# Transmyocardial Laser Revascularization

## Does It Have a Role in the Treatment of Ischemic Heart Disease?

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*Transmyocardial laser revascularization, with or without coronary artery bypass grafting, is an alternative modality for complete revascularization in selected patients with coronary artery disease. Arguably, this modality works by shunting left ventricular blood directly into the ischemic myocardium via laser-mediated transmural channels. In clinical trials, drilling of laser channels has been strongly correlated with long-term improvement of angina, but a causal relationship has not yet been documented. For now, the usefulness of transmyocardial laser revascularization and the nature of its mechanism remain controversial. Some researchers question the existence of myocardial sinusoids altogether. Others question the physiologic possibility of moving blood from the left ventricular cavity into the myocardium against a pressure gradient. Further questions concern the possible routes through which the additional blood gains access to the myocardium; the difficulty of objectively documenting improved myocardial perfusion after transmyocardial laser revascularization; and the nature of the mechanism responsible for the observed clinical benefit. This article examines the different aspects of this controversy and discusses the current status of transmyocardial laser revascularization, as well as possible future directions.* ***(Tex Heart Inst J 1998;25:24-9)***

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Traditional interventional modalities are not always adequate for complete myocardial revascularization in advanced atherosclerotic coronary artery disease. If the lesion is distally located, a target for bypass graft anastomosis may not be identifiable. If the artery is diffusely involved with disease, graft run-off may remain suboptimal. Over the past decade, transmyocardial laser revascularization (TMLR) with[1,2] or without[3,4] coronary artery bypass grafting (CABG) has been proposed as an alternative modality for complete revascularization. Arguably, this method works by shunting left ventricular blood directly into the ischemic myocardium, especially the subendocardial perfusion bed, via laser-mediated transmural channels. Although extensive clinical trials suggest a strong correlation between the drilling of laser channels and long-term improvement in angina, a causal relationship is yet to be documented. Therefore, both the usefulness of the procedure and the nature of its mechanism remain controversial. This article examines the different aspects of this controversy.

### Origins of the Controversy

The rationale behind TMLR, as originally described by Sen and associates[5] and by Mirhoseini and Cayton,[6] involves the presupposition that the laser-created transmyocardial channels will 1) stay patent, 2) establish communications between the endocardium and the myocardial sinusoidal plexus, and 3) through these communications convey oxygenated left ventricular blood to the arteriolar system, thereby reversing ischemia and relieving angina. Through the years, this hypothesis has been challenged at every conceivable level.

### Aspects of the Controversy

*Do Myocardial Sinusoids Exist?* First and foremost, the very existence of myocardial sinusoids in adults has been questioned. The existence of arterioluminal[7] and venoluminal[8] connections was indirectly documented by means of dye injection (into the coronary ostia and the coronary sinus, respectively) at the turn of the 18th century. Wearn and colleagues,[9] in 1933, were the 1st to describe direct histologic and gross evidence of the myocardial sinusoidal plexus with its arte-

riosinusoidal, luminosinusoidal, and arterioluminal components. However, this evidence was later criticized as being a mere dehydration artifact.[10] Moreover, it has been theorized that these structures exist only in the human fetal circulation and undergo atrophy during the postpartum period, to be replaced by the epicardial coronary arteries and intramyocardial arteriocapillary system.[11] Although this argument regarding myocardial vasculature is not likely to be settled on purely anatomic grounds in the foreseeable future, indirect evidence supporting the existence of a myocardial sinusoidal plexus can be found in the successful work of innovative surgeons such as Beck[12] and Vineberg.[13] Beck's experimental and clinical research on omentopexy, pericardiopexy, and poudrage proved the feasibility of 1) bringing an arterial source of blood (e.g., the omentum) into the vicinity of the epicardium (the vascularity of which was enhanced by application of an inflammatory agent such as asbestos or talc) and 2) relieving chest pain, arguably by increasing myocardial perfusion. Vineberg, on the other hand, implanted the left internal mammary artery (LIMA) directly into tunnels formed in the myocardium. Up to 25 years later, he noted that the arteriomyocardial connections were patent and that significant myocardial "blushing" could be induced by selectively injecting the LIMA.

Nevertheless, shunting of intraventricular, rather than arterial, blood into the myocardium, is a different matter, which raises concerns about the physiologic possibility of transferring blood from the left ventricular cavity into the myocardium against a pressure gradient. After all, it is contraction of the myocardium that generates pressure in the left ventricular cavity, and it is intuitive that the force of the contraction must be greater than the internal chamber pressure that the contraction generates.

*Is It Physiologically Possible to Transfer Blood from the Left Ventricle into the Myocardium Against a Pressure Gradient?* This issue constitutes the 2nd aspect of the controversy that surrounds TMLR. According to the observations and speculations of Leary and Wearn[14] in the 1930s, the thebesian system can assume the task of myocardial perfusion when a chronic disease process such as syphilitic aortitis slowly obliterates the coronary ostia and occludes much of the coronary arterial tree. In the opinion of Leary and Wearn, the fact that patients with this condition lead moderately active lives for prolonged periods shows that ventricular blood can seep into the myocardium in the absence of coronary arterial pressure. Early attempts to calculate the difference between the left ventricular pressure (LVP) and the intramyocardial generated pressure (IMP) yielded contradictory results,[15,16] mainly because of inaccuracies in the pressure measurement techniques. In our laboratory, however, studies using transducer-tipped catheters have indicated that the LVP is consistently greater than the IMP during the systolic ejection period.[17] Therefore, a positive gradient does exist in the luminoendocardial direction, and this gradient provides the driving force for the blood supply believed to occur after TMLR. In support of pure experimental data, recent clinical observations of high-resolution echocardiographic contrast medium injected into the left ventricular cavity of laser-treated patients have provided direct testimony that blood does move into the myocardium during each systolic contraction of the heart wall.[18]

*Through What Routes Could the Additional Blood Gain Access to the Myocardium?* The possible routes through which the additional blood gains access to the myocardium, if indeed it does, constitute the 3rd aspect of the TMLR controversy. If, for rhetorical purposes, we assume that laser channels enhance existing luminosinusoidal pathways and allow blood to flow in the desired direction, the question of whether the channels will preserve patent, long-term endocardial connections gains relevance. This issue is hotly debated, and opinions vary widely, even among investigators who examine similar histologic specimens from patients who die after undergoing TMLR.[19,20] Some experts propose that the term "patent channels" be replaced by "channel remnants" and that angiogenesis be recognized as an alternative, or adjunctive, mechanism to that of channel remnants.[21] The latter proposal is supported by the fact that laser irradiation produces heat-shock proteins and oxygen free radical scavengers, which themselves are known to possess angiogenic properties.[22] In the final analysis, the laser channels may become occluded by thrombosis acutely, only to serve as foci for the formation of new vessels via the influx of growth factors that promote endothelialization and angiogenesis in the long term.[23] Experimental studies have shown that, during the first 4 postoperative weeks, drilling of laser channels in myocardial tissue induces up to a 35-fold increase in capillary density, when compared with mechanical drilling of control channels in ovine[24] and canine[25] hearts. Furthermore, incorporation of bromodeoxyuridine into capillary walls, which is an indicator of new vessel formation, increases by 4 times in laser-treated hearts.[25] The expression of beta-galactosidase increases 4-fold in the vicinity of laser-created channels when the target tissue is infected with the encoding gene bound to either naked plasmid or plasmid infected with the hemagglutinating virus of Japan (HJV). This latter finding suggests that nonviral transgenic expression is feasible, as an adjunct to laser thermal injury, for enhancing the angiogenic properties of laser irradiation.[26]

*How Can Improved Myocardial Perfusion Be Objectively Documented after TMLR?* A 4th source of controversy arises from failure to objectively document a frank improvement in myocardial perfusion after laser therapy. The major contributors to this problem are the inherent inaccuracy and insensitivity of available direct diagnostic techniques—such as thallium single-photon emission tomography (TI:SPECT) and positron emission tomography (PET)—and the subtlety of perfusional changes after TMLR. We used computer-aided techniques that allowed PET tracer concentrations in the myocardium to be assessed according to subendocardial and subepicardial regions of interest.[3] In this way, we were able to detect a significant increase in the relative subendocardial blood flow as early as 3 months after TMLR; the increase in flow persisted throughout the entire year of the study. The predictive accuracy of subregional PET, thus increased over that of conventional transmural analysis, correlated well with the degree of clinical improvement. Unfortunately, the high cost of PET limited the size and scope of this uncontrolled longitudinal study and prevented other centers from contributing to the data pool. Currently, TI:SPECT is being used to assess myocardial perfusion in controlled, randomized studies. The increasing sample size is improving the statistics, so that scientifically acceptable documentation of clinical efficacy may eventually be obtained.

*What Is the Nature of the Mechanism Responsible for the Observed Clinical Benefit?* At present, all parties involved in the TMLR controversy, including clinical investigators, patients, and regulatory agencies, seem to be in agreement that TMLR significantly reduces anginal symptoms in as many as 75% of the patients treated with this modality. It is, however, the nature of the mechanism responsible for this observed clinical benefit that is being debated. This issue constitutes the 5th aspect of the TMLR controversy. Although the most straightforward explanation for the benefit would be direct reversal of ischemia owing to improved perfusion status, the above-mentioned deficiencies in diagnostic technique have caused some experts to propose alternative theories such as cardiomyocyte denervation or the placebo effect. The placebo-effect theory would be unlikely to persist beyond the 1st 6 months after any intervention that yielded no substantial revascularization. Therefore, the placebo-effect theory is discredited by the fact that more than 50% of those who undergo TMLR as sole therapy continue to lead relatively symptom-free lives up to 3 years afterward. On the other hand, denervation is a more realistic possibility, owing to the traumatic effect of laser irradiation in myocardial tissue. There has been no reported increase in the extent of fixed perfusion defects (myocardial infarctions) in TMLR-treated populations but, again, TI:SPECT may be insufficiently specific to detect subtle laser-induced microinfarcts. A recent study compared the degree of central-nervous-system–mediated decrease in the mean systemic arterial pressure after either TMLR with a holmium:yttrium aluminum garnet (Ho:YAG) laser or destruction of epicardial nerves by topically applied phenol in normoperfused dogs.[27] The response to topical bradykinin, a potent analgesic, was equally decreased in both groups, leading the investigators to conclude that TMLR destroys cardiac nerve fibers and, thus, helps reduce angina pectoris.

The destruction associated with TMLR may depend on the wavelength of the laser used. In addition to the carbon dioxode ($CO_2$) laser, 2 Ho:YAG systems (CardioGenesis, Inc., and Eclipse Surgical Tech, Inc.; Sunnyvale, Calif) and 1 excimer (Xe:Cl) laser system (United States Surgical Corporation; Norwalk, Conn) are currently being proposed for clinical use. The Xe:Cl laser operates in the ultraviolet wavelength, but the rest are near-infrared lasers. The mechanisms of tissue removal are mainly water absorption and heating with the near-infrared lasers and breakdown of the peptide bonds with the ultraviolet laser. In comparison with the $CO_2$ or Xe:Cl lasers, Ho:YAG lasers are limited by their propensity to cause excessive structural damage to adjacent tissue. This problem may be a disadvantage with respect to channel patency, because the reparative tissue response is proportional to the amount of damage, and, when damage is excessive, the channel may undergo early closure by scar tissue. However, because the upregulation of angiogenic factor release also increases in direct proportion to the volume of the affected tissue, compensatory mechanisms may improve the final perfusion status of Ho:YAG-treated tissue. The Ho:YAG debate is not resolved yet, but research is underway.[28]

In our laboratory, comparative studies of normally perfused pig hearts have suggested that thermal and structural damage to the myocardium during TMLR is indeed proportional to the laser wavelength. In a series of 9 pigs, we created 30 laser channels in the cardiac wall (thickness, approximately 2 cm) of each animal. Each laser modality was used exclusively in 3 animals. We then measured the amount of excised and damaged tissue in cross-sections. Assuming that the geometry of the channels was cylindrical, we extrapolated the results to determine the degree of volumetric damage. In cubic centimeters, the results were $1.48 \pm 1.03$, $1.87 \pm 0.72$, and $8.45 \pm 5.36$ for the $CO_2$, Xe:Cl, and Ho:YAG lasers, respectively. The relatively large increase in damage imposed by the Ho:YAG laser was to be expected, given the explosive ablative processes that govern this laser's interactions with cardiovascular tissue.[29] Whether this

degree of damage is sufficient to account for the loss of sympathetic response in the experience of Kwong and associates[27] remains to be elucidated by further, comparative experiments using the other, less traumatic laser modalities. Meanwhile, alternative diagnostic methods can be explored to confirm or deny the theory of cardiomyocyte denervation. Of these diagnostic methods, the most promising is myocardial scintigraphy with $^{123}$I-metaiodobenzylguanidine (MIBG), a guanethidine analogue compound that is homologous to norepinephrine at sympathetic nerve endings.[30] The uptake, storage, and release of MIBG can be measured with nuclear scanning techniques before and after TMLR; in this manner, potential alterations in sympathetic afferent nerve signals can be documented in direct proportion to levels of perceived angina both experimentally and clinically.

### Current Status

Multicenter randomized clinical trials are currently being conducted using the laser wavelength modalities mentioned above.[3,31,32] The $CO_2$ laser (PLC Medical Systems, Inc.; Franklin, Mass) was the 1st system to be made available and, therefore, is the one for which the most clinical data exist. To date, clinical studies with this laser have invariably yielded a decrease in angina by more than 2 Canadian Cardiovascular Society classes, as well as improved clinical status and exercise tolerance for more than 2 years after TMLR, with mild to moderate improvement in regional cardiac perfusion.[1-4,21] Unfortunately, except for isolated reports from investigators in the multicenter study,[33,34] no evidence of a parallel increase in overall cardiac function has been observed. The reason may be that the minimum baseline ejection fraction required by enrollees is kept relatively high to prevent pre- and postoperative complications. Therefore, the improvement in systolic function, if any, becomes too subtle to be detected by conventional diagnostic techniques. On the other hand, the 1-year mortality rate of TMLR patients is the same as, if not less than, that of control patients undergoing maximal medical management (12% to 15%).

In summary, recent clinical trials have established TMLR as a relatively low-risk therapy in end-stage ischemic heart disease. This therapy is more effective in improving the quality of life than in improving survival in patients otherwise incapacitated by angina. The recent trials have also helped define the optimal subset that may benefit from the procedure: patients who suffer primarily from angina (chest pain) rather than congestive heart failure (shortness of breath), whose systolic function is not compromised (left ventricular ejection fraction greater than 40%) and who do not have morbid arrhythmias, are most likely to have a favorable prognosis. With these inclusion criteria in mind, surgeons can reduce the mortality rate associated with TMLR until it resembles that associated with a left thoracotomy under general anesthesia; moreover, they can maximize TMLR's clinical benefits so that they exceed the benefits of medical management or technically suboptimal CABG or percutaneous transluminal coronary angioplasty.

### Future Directions

To reduce the traumatic effect of TMLR, cardiologists have begun to use a catheter-based technology based on the percutaneous, transluminal approach. In this manner, the myocardium is accessed from the left ventricular cavity, and the channels are created from the endocardial surface. The Ho:YAG and Xe:Cl lasers lend themselves readily to this approach, for which clinical evaluation has already been initiated.[35] On the other hand, the wavelength of the $CO_2$ laser is not transmittable through currently available fiberoptic catheters, and further research is needed to develop the appropriate technology. Because the percutaneous approach will eliminate the need for general anesthesia and for surgical dissection of pulmonary and pericardial adhesions, TMLR therapy will be expanded to include the severely depressed left ventricle. It will also allow treatment of the interventricular septum. Additionally, percutaneous TMLR will be an interesting means of determining whether the symptomatic relief provided by intraoperative TMLR is indeed a placebo effect associated with a left thoracotomy.

One potential problem with percutaneous TMLR involves navigating the catheter within the left ventricular cavity. Several innovative designs are being developed to yield a flexible, steerable catheter that can control both the 3-dimensional location of the catheter tip in situ and the depth of ablation during TMLR. Another potential problem is arrhythmia caused by paroxysmal irradiation of the heart during portions of the cardiac cycle, specifically during the T-wave. The Xe:Cl laser seems especially prone to this problem because of the relatively high number of pulses delivered per unit time. One solution would be to synchronize the activity of the laser so as to avoid the T-wave; this approach is being used in some other interventional modalities.

Clinical trials of percutaneous TMLR with a Ho:YAG laser have recently begun at the Texas Heart Institute. Consequently, our center has become one of the few where TMLR is being performed by both the surgery and cardiology departments.

## Conclusion

Over the past decade, solid progress has been made in establishing TMLR as an alternative therapy for end-stage ischemic heart disease in patients with distal, diffuse atherosclerotic involvement and ad-

equate left ventricular systolic function. Although further basic research is needed to clarify the involved mechanisms of TMLR, tangible results are accumulating, and multicenter clinical trials are elucidating optimal patient populations for "total revascularization" of the myocardium. From a pragmatic point of view, discussions that have historically focused on the anatomic, physiologic, histologic, diagnostic, and clinical aspects of this interesting technology are likely to be replaced by discussions regarding the choice of "surgical vs percutaneous" or "sole vs adjunctive" TMLR in treating a given coronary occlusive lesion.

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