JACC Vol. 30, No. 3
September 1997:607–12

Improvement in Inducible Ischemia During Dobutamine Stress Echocardiography After Transmyocardial Laser Revascularization in Patients With Refractory Angina Pectoris

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Objectives. **The purpose of this ongoing study is to determine whether transmyocardial laser revascularization (TMLR) can lessen inducible ischemia and improve contractile reserve in patients with refractory angina pectoris.**

Background. **TMLR is an emerging surgical technique for the treatment of myocardial ischemia and angina pectoris not amenable to conventional percutaneous or surgical revascularization. Objective data documentating a reduction in ischemia during noninvasive stress testing after TMLR are rare.**

Methods. **Fifteen patients with severe coronary artery disease unsuitable for treatment with standard revascularization techniques were studied with dobutamine stress echocardiography (DSE) before TMLR. Of the 12 patients who underwent TMLR, DSE was repeated at 3 months postoperatively in 11 patients and at 6 months in 9 patients. Stress echocardiograms were analyzed for inducible ischemia, with calculation of the wall motion score index (WMSI). Heart rate and dobutamine dose achieved at peak stress were also assessed as indexes of stress tolerance.**

Results. **Compared with that before TMLR, wall motion at rest for all myocardial segments did not change significantly after TMLR, although there was a mild improvement in the WMSI of the lased myocardial regions ([mean ± SD] 1.64 ± 0.34 after vs. 1.78 ± 0.34 before TMLR, $p < 0.05$). Overall WMSI at peak stress improved markedly after TMLR (1.70 ± 0.30 after vs. 2.06 ± 0.31 before TMLR, $p < 0.002$), with the improvement in WMSI limited to the lased segments only (1.47 ± 0.31 after vs. 2.15 ± 0.34 before TMLR, $p < 0.0004$). The improvement in WMSI with stress resulted primarily from a decrease in the percentage of ischemic segments (47% before vs. 23% after TMLR, $p < 0.0008$), with no change in the percentage of infarcted segments (23% before vs. 26% after TMLR). Heart rate (83 ± 5 beats/min before vs. 102 ± 21 beats/min after TMLR, $p = 0.01$) and dobutamine infusion rate (26 ± 9 μg/kg body weight per min before vs. 34 ± 9 μg/kg per min after TMLR) achieved at peak stress also increased postoperatively, consistent with improved stress tolerance. The reduction in ischemic wall motion abnormalities and improved stress tolerance persisted at 6 months, without evidence of further improvement or deterioration of function over time.**

Conclusions. **TMLR performed in patients with refractory angina pectoris reduces ischemic wall motion abnormalities and improves stress-induced tolerance during dobutamine echocardiography. These beneficial effects persist up to 6 months postoperatively.**

(J Am Coll Cardiol 1997;30:607–12)

Transmyocardial laser revascularization (TMLR) is an emerging surgical technique using a high energy laser beam to create channels from the epicardial to endocardial surface of the heart to allow oxygenated left ventricular blood to directly perfuse ischemic myocardium. This technique is based in theory on the reptilian model of circulation, which is devoid of epicardial coronary arteries. Blood is delivered to the myocardium through an extensive vascular network comprising intramyocardial sinusoids that directly connect the ventricle, arteries and veins (1). Although an analogous network of myocardial sinusoids exists in humans, its role in perfusion remains poorly defined Myocardial needle acupuncture was performed as an initial attempt to create transmural channels to deliver oxygenated left ventricular blood directly into the myocardial sinusoids (2,3). However, the success of this technique was limited by premature channel closure due to fibrous ingrowth (4). To minimize local tissue destruction and thereby improve channel patency, Mirhoseini et al. (5–7) proposed the use of a CO_2 laser to create transmyocardial channels. Transmyocardial revascularization using laser technology has

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Manuscript received February 17, 1997; revised manuscript received May 16, 1997, accepted May 30, 1997.

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Published by Elsevier Science Inc.

0735-1097/97/$17.00
PII S0735-1097(97)00219-2

Abbreviations and Acronyms

CCS = Canadian Cardiovascular Society
DSE = dobutamine stress echocardiography (echocardiographic)
ECG = electrocardiogram, electrocardiographic
TMLR = transmyocardial laser revascularization
WMSI = wall motion score index

recently been demonstrated (8,9) to improve functional class of angina pectoris and relative endocardial perfusion in patients with ischemic heart disease.

Dobutamine stress echocardiography (DSE) is a widely accepted noninvasive imaging modality used for the detection of myocardial viability and ischemia (10–13). Dobutamine is infused in incremental doses, with echocardiographic imaging of regional and global left ventricular function performed at each stage. A number of variables, including the number and severity of ischemic wall myocardial segments; the differentiation between normal, viable, ischemic or infarcted myocardial segments; and the ischemic threshold (defined as the heart rate or dobutamine infusion rate, or both, at which ischemia develops) are available to quantitate changes over time. The present study was performed to test the hypothesis that TMLR can reduce inducible ischemia, improve the ischemic threshold and increase contractile reserve during DSE in patients with refractory angina pectoris.

Methods

Study patients. Between September 1, 1995 and July 7, 1996, 15 patients (6 women, 9 men; mean [±SD] age 63 ± 9 years, range 45 to 75) with severe, diffuse coronary artery disease not amenable to percutaneous or surgical revascularization were considered eligible for TMLR. As part of the enrollment criteria, patients were also required to have evidence of ischemia demonstrated by thallium scintigraphy that was not limited to the septum. Patients were enrolled as part of the Phase III clinical investigation evaluating the safety and effectiveness of TMLR using The Heart Laser (PLC Medical Systems, Inc.). Patients initially enrolled in this study were randomized to treatment with TMLR (n = 7) or to medical therapy (n = 8). Of the 8 patients initially randomized to medical therapy, 5 crossed over to the TMLR group within the first month of randomization, yielding a TMLR study group of 12 patients. Due to a high early crossover rate among all study centers, the protocol was subsequently changed, so that patients were required to receive at least 6 months of medical therapy before crossover to TMLR. The remaining three patients in the medical therapy group were enrolled after this protocol change. These three patients were assessed at 3 and 6 months for efficacy of medical therapy. Because the protocol was again modified, excluding the medical control group altogether, no additional patients were randomized.

Study design. At the time of enrollment in the study, all 15 patients underwent DSE for assessment of inducible myocardial ischemia. Of the 12 patients treated with TMLR, DSE was repeated postoperatively at 3 months in 11 patients and at 6 months in 9. Two patients died, yielding a 6-month follow-up group of 10 patients. The tenth patient did not return for 6-month DSE. Of the patients randomized to medical therapy, all three underwent repeat DSE at 3 and 6 months after enrollment.

Dobutamine stress echocardiography. DSE was performed using a Hewlett-Packard Sonos 2500 (2.5-MHz transducer) equipped with specialized software designed for stress echocardiographic imaging. Due to the severity of coronary disease, all medications, including beta-adrenergic blocking agents, were continued before DSE both before and after TMLR. Dobutamine was infused in 6-min stages at rates of 5, or 10, 20, 30 and 40 μg/kg body weight per min. The use of 6-min stages relates to preliminary data from our laboratory demonstrating a more consistent heart rate response at lower doses of dobutamine, in addition to a decreased requirement for atropine administration when DSE is performed in 6-min stages compared with 3-min stages. These benefits are particularly evident in patients treated with beta-blockers (14). Given the high (83%) percentage of patients treated with beta-blocker therapy, in addition to the severity of coronary artery disease warranting cautious use of atropine, 6-min stages were used. Imaging was performed using standard views, including the parasternal long- and short-axis and apical four- and two-chamber views. Digital images were acquired at rest and at low (5 or 10 μg/kg per min), mid and peak dose and then displayed in a quad-screen format for subsequent analysis. Blood pressure and continuous electrocardiographic (ECG) monitoring was performed throughout the dobutamine infusion. Tests were terminated for angina with associated ECG changes or regional wall motion abnormalities; the development of new, extensive regional wall motion abnormalities; or completion of the infusion. All test end points were achieved either before or by the end of the completion of the 40-μg/kg infusion; hence, no patient required atropine administration.

Echocardiograms were analyzed for inducible ischemia using a standard 16-segment model proposed by the American Society of Echocardiography. Regional wall motion was scored as follows: 1 = *normal*; 2 = *hypokinetic* (reduced systolic wall thickening); 3 = *akinetic* (absent systolic wall thickening); and 4 = *dyskinetic* (outward systolic wall motion). The wall motion score index (WMSI) was calculated at rest, low dose and peak stress by two independent observers (C.D., T.R.).

In addition to evaluation of the global (all 16 segments) WMSI and lased and nonlased segments were analyzed separately. To define the lased myocardial regions, an intraoperative map was created for each patient documenting the location of the laser channels. For this purpose, the heart was divided into the basal, mid and apical segments of the anterior, lateral, posterior and inferior walls (total 12 segments). The septum was excluded because it is not approachable by TMLR. Lased and nonlased segments were differentiated on the basis of an intraoperative map. Because these segments have analogous echocardiographic correlates, a corresponding map of

Table 1. Interpretation of Regional Wall Motion During Dobutamine Stress Echocardiography

Wall Motion Analysis			
Rest	Low Dose	Peak	Interpretation
Normal	Normal	Normal	Normal
Normal	No change or worse	Worse	Ischemic
Abnormal	Improved	Worse	Ischemic (biphasic)
Abnormal	Improved	Improved	Viable/nonischemic
Abnormal	No change	No change	Infarcted

Table 2. Patient Demographics

MI	9 (75%)
CABG	11 (92%)
Repeat CABG	7 (58%)
No. of patent grafts	1.6 ± 1.0
Range	0–3
LVEF (%)	52 ± 11
Range	39–71
Admissions for unstable angina (per yr)	2.8 ± 1.4

Data presented are mean value ± SD, range or number (%) of patients. CABG = coronary artery bypass graft surgery; LVEF = left ventricular ejection fraction; MI = myocardial infarction.

lased and nonlased segments based on the 16 segment echocardiographic model (excluding the basal and mid anterior septum and basal, mid and apical septum, yielding a total of 11 segments) was subsequently created. All echocardiographic segments correlated with the intraoperative segments, with the exception of the apical posterior wall, for which there is no defined echocardiographic segment. Laser holes drilled in this segment were therefore assigned to the apical inferior wall of the echocardiographic model.

On the basis of regional LV function and response to low and peak dobutamine stress, individual segments were also classified as *normal*, *viable*, *ischemic* or *infarcted* (Table 1). *Viable segments* were defined as those with abnormal rest regional function that demonstrated sustained improvement with dobutamine infusion and no evidence for ischemia. *Ischemic segments* were defined as those with deterioration of rest regional function during stress or segments exhibiting a "biphasic" response to dobutamine (i.e., improved wall motion with low dose and deterioration at peak dose). Note that all ischemic segments are also viable; however, segments referred to as "viable" specifically denote those without ischemia. Segments with abnormal rest regional function and no change with stress were classified as *infarcted*.

Other end points assessed during DSE included peak heart rate and dobutamine infusion rate tolerated at peak stress.

Transmyocardial laser revascularization. TMLR was performed through a left anterior thoracotomy without cardiopulmonary bypass using The Heart Laser (PLC Medical Systems, Inc.). The Heart Laser is a 1000-W CO_2 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 thallium scintigraphy. Transmyocardial penetration of laser pulses was confirmed by intraoperative transesophageal echocardiography that demonstrated intracavitary microbubble formation on contact of the laser beam with ventricular blood. Hemostasis from the laser channel was achieved by manual compression or rarely by epicardial suture placement. The mean number of confirmed laser channels drilled/patient was 30 ± 9 (range 15 to 45).

Data analysis. Results are expressed as mean value ± SD, unless specified otherwise. Comparisons between study end points before and after TMLR were made using paired Student *t* tests. Differences were considered significant at $p < 0.05$.

Results

Patient demographics. Demographic and clinical characteristics of the patients enrolled in this study are summarized in Table 2. All patients enrolled had Canadian Cardiovascular Society (CCS) class III or IV angina pectoris. The majority of patients had at least one previous myocardial infarction and had undergone coronary artery bypass graft surgery. The range of cardiac medications taken by the patients at the time of enrollment included beta-blockers in 10 (83%), nitrates in 12 (100%), calcium-channel blocking agents in 11 (92%), diuretic drugs in 7 (58%), angiotensin-converting enzyme inhibitors in 7 (58%) and lipid-lowering agents in 11 (92%). There were no significant changes in the number or dosages of cardiac medications at the 3- or 6-month clinical follow-up periods.

Dobutamine stress echocardiography. Comparisons between the mean wall motion score index before and 3 months after TMLR for all segments (global) and for lased and nonlased segments at rest and peak dobutamine stress are

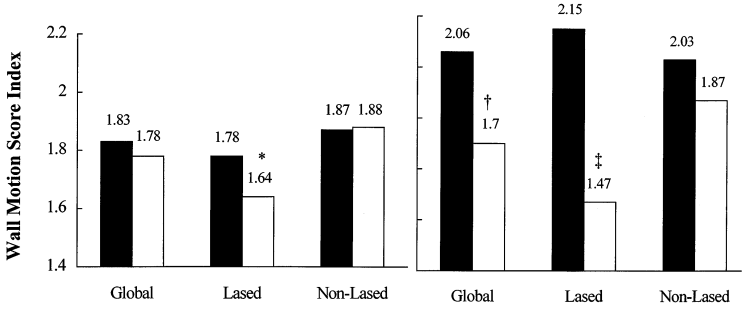


Figure 1. WMSI at rest **(left)** and peak dobutamine stress **(right)** for all segments (Global) and lased and nonlased segments before **(solid bars)** versus after TMLR **(open bars),** demonstrating postoperative improvement in WMSI of the lased segments at rest and improvement in global and lased segment WMSI at peak stress. *p = 0.05. †p = 0.002. ‡p = 0.0004.

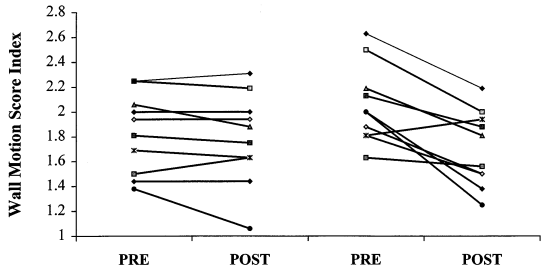
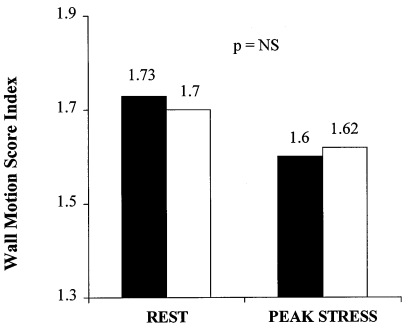


Figure 2. Global WMSI at rest **(left)** and peak dobutamine stress **(right)** for individual patients before (PRE) versus after TMLR (POST), illustrating a uniform improvement in WMSI for the majority of patients after TMLR.

presented in Figure 1. Interobserver agreement for assessment of the WMSI was excellent (r = 0.94). At rest, there was no overall change in regional myocardial function assessed by WMSI after TMLR. Analysis of the lased and nonlased segments separately demonstrated a slight improvement in rest function among the lased segments after TMLR. In contrast, wall motion score at peak stress was significantly improved after TMLR compared with the preoperative study, consistent with a reduction in inducible ischemia with stress. Analysis of the lased and nonlased segments separately demonstrated that the improvement in global wall motion score with stress was due to a reduction in ischemia of the lased segments, with no significant change in nonlased regions. Figure 2 illustrates the change in WMSI for each individual patient before and 3 months after TMLR at rest and at peak dobutamine stress. In the majority of subjects, regional function at rest did not change significantly after TMLR. More important, Figure 2 illustrates that the improvement in overall WMSI with stress was due to a uniform reduction in inducible ischemia in all but one patient as opposed to a dramatic improvement in a few patients.

Figure 3 depicts the mean WMSI at rest and with peak stress at 3 months after TMLR compared with 6 months after TMLR. This graph illustrates that the beneficial effects of TMLR on left ventricular function evident at 3 months persist

Figure 3. Global WMSI at rest **(left)** and peak dobutamine stress **(right)** at 3 months **(solid bars)** versus 6 months after TMLR **(open bars),** demonstrating a persistent beneficial improvement in WMSI over time.



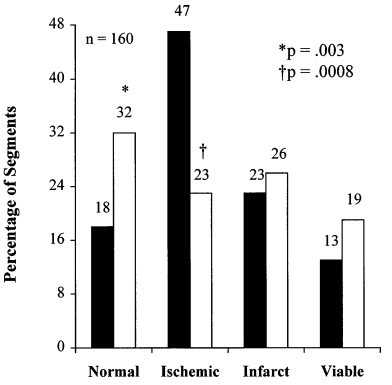


Figure 4. Classification of all myocardial segments as normal, ischemic, infarcted or viable before **(solid bars)** versus after TMLR **(open bars),** illustrating a reduction in the percentage of ischemic and an increase in the percentage of normal segments after TMLR.

at 6 months, without evidence for further improvement or deterioration of regional function.

Change in regional wall motion. To account for the observed changes in regional wall motion score after TMLR, individual segments were classified as normal, ischemic, viable or infarcted (Table 2). Figure 4 illustrates the analysis of 160 individual segments analyzed accordingly, demonstrating an increase in the percentage of normal segments (from 18% before to 32% after TMLR, p = 0.003) and a decrease in the percentage of ischemic segments (from 47% before to 23% after TMLR, p = 0.0008). Separate analysis of the lased and nonlased segments (Fig. 5) revealed that the reduction in ischemia occurred predominantly among the lased segments, with no significant change in the nonlased segments. Among lased segments, there was no significant increase in the percentage of infarcted segments and a trend toward an increase in the percentage of viable nonischemic segments. Among the nonlased segments, the percentage of normal segments increased significantly, from 26% to 31% (p = 0.02), but there was no change in the percentage of ischemic, infarcted or viable segments.

Heart rate and dose response during DSE. The hemodynamic response during DSE and the dose of dobutamine reached at peak stress were also assessed before and after TMLR as indexes of stress tolerance. There were no significant differences in rest heart rate or systolic blood pressure before versus 3 or 6 months after TMLR. Mean heart rate achieved at peak stress increased from 83 ± 5 beats/min before to 102 ± 21 beats/min after TMLR (p = 0.01). Mean dobutamine infusion rate reached at peak stress also increased from 26 ± 9 μg/kg per min before to 34 ± 9 μg/kg per min after TMLR (p = 0.03). There were no significant differences in peak heart rate or peak infusion rate at 6 compared with 3 months after TMLR. Although all tests were terminated for ischemic wall motion abnormalities or angina pectoris after TMLR, these end points occurred at higher heart rates and higher dobutamine infusion rates after than before TMLR.

Medical therapy group. Although limited conclusions may be drawn given the small patient number, among the three

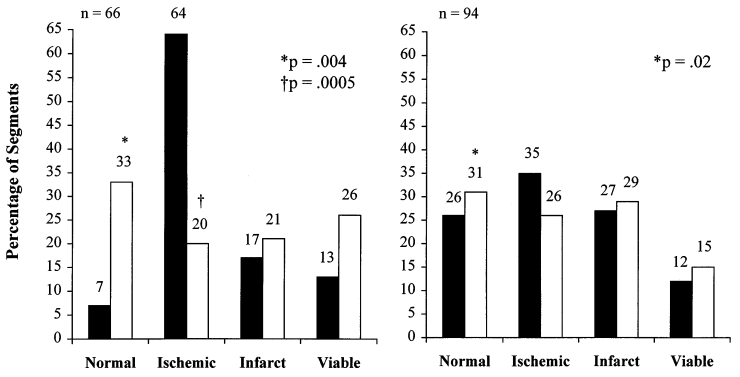
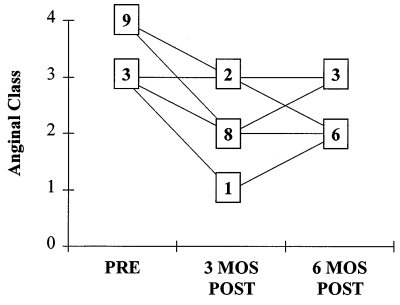


Figure 5. Classification of lased (**left**) and nonlased segments (**right**) as normal, ischemic, infarcted or viable before (**solid bars**) versus after TMLR (**open bars**), illustrating that the overall reduction in the percentage of ischemic and the increase in the percentage of normal segments were predominantly due to improvement in the lased myocardial regions.

patients in the medical therapy group, mean rest wall motion score remained unchanged at 3 months (1.66 ± 0.41) and at 6 months (1.60 ± 0.40) compared with the baseline study at randomization (1.66 ± 0.41). Despite continued aggressive medical therapy, mean wall motion score at peak stress at 3 months (1.97 ± 0.04) was slightly worse than that at the baseline study (1.75 ± 0.27). Mean wall motion score at peak stress similarly did not change at 3 months (1.97 ± 0.04) compared with that at 6 months (1.91 ± 0.04).

Clinical assessment of angina. CCS angina class before and after TMLR is presented in Figure 6. Before TMLR, nine patients (75%) were in CCS class IV, and three (25%) were in CCS class III. Two patients died within the 6-month follow-up period, yielding a study group of 11 patients at 3 months and 10 at 6 months. One patient died perioperatively due to myocardial ischemia and congestive heart failure. The second patient died 4 months postoperatively due to acute myocardial infarction from occlusion of a saphenous vein graft. Among the 11 patients available for 3-month post-TMLR follow-up, 10 had clinical improvement in angina by at least one functional class. Of the 10 surviving patients at 6 months, 9 returned for clinical follow-up. No patients had CCS class IV symptoms; three were in CCS class III; five were in CCS class II; and one was in CCS class I.

Figure 6. CCS angina pectoris class before (PRE [n = 12]) versus 3 (3 MOS POST [n = 11]) and 6 months after TMLR (6 MOS POST [n = 9]). The differences in number of patients at follow-up reflects two patients who died and one patient who did not return for the 6-month follow-up visit.



Discussion

The current data demonstrate that TMLR results in an improvement in inducible ischemia during DSE as early as 3 months postoperatively. *Inducible ischemia* is a general term that incorporates several different variables, including the severity and extent of ischemic wall motion abnormalities, the threshold (i.e., heart rate or dobutamine infusion rate) at which ischemic wall motion abnormalities occur and the development of symptoms such as angina pectoris. DSE is both sensitive and specific for the detection of inducible ischemia in patients with coronary artery disease and for the identification of hibernating myocardium in patients with ischemic left ventricular dysfunction (12,15,16). DSE has also been used to predict improvement in regional and global left ventricular function after coronary revascularization with either percutaneous transluminal coronary angioplasty or coronary artery bypass graft surgery (12,13,16).

In the present study, global wall motion at rest did not change significantly after TMLR, although there was a slight but significant improvement among the lased segments only. Wall motion score at peak DSE decreased significantly after TMLR due to a reduction in the number of lased segments that became ischemic at peak stress. Further evidence for an improvement in contractile reserve after TMLR was suggested by a greater tolerance to higher doses of dobutamine and achievement of higher heart rates at peak stress. The improvement in contractile reserve during stress after TMLR paralleled the observed benefits in anginal function class. These beneficial effects in terms of angina, reduction in inducible myocardial ischemia and greater stress tolerance were evident by 3 months and persisted at 6 months.

Although the precise mechanisms for the beneficial effects of TMLR remain elusive, the success of TMLR is based in theory on the supposition of improved regional blood flow to ischemic myocardium. The present study demonstrates that the reduction in WMSI during stress after TMLR was related to a decrease in viable ischemic myocardial segments and a trend toward an increase in the number of viable nonischemic segments, with no increase in the number of infarcted segments. These data suggest that TMLR does, in fact, improve

local perfusion to ischemic regions and does not create regions of microinfarction. Interestingly, there was a slight improvement in the percentage of normal segments within nonlased regions. One potential explanation for this finding may be that the increased perfusion in lased regions resulted in an overall improvement in systolic function of adjacent myocardial segments.

Because of the small number of patients in the medically treated group, statistical inferences and a reliable comparison between medical and surgical groups could not be drawn. The limited number of patients in the control group reflects the early protocol design, which allowed for immediate crossover to TMLR after hospital admission for unstable angina after enrollment and the latter elimination of the medical therapy group altogether. Nonetheless, overall wall motion score at rest and with stress did not appear to significantly change over the follow-up period, despite similar follow-up and aggressive pharmacologic therapy. Although this observation does not indicate a failure of medical therapy, it does suggest that aggressive medical therapy alone was unlikely to account for the reduction in inducible ischemia and improved stress tolerance in the TMLR group.

The reduction in ischemic wall motion abnormalities during peak dobutamine stress implies an improvement in local perfusion to these regions. The mechanisms for improved local perfusion to ischemic regions have not been well elucidated; however, direct perfusion from channels and neovascularization are among the proposed hypotheses. Anatomic evidence for channel patency has been demonstrated in the animal model (17) and in humans (18). Preliminary evidence for neovascularization and smooth muscle cell proliferation after TMLR has also been demonstrated in animal models (17,19).

Study limitations. The major limitations of this study are the relatively small patient cohort, lack of adequate medical control group and limited long-term follow-up. Despite these limitations, this study does provide evidence for a reduction in ischemia after TMLR as early as 3 months postoperatively. Larger, long-term studies will be needed to determine the specific patient groups that benefit most from this procedure, the specific myocardial regions that respond the most effectively to TMLR, whether the beneficial effects persist long term and the overall impact of the procedure on mortality.

Implications. In addition to a subjective improvement in symptoms, the data obtained from this study provide objective evidence for a reduction in inducible ischemia after TMLR in patients with refractory angina pectoris. Documentation of functional improvement as such may lead to more widespread acceptance of this procedure for patients with severe coronary artery disease not amenable to standard revascularization techniques. DSE also provides a means to document functional change after TMLR, thereby enabling future studies to be conducted with objective end points.

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