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 TRANSMYOCARDIAL REVASCLARIZATION FOR END-STAGE CORONARY ARTERY DISEASE
 

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 TRANSMYOCARDIAL REVASCLARIZATION WITH A CARBON DIOXIDE LASER  
 IN PATIENTS WITH END-STAGE CORONARY ARTERY DISEASE

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**ABSTRACT**

**Background** The construction of subendocardial channels to perfuse ischemic areas of the myocardium has been investigated since the 1950s. We assessed the safety and efficacy of transmymocardial revascularization with a carbon dioxide laser in patients with refractory angina and left ventricular free-wall ischemia that was not amenable to direct coronary revascularization.

**Methods** In a prospective, controlled, multicenter trial, we randomly assigned 91 patients to undergo transmymocardial revascularization and 101 patients to receive continued medical treatment. The severity of angina (according to the Canadian Cardiovascular Society [CCS] classification), quality of life, and cardiac perfusion (as assessed by thallium-201 scanning) were evaluated at base line and 3, 6, and 12 months after randomization.

**Results** At 12 months, angina had improved by at least two CCS classes in 72 percent of the patients assigned to transmymocardial revascularization, as compared with 13 percent of the patients assigned to medical treatment who continued medical treatment ( $P < 0.001$ ). Patients in the transmymocardial-revascularization group also had a significantly improved quality of life as compared with the medical-treatment group. Myocardial perfusion improved by 20 percent in the transmymocardial-revascularization group and worsened by 27 percent in the medical-treatment group ( $P = 0.002$ ). In the first year of follow-up, 2 percent of patients assigned to undergo transmymocardial revascularization were hospitalized because of unstable angina, as compared with 69 percent of patients assigned to medical treatment ( $P < 0.001$ ). The perioperative mortality rate associated with transmymocardial revascularization was 3 percent. The rate of survival at 12 months was 85 percent in the transmymocardial-revascularization group and 79 percent in the medical-treatment group ( $P = 0.50$ ).

**Conclusions** In patients with angina refractory to medical treatment and coronary artery disease that precluded coronary-artery bypass surgery or percutaneous transluminal coronary angioplasty, transmymocardial revascularization improved cardiac perfusion and clinical status over a 12-month period. (N Engl J Med 1999;341:1021-8.)

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**I**N the 1950s, Goldman and associates<sup>1</sup> and Massimo and Boffi<sup>2</sup> proposed that natural or artificial conduits could be implanted in the subendocardium to direct left ventricular blood through the coronary sinusoids and into ischemic areas of the myocardium. In 1968, after extensive experiments in animals, Sen and colleagues<sup>3</sup> described transmymocardial revascularization through transmural channels created with a 16-gauge intravenous cannula. In 1981, Mirhoseini and Cayton<sup>4</sup> used a laser to create transmymocardial channels in animals; five years later, Okada and colleagues<sup>5</sup> did the same in humans. Investigators have continued to test transmymocardial revascularization in both animals<sup>6-9</sup> and humans.<sup>10</sup>

In a nonrandomized, longitudinal trial undertaken to establish the safety, efficacy, and value of transmymocardial revascularization performed with a laser in 201 patients at eight U.S. centers, angina was relieved and cardiac perfusion improved in 75 percent of the patients over a 12-month period.<sup>10</sup> We conducted a prospective, randomized, multicenter trial to examine further the safety and efficacy of transmymocardial revascularization in patients with refractory angina and documented left ventricular free-wall ischemia that was not amenable to direct coronary revascularization and to compare this treatment with maximal medical therapy.

## METHODS

### Study Design

Between July 1995 and September 1997, 12 U.S. centers participated in this prospective, randomized, controlled study. Written informed consent was obtained from each patient before enrollment. By means of randomization at a central institution, patients were assigned, in a 1:1 ratio, to undergo transmymocardial revascularization with a carbon dioxide laser (the Heart Laser System, PLC Medical Systems, Franklin, Mass.) or to receive continued medical treatment. Patients were selected by the attending cardiologist, interventional cardiologist, or surgeon after a review of clinical symptoms, recent angiograms, and perfusion scans.

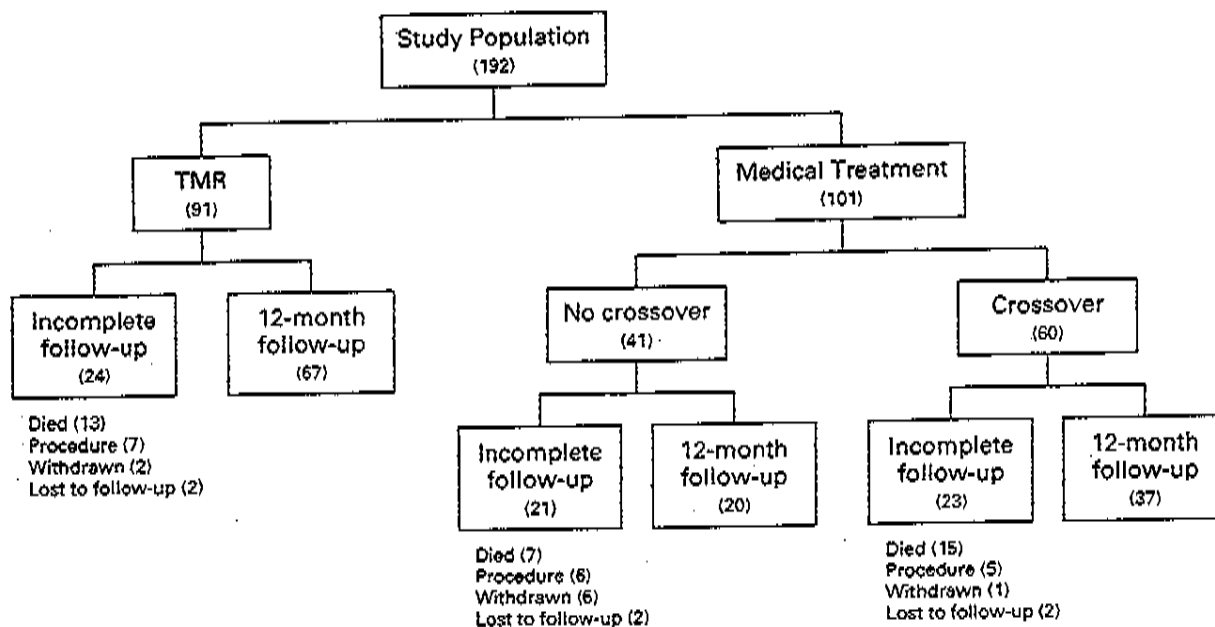
To be enrolled in the trial, patients were required to meet the following criteria: Canadian Cardiovascular Society (CCS) class

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\*Other members of the Transmymocardial Carbon Dioxide Laser Revascularization Study Group are listed in the Appendix.

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**Figure 1.** Overview of the Outcomes of Patients Assigned to Undergo Transmyocardial Revascularization (TMR), Those Assigned to Receive Medical Treatment Alone, and Those Crossed over from Medical Treatment to TMR.

Numbers in parentheses are numbers of patients. "Procedure" refers to any additional revascularization procedure, including percutaneous transluminal coronary angioplasty or coronary-artery bypass grafting.

III or IV angina that was refractory to medical treatment, reversible ischemia of the left ventricular free wall, and coronary disease that was not amenable to coronary-artery bypass grafting or percutaneous transluminal coronary angioplasty. Patients whose coronary disease was severe and diffuse or who did not have a target vessel or conduit suitable for grafting were considered to have disease not amenable to the latter two procedures. Patients were excluded if the left ventricular ejection fraction was less than 20 percent or if they had a concurrent major illness.

Crossover from medical treatment to transmyocardial revascularization was allowed if a patient had unstable angina that necessitated intravenous antianginal therapy for 48 hours or more in an intensive care unit. After crossover, patients were followed for an additional 12 months, regardless of how long they had been in the group assigned to medical treatment. These patients were considered part of the medical-treatment group until crossover, after which they were followed separately.

#### Clinical Evaluation

The patients' clinical status was evaluated with respect to CCS angina class, use of cardioactive medications, and responses on quality-of-life questionnaires. Angina was classified at enrollment and at 3, 6, and 12 months according to CCS guidelines. To eliminate potential bias, angina was also classified in a blinded manner by an independent evaluator. Success at follow-up was defined as an angina class at least two classes below that at base line.

To study fully the effects of transmyocardial revascularization in comparison with medical treatment, both intention-to-treat and "on-treatment" analyses of angina were conducted. The intention-to-treat analysis, which included patients who remained in the medical-treatment group as well as patients who were crossed over to transmyocardial revascularization as part of the medical-treatment group, provided a conservative estimate of the effect of transmyocardial revascularization, preventing overly op-

timistic conclusions. The on-treatment analysis, which did not include patients who were crossed over to transmyocardial revascularization, was considered the best way to evaluate the results from a clinical perspective. Thus, patients assigned to transmyocardial revascularization were compared first with all the patients assigned to medical treatment and then separately with those assigned to medical treatment and not crossed over.

Quality of life was assessed in all patients at enrollment and at 3, 6, and 12 months during follow-up. At these times, each patient completed two questionnaires: the 36-item Medical Outcomes Study Short-Form General Health Survey (SF-36)<sup>11</sup> and the Seattle Angina Questionnaire.<sup>12</sup>

#### Single-Photon-Emission Computed Tomography

The extent and reversibility of myocardial ischemia at rest and during exercise were assessed in each patient at enrollment and at 3, 6, and 12 months. Patients underwent thallium-201 single-photon-emission computed tomography (SPECT) with pharmacologic stress testing (with dipyridamol at a dose of 0.56 mg per kilogram of body weight, to a maximum of 6 mg) and four-hour redistribution-reinjection imaging. All the images were processed according to a standard protocol by a single technician at Cedars-Sinai Medical Center. Every image was then analyzed by an experienced nuclear cardiologist who was unaware of the patient's identity, treatment assignment, and scan date.

Each image was divided into three cross sections (apical, mid-ventricular, and basal) parallel to the atrioventricular groove. Each of these cross sections was then divided into eight segments, which were individually analyzed to assess perfusion status. Each segment was examined for the presence of normal tissue, a fixed defect (scar), a reversible defect (ischemic or hibernating myocardium), or both fixed and reversible defects. The sum of the number of segments in each perfusion category is expressed as a percentage of all 24 segments and used to characterize the perfusion of the left side of the heart. Perfusion re-

## TRANSMYOCARDIAL REVASCUARIZATION FOR END-STAGE CORONARY ARTERY DISEASE

sults at 3, 6, and 12 months were compared with the scores at base line for each patient.

### Transmyocardial Revascularization

The technique of transmyocardial revascularization has been described in detail elsewhere.<sup>10</sup> Transmural channels approximately 1 mm in diameter were created with a single pulse of the carbon dioxide laser (peak power, 850 W) through the left ventricle. Approximately one channel was created per square centimeter of myocardial surface. Transmural penetration by the laser was confirmed by transesophageal echocardiography.

### Statistical Analysis

Analyses were performed with a two-sided standard t-test, paired t-test, or analysis of variance for normally distributed continuous variables; with a two-sided Wilcoxon signed-rank test, the Wilcoxon rank-sum test, or the Kruskal-Wallis test for variables not normally distributed; with a two-sided chi-square test or Fisher's exact test for discrete variables; and with the Kaplan-Meier test or a log-rank test for survival free of cardiac events. P values of less than 0.05 were considered to indicate statistical significance.

To determine whether specific outcomes, such as treatment success or mortality, could be predicted on the basis of the patient's characteristics at base line, multivariate logistic-regression analyses were conducted with stepwise regression (SAS software, version 6.12, SAS, Cary, N.C.).

## RESULTS

### Characteristics of the Study Population

Ninety-one patients were randomly assigned to undergo transmyocardial revascularization, and 101 patients were assigned to receive medical therapy (Fig. 1). The groups were balanced at base line with respect to sex, age, cardiac status, medical history, and cardiac risk factors (Table 1). Approximately 60 percent of the patients in each group were considered to be at high risk for a poor outcome as determined by the established scoring system of the Cleveland Clinic for surgical revascularization.<sup>13</sup> All the patients in both groups had severe coronary disease with lesions in all three major vessels.

### Results of Transmyocardial Revascularization

During surgery, a mean ( $\pm$ SD) of  $36 \pm 13$  channels were created,  $30 \pm 8$  of which were confirmed by transesophageal echocardiography to be transmural. Epicardial sutures were needed for hemostasis in 1 percent of the patients. There were no intraoperative deaths. The median stay in the intensive care unit for the patients who underwent transmyocardial revascularization was two days, for a median hospital stay of seven days.

### Clinical Status

Two patients assigned to transmyocardial revascularization and four assigned to medical treatment were lost to follow-up. Two of the four patients in the medical-treatment group had been crossed over to transmyocardial revascularization; thus, the six patients were evenly distributed among the three groups analyzed (Fig. 1) and their exclusion did not modify the results, regardless of the outcome.

TABLE 1. CHARACTERISTICS OF THE PATIENTS AT RANDOMIZATION.\*

VARIABLE	TMR (N=91)	MEDICAL TREATMENT (N=101)	CROSSOVER (N=60)†
Female sex (% of patients)	19	23	18
Age (yr)	$61 \pm 10$	$61 \pm 10$	$61 \pm 11$
Cardiac status			
CCS class IV angina (% of patients)	69	63	100
CCS class III angina (% of patients)	31	37	0
Unstable angina (% of patients)	8	13	70
LVEF (%)	$50 \pm 11$	$50 \pm 11$	$51 \pm 11$
LVEF $\leq 45\%$ (% of patients)	47	58	30
Acute myocardial infarction			
History (% of patients)	82	77	78
No. of episodes	$1.8 \pm 1.1$	$1.8 \pm 1.2$	$1.8 \pm 1.1$
Congestive heart failure (% of patients)	34	35	37
CABG			
History (% of patients)	92	91	93
No. of episodes	$1.6 \pm 0.7$	$1.6 \pm 0.7$	$1.6 \pm 0.7$
PTCA			
History (% of patients)	47	58	53
No. of procedures	$2.4 \pm 2.0$	$2.9 \pm 3.3$	$3.1 \pm 4.0$
Risk factors (% of patients)			
Hypertension	65	64	68
Diabetes	40	51	47
Hypercholesterolemia	57	65	62
Current tobacco use	9	7	10
Risk associated with CABG‡			
Score	$6.1 \pm 3.4$	$5.8 \pm 2.9$	$9.3 \pm 3.6$
High risk (% of patients)	59	57	87

\*Plus-minus values are means  $\pm$ SD. TMR denotes transmyocardial revascularization, CCS Canadian Cardiovascular Society, LVEF left ventricular ejection fraction, CABG coronary-artery bypass grafting, and PTCA percutaneous transluminal coronary angioplasty.

†The crossover group consisted of 60 patients randomly assigned to receive medical treatment who subsequently underwent transmyocardial revascularization because of unstable angina that required antianginal therapy for at least 48 hours. These patients are also included in the medical-treatment group.

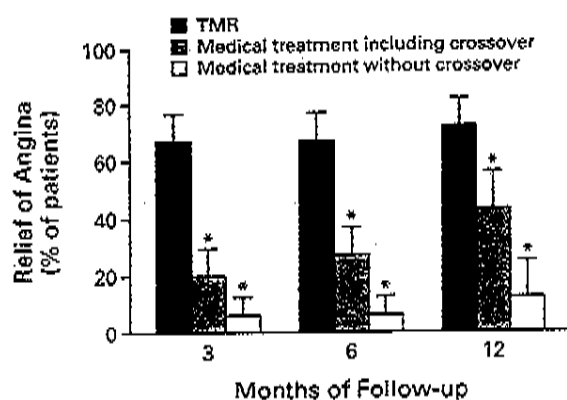
‡The risk associated with coronary-artery bypass grafting was assessed with the scoring system of the Cleveland Clinic.<sup>13</sup> A score of  $\geq 5$  indicates a high risk.

### Angina Class

With success at follow-up defined as a reduction of at least two angina classes as compared with base line, transmyocardial revascularization was significantly more successful in both analyses (Fig. 2). At three months, 67 percent of the patients assigned to transmyocardial revascularization, 20 percent of those assigned to medical treatment (including those crossed over), and 6 percent of those assigned to medical treatment and not crossed over had a clinically successful result ( $P < 0.001$  for the comparison between the transmyocardial-revascularization group and each medical-treatment group) (Fig. 2). At 6 months, the success rates were 67 percent, 27 percent, and 6 percent, respectively, and at 12 months, the success rates were 72 percent, 43 percent, and 13 percent, respectively ( $P < 0.001$  for both sets of comparisons).

A blinded, independent assessment of angina was

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## No. OF PATIENTS

TMR	78	67	61
Medical treatment including crossover	77	67	54
Medical treatment without crossover	24	24	20

Figure 2. Relief of Angina According to Treatment Group.

Results are shown for both intention-to-treat and on-treatment analyses. The intention-to-treat analysis included all patients assigned to the medical-treatment group, including those crossed over to transmyocardial revascularization (TMR). Relief was defined as an improvement in angina by at least two Canadian Cardiovascular Society classes from base line. The T bars indicate standard deviations. Asterisks indicate  $P < 0.001$  for the comparison with the transmyocardial-revascularization group.

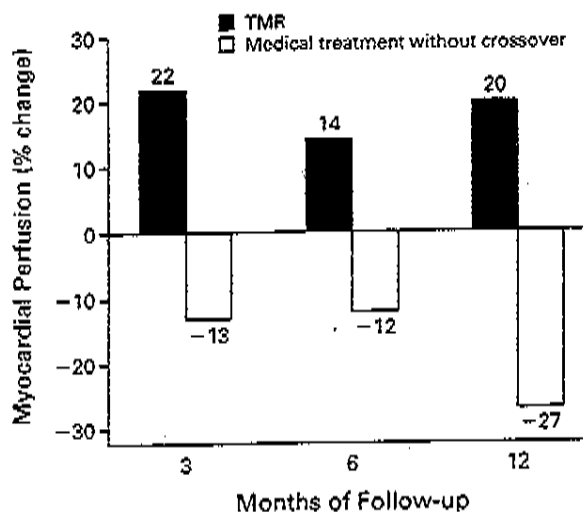
conducted in addition to the on-site evaluations. For 80 percent of the patients, the result of the independent assessment was within one CCS class of the result of the on-site assessment, indicating consistency in the evaluations. When the on-site and independent evaluations were compared, no significant differences were found ( $P = 0.20$ ).

#### Cardioactive Medications

Changes in the use of cardioactive medications (nitrates, beta-blockers, and calcium-channel blockers) from base line to follow-up were analyzed for their potential influence on outcomes with respect to angina. The clinical success of transmyocardial revascularization was not due to changes in medication; the use of medications decreased or remained unchanged in 83 percent of the patients in whom transmyocardial revascularization was successful. Conversely, the use of medications increased or remained unchanged in 86 percent of the patients assigned to medical treatment.

#### Quality of Life

According to the responses on the SF-36 questionnaire, patients in the transmyocardial-revascular-



## No. OF PATIENTS

TMR	50	47	38
Medical treatment	38	35	13

Figure 3. Change in Left-Sided Myocardial Perfusion during Follow-up, According to Treatment Assignment.

The percent change in myocardial perfusion differed significantly between the groups at each time point ( $P = 0.001$  at 3 months,  $P = 0.002$  at 6 months, and  $P = 0.002$  at 12 months). The percentage change in myocardial perfusion is calculated as the number of defects at base line minus the number of defects at follow-up, divided by the number of defects at base line. Numbers shown represent results from patients with usable data. TMR denotes transmyocardial revascularization.

ization group had a greater improvement in their quality of life (38 percent improvement) than patients in the medical-treatment group (6 percent improvement) as compared with base line at three months ( $P < 0.001$ ). This difference was also significant at 6 and 12 months ( $P = 0.01$  and  $P < 0.001$ , respectively). For each of 15 components of the Seattle Angina Questionnaire, transmyocardial revascularization was associated with a significantly better result than medical treatment.

#### SPECT Scans

The rates of compliance with the protocol and the proportion of scans that were usable during follow-up were similar in the two groups (81 percent and 72 percent, respectively, in the transmyocardial-revascularization group and 79 percent and 69 percent, respectively, in the medical-treatment group). The mean number of segments with reversible perfusion defects at enrollment was  $7.1 \pm 3.7$  per patient in the transmyocardial-revascularization group and  $6.8 \pm 3.3$  in the medical-treatment group ( $P = 0.60$ ). At enrollment, the mean number of segments that were judged to have fixed defects was

## TRANSMYOCARDIAL REVASCULARIZATION FOR END-STAGE CORONARY ARTERY DISEASE

9.0±3.6 in the transmyocardial-revascularization group and 9.0±3.3 in the medical-treatment group ( $P=0.96$ ).

Medications were not stopped before the performance of SPECT imaging. Use of medications was balanced between the groups at each time point. Figure 3 shows the percent change in left-sided myocardial perfusion at 3, 6, and 12 months. In the group assigned to transmyocardial revascularization, reversible ischemia decreased by an average of 1.5 segments per patient at 3 months, 0.8 segment at 6 months, and 1.4 segments at 12 months. In contrast, in the group assigned to medical treatment, reversible ischemia increased by an average of 0.8, 0.8, and 1.3 segments, respectively ( $P=0.001$  for the comparison between groups at 3 months,  $P=0.02$  for the comparison at 6 months, and  $P=0.002$  for the comparison at 12 months). However, there were no statistically significant differences between the groups at any of these time points in the number of fixed defects per patient.

### Morbidity

During the first 30 days after transmyocardial revascularization, 6 patients (7 percent) had acute myocardial infarction, 10 (11 percent) had congestive heart failure, 7 (8 percent) had ventricular tachycardia or ventricular fibrillation, and 1 (1 percent) had unstable angina. Sixty-two patients had no complications, 18 had one, 7 had two, 1 had three, 1 had four, and 2 had five. The only complication resulting specifically from the surgical procedure was an accidental laser-induced injury of the mitral apparatus, which was repaired, in one patient.

During the 12-month follow-up period, the rate of hospital admission due to unstable angina was 2 percent among patients assigned to transmyocardial revascularization and 69 percent among patients assigned to medical treatment ( $P<0.001$ ). Rates of admission to the intensive care unit during the 12-month period were 0.02 admission per patient in the transmyocardial-revascularization group and 1.37 admissions per patient in the medical-treatment group. There was no significant difference in the rate of freedom from acute myocardial infarction between patients assigned to transmyocardial revascularization (87 percent) and those assigned to medical treatment who did not cross over (80 percent,  $P=0.24$ ), but the rate of freedom from unstable angina was significantly higher after transmyocardial revascularization (84 percent, as compared with 25 percent after medical treatment only;  $P<0.001$ ). The proportion of patients who did not die and who were free of acute myocardial infarction, unstable angina, and class IV angina was also significantly higher in the transmyocardial-revascularization group (66 percent, as compared with 11 percent in the medical-treatment group;  $P<0.001$ ). Event-free survival is shown in Figure 4.

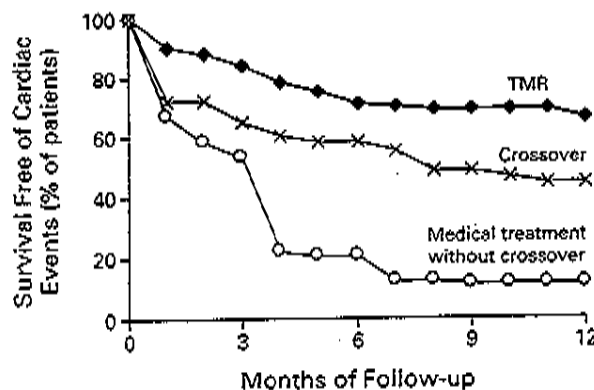


Figure 4. Event-free Survival According to Treatment Group.

Cardiac events were defined as acute myocardial infarction, unstable angina, or class IV angina. TMR denotes transmyocardial revascularization.

### Mortality

There were no intraoperative deaths among the patients assigned to transmyocardial revascularization; the 12-month survival rate was 85 percent. In comparison, the 12-month survival rate was 79 percent among the 41 medically treated patients who were not crossed over to transmyocardial revascularization ( $P=0.50$ ). Of the patients assigned to transmyocardial revascularization, 3 (3 percent) died perioperatively, and 10 (11 percent) died from cardiac causes during follow-up (Table 2).

The sole predictor of perioperative mortality was the occurrence of unstable angina. The time between an occurrence of unstable angina and surgery was significantly related to the risk of perioperative death ( $P<0.001$ ): the risk increased by a factor of 22.9 when the time between angina and surgery decreased to less than 2 weeks (1 to 7 days: 8 of 30 patients died [27 percent; 95 percent confidence interval, 11 to 43 percent]; 8 to 14 days: 3 of 19 died [16 percent; 95 percent confidence interval, 0 to 32 percent];  $\geq 15$  days: 1 of 102 died [1 percent; 95 percent confidence interval, 0 to 3 percent]) ( $P<0.001$ ). A low left ventricular ejection fraction was a significant predictor of overall mortality in the transmyocardial-revascularization group ( $P=0.02$ ). The incidence of acute myocardial infarction during the study was significantly associated with overall mortality in both groups (transmyocardial revascularization,  $P=0.05$ ; medical treatment,  $P=0.03$ ). The treatment-group assignment was not predictive of mortality, confirming the similarity of overall mortality in the two groups.

### Crossover Group

Of the 101 patients assigned to medical treatment 60 (59 percent) were crossed over to transmyocar-

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TABLE 2. CAUSES OF DEATH ACCORDING TO TREATMENT GROUP.

CAUSE OF DEATH	No. OF PATIENTS	STUDY DAY*
<b>Group assigned to transmyocardial revascularization</b>		
Early deaths		
Intraoperative or perioperative acute myocardial infarction	3	5, 9, 12
Late deaths from cardiac causes		
Sudden cardiac death after low cardiac output syndrome	1	86
Acute myocardial infarction after multiple-organ failure	1	119
Congestive heart failure due to ventricular fibrillation	1	124
Unstable angina	1	194
Stroke	1	198
Ventricular fibrillation after gallbladder surgery	1	324
Low cardiac output syndrome after laser revascularization	1	72
Acute myocardial infarction	2	38, 161
Late deaths from noncardiac causes		
Dehydration due to viral infection	1	157
<b>Group assigned to medical treatment without crossover</b>		
Early deaths		
Acute myocardial infarction	2	13, 24
Late deaths		
Acute myocardial infarction preceded by unstable angina	1	204
Sudden death at home from presumed arrhythmia	3	30, 99, 246
Late deaths from noncardiac causes		
Non-cardiac-related cancer	1	246
<b>Group crossed over to transmyocardial revascularization</b>		
Early deaths		
Ventricular fibrillation	3	0, 0, 2
Cardiac arrest	2	7, 14
Perioperative acute myocardial infarction	2	7, 9
Perioperative low cardiac output syndrome	2	8, 11
Late deaths from cardiac causes		
Arrhythmias	4	45, 158, 201, 203
Acute myocardial infarction	2	58, 273

\*Day 0 is the day of operation.

dial revascularization a mean of  $107 \pm 89$  days after randomization. Because of their unstable angina, these patients were considered to be at high risk for a poor outcome (Cleveland Clinic risk score,  $9.3 \pm 3.6$ , as compared with a score of  $5.8 \pm 2.9$  at enrollment for all patients assigned to medical treatment, where a score of  $\geq 5$  indicates a high risk;  $P=0.02$ ). During the first 30 days after surgery, 3 of the 60 patients (5 percent) had acute myocardial infarction, 2 (3 percent) had unstable angina, 3 (5 percent) had arrhythmias, and 3 (5 percent) had congestive heart failure. One patient sustained laser-induced damage to the mitral apparatus during surgery. Twenty-three of the patients who were crossed over underwent the 12-month follow-up assessment of angina; 16 of these

23 patients (70 percent) had CCS class I or II angina, 3 (13 percent) had class III, and 4 (17 percent) had class IV.

## DISCUSSION

Before this study was conducted, the potential benefits of transmyocardial revascularization performed with a carbon dioxide laser had been observed in most of the 2500 patients who had undergone this treatment. A nonrandomized study of these patients showed significant improvement in symptoms and perfusion after the laser treatment.<sup>10</sup> Whether this improvement would have occurred without transmyocardial revascularization was unknown. This question prompted the current randomized investigation.

In this study, the proportion of patients who had relief from angina was greater in the group assigned to undergo transmyocardial revascularization (72 percent) than in the patients in the group assigned to receive maximal medical therapy who did not cross over to transmyocardial revascularization (13 percent). This significant decrease in the patients' CCS class was confirmed by a blinded, independent assessment and with use of the Seattle Angina Questionnaire. Moreover, patients who were assigned to medical treatment had a rate of hospital admission for unstable angina of 69 percent, as compared with only 2 percent in the transmyocardial-revascularization group. Among patients who underwent transmyocardial revascularization, relief of acute and chronic angina resulted in an improved quality of life, as measured by the SF-36 questionnaire, and reduced use of antianginal medications.

In addition, myocardial perfusion improved after transmyocardial revascularization and worsened with medical treatment alone. The price of the benefits of transmyocardial revascularization was a 3 percent rate of perioperative mortality. If the procedure was deferred for two weeks, this rate decreased to 1 percent, making the mortality associated with transmyocardial revascularization less than that associated with coronary-artery bypass grafting.<sup>14</sup> Overall survival at 12 months was similar in the two groups (transmyocardial revascularization, 85 percent; medical treatment, 79 percent;  $P=0.50$ ).

This study did not directly address the mechanisms underlying the benefits of transmyocardial revascularization; however, several inferences can be made. There may be a short-lived placebo effect. In a nonrandomized trial, long-term follow-up of patients who underwent transmyocardial revascularization showed no change in the improvement in symptoms after 3 years (average CCS class,  $3.8 \pm 0.4$  at base line,  $1.4 \pm 1.2$  at 12 months, and  $1.5 \pm 1.2$  at 36 months).<sup>15</sup> The conversion of ischemic myocardium to infarcted myocardium may also improve anginal symptoms. In our study, however, the extent of fixed defects in perfusion over the 12-month period

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was similar in the two groups, and there was no significant increase in fixed defects after transmymocardial revascularization as compared with medical treatment. Denervation is another possible mechanism of the benefit. If this were the explanation, however, one would expect to see an increase in myocardial infarction, sudden death, and heart failure with transmymocardial revascularization — none of which increased in the patients assigned to this treatment.

Improved perfusion and relief of symptoms after transmymocardial revascularization could result from patent channels created by the laser or from laser-induced angiogenesis. Isolated anatomical evidence of patent channels has been reported.<sup>16,17</sup> In addition, real-time, high-resolution contrast echocardiography has shown patent laser channels perfusing a 1.5-cm<sup>3</sup> section of myocardium with each systole.<sup>18</sup> In our study, perfusion improved over a period of 12 months, indicating that the laser may increase perfusion by stimulating angiogenesis.

Although we assume that transmymocardial revascularization directly enhances myocardial perfusion, providing relief of angina, we cannot establish a direct correlation. Changes in clinical symptoms and changes on perfusion scans reflect two related but distinct phenomena, and in our study the degree of symptomatic improvement was not necessarily matched by the degree of improvement in the results on scanning. Symptoms and perfusion improved in most of the patients assigned to transmymocardial revascularization but not in those assigned to medical treatment who did not cross over to transmymocardial revascularization.

The option for crossover from the medical-treatment group to the transmymocardial-revascularization group was the greatest limitation of this study. Crossover was allowed as an incentive for patients assigned to maximal medical therapy to remain in the study if medical therapy failed. The attrition rate in this group was considerable because the condition of these patients did not improve substantially and because, by definition, they had unstable angina that required intravenous medication. Despite the limitation inherent in the crossover design, the patients assigned to transmymocardial revascularization showed improvement at three and six months as compared with their base-line values and as compared with values in their medically treated counterparts. In addition, although lifestyle changes can be limiting factors in clinical trials, there were no significant differences in lifestyle or medication use that might have influenced the outcomes.

In a recent report on a randomized study at a single center,<sup>19</sup> Schofield et al. concluded that transmymocardial revascularization should not be recommended because it did not significantly increase exercise capacity or 12-minute walking distance at 12 months. However, the patients who underwent transmymocar-

dial revascularization did have significantly decreased angina (as indicated by the CCS class), increased functional capacity, less need for antianginal medications, and fewer hospital admissions as compared with medically treated patients. With respect to exercise capacity and walking times, comparisons were made between the groups at each follow-up period, not between base line and follow-up within each group. The authors reported similar decreases in reversible defects in the two groups. However, they did not consider the effect of changes in fixed defects.

With regard to fixed defects, there was no significant change from base line to 12 months in the transmymocardial-revascularization group.<sup>19</sup> The medically treated group, however, had a significant increase in fixed defects from base line (38 segments [8 percent]) to 12 months (68 segments [17 percent]); in other words, reversible defects decreased when fixed defects increased, as ischemic areas became scarred. In addition, follow-up data on perfusion were pooled, and comparisons were again made between the groups rather than between base line and follow-up.

In general, the study by Schofield et al.<sup>19</sup> is not closely comparable with our multicenter trial. Patients in our trial were much sicker (70 to 80 percent had CCS class IV angina at base line, as compared with 27 percent in the study by Schofield et al.<sup>19</sup>), and we did not exclude patients with unstable angina, whereas Schofield et al. did. If patients with unstable angina are excluded, the perioperative mortality rate in our study falls to 1 percent, which is less than the 5 percent reported in the other series.<sup>19</sup>

In summary, we conducted this multicenter, randomized, controlled trial to determine the effect of transmymocardial revascularization with a carbon dioxide laser on symptoms and cardiac perfusion in patients with end-stage coronary disease. We found that transmymocardial revascularization significantly alleviated angina and improved cardiac perfusion in patients with severe angina that was refractory to conventional medical therapy or revascularization procedures.

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#### APPENDIX

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