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Results of Prospective Randomized Controlled Trials of Transmyocardial Laser Revascularization

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ABSTRACT

Over 6,000 patients worldwide have undergone transmyocardial laser revascularization (TMR) for the treatment of myocardial ischemia due to end-stage coronary artery disease since 1990. Four prospective randomized controlled trials have reported their results in comparing TMR to maximum medical therapy. All of the trials demonstrated that TMR provided significant relief of angina when compared to medical management. Additional objective data in the form of exercise tolerance and myocardial perfusion scanning was used to support the symptomatic improvement. Recent reports of the failure of percutaneous transmyocardial laser revascularization (PMR) to provide angina relief greater than that seen in a placebo group underscore the need for better understanding of TMR. While all of these trials are similar, they are not identical and this review provides an update and comparison of the results.

INTRODUCTION

Prior to the advent of coronary artery bypass grafting (CABG) or percutaneous transluminal coronary angioplasty (PTCA), attempts were made to revascularize the heart by direct perfusion. These were first described by Beck [Beck 1935], who through a number of means achieved at least superficial angiogenesis, primarily as a response to epicardial and pericardial inflammation. Later, Vinberg demonstrated that direct perfusion was possible by implanting the internal mammary artery into the myocardium [Vinberg 1954]. Results of this procedure lead to neovascularization and collateral formation in some cases. In an effort to recreate the anatomy of the reptilean heart, Sen [Sen 1968] and others [Goldman 1956, Massimo 1957] performed direct perfusion by transmyocardial acupuncture. While these results yielded some success, they were not long lasting, difficult to reproduce and more importantly, were eventually overshadowed by the ability to perform CABG. While most patients can be treated with conventional methods, such as CABG or PTCA with stenting, there are a significant and growing number of patients who have exhausted the ability to repeatedly undergo these procedures, primarily due to the diffuse nature of their coronary artery disease. As a result of this severe disease, they have chronic disabling angina that is refractory to medical therapy. Transmyocardial laser revascularization (TMR) was developed to treat these patients.

While Mirhoseini [Mirhoseini 1981a, Mirhoseini 1981b] and Okada [Okada 1986] used a laser to perform this type of revascularization in conjunction with CABG in the early 1980's, the use of a laser as sole therapy required advancements in the technology. After improvements in the laser allowed TMR to be performed on a beating heart, results from individual institutions [Frazier 1995, Horvath 1996] and from multi-center trials [Vincent 1997, Horvath 1997, Dowling 1998] were reported. While the outcomes of these trials were encouraging, they lacked an appropriate control group. Recently four prospective randomized control trials have been published comparing medical management versus TMR in patients with severe angina. Eight hundred thirty-seven patients were enrolled in these trials and by virtue of the one-to-one randomization, half of them were treated with the laser, and the others continued on maximal medical therapy. All patients were followed for twelve months. One important similarity of these trials was that TMR provided significant symptomatic improvement when compared to maximal medical therapy. While there are other similarities between these studies, there are also significant differences. This review will examine the results from these trials with an attempt to provide the reader with an understanding of the clinical efficacy and current experience with TMR.

METHODS

Patients

The baseline characteristics of patients who underwent transmyocardial laser revascularization are listed in Table 1 (◉). While the numbers listed pertain to the transmyocardial laser revascularization patients, since the patients were equally randomized to the medical management group, there were no demographic differences between the groups for any of these trials. The trials employ two different wavelengths of light as their laser source. Burkhoff et al. [Burkhoff 1999] and Allen et al. [Allen 1999] employed a Holmium YAG laser (Ho:YAG). Schofield et al. [Schofield 1999] and Frazier et al. [Frazier 1999] used a carbon dioxide laser (CO_2). Schofield's data comes from a single institution whereas the others are multi-institutional trials. Approximately 200 patients were enrolled for each study. The average patient age was similar at 61 years and the

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Table 1. Baseline characteristics of TMR patients

Study	Laser	n	Average Age	Female %	CCS Angina Class III	CCS Angina Class IV	Unstable Angina	EF% (mean ± SD)	Previous MI	Previous CABG	Previous PTCA	IDDM	CHF
Schofield et al	CO_2	188	60	10%	73%	27%	0%	48 ± 9	73%	95%	29%	19%	9%
Burkhoff et al	Ho:YAG	182	63	11%	37%	63%	0%	50 ± 8	70%	91%	54%	33%	NA
Frazier et al	CO_2	192	61	19%	31%	69%	8%	50 ± 11	82%	92%	47%	40%	34%
Allen et al	Ho:YAG	275	60	26%	0%	100%	0%	47 ± 11	64%	86%	63%	46%	17%

CCS = Canadian Cardiovascular System; EF = Left Ventricular Ejection Fraction; MI = Myocardial Infarction; CABG = Coronary Artery Bypass Grafting; PTCA = Percutaneous Transluminal Coronary Angioplasty; IDDM = Insulin Dependent Diabetes Mellitus; CHF = Congestive Heart Failure; NA = Not Available.

majority were male. There were significant differences in the baseline distribution of patients according to CCS angina class. The majority of the patients in Schofield's trial (73%) were in angina class III, with 27% in class IV. These numbers were reversed for the Burkhoff and Frazier trials. One hundred percent of the patients in Allen's trial were in angina class IV. Only Frazier's trial had patients with unstable angina. The ejection fractions for all of the patients were relatively well preserved at 50%. The majority of the patients in all of the trials had a previous myocardial infarction and some previous revascularization attempt, either CABG and/or PTCA. Diabetes was prevalent in three of the trials (40%), whereas only 19% of the Schofield were diabetic. The incidence of preoperative congestive heart failure had a wide range as the Schofield trial had a 9% incidence and the Frazier trial had a 34% incidence. The entry criteria were similar. The patients had refractory angina that was not amenable to standard methods of revascularization. They had reversible ischemia based on myocardial perfusion scanning, with ejection fractions of ≥ 25%.

Two of the trials, Frazier et al. [Frazier 1999] and Allen et al. [Allen 1999], permitted a crossover from the medical management group to laser treatment for the presence of unstable angina. This necessitated intravenous anti-anginal therapy for which they were unweanable over a period of at least 48 hours. By definition, these crossover patients were therefore less stable and significantly different from those who had been initially randomized to transmyocardial laser revascularization or medical management alone.

Operative Technique

All patients underwent a small anterio-lateral thoracotomy under general anesthesia. The CO_2 laser Schofield et al. [Schofield 1999] and Frazier et al. [Frazier 1999] used to create a 1mm channel with a single 25-30J pulse. Transesophageal echocardiography was employed on all of these CO_2 treated patients to confirm transmural penetration of the laser. The Ho:YAG laser used by Burkhoff et al. [Burkhoff 1999] and Allen et al. [Allen 1999] achieved a similar 1mm channel by manually advancing a fiber through the myocardium while the laser fires. Typical pulse energies are 2J for this laser with 20-30 pulses required to traverse the myocardium. Detection of transmural penetration was primarily by tactile and auditory feedback.

Endpoints

The principal subjective endpoint for all 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 36 Questionnaire (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

Mortality

All the studies reported low perioperative mortality rates, ranging from 1-5% (Table 2, ◉). Predictably, the studies with more patients in class IV (unstable patients) had higher mortality rates [Allen 1999, Frazier 1999]. Meta-analysis of

Table 2. 12 Month Morbidity and Mortality

Study	Perioperative Mortality	1 Yr. Survival		CHF		MI		Arrhythmias	
	TMR	MM	TMR	MM	TMR	MM	TMR	MM	TMR
Schofield et al	5%	96%	89%	NA	12%	NA	NA	NA	15%
Burkhoff et al	1%	90%	95%	14%	32%	11%	18%	14%	14%
Frazier et al	3%	79%	85%	NA	11%	NA	7%	13%	8%
Allen et al	5%	84%	89%	NA	NA	11%	14%	NA	22%

MM = Medical Management; TMR = Transmyocardial Laser Revascularization; CHF = Congestive Heart Failure; MI = Myocardial Infarction; Arrhythmias = Ventricular and Atrial Arrhythmias; NA = Not Available

Table 3. One year success rate

Study	MM	TMR
Schofield et al	4%	25%
Burkhoff et al	11%	61%
Frazier et al	13%	72%
Allen et al	32%	76%

Success Rate = Proportion of patients who experienced a decrease of two or more angina classes.

the one year survival demonstrated no statistically significant difference between the patients treated with the laser or those that continued their medical therapy. The odds ratio for one year survival in the laser treated group was 0.988 that of the one year survival in the medically treated group, with 95% confidence interval (0.637, 1.534).

Morbidity

A comparative assessment for morbidity is difficult as the baseline demographics were not identical between the studies. Additionally, unlike mortality, the exact definition of the various complications vary from one study protocol to the next. However, review of the available rates of postoperative congestive heart failure, myocardial infarction, and arrhythmias, demonstrated a higher rate of all of these complications for patients treated with the Ho:YAG laser (Table 2, ◎).

Angina Class

Angina class assessment was performed by a blinded independent observer in all studies. This was done as either the only angina assessment or as comparison with the investigator's assessment. Significant symptomatic improvement was seen in all studies for patients treated with a laser. Using a definition of success as a decrease of two or more angina classes, all of the studies demonstrated a significant success rate for treatment with the laser, with success rates ranging from 25% to 76% (Table 3,◎). A smaller portion of patients in the medical management group also experienced symptomatic improvement and the success rate for these patients ranged from 4% to 32% (Table 3, ◎). Schofield's study that started with most of its patients in class III, not surprisingly, showed the lowest success rate. In contrast, Allen showed the largest success rate with all of the patients in class IV at enrollment. Of note, the medical management patient group in Allen's study also showed the largest success rate at 32%.

Quality of Life and Myocardial Function

Quality of life as assessed by the Seattle Angina Questionnaire, the SF-36, and the Duke activity status index, demonstrated significant improvement in the quality of life by all of these indices in the TMR group versus the medical management group for each study. Global assessment of myocardial function by ejection fraction using echocardiography or radionuclide multigated acquisition scans showed no significant change in the ejection fraction of any of the patients, regardless of group assignment or study.

Hospital Admissions

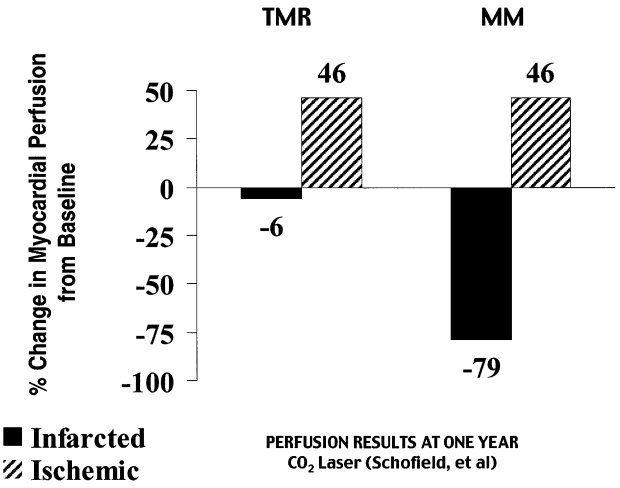
Another indicator of the efficacy of the treatments is demonstrated in the hospital admissions for unstable angina or cardiac related events for all the patients. Meta-analysis of the data provided indicates that the one year hospitalization rate for patients in the laser treated groups was statistically significantly less then those treated medically. The odds ratio for one year hospitalization in the laser treated group was 0.28 that of the one year hospitalization for the medically treated group, with an associated 95% confidence interval of 0.192 to 0.408.

Myocardial Perfusion

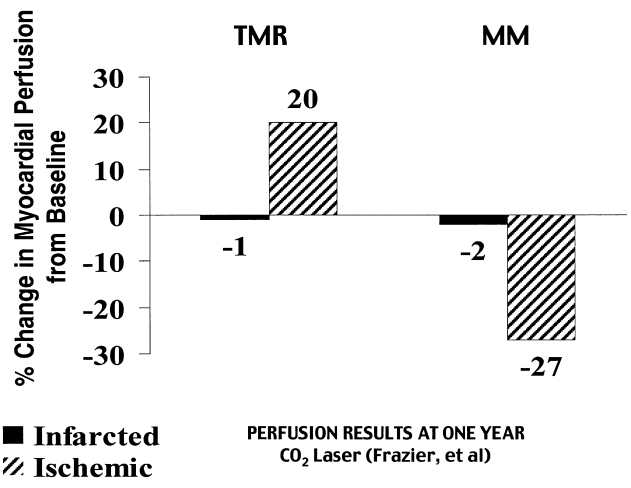
As mentioned, myocardial perfusion scans were obtained preoperatively to verify the extent and severity of reversible ischemia. The perfusion results from all of the studies are represented in Figure 1 (◎) and are expressed as changes in infarcted or ischemic myocardium at one year. Postoperative scans demonstrated differing results between the studies. Schofield et al. [Schofield 1999] divided the left ventricular into five segments and tallied the number of reversible (ischemic) and fixed (scar) defects for both groups. The data was then analyzed and presented as a pooling of all of the defects for all of the patients. Their results demonstrated a decrease in the number of reversible defects for both the TMR and medical management patients. There were 144 reversible defects in the TMR group at baseline and 160 in the medical management group. At twelve months, the TMR group had 78 reversible defects and the medical management group had 86. These numbers result in an overall improvement for both groups. The fixed defects showed little change in the TMR group, 65 at baseline and 69 at twelve months. However, there was a near doubling of the fixed defects in the medical management group from 38 at baseline to 68 at twelve months. These totals yield a 5% change for the TMR group and a doubling of the percentage for the medical management group (8 to 17%) over one-year follow-up (Figure 1A, ◎).

Burkhoff et al. [Burkhoff 1999] using polar plot analysis of the perfusion data, reported their results in percentage of ischemic (reversible) myocardium, which on average was 14% for TMR patients and 13% for the medical management patients at baseline. The percentage of infarcted myocardium (fixed defects) was 9% for TMR patients and 13% for the medical management patients at baseline. At twelve months, the reversible myocardium was 11.5% in the TMR group and 12% in the medical management group. The percent of infarcted myocardium was 11% in both groups at twelve months. These values for both types of defects did not differ significantly from each other or from the baseline measurement (Figure 1B, ◎).

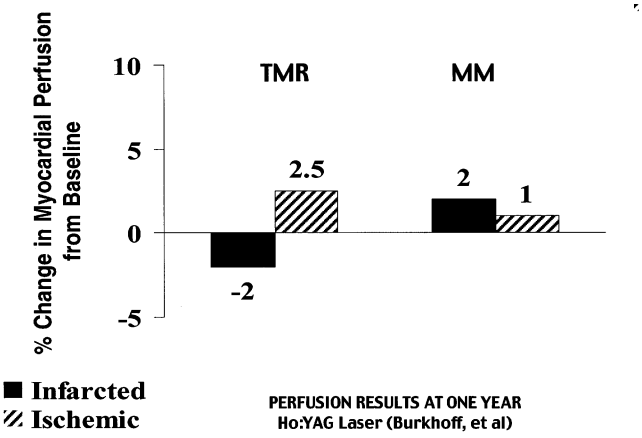
Frazier using a 24-segment model also determined the number of reversible and fixed defects at baseline, which was the same for both groups. There was a 20% improvement in the perfusion of previously ischemic areas in the TMR group, whereas there was a 27% worsening of the perfusion of ischemic areas in the medical management group at twelve months. There was no difference in the number of fixed defects (scar) between both groups at twelve months, nor was there a significant change versus the number of fixed



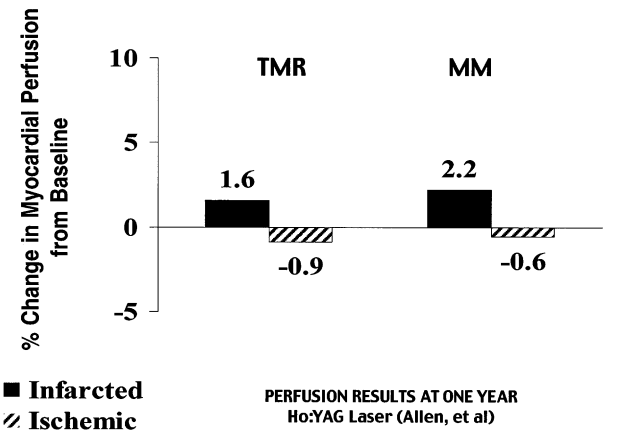
1A. Significant improvement in perfusion of ischemic myocardium treated CO_2 TMR ($p < 0.05$) without a significant change in infarcted areas. Similar "improvement" in ischemic myocardium for MM patients is due to a concomitant change in infarcted myocardium.



1C. Significant improvement in perfusion of ischemic myocardium treated with CO_2 TMR, coupled with a significant worsening in perfusion of ischemic myocardium for MM patients ($p < 0.05$). No significant change in infarcted areas for either group.



1B. Perfusion was not changed after Ho:YAG TMR.



1D. Perfusion was not changed after Ho: YAG TMR.

Figure 1. Change in myocardial perfusion one year after medical management (MM) or transmyocardial laser revascularization (TMR). The percentage change is calculated as baseline perfusion results minus follow-up results, divided by the baseline results. Bars above the abscissa indicate an improvement in perfusion.

defects for each patient when compared to their baseline scans (Figure 1C, ◎).

The perfusion analysis employed by Allen is not delineated in their text. However, they report no significant differences between the TMR group and medical management group with respect to reversible or fixed defects at baseline. There was no significant change from the baseline at twelve months in either the fixed or reversible defects in either group as well (Figure 1D, ◎).

Exercise Tolerance

The aforementioned are the results that are common to all of the studies. Additional functional assessment by exercise tolerance testing was also performed. Treadmill testing employed the modified Bruce protocol, in which exercise intensity is increased every three minutes. TMR patients by Schofield et al. [Schofield 1999] had a 40-second increase in their exercise time when compared to the medical management group at twelve months. This difference between the groups was not statistically significant. However, this was a 70-second improvement over the baseline for the TMR group and only a 5-second improvement for the medical management group. Burkhoff et al. [Burkhoff 1999] reported an average of a 65 second increase in the TMR group at twelve months compared to their baseline with an average of a 46 second decrease in the medical management group over the same interval. This created a median difference between the groups of 111 seconds. Allen et al. [Allen 1999] instituted exercise treadmill testing in substitution for thallium scanning midway through their study. Treadmill tests were performed at baseline. Using the

Naughton protocol for a subset of patients, they showed a statistically significant improvement in exercise tolerance in the TMR versus the medical management group as measured by metabolic equivalents at twelve months. Exercise treadmill testing was not part of Frazier's study.

Medications

The protocols were established that the TMR patients would continue on their maximum medical therapy and be weaned as tolerated. For each study, the frequencies of antianginal and cardiovascular drugs were similar between the two groups at baseline. Schofield reported a decrease in TMR patient's nitrate use at twelve months from 86% to 69%, compared with the medical management patients, which increased slightly from 79% to 82%. Burkhoff et al. reports "little change in overall pattern of medications during the study" for both groups. Frazier et al. [Frazier 1999] reported 60% decrease in the nitrate usage among the TMR patients, whereas the medical management patients had a 22% increase in their use of nitrates. They also note that the overall medications 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.

Crossover

As previously mentioned, Allen and Frazier had crossover groups for patients who failed medical therapy. These crossover rates were 32% and 60% respectively. Once treated with transmyocardial laser revascularization, the crossover patients had a higher perioperative mortality rate, 9%. After the initial perioperative period, their survival was the same as the other group and their angina relief was the same as those originally assigned to the TMR group.

SUMMARY

Almost ten years have passed since the first patients were treated with a laser as sole therapy for their end-stage coronary artery disease. Since then, over 6,000 patients have undergone the procedure around the world. In addition to these patients who have undergone the procedure sole therapy, an increasing number of patients are being treated with TMR in combination with CABG [Trehan 1998]. The procedure has also been performed via percutaneous access (PMR) in a smaller number of patients [Kim 1997, Oesterle 1998, Lauer 1999a, Lauer 1999b, Shawl 1999, Leon 2000, Oesterle 2000, Stone 2000]

The purpose of this review was to examine the clinical efficacy of TMR based on the most recent publications of prospective randomized controlled trials using as sole therapy for severe angina. There is a growing body of literature, both experimental and clinical on this topic. The four studies reviewed here, highlight important issues in understanding and applying transmyocardial laser revascularization.

In evaluating the results, particularly in making comparisons, it is critical to determine whether the patients selected for the procedure are the same between the studies under comparison. In this series, the study by Schofield had significantly fewer patients in angina class IV. The result is that a less dramatic success rate was seen. Additionally, fewer patients were at risk of becoming unstable or needing to crossover. This is an important distinction. One of the lessons learned from Frazier's study was that patients that underwent TMR less than two weeks after an episode of unstable angina requiring intravenous medications had a significantly higher perioperative mortality rate (22% for the unstable patients and 1% for the stable patients).

For all of the patients in all of the studies, there was a similar symptomatic response. This success rate in the relief of angina, as a result of TMR, was accompanied by improvements in the quality of life for these patients. Interestingly, the perfusion results did not mirror these clinical outcomes. One would not expect an anatomic study (perfusion scan) to correlate perfectly with symptoms. For example, the size of a patient's reversible defect is not always reflected by the severity of his/her symptoms. Be that as it may, there was a significant perfusion benefit noted in Frazier's study. Schofield's results indicate a similar decrease in the number of reversible defects for TMR and medical management patients. A careful review of Schofield's data indicates that the decrease in the number of reversible defects for the medical management patients is likely due to a doubling of the number of fixed defects for the same patients. The TMR patients did not exhibit this increase in fixed defects. As a result, for both of these studies, an argument could be made that perfusion is improved for patients treated with transmyocardial laser revascularization. A similar perfusion benefit was not seen by Burkhoff or Allen. The principal difference being that a Ho:YAG laser was used in the latter studies and a CO_2 laser in the former. The argument is made that the present methods of perfusion imaging may not be sensitive enough, however, they appear sensitive enough to detect improvement in patients treated with the CO_2 laser. It may also indicate that the mechanism of action for Ho:YAG TMR is not an increase in myocardial perfusion.

The lack of improvement in myocardial perfusion after Ho:YAG TMR may be one reason that a recent report documents a loss of the long-term symptom relief in patients treated with a Ho:YAG laser [De Carlo 2000]. Significant short-term angina relief was demonstrated at one year as the average angina class fell from 3.5 ± .5 at baseline to 1.8 ± .8 at one year ($p < 0.01$). However, the average angina class at three years after Ho:YAG TMR had significantly increased to 2.2 ± 0.7 ($p = 0.003$ versus 1 year). Additionally, at three years only 30% of the patients had a class two angina improvement compared to their baseline and 70% had a class oneimprovement. Long-term results with a carbon dioxide laser are markedly different. Recently reported, these results demonstrate a decrease in angina class from 3.7 ± 0.4 at baseline to 1.6 ± 1 at five years ($p = 0.0001$) [Horvath 2001]. This was unchanged from the 1.5 ± 1 average angina class at one year of follow-up (p = ns vs 5 years). Additionally, 68% of the patients at 5 years had 2 or more angina class improvement and 23% had a 1 class improvement. This loss of clinical effectiveness seen with a Ho:YAG laser has also been noted in a direct clinical comparison [Lansing 1998, Lansing 2000]. A review of 460 patients treated by a single investigator using both devices, the angina

improvements seen with CO_2 was greater than Ho:YAG [Lansing 2000]. At twelve months, the majority of CO_2 patients were in class one or angina free where as the majority of the Ho:YAG patients were in class two.

This distinction in wavelengths of light between Ho:YAG and CO_2 may have increasing importance as PMR (which also employs a Ho:YAG laser) has failed to demonstrate a perfusion benefit and perhaps even a significant clinical benefit. PMR employs a Ho:YAG laser and a catheter based delivery system where the laser fiber is placed against the endocardium and fired creating a nontransmural 3-4mm depression in the subendocardial layer [Kim 1997, Oesterle 1998, Lauer 1999a, Lauer 1999b, Shawl 1999, Leon 2000, Oesterle 2000, Stone 2000]. In a randomized controlled trial, comparing PMR versus maximal medical therapy, the results at 12 months indicate a significant a significant increase in exercise tolerance and a decrease in symptoms for PMR treated patients [Oesterle 2000]. However, the symptomatic improvement with PMR was not as great as had been seen with TMR with only 34% of the patients in angina class two or lower. Additionally, the improvement in exercise tolerance was less than PMR treated patients with an average increase of 90 seconds for the PMR patients and 150 seconds for the TMR patients [Oesterle 2000]. This comparison of PMR versus TMR indicates that the revascularization is more effective with TMR.

One advantage that PMR trials have over the surgical TMR trials is the ability to perform a double blind randomized placebo controlled trial. The catheter may be placed against the subendocardium and the laser not fired. Recent reports of the six month data of such a trial [Leon 2000] have indicated that the placebo group had the same results as the PMR treated group. There was no difference in the exercise tolerance at six months between the groups, despite a significant increase in exercise tolerance for each group versus their baseline. Forty-two percent of the placebo group achieved a >2 angina class reduction in symptoms at six months. These results further confirm the lack of effectiveness of PMR and are noteworthy in that this trial employed an intraventricular mapping system that allowed for optimal localization of the catheter.

As a result of the improvement in the PMR placebo group, it has been suggested that the placebo effect may be an important mechanism of surgical TMR as well. Unfortunately, it is impossible to run a double-blind placebo controlled surgical trial. Patient expectations with the surgical procedure certainly may generate a placebo effect. However, the long-term benefits seen with the CO_2 laser argues against the placebo effect and more salient objective data have also been obtained. In addition to the symptomatic improvement, CO_2 TMR has been demonstrated via numerous studies to improve myocardial perfusion by nuclear SPECT scans [Horvath 1997, Frazier 1999, Schofield 1999] as well as PET scans [Frazier 1995, Cooley 1996, Kadipasaoglu 1999]. A significant decrease in number of reversible or ischemic myocardial defects without an increase in the number of fixed or infarcted areas has been demonstrated, with CO_2 both in comparison of TMR patients versus their baseline and versus patients randomized to medical management [Frazier 1999, Schofield 1999]. Further evaluation employing other objective measures such as dobutamine stress echocardiography [Donovan 1997] CINE and contrast enhanced MRI [Horvath 2000] show improvement in myocardial function, decrease in myocardial ischemia without an increase in myocardial infarction in patients treated with CO_2 TMR. This evidence is not subject to the placebo effect and has been analyzed by researchers blinded to the treatments that the patients received. A better understanding of the mechanisms whereby TMR does achieve its effect is needed and is the impetus for ongoing studies. Additionally, the enhancement of these results by combining laser revascularization with conventional revascularization (CABG), as well as in combination with other types of unconventional revascularization (gene therapy), will undoubtedly be the investigations of the future.

CONCLUSION

Review of the perspective randomized controlled trials employing TMR as sole therapy for end-stage coronary disease demonstrates significant symptomatic improvement for patients who were treated with the laser versus similar patients who continued on their maximal medical therapy. These symptomatic improvements were measured by a reduction of two or more CCS angina classes and the Seattle Angina Questionnaire, the SF36 or the Duke Activity Status Index. Objective data to support these subjective findings was provided by myocardial perfusion and exercise tolerance results. While the symptomatic improvement was seen regardless of the type of laser employed, there were marked differences in the perfusion results according to laser wavelength.

The carbon dioxide laser provided a significant improvement in perfusion. The lack of documented improvement in perfusion with the Ho:YAG laser may be a reason that long-term results indicate a loss of angina relief in patients treated by Ho:YAG TMR. It may also play a significant role in the failure of the partial thickness treatment obtained with Ho:YAG PMR

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REVIEW AND COMMENTARY

1. Editorial Board Member XA5 writes:

I think it's clear that the holmium lasers have different results which aren't as good as the CO_2 lasers. Thus, it would seem to me logical to leave the papers using lasers other than the CO_2 laser out of the comparisons. Perhaps the best way to set the study up is to compare the CO_2 laser papers with the holmium papers or to have 3 groups: $C0_2$, transmyocardial holmyium, and percutaneous holmium lasers.

Author's Response by Keith A. Horvath, MD:

We agree with the reviewer that there are differences between the Ho:YAG and CO_2 lasers. The purpose of the paper was to report on all of the prospective randomized controlled trials involving lasers for transmyocardial revascularization that are FDA approved and therefore clinically available. As a result, I have included all such trials in the review and allow the reader to decide which laser is more efficacious.

2. Editorial Board Member PB44 writes:

This is a meta-analysis of four major studies of TMR. Did the authors have access to the original data from the studies?

Author's Response Keith A. Horvath, MD:

The meta-analysis that is provided is based on the data that was presented in the manuscripts. I did not have access to the original data from all of the studies.

3. Editorial Board Member AR11 writes:

a) In Figure 1, perfusion data for Allen et al. are not presented, despite discussing the findings in the text. Burkhoff et al.'s data are presented, showing no change — why not the data of Allen et al. as well?

b) Table 2 data seem incomplete, as CHF, MI and ARRHYTHMIA data are not presented for all of the groups across the table. While I recognize that the data may not have been available in the manuscript, these omissions make the Table less useful. Table 3 might be more useful if the longer term results are also included (perhaps up to 5 years) and perhaps offer the cited PMR data as well.

Author's Response Keith A. Horvath, MD:

a) The reviewer notes that perfusion data was not presented from the trial conducted by Allen et al. In their report, Allen et al. did not delineate the methodology used for their perfusion scanning. As a result, it is very difficult to make an absolute comparison with the other trials. However, I have incorporated their graph of perfusion results as Figure 1D to provide the comparison that was requested.

b) The reviewer is correct that Table 2 is incomplete with regard to the incidence of various morbidities. Unfortunately, this information is not available from the manuscripts and as opposed to providing a table that has only the mortality and one-year survival, I have listed other significant adverse events as they were reported, even though they were not reported for each trial.

4. Editorial Board Member GX21 writes:

a) In Table 1, there is no information about the control patients. Also, the n for Frazer et al. of 192 is the sum of the TMR (n=91) plus MM (n=101) patients, 60 of whom crossed over to TMR. But the baseline characteristics are given only for the original TMR patients. Figure 1b uses only 13 of the MM patients who did not crossover to TMR. The numbers contributing to each bar in Figure 1 should be given.

b) In the Results section ("mortality"), it is only correct to compare long-term survival rates if the rates for each study were calculated in the same way. It is unclear if the survival estimates are simple proportions or Kaplan Meier estimates; the latter should be used when there are censored data. How was the meta analysis performed? How were the survival estimates compared? How were the odds ratio for one year survival calculated?

Author's Response Keith A. Horvath, MD:

a) The reviewer is concerned regarding Table 1's lack of information about the control patients. To simplify the table, and specifically, to provide information with regard to the patients that underwent TMR, those baseline characteristics are listed for TMR patients. As each study was a one-to-one randomization, the baseline characteristics of the medical management group or for each study were the same as the TMR group. Therefore, the baseline information for the TMR patients applies to the control patients as well. The concern regarding Figure 1 and the numbers of patients that each bar represents is difficult, as those data are not reported in each manuscript. Additionally, the methodology, whereby the perfusion scanning was done is either not defined or is different from study to study.

b) With regard to survival estimates, these were taken as the percentage of patients alive or the number of deaths that were recorded in each study. When these numbers were not directly provided in the manuscript, they were taken from the survival curves that were provided. It is from this data that the meta-analysis was performed and that the odds ratio was calculated.

4. Editorial Board Member SC389 writes:

It would be better if we had the data for how the patients receiving medical management fared in their morbidity. This is not clear to me and is reported as NA in table 2.

Author's Response Keith A. Horvath, MD:

We agree with the reviewer that it would be of interest to know the morbidity of patients randomized to continuing their maximal medical therapy. The studies were designed to have the first official point of follow-up at three months and this was the first time that patients in the medical management group returned to their physicians. Early morbidity was therefore poorly captured for those medical management patients. Additionally, as an example, the TMR patients were typically on telemetry in the early postoperative period and some of the morbidity reported may simply reflect this monitoring. The medical management patients were not monitored after enrollment and therefore the incidences of arrhythmias would not have been captured. In an attempt to capture such data for the medical management group as part of the post-FDA approval process, patients were randomized to having their procedure without delay (within a week) or with a delay (after 30 days). This is an attempt to determine the morbidity and mortality of patients who continue on the their medical therapy. This registry has been submitted to the FDA by the CO_2 laser users and the final analysis is pending.