Intermediate-Term Clinical Outcome Following Transmyocardial Laser Revascularization in Patients With Refractory Angina Pectoris

Carolyn K. Landolfo, MD; Kevin P. Landolfo, MD; G. Chad Hughes, MD; Edward R. Coleman, MD; Robin B. Coleman, RN; James E. Lowe, MD

**Background**—This study was conducted to examine the intermediate-term clinical outcomes in patients with refractory angina pectoris treated with transmyocardial laser revascularization (TMR) at our institution. TMR is an alternative surgical technique for the treatment of myocardial ischemia and angina pectoris not amenable to conventional percutaneous or surgical revascularization. Limited data exist evaluating the natural history and duration of clinical improvement in angina pectoris following TMR.

**Methods and Results**—Thirty-four patients with severe coronary artery disease unsuitable for treatment with standard revascularization techniques underwent TMR in myocardial regions determined to be ischemic by preoperative SPECT 201 Tl perfusion imaging following dipyridamole stress. Patients were assessed postoperatively at 3, 6, and 12 months for clinical outcomes including death, myocardial infarction, functional class of angina pectoris, and hospitalizations for unstable angina. Myocardial perfusion imaging by 201 Tl scintigraphy was also assessed at these temporal end points. Overall mortality at 1 year was 14.7% (n = 5). Nonfatal myocardial infarction occurred in 3 patients (8.8%). Among the patients with complete 12-month follow-up (n = 27), mean anginal class improved from 3.5 ± 0.5 pre-TMR to 2.8 ± 0.7 and 2.5 ± 0.7 at 3 and 6 months, respectively, and 2.8 ± 0.9 at 12 months. Overall improvement in angina pectoris was sustained at 1 year by at least one functional class in 50% of patients. Mean hospitalizations per year for unstable angina declined from 2.4 ± 1.6 pre-TMR to 1.7 ± 2.0 post-TMR (P = 0.01). There was no significant improvement in perfusion by SPECT 201 Tl imaging at any temporal end point post-TMR.

**Conclusions**—Despite the lack of demonstrable improvement in perfusion by SPECT 201 Tl imaging, TMR improved the functional class of angina pectoris in patients with end stage coronary artery disease to a modest degree. Although the maximal benefit in symptoms occurred at 6 months post-TMR, mild sustained clinical improvement above baseline was evident in 50% of patients at 1 year. (Circulation. 1999;100[suppl II]:II-128–II-133.)

Key Words: coronary disease ■ revascularization ■ angiogenesis ■ lasers ■ perfusion

Transmyocardial laser revascularization (TMR) is an emerging surgical therapy for the treatment of ischemic heart disease not amenable to conventional percutaneous or surgical revascularization techniques.1–4 TMR uses a high energy laser beam to create channels from the epicardial to endocardial surface of the heart in order to improve perfusion to ischemic myocardium. Although the mechanism underlying increased perfusion following TMR remain elusive, this technique is based in theory on the reptilian model of circulation which, being devoid of epicardial coronary arteries, relies on delivery of blood to the myocardium through an extensive vascular network composed of intramyocardial sinusoids directly connecting the ventricle, arteries, and veins.5 Although an analogous network of myocardial sinusoids exists in humans, its role in perfusion remains poorly defined. Myocardial needle acupuncture was an earlier attempt to model the reptilian circulation;6,7 however, the success of this technique was limited by premature channel closure due to fibrous ingrowth.8 In order to minimize fibrosis, thereby improving channel patency, Mirhoseini et al proposed the use of a CO2 laser to create transmyocardial channels.9–11 The majority of human and animal studies, however, have failed to demonstrate channel patency following TMR. Alternative mechanisms such as denervation and angiogenesis have more recently been promoted as the explanations underlying the clinical benefits following TMR.12–17

Transmyocardial revascularization using laser technology has been demonstrated to improve functional class of angina pectoris, reduce ischemia during noninvasive stress testing, and increase relative endocardial perfusion in patients with ischemic heart disease.18–21 This study was conducted to...
evaluate the intermediate clinical outcomes among patients at our institution treated with TMR.

Methods

Study Population
Between October 4, 1995 and August 6, 1997, 34 patients (14 women, 20 men; mean age 61±9, range 43 to 75) with severe, diffuse coronary artery disease not amenable to percutaneous or surgical revascularization were considered eligible for TMR. As part of the enrollment criteria, patients were also required to have preoperative evidence of ischemia (not limited to the septum) by noninvasive nuclear stress testing. Patients were initially enrolled as part of the Phase III clinical investigation evaluating the safety and effectiveness of TMR using The Heart Laser (PLC Medical Systems, Inc). In the initial phase of this trial, patients were randomized to medical therapy or TMR therapy. After multiple protocol changes, a total of 34 patients, including 8 patients initially randomized to medical therapy, underwent TMR.

Of the 34 patients undergoing TMR, 27 were available for follow-up at 1 year. Within the first year following TMR, there were a total of 5 deaths. Two additional patients underwent percutaneous intervention for newly evolved saphenous vein bypass graft lesions, thereby excluding them from the final analysis.

Study Design
Clinical evaluation, including history and physical examination, was performed immediately before TMR and then at 3, 6, and 12 months postoperatively by the same physician (C.L.D.) and nurse clinician (R.B.C.). Clinical follow-up >12 months was conducted by telephone interview and communication with primary care physicians or referring cardiologists. Pertinent demographic data obtained preoperatively are listed in Table 1. Canadian Cardiovascular Class (CCS) of angina was recorded at each follow-up end point. The number of hospitalizations for cardiac-related etiologies, including unstable angina pectoris, myocardial infarction, and congestive heart failure, were recorded pre- and postoperatively. Hard clinical end points assessed were cardiac-related death (including fatal myocardial infarction) and nonfatal myocardial infarction. Other end points evaluated included change in CCS of angina, number of hospitalizations for unstable angina pectoris, change in dosage and/or numbers of cardiac medicines, and changes in perfusion by 201 Tl SPECT imaging.

Transmyocardial Laser Revascularization
TMR was performed through a left anterior thoracotomy without cardiopulmonary bypass using The Heart Laser. The Heart Laser is a 1000-W CO2 laser with an energy range of 8 to 80 J delivered in 10- to 99-ms pulses. Laser pulses were delivered to regions of myocardium determined to be ischemic preoperatively by noninvasive nuclear imaging. Transmyocardial penetration of laser pulses was confirmed by intraoperative transesophageal echocardiography. Hemostasis from the laser channel was achieved by manual compression or (rarely) by epicardial suture placement. The mean number of confirmed laser channels drilled per patient was 22±10 (range, 10 to 44).

Nuclear Perfusion Imaging
All patients underwent pharmacologic stress and redistribution perfusion imaging with 201 Tl to assess the extent of myocardial ischemia. Pharmacologic stress was performed using dipyridamole at a dose of 140 μg/kg infused over 4 minutes. An initial injection of 3.5 to 4.0 mCi of 201 Tl was administered immediately following pharmacological stress. Imaging was performed using a CardiA (Elscint), dual head camera. A second injection of 1.5 to 2.0 mCi of 201 Tl was then given, and redistribution imaging was performed 4 hours after the initial images were obtained. Images were analyzed according to a 12-segment model. Based on perfusion analysis of the left ventricle, individual segments were assessed as normal, ischemic, or infarcted. Segments with mixed infarction and ischemia were graded according to the predominant component. Analysis of the mixed segments as a separate group was also performed; however, the overall results did not statistically change from those obtained by assigning these segments to ischemic or infarcted groups. Hence, only normal, ischemic, and infarcted groups were reported in the results section. The percentage of segments analyzed as normal, ischemic, or infarcted were analyzed for each patient pre-TMR compared with 3, 6, and 12 months post-TMR. In addition, an overall perfusion score index was created by assigning segments a numerical score (normal=1, ischemic=2, and infarcted=3) and dividing by the total number of segments (n=12). The perfusion score index was compared pre-versus post-TMR.

Data Analysis
All data are expressed as the mean±1SD unless specified otherwise. One-way ANOVA was used to compare CCS anginal scores and thallium perfusion score indices at baseline, 3, 6, and 12 months post-TMR. When overall significance (P<0.05) was present with ANOVA, Tukey’s honest significant difference test was used posthoc to delineate comparisons between paired groups. The χ² test was used to compare differences for nominal data, including the temporal changes between the numbers of normal, ischemic or infarcted segments.

Results

Patient Demographics
Preoperative demographic and clinical characteristics of the patients enrolled in this study are summarized in Table 1. All patients enrolled had CCS III or IV angina pectoris. A history of previous myocardial infarction was present in 76% of patients, and 91% had undergone at least one coronary artery bypass operation (redo in 47%). The range of cardiac medications being taken by patients at the time of enrollment included β-blockers in 31 (91%), nitrates in 33 (97%), calcium-channel blockers in 30 (88%), diuretics in 19 (56%), angiotensin-converting enzyme inhibitors in 23 (68%), and lipid-lowering agents in 31 (91%).

<table>
<thead>
<tr>
<th>TABLE 1. Patient Demographics (n=34)</th>
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<tr>
<td><strong>Patient characteristics</strong></td>
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<tr>
<td>Age, y 61±9</td>
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<tr>
<td>Sex, F/M 14/20</td>
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<tr>
<td>Left ventricular ejection fraction, 51±9%, (35%–70%)</td>
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<tr>
<td>Risk factors for CAD</td>
</tr>
<tr>
<td>Diabetes mellitus 24 (71)</td>
</tr>
<tr>
<td>Hypertension 32 (94)</td>
</tr>
<tr>
<td>Recent smoking 6 (18)</td>
</tr>
<tr>
<td>Hyperlipidemia 32 (94)</td>
</tr>
<tr>
<td>Family history 21 (62)</td>
</tr>
<tr>
<td>CAD history</td>
</tr>
<tr>
<td>Myocardial infarction 26 (76)</td>
</tr>
<tr>
<td>Native 3-vessel CAD 34 (100)</td>
</tr>
<tr>
<td>Coronary artery bypass surgery 31 (91)</td>
</tr>
<tr>
<td>Redo coronary artery bypass surgery 16 (47)</td>
</tr>
<tr>
<td>No. of patent bypass grafts pre-TMR 1.8±0.9 (0–3)</td>
</tr>
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CAD indicates coronary artery disease. Numbers in parentheses indicate percentage or range.
Clinical Outcomes

Mortality
Among the 34 patients treated with TMR, 30-day in-hospital mortality was 6% (n=2). Both deaths were attributed to cardiogenic shock from perioperative myocardial infarction. Both of the deceased patients had antecedent unstable angina requiring therapy with intravenous heparin and nitroglycerin within the week before TMR. Total mortality at 1-year was 14.7% (n=5). Two additional deaths occurred in the ensuing 6 months, yielding an 18-month mortality rate of 21%. Of the late (>1 month) mortality, 2 patients died suddenly at home. The remaining 3 patients died of myocardial infarction complicated by congestive heart failure, 2 of whom were found to have acute saphenous vein bypass graft closure. The third patient refused cardiac catheterization.

Nonfatal Myocardial Infarction
A total of 6 nonfatal myocardial infarctions occurred in 3 patients over the 12-month follow-up period. Two of these patients were among those who succumbed to subsequent fatal myocardial infarctions. The third patient sustained a perioperative myocardial infarction in the setting of noncardiac surgery complicated by significant blood loss.

Angina Pectoris
The distribution of patients within each functional class of angina pectoris at 3, 6, and 12 months following TMR is illustrated in Figure 1 for the 27 patients with complete 12-month follow-up. The mean anginal class for patients with complete 1-year follow-up was 3.5 ± 0.5 pre-TMR, improving to 2.8 ± 0.7 (P<0.003) and 2.5 ± 0.7 (P=0.002) at 3 and 6 months, respectively, and remaining stable at 2.8 ± 0.9 (P=0.006) at 12 months. Before TMR, all patients had class III or IV symptoms of angina pectoris. Post-TMR, functional class of angina pectoris improved by at least 1 grade in 65% of patients by 3 months and in 73% by 6 months (Table 2). At 12 months, 50% of patients had sustained improved in symptoms by at least 1 functional class. The number of patients with class IV symptoms decreased from 59% pre-TMR to 17% at 6 months post-TMR, with 57% of patients achieving class II status. Among the 27 patients with complete 1-year follow-up, 30% of patients had worsening of their symptoms at 12 compared with 6 months, with 41% remaining class II and 33% reverting to class IV. Despite symptomatic improvement in a majority, none of the patients in this series reported complete resolution of symptoms.

Elecive cardiac catheterization was performed at the discretion of the primary care physician in 6 patients who had deterioration in clinical status (excluding the patients who died of acute myocardial infarction and had documented saphenous bypass graft closure as noted above). Coronary angiography revealed no change in the patency of bypass grafts in 5 of 6 patients but severe diffuse distal disease. The sixth patient had progression of saphenous graft bypass disease and was subsequently treated with angioplasty and stenting of 2 bypass grafts.

Unstable Angina Hospitalizations
The annual number of hospitalizations for unstable angina pectoris decreased significantly post-TMR compared with pre-TMR (2.4 ± 1.0, pre-TMR compared with 1.7 ± 2.0, post-TMR, P=0.01) (Figure 2). This analysis, however, excludes one patient who had at least 10 post-TMR hospitalizations at multiple institutions for reported unstable angina. This particular patient also had profound depression with at least one suicide attempt in the post-TMR period. Due to her psychological instability, it was questioned on several occasions as to whether or not all chest pain admissions were truly due to angina pectoris. If this patient is included in the analysis, then the number of hospitalizations for unstable angina pre-TMR compared with post-TMR no longer remains significant (2.4 ± 1.6, pre-TMR compared with 2.0 ± 2.6, post-TMR, P=NS). Figure 3 illustrates the time course of hospitalizations for unstable angina post-TMR. The number of post-TMR hospitalizations peaked during the initial 3 months.

![Figure 1. Distribution of patients defined by CCS class of angina pectoris as function of months post-TMR.](image)

![Figure 2. Mean number of hospitalizations per year for unstable angina pectoris pre-TMR compared with post-TMR.](image)

| TABLE 2. Percentage of Patients With Improvement by 1 or 2 Functional CCS Classes of Angina Pectoris Post-TMR |
|-------------------|-------------------|-------------------|-------------------|
| Months            | Post-TMR n        | 1 CCS Class       | 2 CCS Classes     |
| 3                 | 31                | 65%               | 13%               |
| 6                 | 30                | 73%               | 17%               |
| 12                | 30                | 50%               | 13%               |
| >12               | 27                | 41%               | 11%               |

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with a nadir at 6 to 9 months. A second peak occurred in the 9- to 12-month post-TMR period, concomitant with the observed deterioration in clinical status.

**Cardiac Medications**
All patients participating in this study were on maximal medical therapy at the time of enrollment. There were no significant changes in the number or dosages of medications taken by patients pre-TMR compared with post-TMR.

**Thallium Perfusion Imaging**
Results of perfusion imaging with $^{201}$Tl are presented in Figure 4. The changes in percentages of segments characterized as normal, ischemic (reversible defects), or infarcted (fixed defects) are compared pre- and post-TMR. There was no significant decrease in the number of ischemic segments pre-TMR compared with 3 months post-TMR. There was also no change in the number of fixed defects at 3 months compared with baseline. An overall semiquantitative perfusion index was created by assigning a numerical score to each segment on the basis of the presence of normal perfusion, ischemia, or infarction. The perfusion score index presented as a function of time post-TMR is presented in Figure 5. There was no significant change in the perfusion score index pre-TMR compared with post-TMR.

**Discussion**
This study describes the change in functional class of angina pectoris over a 12-month period following TMR in patients with severe coronary artery disease. Clinical improvement in symptoms, defined by an improvement by at least 1 functional class, occurred in 73% of patients with a maximum benefit evident at 6 months. Sustained improvement at 12 months was present in 50%, evidenced by a decrease in the number of hospitalizations for unstable angina.

Although limited data exist, other published series have reported a greater and more sustained improvement in functional class of angina pectoris at 1-year follow-up. Among 20 patients treated at Brigham and Women’s Hospital in Boston, Horvath et al reported mean angina class of $1.0_{\pm0.9}$ at an average follow-up of $11_{\pm8}$ months. Horvath et al also reported the results of a multicenter, nonrandomized trial involving 200 patients treated with TMR at a mean follow-up of $10_{\pm3}$ months. Pre-TMR, all patients were either class III or IV for angina pectoris. Post-TMR, the majority of patients (approximately 28%) reported no residual angina at 12 months, with only 10% of patients remaining class III or class IV.

Our data do not corroborate the findings of other investigators, and the reasons for these differences are not entirely clear. Although the patients in our series treated with TMR did exhibit clinical improvement, the magnitude of improvement was not as great, nor was the duration of benefit sustained as reported in other studies. In terms of the study population, our patient characteristics appear similar in terms of severity of underlying coronary artery disease, history of prior bypass surgery, left ventricular function, and extent of medical therapy. Similarly, the operative technique, type of laser, and the number of laser channels drilled were also comparable. One important explanation for the differences in clinical outcome may be related to the subjective component on the part of a patient in his/her assessment of improvement in angina pectoris. The majority of patients referred for TMR have often been told that there is nothing else that can be done for them. This procedure is often viewed as a last hope, and patients are desperate to receive and benefit from the procedure. Therefore, the positive psychological benefits on the patient derived from undergoing what he or she views as a last hope procedure cannot be overemphasized, especially in the short-term. Furthermore, there is also a subjective component on the part of the physician, who wants to reassure the patient that the procedure itself was worth the risk and cost. Our patients were assessed pre- and postoperatively by a
single cardiologist in order to help remove the subjective bias in the functional assessment of angina among multiple treating physicians.

One additional factor for the discrepancy in our data with other published works potentially relates to the use the CCS functional classification of angina among a population of patients who, by necessity, have adopted a relatively sedentary lifestyle. By definition, a patient with class IV angina can perform minimal or no activities without angina, and patients with class I angina should be able to perform strenuous or prolonged recreational or strenuous work activities without symptoms. Among a sedentary population who has angina with minimal activity, a significant improvement in functional class would be defined as no angina occurring at the same or at a slightly higher level activity. Although these patients may now be able to perform daily activities of living with minimal or no symptoms, it is not the equivalent of an improvement to class 0 or I symptoms. Many of these patients do not attempt any activity which requires significant exertion. Hence, although there may be an improvement in symptoms, the functional class should be interpreted in light of a patient’s baseline functional capacity. In our experience, although many patients had improvement in symptoms, none of the patients were engaging in strenuous physical activities that would allow them to be classified as class 0 or I. Hence, our patients may have had similar improvements in angina to those reported in other studies, but the precise classification scheme may have been interpreted differently based on the patient’s overall level of functioning.

Because the mechanisms underlying the clinical improvement following TMR remain elusive, it is difficult to speculate on the pattern of clinical improvement and deterioration observed in this study. Although direct myocardial perfusion through the laser channels themselves has been proposed as a mechanism for the observed increase in myocardial perfusion,24,25 this hypothesis has not been supported in animal and human studies.25–29 More recently, angiogenesis has been proposed as the mechanism for improved perfusion in laser-treated regions of ischemic myocardium.13–17 It has also been speculated that denervation of laser-treated myocardium may also contribute to the observed clinical improvement, particularly among patients who seem to have an immediate benefit from the procedure. In our study, the beneficial effects of TMR appeared to have plateaued at 6 months. Although many patients exhibited a gradual worsening of symptoms over the next 6 months, it cannot necessarily be assumed that clinical deterioration was solely related to diminishing effects of TMR. Several patients exhibited progression in native and bypass graft disease during the latter 6 months following TMR, suggesting that the natural history of underlying severe native coronary disease and deterioration in old bypass grafts were at least partially responsible for the clinical deterioration in status. In addition, patients were treated with the laser only in areas that were ischemic preoperatively. Although it is possible that these positive effects waned over time, it is equally likely that progression of native and bypass graft disease in nonlased areas could have resulted in a clinical decline.

The results of perfusion imaging reported in the literature have been inconsistent with regard to improvement in perfusion post-TMR. Several studies have shown no improvement in reversible ischemia,18,21,30 whereas the results of the multicenter trial demonstrated a significant improvement at 12 months.23 Myocardial perfusion post-TMR in our series is more consistent with the former results. The number of segments with reversible ischemia did not significantly change over the 12-month period following TMR. There was a nonsignificant trend toward a decrease in ischemic segments with a concomitant increase in infarcted segments. These data are compatible with the histologic findings reported by Burkhoff et al, demonstrating the presence of fibrous transmural scars extending from the epicardium to endocardium in previously lased regions.28 Our data, therefore, support a symptomatic improvement in angina pectoris following TMR, but only to a modest degree.

**Limitations/Future Implications**
The major limitation of this study is the relatively small patient population. Second, the findings reported in this study were limited to patients who received treatment only. Given the numerous changes in protocol in the initial randomized study, an adequate medical control group for comparison of outcomes is lacking. Finally, the follow-up reported in this study is limited to 1 year. Despite these limitations, this study does provide evidence for a reduction in angina pectoris following TMR as early as 3 months postoperatively, with an overall improvement in 50% of patients by at least 1 functional class at 1 year. Larger, long-term studies will be needed to determine the specific populations that benefit most from this procedure, the specific myocardial regions which respond the most effectively to TMR, and the overall impact of the procedure on mortality. In order to improve the long-term benefits of the procedure, the mechanisms underlying TMR, especially with regard to the role of angiogenesis, need to be elucidated.

**References**


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