Cardiac Sympathetic Denervation After Transmyocardial Laser Revascularization

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Background—Transmyocardial laser revascularization (TMR) has been shown to improve refractory angina not amenable to conventional coronary interventions. However, the mechanism of action remains controversial, because improved myocardial perfusion has not been consistently demonstrated. We hypothesized that TMR relieves angina by causing myocardial sympathetic denervation.

Methods and Results—PET imaging of resting and stress myocardial perfusion with $^{13}$NH$_3$ and of sympathetic innervation with $^{11}$C-hydroxyephedrine (HED) was performed before and after TMR in 8 patients with class IV angina ineligible for CABG or PTCA. A mean of $50\pm11$ channels were created in the left ventricle (LV) with a holmium:YAG laser. A semiautomated program was used to determine NH$_3$ uptake and HED retention in the LV. Perfusion and innervation defects were defined as the percentage of LV with tracer uptake or retention $>2$ SD below normal mean values. All patients experienced improvement in their angina by $2.4\pm0.5$ angina classes after surgery, $P=0.008$. Sympathetic innervation defects exceeded resting perfusion defects in all patients before TMR ($34.6\pm27.3\%$ for HED versus $9.4\pm10.8\%$ for NH$_3$, $P=0.008$). TMR did not significantly affect resting or stress myocardial perfusion but increased the extent of sympathetic denervation in 6 of 8 patients by $27.5\pm15.9\%$, $P=0.03$. In the remaining 2 patients, both sympathetic denervation and stress perfusion defects decreased after surgery.

Conclusions—TMR causes decreased myocardial HED uptake in most patients without significant change in resting or stress myocardial perfusion, suggesting that the improvement in angina may be at least in part due to sympathetic denervation. (Circulation. 1999;100:135-140.)

Key Words: angina ▪ lasers ▪ revascularization ▪ nervous system, autonomic

Transmyocardial laser revascularization (TMR) is a new surgical technique that has recently been approved by the Food and Drug Administration as a therapeutic modality to treat patients with intractable angina and severe coronary artery disease not amenable to coronary artery bypass graft surgery (CABG) or coronary angioplasty (PTCA). The concept of this technique is based on the anatomy of the reptile heart, in which myocardial perfusion is achieved primarily via direct blood flow from the ventricle through transmural channels. Results of clinical studies continue to show that TMR is effective in relieving angina. However, the exact mechanisms by which TMR exerts its effects and relieves angina are still controversial. The main proposed mechanisms include direct blood flow from the ventricular cavity to the ischemic myocardium through laser-created channels and increased myocardial blood flow through neovascularization mediated by thermal or mechanical laser injury.

However, the majority of human and experimental studies have not been able to demonstrate histologically sustained patency of the channels created. Objective improvement in myocardial perfusion by thallium imaging studies has also been an inconsistent finding. Furthermore, improvement in myocardial perfusion has been documented primarily several months after TMR, whereas the improvement in angina is observed in most patients within a few days after the procedure. As an alternative mechanism to explain the improvement in angina immediately after TMR, we hypothesized that TMR causes damage to the epicardial sympathetic fibers. This hypothesis is based on the following observations: the perception of anginal pain is believed to be conveyed via afferent sympathetic fibers, postganglionic sympathetic fibers to the left ventricle (LV) are known to be located superficially in the epicardium, and silent myocardial ischemia, i.e., no anginal pain, is a frequent observation in diabetic patients, who often have autonomic neuropathy. Therefore, in this study we assessed resting and stress-induced myocardial blood flow and sympathetic innervation of the LV using positron emission tomography (PET) before and after TMR.
Methods

Patient Population
This study included 8 patients (1 woman, 7 men), mean age 60±11 years, who underwent TMR as part of a larger prospective randomized trial of TMR versus maximum medical management in patients with class IV angina. The inclusion criteria for this study were class IV angina according to the Canadian Cardiovascular Society classification (CCS); ejection fraction >50%, based on preprocedure angiography, multigated acquisition scan, or echocardiogram; the patient not a candidate for other forms of coronary interventions; and evidence of ischemic or viable myocardium (defined as ≥10% reversibility in the myocardial defect based on preprocedure myocardial perfusion study) in the apical two thirds of the LV free wall. Five patients had type II diabetes mellitus. All patients had previous CABG 9.5±5 years before the TMR procedure, 3 had reoperation for CABG, and 3 had additional coronary angioplasty. None had recent (within the 6 months preceding TMR) myocardial infarction. As defined by the larger trial, all patients had intractable class IV angina and were not candidates for conventional coronary interventions.

Study Protocol
All patients underwent positron emission tomography (PET) imaging to evaluate LV perfusion and sympathetic innervation before and after TMR. All patients were evaluated for angina according to the CCS classification. Angina class was determined at the time of PET imaging before TMR, after surgery at the time of hospital discharge, and at the time of the second PET imaging after TMR. The medical regimen was also reviewed at the time of angina class evaluation. TMR surgery was performed at St Vincent Hospital and the PET studies at Indiana University Hospital. The study protocol was approved by the Institutional Review Board, and written informed consent was obtained from all subjects before the study.

TMR Technique
The heart was exposed through a limited fifth interspace left anterolateral thoracotomy. The pericardium was identified and opened longitudinally and anterior to the phrenic nerve. Adhesions, which were typically present from previous coronary procedures, were divided to expose the apical two thirds of the LV. Previous bypass grafts, if still patent, were left undisturbed to avoid distal embolization. Cardiopulmonary bypass was not used. The laser system was a 20-W pulsed holmium:yttrium-aluminum-garnet (Ho:YAG) laser (Eclipse Surgical Technologies, Inc) with fiber-optic delivery. Power output was set at 7 W with a frequency of 5 Hz (12 frames ×5, 6×10, 3×60, and 5×300 seconds). Continuous ECG monitoring was maintained throughout the procedure.

Image Reconstruction and Analysis
After image acquisition, a semiautomated analysis program was used to quantify abnormalities. Analysis was performed on composite images representing data acquired from 10 to 30 minutes after injection of NH₃ and 30 to 60 minutes after HED injection. All images were reoriented to a long-axis projection. The location of the cardiac base and apex and the inner and outer boundaries of the myocardial wall were manually defined, and the images were sliced to 11 short-axis planes between the base and the apex. The short-axis images were oriented with the LV septum on the left. Tracer uptake was then determined by circumferential profile analysis of the composite short-axis images. By use of a maximal-search algorithm, each of the 11 short-axis slices was divided into 16 equal regions of interest (ROIs) that, when combined with 1 apical region, resulted in 177 ROIs encompassing the LV. Tracer uptake was integrated in each of the 177 ROIs. The integrated images were converted into polar maps. Each polar map depicts the 177 ROIs in the LV, with the LV base on the outside and the apex in the center. The polar maps of each tracer were normalized to the top 5% of ROIs of the resting ammonia scan. Finally, the normalized polar maps of each patient were compared with the corresponding tracer polar maps derived from a database of 30 normal volunteers (Figure 1). Abnormal tracer uptake was defined as uptake of ≥2 SD below database mean. The defect size is expressed as percentage of the LV with abnormal tracer uptake. For each patient, cardiac perfusion (NH₃) and sympathetic innervation (HED) polar maps were compared with regard to the location and the extent of the tracer uptake defect before and after TMR procedure (Figure 2).

Data Analysis
Results are expressed as mean±SD. Because there was no normal distribution of the values, a nonparametric test (Wilcoxon signed rank test) was used to compare the results of LV NH₃ and HED defects before and after TMR. Differences were considered statistically significant at P<0.05.

Results
Improvement in Angina
As part of their enrollment criteria, all of the 8 subjects had CCS class IV angina before surgery. After TMR, all patients experienced immediate (before hospital discharge) improvement in their angina class. Seven patients were free of angina at the time of hospital discharge, and 1 had CCS class II angina. The mean hospital stay was 4.5±1 days. At the time of their postoperative PET studies, 5 patients had angina class II and 3 had angina class I (mean improvement, 2.4±0.5 angina classes, P=0.008) (Figure 3). Despite the significant symptomatic improvement in the patients’ symptoms, no...
A major change was made in the antianginal medical regimen, as dictated by the TMR study protocol. 5

**Functional Exercise Capacity**

Only 4 patients (subjects 1, 6, 7, and 8) had functional stress testing before and after TMR. There was no significant difference in maximal exercise capacity after TMR (5.5±1.0 METs before and 5.6±1.1 METs after TMR). However, post-TMR exercise testing induced similar angina in 1 patient, less angina in 1, and no angina in the other 2 patients. In these 2 patients, testing was stopped secondary to fatigue in 1 and to fatigue and significant drop in blood pressure in the other. Postoperative (without preoperative) treadmill exercise testing was performed in another patient in whom testing was terminated secondary to fatigue without inducible angina.

**Myocardial Perfusion and Sympathetic Innervation**

PET studies of myocardial perfusion (NH₃) and of myocardial sympathetic innervation (HED) were performed 6±3 days before and 67±14 days after TMR. A mean of 50±11 channels were created in the apical two thirds of the LV. The extent of LV resting and stress myocardial perfusion and sympathetic innervation defects before and after TMR is shown in the Table. Before TMR, the mean extent of resting perfusion defects was 9.4±10.8% (0% to 29%). All patients had evidence of ischemia, as manifested by a larger area of perfusion defects with stress: mean, 22.5±5.9% (range, 14% to 30%), \( P=0.008 \) (Figure 4). The extent of sympathetic denervation significantly exceeded that of resting perfusion defects in all patients before and after TMR (34.6±27.3% before and 49.6±28.5% after TMR), \( P=0.008 \) for both comparisons (Figure 4). The extent of sympathetic denervation was larger than but not significantly different from that of stress perfusion defects before and after TMR (Figure 4).

After TMR, there was no significant change in resting or stress-induced myocardial perfusion defect size (8.1±10.6% for rest and 24.2±16.4% for stress, \( P=0.77 \) and 0.84, respectively, versus pre-TMR) (Figure 5). However, 6 of the 8 patients had significant increases in the extent of the sympathetic innervation defects after surgery (29.8±27.9% before and 57.3±26.4% after TMR, \( P=0.031 \)). The other 2 patients (patients 7 and 8) had a decrease in HED defects; both patients with marked parallel decrease in the extent of stress-induced perfusion defect (Table). The location of the HED defects remained consistent after surgery, irrespective of whether the defect increased or decreased in size. Apical
regions of the LV were consistently involved in the innervation defect after TMR.

Discussion

The main finding of this study is that transmyocardial laser revascularization causes LV cardiac sympathetic denervation without affecting myocardial blood flow at rest or during stress, as determined by PET imaging. Consistent with previous studies, all the patients in this study experienced significant improvement in their anginal symptoms after TMR.

Since laser was first introduced to create the transmural channels, many clinical studies in animals and humans have tried to explore the mechanisms by which this procedure works. Increased myocardial perfusion, directly through the patent channels or indirectly via laser-induced neovascularization, has been the main proposed mechanism of angina relief. Angina relief has been a consistent finding of most clinical studies regardless of the kind of laser used, CO₂ or Ho:YAG. However, increased perfusion, channel patency, and neovascularization have all been very variable findings. Human autopsy studies showed occluded channels as early as 2 days after surgery. Few studies have shown an increase in myocardial perfusion after TMR. Increased perfusion, when present, was not correlated with channel patency. Horvath et al showed some protective effect against acute ischemia 1 month after creating the channels in normal sheep myocardium, with evidence of improved contractility and reduced infarct size in the laser-treated ischemic myocardium. TMR failed to protect against acute ischemia when created around the time that ischemia was created in canine models. This observation raises the question of whether the channels behave differently if created in normal versus ischemic myocardium. Our findings again failed to confirm a significant change in resting myocardial perfusion or the extent of ischemic myocardium in most patients as determined by PET imaging performed 2 months after TMR.

Laser-mediated vascular growth is a time-consuming process, and the earliest it has been shown to exist is 2 to 3 weeks after TMR, with progressive increase thereafter. Its ability to provide blood flow is yet to be demonstrated, and controversy still exists regarding its actual histological nature and whether it represents true vessels or pseudovascular tubes. Whether this process contributes to improved myocardial perfusion several months after TMR, at a time later than we imaged our patients after surgery, remains open.

Most TMR clinical studies, including ours, show relief of angina without concomitant improvement in myocardial perfusion. In addition, there is a significant lag time between chest pain relief and increased myocardial perfusion and neovascularization when present, and the histological evidence indicates early occlusion of most of the channels. These data call for an alternative explanation for the rapid clinical relief of angina after TMR. Our study suggests that TMR causes cardiac sympathetic denervation in most patients. Such a response can provide immediate relief of angina by damaging the afferent nerves that convey anginal pain. The apex was involved in the innervation defect after TMR in all patients, suggesting that more proximal laser lesions interrupt the sympathetic nerve fibers traveling to the apex and cause distal denervation beyond the actual lesion area. This sympathetic denervation pattern is consistent with the denervation noted distal to the infarcted area in other studies.

<table>
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<tr>
<th>Patient</th>
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<th>Sympathetic Innervation, %LV</th>
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Sympathetic denervation after TMR has been discussed in previous studies as a possible mechanism. But only 2 published experimental studies suggest that TMR with Ho:YAG laser destroys cardiac nerve fibers. Kwong et al evaluated cardiac afferent nerve function by hemodynamic response to bradykinin application to the laser-treated areas of a canine model. Stoll et al showed that TMR performed in nonischemic porcine heart causes significant HED defects consistent with sympathetic denervation. That study used tracers, imaging studies, and data analysis methods similar to the ones we used. Our data are the first to show that TMR causes reduced HED uptake in humans.

The increase in HED defects noted in our study could not be attributed to myocardial infarction or ischemia, because there was no significant change in resting or stress-induced myocardial perfusion defects after TMR. Functional stress testing results are consistent with the concept that TMR causes sympathetic denervation, masking ischemic symptoms and reducing stress-induced angina without actually improving maximal exercise capacity. The sympathetic innervation defects were significantly larger than the perfusion defects before the intervention, which could be a result of chronic ischemia, previous myocardial infarction, and/or diabetic autonomic neuropathy. Whether the extent of sympathetic denervation noted in our study after TMR can alone explain the improvement in angina is yet to be determined. Partial or total cardiac surgical sympathectomy has been shown to relieve angina. However, to the best of our knowledge, no study has correlated the degree of sympathetic denervation and angina class.

The 2 patients with decreased innervation defects after surgery also experienced immediate and sustained angina relief. These 2 patients were similar in clinical data and antianginal treatment to the other patients. This continues to add to the complexity of this issue and implies that other mechanisms in addition to sympathetic denervation are involved. In these patients, improvement in myocardial ischemia with increased perfusion and delivery of the tracer to the nerve endings could be inferred, because they had parallel decreases in both innervation and stress-induced perfusion defects. It is unclear whether the postoperative improvement in ischemia was a result of silent ischemia at the time of the preoperative PET study or secondary to TMR.

Clinical Implications
TMR causing sympathetic denervation may have significant clinical implications. It can result in “denervation supersensitivity” to circulating catecholamines and can be potentially arrhythmogenic. A recent study of diabetics with autonomic neuropathy showed that apical LV denervation is associated with proximal sympathetic hyperinnervation. This sympathetic dysinnervation pattern could occur in TMR and could further increase the risk of potential life-threatening arrhythmias. Sympathetic denervation as a mechanism for angina relief raises the question of whether a percutaneous endocardial approach of laser TMR would be as effective in relieving angina as the epicardial approach, because it is less likely to damage the epicardial sympathetic fibers.

Study Limitations
The major limitation in our study is the small patient cohort. Another limitation is that most of our study patients had diabetes mellitus, which can result in autonomic neuropathy and potentially interfere with our results. However, diabetic neuropathy is not expected to occur or progress over a 3-month interval, the maximum time interval between the preoperative and postoperative PET studies. Correlation between the location of the TMR lesions and the HED defects was not possible in our study because no accurate anatomic maps of the lesions were available. This correlation has been shown to exist in animal study data from our institution using the Ho:YAG system to create myocardial transmural channels in nonischemic porcine myocardium.

Conclusions
Our study indicates that TMR causes reduced myocardial HED uptake consistent with sympathetic denervation of the LV in most patients, without a significant change in resting or stress myocardial perfusion. This suggests that 1 mechanism by which TMR improves angina is LV sympathetic denervation.

Acknowledgment
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