Transmyocardial laser revascularization for diffuse coronary artery disease: Early results

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Transmyocardial revascularization (TMR) using a high energy CO_2 laser has emerged as a new therapeutic option for patients with severe diffuse coronary artery disease refractory to conventional modes of therapy. TMR has shown symptomatic benefit and improvement in the exercise tolerance in a group of patients suffering from disabling angina, not amenable to other modes of treatment. However, this procedure resulted in 14 to 18% high early mortality in various series. The univariate predictors of mortality were age > 55 years, female sex, CKP > 1600 IU, absence of inter coronary collaterals, and mean PAP > 21 mm Hg. At one-year follow-up studies, a significant improvement in the angina class (II, III, IV), and treadmill testing (TMT) effort tolerance were observed; but without any significant change in the left ventricular ejection fraction. The high early mortality can be brought down with strict patient selection criteria. The mechanism of beneficial effects remains uncertain, and the patency of laser channels is controversial; but laser-induced neoangiogenesis is being looked upon as a plausible explanation.

TRANSMYOCARDIAL revascularization (TMR), using a high energy CO_2 laser[1], has emerged as a useful alternative mode of therapy for patients with severe refractory angina and coronary anatomy unsuitable for conventional modes of treatment. The procedure is based on the premise that the laser-created transmural channels allow blood to flow directly from the left ventricle to the myocardial vascular plexus and thereby alleviate ischaemia in potentially viable myocardium. Although the early follow-up data from various centers have shown a remarkable symptomatic benefit in angina class II, III, IV (refs 2–4), concrete objective evidence regarding improvement in myocardial perfusion is still lacking. The procedure has also been criticized due to its high early mortality[2,4,5], and there have been reports in the literature claiming that these laser-created channels get blocked early postoperatively, and that the beneficial effects of this procedure cannot be attributed to 'the reptilian heart' phenomenon[6].

We have therefore reviewed the data on patients who underwent transmyocardial laser revascularization at the Institute of Cardiovascular Diseases, Chennai, and present the results of early studies as well as of one-year follow-up studies.

Patient and methods

From December 1994 to September 1997, 102 patients underwent TMR as the sole mode of myocardial revascularization. During the same period, an additional 43 patients underwent TMR combined with coronary artery bypass grafting (CABG) (Table 1), but have not been included in this study. The mean age of the patients was 56.7 ± 9.2 years and most of the patients were between 51 and 70 years of age. All the patients were males. The mean preoperative angina class and rejection fraction of the patients were 2.6 ± 0.7 and 44.7 ± 10.5%, respectively; 49.01% patients were diabetic, 32.3% had history of previous myocardial infarction (MI), 12.7% had undergone a previous CABG and 9 patients (8.9%) had unstable angina at the time of surgery. Patient demographics are outlined in Table 2.

Patients suffering with severe angina, refractory to maximal medical therapy (Nitrates, Beta blockers, Ca channel blockers, and Trimetazidine), and who were not amenable to conventional percutaneous transluminal coronary angioplasty (PTCA) or CABG were enrolled in this study after explaining the nature of the procedure and obtaining informed consent. Patients with ejection fraction < 30% and scant evidence of reversible ischaemia on thallium myocardial perfusion scan were excluded.

Table 1. TMR and associated procedures

Procedure	Numbers of patients
Isolated TMR	102
TMR + CABG	25
TMR + CABG with endarterectomy	17
TMR + CABG + ASD closure	1
Total	145

TMR = Transmyocardial laser revascularization.
CABG = Coronary artery bypass grafting.
ASD = Atrial septal defect.

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Preoperative workup included 2D echocardiography for regional wall motion abnormality and estimation of ejection fraction. The patients underwent a symptom-limited treadmill testing (TMT) to record the baseline exercise tolerance, using a modified Bruce protocol, and stress thallium was performed to map region of reversible ischaemia.

Patients were operated using a left anterolateral thoracotomy through the 5th intercostal space. A 800 watt CO_2 laser (The Heart Laser, PLC Medical Inc., Milford, MA) was used to drill the laser channels employing an energy output of 40 J and pulse duration of 50 ms. An average number of 23 ± 8 channels were created in each patient. Of late we have reduced the pulse duration to 25 ms, as an experimental study recently has shown that increasing the pulse duration carries an increased risk of thermal damage to the surrounding tissues[7]. The laser was synchronized to the EKG signal and fired at the peak of 'R' wave. Transoesophageal echocardiography was employed to confirm the transmural penetration of laser. Intraoperatively the patients were monitored using continuous EKG and ST segment analysis. Pulmonary artery pressures and cardiac index were monitored employing a Swan Ganz thermodilution catheter. Postoperatively cardiac enzymes were measured at intervals of 4 h for 24 h, and the pattern of rise of the enzymes was recorded and analysed.

The patients were extubated after 6–8 h of elective ventilation, whenever possible. They were discharged home after 8 to 10 days of the operation. A follow-up study was undertaken at intervals of one month, three months, six months, and twelve months, postoperatively. At the time of follow-up, data regarding angina class, ejection fraction, and effort tolerance were recorded, and analysed using SPSS statistical package. Thallium myocardial perfusion scans were performed pre- and postoperatively to assess improvement in regional myocardial perfusion.

Autopsies on 8 patients, who died in hospital, involved the removal of 2–4 channels completely from each of the hearts after fixing them in buffered neutral formalin for 14 days. The entire blocks were sectioned serially from epicardial to endocardial surface, and were subjected to histopathological examination.

Results

The various perioperative parameters have been listed in Table 3. Most of the patients were extubated within 8 to 12 h of operation. The mean duration of ventilation was 10.2 ± 4.4 h and the patients stayed in the ICU for a mean period of 2.6 ± 1.2 days. 17 patients (14.7%) died within 30 days of the operation due to several factors (Table 4).

The use of intra aortic balloon pump (IABP) in 11 patients, due to persistent myocardial ischaemia, evolving myocardial infarct, low cardiac output and increasing need for inotropic supports, resulted in 8 mortalities due to cardiac failure.

A univariate analysis of the predictors of early mortality revealed that female sex, advanced age and perioperative MI were factors significantly affecting the early mortality (Table 5). The mean age of the patients who died was 63.1 years compared to 56.6 years for those who survived the operation. Other variables like perioperative angina class, associated risk factors, previous MI, and the number of laser channels were not observed to be predictors of early mortality.

A multivariăte logistic regression analysis, using SPS software V.4.0, showed age > 55 years as a statistically significant predictor of early mortality (odds ratio 7.7; 95% CI = 1.6–36.7; $P < 0.01$).

Table 2. Patient profile (n = 102)

	Patients	
Characteristic	Number	Percentage
Angina class II	47	46.07
III	44	43.13
IV	11	10.78
Risk factors		
Diabetes mellitus	50	49.01
Hypertension	51	50.0
Previous MI	33	32.35
Smoking	20	19.6
Hyperlipidaemia	43	42.15
Previous CABG	13	12.74
Left main disease	13	12.74

MI = Myocardial infarction.
CABG = Coronary artery bypass grafting.

Table 3. Perioperative characteristics

Average number of channels	23 ± 8
Mean pulmonary artery pressure	15 ± 4.5 mm Hg
Mean cardiac index	3.3 ± 0.8 L/min/m^2
Mean CPK	352 ± 276 IU
Mean CKMB	3.1 ± 1.6%
Perioperative use of IABP	11 (10.8%)

CKP = Creatinine phosphokinase.
CKMB = Creatinine phosphokinase-MB fraction.
IABP = Intra-aortic balloon pump.

Table 4. Causes of mortality

	Number of patients showing mortality
Early	
Perioperative myocardial infarction	9
Cardiac tamponade	1
Massive GI bleeding	1
Sepsis and multi organ failure	2
Sudden death (? arrhythmia)	2
Late	
Myocardial infarction	1
Sudden death	1
Total	17

Two patients died during follow-up studies, one due to MI and the other due to sudden cardiac death, while the follow-up studies of other patients have shown an improvement in anginal status even after one year. The exercise capacity on treadmill, both in exercise duration and met load, which was not showing any significant change up to six months postoperatively, improved remarkably, acquiring statistical significance. Ejection fraction did not improve and registered a marginal, though statistically insignificant drop at one year (Table 6). Thallium myocardial perfusion scans, preoperative and three months after operation did not reveal any significant improvement in myocardial perfusion. There was no difference in perfusion of the lased and nonlased (septal) segments.

Histopathology of serial sections derived from the hearts of the patients who died in the hospital revealed that the epicardial end of the channel appeared depressed and filled with thin or thick bands of fibrin. One of the features observed was that none of the channels was in straight line, but were twisted and spiralling, and unless care was taken to cut large sections through and through, there was a likelihood to miss the course of the channels, thereby wrongly concluding that the channels were closed. The apparent twisting of the channels is presumably due to the architecture of the cardiac muscle itself. The channels were generally observed to be filled with plasma and erythrocytes, separated by fibrin strands. Invariably, the channels showed communication with sinusoids in large number of areas entering either into sinusoids or opening into the endocardium. The endocardial end however, did show a few fibrin strands, but these appeared to be of recent origin indicating patency during life.

Table 5. Univariate predictors of mortality

Variables	Significance
Age > 55 years	$P < 0.006$
Female sex	$P < 0.03$
Mean CKP > 1600 IU	$P < 0.006$
No collaterals	$P < 0.004$
Mean PAP > 21 mm Hg	$P < 0.02$

CKP = Creatinine phosphokinase.
PAP = Pulmonary artery pressure.

Discussion

The conventional modes of treatment of coronary artery disease, i.e. PTCA and CABG have stood the test of time, improving the quality of life as well as its longevity. But, a substantial group of patients with diffuse small vessel coronary artery disease, especially in the Indian subcontinent, who are young and healthy in other respects and therefore could lead an active and productive life, cannot be offered these standard modes of treatment. Despite multiple endarterectomies, it is often not possible to achieve complete revascularization in these patients. For such patients despite maximal medical therapy, transmyocardial laser revascularzation has a definite role.

Our study differs from other western reports on TMR in many respects. Mainly, we are dealing with a younger group of patients (mean age 56.7 ± 9.2 years), 49.5% of them being diabetic, and therefore, underwent TMR as a primary procedure (87.4%) because their diffusely diseased small calibre vessels are not amenable to PTCA or CABG[4].

The operative technique and laser energy used for creating the channels has been fairly standardized for all the series, and similar settings were used in the present study as well. An experimental study recently showed that a pulse duration of 25 ms (energy output of 20 J) was sufficient to traverse the human myocardium, which is usually 20 mm thick[7]. Increasing the pulse duration provides only a marginal benefit; though thicker areas of myocardium can be accessed, it is at the expense of increased thermal damage to the surrounding tissue. Of late, we have reduced the pulse duration to 25 ms, and

Table 6. Postoperative follow-up studies

Parameter	Preoperative (n = 108)	Postoperative 1 month (n = 70)	3 months (n = 67)	6 months (n = 51)	12 months (n = 44)
Angina class	2.56 ± 0.7	0.7 ± 1.1	0.7 ± 1.0	0.8 ± 1.1	0.8 ± 0.9
Angina	100%	33%	35%	40%	46%
TMT					
Duration (min)	5.5 ± 3	6.5 ± 3.4	6.5 ± 3.4	8 ± 3.7	9.7 ± 4.0 ($P < 0.008$)
Workload (mets)	3.6 ± 1.7	3.7 ± 2.1	4.3 ± 2.3	5.4 ± 2.6	6.0 ± 3.4 ($P < 0.005$)
MUGA LVEF %	44.7 ± 10.5	42.2 ± 11.7	45.6 ± 18	46 ± 11.6	42 ± 11.7

TMT = Treadmill test.
LVEF = Left ventricular ejection fraction.

transoesophageal echocardiography has confirmed transmyocardial penetration of laser. The beneficial effects, if any, of this modification are yet to be documented.

The major criticism of this procedure is its high early mortality (reported to be 14 to 18% in various series), and in a significant number of cases it has been attributed to perioperative MI leading to cardiac failure[2,4]. Although some degree of rise in cardiac enzymes has been noticed in all the cases, postoperatively, the analysis of risk factors of early mortality has revealed that patients having creatinine phosphokinase (CKP) > 1600 IU and creatinine phosphokinase-MB fraction (CKMB) > 10% are at a higher risk of an unfavourable outcome. The factors contributing to perioperative infarction were the presence of left main disease and absence of well-developed inter coronary collaterals. We feel that early high mortality can be brought down with strict patient selection criteria.

But, patients have indeed benefited symptomatically, and the positive trend in the relief of angina has continued at one-year follow-up studies (Table 6). They definitely performed better on TMT, in both the duration of exercise as well as the metabolic equivalent (mets) achieved. Not only was this change most marked but also became statistically significant between six months and one-year follow-up studies. This observation perhaps supports the theory of laser-induced neovascularization, which requires time to develop to beneficially effect the myocardium. Thallium perfusion scans were not repeated in this study, as they did not show any improvement at three-months follow-up. However, with the availability of the data on improvement in exercise tolerance we plan to repeat the perfusion scans at one year after TMR to evaluate the improvement in regional perfusion.

Patients with impaired left ventricular (LV) function (mean PAP > 21 mm Hg), showing higher risk of early death, were not considered as good candidates for isolated TMR. Moreover, a marginal drop in ejection fraction at one-year follow-up was observed, which may tilt the balance in a patient with preexisting LV dysfunction, leading to an unfavourable outcome. For patients with poor LV ejection fraction and left main disease, we have now adopted a policy of combining TMR with CABG to at least one important vessel, and carry out extensive endarterectomies with onlay patch in such cases; as we believe that this graft supports the myocardium during the early postoperative period, improving the postoperative outcome.

Conclusion

We believe there is enough data to suggest that TMR provides symptomatic benefit and improves quality of life as well as the patient's ability to undergo stress. Although we do not have any evidence at present to show an improvement in regional myocardial perfusion, Cooley *et al.*[8] have demonstrated better subendocardial perfusion after TMR using PET scan. The mechanism of beneficial effects provided by TMR is still uncertain and controversial, but the focus is shifting towards laser-induced neoangiogenesis[9].

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