Sustained Angina Relief 5 Years After Transmyocardial Laser Revascularization With a CO_2 Laser

Keith A. Horvath, MD; Sary F. Aranki, MD; Lawrence H. Cohn, MD; Robert J. March, MD; O. Howard Frazier, MD; Kamuran A. Kadipasaoglu, PhD; Steven W. Boyce, MD; Bruce W. Lytle, MD; Kevin P. Landolfo, MD; James E. Lowe, MD; Brack Hattler, MD; Bartley P. Griffith, MD; Allan M. Lansing, MD, PhD

Background—Although transmyocardial laser revascularization (TMR) has provided symptomatic relief of angina over the short term, the long-term efficacy of the procedure is unknown. Angina symptoms as assessed independently by angina class and the Seattle Angina Questionnaire (SAQ) were prospectively collected up to 7 years after TMR.

Methods—Seventy-eight patients with severe angina not amenable to conventional revascularization were treated with a CO_2 laser. Their mean age was 61±10 years at the time of treatment. Preoperatively, 66% had unstable angina, 73% had had ≥1 myocardial infarction, 93% had undergone ≥1 CABG, 42% had ≥1 PTCA, 76% were in angina class IV, and 24% were in angina class III. Their average pre-TMR angina class was 3.7±0.4.

Results—After an average of 5 years (and up to 7 years) of follow-up, the average angina class was significantly improved to 1.6±1 (P=0.0001). This was unchanged from the 1.5±1 average angina class at 1 year postoperatively (P=NS). There was a marked redistribution according to angina class, with 81% of the patients in class II or better, and 17% of the patients had no angina 5 years after TMR. A decrease of ≥2 angina classes was considered significant, and by this criterion, 68% of the patients had successful long-term angina relief. The angina class results were further confirmed with the SAQ; 5-year SAQ scores revealed an average improvement of 170% over the baseline results.

Conclusions—The long-term efficacy of TMR persists for ≥5 years. TMR with CO_2 laser as sole therapy for severe disabling angina provides significant long-term angina relief. **(*Circulation*. 2001;104[suppl I]:I-81-I-84.)**

Key Words: laser ■ revascularization ■ coronary disease ■ angina

Since 1993, >6000 patients around the world have undergone transmyocardial revascularization (TMR) with a CO_2 laser. This procedure is designed to treat patients with severe disabling angina due to end-stage coronary disease. Typically, the patients are in Canadian Cardiovascular System (CCS) angina class III or IV at the time of treatment. Recently, randomized controlled trials that compared the effects of surgical TMR with those of maximal medical management were published.[1–4] In these reports, TMR was shown to significantly relieve angina, improve quality of life, increase exercise tolerance, and reduce hospital admissions for >800 patients. For patients with stable angina, this benefit was accomplished with a low perioperative mortality rate (1% to 3%).[1–4] As a result, surgical TMR received Food and Drug Administration approval.

In an attempt to further decrease the morbidity rate of this procedure while attempting to obtain the same clinical results, percutaneous transmyocardial laser revascularization (PMR) was used in trial.[5–7] These recent reports have indicated some improvement with regard to symptoms and exercise tolerance at 6 months to 1 year after PMR.[5–7] However, in the only double-blinded, randomized controlled trial,[6] there was no difference between the placebo group and the PMR-treated group. This has raised the question of whether the clinical results from laser revascularization were largely a placebo effect. We collected data on 78 patients who underwent CO_2 TMR an average of 5 years ago and report on their clinical status and angina class postoperatively.

Methods

From 1993 to 1996, patients were enrolled in phase II and phase III Food and Drug Administration–approved trials at 8 institutions across the United States. All sites had approval from local institutional review boards, and informed consent was obtained before enrollment. The original selection criteria were that the patient (1) be in CCS angina class III or IV, (2) be >18 years old, (3) have an ejection fraction of ≥20%, (4) have evidence of reversible ischemia, and (5) not be candidates for CABG or PTCA. Patients had their baseline angina class assessed by their cardiologist and the investigator and further confirmed with the self-administered Seattle

From the Northwestern University Medical School (K.A.H.), Chicago, Ill; Brigham and Women's Hospital (S.F.A., L.H.C.), Boston, Mass; Rush-Presbyterian-St Luke's Medical Center (R.J.M.), Chicago, Ill; Texas Heart Institute (O.H.F., K.A.K.), Houston, Tex; Washington Hospital (S.W.B.), Washington, DC; Cleveland Clinic (B.W.L.), Cleveland, Ohio; Duke University Hospital (K.P.L., J.E.L.), Durham, NC; University of Pittsburgh Hospital (B.H., B.P.G.), Pittsburgh, Pa; and Norton Audubon Hospital (A.M.L.), Louisville, Ky.

Correspondence to Keith A. Horvath, MD, Division of Cardiothoracic Surgery, Northwestern University Medical School, 201 E Huron St, Galter 10-105, Chicago, IL 60611. E-mail khorvath@nmh.org

© 2001 American Heart Association, Inc.

Circulation **is available at http://www.circulationaha.org**

Baseline Patient Characteristics

Age, y	61±10.3 (range 30–83)
Sex, % male	79
Unstable angina, %	66
History of smoking, %	83
Hypertension, %	66
Hypercholesterolemia, %	68
Diabetes, %	28
Cardiac history, mean±SD (range; %)	
Previous myocardial infarctions	1.9±1.1 (1–6; 73)
Previous CABG	1.5±0.60 (1–3; 93)
Previous PTCA	2.5±2.6 (1–12; 44)

Angina Questionnaire. Details of the enrollment, baseline, and 1-year follow-up data were previously reported.[2,8] From that original enrollment, 195 patients underwent TMR an average of 5 years before this report. Patients who died or who underwent an additional revascularization procedure were not included in the present analysis. Forty-one patients (21%) died during the first year after TMR. Of these patients, 28 died of cardiovascular causes, 9 of noncardiovascular causes, and 4 of unknown causes. Sixteen patients underwent an additional revascularization procedure during the first year. Therefore, for this report of long-term follow-up, 138 patients remained. Between the previous reports[2,8] of 1 year and this report, an additional 41 patients died (21 of cardiovascular causes, 18 of noncardiovascular causes, and 1 of unknown cause). Seventeen patients underwent revascularization procedures in the interim. Of the 80 remaining patients, 2 were lost to follow-up. The results for the remaining 78 patients, who underwent their TMR procedure an average of 5 years earlier, were collected. This long-term follow-up was performed in the first quarter of 2000, and the maximum follow-up period for these patients was 7.2 years. Interviews were conducted by research coordinators at the individual sites. The results of the angina class status were confirmed by contacting the patient's physician and by repeating the self-administered Seattle Angina Questionnaire as needed. A comparison between the patients' status at baseline, at 1 year, and then at an average of 5 years is reported.

The patient demographics are outlined in the Table. As noted, these patients had a significant incidence of cardiac risk factors, as well as previous myocardial infractions and prior conventional revascularizations.

TMR Technique

The surgical technique of CO_2 TMR (PLC Medical Systems) has been previously described.[8] With the patient under general anesthesia, transmural channels of ≈1-mm diameter were created with a single pulse of the CO_2 laser (peak power 850 W) through the myocardium of the left ventricle. Approximately 1 channel was created per square centimeter of myocardial surface. Complete transmural penetration by the laser was confirmed with intraoperative transesophageal echocardiography. All areas of reversible ischemia were targeted for treatment.

Statistical Analysis

Analyses were performed with a 2-sided standard *t* test, and paired *t* test was used for normally distributed continuous variables. The appropriateness of this analysis was confirmed by performing a marginal homogeneity test that compared the baseline with the long-term follow-up. $P<0.05$ is considered to indicate statistical significance (SAS Software, Version 6.12; SAS).

Results

Seventy-eight patients underwent CO_2 TMR as sole therapy for their disabling angina an average of 5 years earlier. The data collected represent 359 years of patient follow-up. To accurately assess the durability of angina relief over the long term for these patients, only those who survived and did not have additional revascularization procedures were included in this analysis. Of note, there were no differences in outcomes on the basis of the number of channels created, the site at which the patient was enrolled, or the investigator who performed the procedure.

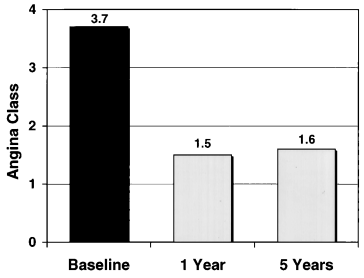


Figure 1. Average CCS angina class at baseline and 1 and 5 years of follow-up. $P=0.0001$ for baseline vs 1 or 5 years. P=NS for 1 vs 5 years.

TMR Results

Intraoperatively, 20±8 channels (range, 13 to 44 channels) were created as confirmed with transesophageal echocardiography. There were no intraoperative deaths. The median stay in the intensive care unit was 2 days, and the median hospital stay was 8 days.

Angina Class

The majority of the patients (74%) were in angina class IV and the remainder (26%) were in class III at baseline, for an average angina class of 3.7±0.4 (Figure 1). At 1-year follow-up, the angina class distribution was markedly different, with 81% of the patients having no angina or being in CCS class I or II. The average angina class at 1 year was 1.5±1.1 (Figure 1). The distribution of the same patients at 5 years was not significantly changed, with 80% of the patients having no angina or being in class I or II. The average angina class at 5 years is 1.6±1.1, which is unchanged from the 1-year follow-up (P=NS).

Although these figures depict the change in angina class for the group, a comparison of angina class status for each patient versus the baseline can also be measured by considering the degree of reduction in angina class for each patient. The majority of these patients had a >2 angina class reduction at both 1 and 5 years ($P=0.001$). The distribution of patients according to their decrease in angina class is depicted in Figure 2. At 1 year, 77% of the patients had a ≥2 angina class decrease, with only 1% having an increase (Figure 2A). Again, this is unchanged when values for these patients at 5 years are compared with the baseline values (68% of the patients had the same anginal improvement) (P=NS) (Figure 2B). Only 1% had an increase in angina class at 5 years.

Seattle Angina Questionnaire

For the 5 parameters measured via the Seattle Angina Questionnaire, the long-term follow-up indicates significant improvement in exercise capacity, angina stability, angina

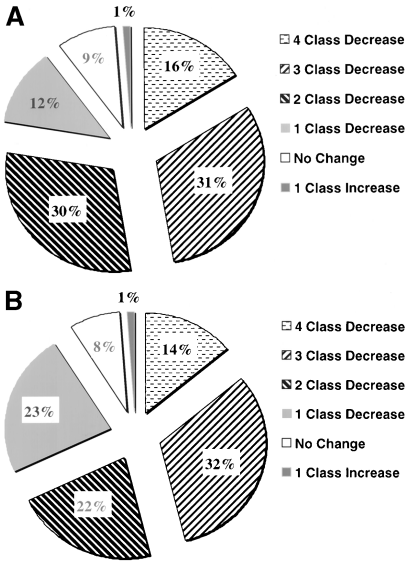


Figure 2. Distribution of patients by decrease in CCS angina class vs baseline at 1 year (A) and at 5 years (B). P=NS for 1 year vs 5 years.

frequency, treatment satisfaction, and disease perception. This improvement is reflected in a significant increase in Seattle Angina Questionnaire scores ($P<0.001$ versus baseline for all scores) (Figure 3). The percentage increase from baseline to 5 years for the majority of these scores was 150% to 250%.

Discussion

The short-term ability of TMR to provide angina relief has been previously demonstrated.[1–4,8] These previous reports from randomized controlled trials demonstrate significant symptomatic relief, improved exercise tolerance, and improved quality of life for laser-treated patients versus patients who continued their maximal medical therapy. These trials reported on the results at 12 months, and although these results were significant then, it is noteworthy that the same symptomatic improvement has been documented now, up to 7 years postoperatively.

The limitations of the present study include the lack of a control group against which to measure the symptomatic improvements that were seen. A significant improvement has been previously demonstrated in a randomized controlled trial.[2] In that study, patients who continued their maximum medical therapy had a similar 1-year mortality rate and revascularization rate and no significant improvement in angina class or Seattle Angina Questionnaire scores compared with CO_2 TMR–treated patients. Whether these medical management patients would have improved at 5 years is unknown. Also, as noted earlier and confirmed by this study, TMR provides an improvement in quality of life but does not confer a survival benefit. Finally, the angina class assessment is subjective but was performed by research coordinators who were not in contact with the patient between the protocol-mandated 1-year follow-up and the long-term follow-up reported here. The assessments that were made were confirmed by the patient's physician in an attempt to eliminate bias. No investigators performed the assessments. This study was also conducted with patients who were prospectively enrolled but retrospectively contacted for follow-up. Additional prospective studies with objective measurements are planned for the future.

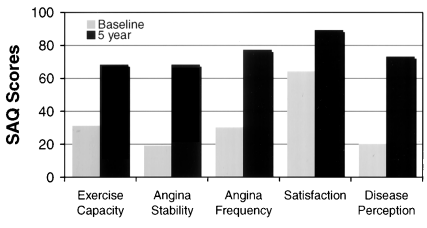


Figure 3. Seattle Angina Questionnaire Scores at baseline vs 5 years. $P<0.0001$ for all scores for baseline vs 5 years.

This report documents the longest follow-up period for TMR with CO_2 laser. Recently, 3-year results after TMR with an Ho:YAG laser were reported.[9] Patients in the Ho:YAG study met the same inclusion criteria and had the same baseline demographics as those in our study. Significant short-term angina relief at 1 year was also documented with the Ho:YAG device. The average angina class was 3.5 ± 0.5 at baseline and 1.8 ± 0.8 at 1 year ($P<0.01$). However, in distinction to the CO_2 TMR results, the average angina class at 3 years after Ho:YAG TMR had significantly increased to 2.2 ± 0.7 ($P=0.003$ versus 1 year). In addition, at 3 years, only 30% of the patients had a 2–angina class improvement compared with their baseline, and 70% had only a 1-class improvement. This is a marked contrast to the CO_2 laser results, which demonstrated that 68% of the patients had a $\geq$2–angina class improvement and 23% had a 1–angina class improvement after 5 years. This loss of clinical effectiveness seen with an Ho:YAG laser has also been noted in a direct clinical comparison.[10,11] In a review of 460 patients treated by a single investigator who used both devices, the angina improvement seen with CO_2 laser was greater than that seen with Ho:YAG laser.[11] At 12 months, the majority of the CO_2 patients were in class I or were angina free, whereas the majority of the Ho:YAG patients were in class II. There is a significant difference in the laser tissue interaction between the CO_2 and Ho:YAG lasers. The CO_2 laser is able to create a transmural channel with a single pulse and with minimal collateral damage. The Ho:YAG laser requires multiple pulses to create a channel, and with each pulse, an explosion occurs at the tissue level. This increases the collateral damage and creates a photoacoustic effect in which shock waves of energy are transmitted through the myocardium. In addition, the Ho:YAG laser energy is delivered via fiber. This fiber is manually advanced through the myocardium during Ho:YAG TMR. It is difficult to ensure that the injury induced is not primarily mechanical in nature rather than due to laser ablation of the tissue. This increased damage with the Ho:YAG laser has been demonstrated experimentally.[12]

More recently, results from various PMR trials have been reported.[5–7] With PMR, an Ho:YAG laser and a catheter-based delivery system are used; the laser fiber is placed against the endocardium and fired, creating a nontransmural 3- to 4-mm depression in the subendocardial layer.[5–7] In a randomized controlled trial that compared PMR with maxi-

mal medical therapy, the results at 12 months indicate a significant increase in exercise tolerance and a decrease in symptoms for PMR-treated patients.[5] However, the symptomatic improvement with PMR was not as great as had been seen with TMR, with only 34% of the patients in angina class II or lower. Also, the improvement in exercise tolerance was less in PMR-treated patients, with an average increase of 90 seconds for the PMR-treated patients and 150 seconds for the TMR-treated patients.[5] This comparison of PMR with TMR indicates that the revascularization is more effective with TMR.

One advantage that the PMR trials have over the surgical TMR trials is the ability to perform a double-blind randomized placebo-controlled trial. The catheter is placed against the subendocardium and the laser is not fired. Recent reports of the 6-month data for such a trial[6] indicated that the placebo group had the same results as the PMR-treated group. There was no difference in exercise tolerance at 6 months between the groups, despite a significant increase in exercise tolerance for each group versus the baseline value. Of the placebo group, 42% achieved a >2–angina class reduction in symptoms at 6 months. These results further confirm the lack of effectiveness of PMR and are noteworthy in that this trial used an intraventricular mapping system that allowed for optimal localization of the catheter.

The significant improvement in the PMR placebo group suggests that the placebo effect may be an important mechanism of surgical TMR results as well. Unfortunately, it is impossible to run a double-blind surgical trial. Patient expectations with a surgical procedure may generate a placebo effect. Previous placebo-controlled surgical trials have demonstrated an average 35% to 40% improvement.[13,14] These investigators investigated the surgical treatment of angina pectoris by internal mammary artery ligation. Patients were randomized to mammary ligation or to a sham operation in which they received only a skin incision. A symptomatic improvement was seen for both groups and is similar to what has been seen with PMR but is less than what has been reported for TMR; more important, the benefit was largely erased by 9 months and gone at 1 year. Although the present report of long-term benefit argues against a placebo effect, more salient and objective data have also been obtained. In addition to the symptomatic improvement, CO_2 TMR has been demonstrated in numerous studies to improve myocardial perfusion by nuclear SPECT scans[1–2,8] and by PET scans.[15] A significant decrease in the number of reversible or ischemic myocardial defects without an increase in the number of fixed or infarcted areas has been demonstrated with the CO_2 laser in comparisons of TMR-treated patients both with their baseline values and with patients randomized to medical management.[1,2] Further evaluation using other objective measures, such as dobutamine stress echocardiography[16] and CINE and contrast-enhanced MRI,[17] shows an improvement in myocardial function and a decrease in myocardial ischemia without an increase in myocardial infarction in patients treated with CO_2 TMR. This evidence is not subject to the placebo effect and has been analyzed by readers blinded to the treatments that the patients received. In the only Ho:YAG TMR report that followed myocardial perfusion, no improvement was seen.[4]

Conclusions

The long-term follow-up of patients with severe disabling angina treated with CO_2 TMR reveals sustained angina relief over 5 years (and up to 7 years) postoperatively. The average angina class improvement and distribution at 5 years were not significantly changed from the results seen at 1 year postoperatively. These angina class results were confirmed by a significant improvement in Seattle Angina Questionnaire scores.

References

1. Schofield PM, Sharples LD, Caine N, et al. Transmyocardial laser revascularization in patients with refractory angina: a randomized controlled trial. *Lancet*. 1999;353:519–524.
2. Frazier OH, March RJ, Horvath KA. Transmyocardial revascularization with a carbon dioxide laser in patients with end-stage coronary artery disease. *N Engl J Med*. 1999;341:1021–1028.
3. Burkhoff D, Schmidt S, Schulman SP, et al. Transmyocardial laser revascularization compared with continued medical therapy for treatment of refractory angina pectoris: a prospective randomized trial. *Lancet*. 1999;354:885–890.
4. Allen KB, Dowling RD, Fudge TL, et al. Comparison of transmyocardial revascularization with medical therapy in patients with refractory angina. *N Engl J Med*. 1999;341:1029–1036.
5. Oesterle SN, Sanborn TA, Ali N, et al. Percutaneous transmyocardial laser revascularization for severe angina: the PACIFIC randomized trial. *Lancet*. 2000;356:1705–1710.
6. Leon MB, Baim DS, Moses JW, et al. A randomized blinded clinical trial comparing percutaneous laser myocardial revascularization (using Biosense LV mapping) vs placebo in patients with refractory coronary ischemia. *Circulation*. 2000;102(suppl II):II-565. Abstract.
7. Stone GW, Rubinstein P, Schmidt D, et al. A prospective, randomized, multicenter trial of percutaneous transmyocardial laser revascularization in patients with non-recanalizable chronic total occlusions. *Circulation*. 2000;102(suppl II):II-689. Abstract.
8. Horvath KA, Cohn LC, Cooley DA, et al. Transmyocardial laser revascularization: results of a multi-center trial using TLR as sole therapy for end- stage coronary artery disease. *J Thorac Cardiovasc Surg*. 1997;113:645–654.
9. De Carlo M, Milano AD, Pratali S, et al. Symptomatic improvement after transmyocardial laser revascularization: how long does it last? *Ann Thorac Surg*. 2000;70:1130–1133.
10. Lansing AM. Transmyocardial revascularization: mechanism of action with CO_2 and Ho:YAG lasers. *J Thorac Cardiovasc Surg*. 1998;115:1392.
11. Lansing AM. Transmyocardial revascularization: late results and mechanisms of action. *J Ky Med Assoc*. 2000;98:406–412.
12. Kadipasaoglu KA, Sartori M, Takafumi M, et al. Intraoperative arrhythmias and tissue damage during transmyocardial laser revascularization. *Ann Thorac Surg*. 1999;67:423–431.
13. Cobb LA, Thomas GI, Dillard DH, et al. An evaluation of internal-mammary-artery-ligation by a double-blind technic. *N Engl J Med*. 1959;260:1115–1118.
14. Dimond EG, Kittle CF, Crockett JE. Comparison of internal mammary ligation and sham operation for angina pectoris. *Am J Cardiol*. 1960;5:483–486.
15. Frazier OH, Cooley DA, Kadipasaoglu KA, et al. Myocardial revascularization with laser: preliminary findings. *Circulation*. 1995;92(suppl II):II-58–II-65.
16. Donovan CL, Landolfo KP, Lowe JE, et al. Improvement in inducible ischemia during dobutamine stress echocardiography after transmyocardial laser revascularization in patients with refractory angina pectoris. *J Am Coll Cardiol*. 1997;30:607–612.
17. Horvath KA, Kim RJ, Judd RM, et al. Contrast enhanced MRI assessment of microinfarction after transmyocardial laser revascularization. *Circulation*. 2000;102(suppl II):II-765. Abstract.