

COMPARISON OF TRANSMYOCARDIAL REVASCULARIZATION WITH MEDICAL THERAPY IN PATIENTS WITH REFRACTORY ANGINA

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ABSTRACT

Background Transmyocardial revascularization involves the creation of channels in the myocardium with a laser to relieve angina. We compared the safety and efficacy of transmyocardial revascularization performed with a holmium laser with those of medical therapy in patients with refractory class IV angina (according to the criteria of the Canadian Cardiovascular Society).

Methods In a prospective study conducted between March 1996 and July 1998 at 18 centers, 275 patients with medically refractory class IV angina and coronary disease that could not be treated with percutaneous or surgical revascularization were randomly assigned to receive transmyocardial revascularization followed by continued medical therapy (132 patients) or medical therapy alone (143 patients).

Results After one year of follow-up, 76 percent of the patients who had undergone transmyocardial revascularization had improvement in angina (a reduction of two or more classes), as compared with 32 percent of the patients who received medical therapy alone ($P < 0.001$). Kaplan-Meier survival estimates at one year (based on an intention-to-treat analysis) were similar for the patients assigned to undergo transmyocardial revascularization and those assigned to receive medical therapy alone (84 percent and 89 percent, respectively; $P = 0.23$). At one year, the patients in the transmyocardial-revascularization group had a significantly higher rate of survival free of cardiac events (54 percent, vs. 31 percent in the medical-therapy group; $P < 0.001$), a significantly higher rate of freedom from treatment failure (73 percent vs. 47 percent, $P < 0.001$), and a significantly higher rate of freedom from cardiac-related rehospitalization (61 percent vs. 33 percent, $P < 0.001$). Exercise tolerance and quality-of-life scores were also significantly higher in the transmyocardial-revascularization group than in the medical-therapy group (exercise tolerance, 5.0 MET [metabolic equivalent] vs. 3.9 MET; $P = 0.05$; quality-of-life score, 21 vs. 12; $P = 0.003$). However, there were no differences in myocardial perfusion between the two groups, as assessed by thallium scanning.

Conclusions Patients with refractory angina who underwent transmyocardial revascularization and received continued medical therapy, as compared with similar patients who received medical therapy alone, had a significantly better outcome with respect to improvement in angina, survival free of cardiac events, freedom from treatment failure, and freedom from cardiac-related rehospitalization. (N Engl J Med 1999;341:1029-36.)

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DESPITE the success of current medical and surgical management of ischemic heart disease, a growing number of patients have diffuse obstructive coronary artery disease that is not amenable to coronary-artery bypass grafting or catheter-based interventions. This problem has stimulated interest in developing alternative therapeutic approaches. Early attempts at indirect myocardial revascularization had limited success. Beck's use of omentopexy, reported in 1935,¹ and Vinberg's use of thoracic-artery implantation, reported in 1954,² were attempts to provide direct myocardial perfusion and were based on the description by Wearn et al., in 1933,³ of a sinusoidal network in the human heart. In 1965, Sen et al. proposed the creation of transmural channels in the left ventricular wall to permit direct perfusion of ischemic myocardium with oxygenated left ventricular blood.⁴ This concept was based on the model of the reptilian heart, in which the left ventricle is directly perfused from endothelium-lined channels that radiate out from the left ventricular cavity. Mirhoseini and associates^{5,6} advanced the concept by using laser energy rather than mechanical energy to create the transmural channels. Subsequent clinical trials using a carbon dioxide laser⁷⁻¹³ or a holmium:yttrium-aluminum-garnet laser¹⁴⁻¹⁶ (hereafter referred to as a holmium laser) demonstrated that transmyocardial revascularization significantly improved angina in patients who were not candidates for conventional therapies.

We conducted a prospective, randomized, multicenter trial to compare the safety and efficacy of transmyocardial revascularization, performed with a holmium laser and followed by continued medical therapy, with the safety and efficacy of medical ther-

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The centers and investigators participating in the study are listed in the Appendix.

apy alone in patients with refractory class IV angina (according to the classification system of the Canadian Cardiovascular Society [CCS]). Eighteen centers in the United States participated in the study.

METHODS

Patients

Between March 1996 and July 1998, 275 patients with medically refractory class IV angina and coronary artery disease that could not be treated with percutaneous or surgical revascularization were randomly assigned to undergo transmyocardial revascularization and continued medical therapy (132 patients) or medical therapy alone (143 patients). Randomization was performed by each center on a 1:1 basis, with a block size of six patients per center. The demographic and clinical characteristics of the patients in the two treatment groups were similar (Table 1). A blinded, independent data and safety monitoring committee monitored the study. Study approval was obtained from the Food and Drug Administration (FDA) and the institutional review board of each participating center. Informed consent was obtained from each patient before enrollment.

The criteria for enrollment were refractory class IV angina that was not amenable to coronary-artery bypass grafting or percutaneous transluminal coronary angioplasty (as determined by a surgeon and an interventional cardiologist at each center); reversible ischemia, as determined by myocardial perfusion scanning, within the distal two thirds of the left ventricle (i.e., the area of the ventricle amenable to transmyocardial revascularization); and a left ventricular ejection fraction greater than 25 percent. Exclusion criteria were a contraindication to general anesthesia; severe chronic obstructive pulmonary disease (indicated by a forced expiratory volume in one second that was less than 55 percent of the predicted value); the need for continued use of intravenous antianginal medications; an inability to undergo dipyridamole-thallium stress scintigraphy; a non-Q-wave myocardial infarction within the

previous two weeks or a Q-wave myocardial infarction within the previous three weeks; the need for long-term anticoagulant therapy; the presence of a ventricular mural thrombus; severe arrhythmias; and decompensated congestive heart failure.

Medically refractory angina was defined as CCS class IV angina that was present despite maximal tolerated doses of multiple antianginal medications (nitrates, calcium-channel blockers, and beta-blockers). At the time of enrollment, 91 percent of the patients (250 of 275) were taking two or more antianginal medications, and 31 percent (85 of 275) were taking analgesics or narcotics.

Forty-six patients (32 percent) initially assigned to receive medical therapy alone met the a priori criteria for treatment failure and could not be weaned from intravenous antianginal medication on two attempts over a period of 48 hours. They were withdrawn from the study and underwent transmyocardial revascularization under a parallel, FDA-approved protocol for patients who could not be weaned from intravenous antianginal medications. Thus, there were three groups of patients: those randomly assigned to undergo transmyocardial revascularization and to receive continued medical therapy (132 patients), those who received medical therapy alone throughout the study (97), and those randomly assigned to receive medical therapy alone who met the criteria for treatment failure and underwent transmyocardial revascularization as part of a separate protocol (46). The third group of patients is hereafter referred to as the crossover group.

Operative Technique and Laser Procedure

The operative procedure has been described in detail elsewhere.^{14,15} Cardiac exposure was accomplished through a limited left anterior thoracotomy. The administration of intravenous fluids was minimized to prevent fluid overload. A 20-W, pulsed holmium laser (Eclipse Surgical Technologies, Sunnyvale, Calif.) was used to create transmyocardial channels. The laser, which has been approved by the FDA, was calibrated to deliver 6 to 8 W per pulse, and energy was delivered at the rate of five pulses per second through a flexible 1-mm optical fiber. Energy application was not gated to the cardiac cycle. Channels were placed every square centimeter throughout the distal two thirds of the left ventricle. Three to five channels were placed, followed by the application of digital pressure for two to three minutes to obtain hemostasis and allow for myocardial recovery. Mechanical manipulation of the heart was minimized. A mean (\pm SD) of 39 ± 11 channels were created per patient. The mean durations of surgery and laser use were 99 ± 43 and 25 ± 13 minutes, respectively.

Primary End Points

The primary end points were a change in angina symptoms, treatment failure, and a change in myocardial perfusion. Angina was evaluated at 3, 6, and 12 months in all surviving patients who were not crossed over to surgical treatment and who had reached the designated follow-up time (hereafter referred to as eligible patients): 213 of 221 patients (96 percent) at 3 months, 172 of 183 (94 percent) at 6 months, and 126 of 136 (93 percent) at 12 months. Improvement in angina was defined as a reduction of two or more CCS angina classes from base line. An independent laboratory (at the Cleveland Clinic Foundation, Cleveland) conducted a masked assessment of angina and quality of life at 12 months. Angina was assessed with the use of a questionnaire designed to classify the symptoms of angina according to the CCS class (with class 0 indicating the absence of angina). The Duke Activity Status Index¹⁷ was used to assess the quality of life. The index is based on a scale from 0 to 58, with higher scores indicating greater functional capacity. Among the first 160 patients enrolled in the study, these assessments were performed at 12 months in 112 of 132 eligible patients (85 percent).

Treatment failure in both the transmyocardial-revascularization group and the medical-therapy group was defined a priori as death, Q-wave myocardial infarction, two cardiac-related hospitalizations within a 3-month period, three cardiac-related hospitalizations within a 12-month period, or an inability to withdraw in-

TABLE 1. CHARACTERISTICS OF THE PATIENTS AND CARDIAC RISK FACTORS.*

VARIABLE	TRANSMYOCARDIAL REVAS- CULARIZATION (N=132)	MEDICAL THERAPY (N=143)
Age — yr	60 \pm 10	60 \pm 11
Preoperative ejection fraction — %	47 \pm 11	47 \pm 10
Male sex — no. (%)	98 (74)	109 (76)
History of diabetes — no. (%)	61 (46)	69 (48)
History of hypertension — no. (%)	92 (70)	102 (71)
History of hypercholesterolemia — no. (%)	104 (79)	120 (84)
Tobacco use — no. (%)	95 (72)	103 (72)
Family history of premature CAD — no. (%)	66 (50)	64 (45)
History of myocardial infarction — no. (%)	84 (64)	92 (64)
History of congestive heart failure — no. (%)	22 (17)	37 (26)
Previous PTCA — no. (%)	63 (48)	67 (47)
Previous CABG — no. (%)	114 (86)	123 (86)
Previous PTCA or CABG — no. (%)	121 (92)	124 (87)

*Plus-minus values are means \pm SD. None of the differences between the treatment groups were statistically significant. CAD denotes coronary artery disease, PTCA percutaneous transluminal coronary angioplasty, and CABG coronary-artery bypass grafting.

travenous antianginal medications on at least two attempts in a 48-hour period. Data on treatment failure were available at 12 months for 273 of 275 patients (99 percent).

Myocardial perfusion was assessed with the use of dipyridamole-thallium stress testing, with images obtained while the patient was at rest, under conditions of drug-induced stress, and after a four-hour delay. Imaging was performed at base line in all patients and at 3, 6, and 12 months in the first 160 patients enrolled in the study. Computerized quantification of ischemic changes, perfusion defects at rest, and delayed perfusion defects was performed in a masked manner by an independent laboratory (at Brigham and Women's Hospital, Boston), with the use of the validated Emory/Cedars-Sinai software package, version 1.0. A change in perfusion was defined as a difference of more than 10 percent from the base-line value. The 46 patients in the crossover group underwent follow-up thallium scanning only at rest and were excluded from this analysis. Computer-quantified, paired scans (base-line and 12-month follow-up) were available for 61 of 95 eligible patients (64 percent).

Secondary End Points

Secondary end points included freedom from cardiac-related rehospitalization, survival free of cardiac events, use of cardiac medications, performance on an exercise treadmill test, and quality-of-life score. Freedom from cardiac-related rehospitalization, occurrence of Q-wave and non-Q-wave myocardial infarction, and survival free of cardiac events were evaluated at 3, 6, and 12 months. Survival free of cardiac events was defined as freedom from death, Q-wave myocardial infarction, cardiac-related hospitalization, and subsequent coronary-artery bypass grafting or percutaneous angioplasty.

The rates of use of cardioactive medications (calcium-channel blockers, beta-blockers, and nitrates) and doses were determined at base line and at 3, 6, and 12 months. The use of cardiac suppressants (beta-blockers and calcium-channel blockers) was avoided during the first 48 hours after surgery, but treatment with nitrates, angiotensin-converting-enzyme inhibitors, and diuretics was resumed after the operation. Cardioactive medications that had been administered before surgery were continued for two months after surgery and then gradually withdrawn, as tolerated, on the basis of the patient's anginal symptoms. An independent laboratory (at Stanford University Medical Center, Stanford, Calif.) performed a masked analysis of medication use at 12 months for the first 160 patients enrolled in the study. Data were available for 126 of the 132 eligible patients (95 percent).

Exercise treadmill testing was not part of the original study design. Following a recommendation by the FDA, however, we modified the protocol after the first 160 patients had been enrolled, eliminating follow-up thallium scanning and substituting treadmill testing according to the Naughton protocol at 12 months. No treadmill tests were performed at base line. Analysis of total exercise time included only the 81 patients who underwent Naughton testing; the 9 patients who underwent other types of treadmill testing were excluded. To determine the average workload, expressed as metabolic equivalents (MET), Naughton and non-Naughton test results were combined. The 11 patients who were unable to exercise because of angina were assigned a score of 1 MET. Exercise treadmill tests were performed in 90 of 132 eligible patients (68 percent) at 12 months.

Statistical Analysis

Since 32 percent of the patients assigned to receive medical therapy alone met the predefined criteria for treatment failure and were withdrawn from this study to undergo transmyocardial revascularization in a parallel, nonrandomized study, a modified approach to the statistical analysis was required for certain end points. For definitive end points recorded before crossover (treatment failure, survival free of cardiac events, and cardiac-related rehospitalization), an intention-to-treat analysis was used. For end points measured at 12 months (improvement in angina, results of

thallium scanning, myocardial-infarction rates, medication use, quality-of-life scores, and performance on an exercise treadmill test), the patients who underwent transmyocardial revascularization were compared with the patients who received medical therapy alone throughout the study. Survival at one year was determined with the use of both types of analyses.

A central laboratory using Statgraphics Plus, version 2.1, performed all analyses of thallium scans. Base-line scans obtained at rest, under conditions of stress, and after a four-hour delay were compared with follow-up scans. Mean changes were calculated for each variable, and Student's t-test was used to analyze unpaired data.

Kaplan-Meier estimates were used to compare the treatment groups at one year with respect to mortality, survival free of cardiac events, freedom from treatment failure, freedom from cardiac-related hospitalization, and myocardial infarction. With the exception of the analysis of thallium scans, all analyses were performed with the use of SAS software, versions 6.11 and 6.12 (SAS Institute, Cary, N.C.). The chi-square test and Student's t-test were used to compare qualitative and continuous variables, respectively, and P values of 0.05 or lower on two-tailed testing were considered to indicate statistical significance.

RESULTS

Primary End Points

Angina improved in a significantly larger proportion of patients in the transmyocardial-revascularization group than in the medical-therapy group at 3, 6, and 12 months (P<0.001 for all three comparisons) (Fig. 1). At 12 months, 76 percent of the patients in the transmyocardial-revascularization group had improvement in angina (a reduction of two or more CCS classes), as compared with only 32 percent of

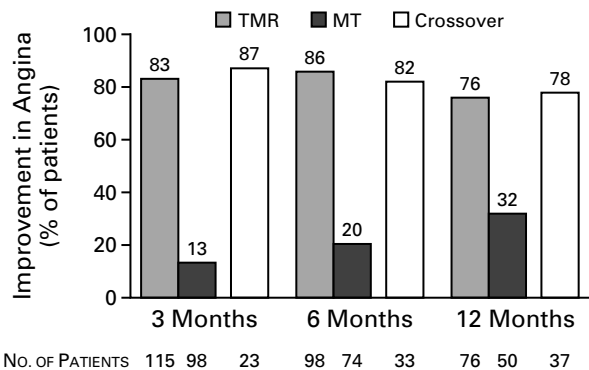


Figure 1. Improvement in Angina at 3, 6, and 12 Months in Patients Randomly Assigned to Undergo Transmyocardial Revascularization (TMR), Patients Who Received Medical Therapy Alone Throughout the Study (MT), and Patients Assigned to Receive Medical Therapy Who Met the Criteria for Treatment Failure and Underwent Transmyocardial Revascularization (Crossover).

All patients had class IV angina at base line. The improvement in angina in the medical-therapy group at 12 months reflects the reduction in the number of patients in this group as the sicker patients were withdrawn so that they could undergo transmyocardial revascularization under a separate protocol. P<0.001 for the comparison between the transmyocardial-revascularization and medical-therapy groups at all three points in time. The numbers at the bottom of the graph are numbers of patients.

patients in the medical-therapy group ($P < 0.001$). The proportion of patients in the crossover group who had improvement in angina at 12 months was similar to that in the transmyocardial-revascularization group. The results of the masked assessment of angina were closely correlated with the study investigators' assessment and differed by no more than one CCS class 80 percent of the time.

In the intention-to-treat analysis, the rate of freedom from treatment failure at one year was significantly higher in the transmyocardial-revascularization group than in the medical-therapy group (73 percent vs. 47 percent, $P < 0.001$) (Fig. 2). Patients randomly assigned to receive medical therapy alone

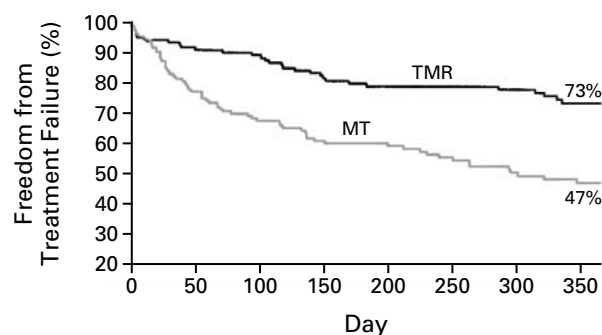


Figure 2. Kaplan-Meier Estimates of Freedom from Treatment Failure at One Year for the 132 Patients Randomly Assigned to Undergo Transmyocardial Revascularization (TMR) and the 143 Patients Assigned to Receive Medical Therapy Alone (MT) in the Intention-to-Treat Analysis.

The difference between the groups was significant ($P < 0.001$ by the log-rank test).

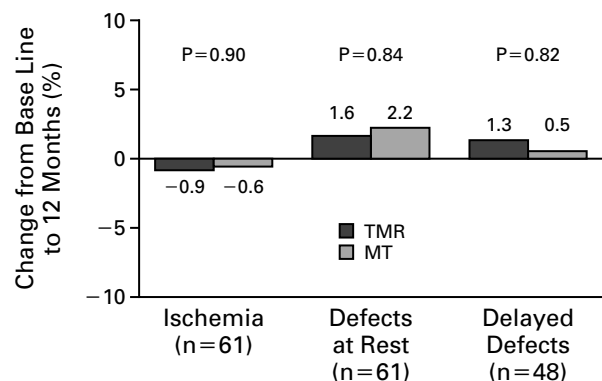


Figure 3. Changes from Base Line to 12 Months in Ischemia, Perfusion Defects at Rest, and Delayed Defects.

TMR denotes transmyocardial revascularization, and MT medical therapy.

were twice as likely to meet the a priori criteria for treatment failure at 12 months as patients randomly assigned to undergo transmyocardial revascularization.

Computer-quantified changes in perfusion between base line and 12 months are shown in Figure 3. There were no significant differences between the transmyocardial-revascularization group and the medical-therapy group with respect to changes in ischemia, defects in perfusion at rest, or delayed defects. Furthermore, no correlation was noted between improvement in angina and the results of thallium scanning. Since laser energy ablates myocardial tissue, there was concern that transmyocardial revascularization might improve angina by creating zones of infarction; however, no differences in fixed defects were noted.

Perioperative Morbidity and Mortality

The rate of perioperative (in-hospital or 30-day) mortality after transmyocardial revascularization was 5 percent (7 of the 132 patients died), which included 1 patient who died after randomization but before undergoing transmyocardial revascularization. Five patients (4 percent) died from cardiac causes: two from left ventricular dysfunction and three from ventricular fibrillation. Two patients died from non-cardiac causes: one each from respiratory insufficiency and multisystem organ failure. The perioperative mortality rate among the last 100 consecutively enrolled patients was 2 percent. Perioperative adverse events in the transmyocardial-revascularization group are shown in Table 2. The perioperative mortality rate in the crossover group was 9 percent (4 of the 46 patients died). Two of the 97 patients (2 percent) who received medical therapy alone throughout the study died within 30 days after enrollment; both deaths resulted from myocardial infarctions. The mortality rates at 30 days in the transmyocardial-revascularization, medical-therapy, and crossover groups did not differ significantly ($P = 0.07$).

In the intention-to-treat analysis, Kaplan-Meier survival estimates at one year for the transmyocardial-revascularization and medical-therapy groups did not differ significantly (84 percent and 89 percent, respectively; $P = 0.23$) (Fig. 4). When the crossover patients were considered separately, there were also no significant differences in survival at one year (transmyocardial-revascularization group, 84 percent; medical-therapy group, 88 percent; and crossover group, 91 percent; $P = 0.47$) (Fig. 5).

Secondary End Points

In the intention-to-treat analysis, the Kaplan-Meier estimate of survival free of cardiac events at one year was significantly higher in the transmyocardial-revascularization group than in the medical-therapy group (54 percent vs. 31 percent, $P < 0.001$). The rate of freedom from cardiac-related rehospitalization was also significantly higher in the transmyocardial-

TABLE 2. PERIOPERATIVE (IN-HOSPITAL OR 30-DAY) MORTALITY AND COMPLICATIONS AMONG THE 132 PATIENTS RANDOMLY ASSIGNED TO UNDERGO TRANSMYOCARDIAL REVASCULARIZATION.

VARIABLE	No. OF PATIENTS (%)
Death	7 (5)
Atrial arrhythmias	13 (10)
Hypotension	13 (10)
Ventricular arrhythmia	16 (12)
Non-Q-wave myocardial infarction	6 (5)
Congestive heart failure	5 (4)
Respiratory insufficiency	4 (3)
Q-wave myocardial infarction	1 (1)
Transfusion due to blood loss from transmyocardial revascularization	0

revascularization group (61 percent vs. 33 percent, $P < 0.001$) (Fig. 6). The transmyocardial-revascularization group and the medical-therapy group did not differ significantly with respect to freedom from Q-wave infarction (98 percent and 96 percent, respectively; $P = 0.56$) or freedom from non-Q-wave infarction (88 percent and 93 percent, respectively; $P = 0.17$).

The rate of use of calcium-channel blockers at 12 months was lower in the group of patients who underwent transmyocardial revascularization (44 percent [26 of 59 patients]) than in the group that received medical therapy alone (76 percent [32 of 42], $P = 0.002$). Similarly, the use of beta-blockers was reduced or discontinued in 39 percent of the transmyocardial-revascularization group (28 of 72 patients), as compared with 17 percent of the medical-therapy group (7 of 42, $P = 0.02$). Although the percentage of patients who decreased or discontinued their use of nitrates was greater in the transmyocardial-revascularization group than in the medical-therapy group, the difference was not significant ($P = 0.12$).

The higher rates of improvement in angina and freedom from treatment failure and the reduced rates of cardiac-related rehospitalization and use of cardioactive medications among the patients treated with transmyocardial revascularization, as compared with those receiving medical therapy alone, were reflected in the surgical group's greater tolerance of exercise (5.0 ± 0.7 vs. 3.9 ± 0.8 MET, $P = 0.05$) and higher quality-of-life score (21 ± 14 vs. 12 ± 11 , $P = 0.003$) at 12 months.

DISCUSSION

Direct surgical or percutaneous revascularization remains the mainstay of treatment for angina. Unfortunately, a subgroup of patients with medically

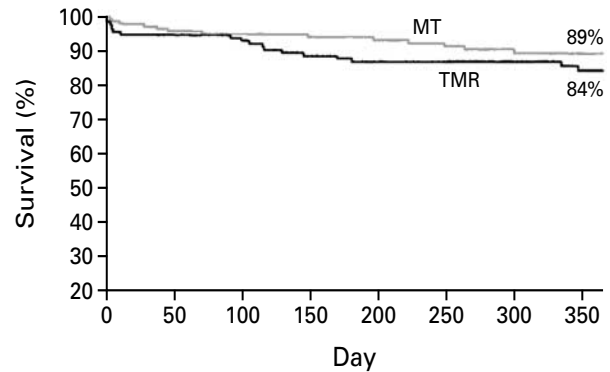


Figure 4. Kaplan–Meier Estimates of Survival at One Year in the Intention-to-Treat Analysis. The difference in survival between the groups was not significant. TMR denotes transmyocardial revascularization, and MT medical therapy.

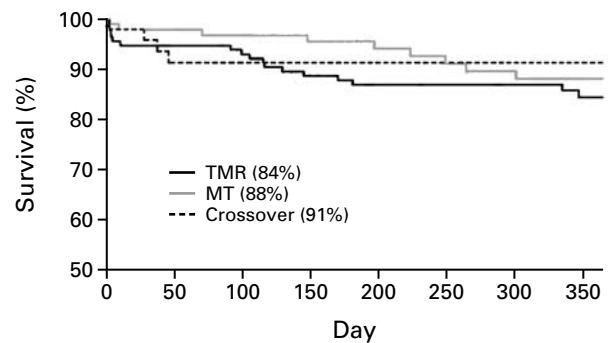


Figure 5. Kaplan–Meier Estimates of Survival at One Year for the 132 Patients Randomly Assigned to Undergo Transmyocardial Revascularization (TMR), the 97 Patients Who Received Medical Treatment Alone Throughout the Study (MT), and the 46 Patients Assigned to Receive Medical Therapy Who Met the Criteria for Treatment Failure and Underwent Transmyocardial Revascularization (Crossover). The differences in survival were not significant.

refractory angina have small or diffusely diseased distal vessels that are not amenable to conventional revascularization therapies. Transmyocardial revascularization has been introduced to supplement medical management of this difficult condition.

The perioperative mortality rate after transmyocardial revascularization performed with a carbon dioxide laser in patients with stable angina ranges from 1 to 20 percent.^{8,9,13} We performed transmyocardial revascularization with a holmium laser in patients with medically refractory class IV angina. The perioperative mortality rate in this group of patients was 5 percent (7 of 132 patients died); 5 of the 7 deaths occurred during the first three months in which the

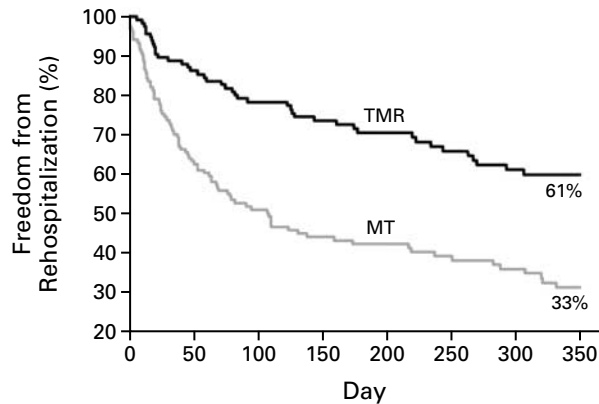


Figure 6. Kaplan-Meier Estimates of Freedom from Cardiac-Related Rehospitalization at One Year in the Intention-to-Treat Analysis.

The difference between the groups was significant ($P < 0.001$ by the log-rank test). TMR denotes transmyocardial revascularization, and MT medical therapy.

study was conducted. The perioperative mortality rate in the last 100 consecutively enrolled patients was 2 percent, which was the same as the rate in the group of patients who received medical therapy alone. The rate of perioperative complications was low in view of the coexisting conditions in this patient population.

In one study, transmyocardial revascularization with a carbon dioxide laser resulted in a higher perioperative mortality rate in patients with unstable angina than in those with stable angina (27 percent vs. 1 percent).¹³ In a study of transmyocardial revascularization with a holmium laser in 85 patients who could not be weaned from intravenous antianginal medications, Dowling and associates reported an operative mortality rate of 12 percent (10 of 85 patients died).¹⁵ In our study, the crossover group (patients in the medical-therapy group who could not be weaned from intravenous antianginal medications and underwent transmyocardial revascularization as part of a separate protocol) and the transmyocardial-revascularization group had similar rates of perioperative mortality (9 percent and 5 percent, respectively; $P = 0.48$), survival in the Kaplan-Meier analysis (91 percent and 84 percent, respectively; $P = 0.53$), and improvement in angina at one year. These results suggest that transmyocardial revascularization with a holmium laser should be performed, when possible, in patients with stable angina but that those with unstable angina should not be denied this procedure.

Ventricular arrhythmia was an early concern with the use of lasers that were not gated to the cardiac cycle. The perioperative rate of ventricular arrhythmia in our trial was 12 percent, which is similar to the 10 percent rate in clinical trials using a gated carbon dioxide laser.¹⁸

Transmyocardial revascularization performed with a holmium laser resulted in a significant improvement in angina at one year in 76 percent of the patients in our study who underwent the procedure, as compared with 32 percent of the patients who received medical therapy alone. The subjective nature of angina assessment introduces the possibility of bias. Unlike previous studies,^{7-13,19} ours included an independent, masked evaluation of angina. There was a strong correlation between the independent evaluation and that performed by the investigators, with a discrepancy of no more than one CCS class 80 percent of the time. The proportion of patients who reduced or ceased their use of cardioactive medications was significantly larger in the transmyocardial-revascularization group than in the medical-therapy group. Our findings are in agreement with those reported by other investigators^{8,9,13} and support the suggestion that relief of angina in patients treated with transmyocardial revascularization is not due to increased use of antianginal medications. Relief of angina for up to four years has been reported in patients who underwent transmyocardial revascularization with a carbon dioxide laser.²⁰ Although the benefit of transmyocardial revascularization in our patients may have been due in part to a placebo effect, sustained relief of angina and widely divergent Kaplan-Meier curves at one year ($P < 0.001$) for freedom from treatment failure help refute the argument that a placebo effect is an important mechanism for the favorable results of transmyocardial revascularization.

The success of transmyocardial revascularization is thought to be due to improved regional blood flow to ischemic myocardium, but the precise mechanisms of its effects remain unclear. Although in our study the patients treated with transmyocardial revascularization had higher rates of improvement in angina, freedom from treatment failure, and freedom from cardiac-related rehospitalization, as well as better exercise tolerance and higher quality-of-life scores at 12 months, than the patients treated with medical therapy alone, no significant differences in computer-quantified reversible or fixed perfusion defects were noted between the two groups.

Horvath and associates⁹ reported a small improvement in perfusion after transmyocardial revascularization performed with a carbon dioxide laser. These results seemingly supported the hypothesis that transmyocardial revascularization improved myocardial perfusion. However, the follow-up was incomplete, the analysis was not computer-quantified, and improved perfusion was poorly correlated with relief of angina.²¹ In a prospective, randomized trial involving primarily patients with class III angina, Schofield and associates¹⁹ compared transmyocardial revascularization (performed with a carbon dioxide laser) with medical therapy alone and were unable to demonstrate improved perfusion on thallium scans ob-

tained after transmymocardial revascularization. Although the proportion of patients with improvement in angina was significantly larger in the transmymocardial-revascularization group, it was lower than that reported in previous studies.^{9,16} The lower rate of improvement in angina may reflect the enrollment of patients with class III angina rather than class IV angina. The failure to demonstrate improved perfusion after transmymocardial revascularization may be due to the low sensitivity of thallium scanning rather than to the absence of an effect. Using positron-emission tomography, Frazier and associates⁷ demonstrated an improvement in subendocardial blood flow in 11 patients treated with transmymocardial revascularization.

Angiogenesis²²⁻²⁴ and sympathetic denervation²⁵⁻²⁷ are plausible mechanisms for the clinical results achieved with transmymocardial revascularization. Inflammatory cells recruited in response to laser-induced myocardial injury may release angiogenic growth factors, and the actions of these growth factors may result in neovascularization and improved regional collateral flow. Sympathetic denervation may relieve angina without influencing myocardial perfusion; this would explain the immediate relief experienced by some patients. The possibility that denervation may lead to silent ischemia or infarction after transmymocardial revascularization is less likely, since there was no increase in fixed perfusion defects in our transmymocardial-revascularization group. The mechanism of action of transmymocardial revascularization is probably multifactorial, with angiogenesis and denervation occurring concurrently.

In this prospective, randomized, multicenter trial, patients with medically refractory class IV angina who underwent transmymocardial revascularization and continued medical therapy had significantly higher rates of improvement in angina, survival free of cardiac events, freedom from treatment failure, and freedom from cardiac-related rehospitalization than patients who received medical therapy alone. Mortality did not differ significantly between the two groups. Although its mechanism of action is unknown, transmymocardial revascularization is a treatment option for patients with medically refractory angina who are not candidates for conventional revascularization.

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APPENDIX

The following centers and investigators participated in the study; the number of patients enrolled at each center is shown in parentheses: Albany Hospital, Albany, N.Y. — J.M. Luber, Jr., and J.M. Kelley (3); Audubon Hospital, Louisville, Ky. — T. Matthew (8); Brook Army Hospital, Fort Sam Houston, Tex. — D. Cohen (1); Bryan Memorial Hospital, Lincoln, Nebr. — D.M. Gangahar (15); University of Louisville, Jewish Heart and Lung Institute, Louisville, Ky. — R.D. Dowling, A. Lansing, and A.D. Slater (31); Memorial Hospital, Springfield, Ill. — J.A. Schneider (11); Methodist Hospital, Memphis, Tenn. — G.P. Schoettle (25); Ochsner

Hospital, New Orleans — J.L. Ochsner (2); Sacred Heart Hospital, Spokane, Wash. — S.L. Selinger, S.M. Cattaneo, and D. Sandler (21); St. John Hospital, Detroit — A. Kafi and T. Schreiber (5); St. Joseph's Hospital, Atlanta — D. Murphy and J.A. Wolfe (8); St. Thomas Heart Institute, Nashville — M.R. Petracek (14); St. Vincent Hospital and Indiana Heart Institute, Indianapolis — K.B. Allen, D.A. Heimansohn, and J.J. Schier (64); Tampa General Hospital, Tampa, Fla. — W.W. Angell, F. Matar, P.P. McKeown, and N.J. Sears (15); Terrebonne General Medical Center, Houma, La. — T.L. Fudge (32); University of Colorado Hospital, Denver — R.K. Brown (3); University of Iowa Hospital, Iowa City — W.E. Richenbacher (12); and William Beaumont Hospital, Royal Oak, Mich. — J.S. Bassett (5).

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