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Transmyocardial laser revascularization: Subjective success, objective controversy

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Low powered lasers were first used in the early 1980s to produce transventricular channels as an adjunct to coronary artery bypass graft surgery (CABG). Early results were encouraging, but because of the combined procedure, could not be attributed directly to use of the laser.[1] High powered lasers were introduced into clinical practice in 1990.[2] These lasers are powerful enough to create a transmyocardial channel with minimal thermal damage to surrounding tissues.[3] Clinical studies, using transmyocardial laser revascularization (TMR) as the sole operative therapy for patients with severe and diffuse coronary artery disease (CAD) who have Class III or IV angina, and are on medical therapy, have been conducted since 1993. Based on the results of these studies, the FDA granted approval for the use of TMR as a sole therapy. Clinical studies are currently underway to assess the results of combined TMR and CABG.[4] Over the last year, the results of four controlled randomized studies have been published.[5-8] The data from two of these studies formed the basis for FDA approval of two different types of laser systems. The results of these randomized trials are not identical, and in fact, are contradictory in some major aspects such as the evidence for improved myocardial perfusion. The results of these studies have not provided any additional insights into the mechanism of action of TMR which remains the Achilles'heel of this procedure. Consequentially, TMR continues to be a controversial issue and will remain so until the exact mechanism of action is deciphered. In this review, background information about the TMR procedure will be discussed along with an analysis of the recently published randomized studies.

What is TMR?

In TMR, a high energy laser is used to create a channel from the epicardial surface into the left ventricular chamber. The concept of connecting oxygenated blood from the left ventricular cavity to pre-existing myocardial sinusoids and to ischemic myocardium was the initial hypothesis behind the use of TMR.[9,10] Although sinusoids may occur in reptilian hearts, their existence and role in mammalian hearts is doubtful.[11] Even if these channels remain open, there might be a physiologic hindrance to blood flow through these channels during myocardial contraction accompanied with a siphoning effect during myocardial relaxation.[12]

Histology studies have shown that laser energy causes an injury and a healing-inflammation sequence that result in scar formation and channel closure.[13] Although there is an increased blood vessel formation within and around these channels, their role in improving myocardial perfusion remains undetermined.[14] However, this increase in vascular density around the channels may be beneficial in diminishing anginal symptoms. Direct damage of ischemic tissue, secondary to laser-induced myocardial infarction, has also been postulated as contributing to the relief of angina. In addition,sympathetic denervation secondary to tissue damage or nerve injury as a result of direct laser energy may

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also be responsible for the relief of angina. Finally, a placebo effect should always be considered when a new unblinded therapy without a definitive mechanism of action is introduced. It is feasible that one or more of these various mechanisms may be responsible at different time periods for the relief of angina.[15]

Laser-tissue interactions

Laser-tissue interactions and the desired effects needed determine which type of laser is used. Different types of lasers are used for different biological purposes.[16] The laser wave length and frequency, along with the optical properties of target tissues, determine the type of laser-tissue interaction. In turn, this is determined by photonic absorption and scattering by the target tissue, pulse energy and duration, and the peak power generated.[17] The lasers used need to be powerful enough to cause controlled destruction and ablation of myocardial tissues, without causing unwanted structural, thermal, and/or acoustic damage.

The types of lasers currently used for TMR are mainly the carbon dioxide (CO_2) and the Holmium-Yag (Ho:Yag) lasers. Another type of laser is the Excimer laser. The CO_2 and Ho:Yag lasers are infrared lasers exerting their effect by vaporizing water molecules. These lasers have frequencies similar to the vibration frequency of water. Absorption of laser energy by water molecules results in heating, evaporation, and tissue ablation. The Excimer laser, on the other hand, operates in the ultraviolet range and exerts its effect by dissociating the dipeptide bonds of proteins. Because the myocardium is composed predominantly of water and proteins, these types of lasers are ideal for creating transmyocardial channels.[18]

Candidates for TMR

Patients selected for TMR are more likely to have diabetes and multiple risk factors for CAD and usually have had prior conventional coronary revascularization. Indeed, multiple prior procedures are common. In spite of this, severe angina – not controlled with intense medical therapy and present as Class III or IV symptoms and poor quality of life – is the indication for the procedure. Patients with congestive heart failure and poor left ventricular function are not good candidates for TMR. Objective evidence for ischemia of the free wall of the left ventricle is an essential pre-requisite for this procedure. Septal ischemia alone is a contra indication for TMR, since the epicardially applied laser beam cannot reach the septum.[19]

An increasing number of these medically refractory, unsuitable for standard revascularization patients are being referred to tertiary centers where TMR is performed. Nevertheless, the number of those requiring TMR as a sole therapy is very small compared to patients undergoing CABG or PTCA.[20] Since 1993, the proportion of patients enrolled in phase II and III studies at the Brigham and Women's Hospital accounted for only 0.1% of primary CABG procedures and 1% of reoperative CABG procedures. However, it is probably more likely that patients requiring a combined TMR and CABG may represent a much larger proportion of CABG procedures.

The TMR operative procedure

The procedure is performed under general anesthesia through a limited left anterior thoracotomy. The majority of these patients have had previous CABG procedures and thick scar tissue is usually abundant. Care must be taken to prevent injury to the left phrenic nerve, left ventricle, epicardial vessels, as well as to any patent or diseased grafts. When the free wall of the left ventricle is exposed, TMR is performed. With CO_2 laser, a single energy pulse is used to create the laser channel. With the Ho:Yag laser, multiple pulses with a laser probe are required. The laser energy causes tissue ablation and vaporization that can be detected as a puff of smoke on transesophageal echocardiogram when the laser transverses the free wall of the left ventricle.[21] Laser energy is dissipated by the blood in the left ventricle which minimizes injury to the mitral valve apparatus.[19]

After the laser channels are created, blood spurts through until a clot is formed on the epicardial surface. Hemostasis is achieved by digital compression. This pulsatile bleeding is the only irrefutable evidence that blood is flowing through the newly created channels.[22] How long these channels remain open and to what extent the blood flows through them to contribute to angina relief remains a matter of controversy.

Cardiopulmonary bypass is not necessary and the procedure is performed on a beating heart. The CO_2 laser is synchronized to the electrocardiogram. The laser pulse is fired on the peak of the R-wave when the heart is electrically and mechanically quiescent. This reduces the incidence of arrhythmias and structural damage to the mitral valve apparatus.[23] Ten to fifty 1-mm channels are created in the ischemic zone of the left ventricular free wall. Besides the exposure and localization, the actual operative technique of TMR is fairly simple.

Perioperative management

Perioperative management of these patients presents a major challenge.[19] Unlike CABG or PTCA, where direct myocardial revascularization and improvement in coronary blood flow is achieved at the end of the procedure, the luxury of promptly reversing ischemia with TMR does not exist. Patients selected for TMR generally have severe forms of refractory ischemia and the addition of anesthesia and surgery, without improving myocardial blood supply, is a source of major stress. It is not surprising that these patients can develop acute ischemic episodes during or after surgery. As such, we have employed an aggressive monitoring, pharmacological, and mechanical support protocol for these patients at the Brigham and Women's Hospital that has resulted in improvements in perioperative morbidity and mortality.[15] Pulmonary-

artery catheter, radial arterial line, transesophogeal echocardiograms, prophylactic intravenous nitrates, and intra-aortic balloon counterpulsation (when possible) are routinely used. As the clinical condition allows for intravenous nitrates and intra aortic balloon counterpulsation to be withdrawn in 24 to 48 hours, depending on the hemodynamic stability of these patients, oral preoperative anti-anginal medications are re-initiated as soon as possible. These medications should be titrated to pre-operative levels and close cooperation with the treating cardiologist is important. Intravenous heparin is added when there is no evidence of bleeding through the thoracic tubes. Blood loss is usually between 100-500 cc's and blood transfusion is rarely required.

In summary,the operative procedure is simple and straightforward, but the perioperative management is far more complex and demanding than routine CABG. Further improvements can be expected with further refinement and fine-tuning of perioperative management for this group of potentially acute ischemic patients.

Clinical trial results with TMR

By the nature of the operative procedure, double-blind randomized trials have not been conducted with TMR. The largest clinical experience to date has been with the CO_2 laser (PLC Medical Systems, Franklin, MA). Horvath[24] reported that over 2500 patients worldwide underwent TMR with this system. Most published reports prior to 1999 were either retrospective or non-randomized prospective studies.[3,18,21,23] In 1999, four prospective randomized studies were published. One study was from the United Kingdom where the CO_2 laser was used (UK/CO_2).[5] The other 3 studies are from the United States; one of these studies used CO_2 laser (US/CO_2)[6] and the other 2 studies used the Holmium-Yag laser (US/HY_1[7] and US/HY_2[8]).

Three of these studies were industry-sponsored and their conclusions were favorable for the endorsement of TMR use for patients with severe angina on maximal medical therapy who were not suitable for CABG or PTCA. The fourth study which showed improvements in angina and exercise capacity (not as significant as the other studies) concluded that adoption of TMR cannot be advocated. This study was sponsored by the National Health Service and by a third-party payer. Regardless of the conclusion of each individual study, it is prudent perhaps to interpret them by analyzing a patient's characteristics, operative techniques, and various endpoints collectively in order to get a broader view about the potential therapeutic role of TMR.

Patient characteristics

A total of 837 patients were randomized to have TMR (n=409) or medical therapy (n=428). The rate of enrollment of eligible patients was reported in 2 studies (UK/CO_2 and US/HY_1) and varied from 55-60%. The main reasons for exclusion of eligible patients were: there was no evidence for reversible ischemia or suitability for conventional revascularization procedures, low ejection fraction, and refusal to participate in the study. Age and gender distribution was similar in all 4 studies. All patients had class III or IV CCS angina class. In one study (US/HY_2), all patients (100%) were in class IV angina. In the UK/CO_2 study, 25% of the patients were in class IV and in the other two studies, at least two-thirds were in class IV angina. The majority of these patients had a previous CABG (55-95%) and an ejection fraction of over 45%. History of previous myocardial infarction, diabetes, hypertension, hypercholesterolemia, smoking, and family history was similar for the 4 studies. The higher percentage of diabetic patients compared to CABG patients in these studies patients reflects the severe and diffuse nature of CAD in this patient population, selected as unsuitable for conventional revascularization procedures. In the US/HY_1 study, an additional inclusion criteria of a protected region of the left ventricle was required. This was defined as a territory that was supplied by an unobstructed blood flow (no lesions >50%) through a major native vessel or previously placed bypass grafts. This inclusion requirement was based on previously reported data of increased operative mortality in the absence of such protection.[25]

The operative technique was essentially the same in the 4 studies. In 3 of the studies, through a limited left anterior thoracotomy, a mean of 30-39 channels were created in the free wall of the left ventricle. The US/HY_1 reported a median of 19 channels with a range of 9-42. The channels were about 1mm in diameter placed at a density of 1 channel/cm^2.

Mortality and morbidity

The 30-day mortality ranged from 1-5%. The US/HY_1 study had a mortality of 1% and the authors contributed this low mortality to the presence of a protected region of the left ventricular myocardium. The 30-day mortality for patients randomized to medical therapy was 2% as reported by the US/CO_2 and US/HY_2 studies. These two studies allowed patients to cross over from medical to laser therapy for unstable angina. The operative mortality for this group (cross-over patients) was 15% and 9%, respectively. The US/CO_2 study found that unstable angina and low ejection fraction were independent predictors of perioperative mortality. The risk of death increased by over 20-fold when the time between unstable angina and surgery was less than 2 weeks.

Perioperative morbidity included myocardial infarction, atrial arrhythmias, worsening congestive heart failure, pneumonia, and wound cellulitis. As expected, the overwhelming causes of mortality and morbidity were cardiac in origin. There was one procedure-specific complication with laser-induced injury to the mitral valve apparatus that required repair.

Survival at 12-months ranged from 85% to 96% in TMR patients compared to a range of 79% to 96% for medical

Table 1: Objective results: Nuclear scans.

Study		Reversible Sites (%)		Fixed Sites (%)	
		TMR	MED	TMR	MED
UK/CO_2	Baseline	31	34	14	8
	12 months	21	22	19	7
US/HY_1	Baseline	14 (0-63)	13 (0-51)	9 (0-45)	13 (0-51)
	12 months	11.5 (0-65)	12 (0-50)	11 (0-63)	11 (0-39)
US/CO_2	Baseline	7.1 ± 3.7	6.8 ± 3.3	9 ± 3.6	9 ± 3.3
	12 months	↓ 1.4 segments	↑ 1.3 segments*	No Change	No Change
US/HY_2	Baseline	No numbers given – No change			
	12 months				

*only statistical difference

therapy patients. In none of the studies was there a significant prolongation of survival in the TMR group.

Results of treadmill stress test

Two of the studies had duration of treadmill exercise as a primary end point. In the UK/CO_2 study, the difference in exercise time at 12 months was 40 seconds in favor of TMR, but this difference was not significant. The test was stopped more frequently for angina in medical patients and for dyspnea or fatigue in TMR patients. In the US/HY_1 study, there was a median of a 60-second improvement in exercise duration at 12 months in TMR patients, while more than 50% of medical patients had a 64% reduction in exercise tolerance. Overall total exercise tolerance increased by a median of 65 seconds in TMR patients compared to a median reduction of 46 seconds in medical patients. This difference was significant ($p<0.0001$). A deterioration of exercise duration by 60 seconds or more occurred in 17% of TMR patients as compared to 45% of medical therapy patients. The US/HY_2 study did not have a baseline treadmill exercise evaluation. However, in a subgroup of 90 of the 275 patients, there was a greater exercise tolerance of TMR patients (5± 0.7 MET vs 3.9± 0.8 MET, TMR vs. medical therapy, $p=0.05$).

Angina status and medications

In all 4 studies, there was a significant improvement in the frequency and severity of angina after TMR. The extent of improvement varied from 25% for the UK/CO_2 study to 65-75% in the 3 US studies. Clinical success was defined as a reduction of 2 CCS angina classes at follow-up. The US/HY_1 showed that TMR had a differential effect on angina improvement in relation to baseline severity. In patients with class IV angina, 67% were improved vs. 59% for class III. This is compared to 12% vs. 10%, respectively, for medical patients. All 4 studies showed a significant reduction in the number of hospital admissions for unstable angina or for cardiac-related causes in the TMR group compared to medical treatment patients.

Anti-anginal medications were significantly reduced in the UK/CO_2 and the US/HY_2 studies following TMR. The other 2 studies showed no such significant reduction.

Nuclear scans (Table 1)

The UK study used technetium-99m-labelled sestamibi, while the 3 US studies used dipyridamole thallium stress testing. All four studies showed no change in the proportion or number of fixed segments from baseline to 12-months following randomization. Three of the studies showed no significant change in the proportion of ischemic segments at baseline and follow-up. However, the US/CO_2 study showed a reduction in ischemic segments following randomization to TMR and an increase in ischemic segments following randomization to medical therapy ($p=0.002$). Symptomatic relief of TMR patients was not generally supported by objective improvements in perfusion imaging.[26]

Cardiac events and quality of life

There was no significant difference in cardiac events such as acute myocardial infarction and congestive heart failure between patients randomized to TMR or medical therapy. In addition, in two of the studies (UK/CO_2 and US/HY_1), no changes in left ventricular function were detected as measured by ejection fraction changes from baseline to 12-month follow-up.

The UK/CO_2 study collected information on health-related quality of life and detailed resources used,but the results were not reported. In the US/HY_1 and US/CO_2

studies, the Seattle Angina Questionnaire (SAQ) was used to assess quality of life at 12-month follow-up. Both studies reported that quality of life ind6ex scores were significantly better for the TMR group. In addition, the US/CO_2 study also used the short form questionnaire (SF-36) and reported 38% improvement for TMR patients in general physical and mental perception, compared to 6% for medical patients ($p<0.001$). In the US/HY_2 study,the Duke activity status index was used to assess the quality if life. This is based on a scale from 0-58 with higher scores indicating greater functional capacity. At 12-months, the score was 21± 14 for TMR patients and 12 ±11 for medical patients ($p=0.003$).

Summary of randomized trials

The results of these randomized studies show a definite improvement in anginal symptoms in TMR patients, without any substantial change in pre-operative anti-anginal medications. These symptomatic improvements are translated into better quality of life as self-reported by patients on questionnaires. In addition, there was a significant reduction in the need for hospital admissions for unstable angina and for cardiac causes following TMR. If this pattern holds for the long term, it may have an impact on cost reduction after TMR compared to medical therapy, but such outcomes were not part of the original design of these trials.

The objective evidence for increased perfusion following TMR to explain these improvements in symptoms has not been forthcoming. Only one study showed some improvement in myocardial perfusion following TMR, but this increase was disproportionate to the improvement in symptoms. Another objective assessment was the duration of exercise. Only two studies assessed exercise duration at baseline and following randomization.[5,6] One study[5] showed some improvement that was not statistically significant, while the other showed significant increase. In the other 2 studies, there were no baseline stress data and only one had such data at 12 months in only one-third of the patients, where TMR patients had better exercise durability.[8] One possible reason for this discrepancy in results is the sensitivity of nuclear scans in measuring any changes in perfusion following TMR. However, such a question needs to be answered by people experienced in these techniques.

Other interesting results not highlighted by the investigators of these studies were survival, ejection fraction, freedom from cardiac events, and the extent of fixed defects on nuclear scans. Analyzing these results may provide some circumstantial evidence either for or against some proposed mechanisms of action of TMR. Survival at 12-months following TMR was similar to that in medical therapy patients, despite the operative mortality. Similarly, there was no difference in ejection fraction, the rate of cardiac events, and the proportion of fixed defects on nuclear scans between the two groups. These findings argue against important laser-induced myocardial damage. In addition, sympathetic denervation as a reason for symptomatic improvement might be doubtful. Denervation can lead to silent ischemia, myocardial infarctions, and death. Such findings were not reported following TMR.

Is TMR the only alternative for these patients? The answer is definitely no. Other novel non-invasive therapies have been recently introduced. Such therapies include external balloon counterpulsation,[27] neurostimulation,[28] and catheter-based laser revascularization.[29] However, long term results are not yet available. Assuming that such therapies are comparable to TMR, it is most likely that TMR primary indications will be used in combination with CABG in patients with three-vessel disease and at least one inoperable region, unless of course, irrefutable evidence emerges to show that TMR is no more effective than placebo.

We are currently using the CO_2 laser, based on the FDA recommendations. The FDA is monitoring the results closely and sole therapy patients are entered into a randomized registry,where they will be randomized for the TMR procedure within 5 days from agreeing to participate in the study vs 30 days. We are also using the TMR procedure in conjunction with CABG surgery for patients with one or more inoperable regions of the myocardium. This combined procedure is not under any protocol at the present time and is being performed because of medical necessity only. The future of TMR is continually evolving and will greatly depend on the results of latter base laser revascularization. If this becomes an established therapy, it would undoubtedly become the treatment of choice for sole therapy, and TMR would continue the treatment of choice of combined therapy (TMR and CABG).

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