A Prospective, Multicenter, Randomized Trial of Percutaneous Transmyocardial Laser Revascularization in Patients With Nonrecanalizable Chronic Total Occlusions

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OBJECTIVES

We sought to evaluate the safety and efficacy of percutaneous transmyocardial revascularization (PTMR) in patients with refractory angina caused by one or more chronic total occlusions (CTOs) of a native coronary artery.

BACKGROUND

Previous unblinded, randomized trials of PTMR in patients with end-stage coronary artery disease and refractory angina have demonstrated significant relief of angina and increased exercise duration. Whether such benefits would be realized in blinded patients with less extensive coronary artery disease is unknown.

METHODS

A total of 141 consecutive patients with class III or IV angina caused by one or more chronically occluded native coronary arteries in which a percutaneous coronary intervention (PCI) had failed were prospectively randomized, at 17 medical centers, in the same procedure, to PTMR plus maximal medical therapy (MMT) (n = 71) or MMT only (n = 70). Blinding was achieved through heavy sedation, dark goggles and the concurrent performance of PCI in all patients.

RESULTS

Baseline characteristics were similar between the two groups. A median number of 20 laser channels were created in patients randomized to PTMR. At six months, the anginal class improved by two or more classes in 49% of patients assigned to PTMR and in 37% of those assigned to MMT (p = 0.33). The median increase in exercise duration from baseline to six months was 64 s with PTMR versus 52 s with MMT (p = 0.73). There were no differences in the six-month rates of death (8.6% vs. 8.8%), myocardial infarction (4.3% vs. 2.9%) or any revascularization (4.3% vs. 5.9%) in the PTMR and MMT groups, respectively (p = NS for all).

CONCLUSIONS

In patients with class III or IV angina caused by nonrecanalizable CTOs, the performance of PTMR does not result in a greater reduction in angina, improvement in exercise duration or survival free of adverse cardiac events, as compared with MMT only. (J Am Coll Cardiol 2002;39:1581–7) © 2002 by the American College of Cardiology Foundation

The inability to successfully pass a guidewire into the true distal lumen of a chronically occluded coronary artery is the most frequent cause of failed percutaneous coronary intervention (PCI) and one of the most common indications for coronary artery bypass graft surgery (CABG) (1–6). Furthermore, many more patients with occluded vessels not amenable to PCI are treated conservatively with antianginal medication. The likelihood of successful recanalization of chronic total occlusions (CTOs) has reached a plateau at ~50% to 70% over the last decade, despite steady improvements in angioplasty equipment, operator technique and the introduction of new devices (1–6).

Percutaneous transmyocardial revascularization (PTMR) is a technique whereby holmium/yttrium aluminum garnet (YAG) laser energy is transmitted to the endocardial surface through fiberoptic cables to photoacoustically create partial-thickness myocardial channels (7–9). In two separate randomized trials, PTMR, as compared with maximal medical therapy (MMT), was found to reduce angina and improve exercise capacity in patients with advanced ischemic heart disease and class III or IV angina (10,11). The results of these studies, however, have been questioned because of a lack of blinding, raising the possibility that the benefits observed with PTMR may have been due to the placebo effect (12,13). Moreover, a third trial in which a different laser system was used (but which was blinded), found no incremental improvement in symptoms or functional capacity with PTMR (14).
Therefore, we performed a prospective, multicenter, single-blinded, randomized trial of PTMR versus MMT in patients with a nonrevascularizable CTO and class III or IV angina in whom continued medical therapy was planned.

**METHODS**

**Patient group.** Consecutive patients meeting each of the following inclusion criteria were considered for enrollment: 1) Canadian Heart Association class III or IV angina, despite maximally tolerated anti-anginal medications; 2) planned PCI of CTO in a native coronary artery; 3) no other lesions present requiring PCI or CABG; 4) myocardial viability in the distribution subtended by the CTO, as verified either by thallium scintigraphic imaging, echocardiography, radionuclide ventriculography or left ventriculography; 5) myocardial wall thickness ≥9 mm in the area intended for treatment by PTMR (i.e., the nonrevascularizable region and surrounding margin), as measured by two-dimensional echocardiography; and 6) continued medical management if PCI was unsuccessful.

Patients were excluded if any of the following conditions were present: 1) left ventricular ejection fraction <30%; 2) myocardial infarction (MI) within three months, left ventricular aneurysm or mural thrombus; 3) aortic stenosis, aortic regurgitation or a prosthetic aortic valve; 4) decompensated heart failure; 5) ventricular tachycardia or fibrillation within one week; 6) the inability to perform a baseline modified Bruce exercise stress test for any reason other than severe angina, or if the electrocardiogram was uninterpretable for ischemia (e.g., left bundle branch block, left ventricular hypertrophy or Wolf-Parkinson-White syndrome); 8) a previous PCI was performed within the last six months; 9) a noncardiac condition with anticipated life expectancy <1 year; 10) participation in other investigational drug or device studies; or 11) the inability or unwillingness to comply with the follow-up procedures or provide informed consent.

The protocol was approved by the Human Investigational Review Board at each site, and all patients provided written, informed consent.

**Study protocol and procedure.** A modified Bruce exercise test and transthoracic echocardiography for the assessment of left ventricular ejection fraction, regional wall motion and myocardial thickness were performed at baseline in eligible patients who gave consent. Cardiac catheterization was performed, and PCI of the CTO was attempted according to routine practice. If the PCI was successful, or unsuccessful but complicated, the procedure was completed, and the patient was not enrolled. If the PCI was unsuccessful (with >5 min of time spent attempting to cross the CTO with the guide wire) and uncomplicated, the patient was randomized to PTMR plus MMT or MMT only. In patients assigned to PTMR, laser revascularization was performed in the myocardial territories subtended by the CTO, using the Eclipse holmium/YAG laser with fluoroscopic guidance, as previously described (15).

After the procedure, creatine kinase-MB isoenzyme levels were measured every 8 h (3 times/day). Patients were discharged when clinically stable. After hospital discharge, the anti-anginal medication was adjusted in all patients to minimize symptoms and maximize functional status. Clinical follow-up was performed by office visit, interview or telephone call at 3, 6 and 12 months after discharge. Repeat exercise testing (using the same modified Bruce protocol as in the baseline study) was scheduled at 6 and 12 months.

**Blinding.** Blinding was attempted by use of heavy sedation and placement of dark goggles over the patient’s eyes during the entire PCI (with or without PTMR) procedure. Moreover, the seamless transition after randomization from unsuccessful PCI to either PTMR or conclusion of the procedure was not revealed to the patient. The physician investigator was not blinded out of necessity. However, the randomization assignment was not revealed to the patient, family or treating physician, was not recorded in the chart and was not available to the individuals supervising the follow-up exercise tests. The study blind was not broken until after the last follow-up period. Finally, to assess the success of blinding, a questionnaire was completed by the patient at hospital discharge, designed to elicit the patient’s perceptions as to treatment assignment (1 = PTMR certain; 2 = PTMR probable; 3 = randomization uncertain; 4 = MMT [no PTMR] probable; and 5 = MMT [no PTMR] certain).

**End points, power analysis and statistics.** The trial was powered to assess the improvement in exercise duration from baseline to late follow-up in patients undergoing paired (modified Bruce) exercise tests. In patients unable to exercise because of refractory angina, the exercise duration for that test was imputed to 0 s. Assuming that the change in exercise duration between the baseline and follow-up exercise test would be 1.5 ± 3.0 min greater in the PTMR arm than in the MMT arm, the sample size was calculated to be 64 subjects per group, using a two-tailed analysis with alpha = 0.05 and 80% power. Thus, allowing for dropout and noncompliance, enrollment of 140 total patients was planned. Secondary end points included anginal status and the cumulative occurrence of adverse cardiac events at each follow-up period.
were performed on an intention-to-treat basis. Significance was established at \( p = 0.05 \).

**RESULTS**

A total of 141 patients at 17 medical centers were randomized after failed but uncomplicated PCI of CTO: 71 to PTMR and 70 to MMT only. The baseline clinical and angiographic characteristics of the two groups were similar (Table 1). The patient group was characterized by a high incidence of diabetes, previous MI, previous CABG and extensive coronary artery disease (Table 1). The distribution of failed recanalization of CTO during the procedure was also similar between the two groups (Fig. 1).

Among patients randomized to PTMR, a total of 20 channels (range 15 to 25 channels) was created in an average of 1.6 myocardial territories per patient (32% anterior, 62% inferior, 54% posterolateral and 14% apical). The laser procedural time was 16 min (range 11 to 30 min).

**Clinical outcomes and adverse events.** In-hospital complications tended to occur more frequently in patients assigned to PTMR, as compared with MMT, although there were no differences in the rates of major adverse cardiac events at six months (Table 2). Angina was significantly improved in both groups at six months (Fig. 2). Angina improved by two or more classes in 56% of patients who had PTMR and in 38% who received MMT at three months (\( p = 0.12 \)); at six months, these rates were 49% vs. 37%, respectively (\( p = 0.33 \)). Paired modified Bruce exercise tests were completed at baseline and at six months in 71 patients (36 treated patients and 35 control subjects; \( p = 0.97 \)). The exercise duration significantly and similarly improved from baseline to six months in both groups (86 ± 38 s after PTMR vs. 69 ± 29 s after MMT [median 64 vs. 52 s]; \( p = 0.73 \)). The numbers of patients in the PTMR and MMT groups who could not exercise due to refractory angina were seven and five at baseline and three and three at six months, respectively.

**Efficacy of blinding.** Attempts at blinding (through hospital discharge) were reasonably successful in both groups (Fig. 3). Of patients randomized to PTMR, 44% either
believed that they did not receive PTMR or were not certain. Of patients randomized to MMT, 75% either thought they received PTMR or were not certain.

**DISCUSSION**

This randomized trial demonstrates that in patients with class III or IV angina due to one or more CTOs that cannot be percutaneously revascularized, the creation of partial-thickness myocardial channels with a holmium/YAG laser does not significantly prolong exercise time or improve anginal symptoms at intermediate-term follow-up. Moreover, the 82.3% six-month rate of survival free from MI or revascularization after MMT was not enhanced by PTMR.

**Comparison with previous studies.** In contrast to the present study, two previous multicenter, randomized trials have demonstrated that fluoroscopically guided PTMR may alleviate angina and prolong the exercise duration in patients with refractory angina due to end-stage ischemic heart disease and with no potential for surgical or catheter-based revascularization—so called “no-option” patients. In the Potential Angina Class Improvement From Intramyocardial Channels trial, in which 221 no-option patients were enrolled, the anginal status at six months was improved by two or more classes in 46% of patients randomized to PTMR with the Cardiogenesis (Sunnyvale, California) holmium/YAG laser and in 6% of those treated conservatively (p < 0.001), and the exercise duration increased correspondingly (10). In a randomized trial of 325 no-option patients, in whom the same Eclipse laser as in the current study was utilized, patients assigned to PTMR had an 85-s improvement in exercise time from baseline to six months, compared with a 58-s decline in control subjects (p < 0.0001); anginal improvement by two or more classes was present in 55% versus 31% of patients at 12 months, respectively (p < 0.001) (11).

Several patient- and method-related differences between these previous studies and the present trial may explain the variance in outcomes. First, the extent of coronary artery disease and, thus, the degree of ischemia, may have been greater in the earlier studies. “No-option” patients typically have diffuse, obliterative coronary atherosclerosis, whereas patients in the current trial had at least one CTO with a distal lumen that could be visualized and possibly amenable to PCI or CABG. However, the number of diseased epicardial vessels and the incidence of previous MI, PCI, and CABG were similar across the three studies, as was the myocardial density of the laser channels created (10,11).

**Blinding and the placebo effect.** A notable difference between the current and previous trials is that in the present study, extensive efforts were made to blind the patients to the treatment assignment, by the use of dark goggles and heavy sedation, and this effort was aided by the performance of an extended procedure (unsuccessful, uncomplicated PCI) in all patients before randomization. Blinding of caregivers was also promoted by restricting access to the randomization status beyond the catheterization laboratory. The efficacy of these blinding measures was assessed by a

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**Table 2.** Adverse Events in Randomized Patients

<table>
<thead>
<tr>
<th></th>
<th>PTMR (n = 71)</th>
<th>MMT (n = 70)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>In-hospital complications</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>0%</td>
<td>1.4%</td>
<td>0.49</td>
</tr>
<tr>
<td>MI (CK-MB &gt;3× normal)</td>
<td>2.8%</td>
<td>1.4%</td>
<td>0.99</td>
</tr>
<tr>
<td>Stroke</td>
<td>0%</td>
<td>0%</td>
<td>—</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>1.4%</td>
<td>0%</td>
<td>0.99</td>
</tr>
<tr>
<td>Ventricular tachycardia or fibrillation</td>
<td>7.0%</td>
<td>0%</td>
<td>0.06</td>
</tr>
<tr>
<td>Cardioversion</td>
<td>4.5%</td>
<td>0%</td>
<td>0.12</td>
</tr>
<tr>
<td>Pericardial tamponade</td>
<td>4.2%</td>
<td>0%</td>
<td>0.24</td>
</tr>
<tr>
<td>Effusions without tamponade</td>
<td>2.8%</td>
<td>0%</td>
<td>0.50</td>
</tr>
<tr>
<td><strong>Cumulative 6-month adverse events</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>8.6%</td>
<td>8.8%</td>
<td>0.91</td>
</tr>
<tr>
<td>MI</td>
<td>4.3%</td>
<td>2.9%</td>
<td>0.68</td>
</tr>
<tr>
<td>Any revascularization (PCI or CABG)</td>
<td>4.3%</td>
<td>5.9%</td>
<td>0.65</td>
</tr>
<tr>
<td>Death, MI or any revascularization</td>
<td>17.1%</td>
<td>17.7%</td>
<td>0.87</td>
</tr>
</tbody>
</table>

*Kaplan-Meier estimates. Data are presented as the percentage of patients.
CK-MB = creatine kinase-MB isoenzyme; PCI = percutaneous coronary intervention; other abbreviations as in Table 1.

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**Figure 2.** Canadian Heart Association angina class at six months in the study group. PTMR = percutaneous transmyocardial revascularization; MMT = maximal medical therapy.
pre-discharge questionnaire, which verified that most patients in both groups were uncertain of their treatment allocation. Indeed, 75% of patients treated conservatively mistakenly believed they had either received or may have received the active therapy (PTMR), and as a group, their exercise tolerance improved by 52 s from baseline to follow-up. In contrast, conservatively treated no-option patients in the earlier Eclipse study had a marked decline in their exercise time during follow-up (11), perhaps a consequence of less successful blinding and the patient’s resignation to continued symptoms (Fig. 4). Importantly, these data are concordant with the findings of Direct myocardial revascularization In Regeneration of Endomyocardial Channels Trial (DIRECT), a recently reported randomized, blinded study of PTMR in 298 no-option patients treated with the Johnson & Johnson (Warren, New Jersey) holmium/YAG laser with electromechanical map guidance, in whom no incremental improvement in angina or exercise capacity was found after PTMR (14). The DIRECT data are particularly relevant, as anginal status and exercise duration had improved in a previous unblinded registry using this system (16). Thus, these studies reinforce the power of the placebo effect, as well as the importance of adequate blinding whenever possible (12,13).

Finally, the results of a fourth, smaller, randomized trial, the Blinded Evaluation of Laser Intervention Electively for Angina Pectoris study, in which PTMR with the Eclipse holmium/YAG laser was compared with a truly blinded sham procedure in 82 no-option patients, were recently reported (17). Compared with the sham control group, PTMR resulted in a greater relief of angina at six months (≥2 class improvement in 41% vs. 13%, p = 0.004). However, the total exercise duration from baseline to six months increased by just 10 s in the PTMR arm and 7 s in the sham arm (p = NS), suggesting that the laser’s photo-

**Figure 3.** Results of the pre-discharge questionnaire of treatment assignment. PTMR = percutaneous transmyocardial revascularization; MMT = maximal medical therapy.

**Figure 4.** Improvement in exercise duration from baseline to six months in patients randomized to percutaneous transmyocardial revascularization (white bars) with the Eclipse holmium/yttrium aluminum garnet laser versus maximal medical therapy (black bars) in the present study (patients with non-revascularizable chronic total occlusions (CTOs); left bars) compared with a previous study with the same device in a different patient group (patients with end-stage ischemic heart disease with no revascularization options; right bars).
acoustic effect may reduce some patient’s pain perception, without relieving ischemia (18,19).

**Study limitations.** The principal limitation of the study is that only 71 of 141 randomized patients had paired baseline and follow-up exercise tests, rather than 128, for which the sample size of 140 was chosen. However, the principal end point—the difference in improvement in exercise time from baseline to six months between the two groups—was powered to 90 s; given the observed mean difference of only 17 s in 71 patients, the average increment in exercise duration improvement would have had to be ~181 s in 57 additional patients for the study to be statistically positive, a magnitude of improvement which has not yet been seen in any PTMR investigation. Also, data from the 12-month planned functional tests and clinical status are not currently available, although the trend toward a reduction in angina seen at three months was less apparent at six months, making it doubtful that longer follow-up would have been revealing. Nonetheless, a small benefit of PTMR in improving exercise capacity or relieving angina in patients with a nonrecanalizable CTO cannot be excluded, and may have been revealed by a larger sample size and more extended follow-up. However, the trend observed in the present study—that is, greater procedural complications in patients undergoing PTMR—may also have become significant in a larger trial. As collateral vessels were not quantified, the impact of angiographically visible collateral blood flow to the myocardial target zones on the outcome of PTMR is unknown. Finally, myocardial perfusion or metabolic imaging was not performed, although most previous studies have not demonstrated improved perfusion with PTMR (20,21).

**Clinical implications.** Based on this study, PTMR should not be considered for patients with class III or IV angina caused solely by a nonrecanalizable CTO. However, given the conflicting results in the aforementioned randomized trials, which included different patient groups, different degrees of blocking and different holmium/YAG systems, one final, large-scale, blinded, randomized trial (preferably with the Cardiogeneration/Eclipse laser system, in which positive results in no-option patients have been reported) would be essential to definitively exclude (or potentially establish) a role for PTMR in patients who are otherwise poor candidates for traditional revascularization modalities.

**REFERENCES**


14. Leon MB. DIRECT (DMR In Regeneration of Endomyocardial Channels Trial). Presented at: Late-Breaking Trials, Transcatheter Cardiovascular Therapeutics; October 19, 2000, Washington DC.


**APPENDIX**

**PARTICIPATING SITES AND PRINCIPAL INVESTIGATORS (PI)**

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