

# Transmyocardial laser revascularisation compared with continued medical therapy for treatment of refractory angina pectoris: a prospective randomised trial

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## Summary

**Background** Transmyocardial revascularisation (TMR) is an operative treatment for refractory angina pectoris when bypass surgery or percutaneous transluminal angioplasty is not indicated. We did a prospective randomised trial to compare TMR with continued medication.

**Methods** We recruited 182 patients from 16 US centres with Canadian Cardiovascular Society Angina (CCSA) score III (38%) or IV (62%), reversible ischaemia, and incomplete response to other therapies. Patients were randomly assigned TMR and continued medication (n=92) or continued medication alone (n=90). Baseline assessments were angina class, exercise tolerance, Seattle angina questionnaire for quality of life, and dipyridamole thallium stress test. We reassessed patients at 3 months, 6 months, and 12 months, with independent masked angina assessment at 12 months.

**Findings** At 12 months, total exercise tolerance increased by a median of 65 s in the TMR group compared with a 46 s decrease in the medication-only group ( $p<0.0001$ , median difference 111 s). Independent CCSA score was II or lower in 47.8% in the TMR group compared with 14.3% in the medication-only group ( $p<0.001$ ). Each Seattle angina questionnaire index increased in the TMR group significantly more than in the medication-only group ( $p<0.001$ ).

**Interpretation** TMR lowered angina scores, increased exercise tolerance time, and improved patients' perceptions of quality of life. This operative treatment provided clinical benefits in patients with no other therapeutic options.

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## Introduction

Standard treatments for angina pectoris are effective for most patients. Some patients with advanced disease, however, become less responsive to medication but are not candidates for percutaneous transluminal coronary angioplasty or coronary-artery bypass grafting because the atherosclerotic lesions are too diffuse. These patients have frequent angina, limited exercise tolerance, and poor quality of life. Transmyocardial revascularisation (TMR) was developed to treat such patients.<sup>1</sup> TMR is a surgical procedure that uses a laser to create channels through the myocardial wall to the ventricular chamber. Although there is controversy about the mechanism of action, early clinical trials of TMR in the USA with carbon-dioxide lasers showed encouraging results.<sup>2–5</sup> However, these results have been challenged because of high crossover rates and lack of masked assessment of symptoms. A subsequent study that used a carbon-dioxide laser but did not allow for crossover in the study design showed limited clinical benefits in patients with predominantly class III angina.<sup>6</sup>

We designed the Angina Treatments—Lasers and Normal Therapies in Comparison (ATLANTIC) prospective randomised study to compare TMR with continued medical therapy in patients with medically refractory angina.

## Patients and methods

### Patients

We recruited 337 patients from 16 US centres who were assessed by their treating physician and referred for this study (figure 1). After a medical history was taken, the most recent angiogram reviewed, and informed consent obtained, patients underwent baseline testing. Tests were echocardiography, a dipyridamole thallium stress test, treadmill exercise-tolerance testing (Modified Bruce Protocol), and a self-administered Seattle angina questionnaire. The Seattle angina questionnaire consists of 19 questions, from which five quality-of-life indices specific for patients with angina are derived. Higher scores for each index signify better quality of life. Eligible patients had Canadian Cardiovascular Society Angina (CCSA) scores of III or IV, despite maximum tolerated doses of at least two antianginal drugs. Entry criteria were a left-ventricular ejection fraction of 30% or more and reversible perfusion defects on dipyridamole thallium stress test.

We designed the baseline exercise-tolerance-test protocol to obtain evidence that the patients' angina was refractory to medical treatment, to account for possible exercise habituation effects, and to ensure test consistency. With the exception of sublingual nitroglycerine within 4 h, prescribed cardiovascular drugs were continued before the exercise-tolerance test. Each eligible patient had to have two consecutive exercise-tolerance tests (of a

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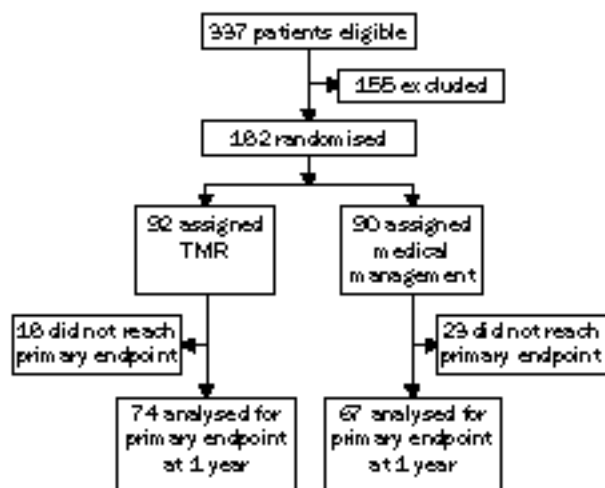


Figure 1: Trial profile

maximum of four tests) with durations within 15% of each other. The test could be limited by symptoms or ischaemic changes on electrocardiography, but typical angina occurring during at least one test was required for inclusion in the study.

We enrolled only patients with at least one region of protected myocardium. We defined a protected region angiographically as a vascular territory that was perfused by unobstructed blood flow (no lesion >50%) through a major vessel or through a previously placed bypass graft inserted into a major vessel that was free from distal disease. We developed this criterion from a previous retrospective study, which reported that patients with no protected regions were at higher risk of mortality after TMR.<sup>7</sup>

Patients who had been admitted to hospital for unstable angina, substantial change in angina pattern, or change in antianginal drugs were not included until 21 days after the last event. We excluded patients who had had myocardial infarction within 3 months, severe symptomatic heart failure (requiring  $\geq 40$  mg furosemide daily), a history of clinically important ventricular arrhythmias, or a cardiac transplant, or who were judged to be poor surgical candidates.

#### Randomisation and treatment

Patients who met the inclusion criteria were randomly assigned TMR with continued medication (n=92) or continued medication only with their current treatment regimen (n=90, figure 1). We used block randomisation according to site to achieve roughly equal distribution between groups at each site. Randomisation was done by a central coordinating centre by telephone. The coordinating centre confirmed eligibility criteria before it provided a randomisation assignment. Six patients had minor deviations from protocol related to entry criteria but were included in analyses.

Under general anaesthetic, a limited muscle-sparing left thoracotomy was done and transmyocardial laser channels were created in and around previously identified areas of reversible ischaemia with a density of about one channel per 1.0–1.5 cm<sup>2</sup>. A median of 18 (range 9–42) channels were created with a holmium:YAG (CardioGenesis Corp, Sunnyvale, CA, USA). Bleeding from most channels stopped spontaneously or with finger pressure. No patient had recurrent bleeding after initial control. Patients were monitored in intensive care immediately after surgery.

We assessed patients at 3 months, 6 months, and 12 months for angina class (unmasked assessment by investigators) exercise tolerance, dipyridamole thallium stress test, and Seattle angina questionnaire. Echocardiography was done at 3 months. Angina class was also assessed by standard protocol at 12 months by trained independent interviewers unaware of treatment group. We established central laboratories for on-site training and to review results of exercise-tolerance tests, echocardiography, dipyridamole thallium stress test, Seattle angina questionnaire, and independent angina assessments. All endpoint data were assessed by central laboratory investigators who were unaware of treatment group.

	TMR (n=92)	Medication only (n=90)
<b>Demography</b>		
Age (years)	63 (42–78)	65 (36–78)
Sex (M/F)	10 (11%)/82 (89%)	7 (8%)/83 (92%)
<b>Clinical characteristics</b>		
Diabetes	33 (36%)	31 (34%)
Hypertension	68 (74%)	79 (88%)*
Hyperlipidaemia	71 (77%)	81 (90%)†
History of smoking	77 (84%)	73 (81%)
Family history of coronary-artery disease	66 (73%)‡	70 (78%)
Previous myocardial infarction	64 (70%)	62 (69%)
Previous interventions		
None	3 (3%)	6 (7%)
CABG alone	40 (44%)	27 (30%)
PTCA alone	6 (7%)	8 (9%)
CABG and PTCA	43 (47%)	49 (54%)
<b>Baseline tests</b>		
CCSA score		
III	34 (37%)	36 (40%)
IV	58 (63%)	54 (60%)
Exercise tolerance (s)	364 (105–981)	381 (89–747)
Left-ventricular ejection fraction (%)	50 (31–68)	45 (31–68)
Left-ventricular myocardium with ischaemia	14 (0–63)	13 (0–51)
Left-ventricular myocardium with infarction	9 (0–45)	13 (0–51)
Seattle angina questionnaire		
Angina frequency	20 (0–90)	20 (0–80)
Angina stability	25 (0–100)	50 (0–100)
Physical limitation	25 (0–100)	31 (0–64)
Disease perception	17 (0–67)	25 (0–75)§
Treatment satisfaction	69 (0–100)	63 (13–100)

Data are median (range) or n (%). CABG=coronary-artery bypass grafting; PTCA=percutaneous transluminal coronary angioplasty. \*p=0.02. †p=0.03. ‡History unknown for two patients in TMR group. §p=0.02.

Table 1: Baseline demography and test results

#### Statistical analysis

The primary outcome measure was the change in exercise duration on a standard protocol. We designed the study to detect a difference of 60 s, which we took to be clinically important, in the mean change from baseline in the TMR group compared with the medication-only group, with a power of 80% and a level of significance of 0.05. We assumed that the change was normally distributed with an SD of 135 s on the basis of a preliminary feasibility study. We therefore estimated that we needed to recruit 80 patients per group. We anticipated about a 10% loss to follow-up and increased the sample size to 90 per group.

Angina, quality of life, and dipyridamole thallium stress test were taken to be secondary outcome measures. The study proceeded until completion of planned enrolment and was not stopped prematurely. Since all patients received assigned treatment and there was no crossover, we did analyses by treatment group. We excluded from analyses patients who died or withdrew from the study. Results are presented as medians and ranges or IQR. We compared baseline characteristics with Fisher's exact test for dichotomous data, the Mantel-Haenszel<sup>2</sup> test for ordered categorical data, or Wilcoxon's rank-sum test for continuous data. We estimated survival curves by Kaplan-Meier method and used the log-rank test to compare groups. Changes from baseline in exercise-tolerance tests, Seattle angina questionnaire, dipyridamole thallium stress test, and ejection fraction between groups were compared with Wilcoxon's test, whereas the difference in the distribution of angina between

Protected regions	TMR	Medication only*
Anterior only	32 (35%)	31 (34%)
Lateral only	14 (15%)	14 (16%)
Inferior only	14 (15%)	10 (11%)
Anterior and lateral	10 (11%)	13 (14%)
Anterior and inferior	8 (9%)	13 (14%)
Lateral and inferior	11 (12%)	5 (6%)
Anterior, lateral, and inferior	3 (3%)	3 (3%)

\*One patient had no protected region and is not included in table.

Table 2: Severity of coronary disease by number of protected regions

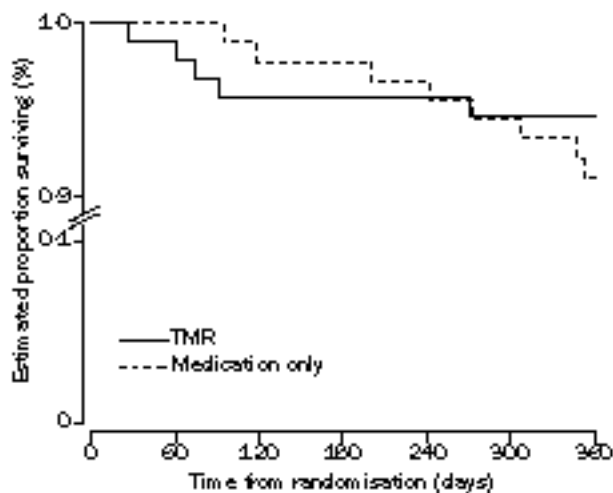


Figure 2: Kaplan-Meier survival curves

One additional death in medication-only group at 379 days not shown in curves.

groups according to independent scores was assessed with the Mantel-Haenszel test. We compared ejection fraction over time within groups with a signed-rank test. All p values are two-sided.

## Results

182 of 337 patients were enrolled (figure 1). The main reasons for exclusion were absence of objective evidence of ischaemia on dipyridamole thallium stress test (34), patient's decision not to participate (23), eligibility for coronary-artery bypass graft or percutaneous transluminal coronary angioplasty decided by the central laboratory (23), insufficient region of protected myocardium (20), absence of angina on exercise testing (20), and left-ventricular ejection fraction of less than 30% (12). Age, sex, and baseline variables were similar in the two groups, although there were higher frequencies of hypertension and hypercholesterolaemia and higher disease perception score on the Seattle angina questionnaire in the medication-only group (table 1). More men than women were enrolled.

Most patients had previous myocardial infarction and coronary-artery bypass grafting or percutaneous

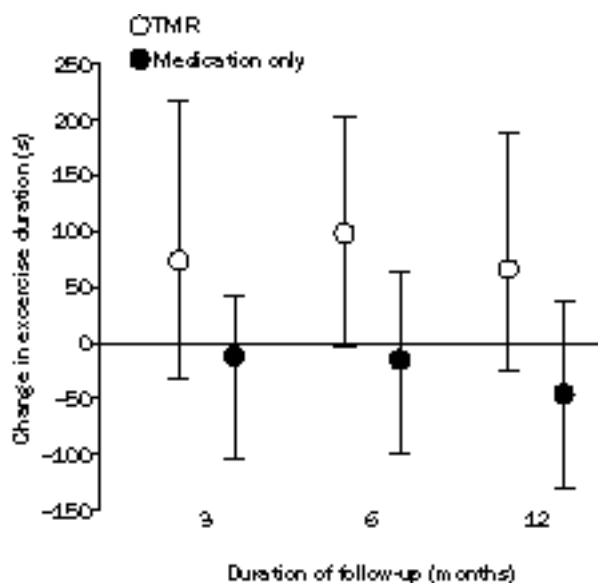


Figure 3: Median (IQR) changes in total exercise duration at each follow-up visit

Event	TMR	Medication only
Death	5	9
Unstable angina	37	69
Heart failure or left-ventricular dysfunction	25	10
Myocardial infarction	14	8
Arrhythmias	11	10
Other cardiovascular disorder	11	12
Thromboembolic disorder	9	3
Respiratory failure	5	1
Pneumonia	5	1
Cellulitis	4	0
Phrenic-nerve paresis	3	0

Table 3: Serious adverse events

transluminal coronary angioplasty. Two-thirds had class IV angina at baseline. Ventricular function was well preserved (median left-ventricular ejection fraction 50%) but baseline exercise tolerance was poor (median total exercise duration 364 s). The two groups showed a median of 14% ischaemic myocardium and 11% infarction, measured by quantitative polar analysis of the dipyridamole thallium stress test (available from 87% of participants at baseline). Severity of coronary-artery disease, indexed at the central laboratory by the number of protected regions, was also similarly distributed between groups (table 2). 115 patients had only a single protected region, most commonly a protected anterior wall that was the result of a previously placed internal mammary artery to a patent distal left anterior descending artery.

The frequencies of use of individual cardiovascular drugs were similar in the two groups. In addition, 102 (56%) patients were taking combinations of  $\beta$ -blockers, nitrates, and calcium-channel blockers, 38 (21%) were taking  $\beta$ -blockers and nitrates, and 29 (16%) were taking nitrates and calcium-channel blockers. 147 (81%) patients used daily aspirin at baseline. 137 (75%) patients were taking lipid-lowering agents. There was little change in the overall pattern of medications during the study.

14 patients died during the study, (five [5%] in the TMR group, nine [10%] in the medication-only group). Four of the deaths in the TMR group were attributed to myocardial infarction and one to respiratory failure. Only one of these occurred within 30 days of surgery. All nine deaths in the medication-only group happened more than 30 days after randomisation, seven because of cardiac causes and two because of unknown causes. Survival did not differ significantly between groups (figure 2).

The number of episodes of unstable angina requiring admission to hospital was higher in the medication-only group than in the TMR group, whereas the rate of heart failure (defined as the need for a new prescription of a diuretic or doubling of a pre-existing diuretic regimen) or left-ventricular dysfunction ( $\geq 10\%$  point decrease in ejection fraction) were higher in the TMR group. Other adverse events arose with low frequency (table 3).

16 patients withdrew from the study, nine in the TMR group and seven in the medication-only group, all voluntarily. Although complete follow-up test results were not available for these patients, each one was contacted and was alive at 12 months. After deaths and withdrawals had been accounted for, 152 patients (78 in the TMR group, 74 in the medication-only group) reached the end of the study and were assessed for angina. Of these, 74 (95%) in the TMR group and 67 (91%) in the medication-only group completed the exercise-tolerance test at 12 months (figure 1).

Postoperative electrocardiography showed no significant changes in any patient and were typically unchanged from

CCSA classification by independent assessment	CCSA classification by investigator assessment							
	TMR				Medication only			
	I	II	III	IV	I	II	III	IV
I	16	4	0	1	0	0	2	0
II	15	7	4	1	2	3	8	0
III	13	7	7	4	2	3	11	13
IV	0	10	1	6	3	2	8	44

Table 4: Comparison of proportion (%) of investigator and independent scores in each CCSA class at 12 months

baseline; changes that were seen were non-specific ST and T-wave changes. At 3-month follow-up, only two patients in the TMR group had new Q waves; no patient in the medication-only group had new Q waves.

TMR channels have a central region of vaporised myocardium surrounded by a thin rim of necrosis due to thermal damage.<sup>8</sup> Induction of myocardial necrosis is inherent to the procedure. Serum creatine phosphokinase and its MB fraction (available in 96% of patients) peaked at 16–24 h after the procedure. The highest mean concentration was 1387 IU/L and was less than 1095 IU/L in 50% of patients. Mean overall creatine phosphokinase concentration was 45 IU/L and was less than 20 IU/L in 50% of patients.

There was an improvement in exercise duration in patients in the TMR group at all time points, with median values of more than 60 s. More than 50% of patients in the medication-only group had decreased exercise tolerance at all time points (59% at 3 months, 55% at 6 months, and 64% at 12 months; figure 3). At 12 months, total exercise tolerance increased by a median of 65 s in the TMR group compared with a 46 s fall in the medication-only group ( $p < 0.0001$ ); the median difference between groups was 111 s. Exercise duration at 12 months had decreased by 60 s or more in only 17% of patients in the TMR group compared with 45% in the medication-only group. Despite the longer exercise duration, only 26% of patients in the TMR group had angina during the final test, compared with 58% of those in the medication-only group. The major reason for stopping the exercise test in patients who did not have angina was fatigue.

Unmasked assessment of angina showed substantial improvement in angina in the TMR group at each follow-up visit. At 12 months, CCSA score had decreased by two or more classes in 47 (61%) of 77 TMR-treated patients compared with only eight (11%) of 73 treated with medication only, in whom CCSA class remained mostly unchanged. Additionally, patients with more severe angina at baseline were more likely to show more improvement; 32 (67%) of 48 patients in the TMR group with baseline CCSA class IV angina were more likely to show a decrease of two or more classes compared with 15 (52%) of 29 in the medication-only group with baseline CCSA class III angina. In the medication-only group, such changes were seen in five (12%) of 43 and three (10%) of 30, respectively. Findings were similar at each follow-up visit.

Comparison of investigator scores and masked independent scores for angina at 12 months showed that investigators generally assigned lower angina scores to patients in the TMR group than did independent assessors (table 4). In the medication-only group, the proportion of patients for whom investigators assigned lower or higher scores than independent assessors (14% and 12%, respectively) showed no systematic bias in class assignment. In the TMR group, a significantly higher proportion of patients were assigned higher scores than lower scores by the investigators than by the independent

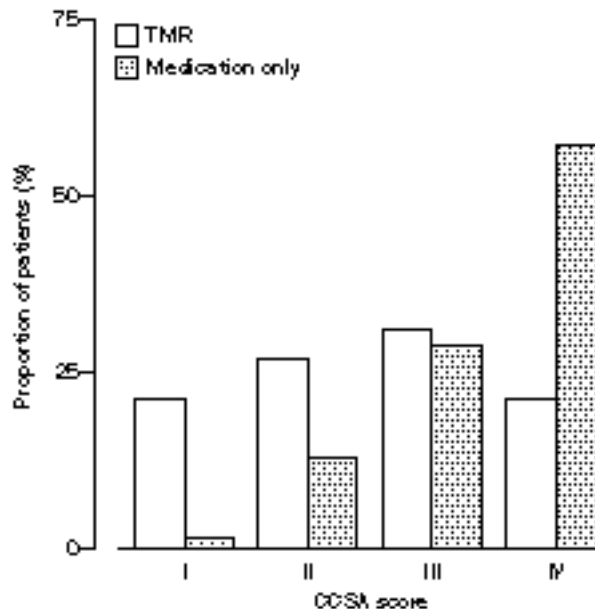


Figure 4: Distribution of CCSA scores by independent assessors

assessors (32 vs 11%), which showed bias in favour of the therapy. It was therefore deemed inappropriate to rely on the investigator CCSA scores as a measure of efficacy. CCSA scores obtained from the masked assessment of angina at 12 months (figure 4) were significantly lower in the TMR group than in the medication-only group ( $p < 0.001$ ). 48% of patients in the TMR group were in class II or lower, compared with 14% of those in the medication-only group at the end of the study.

At 3 months, 6 months, and 12 months, scores of each quality-of-life index in the Seattle angina questionnaire rose significantly more in the TMR group than in the medication-only group (figure 5). The reported quality of life was therefore better in the TMR group.

The change in the percentage of myocardium with fixed and reversible defects from baseline to the 3-month, 6-month, and 12-month visits did not differ significantly between the two treatment groups. TMR did not, therefore, influence myocardial perfusion as assessed by this technique. For example, at 12 months, the median proportion of the myocardium affected by ischaemia on polar analysis was 11.5% (range 0–65,  $n=66$ ) in the TMR group and 12% (0–50,  $n=65$ ) in the medication-only group, which are similar to each other and to the baseline values (table 1). Similarly, the median proportion of the myocardium with infarction was 11% (0–63,  $n=66$ ) in TMR and 11% (0–39,  $n=66$ ) in the medication-only group; these values did not differ significantly from each other or baseline.

Left-ventricular ejection fraction did not change significantly in the medication-only group from baseline to 3 months (median change 0% [–25 to 20],  $p=0.21$ ). In the TMR group, the median change in ejection fraction from baseline to 3 months was a decrease from baseline by 3% (–28 to 20,  $p < 0.0001$ ). A more detailed analysis, based on a qualitative grading of 15 different myocardial segments, showed no change in the proportion of segments graded as normal or hypokinetic, compared with those graded akinetic, dyskinetic, or aneurysmal in patients in each treatment group.

## Discussion

All previous studies of TMR have limited selection of patients to those with the most advanced forms of

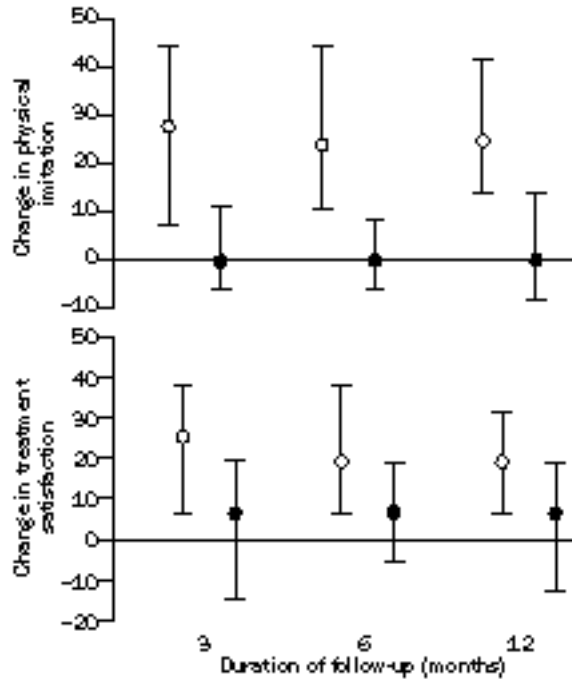
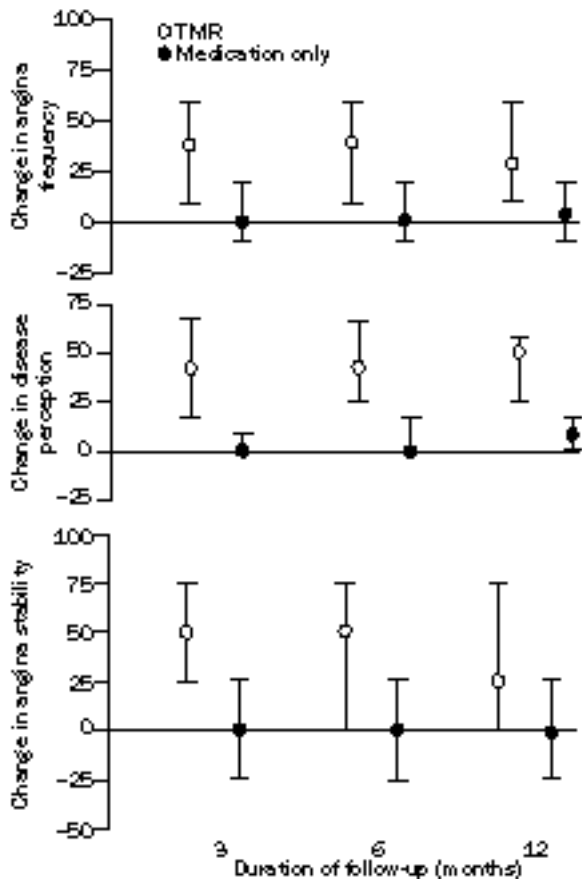


Figure 5: Median (IOR) changes in values of individual indexes derived from the Seattle angina questionnaire

ischaemic heart disease and the worst symptoms, and those ineligible for standard interventions. Our entry criteria were intended to select such patients. Most of our patients had class IV angina and poor exercise tolerance and were in a stable stage of their disease. There was a high frequency of cardiac risk factors, previous myocardial infarctions, multiple previous invasive therapies, and reasonably well preserved left-ventricular function without symptoms of heart failure. The mortality rate in our study was lower than that in previous studies of TMR. Factors contributing to the low mortality could include exclusion of patients with no region of protected myocardium, acute ischaemia, low ejection fractions (<30%), or refinement of surgical technique.

Postoperative echocardiography, electrocardiography, and dipyridamole thallium stress tests showed that TMR did not infarct the treated region on a large scale. Enzymatic evidence showed mild myocardial necrosis, but creatine phosphokinase MB concentrations of up to 30 IU/L are common. Concentrations were higher in a few patients, but other tests showed no evidence of substantial major myocardial damage. Echocardiography showed a small but significant reduction in global ejection fraction, although a more detailed segmental analysis showed no significant change from baseline. Such a decrease was not seen in a previous study of TMR with a carbon-dioxide laser,<sup>6</sup> but differences in lasers or in study populations have not been established. For the group as a whole, this apparently minor change in left-ventricular function did not adversely impact on survival, exercise tolerance, or angina in the TMR group.

Angina relief and improvement in quality of life were significant. Although we were able to eliminate bias in angina scoring by using only the independent scores, bias among patients could not be eliminated. There was a

significant increase in exercise tolerance in the TMR group, which provided objective evidence of improved functional capacity after TMR. No exercise training effect, commonly seen in studies of heart failure patients,<sup>9</sup> was shown in patients in the medication-only group with angina but no heart failure; overall, exercise tolerance declined in this group. Thallium scans done under a fixed degree of chemically induced vasodilatory stress showed no improvement in blood flow after TMR. This finding raises questions about the mechanisms contributing to clinical benefits, but does not exclude the possibility of an improvement in perfusion undetectable by this technique.

Several previous clinical studies of TMR focused on angina relief compared with a control group receiving medical therapy. Researchers in one study that used a carbon-dioxide laser concluded that TMR improves myocardial perfusion, although the high rate of crossover limited the validity of the conclusions.<sup>5</sup> In another study that also used a carbon-dioxide system in mainly class III patients, the investigators reported a low rate of improvement in angina, a non-significant increase in exercise duration at 1 year, no improvement in perfusion, and a slightly higher 1-year mortality with TMR (11 vs 4%,  $p=0.14$ ).<sup>6</sup>

There is controversy about the mechanism of action of TMR. Early claims of channel patency and direct transmyocardial blood flow<sup>10-13</sup> have mainly been refuted.<sup>5,8,14-21</sup> Preclinical studies have shown vascular growth (angiogenesis) after TMR that can increase blood reserve by about 30%,<sup>22,23</sup> which may potentially improve symptoms. Angiogenesis and growth of existing vessels are thought to be due to the inflammation occurring in response to the microinjuries<sup>24</sup> around the original laser channels.<sup>16</sup> Myocardial denervation has been seen in laboratory animals,<sup>25</sup> but no harmful clinical consequences of creating silent ischaemia have emerged, as shown by the low mortality rate after TMR. Analysis of electrocardiograms, nuclear scans, and echocardiograms

has excluded the possibility that angina relief is provided by infarcting large regions of treated myocardium. Angina improvement may be due to a placebo effect, a factor that cannot be excluded in unmasked studies of angina relief.

Continued refinements in surgical therapy have lowered morbidity and mortality among patients with ischaemic heart disease. Our study showed significant improvements in symptoms and function after 12 months among non-option patients treated with TMR.

#### Contributors

Daniel Burkhoff was a coprincipal investigator, designed the study, oversaw data collection and analysis, and drafted the paper. James W Jones was a coprincipal investigator, participated in study design, performed surgery and cared for most of the patients, trained many of the participating surgeons, and oversaw data analysis. Sheila Schmidt recruited, interviewed, and cared for many patients. Steven P Schulman did the masked CCSA assessments. Jonathan Myers headed the exercise test central laboratory and reviewed all tests. Jon Resar headed the angiography central laboratory and analysed the changes in medication use. Lewis C Becker headed the central nuclear cardiology laboratory and analysed all of the scans. James Weiss headed the central echocardiography laboratory and analysed all of the images. All authors participated in writing of the paper.

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