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TRANSMYOCARDIAL LASER REVASCULARIZATION: RESULTS OF A MULTICENTER TRIAL WITH TRANSMYOCARDIAL LASER REVASCULARIZATION USED AS SOLE THERAPY FOR END-STAGE CORONARY ARTERY DISEASE

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Background: Transmyocardial laser revascularization was used as the sole therapy for patients with ischemic heart disease not amenable to percutaneous transluminal coronary angioplasty or coronary artery bypass grafting. This technique uses a carbon dioxide laser to create transmyocardial channels for direct perfusion of the ischemic heart. **Methods:** Since 1992, 200 patients, at eight hospitals in the United States, have undergone transmyocardial laser revascularization. The patients have a combined 1560 months of follow-up for an average of 10 ± 3 months per patient. Their age was 63 ± 10 years and their ejection fraction was $47\% \pm 12\%$. Eighty-two percent had at least one previous bypass graft operation and 38% had a prior angioplasty. Preoperatively, the patients underwent nuclear single photon emission computed tomography perfusion scans to identify the extent and severity of their ischemia. These scans were repeated at 3, 6, and 12 months. Angina class, admissions for angina, and medications were recorded. **Results:** The perioperative mortality was 9%. Angina class decreased significantly from before treatment to 3, 6, and 12 months ($p < 0.001$). Likewise, there was a significant decrease in the number of perfusion defects in the treated left ventricular free wall. Concomitantly, there was a significant decrease in the number of admissions for angina

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in the year after the procedure when compared with the year before treatment (2.5 vs 0.5 admissions per patient-year). **Conclusion:** These combined results indicate that transmymocardial laser revascularization provides angina relief, decreases hospital admissions, and improves perfusion in patients with severe coronary artery disease. (*J Thorac Cardiovasc Surg* 1997;113:645-54)

Transmymocardial laser revascularization (TLR) is a new technique that creates transmural channels in ischemic myocardium via laser ablation. Conceptually, this allows direct perfusion of the myocardium with ventricular blood. Since 1992, eight medical centers in the United States have used a high-powered carbon dioxide laser to perform TLR. Several previous reports have investigated the use of this technique both clinically and experimentally.¹⁻¹⁹ The ability of TLR alone to provide relief of angina and improve myocardial perfusion was assessed in a cohort of patients with disabling angina refractory to medical therapy and untreatable by conventional means of revascularization.

Patients and methods

Between August 1992 and July 1995, 200 patients were treated with TLR at the following institutions: Seton Medical Center, San Francisco; St. Luke's Hospital, Milwaukee; Brigham and Women's Hospital, Boston; Texas Heart Institute, Houston; Audubon Regional Medical Center, Louisville; University of Pittsburgh Medical Center, Pittsburgh; Rush-Presbyterian-St. Luke's Medical Center, Chicago; and Columbia Presbyterian Medical Center, New York. The study was approved by the Food and Drug Administration and by the institutional review boards at the aforementioned centers. Informed consent was obtained from each patient enrolled.

Patient selection and demographics. Inclusion criteria for the study were threefold: (1) severe angina refractory to medical therapy, (2) reversible ischemia documented by a radionuclide myocardial perfusion scan, and (3) contraindications to percutaneous transluminal coronary angioplasty (PTCA), coronary artery bypass grafting (CABG), or transplantation.

The patient demographics are outlined in Table I. The distribution of patients according to preoperative angina class is depicted in Fig. 1, A. Preoperatively, 80% of the patients were in Canadian angina class IV and 20% were in class III.

Radionuclide scans. Preoperatively, all the patients underwent rest and stress nuclear medicine perfusion scans to assess the extent and reversibility of their myocardial ischemia. The scans were obtained with the use of thallium 201 or technetium 99m sestamibi. A 2 to 3 mCi dose of ²⁰¹Tl was administered at peak stress, and stress images were obtained 15 minutes later. Redistribution images were obtained at 34 hours followed by reinjection of half the stress dose in cases

Table I. Patient demographics

Men	156	78%
Women	44	22%
Age (yr)		
Mean $\pm$ SD	63 $\pm$ 10	
Range	35-85	
Diabetes	69	35%
Hypertension	133	67%
Cholesterol > 200 mg/dl	131	65%
Unstable angina	178	89%
Previous MI	155	78%
Previous PTCA	56	38%
Previous CABG	164	82%
Ejection fraction (%)		
Mean $\pm$ SD	45 $\pm$ 10	
Range	15-75	

MI, Myocardial infarction; SD, standard deviation.

in which the redistribution images were abnormal. ^{99m}Tc sestamibi imaging was performed according to the rest-stress protocol, in which 7 to 9 mCi ^{99m}Tc sestamibi is administered at rest with rest imaging 45 to 60 minutes later, followed by administration of 21 to 25 mCi ^{99m}Tc sestamibi at peak stress and stress imaging 30 to 60 minutes later.

Symptom-limited treadmill stress testing was performed in the preoperative period by means of the Bruce protocol. Postoperative stress testing was done with the use of the same protocol and to the same rate-pressure product as before the operation. The standard dipyridamole protocol was used for pharmacologic stress testing: 0.56 mg dipyridamole infused intravenously over 4 minutes and tracer administration 4 minutes after termination of the infusion.

Single photon emission computed tomographic imaging was performed according to institutional protocols for all patients. The data were reconstructed with filtered back-projection and reformatted into coronal, sagittal, and transaxial slices. Corresponding rest and stress coronal-sagittal-transaxial data were generated and transferred to hard copies.

All studies were read by two observers in a central core laboratory. The observers were blinded to patient information. The observers did not know whether a given study was conducted before or after the operation, and the results of prior studies were unknown. Differences between observers were resolved by consensus.

The left ventricular free wall was divided into twelve segments. There are an additional twelve segments in the septum and one in the apex. Segments with abnormal uptake at rest were scored as having a fixed perfusion defect (i.e., scar). Segments with decreased tracer uptake

Fig. 1. A, Preoperative angina class. B, Angina class at 3 months.

during stress compared with rest were scored as having reversible perfusion defect (i.e., ischemia). The number of segments with fixed perfusion defects and the number of segments showing reversible defects were tabulated for the septum (nontreated portion of the myocardium) and for the left ventricular free wall (treated portion).

Operative technique. The patients were intubated and a transesophageal echocardiography (TEE) probe was inserted. A baseline TEE study was performed to evaluate ventricular function and valvular disease. The TEE was primarily used to confirm transmyocardial penetration of the laser beam. The patients were placed in a 45-degree right lateral decubitus position and underwent a left anterolateral thoracotomy through the fifth or sixth intercostal space depending on the location of the point of maximal impulse. The pericardium was opened and dissected free of the heart. In patients status post-CABG, care was taken to avoid previous bypass grafts. On the

basis of the preoperative nuclear medicine scan, the area of reversible ischemia was exposed.

Laser. The laser is a 1000 watt carbon dioxide device (The Heart Laser, PLC Medical Systems, Milford, Mass.) that delivers 850 watts of peak power to the tissue. The maximum output is 80 joules and the pulse width can be varied from 1 to 99 msec. The operative settings were an average pulse energy of 42 ± 10 joules and a pulse width of 52 ± 12 msec. The carbon dioxide laser is aimed with helium-neon laser guidance, placed against the epicardium, and fired. The laser is triggered to fire on the *r* wave of the electrocardiographic cycle when the ventricle is maximally distended with blood and electrically quiescent. The laser energy is absorbed by the blood in the ventricle, and this produces an acoustic image analogous to steam that is readily visible by TEE in the long-axis four-chamber view. This TEE image denotes transmyocardial penetration. Only laser shots verified by TEE were con-

Fig. 1. C, Angina class at 6 months. D, Angina class at 12 months.

sidered to have traversed the myocardium. On average 30 ± 12 pulses were delivered and 25 ± 9 were confirmed by TEE for each case. The channels are 1 mm in diameter and 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 not adequate.

Follow-up. The 200 patients combined for 1560 patient-months of follow-up. The average length of follow-up was 10 ± 3 months. The patients returned at 3, 6, and 12 months after the operation for physical examination, review of medications, and assessment of angina class. Baseline radionuclide scans were required for preoperative evaluation. Additional radionuclide scans were obtained at 3, 6, and 12 months according to individual institutional protocols of follow-up. At a

given month of follow-up assessments (3, 6, or 12 months), only patients with complete data for that particular month contributed data to the analysis. Angina class data were complete for 156 patients at 3 months, 143 patients at 6 months, and 95 patients at 12 months. Radionuclide studies were complete for 120, 107, and 59 patients at 3, 6, and 12 months, respectively. The follow-up studies were compared with the preoperative baseline scans, and the change in the number of involved segments was calculated. The septum was not treated by TLR and thereby served as a control for each patient. Angina class, medications, activity level, and admissions for angina were assessed by interview and questionnaire.

Statistics. Angina class at baseline and follow-up was compared with the use of the Wilcoxon signed rank test

Fig. 2. Survival after TLR.

and paired *t* test. Differences were considered significant at *p* < 0.05. When necessary, a Bonferroni correction for repeated measures at multiple time points was used. The *p* values listed are two-sided *p* values. Results are expressed as mean $\pm$ standard deviation.

Results

Morbidity. Postoperative morbidity from the procedure was minimal. No intraoperative laser-induced arrhythmias occurred. There was a 9% incidence of atrial fibrillation after the operation (18 patients). Four patients had myocardial infarctions (2%). One patient had acute mitral regurgitation as a result of laser injury of the chordae and underwent mitral valve repair at the time of the procedure. Two patients (1%) required reoperation for bleeding. Intraaortic balloon pump assistance was used after the operation in seven patients (4%). One wound infection occurred and five cases of pneumonia (2.5%). The majority of the patients were extubated within the first 24 hours after the operation (0.8 ± 1.4 days). The average intensive care unit stay was 2 ± 3 days. The average hospital stay was 8 ± 6 days.

Mortality. Eighteen (9%) deaths occurred in the first 30 days after the procedure. The causes of death for these patients are listed in Table II. The majority of these deaths (12) were cardiac in nature. All of these patients had class IV unstable angina in the preoperative period. Fifteen of these patients had had a previous CABG. Autopsies were per-

Table II. Deaths

Cause	No. of patients
Early deaths	
Myocardial ischemia	5
Myocardial failure	5
Sudden death	2
Multisystem organ failure	2
Pulmonary embolism	1
Gastrointestinal bleeding	1
Pneumonia	1
Anesthetic complication	1
Late deaths	
Myocardial ischemia	1
Myocardial failure	4
Sudden death	2
PTCA	2
Heart transplant	1
House fire	1
Unknown	6

formed in eight of the patients and determined the cause of death as listed.

Over the subsequent months of follow-up an additional 17 (9%) deaths occurred, ranging from postoperative day 33 to day 317. The causes of these late deaths are listed in Table II. Of these deaths, seven were related to the heart. Fig. 2 depicts the postoperative survival for all patients after TLR.

Thirteen of the patients had additional procedures in the 12 months after their TLR. Three patients died as a result of these procedures and are

Fig. 3. A, Left ventricular free wall perfusion. B, Septal perfusion.

listed in Table II. The remaining 10 patients underwent the following procedures: one re-TLR (356 days after TLR), three CABGs (106, 126, and 326 days after TLR), and six PTCA's (2, 24, 111, 217, 301, and 313 days after TLR). Data on patients after additional revascularization procedures were not included for analysis.

Medications. All patients were initially restarted on their preoperative medications immediately after their TLR. One year after TLR, 56% of the patients had decreased their usage of cardioactive medications (nitrates, β -blockers, or calcium channel blockers) and 19% had increased their medications.

Hospital admissions. In the year before their TLR, the patients averaged 2.5 ± 2 admissions for angina. In those patients with a full year of follow-up there was a significant decrease in the number of admissions, with an average of 0.4 ± 0.6 admissions for angina after treatment with TLR ($p < 0.001$).

Angina class. Angina class decreased significantly from the preoperative status at 3, 6, and 12 months ($p < 0.001$). The distribution of patients according to Canadian angina class at baseline and at 3, 6, and 12 months of follow-up is depicted in Fig. 1, *A* to *D*. There was a significant redistribution of patients from angina class III and IV to a markedly decreased incidence of angina. In fact, for one third of the patients angina was eliminated and did not recur throughout the average 10 ± 3 months of follow-up. Using the definition that a decrease of two angina classes after the operation is considered a success, the procedure had a 75% success rate for patients at 3 months (117/156 patients, $p < 0.001$), at 6 months (108/143 patients, $p < 0.001$), and at 12 months (70/95 patients, $p < 0.001$).

Radionuclide perfusion scans. The results of the preoperative and postoperative radionuclide perfusion scans are graphically displayed in Fig. 3, *A* and *B*. A significant decrease in the number of segments with reversible perfusion defects in the treated left ventricular free wall was noted at 6 and 12 months (Fig. 3, *A*). With this change there was no increase in the number of segments with fixed defects in the treated area. Results of scans of the untreated septum (Fig. 3, *B*) reveal no significant change in either the fixed or reversible perfusion defects.

Positron emission tomographic scans. One institution (THI) performed positron emission tomographic scans before and after the operations. These confirmed improved subendocardial versus subepicardial resting perfusion in the laser-treated areas at 12 months (0.96 ± 0.07 vs. 1.10 ± 0.04 , $p < 0.001$, $n = 11$).

Discussion

The success of any type of myocardial revascularization is the improvement in the delivery of oxygen-carrying blood to the ischemic area. This has been achieved by manipulation of the existing coronary vasculature by CABG and PTCA. Unfortunately, these conventional methods of revascularization cannot be used in a significant number of patients. These patients may have diffusely small vessels or may have already exhausted their ability to undergo

another PTCA or CABG. It is for these patients that TLR was developed.

Before the advent of PTCA and CABG, attempts were made at direct transmyocardial revascularization.²⁰⁻²⁷ A series of tubes and needles to create transmural channels were used with minimal success.²²⁻²⁷ Conceptually, these methods were based on the knowledge of myocardial sinusoids and the thebesian system.²⁸ These communications were thought to allow direct perfusion of the myocardium by ventricular blood. Other methods of creating myocardial neovascularization by omentopexy and poudrage or by internal thoracic artery implantation were also moderately successful.^{20, 21} TLR incorporates the direct perfusion and neovascularization of these other techniques. Although the exact mechanism of TLR is unknown, there appears to be evidence of channel patency and of angiogenesis.^{1, 4, 7, 9, 14, 15} In theory, the laser-created channels would provide blood to the myocardium and stimulate further vessel formation. This process would take some time and may explain the improvement in angina class and perfusion scan results, particularly between 3 and 6 months after the operation. This improvement persists for 1 year after the procedure. The possibility that this is due to a placebo effect may be a criticism of the angina class data but cannot explain the improved perfusion as seen by single photon emission computed tomography and positron emission tomographic scans.

Symptomatically, the patients have shown initial improvement, which has continued with time. In addition to a significant decrease in their angina class, they have been able to avoid readmissions to the hospital for angina and have decreased their medication usage.

Limitations. This study, albeit prospective, does not have a randomized control group. On the basis of these preliminary results of this study, two separate multiinstitutional randomized controlled trials are in progress comparing TLR versus medical management and TLR versus reoperative CABG. These studies are still accruing patients and the results are pending.

The protocols for radionuclide myocardial perfusion scans varied among the participating institutions but were consistent with regard to the individual patient. Identical protocols at all sites are being applied in the ongoing randomized controlled trial.

Another limitation is the additional procedures that 13 of the 200 patients underwent after their TLR. Unfortunately, several of these procedures

were performed at institutions outside the study group. These additional procedures demonstrate the difficulty in treating these patients, inasmuch as they resulted in three deaths. Patients who survived these procedures were not included in the follow-up because the goal was to evaluate the efficacy of TLR in treating their disease. This was not a study to determine the benefit of TLR in combination with another method of revascularization. Assuming the worst case scenario, that is, that all of these patients were in angina class IV at the time of their procedure and remained in that class for the duration of follow-up, there was no significant change in the success rate of the procedure at 3 ($p < 0.001$), 6 ($p < 0.001$), and 12 months ($p < 0.001$).

This study was designed to observe the patients and collect data for 1 year. Some of the institutions have observed their subgroups of patients for longer periods and have reported continued relief of angina and improved perfusion.^{6, 16, 17} The purpose of this report is to confirm the earlier individual reports in a significantly larger combined group of patients. Further follow-up will obviously allow evaluation of the long-term efficacy of the procedure.

Future investigations experimentally include further elucidation of the mechanism and the use of angiogenic growth factors with TLR. Clinically, the greatest potential future use of TLR is in conjunction with CABG. This would provide an adjunct to CABG in the patient in whom some territories are graftable and others are not. It can be performed thoracoscopically and would also provide a method to expand the areas revascularized during minimally invasive CABG. TLR may also prove beneficial in the treatment of the diffuse atherosclerosis seen in patients having heart transplantation.

Conclusion

The results of this multicenter trial using TLR as sole therapy for severe angina indicate that TLR provides relief of angina and improves myocardial perfusion in patients with end-stage coronary artery disease.

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Discussion

Dr. John L. Ochsner (*New Orleans, La.*). This is an interesting paper in which the results of the procedure were designed to deliver blood to the myocardial sinusoids, somewhat like the Vineberg operation. Also like the Vineberg operation, it carried a very significant mortality, just about the same, 9%, and had a similar 1-year success rate. However, after a Vineberg operation, one can objectively demonstrate blood flow. If the internal thoracic artery is injected, it shows myocardial sinusoid blushing, and frequently even filling of the coronary arteries. However, to the best of my knowledge, I have been unable to find any report of even a myocardial blush from a ventriculogram after a transmyocardial revascularization. In fact, except for a few anecdotal reports, we have been unable to demonstrate any long-term patency of the channels. Yet one cannot argue with the clinical success of the operation. What is the mechanism of the success? Is it perfusion of the sinusoids by ventricular blood? Is it perfusion that occurs from angiogenesis that is a result of a metabolic response in scar tissue? Is it laser destruction of neuron networks within the heart? Or is it just a placebo effect, what we in the deep bowels of Cajun country refer to as voodoo? Of course, these are only hypotheses; we cannot be sure of the source of its beneficial results. On the other hand, for years we did not know the exact mechanism of digitalis or aspirin, and yet we knew they were effective.

We recently extended our indications for transmyocardial revascularization to include patients who had had transplantation. Recently, in one patient who required a CABG operation, we used the transmyocardial revascularization as an adjunct in the hope of treating the small-vessel disease known to occur with allograft vasculopathy.

I would like to ask two questions of the authors. Do you have any long-term data, that is, over a year, particularly in regard to the control of angina? We have seen the angina disappear early only to recur late and then progressively disappear again as we think angiogenesis occurs. Second, do you believe that we should start to include those patients who are in heart failure but without angina but do have evidence of hibernating myocardium?

Dr. Gurukumar B. Parulkar (*Bombay, India*). Dr. Horvath and his colleagues have presented highly scientific data on patients who underwent transmyocardial revascularization during the multicenter clinical trial. In 1965 the

late Dr. Sen and I reported a similar concept of transmyocardial revascularization in experimental animals, using a large-bore needle to make through-and-through punctures in the anoxic left ventricle. It was interesting in those days to observe how these punctures, which did not remain patent after 6 to 8 weeks, could effectively reduce myocardial necrosis after ligation of the left anterior descending artery. We did use this technique occasionally in patients with accidental injury to the coronary arteries or to treat severe anoxic damage after anoxia during cardiac operations; however, we have never reported this work.

I have one question for the authors. Have they thought of using transmyocardial revascularization in patients with cardiogenic shock with very advanced coronary artery disease in whom neither surgery nor angioplasty can be considered?

Dr. Josef G. Vincent (*Kreuzlingen, Switzerland*). In a 2-year period in our clinic we operated on 212 patients using the carbon dioxide laser, and I am extremely happy that our results may confirm your study on the other side of the ocean. The criteria to accept the patients were, without exception, refusal from other centers to operate on them or to do PTCA. The medical therapy was maximal. To our surprise, the patients were able to pass an exercise test 5 days after the operation. Our follow-up study, which contains 146 patients at 3, 6, and 12 months, reveals low grading of the angina class for at least two classes, inasmuch as 82% of our patients were in classes III and IV and now 75% and 89% are in class I or zero. We were not able to confirm these results on echography or on scintiscan on all of our patients, but the quality of life of our patients, voodoo or not, improved considerably. We are happy so far to greet the patients back, walking around, without any pain, and with lower medication doses.

Dr. Todd Rosengart (*New York, N.Y.*). We have been looking at the excimer laser for performing TLR in recent studies in a sheep model. We created a series of excimer-lased channels. We were actually delivering about 1 joule of energy per channel and looked at histology at 30 days. Because there has been some question as to whether nonlased acupuncture might be an effective TLR technique, we also created a series of nonlased channels with the fiberoptic delivery system that we were using. At 30 days, 60% of the lased channels were patent and most of those demonstrated a well-lined endothelium. We also noticed, as have the investigators using the carbon dioxide laser, that there was a significant neovascular response in the lased segments. However, in contrast, none of the nonlased channels was patent at 30 days, and we saw very little in the way of a neovascularization response in these nonlased regions.

Do you think that it is the laser energy delivered, the tissue vaporization, the adjacent tissue injury, or some other effect that at the present time we are not aware of that is causing the results that we are seeing with TLR?

Dr. Horvath. All of these questions are very pertinent, and the majority concern the mechanism. This is an experimental technique, and the clinical results that we have seen are valid. I am not sure what the mechanism is,

whether it is, as Dr. Ochsner outlined and Dr. Rosengart echoed, due to perfusion directly from the ventricle into the myocardium, whether it is due to angiogenesis as a result of delivery of laser energy to the myocardium, or whether denervation plays a role in eliminating the anginal symptoms.

Voodoo is something that I am not familiar with and I hope I never will be. With regard to the possible placebo effect, a similar study was done years ago by E. Grey Diamond. A number of patients underwent internal thoracic artery ligation to relieve their angina. It is the only prospective randomized double blind study of the surgical treatment of angina. The patients were randomized into a placebo and a treated group. Unfortunately, at 9 months none of the patients in either group said that they were in fact angina-free. The fact that patients are free of symptoms after 1 year of follow-up indicates that something beyond a placebo effect is occurring here.

Regarding long-term follow-up, some of our patients were operated on 4 years ago, and their results are the same as they were at 1 year.

As Dr. Rosengart has said, the laser has a major advantage over the needle in that there is actual tissue ablation and the delivery of laser energy. Both the work

done by Dr. Sen, which was alluded to by Dr. Parulkar, and the study that Dr. Rosengart referred to using a needle or fiber demonstrates that a minimum effect can be obtained with these techniques, but the channels do not appear to stay patent.

Finally, regarding the use of this procedure for heart failure, the criteria that we had established was that none of these patients should be transplant candidates. In fact, in reviewing our data for the patients who died early, one of the independent risk factors was an ejection fraction less than 20%. Unless there is a significant area of hibernating myocardium or reversible ischemia delineated by the nuclear medicine scan, I cannot recommend this as a treatment for heart failure.

In summary, a number of these questions will be answered with the ongoing trials approved by the Food and Drug Administration. There are presently two randomized controlled studies, one comparing the laser to continued medical therapy and another comparing the laser to reoperative CABG. In the first study 113 of the 150 patients have been enrolled and the initial 3-month results are encouraging, but further work is needed both clinically and experimentally to answer these questions.