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Transmyocardial Laser Revascularization

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Revascularization of ischemic myocardium is classically achieved by improving perfusion through epicardial coronary arteries. A novel method of enhancing myocardial blood flow in patients who are not candidates for conventional revascularization has received great attention in the scientific and lay press. Transmyocardial laser revascularization (TMLR) is a procedure that attempts to improve myocardial blood flow by using a laser to create multiple channels through the ventricular myocardium. This technique has been studied with varying degrees of success in animal models and has recently been evaluated in several human clinical trials.

History

In the reptilian heart, perfusion occurs when blood courses from the ventricle through nonendothelialized channels in the myocardium. It has been hypothesized that the mammalian heart may be perfused in this way by mechanically creating transmyocardial channels. In 1965, Sen[1] used a 1.5-mm needle to create transmyocardial channels in dog myocardium prior to ligation of the left anterior descending (LAD) coronary artery. Treatment enhanced survival and treated dogs had less ischemic myocardium, compared with controls. Later histological studies have shown that channels created with this acupuncture technique tend to close prematurely with fibrosis and scarring.[2]

The obvious therapeutic role for such an intervention is in patients with ischemic heart disease who are not candidates for coronary artery bypass grafting (CABG) or angioplasty. With the advent of laser technology, transmyocardial channels can be created by using a carbon dioxide (CO2) or holmium yttrium-aluminum-garnet (YAG) laser system.

CO_2 laser-generated channels in dog myocardium have been shown to remain open for up to 2 years and become endothelialized.[3] When Mirhoseini et al[2] revascularized a large area of the left ventricle with laser channels, survival after LAD ligation was 83% (10/12),

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compared to 0% (0/6) among controls. However, Whittaker has reported a lack of effect of holmium-YAG laser revascularization after LAD ligation on ischemic dog myocardium.[4] Using radiolabelled microspheres, he showed that laser-generated myocardial channels had no difference in myocardial blood flow or lactate clearance, compared to controls.

This discrepancy in results was purported to be secondary to the lack of control for collateral vessels in the earlier studies. Possibly, the use of a holmium-YAG laser instead of CO_2 laser may have caused more thermal injury to the myocardium and reduced the efficacy of laser-generated channels.

Early Studies in Patients with Concomitant CABG

In 1983, Mirhoseini described a patient who could not be weaned successfully from cardiopulmonary bypass after CABG.[5] This patient was successfully weaned after a low-power laser was used to revascularize the heart by creating transmyocardial channels.

After this report, a series of 12 cases of laser revascularization with concomitant CABG were presented.[6] These patients had at least one bypassable vessel, but other areas of viable or ischemic myocardium were perfused by coronary arteries that were inadequate for CABG. Pre- and post-operative thallium scans showed improved uptake in the area of laser revascularization in half of (6/12) patients. Patent channels were documented by left ventriculography in half of (6/12) patients and clinical improvement was noted in all patients.

These early experiments used a low-power CO_2 laser on the cooled and arrested heart. Eventually, the development of a feasible high-power CO_2 laser led to the ability to create channels on the beating heart, negating the need for cardioplegia and cardiopulmonary bypass.

Evidence for Perfusion

Studies in animals have relied mainly on autopsy specimens or visual indices to determine the viability of myocardium revascularized by laser-generated channels.[1,3] Radiolabelled microspheres have been used in animals to document increased perfusion in previously ischemic myocardium; however, the results have been inconsistent.[4,7,8,9]

Human studies use thallium scintigraphy or positron emission tomography (PET) to demonstrate perfusion. In a study of 21 patients with refractory angina who were treated with TMLR, 5 were dead at 3 months.[10,11] The 15 remaining patients (one patient was excluded because of surgical complications) had no change in thallium uptake compared to baseline, despite a two-level increase in Canadian Cardiovascular Society (CCS) class. However, a similar trial of 20 patients with equal mortality and clinical improvement showed a significant increase in sestamibi uptake after surgery.[12]

A multicenter trial of 8 U.S. hospitals recruited 200 patients to undergo TMLR.[13] Despite an 8% perioperative mortality rate, admissions for angina fell by 88% (compared to rates for each patient, one year prior to study entry) and the number of ischemic segments on thallium scanning was reduced by 45%.

A recent observational study of 56 patients with CCS class 3 to 4 angina showed an improvement in exercise duration and thallium uptake in patients who underwent TMLR as an adjunct to CABG. Only one death occurred and 92% of patients were free of angina at one year.[14] A study of 16 TMLR-treated patients (no deaths) who had dipyridamole thallium scans at baseline and

3, 6, and 12 months postoperatively showed improved perfusion, which correlated with positive changes in angina class.[15] Yet another study of 64 patients with inoperable coronary disease who underwent TMLR showed a 41% reduction in reversible defects of the left ventricular free wall at 12 months after laser surgery.[16]

Lack of Randomized Data

To date, the majority of published trials with human data have been observational studies without randomization or controls (Table 1). Recently, a randomized study of TMLR versus medical therapy was presented at the American College of Cardiology 46th Annual Scientific Session.[17] Primary endpoints were change in angina class and thallium uptake; the secondary endpoints, change in ejection fraction, quality of life, morbidity, and mortality.

This study enrolled 198 patients: 101 received medical therapy; 97 had TMLR. All patients had CCS class 3 or 4 angina, were not candidates for conventional revascularization, and had ischemic or hibernating myocardium on thallium imaging. Patients randomized to TMLR had an operative mortality of 3%. At 6 months, only 26% of TMLR-treated patients had CCS class 3 or 4 angina, compared to 77% of controls. Hospitalization for unstable angina at 6 months was 13% for TMLR-treated patients and 72% for controls. Patients who underwent TMLR reported an improvement of 139% in quality of life, compared to 23% for controls.

Although imaging data had not yet been analyzed, a representative scintigraph showed remarkable improvement in perfusion after TMLR. Crossover to TMLR was allowed if patients with unstable angina had been admitted to an intensive care unit for at least two days and treated with intravenous medications. Unfortunately, perioperative mortality in the crossover group was 40%.

Certainly, it appears from this randomized trial that subjective measures of angina class seem to improve after TMLR, compared to medical therapy. However, perhaps the comparison of an invasive intervention to medical therapy leads to the corruption of data, merely on the basis of nonblinding. Objective data, such as quantified perfusion imaging, multigated analysis of improvement in ejection fraction, or quantified improvement in exercise duration, are necessary to document the possible benefits of TMLR. Perhaps as more data from this ongoing study are analyzed, this information will become available.

The improvements in angina class certainly raise questions about the pathophysiology of laser-generated perfusion. Two histologic studies on humans who died after TMLR surgery have revealed a high rate of prolif-

Table 1: Published trials of transmyocardial laser revascularization.

Source	Patients	Preoperative CCS class	Mortality	Improvement in CCS class	Scintigraphic Improvement	Exercise Improvement
March[15]	16	3-4	n/a	yes	yes	n/a
Trehan[14]	56	50% 3-4	2%	yes	yes (28%)	yes (81%)
Cooke[16]	64	3	n/a	yes	yes (41%)	n/a
Horvath[13]	200	3-4	8%	yes	yes (45%)	n/a
Frazier[10]	21	3.7	24%	yes	no	n/a
Horvath[12]	20	3.7	25%	yes	yes	n/a
Lowe[17]	97	3-4	3%	yes	? yes	n/a

eration of vascularized fibrous tissue within laser-generated channels. Neither study was able to demonstrate a connection between the vascular network developing within transmyocardial channels and the remaining intramyocardial vascular network or left ventricle.[2,18]

These data suggest the need for long-term studies to assess myocardial perfusion after TMLR. It is possible that, since most autopsy specimens came from patients who died within the first few weeks after TMLR, the vascular network had not yet had a chance to develop fully. Meanwhile, with no clear-cut pathophysiologic mechanism by which TMLR improves myocardial perfusion and function, the results of this study must be interpreted with caution.

Some authors[18] believe that laser-generated channels cause a sufficient loss of myocardium to reduce the ratio of myocardial demand and supply, thereby reducing angina without actually improving perfusion. However, 25 1-mm-diameter laser channels in 1.5-cm-thick myocardium only leads to a 0.3 cm^3 loss of myocardium.

Future Directions

The holmium-YAG laser provides surgeons with an opportunity to advance TMLR to a thoracoscopic route. Because of its properties, this laser can work in fiberoptic systems, allowing for a minimally invasive approach to revascularization. However, histologic studies have demonstrated that this type of laser creates more thermal damage and charring than does the CO_2 laser. Nevertheless, a small holmium-YAG laser trial has shown improvement in symptoms without change in postoperative ejection fraction or wall motion by echocardiography.[19]

Cardiac allograft vasculopathy (CAV) is a form of coronary disease that perplexes transplant physicians. Few options exist for optimal treatment of these patients. A study of 28 cardiac transplant patients with CAV who underwent TMLR (18 as sole therapy; 10 with concurrent CABG) reported 3-month follow-up studies on 12 patients.[20] Initially, 11 patients were CCS class 4, while 1 was CCS class 3. At 3 months after TMLR, only 1 patient was CCS class 4, while 2 were CCS class 3. Regional myocardial dipyridamole imaging was reportedly improved at 3 months. Interestingly, the greatest improvement was seen in the septum, which is inaccessible to TMLR. Unfortunately, the authors do not report which of the 12 patients had concomitant CABG and do not analyze separately the results in TMLR-only patients.

Conclusions

TMLR has been shown to prevent ischemia in animal models with coronary artery ligation. As a result, observational studies in humans have been performed worldwide with variable success. The average mortality rate of observational and randomized studies evaluating TMLR is 7.6%. All studies show improvement in CCS class, and the majority have objective evidence of improved myocardial perfusion.

Despite this, the pathophysiology of such improvement is poorly understood. Objective measures of improvement in exercise and left ventricular function are lacking. Overall, although TMLR initially sounds promising, without pathophysiologic correlates, objective evidence of improvement in myocardial perfusion and function, and high operative mortality rates, it is difficult to recommend this procedure to all patients who are not candidates for conventional revascularization.

References

1. Sen PK, Udwadia TE, Kinare SG. Transmyocardial acupuncture. *J Thoracic Cardiovasc Surg* 1965;50:181-9.
2. Krabatsch T, Schaper F, Leder C, et al. Histological findings after transmyocardial laser revascularization. *J Card* Surg 1996;11(5):326-31.
3. Mirhoseini M, Cayton M. Revascularization of the heart by laser. *J Microvas Surg* 1983;2:253.
4. Whittaker P, Kloner RA, Przyklnek K, et al. Laser-mediated transmural myocardial channels do not salvage acutely ischemic myocardium. *JACC* 1993;22(1):302-9.
5. Mirhoseini M, Fisher JC, Cayton MM. Myocardial revascularization by laser. *Laser Surg Med* 1983;3:241-5.
6. Mirhoseini M, Shelgikar S, Cayton MM. New concepts in revascularization of the myocardium. *Ann Thorac Surg* 1988;45:415-420.
7. Mirhoseini M, Cayton M, Wong Y, et al. Endocardial blood flow in acute ischemia following transmyocardial laser revascularization. *JACC* 1997;29(2, Suppl A):769-4A.
8. Almanza O, Wassmer P, Moreno CA, et al. Laser transmyocardial revascularization (LTMR) improves myocardial blood flow via collaterals. *JACC* 1997;29(2, Suppl A):929-162A.
9. Yano OJ, Bielfield MR, Jeevanandam V, et al. Prevention of acute regional ischemia with endocardial laser channels. *Am Thorac Surg* 1993;56:46-53.
10. Frazier OH, Cooley DA, Kadipasaoglu KA, et al. Myocardial revascularization with laser. Preliminary findings. *Circulation* 1995;92(9,Suppl II):II58-65.
11. Cooley DA, Kadipasaoglu KA, Frazier OH, et al. Transmyocardial laser revascularization: clinical experience with 12-month follow-up. *J Thorac Cardiovasc Surg* 1996; 111(4):791-7.
12. Horvath KA, Mannting F, Cummings N, et al. Transmyocardial laser revascularization: operative techniques and clinical results at two years. *J Thoracic Cardiovasc Surg* 1996; 111(5):1047-53.
13. Horvath KA, Cohn LH, Cooley DA, et al. Transmyocardial laser revascularization: results of a multicenter trial using TMLR as a sole therapy for end-stage coronary artery disease. Presented at the American Association of Thoracic Surgery meeting, Apr-May 1996.
14. Trehan N, Bapna R, Mishra A, et al. Complete myocardial revascularization with transmyocardial laser as an adjunct to CABG without cardiopulmonary bypass. *JACC* 1997;29 (2,Suppl A):141A.
15. March RJ, Ali A, Bouzoukis M, et al. Effects of transmyocardial laser revascularization on myocardial perfusion. *JACC* 1997;29(2,Suppl A):121A.
16. Cooke RH, Boyce SW, Aranki S, et al. Myocardial perfusion imaging following transmyocardial laser revascularization. *JACC* 1997;29(2,Suppl A):72A.
17. Lowe JE. Transmyocardial laser revascularization (TMLR) versus medical management in patients unamenable to conventional revascularization. As presented at the American College of Cardiology Scientific Session, Anaheim, March 1997.
18. Schaper F, Lippek F, Krabatsch T, et al. Results of histomorphological and histomorphometrical investigations of left ventricular myocardium after transmyocardial laser revascularization (TMLR). JACC 1997;29(2,Suppl A):72A.
19. Sundt TM, Carbone KA, Oesterle SN, et al. The holmium-YAG laser for transmyocardial laser revascularization. Initial clinical experience. Presented at the American Heart Association Meeting, New Orleans, November 1996.
20. March RJ, Guynn Todd. Cardiac allograft vasculopathy: the potential role for transmyocardial laser revascularization. *J Heart Lung Transplant* 1995;14:S242-6.

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Abstracts of Interest

Results of Histomorphological and Histomorphometrical Investigations of Left Ventricular Myocardium After Transmyocardial Laser-Revascularisation. (TMLR)

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Although most of the patients, who are treated with TMLR, benefit from the procedure, the question of long-term patience of the channels is still not answered. Contradictory histological findings of TMLR-treated hearts suggest that there is no agreement about the histomorphology of laser-induced myocardial channels (LIMC). Furthermore there is no clarity about the tissue damage due to heat trauma. We investigated 8 hearts of patients who underwent TMLR and died 3-72 days postoperatively. Regions with LIMC were marked by the surgeon. The myocardium of this regions was cut in pieces, transverse and longitudinal sections were stained with Hematoxylin/Eosin (HE), in parallel sections Elastica-van-Gieson (EvG) staining was used for detection of kollagenous and elastic fibres. Morphometric measurements were performed using a computer assisted image analyser system. We found, that the LIMC measured 1.13 ± 0.09 mm (average ± standard deviation, n = 48) in diameter, the circular zone of necrosis was 0.58 ± 0.23 mm. Structural features of fresh LIMC were transverse aligned cylindrical zones of necrosis, accompanied by thin carbonisation, moreover cell detritus, fibrin and clotted blood. The LIMC were surrounded by high concentration of inflammatory cells. In the endocardium a defined destruction of kollagenous and elastic fibres was evident; the endocardial leak was filled with blood clot. Structural features of elder LIMC were transverse aligned oblong zones of abundantly vascularised fibrous tissue with high proliferation rate. In the endocardium only the kollagenous fibres were repaired, the elastic fibres didn't regenerate. The formerly endocardial leak was closed by a defined scar. Conclusion: LIMC are characterised by necrosis, carbonisation and inflammation or well vascularised fibrous tissue, depending on age. There is no evidence for connections between the left ventricular cavity and the intramyocardial vascular network. A treatment with 25 LIMC in heart with a wall-thickness of 1.8 cm means a loss of more than $3cm^3$ of myocardial tissue.

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Effects of Transmyocardial Laser Revascularization on Myocardial Perfusion

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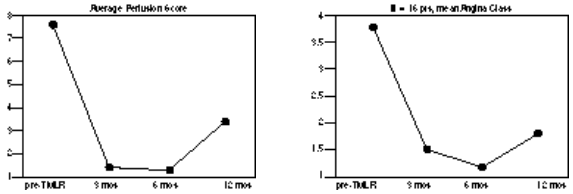
The effects of Transmyocardial Laser Revascularization (TMLR) on left ventricular (LV) Myocardial Perfusion (MP) have not been thoroughly examined. 16 consecutive patients (pts), ten men and six women (age range 45-76 yrs, mean 64) were followed at 3, 6 and 12 month intervals following TMLR. MP studies were obtained using IVdipyridamole over 4 min with 3.5 mCi of Thallium-201 (Tl) given 3 min later. MP imaging was done both immediately and at 3 hours following Tl infusion. Finally, 1.5 mCi of Tl was given and a third set of images was obtained. All images of the LV segments: anterior, lateral, inferior, posterior and septal were scored on a scale of 0-4+ by two independent observers who were blinded as to the lased segments (0 = nl, 2+ to 3+ = moderately severe ischemia, 4+ = severe ischemia). There were no deaths, myocardial infarctions or further revascularization procedures done on these pts during their first year of follow-up.



MP improves during the first year after TMLR, and parallels the changes observed in angina pectoris.

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