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Myocardial Revascularization With Laser: Preliminary Findings

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Abstract

Background: We assessed the transmyocardial laser revascularization (TMLR) as sole therapy in patients with symptomatic coronary artery disease refractory to interventional or medical treatment.

Methods and Results: Thirty-one patients were evaluated with positron emission tomography (PET), dobutamine echocardiography, ^{201} Thallium single-photon emission computed tomography (^{201}) Thallium-SPECT), and multigated acquisition radionuclide ventriculography (MUGA). TMLR was performed in 21 patients who had demonstrable ischemia in viable myocardium. The mean Canadian Cardiovascular Society (CCS) angina class was 3.70 plus/minus 0.7 (4 patients with unstable angina). Untreated septal segments were used as controls. At 3 months, (n = 15 patients), the mean CCS angina class was to 2.43 plus/minus 0.9 (P < .05). On dobutamine echocardiography, the mean resting wall motion score index was improved by 16% in lased segments (P < .03 vs control), and mean LVEF at peak stress increased by 19% (P = NS vs baseline). On^{201} Thallium-SPECT, perfusion of lased and nonlased segments did not change. On PET, the mean ratio of subendocardial to subepicardial perfusion (SEn/SEp) increased 14% over baseline (P < .001 vs control). At 6 months (n = 15 patients), the mean CCS angina class was 1.7 plus/minus 0.8 (P < .05). The mean resting wall motion score index was up by 13% in lased segments (P < .05 vs control). Resting LVEF was unchanged. Stress LVEF increased 21% (P = NS vs baseline). Myocardial perfusion remained unchanged by^{201} Thallium-SPECT. On PET, 36% of the lased segments were better, and 25% were worse compared with baseline. The resting SEn/SEp by PET was up 21% (P < .001 vs control). All deaths (two perioperative and three late) occurred in patients with preoperative congestive heart failure. Two patients required repeat revascularization of new coronary lesions.

Conclusions: These results suggest that TMLR improves anginal status, relative endocardial perfusion, and cardiac function in patients who do not have preoperative congestive heart failure. (Circulation. 1995;92[suppl II]:II-58-II-65.)

Key Words: lasers, coronary disease, ischemic, revascularization, myocardium.

In 1933, Wearns and colleagues [1] described a unique aspect of the myocardial microanatomy involving the presence of myocardial sinusoids. These sinusoidal communications vary in size and structure but represent a network of direct arterial-luminal, arterial-arterial, arterial-venous, and venous-luminal connections. This vascular mesh forms an important source of myocardial blood supply in reptiles, but its role in humans is poorly understood. Shortly after Wearns' report, in an attempt to restore blood flow to the ischemic myocardium, several investigators began to devise methods for delivering oxygenated blood to the vicinity of the spongelike sinusoidal plexus. Beck [2] attempted revascularization by grafting the omentum, parietal pericardium, or mediastinal fat to the surface of the heart. His technique seemed to have limited success. Independently, Vineberg [3] attempted to restore arterial flow to the sinusoids by implanting the left internal mammary artery into the myocardium. Although Vineberg's technique was promising and, indeed, appeared successful in some patients at long-term follow-up, [4] it was overshadowed by the emergence of coronary artery bypass (CAB) surgery.

Other investigators attempted to deliver oxygenated blood directly from the left ventricle into the myocardial sinusoids: Sen et al, [5] followed by Hershey and White, [6] used needle acupuncture to create transmural channels; Massimo and Boff [7] implanted T-shaped tubes into the myocardium. However, fibrous tissue ingrowth, thought to be a reaction to acute mechanical trauma, caused early closure of the communications. [8] Mirhoseini et al [9] proposed using a laser to create transmyocardial channels and to prevent fibrosis. After conducting extensive experiments in animals, Mirhoseini et al [10] performed transmyocardial laser revascularization (TMLR) clinically, as an adjunct to CAB, with an 80-W CO_2 laser. In 1986, Okada and coworkers [11] used a CO_2 laser (output range, 60 to 90 W) to create six holes in the heart of a patient who was in ventricular fibrillation. In 1991, Mirhoseini et al [12] began clinical

studies of TMLR with an 800-W CO ($_2$) laser, which made it possible to create channels in the contracting myocardium.

The present study was conducted to evaluate the suitability of TMLR as an alternative treatment for patients who have symptomatic coronary artery disease that is refractory to maximal medical therapy and who are unsuitable candidates for CAB surgery or percutaneous transluminal coronary angioplasty. Our first objective was to establish guidelines for identifying the candidates in whom hibernating myocardium, reduced coronary flow reserve, or both have been documented through positron emission tomography (PET). Our second objective was to evaluate the long-term effects (3 and 6 months) of TMLR on left ventricular perfusion and metabolism with PET scans and assess left ventricular function with dobutamine echocardiography and MUGA. Our third objective was to determine predictors for mortality and morbidity after TMLR. This paper presents the preliminary results at 3 and 6 months after the laser procedure in 21 patients who underwent TMLR as sole interventional therapy.

Methods

Study Design

Baseline myocardial perfusion (at rest and with dipyridamole infusion-handgrip stress) and viability status were documented by PET. Also, baseline resting left ventricular ejection fraction (LVEF) was assessed by multigated acquisition radionuclide ventriculography (MUGA); segmental wall motion and LVEF, both at rest and with dobutamine infusion, were assessed by two-dimensional echocardiography; and perfusion status, both at rest and/or at peak stress (treadmill or dipyridamole infusion) was assessed using^{201} Thallium chloride (^{201}) Thallium single-positron emission computed tomography [(^{201}) Thallium-SPECT]). The studies were conducted at baseline (before TMLR) and then repeated at 3 and 6 months.

Baseline Patient Characteristics

Between July 1, 1993, and July 6, 1994, 31 consecutive patients with severe chronic ischemic heart disease characterized by distal, diffuse coronary artery disease unsuitable for routine treatment with CAB or percutaneous transluminal coronary angioplasty were screened for possible inclusion in the study. Of the 31 patients who underwent initial screening, the presence of potentially viable myocardium was observed in 21 who were enrolled into the study (mean age, 62.6 plus/minus 9.7 years) Table 1. By the Canadian Cardiovascular Society (CCS) system for assessing angina, 4 of the 21 patients had class III angina, 13 had class IV angina, and 4 had unstable angina, despite maximal medical therapy. Five patients were being treated for congestive heart failure with combined cardiotonics and diuretics. Of the 21 patients, 19 had previously undergone CAB: once in 8 patients, twice in 7, and three times in 4. In addition, 4 patients had undergone PTCA of native vessels and/or CAB grafts. The average time from the previous surgery to the present procedure was 9.3 years (range, 1 to 16 years).

Characteristic	No. of Patients
Angina	
Stable (CCS class III or IV)	17
Unstable	4
Left ventricular ejection fraction	
<50%	14
>50%	7
Number of previous procedures*	
0	2
1	8
≥2	11
Concomitant disease(s)	
Diabetes mellitus	3
High blood pressure	12
Peripheral vascular disease	8

CCS indicates Canadian Cardiovascular Society.
*Coronary artery bypass, percutaneous transluminal coronary angioplasty, or both.

Table 1. Preoperative Characteristics in 21 Patients

PET

Before PET, patients who had not fasted were given 50 mg glucose (Glucola) orally. PET was performed using a nine-slice tomograph. [13-15] [(^{13}) N]ammonia (40 to 50 mCi IV) was infused for 20 to 60 seconds. Data collection was begun in list mode at 80 seconds after the beginning of the infusion (to allow for blood pool clearance) and was continued through 360 seconds.

After completion of [(^{13}) N]ammonia imaging, F-18 deoxyglucose 10 mCi IV was injected. Forty-five minutes later, F-18 deoxyglucose images were acquired for 30 minutes. Each original nine-slice image set of paired early and late [(^{13}) N]ammonia data and late [(^{13}) N]ammonia images paired with F-18 deoxyglucose images were reformatted into true short-axis, true long-axis, and polar maps for side-by-side display. Early (S_1) PET images were reconstructed from data collected between 15 and 110 seconds and late (S_2) images from data collected between 120 and 360 seconds. A relative ratio image of the late to early [(^{13}) N]ammonia polar maps was also displayed as a ratio polar map for quantitative analysis, as previously described. [13-15].

It is believed that the TMLR channels occlude toward the epicardial surface but that their subendocardial section remains patent and establishes camerosinusoidal connections. We therefore hypothesized that only the subendocardial perfusion would be improved, as evidenced by an increase in the mean ratio of subendocardial to subepicardial perfusion (SEn/SEp).

Using automated software, we conducted a detailed analysis by region of interest. On short-axis images, the left ventricular wall and the septum were divided into a subepicardial region and a subendocardial region Figure 1. Tracer uptake in each region was measured separately and expressed as the SEn/SEp to normalize for the dosage of radioisotope injected in each patient during different studies. Although imaging of endocardial to epicardial perfusion by PET is limited by partial volume errors associated with a resolution of 14 mm, qualitative directional trends in SEn/SEp are possible with limited accuracy.

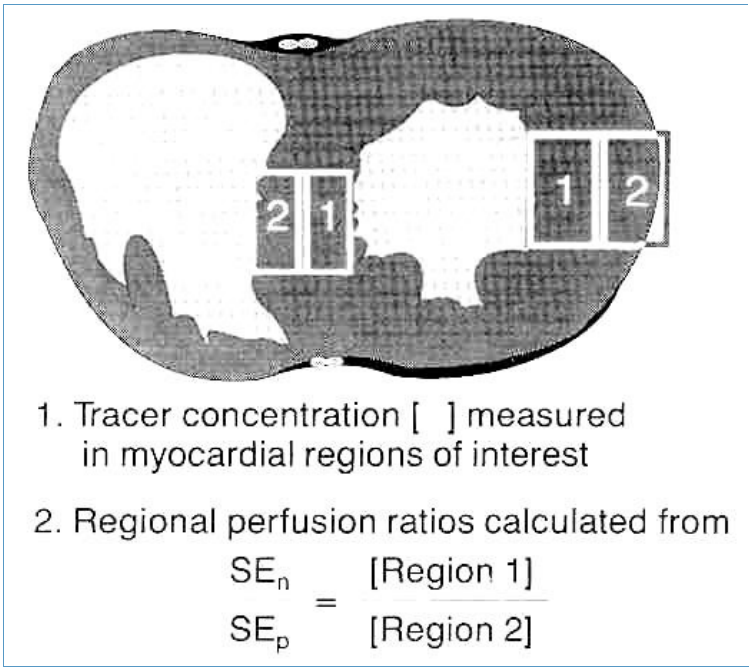


Figure 1. Short-axis diagrammatic image of the myocardium showing subendocardial (SEn) (1) and subepicardial (SEp) (2) regions in which radioisotopic tracer was measured by positron emission tomography to determine perfusion. Tracer uptake was measured separately in each region and expressed as a ratio of SEn to SEp perfusion.

Treadmill

Exercise tolerance of the patients was evaluated by the standard treadmill test by use of a modified Bruce protocol Table 2. [16] Relevant parameters were time on treadmill (minutes), computer-estimated average metabolic equivalents (METs) of maximum rate of Oxygen$_2$ consumption [VO_{2max} (mL O_2 *symbol* kg^{-1} *symbol* min^{-1}) = 3.5 METs], and the maximum heart rate-systolic blood pressure double product (RPP, beats *symbol* min^{-1} *symbol* mm Hg). Time on treadmill and RPP at peak stress for patients who could not perform the test because of unstable angina were considered to be 0 at baseline. METs for these patients were assumed to be 3.0, which represents the basal metabolic rate of oxygen consumption. The treadmill parameters for patients who could not perform the test because of any noncardiac condition were not included in the calculation of sample means.

Stage	Speed, mph	Grade, %	Time, min	METs*
1	1.2	0	3	1.9
2	1.7	5	3	3.5
3	1.7	10	3	4.6
4	1.7	12	3	5.1
5	2.2	12	3	6.3
6	2.5	12	3	7.0

*Metabolic equivalents of oxygen consumption. 1 MET=3.5 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$; METs×3.5=peak maximum oxygen consumption.

Table 2. A Modified Bruce Protocol for Evaluation of Patients Before and After Surgery for Treatment With Transmyocardial Laser Revascularization

(^{201}) Thallium Scintigraphy

An initial injection of 3 mCi of^{201} Thallium chloride was administered during exercise or pharmacological stress. Imaging by use of SPECT with a high-resolution parallel-hole collimator on a single-head, single-crystal scintillation camera was begun 10 minutes after injection. Redistribution imaging was performed at 4 and/or 24 hours after the initial injection. Patients were placed supine on the imaging table, and data were collected over 180 degrees, starting in the right anterior oblique (45 degrees) position and proceeding to the left posterior oblique (135 degrees) position. Acquisition was made in 32 steps (intervals of 6 degrees), each step lasting 40 seconds. Data processing incorporated standard tomographic reconstruction, and display included polar coordinate maps and tomographic slices in orthogonal planes. Stress images were aligned for display with anatomically corresponding slices of initial redistribution collections. Analysis of thallium images included qualitative (visual) and semiquantitative inspection of tomographic data. Tracer uptake in myocardial segments was scored according to severity, on a scale for which 0 denotes normal perfusion and 4 denotes no perfusion. A total of 30 values (15 initial and 15 redistribution) were generated for each study. Myocardial viability scores were generated by comparing perfusion scores at rest and during stress, and then classifying each segment as normal (4), ischemic (2), ischemic with scar (1), and scarred (0). The cumulative viability scores were generated for each study by adding the viability score of individual segments for each patient. These data were normalized by the respective score calculated before TMLR to determine the percent change in perfusion since the operation.

Dobutamine Echocardiography

After patients fasted for 3 hours, dobutamine echocardiography (DE) was performed using a Hewlett-Packard model Sonos 1500 with a 2.5-MHz transducer. Parasternal long-axis, parasternal short-axis (basal, middle, and apical levels), apical four-chamber, and apical two-chamber views were acquired. Blood pressure and ECG measurements were monitored continuously during dobutamine infusion. Dobutamine was administered at 5, 10, 20, 30, and 40 micro gram *symbol* kg^{-1} *symbol* min^{-1} in 5-minute stages for viability and 3-minute stages for ischemia; each stage lasted 5 minutes. The regional wall motion score index (WMSI) estimated by two independent observers was selected as the experimental variable of the echocardiographic studies. A score of 1 indicated normal wall motion and systolic thickening (endocardial excursion of greater or equal to 5 mm and systolic thickening of greater or equal to 25%); 2 indicated hypokinesia (systolic wall thickening of < 5 mm); 3 indicated akinesia (absence of systolic wall thickening or motion); and 4 indicated dyskinesia (systolic wall thinning and outward motion).

Transmyocardial Laser Revascularization

Before surgery, a 5-MHz multiplanar transesophageal probe (Hewlett-Packard) was placed in the esophagus and a baseline study was performed. A left anterolateral thoracotomy in the fourth intercostal space preceded the laser procedure, which was performed on the patient's beating heart using a 1000-W CO_2 heart laser (Laser Engineering, Inc). The energy of each laser pulse was 15 to 60 J, which corresponds to a pulse duration of 20 to 50 ms. The delivery of each laser pulse was synchronized with the R wave on the patient's ECG. Laser pulses were delivered in the area of interest, [nearly equal] 1 cm apart. Transmyocardial penetration of pulses produced intraventricular microcavities (steam bubbles) on contact of the laser beam with intraventricular blood, which was confirmed by transesophageal echocardiography. After each channel was created, adequate hemostasis was ensured by applying external digital pressure or by placing epicardial purse-string sutures. At the completion of the procedure, the incision was closed in the routine manner. A repeat transesophageal study was performed after each operation to rule out injury of the interventricular septum or submitral apparatus.

Data Collection and Statistical Analysis

The LV myocardium was divided into 15 segments Figure 2. The anterior, lateral, and inferoposterior segments of the LV free wall at the basal, mid, and distal levels at which the laser channels were created surgically were considered to be the experimental segments. The anterior septal, septal, and inferior septal segments at the basal, mid, and distal levels, which were technically impossible to reach with the laser probes, were considered to be the control segments. Relevant experimental variables were identified as the SEn/SEp from PET, the WMSI from DE, and

the LV perfusion score from^{201} Thallium-SPECT. Resting and stress LVEF from DE also were considered to be experimental variables. The value of each variable was calculated independently for lased (experimental) and nonlased (control) segments. The values obtained at follow-up were normalized by the respective values of the same variables at baseline. The percentages of change at 3 or 6 months with respect to baseline were averaged within the patient population. Means plus/minus SD of experimental and control segments were compared using a paired, single-tailed Student's t test; a value of P < .05 was considered significant.

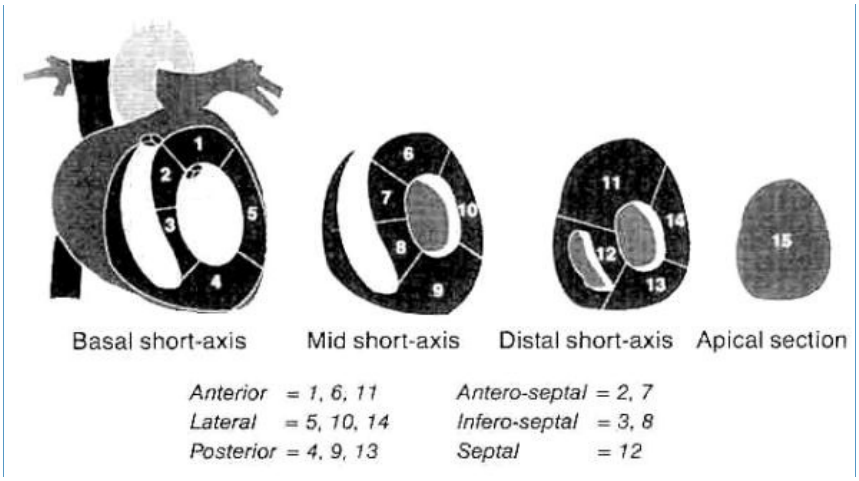


Figure 2. Diagram showing the left ventricular myocardium analyzed by segment. The experimental (lased) regions of interest included the apical (15), anterior (1,6, and 11), lateral (5, 10, and 14), inferoposterior (4, 9, and 13), and apical (15) segments. The control segments were the anteroseptal (2 and 7), septal (12), and inferoseptal (3 and 8).

Results

Before Surgery

In this series of 21 patients, 4 could not undergo the stress protocol for thallium (treadmill or pharmacological) owing to their unstable anginal status. Five other patients had pharmacological stress due to peripheral vascular disease or poor physical condition. One patient had an outside study, and 1 patient did not consent to diagnostic cardiac stress. The remaining 10 patients underwent the treadmill test. The patients who underwent a treadmill or pharmacological stress test (n = 15) were able to increase their RPP by an average of 50 plus/minus 34% at peak stress above the mean resting value of 9109 plus/minus 2738 beats *symbol* min^{-1} *symbol* mm Hg Table 3. The mean METs and time on treadmill were 5.3 plus/minus 2.1 mL O_2 *symbol* kg^{-1} *symbol* min^{-1} and 4.6 plus/minus 2.8 minutes, respectively.

	Baseline, n (n=21)	3 mo, n (n=15)	6 mo, n (n=15)
Mean angina class*	3.7±0.3†	2.4±0.9‡	1.7±0.8‡
Treadmill tolerance, min	4.6±2.8 (14)	8.7±3.1‡ (13)	9.9±3.9‡ (11)
Average METs	5.3±2.1 (14)	5.2±1.8 (13)	5.9±2.0 (11)
ΔRPP	50±34 (19)	83±47	117±66‡ (11)
LVEF, %			
Resting (MUGA)	47±9	51±11	48±12 (13)
Resting (DE)	38±9	45±10 (14)	44±14 (12)
Stress (DE)	42±12 (8)	50±12 (13)	51±21 (10)

Numbers in parentheses indicate number of patients evaluated if different from the number in sample. METs indicates metabolic equivalents: 1 MET=maximum oxygen consumption (mL $O_2 \cdot kg^{-1} \cdot min^{-1}$)/3.5; assumed to be 3.0 for patients who could not exercise owing to unstable angina. RPP indicates heart rate−blood pressure product (beats · min^{-1} · mm Hg); ΔRPP, percent change in RPP at peak stress; LVEF, left ventricular ejection fraction; MUGA, multigated acquisition radionuclide ventriculography; and DE, dobutamine echocardiography.
*Canadian Cardiovascular Society classification of anginal symptoms.
†Includes four patients with unstable angina.
‡*P*<.05 compared with baseline value by paired *t* test.

Table 3. Reevaluation After Transmyocardial Laser Revascularization

Seven patients could not be evaluated with low-dose dobutamine at baseline because of technical difficulties (n = 2) or to chest pain (n = 5). Of the remaining 14 patients, 5 could not be evaluated with maximum-dose dobutamine due to chest pain, and one could not be evaluated because of increased systemic blood pressure. The maximum dose of dobutamine was 40 micro gram *symbol* min^{-1} *symbol* kg^{-1} in 6 patients and 30 micro gram *symbol* min^{-1} *symbol* kg^{-1} in 2 patients.

The mean resting LVEF by echocardiography was 38 plus/minus 9% at rest and 42 plus/minus 12% at peak stress (with low- or high-dose dobutamine). By MUGA (performed on all 21 patients), LVEF was 47 plus/minus 9% (range, 35% to 74%). The LVEF was < 45% in 11 patients. The mean WMSI at resting conditions was 1.91 plus/minus 0.65 in lased

segments and 1.89 plus/minus 0.60 in unlased segments Figure 3.

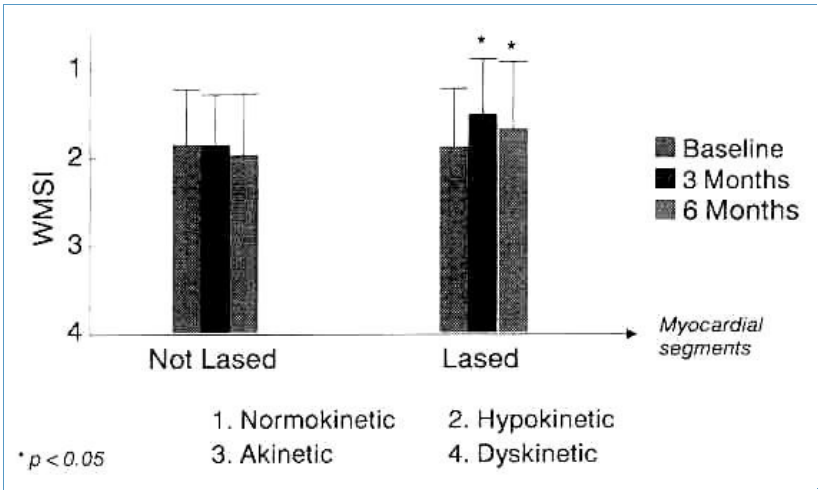


Figure 3. Bar graph showing regional left ventricular wall motion score index (WMSI) assessed by dobutamine echocardiography in the lased and unlased myocardial segments of resting patients. For WMSI, 1 indicates normokinetic; 2, hypokinetic; 3, akinetic; and 4, dyskinetic. From left to right, bars indicate baseline and 3-month and 6-month follow-up scores. *P < .05 vs baseline compared with unlased segments.

All patients were evaluated by^{201} Thallium-SPECT. The mean myocardial perfusion score was calculated to be 1.80 plus/minus 0.85 for the experimental regions to be lased and 2.93 plus/minus 0.87 for the septal segments not to be lased Figure 4.

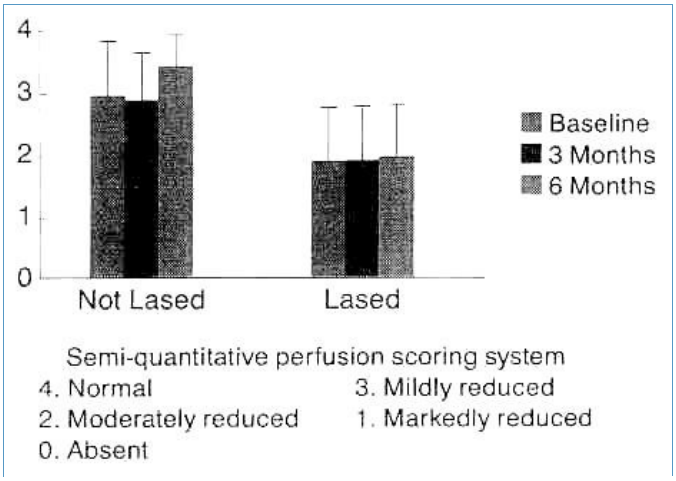


Figure 4. Bar graph showing regional left ventricular viability score assessed by^{201} Thallium scintigraphy in the lased and unlased myocardial segments of patients. There were no significant differences in scores at 3- or 6-month follow-up in either the lased or the unlased segments. For the myocardial viability score, 0, scarred; 1, ischemic surrounding scar; 2, ischemic; and 4, normal. From left to right, bars indicate baseline, 3-month, and 6-month scores.

All but one patient were evaluated by PET at rest before TMLR. Evaluation by PET under conditions of stress was not performed in the first 5 consecutive patients. In 6 other patients in the series, the maximum dose of dipyridamole could not be administered because of their anginal symptoms. Therefore, analysis of results under conditions of stress was conducted on only the 9 remaining patients. The distribution of perfusion and/or metabolic defects by myocardial region was as follows: 9 patients (43%) had anterior defects, 14 patients (67%) had lateral defects, and 18 patients (87%) had inferior or posterior defects. Only 8 patients (38%) had defects involving the intraventricular septum.

Analysis by region of interest showed that, in the left ventricular free wall (containing the segments to be lased), the SEn/SEp was 0.96 plus/minus 0.07 at resting conditions Figure 5 and 0.87 plus/minus 0.10 during dipyridamole-handgrip stress Figure 6. For the septal segments, the SEn/SEp values at rest and under stress were calculated as 1.07 plus/minus 0.07 and 0.96 plus/minus 0.05, respectively Figure 5, Figure 6.

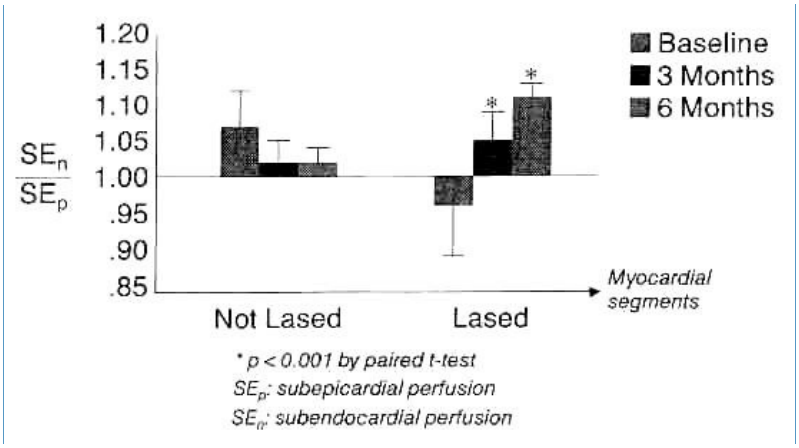


Figure 5. Bar graph showing regional myocardial perfusion assessed by positron emission tomography in the lased and unlased myocardial segments of patients at rest. Perfusion is expressed as a ratio of subendocardial (SEn) to subepicardial (SEp) perfusion. From left to right, bars indicate baseline and 3-month and 6-month follow-up scores. *P < .001 vs baseline.

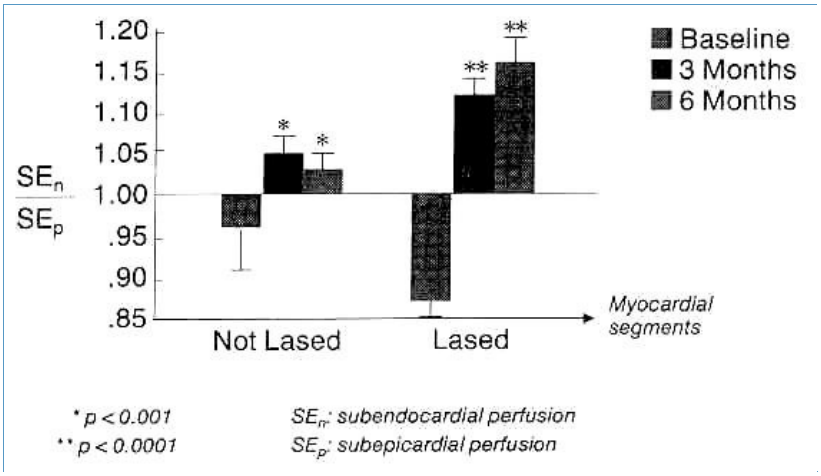


Figure 6. Bar graph showing regional myocardial perfusion assessed by positron emission tomography in the lased and unlased myocardial segments of patients during stress. Perfusion is expressed as a ratio of subendocardial (SEn) to subepicardial (SEp) perfusion. From left to right, bars indicate baseline and 3-month and 6-month follow-up scores. *P < .001 vs baseline; **P < .0001 vs baseline.

During Surgery

Among the 21 patients treated with the laser, the average number of laser pulses delivered per patient was 36 plus/minus 5, and transmyocardial penetration was confirmed by intraoperative transesophageal echocardiography for 79 plus/minus 5% of all delivered pulses. There were no intraoperative complications or deaths, and no cases of postoperative tamponade were reported. The average stay in the intensive care unit was 1.4 days, and the average hospital stay was 6 days.

After Surgery

Exclusions

Seven patients experienced adverse events (death, reoperation) within the first 6 months after TMLR and were excluded from follow-up Table 4. Four of these patients died within the first 3 months after TMLR, but none of the deaths appeared to be directly related to the operation. The other 2 patients required major interventions 3 months after TMLR because new coronary artery stenoses developed, which led to ischemic lesions in nonlased regions of the heart Table 4.

Patient Age, y/Sex, M/F	Event	Postoperative Day
46/M	Coronary artery bypass	87
47/M	Balloon angioplasty	91
59/F	Arrhythmia*	5
80/M	Respiratory failure*	8
56/M	Inferior MI*	94
77/M	Renal insufficiency*	97
72/F	Sudden death (arrhythmia)*	287

MI indicates myocardial infarction.
*Presumed cause of death.

Table 4. Morbidity and Mortality After Transmyocardial Laser Revascularization in Seven Patients

Three-Month Follow-up

Because of the exclusions (n = 6) mentioned above, 15 patients were reevaluated clinically at 3 months. None of the patients had unstable angina or had reported to a hospital for treatment of anginal symptoms within the past 3 months. Subjective reporting of the anginal status was consistent with CCS class I or II angina in 9 patients (60%) and CCS class III or IV angina in 6 patients. There was statistically significant improvement over baseline in the mean CCS angina class, calculated as 2.4 plus/minus 0.9 Table 3.

A treadmill stress test was performed on 13 patients (87% of all who were eligible). The remaining 2 patients were given a pharmacological stress test; 1 declined to take the treadmill test and a second had shortness of breath due to right-sided diaphragmatic hemiparalysis. The average treadmill tolerance (in minutes), and the average RPP at peak stress were both significantly increased compared with baseline values Table 3. The patients undergoing treadmill or pharmacological stress were able to increase their RPP at peak exertion by an average of 83 plus/minus 47% over their resting RPP. This was not significantly different from the value at baseline. Similarly, the mean MET value produced during stress was not statistically significantly different from the value at baseline Table 3.

At 3 months, echocardiographic reevaluation of resting cardiac function was performed on 14 (93%) of the 15 patients eligible for follow-up (1 patient repeatedly missed her appointment). An inadequate acoustic window precluded administration of low-dose dobutamine (10 micro gram *symbol* kg^{-1} *symbol* min^{-1}) in the case of 1 patient. Nine patients received up to 40 micro gram *symbol* kg^{-1} *symbol* min ($^{-1}$) of dobutamine; the maximum dose was limited to 25 micro gram *symbol* kg^{-1} *symbol* min^{-1} in the remaining 4 patients. Figure 3 shows the results obtained with echocardiography from patients at rest. The average WMSI in lased segments changed to 1.54 plus/minus 0.61 (16% improvement of the mean over baseline, Table 5). By contrast, the mean resting WMSI in unlased regions remained unchanged at 1.89 plus/minus 0.56 (3% deterioration of the mean below baseline; Table 5). The change in the WMSI of the nonlased regions was significantly different compared with the postoperative change in the lased regions ($P < .05$). Similarly improving relative trends were observed in the lased segments during low-dose dobutamine infusion, but the difference in the WMSI between the lased and the nonlased segments did not reach statistical significance Table 5. During high-dose dobutamine infusion, both lased and non-lased segments showed worsening of the WMSI compared with the status before TMLR Table 5.

	3 mo		6 mo	
	Lased	Not Lased	Lased	Not Lased
Rest	16±19*	−3±24	13±25*	−9±24
LD	3±27	−10±31	13±23	−7±38
HD	−25±33	−21±31	−16±27	−18±24

Minus sign indicates a worsening of the wall motion score index; LD, low-dose dobutamine; and HD, high-dose dobutamine.
*$P<.05$ with respect to control (not lased) segments by paired, double-tailed Student's *t* test.

Table 5. Percentage Improvement in Wall Motion Score Index (Compared With Before Transmyocardial Laser Revascularization) in Lased and Nonlased Regions by Dobutamine Echocardiography

The mean LVEF by dobutamine echocardiography was 45 plus/minus 10% (improved by 18% over baseline) at resting state and 50 plus/minus 12% during maximum stress (19% increase over baseline). The mean resting LVEF by MUGA was 51 plus/minus 11% (9% increase over baseline). None of these values represented a statistically significant change over baseline Table 3.

Three months after TMLR, 14 patients underwent rest-stress^{201} Thallium-SPECT Figure 4. The mean myocardial perfusion scores of the lased and nonlased segments were calculated as 1.84 plus/minus 0.86 and 2.86 plus/minus 0.76, respectively Figure 4. These represented changes in the sample means over the baseline values of 0.20% and 2.8%, respectively Table 6. The very large standard deviations indicated a high level of data scattering. The changes were not statistically significant.

	3 mo		6 mo	
	Lased	Not Lased	Lased	Not Lased
Perfusion	0.2±18.5	2.8±24.7	5.7±29.7	10.9±23.1

Table 6. Percentage Change in Semiquantitative Myocardial Perfusion Scores (Compared With Before Transmyocardial Laser Revascularization) by (^{201}) Thallium Single-Photon Emission Computed Tomograph

PET reevaluation of 14 patients (48 myocardial regions) revealed improved perfusion and metabolism compared with baseline in a total of 14 regions (6 anterior, 5 lateral, and 3 inferior) on the left ventricular free wall (33% of all the lased regions) and 3 regions in the intraventricular septum (21% of all nonlased regions) Table 7. By contrast, 3 anterior, 5 lateral, and 5 inferior regions (a total of 13 regions, 31% LV free wall) that were lased had poorer perfusion and metabolism Table 7. Two patients had poorer perfusion and metabolism in the septum (14%) Table 7. The status of the remaining regions did not change significantly from baseline.

	Improved		Worsened	
	3 mo	6 mo	3 mo	6 mo
Anterior	6*	6	3	2
Lateral	5	4	5	4
Inferior	3	3	5	3
Septal†	3	4	2	3

*Total number of regions.
†Septal regions were not lased.

Table 7. Myocardial Perfusion and Metabolic Status at 3-Month (14 Patients) and at 6-Month (12 Patients) Follow-up by Positron Emission Tomography

PET analysis by region of interest in the same 14 patients showed that, in the lased segments, the mean resting value of the SEn/SEp significantly increased to 1.05 plus/minus 0.04, a change of 14.27% of the mean over baseline for the lased segments but decreased to 1.02 plus/minus 0.03 for the nonlased segments, a change in the mean of -1.66% below baseline Figure 5, Table 8. By contrast, the SEn/SEp increased significantly during stress for both the lased segments (by 31% over baseline to 1.12 plus/minus 0.05) and the nonlased segments (by 10% over baseline to 1.05 plus/minus 0.02) Figure 6, Table 8. The relative changes in the stress perfusion of the lased segments significantly exceeded that of the unlased segments ($P < .01$).

	3 mo		6 mo	
	Lased	Not Lased	Lased	Not Lased
Rest	14±9*	−2±6	21±11*	−0.5±7
Stress	31±21†	10±6*	37±21†	10±6*

*$P<.001$ vs baseline by paired Student's t test.
†$P<.0001$ vs baseline by paired Student's t test.

Table 8. Percentage Increase in Subendocardial/Subepicardial Ratio Over Baseline Values

Six-Month Follow-up

At 6 months, 6 patients had been excluded from the study for reasons explained above Table 4. One out-of-state patient refused to be evaluated because she was asymptomatic and did not wish to travel. (She later died suddenly, on postoperative day 287, presumably of an arrhythmic event.) Another out-of-state patient missed his reevaluation appointments. These two patients were interviewed over the telephone.

Among a total of 15 patients who were clinically evaluated, there were none with unstable angina. Thirteen (87%) of the 15 reported symptoms equivalent to CCS class I or II angina. One patient continued to have CCS class IV angina, and another patient was still suffering from debilitating shortness of breath due to hemiparalysis of the right diaphragm. The average CCS angina class in this group of patients was 1.7 plus/minus 0.8 ($P < .05$ compared with baseline) Table 3.

Among the 13 patients who were physically present at the 6-month follow-up, 1 repeatedly missed her treadmill and^{201} Thallium-SPECT appointments. Of the remaining 12 patients, all but 1 were able to exercise on the treadmill (pharmacological stress was substituted in 1 patient owing to his shortness of breath). At 6 months, the average time of exercise increased by a statistically significant amount, to 9.9 plus/minus 3.9 minutes Table 3. The mean RPP at rest was calculated as 9339 plus/minus 2132 beats per minute per mm Hg (P = NS), and Delta RPP was 117 plus/minus 66% (P < .05).

At 6-month follow-up, 1 patient missed his echocardiographic evaluation. Of the remaining 12 patients, only 2 did not receive the high dose of dobutamine during echocardiographic evaluation: 1 patient had an inadequate acoustic window; the other had severe systemic hypertension. Therefore, 12 patients were evaluated by dobutamine echocardiography at 6 months. The high dose of dobutamine was 20 micro gram *symbol* kg^{-1} *symbol* min^{-1} in 2 patients, 30 micro gram *symbol* kg^{-1} *symbol* min^{-1} in 1 patient, and 40 micro gram *symbol* kg^{-1} *symbol* min^{-1} in 9 patients. The resting WMSI in lased segments changed to 1.82 plus/minus 0.72 at 6 months Figure 3, representing an improvement in the mean of 13% over baseline Table 5. By contrast, the WMSI in unlased regions changed to 2.07 plus/minus 0.64 at 6 months, which was a deterioration of 9% compared with baseline (P < .05 compared with lased regions). Although a similar trend was observed within the lased and nonlased regions during low-dose dobutamine administration, the differences between the two groups did not reach statistical significance, possibly because of the high standard deviation in the sample Table 5. During high-dose dobutamine infusion, regions in both groups deteriorated by an equal percentage of their respective values at baseline Table 5.

The changes by dobutamine echocardiography in resting LVEF (16% increase over baseline to a mean of 44 plus/minus 14%) and in stress LVEF (21% increase over baseline to a mean of 51 plus/minus 21%) did not reach the level of statistical significance Table 3. The average resting LVEF by MUGA remained unchanged at 48 plus/minus 12%.

At 6 months after TMLR, 13 patients underwent evaluation by^{201} Thallium-SPECT. The mean myocardial perfusion scores were calculated as 1.86 plus/minus 0.79 and 3.12 plus/minus 0.85 for lased and nonlased regions, respectively Figure 4. This represented relative changes of 5.7 plus/minus 29.7% and 10.9 plus/minus 23.1%, respectively, compared with the baseline values of the two samples Table 6. As at 3 months, the differences did not reach statistical significance.

PET analysis in 12 patients showed an improvement over baseline in the perfusion and metabolic status of 13 total regions (6 anterior, 4 lateral, and 3 inferior) in the LV free wall (36% of total regions lased) Table 7. Nine regions that were lased (2 anterior, 4 lateral, and 3 inferior, a total of 25%) had a poorer status than at baseline Table 7. The perfusion and metabolic status of the remaining regions in the LV free wall did not change compared with before TMLR. Perfusion and metabolism in the septal wall were improved in 4 cases (33%), poorer in 3 (25%), and the same in 5 (42%) Table 7. PET analysis by region of interest in 8 patients showed that, in the lased segments, the mean value of the SEn/SEp further increased to 1.11 plus/minus 0.02 (21 plus/minus 11% over baseline, P < .001) at rest and to 1.16 plus/minus 0.03 (37 plus/minus 21% increase over baseline, P < .0001 during stress) Table 8. The average SEn/SEp of the nonlased segments decreased to 1.02 plus/minus 0.01 at rest (-0.5 plus/minus 7% below baseline) but increased to 1.03 plus/minus 0.02 during stress (a change of 10 plus/minus 6% over baseline) Figure 5 and Figure 6, Table 8.

Predictors of Mortality

To find the potential predictors of mortality and morbidity after TMLR, the physiological variables in the patients who experienced a major adverse event (death, re-revascularization) were compared to those in patients whose status had improved Table 9. We observed by intraoperative transesophageal echocardiography that 71% of the adverse-event patients had regurgitant mitral valve disease, whereas only 29% of the other patients had regurgitant mitral valve disease (P < .05). By contrast, the presence of aortic valve disease at the time of surgery did not have a significant effect on the outcome. Left atrial dimension, mean pulmonary arterial pressure, and left atrial pressure were not significant.

Preexisting Condition	No. of Patients With Event (%) (n=7)	No. of Patients Without Event (%) (n=14)	P*
History of MI			
Anterior	4 (57)	0	<.001
Inferior	2 (29)	7 (50)	NS
PAP_m >35 mm Hg	4 (57)	0	<.001
Concomitant cardiotonics and diuretics	6 (86)	5 (36)	<.001
MVR >2+	5 (71)	4 (29)	<.05

MI indicates myocardial infarction; PAP_m, mean pulmonary artery pressure; and MVR, mitral valve regurgitation.
*By paired *t* test.

Table 9. Possible Predictors of Cardiac Events After Transmyocardial Laser Revascularization

Of the 7 patients in our series who experienced adverse events after TMLR, 4 (57%) had a history of anterior or anterolateral myocardial infarction, whereas the 14 patients without adverse events had no such history (P < .001). Furthermore, 6 (86%) of the 7 patients who had adverse events were being treated for congestive heart failure with diuretics and cardiotonics with or without angiotensin-converting enzyme inhibitors at the time they were admitted for surgery, whereas 5 (36%) of the 14 remaining patients who had no adverse events were being so treated (P < .001).

Discussion

Our results suggest that TMLR improves clinical status and produces objective benefits in the cardiac perfusion and function of certain patients. The improvement in the clinical status and exercise time of our initial set of patients was encouraging at 3 months and more so at 6 months. The study showed that relief from angina occurred immediately, and, at follow-up, more patients were able to tolerate increasing levels of cardiac stress for diagnostic purposes. This was consistent with, and possibly secondary to, the significant increase in the relative subendocardial myocardial perfusion as demonstrated on PET scans. The resting myocardial wall kinetics as shown by echocardiography were significantly improved by 3 and 6 months after surgery, but the increase in LVEF, both at rest and during peak stress, did not reach statistical significance. Similarly, the rate of oxygen consumption during exercise (METs) remained essentially constant over the 6-month follow-up period. The patients in our study had long been inactive due to debilitating angina and/or congestive heart failure, hence their cardiovascular, pulmonary, and musculoskeletal conditions in the perioperative period were severely limited. [17] With the improvement of anginal status and the resulting increase in physical activity after laser surgery, LVEF and VO ($_{2max}$) may also be expected to increase significantly in the long term.

Clinical success with TMLR is contingent on the net amount of additional blood brought to the area of the ischemic myocardium and the long-term patency of the laser channels. To assess the efficacy of TMLR in terms of the first requisite, a direct method for the quantitative assessment of regional myocardial perfusion before and after treatment is desirable. In the present study, the task of measuring subendocardial and subepicardial perfusion was performed by use of PET analysis of the lased and nonlased regions. By PET, the mean SEn/SEp values in the lased myocardial segments at rest (0.96 plus/minus 0.07) and during stress (0.87 plus/minus 0.1) were less than unity at baseline. This indicated that, in the preoperative period, perfusion in the epicardial layers of the LV free wall exceeded that in the endocardial layers. After the creation of the laser channels, however, the SEn/SEp values increased significantly beyond unity (1.11 plus/minus 0.02 at rest and 1.16 plus/minus 0.03 during stress at 6 months), which suggests a reversal in the direction of myocardial perfusion in favor of endocardial dominance Figure 5 and Figure 6. This finding is consistent with and supports the rationale for TMLR, which predicts perfusion via subendocardial camerosinusoidal connections established by laser channels. The observation that the resting SEn/SEp in the nonlased septal regions did not change significantly during the postoperative period Figure 5 was consistent with our a priori expectations because the septum was not perforated by laser channels. However, the increase in the septal perfusion ratio during stress was unexpected Figure 6. The increased level of the left ventricular pressure during stress may drive additional blood toward the septum if a collateral network develops postoperatively between the laser-revascularized free wall and the perforating branches of the anterior and posterior descending coronary arteries. [18].

We previously reported [19] anatomic evidence of channel patency, on the other hand, after cardiac autopsy of a patient who died on postoperative day 94 of a myocardial infarction caused by acute occlusion of the mid and distal right coronary arteries. Histological evidence of patent, endothelium-lined tracts within the laser-created channels supports the assumption that the lumen of the laser channels is or can become hemocompatible and that it resists occlusion caused by thrombo-activation and/or fibrosis. The presence of connections between the ventricular cavity and the native intramyocardial sinusoids at 3 months is evidence that TMLR did revascularize a segment of the heart. These initial camerosinusoidal connections may enlarge and become direct arteriolar channels if exposed to a significant pressure gradient. [20] The long-term patency of laser channels is expected to establish systolic contractile function within the preoperatively dyskinetic myocardial segments. It is possible that compression of the laser channels may lead to their occlusion when regional myocardial normokinesia returns. This seems unlikely in normal

physiology, however, because intraventricular pressure has been shown to exceed intramyocardial pressure at all times during the cardiac cycle, especially during the isovolumetric relaxation phase. [21].

It can be argued that acute thrombosis followed by organization and fibrosis of clot is the principal mechanism of channel closure in the case of myocardial acupuncture or boring, which mechanically displace or remove tissue. [8] By contrast, in laser vaporization, a thin zone of charring occurs on the periphery of the transmyocardial channels through the well-known thermal effects of optical radiation on cardiovascular tissue. [22] This type of interface may inhibit the immediate activation of the intrinsic clotting mechanisms because of the inherent hemocompatibility of carbon. [23] In addition, the precise cutting action that results from the high absorption and low scattering of the CO_2 laser may minimize structural damage to collateral tissue, [22] thus limiting the tissue thromboplastin-mediated activation of the extrinsic coagulation. [24].

Our study of the potential predictors of mortality and morbidity after TMLR suggests that patients with unprotected anterior myocardium and those in frank congestive heart failure are less likely to benefit from the laser procedure. On the basis of the promising outcome of the remaining 14 patients, we conclude that TMLR may provide an alternative for treating selected patients who have refractory angina and who are not candidates for conventional revascularization. The results of this preliminary trial indicate the need for further clinical trials to determine the effectiveness of TMLR, and studies that randomize patients to treatment by medication, CAB grafting or TMLR may be useful in this regard. In addition, TMLR merits investigation as an adjunct to routine CAB grafting in certain high-risk patient groups or in patients with transplant graft atherosclerosis.

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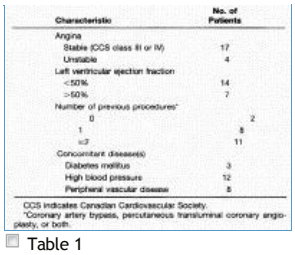
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IMAGE GALLERY

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Characteristic	No. of Patients
Angina	
Stable (CCS class III or IV)	17
Unstable	4
Left ventricular ejection fraction	
<50%	14
>50%	7
Number of previous procedures*	
0	2
1	8
≥2	11
Concomitant disease(s)	
Diabetes mellitus	3
High blood pressure	12
Peripheral vascular disease	5

CCS indicates Canadian Cardiovascular Society.
*Coronary artery bypass, percutaneous transluminal coronary angioplasty, or both.

Table 1

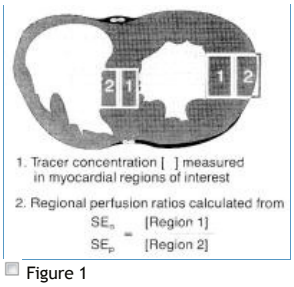


Figure 1

Stage	Speed, mph	Grade, %	Time, min	METs*
1	1.2	0	3	1.9
2	1.7	5	3	3.5
3	1.7	10	3	4.6
4	1.7	12	3	5.1
5	2.2	12	3	6.3
6	2.5	12	3	7.0

*Metabolic equivalents of oxygen consumption. 1 MET=3.5 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$; METs×3.5=peak maximum oxygen consumption.

Table 2

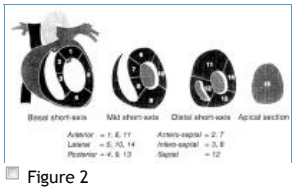


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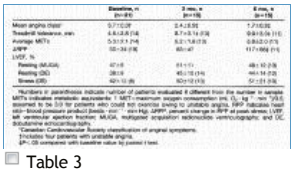


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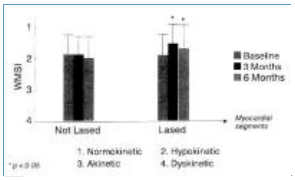


Figure 3

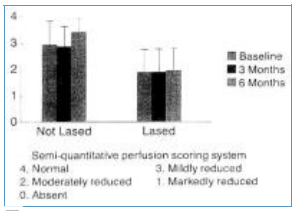


Figure 4

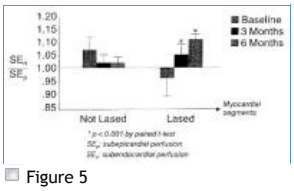


Figure 5

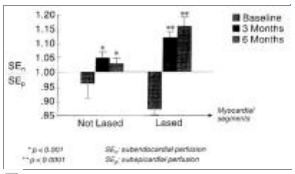


Figure 6

Patient Age, y/Sex, M/F	Event	Postoperative Day
46/M	Coronary artery bypass	87
47/M	Balloon angioplasty	91
59/F	Arrhythmia*	5
60/M	Respiratory failure*	8
56/M	Inferior MI*	94
77/M	Renal insufficiency*	97
72/F	Sudden death (arrhythmia)*	287

MI indicates myocardial infarction.
*Presumed cause of death.

Table 4

	3 mo		6 mo	
	Lased	Not Lased	Lased	Not Lased
Rest	16±19*	−3±24	13±25*	−9±24
LD	3±27	−10±31	13±23	−7±38
HD	−25±33	−21±31	−16±27	−18±24

Minus sign indicates a worsening of the wall motion score index; LD, low-dose dobutamine; and HD, high-dose dobutamine.
*P<.05 with respect to control (not lased) segments by paired, double-tailed Student's *t* test.

Table 5

	3 mo		6 mo	
	Lased	Not Lased	Lased	Not Lased
Perfusion	0.2±18.5	2.8±24.7	5.7±29.7	10.9±23.1

Table 6

	Improved		Worsened	
	3 mo	6 mo	3 mo	6 mo
Anterior	6*	6	3	2
Lateral	5	4	5	4
Inferior	3	3	5	3
Septal†	3	4	2	3

*Total number of regions.
†Septal regions were not lased.

Table 7

	3 mo		6 mo	
	Lased	Not Lased	Lased	Not Lased
Rest	14±9*	−2±6	21±11*	−0.5±7
Stress	31±21†	10±6*	37±21†	10±6*

*P<.001 vs baseline by paired Student's *t* test.
†P<.0001 vs baseline by paired Student's *t* test.

Table 8

Preexisting Condition	No. of Patients With Event (%) (n=7)	No. of Patients Without Event (%) (n=14)	P*
History of MI			
Anterior	4 (57)	0	<.001
Inferior	2 (29)	7 (50)	NS
PAP_m >35 mm Hg	4 (57)	0	<.001
Concomitant cardiotonics and diuretics	6 (86)	5 (36)	<.001
MVR >2+	5 (71)	4 (29)	<.05

MI indicates myocardial infarction; PAP_m, mean pulmonary artery pressure; and MVR, mitral valve regurgitation.
*By paired *t* test.

Table 9

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