

## Clinical Studies of TMR with the CO<sub>2</sub> Laser

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### ABSTRACT

**Objective:** This paper reviews the current status of transmural laser revascularization by a carbon dioxide laser. **Summary:** Since 1990 over 3000 patients worldwide have been treated with a carbon dioxide laser. A nonrandomized phase II trial was completed in 1995. A randomized controlled phase III trial has completed enrollment, and analysis of the follow-up is pending. **Methods:** In each trial 200 patients with endstage coronary artery disease and severe disabling angina that was not amenable to conventional revascularization were enrolled. Preoperative evaluation included confirmation of angina class and evidence of reversible ischemia based on myocardial perfusion scans. Repeat evaluations were done postoperatively at 3, 6 and 12 months. **Results:** 80% of the patients showed a significant improvement in angina class status postoperatively and 30% had no angina at one year of follow-up. Concomitant with this there was significantly less ischemia noted on follow-up perfusion scans. **Conclusions:** Early results from nonrandomized and randomized controlled trials of transmural laser revascularization by carbon dioxide laser indicate that this technique provides an angina relief and improved perfusion in patients with end-stage coronary artery disease.

### INTRODUCTION

The direct perfusion of the heart by transmural channels has been postulated and attempted by a variety of means. Evidence for the feasibility of this type of perfusion exists in human and reptilian anatomy. Human hearts have sinusoidal connections between the ventricular cavity and the coronary vasculature. First described by Wearn, these connections were noted to be endothelial-lined and analogous to the channels seen in snake hearts.<sup>1</sup> The snake myocardium is primarily supplied by multiple interconnecting sinusoids that arise from the ventricle. Only a thin rim of tissue at the epicardial surface is supplied by a rudimentary coronary arterial system.

Attempts to revascularize the heart by direct perfusion were described first by Beck and later by Vineberg.<sup>2,3</sup> The success of Vineberg's technique of internal mammary artery implantation demonstrated that direct perfusion was possible and even led to neovascularization and collateral formation. With these findings and an understanding of the snake heart, Sen and others performed direct perfusion by transmural acupuncture.<sup>4-11</sup> The limited success of these procedures was overshadowed by the discovery of the ability to perform coronary artery bypass grafting (CABG). Interest in direct perfusion has resurfaced as there is a growing number of patients who cannot be treated by either CABG or percutaneous transluminal coronary angio-

plasty (PTCA). A new technique, transmural laser revascularization (TMR), has been developed to treat these patients. The mechanical trauma that resulted in poor long-term patency of transmural acupuncture was overcome, in theory, by the use of a laser to create the channels. The laser channels are a result of tissue ablation with minimal damage, as opposed to the traumatic holes made by needle acupuncture. Mirohseini first employed a laser to perform this type of revascularization and it was used in conjunction with coronary artery bypass grafting in a number of patients in the early 1980s.<sup>12-16</sup> The laser he used was relatively low-powered and, therefore, required an arrested heart. While his results seemed encouraging, it proved difficult to assess the contribution of laser revascularization when combined with CABG. In time, a laser to perform the procedure on the beating heart was developed and this allowed the introduction of TMR as sole therapy for unreconstructable coronary artery disease.

### CLINICAL EXPERIENCE

Currently, three different wavelengths of laser light are being employed clinically to perform TMR: Holmium:YAG, excimer, and CO<sub>2</sub>. The largest series with the longest follow-up has employed the CO<sub>2</sub> laser. Since 1990, more than 3,000 patients

worldwide have been treated with this laser. After an initial study of 15 patients that established the safety of the procedure, a multicenter, non-randomized study was performed on 200 patients.<sup>17</sup> The entry criteria for this study were patients with severe angina that was refractory to medical therapy. They had to have evidence of reversible ischemia. Additionally, they could not be candidates for PTCA, CABG or heart transplantation. Preoperatively, the patients' recent angiograms were reviewed to confirm that they were not candidates for conventional revascularization. Additionally, their anginal class was assessed and their anti-anginal medications were reviewed, as were their admissions to the hospital for angina in the year prior to the procedure. To evaluate the extent and severity of their ischemia, all patients underwent myocardial perfusion scans at rest and with stress. Following the documentation of a significant area of reversible ischemia, the patients were enrolled in the study. Eighty percent of the patients were men and they had an average age of 63 years (range 35–85 years of age). Eighty percent had had a previous CABG and many had had two or three previous bypass operations. Also, 40% of the patients had had a prior PTCA and, in some cases, up to 11 previous angioplasties. Ninety percent of the patients had unstable angina at the time of enrollment. Thirty-five percent had diabetes and seventy percent were hypertensive. The patient's average ejection fraction was 47% (range 15%–77%). All of the patients were in CCS anginal class III (20%) or IV (80%).

Intraoperatively, the patients had a transesophageal echocardiography (TEE) probe inserted. With the patients in a 45° right lateral decubitus position, an anterior thoracotomy was performed through the fifth intercostal space.

The patients received an average of 25 channels, confirmed to be transmural by TEE. The average laser pulse energy was 43 J with a pulse width of 50 milliseconds. The average operative time was two hours with a laser time of 20 minutes. The 1 mm channels were created in a distribution of approximately one per square centimeter. Hemorrhage from the channels was controlled with direct finger pressure or an epicardial suture if pressure was inadequate. The majority of the patients were extubated in the operating room or within the first 18 hours postoperatively. The patients spent an average of two days in the intensive care unit and eight days in the hospital.

While there were no intraoperative laser-induced arrhythmias, early morbidity included a 10% incidence of atrial fibrillation and a 2% incidence of myocardial infarction. Seven of the 200 patients had intraaortic balloon pumps placed intraoperatively or in the initial postoperative period. One patient suffered chordae tendinae rupture as a result of the laser. Mitral regurgitation was noted intraoperatively, and the patient underwent mitral valve repair and was discharged without further complication. The early mortality was 9% and the majority of these deaths was cardiac in nature. All of the patients who died early had unstable angina preoperatively and 15 of the 18 had had a prior CABG. Additionally, patients with ejection fractions <40% and who were older than 80 years were more likely to suffer perioperative mortality. All of the patients were followed for one year, and the late mortality was an additional 9%. Again, an ejection fraction <40% and an age >80 years were independent risk factors of late mortality. There was a 4% reduction in the perioperative mortality from the first 100 patients to the second 100 patients enrolled (11% to 7%). This re-

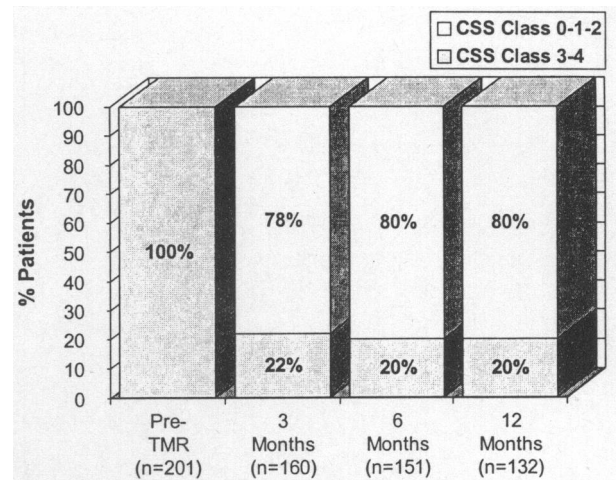


FIG. 1. Phase II angina pectoris class improvement post-TMR.

duction was due to improved patient selection. Postoperatively, the average length of stay in the intensive care unit was two days, with an average hospital stay of seven days.

The patients returned for evaluation at three, six, and twelve months after the procedure. At these times, they underwent repeat radionuclide perfusion scans, had their quality of life and angina classes reassessed, and had their admissions for angina and anti-anginal medications reviewed. The overall survival was 83% at one year.

Preoperatively, the average angina class was 3.8. This improved to 1.46 at three months, 1.36 at six months and 1.44 at twelve months. The distribution of patients according to angina class reflects this improvement (Fig. 1). One hundred percent of the patients were in angina class III or IV preoperatively. Eighty percent of the patients dropped at least two angina classes and thirty percent had no angina at each of the intervals postoperatively. Perfusion scans demonstrated a significant improvement in left ventricular perfusion at six and twelve months (Fig. 2). This decrease in the number of reversible defects was not accompanied by an increase in the number of fixed defects. In comparison, there was no significant difference in the number of fixed or reversible defects in the septum over the twelve months of follow-up. At one institution, perfusion was studied using PET scanning.<sup>18</sup> In this study, subendocardial and subepicardial perfusion were compared. There was

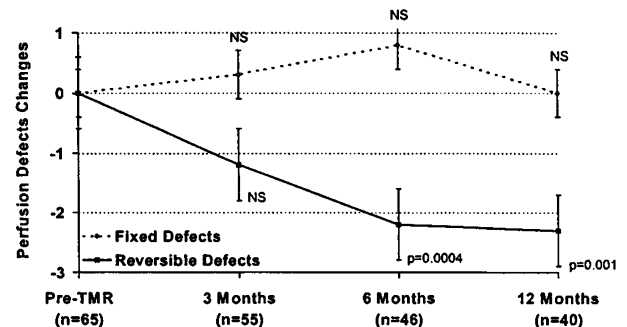


FIG. 2. Phase II Left ventricular perfusion by SPECT. Significant decrease in ischemia after TMR.

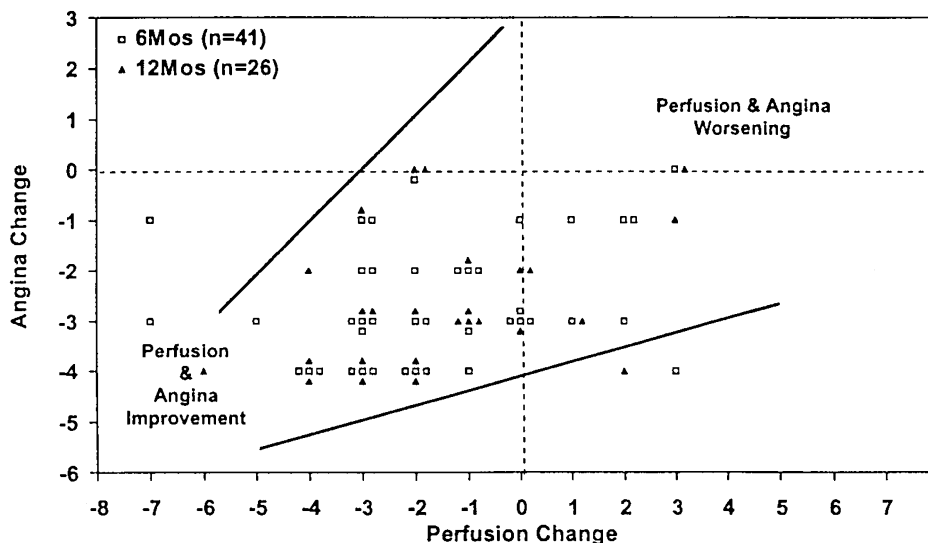


FIG. 3. Phase II Correlation of angina and perfusion changes in patients at 6 and 12 months post-TMR.

a significant improvement in perfusion overall and this was most noticeable in the subendocardial region. Again, when comparing the septum to the left ventricular free wall, there was no change in the resting perfusion of the septal region, whereas there was an improvement in the resting perfusion in the left ventricular free wall. Figure 3 demonstrates the correlation between the angina and perfusion changes. The majority of the patients exhibited an improvement in perfusion and a corresponding improvement in angina class at six and twelve months.

The patients' dosage and usage of nitrates, calcium channel blockers, and beta blockers were monitored throughout the study. All patients were initially re-started on their preoperative medications immediately after the procedure. At one year, 56% of the patients had decreased their usage of these cardioactive medications and 19% had increased their medications.

Because of their endstage coronary disease, these patients were frequently admitted to the hospital for angina. In the year before their transmyocardial laser revascularization, the patients averaged 2.5 admissions for angina. This average decreased to .5 admissions for angina after treatment ( $p > 0.001$ ).

Of note, some patients (15) during the study as well as after the one-year follow-up have undergone additional procedures such as PTCA, CABG or transplant. These patients underwent an additional intervention to treat progression of their disease in their native vessels, in their previous bypass grafts, or as a result of progressive heart failure. Follow-up of patients longer than one year has been reported by individual institutions.<sup>19</sup> The results in these smaller groups of patients have been similar to those seen at one-year follow-up.

Following this, a Phase III trial was started with the same inclusion criteria. But patients enrolled were randomized 1:1 to receive either transmyocardial laser revascularization or continued medical therapy. One hundred and ninety-eight patients were enrolled in this study and were to be followed for one year. The demographics for this study show no difference between the laser group and the medical management group. The average age was 62 years. Ninety percent had undergone a pre-

vious bypass operation, and fifty percent had undergone a previous angioplasty. Forty-five percent have diabetes and sixty percent have hypercholesterolemia. The average ejection fraction is 50% (range 21%–75%). All of the patients were in angina class III or IV at enrollment.

Intraoperatively, patients received an average of 30 channels confirmed by TEE. The median ICU stay was two days and hospital stay eight days. At six months of follow-up, 70% of the patients treated with the laser showed a decrease of at least two angina classes, whereas only 8% of the medical management control group showed a significant improvement in angina class. 30% of the control group had a significant worsening of angina over the period of follow-up. Forty-eight percent of the laser group had a significant decrease in their use of beta blockers, calcium channel blockers, or nitrates over the period of follow-up. In contrast, only one patient in the control group had a significant decrease in his usage of these medications. Event-free survival for death, as well as unstable or class IV angina, at six months was 73% for the TLR group versus 12% for the medical management group ( $p = 0.0001$ ). Quality of life indices increased an average of 130% for patients undergoing TLR compared to no change in the medical management group. The final analysis of the SPECT perfusion data is pending, but preliminary results indicate less ischemia in a follow-up for patients treated with the laser compared to those in the control group.

There was a 6% mortality for the medical patients within the first 30 days of enrollment in the trial. Patients with development of unstable angina were allowed to cross over from the medical group to the laser group. There was a 12% perioperative mortality for this crossover group compared to a 4% perioperative mortality for patients having TLR initially. The crossover patients were, by definition, patients who had not only failed medical therapy but had suffered an acute myocardial infarction and had developed post-infarction angina, or whose angina was unstable and only controlled by intravenous medications. This instability contributed to the higher perioperative mortality in the crossover group.

Final analysis and publication of these Phase III data are forthcoming. At present, the United States Food and Drug Administration is allowing patients to be treated with TLR and, as 100 patients have been enrolled and followed in the medical control group, the randomization has been stopped. Final review and approval of TLR based on these studies is pending.

A retrospective analysis of patients with Class III or IV angina, who were either treated medically or underwent CABG, CABG  $\pm$  PTCA, or PTCA alone, were compared to 100 patients from the same institution who underwent TMR with the CO<sub>2</sub> laser. Angina improvement was the same for TMR, CABG  $\pm$  PTCA, or PTCA alone. The degree of improvement in patients treated with any of these therapies was significant versus improvement in patients treated with medical therapy alone ( $p > 0.001$ ). Mortality at six and twelve months was less than 7% in patients treated with CABG  $\pm$  PTCA or PTCA alone, but was 12% in patients treated with TMR ( $p < 0.05$ ). Mortality in the medical group was 14%. While mortality was the same in the laser-treated and medical-treated groups, the patients treated with the laser had a significant reduction in angina.<sup>20</sup>

In addition to these clinical studies, autopsy studies have been performed on patients who have undergone TMR. One case report demonstrated patent channels in a patient three months after laser therapy.<sup>21</sup> Additional autopsy results from patients who died at 3, 16, and 150 days after TMR have been described.<sup>22</sup> In these cases, 80%–95% of the channels that had been created were found. Early, different stages of wound healing, related to the laser channels, were noted. At day 150 postoperative, the laser-created channels showed scarring as well as an extensive capillary network. Patent or endothelialized channels were not demonstrated in this group of patients who, clinically, were noteworthy for their lack of response to TMR. The patients demonstrated no significant improvement in angina status either short-term or long-term. This same group has demonstrated evidence of blood flow through the patent channels intraoperatively and up to 544 days postoperatively with the use of transesophageal echocardiography. Again, patients who had evidence of doppler blood flow through the channels were “responders” and had a significant clinical improvement in their angina after TMR. Patients whose channels could not be identified were also clinically “nonresponders.”

For these patients with severe coronary artery disease, early postoperative management can be difficult. They should not be treated as being revascularized as they would be if they had undergone a CABG. As a result, postoperative pain control is important and the use of a thoracic epidural can be beneficial. Likewise, some of the morbidity in undergoing TMR can be diminished by performing the operation thoracoscopically. I have performed this procedure with the use of standard thoracoscopic equipment and the carbon dioxide laser and its hand pieces.

## CONCLUSION

Transmyocardial laser revascularization has been shown to improve angina status in patients for whom no other option is available. Clinical studies with the carbon dioxide laser—both

non-randomized and randomized—have yielded similar results regarding this angina class improvement. Perfusion scans have also demonstrated a decrease in the amount of ischemia in these patients. Completion of the randomized controlled study and further investigations are necessary to confirm these findings and to further elucidate the mechanism of TMR.

## REFERENCES

1. Wearn, J.T., Mettier, S.R., Klumpp, T.G., and Zschesche, L.J. (1993) The nature of vascular communications between the coronary arteries and the chambers of the heart. *Am. Heart J.* 9, 143–164.
2. Becks, C.S. (1935) The development of a new blood supply to the heart by operation. *Annals of Surgery* 102, 801–813.
3. Vineberg, A. (1954) Clinical and experimental studies in the treatment of coronary artery insufficiency by internal mammary artery implant. *Jour. Int. Coll. Surgeons* 22, 503–518.
4. Massimo, C. and Boffi, L. (1957) Myocardial revascularization by a new method of carrying blood directly from the left ventricular cavity into the coronary circulation. *J. Thorac. Surg.* 34, 257–264.
5. Goldman, A., Greenstone, S.M., and Preuss, F.S. (1956) Experimental methods for producing a collateral circulation to the heart directly from the left ventricle. *J. Thorac. Surg.* 31, 364–374.
6. Sen, P.K., Udwardia, T.E., Kinare, S.G., and Parulkar, G.B. (1965) Transmyocardial acupuncture: A new approach to myocardial revascularization. *J. Thorac. Cardiovasc. Surg.* 50, 181–189.
7. Khazei, A.H., Kime, W.P., Papadopoulos, C., and Cowley, R.A. (1968) Myocardial canalization: A new method of myocardial revascularization. *Ann. Thorac. Surg.* 6, 163–171.
8. Walter, P., Hundeshagen, H., and Borst, H.G. (1971) Treatment of acute myocardial infarction by transmural blood supply from the ventricular cavity. *European Surgical Research* 3, 130–138.
9. Pifarré, R., Jasuja, M.L., Lynch, R.D., and Neville, W.E. (1969) Myocardial revascularization by transmyocardial acupuncture: A physiologic impossibility. *J. Thorac. Cardiovasc. Surg.* 58, 424–431.
10. Wakabayashi, A., Little, S.T., and Connolly, J.E. (1967) Myocardial boring for the ischemic heart. *Arch. Surg.* 95, 743–752.
11. Anabtawi, I.N., Reigler, H.F., and Ellison, R.G. (1969) Experimental evaluation of myocardial tunnelization as a method of myocardial revascularization. *J. Thorac. Cardiovasc. Surg.* 58, 638–646.
12. Mirhoseini, M., and Cayton, M.M. (1981) Revascularization of the heart by laser. *J. Microsurg.* 2, 253–260.
13. Mirhoseini, M., Fisher, J.C., and Cayton, M.M. (1983) Myocardial revascularization by laser: A clinical report. *Lasers Surg. Med.* 3, 241–245.
14. Mirhoseini, M., Shelgikar, S., and Cayton, M.M. (1988) New concepts in revascularization of the myocardium. *Ann. Thorac. Surg.* 45, 415–420.
15. Mirhoseini, M., Muckerheide, M., and Cayton, M.M. (1982) Transventricular revascularization by laser. *Lasers Surg. Med.* 2, 187–198.
16. Mirhoseini, M., Cayton, M.M., and Shelgikar, S. (1986) Clinical report: Laser myocardial revascularization. *Lasers Surg. Med.* 6, 459–461.
17. Horvath, K.A., Cohn, L.C., Cooley, D.A., et al. (1977) Transmyocardial revascularization: Results of a multi-center trial using TLR as sole therapy for end stage coronary artery disease. *J. Thorac. Cardiovasc. Surg.* 113, 645–654.
18. Horvath, K.A., Mannting, F.R., Cummings, N., Sherman, S.K., and Cohn, L.H. (1996) Transmyocardial laser revascularization: Opera-

- tive techniques and clinical results at two years. *J. Thorac. Cardiovasc. Surg.* 111, 1047–1053.
19. Frazier, O.H., Cooley, D.A., Kadipasaglu, K.A., et al. (1995) Myocardial revascularization with laser: Preliminary findings. *Circulation Supplement II* 92(9), 1158–1165.
  20. Maisch, B., Funck, R., Herzum, M., et al. (1996) Does transmural laser revascularization influence prognosis in endstage coronary disease? *Circulation Supplement I* 94(8), 1295.
  21. Cooley, D.A., Frazier, O.H., Kadipasaglu, K.A., Pehlivanoglu, S., Shannon, R.L., and Angelini, P. (1994). Transmyocardial laser revascularization: Anatomic evidence of long-term channel patency. *Tex. Heart Inst. J.* 21, 220–224.
  22. Gassler, N., Wintzer, H., Stubbe, H., Wullbrand, A., and Helmchen, U. (1997) Transmyocardial laser revascularization: Histologic features in human non-responder myocardium. *Circulation* 95, 371–375.

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