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TRANSMYOCARDIAL LASER REVASCULARIZATION

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Abstract

It has been almost a decade since transmyocardial laser revascularization (TMR) was approved for clinical use in the United States. The safety of TMR was demonstrated initially with non-randomized studies in which TMR was used as the only treatment for patients with severe angina. TMR efficacy was proven after multiple randomized controlled trials. These revealed significant angina relief compared to maximum medical therapy in patients with diffuse coronary disease not amenable to conventional revascularization. In light of these results, TMR has been used as an adjunct to coronary artery bypass grafting (CABG). By definition, patients treated with this combined therapy have more severe coronary disease and the co morbidities that are associated with end stage atherosclerosis. Combination CABG + TMR has resulted in symptomatic improvement without additional risk. The likely mechanism whereby TMR has provided benefit is the angiogenesis engendered by the laser-tissue interaction. Improved perfusion and concomitant improvement in myocardial function has been observed post TMR. Additional therapies to enhance the angiogenic response include combining TMR with stem cell based treatments which appear to be promising future endeavors.

INTRODUCTION

HISTORY

Despite the success of medical therapy, percutaneous coronary interventions (PCI), and coronary artery bypass grafting (CABG) in the treatment of coronary artery disease; there are a significant number of patients with refractory angina due to diffuse coronary artery disease that is not amenable to PCI or CABG. This severe coronary artery disease can lead to incomplete revascularization following CABG and is noted to occur in up to 25% of CABG surgery [1]. This incomplete revascularization is a powerful independent predictor of operative mortality and perioperative adverse events [1-3]. Additionally, the presence of diseased but non-grafted arteries carries a poor prognosis and poses a significant negative influence leading to an increased incidence of death, recurrent angina, myocardial infarction, and the need for repeat CABG [4-6]

Transmyocardial laser revascularization (TMR) was designed to treat patients with end-stage coronary disease. Since the Food and Drug Administration (FDA) approval in 1998

over 20,000 TMR procedures have been performed in the United States and over 50,000 worldwide. Results from individual institutions, multi-center studies and prospective randomized controlled trials have been reported [7-20].

TMR AS SOLE THERAPY

CLINICAL TRIALS

The initial non-randomized trials demonstrated that sole therapy TMR could be performed safely on patients with severe coronary artery disease who previously had no other options. The significant angina relief achieved in these patients led to prospective randomized controlled studies to further demonstrate the efficacy of TMR. In these pivotal trials over 1,000 patients were enrolled and randomized to receiving either TMR or medical management as treatment for their severe angina [14-19].

The enrollment criteria for these sole therapy trials were as follows: Patients had refractory angina that was not amenable to standard methods of revascularization. They had evidence of reversible ischemia based on myocardial perfusion scanning and their left ventricular ejection fractions were greater than 25%.

The typical patient profiles of TMR patients in the randomized controlled trials are listed in Table 1. Because the patients were equally randomized to the medical management group there were no significant demographic differences between the TMR and the control groups for any of these trials. Three studies [14-16] employed a Holmium: yttrium-aluminum-garnet (Ho:YAG) laser and three, [17-19] used a carbon dioxide (CO₂) laser. The average patient age was 62 years and the majority were male (86%). While there were significant differences in the baseline distribution of patients according to Canadian Cardiovascular Society (CCS) Angina Class, the majority of the patients were in angina Class IV (61%). The ejection fractions for all of the patients were mildly diminished at $48 \pm 10\%$. Many of the patients had suffered at least one previous myocardial infarction and most had some prior revascularization, CABG and/or PCI. Two of the trials, [14, 17] permitted a crossover from the medical management group to laser treatment for the presence of unstable angina that necessitated intravenous anti-anginal therapy for which they were unweanable over a period of at least 48 hours. By definition, these crossover patients were less stable and significantly different than those who had been initially randomized to TMR or medical management alone.

OPERATIVE TECHNIQUE

For sole therapy TMR, the patient is placed in a supine position with their left side slightly elevated. General anesthesia may be established using a double-lumen endotracheal tube or a bronchial blocker to help isolate the left lung. This facilitates the operation, particularly as most of the patients have pleural and mediastinal adhesions from previous bypass surgery. Additionally, a thoracic epidural catheter can be employed to provide postoperative pain control.

A left anterior thoracotomy in the fifth intercostal space is the usual incision site. Once the ribs are spread by a retractor, the pericardium is opened to expose the epicardial surface of

the heart (Figure 1). Care must be taken to avoid previous bypass grafts. The left anterior descending artery is identified and used as a landmark for the location of the septum. The inferior and posterior lateral portions of the heart can be reached through this incision with a combination of manual traction, placement of packing behind the heart, and, as illustrated, with the use of a right-angled laser handpiece. Channels are created starting near the base of the heart and then serially in a line approximately 1-cm apart toward the apex; starting inferiorly and working superiorly to the anterior surface of the heart. As there is some bleeding from the channels, commencement of the TMR inferiorly keeps the anterior area clear and expedites the procedure. The number of channels created depends on the size of the heart and on the size of the ischemic area. Myocardium that is thinned by scar, particularly when the scar is transmural, should be avoided as TMR will be of no benefit to these regions and bleeding from channels in these areas may be problematic. The thoracotomy is then closed after the placement of a chest tube and in the majority of the cases, the patient is extubated in the operating room.

The handpiece in Figure 2 is from a CO₂ laser and illustrates one of the differences between the two lasers employed for TMR. The CO₂ laser energy is delivered via hollow tubes and is reflected by mirrors to reach the epicardial surface. 1-mm channels are made with a 15-20 J pulse. The firing of the laser is synchronized to occur on the r wave of the EKG to avoid arrhythmias. The transmural channel is created by a signal pulse in 40 milliseconds and can be confirmed by transesophageal echocardiography (TEE). The vaporization of blood by the laser energy as the laser beam enters the ventricle creates an obvious and characteristic acoustic effect as noted on TEE. The Ho:YAG laser achieves a 1-mm channel by manually advancing a fiber bundle through the myocardium while the laser fires. Typical pulse energies are 2 Js for this laser and at a rate of 5 pulses per second, 10-20 pulses are required to traverse the myocardium. Detection of transmural penetration is primarily by tactile and auditory feedback.

ENDPOINTS

The principal subjective endpoint for all of the trials was a change in angina symptoms. This was assessed by the investigator and/or a blinded independent observer. In addition to assigning an angina class, standardized questionnaires such as the Seattle Angina Questionnaire, the Short Form Questionnaire 36 (SF-36), and the Duke Activity Status Index were employed. These tests were used to detect changes in symptoms and quality of life. Objective measurements consisted of repeated exercise tolerance testing as well as repeat myocardial perfusion scans. Patients were reassessed at 3, 6, and 12 months post-randomization.

RESULTS: SOLE THERAPY

MORTALITY

Prior to the randomized studies, mortality rates in the 10-20% [7-13] range were reported for TMR patients. In the randomized trials, lower perioperative mortality rates were reported ranging from 1-5% [14-20]. One of the important lessons learned from the randomized trials that differ from the earlier studies was a decrease in the mortality when patients taken to the

operating room were not unstable, specifically not on IV heparin or nitroglycerin. When patients were allowed to recover from their most recent episode of unstable angina, and were able to be weaned from intravenous medications such that their operation could be performed two weeks later, the mortality dropped to 1% [17]. The one-year survival for TMR patients was 84-95% and for medical management patients was 79-96%. Meta-analysis of the one-year survival demonstrated no statistically significant difference between the patients treated with a laser to those that continued with their medical therapy [21]. Long term survival of the randomized patients from two of these studies has been reported. Four year follow-up from Aaberge et al in which both the TMR and medical management groups were kept intact demonstrated a 78% survival for TMR vs 76% for medical management ($p=ns$) [22]. In 5 year follow-up using an intent-to-treat analysis Allen reported a survival for TMR patients at 65% vs 52% for medical management patients ($p=0.05$) [23].

MORBIDITY

Unlike mortality, the exact definition of various complications varied from one study protocol to the next, and therefore, morbidity data are difficult to pool. Nevertheless, the typical TMR patient's postoperative course had a lower incidence of myocardial infarction, heart failure, and arrhythmias than what has been documented in a similar cohort of patients, those that have reoperative CABG [14-19].

ANGINA CLASS

The principal reason for performing TMR is to reduce the patient's anginal symptoms. This can be quantified by assessing the angina class, pre- and post procedure. Angina class assessment was performed by a blinded independent observer in all studies. This was done as the only angina assessment or as comparison with the investigators' assessment. Significant symptomatic improvement was seen in all studies for patients treated with the laser. Using a definition of success as a decrease of two or more angina classes, all of the studies demonstrated a significant success rate after TMR with success rates ranging from 25-76% (Figure 3). A meta-analysis of this angina reduction yielded a summary odds ratio of 9.3 (95% CI: 4.6-18.5 $p<0.000001$). Significantly fewer patients in the medical management group experienced symptomatic improvement and the success rate for these patients ranged from 0-32%. The seemingly broad range of success is due to differences between the baseline characteristics of the studies. It is more difficult to achieve a two angina class improvement if the baseline angina class is III. Studies that started with most of their patients in angina class III, not surprisingly showed the lowest success rate. In contrast, the largest success rate for TMR was seen in the trial in which all of the patients were in CCS class IV at enrollment. Of note, the medical management group in this study also showed the largest success rate [14].

QUALITY OF LIFE & VENTRICULAR FUNCTION

Quality of life indices as assessed by the Seattle Angina Questionnaire, the SF-36, and Duke Activity Status Index, demonstrated significant improvement for TMR treated patients vs. medical management in every study. Global assessment of myocardial function by ejection fraction using echocardiography or radionuclide multigated acquisition scans showed no

significant change in the overall ejection fraction for any of the patients, regardless of group assignment or study.

HOSPITAL ADMISSION

Another indicator of the efficacy of TMR was demonstrated in a reduction in hospital admissions for unstable angina or cardiac related events post-procedure. A meta-analysis of the data provided indicates that the one year hospitalization rate of patients in the laser treated group was statistically significantly less than for those treated medically. Medical management patients were admitted four times more frequently than TMR patients over the year of follow-up [21].

EXERCISE TOLERANCE

Additional functional test assessment using exercise tolerance was also performed in three of the trials [15, 18, 19]. While the method of treadmill testing differed between the trials, the results demonstrate an improvement in exercise tolerance for TMR treated patients. Two studies showed an average of 65-70 second improvement in the TMR group at 12 months compared to their baseline, while the medical management group had either an average of 5 second improvement or a 46 second decrease in exercise time over the same interval [18, 19]. One additional trial demonstrated that the time to chest pain during exercise increased significantly and fewer patients were limited by chest pain in the TMR group, whereas the medical management group showed no improvement [19].

MEDICAL TREATMENT

All of the studies employed protocols that continued all of the patients on maximal medical therapy. For each study the frequencies and dosages of antianginal and cardiovascular drugs were similar between the two groups at baseline. TMR patients as a result of their symptomatic improvement, had a reduction in their medication use over the year of follow-up. As many of these patients used a combination of short and long acting nitrates preoperatively, the trials demonstrated a significant decrease in the use of nitrates in TMR treated patients while the medical management patients showed a slight increase in their nitrate usage. At one year, the overall medication use decreased or remained unchanged in 83% of the TMR patients and conversely the use of medications increased or remained unchanged in 86% of the medical management patients [17]. The significant angina relief seen following TMR was not due to medication changes or increases for the TMR treated patients.

MYOCARDIAL PERFUSION

As previously stated, myocardial perfusion scans were obtained preoperatively to verify the extent and severity of reversible ischemia. The four largest randomized trials included follow-up scans as part of their study [14, 15, 17, 18]. These results reflect over 800 of the patients randomized. The methodology of recording and analyzing these results differed in each study so it is difficult to pool the data. Nevertheless, review of the results demonstrated an improvement in perfusion for CO₂ TMR treated patients. Fixed (scar) and reversible (ischemic) defects were tallied for both the TMR treated patients and the medical

management groups. One CO₂ study demonstrated a significant decrease in the number of reversible defects for both the TMR and the medical management patients [18]. This improvement in the reversible defects in the TMR group was seen without a significant increase in the fixed defects at the end of the study. However, the number of fixed defects in the medical management group had nearly doubled over the same 12 month interval. Similarly, there was a 20% improvement in the perfusion of previously ischemic areas in the CO₂ TMR group of another trial and in that same trial there was a 27% worsening of the perfusion of the ischemic areas in the medical management group at 12 months [17]. There was no difference in the number of fixed defects between the groups at 12 months, nor was there a significant change in the number of fixed defects for each patient compared with their baseline scans. The remaining two Ho:YAG studies that obtained follow-up scans showed no significant difference between the TMR and the medical management groups at 12 months and no significant improvement in perfusion in the TMR treated patients over the same interval [14, 15]

Non-randomized data had previously demonstrated an improvement in perfusion using dual isotope scanning at one and two years after CO₂ TMR [24]. Additionally, using N-13 ammonia position emission tomography (PET) assessment, subendocardial perfusion improved significantly compared to the subpericardial perfusion after CO₂ TMR treatment [25, 26].

LONG-TERM RESULTS

Two reports of long-term follow-up of prospectively randomized patients are available. Similar to the one-year results, intention to treat analyses determined that significantly more TMR than MM patients continued to experience at least two-class angina improvement from baseline (88% vs 44%, $p<0.001$) or were free from angina symptoms altogether (33% vs 11%, $p=0.02$) at a mean of five years [23]. In long-term follow-up of the randomized trial that kept both the TMR and MM groups intact (i.e. no cross-over), it was shown that angina symptoms were still significantly improved (24% vs 3%, TMR vs MM, $p=0.001$) and unstable angina hospitalizations were significantly reduced ($p<0.05$) at a mean follow-up of 43 months [22]. Follow-up of a series of nonrandomized patients who received TMR and survived long term, support these findings [27]. At a mean of five years and up to seven years post procedure, 81% of these patients improved to Class II or better, 68% were found to have improved at least two angina classes from baseline, 17% were angina-free, and quality of life remained significantly improved. These last two reports reflect the sustained angina relief seen with CO₂ TMR as these patients had no additional procedures to account for their symptom improvement over the long term.

Based on an assessment of the cumulative results from these multiple randomized trials, the recently updated American College of Cardiology / American Heart Association (ACC/AHA) practice guidelines [20], Society of Thoracic Surgeons (STS) practice guidelines [29] and a consensus statement from the International Society of Minimally Invasive Cardiac Surgery [30] have determined that the weight of the evidence strongly favors the use of TMR in the treatment of stable, medically refractory, angina patients.

TMR AS AN ADJUNCT TO CABG

CLINICAL TRIALS

Owing to its success as sole therapy, TMR has been evaluated in conjunction with CABG in patients with diffuse coronary artery disease who would be incompletely revascularized by CABG alone. The safety and effectiveness of adjunctive TMR have been somewhat difficult to assess due to the influence of coronary bypass grafts and the lack of randomized control arms in some studies [31-33].

Two prospective, randomized, multi-centered controlled trials have been performed using TMR adjunctively with CABG in patients. In these studies patients with one or more viable myocardial target areas served by coronary vessels that were not amenable to bypass grafting received either CABG plus TMR or CABG alone [34, 35]. Baseline and operative characteristics were similar between groups, including the location and number of bypass grafts placed (3.1 ± 1.2 , CABG/TMR; 3.4 ± 1.2 , CABG alone, $p=0.07$). Patients were blinded to their treatment group through one-year follow-up.

RESULTS: TMR AS AN ADJUNCT TO CABG

MORTALITY

Improved outcomes following TMR + CABG versus CABG alone in terms of a reduced operative mortality rate (1.5% vs 7.6%, $p=0.02$), reduced postoperative inotropic support requirements (30% vs 55%, $p=0.001$), increased 30-day freedom from major adverse cardiac events (97% vs 91%, $p=0.04$), and improved one-year Kaplan-Meier survival (95% vs 89%, $p=0.05$) have been reported [34]. Multivariable predictors of operative mortality were CABG alone (odds ratio 5.3, $p=0.04$) and increased age (odds ratio 1.1, $p=0.03$) [34]. A similar beneficial trend in operative mortality following TMR + CABG versus CABG alone (9% vs 33%, $p=0.09$) was reported in a study of high-risk patients [35].

EFFICACY

The use of TMR adjunctively with CABG has been shown to decrease intensive care unit (ICU) times and length of hospitalization stay [33]. In long-term follow-up of the randomized controlled trial, the effectiveness of TMR + CABG vs CABG alone has been reported [36]. At a mean of five years, both groups experienced significant angina improvement from baseline, however, the TMR + CABG group had a lower mean angina-free patients (78% vs 63%, $p=0.08$), compared to CABG alone patients. Long term survival was similar between randomized groups.

Observational data on the practice of TMR + CABG has been collected in the Society of Thoracic Surgeons National Cardiac Database [37, 38]. From 1998 to 2003, 5,618 patients underwent TMR + CABG. These were contemporaneously compared with 932,715 patients who underwent CABG only operations. Table 2 outlines the significant baseline differences between the CABG only patients and the TMR + CABG patients. The TMR + CABG patients have an increased incidence of every surrogate marker of diffuse arterial disease and therefore it is not surprising that their observed mortality was higher at 3.8% (vs 2.7% for CABG only patients, $p<0.001$). When unstable angina patients were removed, the observed

mortality for TMR + CABG was decreased to 2.7% and the O/E ratio was 0.87. Comparison of use and outcomes from sites that have a TMR laser vs those that do not showed no evidence of overuse of TMR or difference in outcomes [38].

MECHANISMS OF ACTION

LASER-TISSUE INTERACTIONS

Understanding the mechanism of TMR starts with understanding the laser-tissue interaction. While numerous devices [39, 40], including ultrasound [41], cryoablation [42], radio frequency [43, 44], heated needles [45, 46], as well as hollow and solid needles have been used; none have engendered the same response that is seen with a laser. Additionally, numerous wavelengths of laser light have also been employed. These include xenon-chloride (XeCl) [47, 48], Neodymium:YAG (Nd:YAG) [49], Erbium:YAG (Er:YAG) [50], and Thulium-Holmium-Chromium:YAG lasers (THC:YAG) [51]. All of these devices have been explored experimentally, but have not been pursued on a significant scale clinically. Only CO₂ and Ho:YAG are clinically approved for TMR. The result of any laser tissue interaction is dependent on both laser and tissue variables [24, 50, 51, 52]. CO₂ has a wavelength of 10,600-nm, whereas Ho:YAG has a wavelength of 2,120nm. These infrared wavelengths are primarily absorbed in water and therefore rely on thermal energy to ablate tissue. One significant difference however is that the Ho:YAG laser is pulsed and the arrival of two successive pulses must be separated by time to allow for thermal dissipation, otherwise the accumulated heat will cause the tissue to explode under pressure. Such explosions create acoustic waves, which travel along the planes of lower resistance between muscle fibers and cause structural trauma as well as thermo coagulation [52]. The standard operating parameters for the Ho:YAG laser, are pulse energies of 1-2 Js and 6-8 watts/pulse. The energy is delivered at a rate of 5 pulses/second through a flexible 1-mm optical fiber bundle. Despite the low energy level and short pulse duration, there are very high levels of peak power delivered to the tissue so that with each pulse there is an explosion (Figure 4). Additionally, the fiber is advanced manually through the myocardium and it is therefore impossible to know whether the channel is being created by the kinetic energy delivered via the mechanical effects of the fiber and whether there has been enough time for thermal dissipation prior to the next pulse.

In contrast the CO₂ was used at an energy level of 15-20 Js/pulse with a pulse duration of 25-40 milliseconds. At this level, the laser photons do not cause explosive ablation and the extent of structural damage is limited. Additionally, a transmural channel can be created with a single pulse (Figure 4). Confirmation of this transmural channel is obtained by observing the vaporization of blood within the ventricle using TEE.

Finally the CO₂ laser is synchronized to fire on the r wave and with its short pulse duration arrhythmic complications are minimized. The Ho:YAG device is unsynchronized and due to the motion of the fiber through the myocardium over several cardiac cycles, is more prone to ventricular arrhythmias.

PATENT CHANNELS

The original concept of TMR was to create perfusion via channels connecting the ventricle with the myocardium. Clinical work has demonstrated some evidence of long-term patency [53, 54]. Additional experimental work showed some evidence of patency as well [55-58]. There are also significant reports from autopsy series and laboratories that indicate that the channels do not remain patent [59-63]. The consensus is that while channels may occasionally remain patent, this is not the principle mechanism of TMR.

DENERVATION

In contrast to the open channel mechanism, damage to the sympathetic nerve fibers may explain the angina relief noted in clinical trials. The nervous system of the heart can function independent of inputs from extra cardiac neurons to regulate regional cardiac function by reflex action. This intrinsic system contains afferent neurons, sympathetic efferent, postganglionic neurons, and parasympathetic efferent postganglionic neurons. Because of this complex system, it is difficult to demonstrate true denervation. However, several experimental studies have demonstrated that denervation may indeed play a role in Ho:YAG TMR [64-67]. Experimental evidence to the contrary was performed in a nonischemic animal model [68]. Although the studies were carefully carried out, it is difficult to isolate the sympathetic afferent nerve fibers and the experiments were in the acute setting and only address short-term effects. Regardless of the methodology employed in the laboratory, there is significant evidence of sympathetic denervation following positron emission tomography of Ho:YAG TMR treated patients [69].

ANGIOGENESIS

The likely underlying mechanism for the clinical efficacy of TMR is the stimulation of angiogenesis. This mechanism fits the clinical picture of significant improvement in symptoms over time as well as a concomitant improvement in perfusion, as seen with the CO₂ laser. Numerous reports have demonstrated a histologic increase in neovascularization as a result of TMR channels [60, 62, 70-76]. More molecular evidence of this angiogenic phenomenon was derived from work that demonstrated an upregulation of vascular endothelial growth factor (VEGF) messenger RNA, expression of FGF2, as well as matrix metalloproteinases following TMR [77-79]. Histologically, similar degrees of neovascularization have been noted after mechanical injury of various types. Needle injury has been demonstrated by immunohistochemistry to also stimulate growth factor expression and angiogenesis. The conclusion is that TMR induced angiogenesis is a nonspecific response to injury [80-82]. Investigation of this using hot and cold needles, radiofrequency energy, and laser energy to perform TMR clearly demonstrates a spectrum of tissue response to the injury [45]. The results in a model of chronic myocardial ischemia to mimic the clinical scenario indicate that indeed neovascularization can occur after mechanical TMR, but if these new blood vessels grow in the midst of a scar, there will be little functional contribution from blood flow through these new vessels. The recovery of function with laser TMR was due to a minimization of scar formation and a maximization of angiogenesis.

This then becomes a critical question that if TMR induces angiogenesis, is there an ensuing improvement in function. Clinically, this has been demonstrated subjectively with quality of

life assessments, but more importantly, it has been demonstrated objectively with multiple techniques, including dobutamine stress echocardiography [83], PET [25], and cardiac MRI [84, 85]. As further evidence of the angiogenic response, experimental data has mirrored the clinical perfusion results noted, with improvements in perfusion in porcine models of chronic ischemia where the ischemic zone was treated with CO₂ TMR [86-89]. This improved perfusion did lead to an improvement in myocardial function as well. Improved perfusion has not been reported in the Ho:YAG clinical trials and experimentally no perfusion benefit is seen [90].

PERCUTANEOUS MYOCARDIAL LASER REVASCULARIZATION

Myocardial laser revascularization has been performed percutaneously [91-93], thoracoscopically [94], via thoracotomy [14-20] and via sternotomy [31-34]. Aside from the percutaneous (PMR) approach, any of the other surgical approaches have yielded similar symptomatic improvement. Several percutaneous trials have attempted to demonstrate a symptomatic improvement with the creation of 2-3mm deep subendocardial divots achieved with a laser fiber fed via a peripheral artery into the left ventricle [91-93]. Even with the use of electromechanical mapping to verify the position of the fiber and the creation of the channel, the results from PMR have been less favorable than those seen with TMR. A double-blinded randomized controlled trial showed no benefit to the laser treated patients compared to the untreated control group [92,93]. As the patients were blinded to their treatment, the possibility of a significant placebo effect for PMR has been raised. Of note, the morbidity and mortality of PMR is reportedly similar to that seen with TMR. As a result, the United States Food and Drug Administration rendered PMR unapprovable.

The failure of PMR to achieve the same clinical results that have been seen with TMR may be due to several significant limitations. The first of which is the partial thickness treatment of the left ventricle. Even at the maximal estimated depth of 6-mm that has been reported with PMR, this is significantly less than the full thickness treatment of the myocardium that is achieved with an open TMR approach. Furthermore, there are typically fewer of these partial thickness channels created with PMR. The exact location of the channel and the establishment of a wide distribution of the channels from inside a moving ventricle is also problematic. Finally, the limitations of Ho:YAG TMR are also applicable to PMR as that is the wavelength of light that has been employed.

FUTURE USES OF TMR

Other potential applications include the use of TMR in the treatment of cardiac transplant graft atherosclerosis. While performed on a small number of patients, the results have indicated a benefit following TMR [95, 96]. Finally, the combination of TMR plus other methods of angiogenesis may provide an even more robust response. Experimental work investigating these combinations has verified a synergistic effect with regard to histologic evidence of significant angiogenesis and, perhaps more importantly, an improvement in myocardial function with a combination of TMR and gene therapy vs. either therapy alone [97-101]. This synergistic response has also been observed in TMR combined with cell based therapies, both clinically and experimentally [102, 103, 104].

CONCLUSIONS

Cardiothoracic surgeons are increasingly faced with more complex patients who have developed a pattern of diffuse coronary artery disease and have exhausted nonsurgical options. Results replicated in multiple randomized, controlled trials augmented by recently available long-term results have validated the safety, effectiveness, and substantially improved health outcomes through the application of TMR for the treatment of selected patients with severe angina due to diffuse disease, when used alone and as adjunctive therapy to achieve a more complete revascularization.

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Fig. 1.

For TMR, channels of one millimeter diameter are created in a distribution of one per square centimeter, starting inferiorly and then working superiorly to the anterior surface of the heart. The number of channels created depends on the size of the heart and on the size of the ischemic area.

Fig. 2.
The CO₂ laser creates a transmural channel in a single 20J pulse. Conceptually direct perfusion may occur via the channel. Evidence indicates the laser stimulates angiogenesis in and around the channel that leads to improved perfusion.

Angina Relief at 12 Months: TMR vs. MM

Fig. 3.

Summary of the angina relief results from five prospective randomized controlled trials comparing transmyocardial laser revascularization (TMR) and medical management (MM). Graph illustrates success rate for TMR or MM as measured by the percentage of patients that had a decrease of 2 or more angina classes. Meta-analysis of these results documents the significant advantage seen with TMR over MM.

Fig. 4. Sequential photography of the firing of a single pulse from a CO₂ laser and a Ho: YAG laser into water. The pulse duration and energy levels are the same as those employed clinically.

TABLE 1

PATIENT CHARACTERISTICS IN RCTS OF SOLE THERAPY TMR

Characteristic	Allen	Frazier	Burkhardt	Schofield	Aaberge
Patients (N)	275	192	182	188	100
Age ¹ (years)	60	61	63	60	61
Male gender (%)	74	81	89	88	92
EF [‡] (%)	47	50	50	48	49
CCS Class III/IV (%)	0/100	31/69	37/63	73/27	66/34
CHF (%)	17	34	nr	9	Nr
Diabetes (%)	46	40	36	19	22
Hyperlipidemia (%)	79	57	77	Nr	76
Hypertension (%)	70	65	74	Nr	28
Prior MI (%)	64	82	70	73	70
Prior CABG (%)	86	92	90	95	80
Prior PCI (%)	48	47	53	29	38

Legend

Baseline patient demographics from prospective randomized controlled trials of TMR.

CABG = Coronary Artery Bypass Grafting; CCS = Canadian Cardiovascular System angina class; CHF = Congestive Heart Failure; EF = Ejection Fraction; MI = Myocardial Infarction; NR = Not Reported; PCI = Percutaneous Coronary Intervention.

TABLE 2**COMPARISON OF CABG ONLY VS TMR + CABG PATIENTS**

STS Adult Cardiac Database 1998-2003			
Characteristic	CABG only	TMR + CABG	P value
N	932,715	5,618	
Body Surface Area, m2 (sd)	1.96 (0.24)	1.99 (0.23)	<0.001
Diabetes (all types)	34%	50%	<0.001
Insulin-dependent Diabetes	10%	19%	<0.001
Renal Failure	5%	7%	<0.001
Dialysis	1%	2%	<0.001
CVA	7%	9%	<0.001
Chronic Lung Disease	14%	17%	<0.001
Peripheral Vascular Disease	16%	20%	<0.001
Cerebral Vascular Disease	12%	17%	<0.001
MI	46%	49%	<0.001
Reoperation	9%	26%	<0.001
3 vessel CAD	71%	80%	<0.001
Hypercholesterolemia	62%	73%	<0.001
Hypertension	72%	80%	<0.001

Legend

Baseline demographics of TMR combined with CABG patients enrolled in the Society of Thoracic Surgeons (STS) National Adult Cardiac Database.

CAD = Coronary Artery Disease; CVA = Cerebral Vascular Accident; MI = Myocardial Infarction.