief from cardiac denervation.[22,23]

Unlike normal coronary arteries that exhibit vasodilation during catecholamine stimulation[24], injured or diseased coronary arteries may exhibit paradoxical vasoconstriction,[25-28] leading to a reduction in MBF and ischemia during stressful situations. We hypothesized that cardiac denervation caused by TMR would lead to attenuation of paradoxical vasoconstriction, thus ameliorating ischemia, which would explain the angina relief and improved exercise tolerance seen in patients undergoing this procedure. We tested our hypothesis in a canine model of chronic ischemic cardiomyopathy previously developed by us.[29,30]

METHODS

Animal Preparation

The study protocol was approved by the animal research committee. Eleven mongrel dogs were pretreated

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with aspirin (75 mg daily) for 3 days, which was continued until euthanasia. They were given gentamicin (80 mg) and cefazolin (1 g) immediately before surgery, and cefazolin was continued through postoperative day 3. Catheters (6 French) were inserted into the right femoral artery for pressure measurements and into the left atrium for injection of microspheres. Up to 4 ameroid constrictors (1.5-3.5 mm) were placed around the dissected left anterior descending coronary artery (LAD) and the left circumflex coronary artery (LCx) and their major branches to create multivessel ischemia. Because the first septal perforator artery in the dog usually comes off of the left main artery, it was always spared. As a result, the basal interventricular septum (IVS) never becomes ischemic.[29,30]

At the completion of the procedure, all dogs were treated with buprenorphine (0.15 μg subcutaneously and 0.15 μg intravenously) and a fentanyl transdermal patch (75 $\mu g \cdot h^{-1}$) for pain control. They were then revived and transferred to the vivarium, where they were examined twice daily and treated appropriately with additional antibiotics or diuretics if infection or heart failure developed. Two-dimensional echocardiography (2DE) was performed weekly to assess LV function. All subsequent studies were performed with the dogs under anesthesia.

Measurement of Regional LV Function and MBF

We performed 2DE from the right thorax with the dog lying on its left side. Three short-axis views (base, papillary muscle, and apex) were acquired during each study. Care was taken to acquire the same views every time in an individual dog. Wall thickening (WT) was measured offline with a previously defined custom program.[31] Regional MBF was measured by use of radiolabeled microspheres as previously described.[32] Normalized MBF was calculated by dividing the averaged MBF of the region of interest by the averaged MBF of the basal IVS (normal segment).

Assessment of Neuron Density With Iodine 123 Metaiodobenzylguanidine Imaging

Labeling of metaiodobenzylguanidine (MIBG), an analog of guanethidine that is taken up in the presynaptic vesicles similar to norepinephrine, was performed with iodine 123 by use of solid-phase ammonium sulfate exchange.[33] Ex vivo I-123 MIBG imaging (159 keV) of myocardial slices corresponding to the 2DE images was performed by placing them directly on the scan head of a gamma camera. Regions of interest were drawn over the LAD and LCx regions at the 3 levels, and counts (per pixel per minute) were computed and normalized to those at the basal IVS level.

Histopathology and Immunohistochemistry

Samples were stained with hematoxylin-eosin for basic architecture and van Gieson's picric acid for fibrosis and collagen. Samples were also immunostained with a monoclonal antibody against tyrosine hydroxylase for noradrenergic nerve terminals (BIOMOL International, Plymouth Meeting, Pa)[34] and a monoclonal antibody against PECAM-1 for measuring blood vessel density (Santa Cruz Biotechnology, Santa Cruz, Calif). Both tyrosine hydroxylase expression and PECAM-1 expression were determined by microscopic observation of the diaminobenzidine reaction product (Dako, Glostrup, Denmark) on the analyzed sections. The regions occupied by fibrosis/collagen (red stain), nerves (dark brown stain), and blood vessels were assessed by use of the following scores based on staining intensity: 0, none; 1, minimal; 2, mild; 3, moderate; and 4, intense. The entire tissue sample (approximately $0.5 \cdot 0.5$ cm) was evaluated for the previously mentioned changes.

Experimental Protocol

Resting hemodynamic and 2DE data were acquired at baseline and at the time of maximal LV dysfunction (before TMR). The pre-TMR evaluation also included MBF and regional WT evaluations at rest and peak dobutamine dose (30-40 $\mu g \cdot kg^{-1} \cdot min^{-1}$) to assess MBF and contractile reserves. For TMR, approximately 35 channels were created percutaneously in the LCx region under fluoroscopy guidance by use of a holmium:yttrium-aluminum-garnet laser catheter (Eclipse Surgical Technologies, Sunnyvale, Calif) via a 9-French sheath in the right femoral artery. Laser energy was delivered at 5 J per pulse and at a rate of 5 Hz from the 1-mm-diameter optical fiber. Maximum penetration (5 mm) was achieved with 3 consecutive pulses, and contact was confirmed by the occurrence of premature ventricular contractions. After the procedure, the femoral artery was ligated and the incision was closed. The LAD region served as the control region in these animals.

Hemodynamic and 2DE data were acquired at rest and peak dobutamine stress at 4, 12, and 24 weeks after TMR. At 24 weeks, MBF was also assessed at rest and peak dobutamine stress to measure MBF reserve. At this time, 5 mCi of I-123 MIBG was injected intravenously; 30 minutes later, the dog was euthanized, the heart was excised, and confirmation of arterial occlusion was achieved by direct examination of the ameroid constrictors. The left ventricle was divided into 0.5-cm short-axis slices of equal thickness. The slices corresponding to the 2DE images were stained for gross infarction.[35] These slices were then processed for radioactivity measurements (MBF and I-123 MIBG). The remainder of the tissue was processed for histopathology (approximately $0.5 \cdot 0.5$–cm samples in duplicate) after triphenyl-tetrazoleum (TTC) staining.

Statistical Methods

Comparisons between stages were performed by use of repeated-measures analysis of variance. The paired Student t test was used to determine the difference between 2 stages. $P < .05$ (2-sided) was considered statistically significant for all comparisons.

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