Do transmyocardial and percutaneous laser revascularization induce silent ischemia? An assessment by exercise testing

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Background Transmyocardial and percutaneous laser revascularization (TMR, PTMR) may reduce angina and increase exercise tolerance in otherwise untreatable angina patients, although the mechanism is unknown and the placebo effect may be significant. One other proposed mechanism is cardiac denervation leading to silent ischemia.

Methods Electrocardiograms obtained during symptom-limited exercise (ETT, modified Bruce protocol) at baseline and 12 months were analyzed (blinded core laboratory) from 182 patients randomized to TMR (n = 92) or medical therapy alone (MEDTMR, n = 90) and 219 patients randomized to PTMR (n = 109) or medical therapy alone (MEDPTMR, n = 110).

Results Exercise duration increased 1 year after TMR or PTMR relative to medically treated patients (6.8 ± 3.4 min vs 8.6 ± 3.5 min for TMR; 7.3 ± 3.1 min vs 9.1 ± 3.6 min for PTMR, P < .05). At baseline, 20% of TMR and MEDTMR subjects had ST depression >1.0 mm, >80% had angina during exercise, but only 3% had ST changes without chest pain (silent ischemia). This did not change after TMR. In the PTMR group, more subjects exercised to >1.0 mm ST depression (from 17% to 34%, P < .05), with no change in MEDPTMR, but the proportion with silent ischemia did not change in either group.

Conclusion Exercise tolerance improved after TMR and after PTMR. Relative to PTMR, TMR more effectively suppressed pain during exercise and ischemic ST depression. However, neither TMR nor PTMR induced significant silent ischemia. These results suggest that denervation may not be a significant factor contributing to angina relief after these procedures. The contribution of the placebo effect was not determined by these results. (Am Heart J 2002;143:1052-7.)

Despite extensive clinical experience with balloon angioplasty (PTCA) and bypass surgery (CABG), there remains a population of severely atherosclerotic patients with medically refractory angina who are not good candidates for these standard therapies. Transmyocardial laser revascularization (TMR, an approved surgical procedure) and percutaneous laser revascularization (PTMR, an investigational, interventional cardiology procedure) have been studied as palliative procedures to treat angina in these patients.1,2 Several recent controlled but unblinded studies have demonstrated that TMR and PTMR each reduce angina, increase exercise tolerance, and improve quality of life.3-7 The initially proposed mechanism of benefit was improved myocardial perfusion by direct flow from the ventricular cavity through laser-created channels,1 mimicking the physiologic mechanisms of blood flow in reptile hearts.8 However, several studies have indicated that this does not occur.9,11 Proposed physiologically based mechanisms include angiogenesis12-16 and myocardial denervation.17-19 In addition, the role of the placebo effect is unclear. The results of one double-blind study of PTMR (the Direct Myocardial Revascularization in Regeneration of Endomyocardial Channels [DIRECT] trial20) suggest that the entire effect was the result of placebo, whereas a more recent double-blind study with a different laser system (the Blinded Evaluation of Laser Intervention Electively For Angina Pectoris [BELIEF] trial21) showed significant angina improvement.

With regard to physiologically based mechanisms, there is evidence of angiogenesis from studies in dogs22 and pigs.14,15 However, clinical studies have thus far failed to demonstrate improved blood flow in treated patients.3-5 In contrast, myocardial denervation has been demonstrated in dog hearts by a reduction in myocardial content of tyrosine hydroxylase (a sympa-
the baseline exercise tolerance test protocol was designed to obtain evidence that the patients’ angina was refractory to medical treatment, to account for possible exercise habituation effects, and to ensure test consistency. Accordingly, with the exception of sublingual nitroglycerin within 4 hours, prescribed cardiovascular drugs were continued before the exercise test. Each eligible subject had to have 2 consecutive tests (out of a maximum of 4 tests) whose durations were within 15% of each other. The test could be limited by symptoms or ischemic echocardiographic changes, but typical angina occurring during at least 1 of the qualifying tests was required for study inclusion. The angina end point was “moderately severe” or a rating of 3 on a scale of 1 to 4.25 The modified Bruce protocol was used for all exercise testing.

Randomization and treatment

Subjects who met inclusion and exclusion criteria for the ATLANTIC study were randomly assigned TMR plus continued maximal medication (TMR + MEDs, n = 92) or continued medical therapy alone (MEDs, n = 90). Subjects who met inclusion and exclusion criteria for the PACIFIC study were randomized to PTMR plus continued maximal medical therapy (PTMR + MEDs, n = 110) or continued medical therapy alone (MEDs, n = 111).

TMR was performed by a limited muscle-sparing left thoracotomy with the patient under general anesthesia. TMR channels were created in and around ischemic regions with a density of —1 per 1.0 cm². A median of 18 (range 9-42) transmyocardial channels were created with a holmium:YAG laser.

PTMR was performed with conscious sedation and anticoagulation (heparin to an activated clotting time —250 s) with use of the Axcis PTMR system (Cardiogenesis Corporation, Sunnyvale, Calif) under biplane fluoroscopic guidance as described previously.26 The median number of channels delivered was 15 (range 8-35).

Follow-up and exercise test analysis

Patients were assessed at 3, 6, and 12 months after randomization for angina class (unblinded assessment by investigators), exercise tolerance and electrocardiographic changes, and Seattle angina questionnaire.27 A central core laboratory was established for onsite training and to interpret the results of the exercise tests. Exercise test results, including electrocardiograms (ECGs), were reviewed and analyzed at the core laboratory that was blinded to treatment group. ECGs were analyzed to determine the number of subjects with interpretable ECGs (ie, those without left bundle branch block or pacemakers) and the number of subjects with 1.0 mm ST depression who were considered to be diagnostic for exercise-induced myocardial ischemia. An association was then made between the occurrence of angina and ST segment depression.

Statistical analysis

Exercise test duration was evaluated in the TMR and PTMR intervention and respective control groups at baseline, 3, 6, and 12 months by the Wilcoxon rank-sum test for continuous data. For the TMR and PTMR interventions, the groups were stratified at each evaluation point by those with 1.0 mm exercise-induced ST depression, the proportion of patients with chest pain during exercise, and the percentage of patients with silent ischemia (1.0 mm ST depression without chest pain). Subjects with ECGs that were uninterpretable for exercise-induced ischemia (eg, left bundle branch block) and missed visits were excluded from analysis, resulting in varying numbers of subjects at each time point, as specified in the tables. For each of these proportions, comparisons
among intervention and control groups were made by χ² distribution.

**Results**

Baseline demographic characteristics and test results of all participating subjects are summarized in Table I. The groups were generally well matched with regard to these characteristics with the exception that a greater proportion of subjects in ATLANTIC were considered to have class IV angina compared with PACIFIC. Despite this, medication use, baseline ejection fraction, exercise tolerance, and extent of myocardial ischemia were similar between the 2 studies. Medication use remained relatively constant throughout the study period.

Exercise duration increased in TMR + MEDs subjects in the ATLANTIC study at each follow-up time point and decreased at each point in MEDsTMR so that there was a statistically significant difference between groups (Table II). In PACIFIC, exercise time also increased significantly in the treated PTMR + MEDs group but remained relatively invariant over time in the MEDsPTMR group; nevertheless, the difference between groups was also statistically significant. Maximal exercise heart rate, which averaged ~100 beats/min at baseline (Table I) increased slightly among TMR + MEDs subjects (~6 beats/min, P < .01 vs MEDsTMR), but did not change significantly in either treated or control groups in the PACIFIC study.

The numbers and percentages of subjects exhibiting 1.0 mm ST-segment depression during exercise at various times are presented in Table III. The number of evaluable subjects at each time point—after accounting for deaths (14 in ATLANTIC and 11 in PACIFIC), missed visits, and subjects with left bundle branch block or pacemakers—is also shown in Table III. No differences were observed in the proportion of subjects exhibiting 1.0 mm ST-segment depression in ei-
Among PTMR + MEDs subjects, 1.0 mm ST depression occurred twice as often at 1 year compared with baseline (17% vs 34%, \( P < .05 \)), but this was unchanged in MEDs PTMR subjects over the study duration.

The frequency with which chest pain occurred during treadmill exercise testing is summarized in Table IV. In TMR-treated subjects, the occurrence of chest pain declined progressively from 82% at baseline to 42% at 1 year \( (P < .01) \). MEDs PTMR subjects had a statistically nonsignificant trend toward a reduction in the occurrence of pain (87% to 72%). In the PACIFIC study, both treatment and control groups exhibited modest reductions in the occurrence of chest pain during exercise; these reductions were significant in PTMR + MEDs subjects at each follow-up but significant in MEDs PTMR subjects only at 12 months \( (P < .05) \).

The proportion of patients who had silent ischemia is summarized in Table V. In both TMR and PTMR studies at baseline, the percentage of patients with silent ischemia was approximately 3%. This did not change significantly in MEDs TMR or MEDs PTMR subjects. There was a trend for the percentage of subjects who...
had silent ischemia to increase in TMR + MEDs subjects at 1 year; this was not statistically significant (P = .06) and was the result of silent ischemia occurring in only 5 additional subjects. Despite the increase in number of PTMR + MEDs subjects having 1.0 mm ST-segment depression, this did not result in a significant increase in the proportion with silent ischemia.

Discussion

The observations presented in this report are a sub-analysis of the recently completed multicenter TMR\(^4\) and PTMR\(^7\) trials performed with the same laser system. As reported in the original studies, angina relief, improved quality of life, and improved exercise tolerance were observed in subjects receiving treatment with either TMR or PTMR. Several mechanisms have been considered as contributing to these benefits. The possibility that denervation may contribute to angina relief after these procedures has been supported by biochemical and physiologic evidence derived from prior preclinical\(^{17,18}\) and clinical studies\(^{19}\) and raises the possibility that patients may still have ischemia during exertion but that the ability to sense angina is impaired (silent ischemia\(^{23,24,28}\)). However, the clinical significance of these prior observations has not been assessed.

The major finding of this study was that neither TMR nor PTMR significantly increased the number of subjects with silent ischemia on standardized exercise tests during the year after the procedure. This was true despite increased exercise duration in treated subjects. Although there was a trend for an increased rate of silent ischemia in TMR + MEDs subjects, this was the result of new occurrence in only 5 additional subjects, too small a number to be able to account for the significant reductions in angina reported after the treatment. These data suggest that denervation is not the dominant mechanism by which TMR or PTMR provide symptomatic relief.

To document that enrolled subjects were refractory to maximal medical therapy, it was required of subjects in both the ATLANTIC and PACIFIC studies to have angina during baseline exercise testing performed on maximal antianginal therapy, which most frequently consisted of triple therapy, including β-blockade. It is likely that this protocol limited the proportion of patients exhibiting ST-segment changes. Nevertheless, as documented previously,\(^4,7\) medications were relatively constant throughout the study period. Accordingly, with the attenuation of angina and increased exercise time after TMR or PTMR, greater ECG evidence of ischemia during follow-up evaluations would still be expected if the procedure enhanced silent ischemia.

Other potential mechanisms of therapeutic action for TMR and PTMR are being investigated. The absence of enzymatic or electrocardiographic evidence of myocardial damage after TMR or PTMR suggests that infarction of treated ischemic myocardium does not contribute. It is important to note that the results of all prior unblinded studies of these procedures cannot exclude the contribution of a placebo effect to the purported benefits. Recent results from the DIRECT trial\(^20\) suggest that the entire effect was the result of placebo, whereas the BELIEF trial\(^21\) (which was performed with the exact same laser system as the ATLANTIC and PACIFIC trials) demonstrated a substantial effect of PTMR on angina reduction. The present analysis provides no further clarification of this issue.

Compared with TMR-treated subjects, a greater percentage of PTMR-treated subjects exhibited significant ST-segment depression during peak exercise at 1 year (Table III). In addition, TMR more effectively suppressed pain (82% at baseline vs 42% with pain during exercise at 1 year). These findings suggest a potential advantage of TMR over PTMR for improving clinical status. Consistent with this concept, our prior results have suggested a greater reduction in Canadian Cardiovascular Society Angina score during daily activities.

### Table V. Number of subjects with silent ischemia (no chest pain with ≥1.0 mm ST change) in the treatment and control groups for the ATLANTIC and PACIFIC studies

<table>
<thead>
<tr>
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<th>Baseline n/T</th>
<th>3 months n/T</th>
<th>6 months n/T</th>
<th>12 months n/T</th>
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<tbody>
<tr>
<td><strong>ATLANTIC (%)</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>3/92 (3.3)</td>
<td>4/83 (4.8)</td>
<td>3/76 (3.9)</td>
<td>8/73 (11.0)</td>
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<tr>
<td>Control</td>
<td>3/90 (3.3)</td>
<td>4/78 (5.1)</td>
<td>4/76 (5.3)</td>
<td>3/67 (4.5)</td>
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<tr>
<td><strong>PACIFIC (%)</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>3/109 (2.8)</td>
<td>5/101 (5.0)</td>
<td>5/91 (5.5)</td>
<td>5/87 (5.7)</td>
</tr>
<tr>
<td>Control</td>
<td>4/110 (3.6)</td>
<td>3/99 (3.0)</td>
<td>6/101 (5.9)</td>
<td>5/92 (5.4)</td>
</tr>
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</table>
and a larger increase in exercise tolerance with TMR compared with PTMR.7

In summary, the results of the present study demonstrate that among the >400 candidates for TMR or PTMR, the prevalence of silent ischemia was low during exercise testing performed on medical therapy. Neither TMR nor PTMR caused a significant increase in the extent to which silent ischemia occurred during exercise testing. These findings provide indirect evidence that denervation is not the dominant mechanism underlying the ability of these procedures to relieve angina. In addition, these data suggest better results with the surgical TMR procedure compared with PTMR.

Since the release of the DIRECT trial results, there has been growing concern among cardiologists that the favorable results generated from unblinded studies such as ATLANTIC and PACIFIC may be solely be the result of a placebo effect. Results of the more recently completed BELIEF study suggest a true, beneficial effect of this procedure, at least with the particular laser system used (the same system used in ATLANTIC and PACIFIC). The present results do not provide any further information concerning the potential role of a placebo effect. Although this technique continues to undergo evaluation, a better understanding of the mechanism underlying myocardial laser treatment will help define the place of this modality in the management of patients with otherwise untreatable angina.

References