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<0.001, 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. 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. 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.

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
maximal 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.

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 myocardial infarction within 3 months, severe symptomatic heart failure (requiring 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.

Randomisation and treatment

Patients who met the inclusion criteria were randomly assigned to 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 cm². 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.

**Table 1: Baseline demography and test results**

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

Data are median (range) or n (%). CABG=coronary-artery bypass grafting; PTCA=percutaneous transluminal coronary angioplasty.

**Table 3: Baseline clinical characteristics**

**Table 4: Baseline laboratory assessments**

**Table 5: Baseline angiographic characteristics**

**Table 6: Baseline exercise-tolerance tests**

**Table 7: Baseline echocardiography results**

**Table 8: Baseline dipyridamole thallium stress test results**

**Table 9: Baseline Seattle angina questionnaire results**

**Table 10: Baseline quality of life results**

**Table 11: Baseline disease perception results**

**Table 12: Baseline physical limitation results**

**Table 13: Baseline angina stability results**

**Table 14: Baseline treatment satisfaction results**

**Figure 1: Trial profile**

*One patient had no protected region and is not included in table.*
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 β-blockers, nitrates, and calcium-channel blockers, 38 (21%) were taking β-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 (>=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 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 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.

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the longer exercise duration, only 26% of patients in the 16–24 h after the procedure. The highest mean concentration and its MB fraction (available in 96% of patients) peaked at baseline; changes that were seen were non-specific ST and improvement in angina in the TMR group at each follow-up visit. For example, at 12 months, the median proportion of the myocardium with fixed 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=65) 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 medicaton-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<0·001). 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

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

There is controversy about the mechanism of action of TMR. Early claims of channel patency and direct transmyocardial blood flow have mainly been refuted. Preclinical studies have shown vascular growth (angiogenesis) after TMR that can increase blood reserve by about 30%, 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 around the original laser channels. Myocardial denervation has been seen in laboratory animals, 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 no-option patients treated with T M R.

Contributors
D aniel 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. Schultz did the masked CCSA assessments. Jonathan M. Mears headed the exercise test center laboratory and reviewed all tests. Jon Resar headed the angiography central laboratory and analysed all of the images. All authors participated in writing of the paper.

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