Myocardial laser revascularization is a novel therapeutic technique aimed at delivering oxygenated blood via a series of channels to the ischemic regions of the heart. These channels may be created surgically or via a less invasive percutaneous approach. In patients with end-stage coronary artery disease, both transmyocardial laser revascularization (TMR) and percutaneous myocardial laser revascularization (PMR) have been associated with a reduction in symptoms, improved exercise tolerance, and enhanced quality of life. However, the mechanism of action of laser therapy is incompletely understood, the results of objective cardiac perfusion measurements are inconclusive, and multiple randomized trials have failed to demonstrate an increase in survival. In addition, the positive results seen in TMR trials have been questioned because of a lack of blinding, raising the possibility that the benefit may have been due to the placebo effect. Finally, two recent sham-controlled, randomized clinical trials of PMR have not shown any benefit of the procedure, but instead have highlighted the important role of the placebo effect in the response to PMR. Further research is, therefore, needed to elucidate the value of myocardial laser revascularization.

Despite the increasing success of percutaneous coronary intervention (PCI) and coronary artery bypass graft surgery (CABG), a significant number of patients with coronary artery disease (CAD) cannot be successfully revascularized, and many continue to experience refractory symptoms despite maximal medical therapy. The morbidity and mortality associated with the care of these patients has led to the development of a novel therapeutic strategy aimed at delivering oxygenated blood to the myocardium: myocardial laser revascularization. This technique involves using a laser to create channels within ischemic regions of the heart. Transmyocardial laser revascularization (TMR) is performed surgically via an epicardial approach, while percutaneous myocardial laser revascularization (PMR) is performed percutaneously via an endocardial approach. In numerous patient series, TMR (1–11) and PMR (12,13) have been associated with significantly reduced anginal symptoms in patients with end-stage CAD. Similar results have also been published in six randomized, controlled trials of TMR (14–19) and one trial of PMR (20). Two of three blinded trials of PMR, however, have not shown any measurable benefit of the procedure. In this article, we review the experimental and clinical experience to date with TMR and PMR. Specifically, we discuss the controversy surrounding its mechanism of action, and we summarize the major clinical studies in this field.

Three types of lasers are being used in clinical trials: the carbon dioxide \( (\text{CO}_2) \), the holmium:yttrium-argon-garnet \( (\text{Ho:YAG}) \), and the excimer lasers. Of these, the Food and Drug Administration (FDA) has approved only the \( \text{CO}_2 \) and \( \text{Ho:YAG} \) lasers for use in TMR. The impact of lasers on myocardial tissue has been examined in detail elsewhere (21). In brief, the \( \text{CO}_2 \) and the \( \text{Ho:YAG} \) lasers rely on thermal energy to create channels, whereas the excimer laser ablates tissue by dissociating molecular bonds. The \( \text{CO}_2 \) laser is transmitted through a series of mirrors and lenses. In contrast, the \( \text{Ho:YAG} \) and the excimer lasers allow the laser beam to be transmitted by an optical fiber. These lasers can, therefore, be used in PMR as well as with minimally invasive surgical techniques (22). Each of the three lasers has been associated with a reduction in angina (23–25), but none have been compared head to head in clinical trials.

In TMR, patients are positioned for a left anterior thoracotomy that is made through the fifth intercostal space. In some patients who have not had previous operations, a thoracoscopic approach has also been used (26). The pericardium is dissected open, and a cradle is made. No heparin is administered, nor is the heart cannulated for cardiopulmonary bypass. The \( \text{CO}_2 \) laser probe (PLC Medical Systems, Franklin, Massachusetts) is placed directly on the myocardium and is synchronized with the electrocardiogram (TEE) is used to confirm transmural
penetration. The Ho:YAG laser (CardioGenesis Corporation, Foothill Ranch, California) requires multiple pulses to create a single channel, is not synchronized to the electrocardiogram, and does not require TEE confirmation. Furthermore, the Ho:YAG laser is delivered through an optical fiber, which must physically puncture the epicardium before the laser is deployed (Fig. 1). A total of 25 to 40 channels are made 1 cm apart in the entire left ventricle (to within 1 cm of the atrioventricular groove). Digital pressure is applied to stop bleeding, but, occasionally, a suture may be necessary to obtain hemostasis. The pericardium is left open, and a single chest tube is placed before thoracotomy closure. Patients are then transferred to the intensive care unit for monitoring (27).

PMR. Three catheter-based PMR systems have been developed, all of which are based on the Ho:YAG laser (13,28,29). These devices are being used in many centers across Europe. However, none have obtained FDA approval. Coronary angiography and biplane left ventriculography are performed to delineate the treatment area. The guiding catheter is introduced into the left ventricle via the femoral artery, and the laser fiber is positioned onto the endocardium. Once good contact is achieved, multiple laser pulses are fired to create a channel. The laser is then repositioned under fluoroscopy for the next channel site (13). Up to 20 channels are thus created. The patient is then monitored as per a routine post-cardiac catheterization protocol. Many are discharged from hospital the same day.

To minimize the need for fluoroscopy and contrast administration, the Biosense (Biosense Webster, Diamond Bar, California) electromechanical mapping system may be used. A real-time three-dimensional image of the left ventricle is created, allowing catheter movements to be tracked and its location on the endocardial surface to be visualized throughout the procedure (30). In contrast with TMR, PMR devices are designed to avoid complete transmural penetration of the left ventricle. Instead, by creating 5- to 6-mm channels in the subendocardial layer (contraindicated if target area wall thickness measures less than 8 mm), the PMR design minimizes the probability of perfo-

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**Figure 1.** A comparison of transmyocardial revascularization, percutaneous myocardial revascularization, and direct myocardial revascularization. (Figure 1 is reproduced with permission of CardioGenesis Corporation, Foothill Ranch, California.)
ration and the possibility of pericardial tamponade. In addition to avoiding the morbidity and mortality associated with thoracotomy, PMR also provides access to portions of the myocardium not approachable from the epicardium (e.g., the interventricular septum). Unfortunately, important limitations to PMR exist. The procedure requires retrograde cannulation of the aortic valve and, therefore, cannot be performed in patients with aortic stenosis or aortic valve prosthesis. Lasing of the inferoposterior wall can be difficult because of hypertrophied papillary muscles. Also, imprecise positioning of the laser under fluoroscopy may result in lack of channel uniformity and wall coverage (31).

SUGGESTED MECHANISMS OF ACTION

Open channel hypothesis. Transmural channels were initially thought to increase myocardial perfusion by delivering oxygen-rich blood from the left ventricle directly into the myocardium, akin to the sinusoids of the reptilian heart. This “open channel” hypothesis was supported by an early study suggesting long-term patency of the lased transmural channels (32). However, there now exists substantial experimental (33–36) and clinical postmortem evidence to the contrary (37–40). These studies suggest that the channels fill with necrotic and inflammatory debris shortly after the procedure and do not remain patent, ultimately being replaced by scarred tissue. Myocardial perfusion studies performed immediately after TMR support this finding (33,35,41–44). For these reasons, the “open channel” hypothesis has been largely abandoned in favor of two other proposed mechanisms of TMR: laser-induced denervation of the myocardium and laser-induced angiogenesis.

Myocardial denervation. Damage to the epicardial sympathetic nerve fibers may explain the immediate relief in angina observed in certain clinical trials (14,23). To test this hypothesis, Kwong et al. (45) studied the effects of TMR on myocardial afferent nerve fibers in a canine model. Two weeks after TMR treatment, no response to bradykinin was seen after stimulation of laser-treated areas of the left ventricle, but a normal hypotensive response was seen after stimulation of untreated areas in these same animals and in control animals. Using immunoblot techniques, Kwong et al. (45) also demonstrated the loss of a neural-specific enzyme, tyrosine hydroxylase, in regions of laser treatment. In a subsequent study (46), these same authors showed that an endocardial approach also achieves at least partial denervation of the myocardium. Finally, Al-Sheikh et al. (47) found that six of eight patients who underwent TMR had a significant decrease in the uptake of the positron emission tomography (PET) tracer \(^{11}C\) hydroxyephedrine, suggesting sympathetic denervation of the left ventricle.

Minisi et al. (48), on the other hand, examined the effect of TMR in dogs with sinoaortic denervation and vagotomy in an effort to isolate the sympathetic afferent fibers that are thought to mediate anginal chest pain. After TMR, there was no significant attenuation in the reflex responses to either epicardial or intracoronary bradykinin. These results indicate that TMR does not acutely interrupt the sympathetic afferent nerve fibers.

Such results notwithstanding, the above studies do not directly assess the functional sympathetic innervation of the heart. To circumvent this problem, Hirsh and colleagues (49) used direct electrical stimulation of sympathetic and parasympathetic efferent cardiac neurons to show that TMR does not affect axonal function in the lased ventricle. Although their data do not address the long-term effects of TMR, Hirsh et al. (49) conclude that it would be unlikely that such revascularization would result in long-term local nerve injury in the absence of immediate and direct neuronal effects. Clearly, more research is needed in this area. Given the current evidence, however, any beneficial effects that TMR may afford cannot be solely ascribed to myocardial denervation.

Angiogenesis. In 1987, Hardy et al. (50) reported new capillary formation in the area of TMR channels (Figs. 2 to 4) (51). Multiple subsequent studies (34–36,38,39,52–55) have since confirmed this finding. Transmyocardial laser
revascularization results in the upregulation of vascular endothelial growth factor (VEGF) messenger RNA (56), and the expression of transforming growth factor β and basic fibroblast growth factor (57). These growth factors appear to mediate the angiogenic process. However, this process is not specific for laser-induced injury. Malekan and coauthors (58) found evidence of neovascularization after creating channels of equal diameter with either a miniature power drill or a CO₂ laser. The degree of angiogenesis observed in this study was independent of the method of channel creation. Moreover, Chu and associates (59), in a porcine model of chronic ischemia, demonstrated that both needle injury and TMR lead to similar degrees of VEGF expression and angiogenesis. Therefore, current evidence suggests that TMR-induced angiogenesis is the result of a nonspecific response to tissue injury.

What is the functional significance of TMR-induced angiogenesis? Early animal models of acute ischemia failed to demonstrate an increase in myocardial blood flow immediately after TMR (32,35,41–44). More recently, however, in a canine model of chronic myocardial ischemia, Yamamoto and colleagues (60) found a 40% increase in coronary flow reserve during stress two months after TMR. In other studies using a porcine model of chronic ischemia, CO₂-laser revascularization was shown to significantly ameliorate microperfusion (61) and regional contractility 12 weeks after treatment (61,62). Finally, in a miniswine model of hibernating myocardium, Hughes et al. (63) demonstrated significantly improved myocardial blood flow in the lased regions at six months. The above results suggest that TMR does not improve blood flow acutely, but may improve regional myocardial blood flow after a period of two to six months. Is this improvement in myocardial perfusion the result of angiogenesis? Future studies, including a time-course assessment of vascular development after TMR, will be needed to answer this question.

**OBSERVATIONAL STUDIES OF TMR**

Since the first reported use of TMR in 1983 (64), over 3,000 patients have now been reported in the literature. Almost all study patients had severe diffuse three-vessel coronary disease. The majority had at least one prior myocardial infarction as well as multiple prior revascularization procedures. All had Canadian Cardiovascular Society (CCS) class III or IV angina on maximal medical therapy, and had demonstrated nonrevascularizable coronary anatomy and viable (hibernating) myocardium by either dobutamine stress echocardiography or nuclear studies.

The 30-day operative mortality with TMR has been reported to be as high as 20% (65). Beyond the operative learning curve, several factors have been associated with an increased risk of mortality after TMR (23,66–69). Chief among these are congestive heart failure, unstable angina, significant mitral regurgitation, and the lack of at least one protected vascular territory through a native artery or patent vascular graft. When eligibility criteria are amended to exclude such patients, operative mortality is reduced to an average of 3% (24). Interestingly, Lutter et al. (66) studied the combined use of an intraaortic balloon pump (IABP) and TMR in seven patients with unstable angina and an ejection fraction <35%, six of whom had clinical signs of congestive heart failure. In this extremely sick patient group, the authors reported a 30-day mortality of 0%, suggesting that the prophylactic use of an IABP during the perioperative period may significantly reduce mortality in high-risk populations.

Up to one-third of patients undergoing TMR may experience procedure-related complications (7,11,23,66,67,70). These complications include atrial and ventricular arrhythmias, pericardial effusion, tamponade, and, in one study, acute mitral regurgitation secondary to laser-induced damage to the mitral valve (70). Hughes et al. (71) demonstrated in swine that TMR significantly increases myocardial water content and impairs diastolic relaxation in lased segments. These same authors also found that the prophylactic use of a furosemide infusion initiated in the immediate postoperative period was associated with a lower incidence of heart failure (27,67). It has been hypothesized that diuretic therapy may reduce adverse events by decreasing myocardial edema and diastolic dysfunction. Additionally, postoperative therapy with aspirin, intravenous nitroglycerin, intravenous beta-blockade, and the early resumption of preoperative cardiac medications may help to improve outcomes (27,67,72).

The most consistently reported finding in each of the clinical studies performed to date has been a decrease in angina score. Of the 18 studies we identified, 11 included a 12-month patient follow-up (Table 1). We chose this length of follow-up as the minimum necessary to demonstrate a sustained effect. It is important to note that these are observational studies and, therefore, do not include a control group (73). Indeed, Prêtre and Turina (74) contend that...
Table 1. Published Series of Transmyocardial Laser Revascularization With 12-Month Follow-Up

<table>
<thead>
<tr>
<th>Author (Reference)</th>
<th>Number of Patients</th>
<th>Laser Used (Mean Number of Channels Produced)</th>
<th>Mean CCS Class: Baseline vs. Follow-Up (p Value)</th>
<th>Improvement in Exercise Time (s) (p Value)</th>
<th>Perfusion Modality: Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burns et al. (1)</td>
<td>967</td>
<td>CO2 (29)</td>
<td>NA*</td>
<td>110 (p &lt; 0.001)</td>
<td>NA</td>
</tr>
<tr>
<td>Hatler et al. (2)</td>
<td>167</td>
<td>CO2 (32)</td>
<td>NA†</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Vincent et al. (3)</td>
<td>140</td>
<td>CO2 (33)</td>
<td>NA‡</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Agarwal et al. (4)</td>
<td>102</td>
<td>CO2 (23)</td>
<td>2.6 vs. 0.8 (NA)</td>
<td>252 (p &lt; 0.008)</td>
<td>2010T1:SPECT: no change</td>
</tr>
<tr>
<td>Dowling et al. (5)</td>
<td>85</td>
<td>Ho:YAG (35)</td>
<td>4.0 vs. 1.6 (NA)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Gasser et al. (6)</td>
<td>61</td>
<td>CO2 (30)</td>
<td>3.5 vs. 1.8 (NA)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Négrel et al. (7)</td>
<td>60</td>
<td>CO2 (33)</td>
<td>3.3 vs. 2.3 (NA)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>De Carlo et al. (8)</td>
<td>34</td>
<td>Ho:YAG (36)</td>
<td>3.6 vs. 1.8 (p &lt; 0.001)</td>
<td>96** (p = 0.005)</td>
<td>NA</td>
</tr>
<tr>
<td>Landolfi et al. (9)</td>
<td>34</td>
<td>CO2 (22)</td>
<td>3.5 vs. 2.8 (p &lt; 0.006)</td>
<td>NA</td>
<td>2010T1:SPECT: no change</td>
</tr>
<tr>
<td>Lee et al. (10)</td>
<td>15</td>
<td>Excimer (41)</td>
<td>3.5 vs. 1.8 (p &lt; 0.002)</td>
<td>96 (p = NS)</td>
<td>2010T1:SPECT: no change</td>
</tr>
<tr>
<td>Cooley et al. (11)</td>
<td>13</td>
<td>CO2 (36)</td>
<td>3.7 vs. 1.8 (p &lt; 0.01)</td>
<td>342 (p &lt; 0.001)</td>
<td>2010T1:SPECT and PET:‡ no change</td>
</tr>
</tbody>
</table>

*Exact data not available, however, 34% of patients improved by at least two CCS classes at 12 months (p = 0.001); †Exact data not available, however, 42% of patients improved by at least two CCS classes at 12 months (p = 0.001); ‡42% were CCS class 0 to 1 at 12 months (p-value not specified); §64% of patients had an improvement in their treadmill time at 12 months (p-value not specified); ¶12-month data not available, however, treadmill time improved by 105 to 130 at six months (p = 0.03); ¶The study presents three-year follow-up data in a smaller subgroup of 19 patients, however, only 12-month data are presented here; #Patient follow-up ranges from 4 to 48 months, however, only 12-month data are presented here; **Analysis of effort tolerance included only 11 patients who underwent exercise testing preoperatively; ††Subregional PET analysis showed improved perfusion in endocardial regions.

The improvement in symptoms appears to peak by six months and persists for at least one year. Two studies have demonstrated sustained angina relief beyond 12 months. The first, a study of 19 patients using the Ho:YAG laser, showed a decrease in CCS class angina from a baseline of 3.3 to 2.6 on three-year follow-up (7). The second, a study of 78 patients using the CO2 laser, showed a decrease in angina class from a baseline of 3.7 to 1.6 after an average of five years of follow-up (75). Transmyocardial laser revascularization has also been associated with improved quality of life (3,64), decreased need for antianginal medication (64,69,76), reduced hospital admissions for unstable angina (65,70), and improved exercise tolerance (1,3,4,6,11,23,24,76).

Results of postoperative perfusion studies have been conflicting. Five studies (11,23,65,70,77) demonstrated improved myocardial perfusion by single-photon emission computed tomography (SPECT) or PET imaging at three to 12 months after TMR. In contrast, seven studies (3,4,6,7,24,76,78) demonstrated diminished perfusion or no change. Two studies (23,79) demonstrated improvements in rest and stress function by dobutamine stress echocardiography at three to six months after TMR, while another (11) found no change in wall motion at 12 months. It has been hypothesized that the progression of disease in native coronaries and bypass grafts may confound the results of postoperative perfusion studies and may potentially explain the disparity of these findings (7,27). It has also been suggested that the lack of improvement in perfusion and myocardial function may be secondary to the limitations of current imaging modalities (e.g., low resolution of perfusion scans and poor echocardiographic imaging windows) (14,16,19). Laham et al. (80) recently reported on the use of magnetic resonance imaging (MRI) to investigate the revascularization effect of the Ho:YAG laser. In this small (n = 15), open-label study, the authors reported significantly improved target wall thickening and wall motion at 30 days and at six months. Importantly, no improvement was seen with SPECT imaging. The authors conclude that MRI may be a promising modality for the demonstration of a true revascularization effect, which is crucial to the acceptance of TMR, particularly in the absence of hard clinical end points.

**RANDOMIZED CONTROLLED TRIALS OF TMR**

To date, there have been six prospective, randomized, controlled trials of TMR versus medical therapy (Table 2). The largest trial, conducted by Allen et al. (14), randomized 275 CCS class IV patients with CAD not amenable to PCI or CABG. Crossover from medical to surgical groups was allowed for patients requiring intravenous antianginal therapy despite two attempts at weaning over a 48-h period. In the final analysis, 132 patients were treated primarily with TMR and 143 patients with medical management, of whom 32% crossed over to the TMR arm from the medical therapy group. Follow-up results, including anginal class assessment, exercise tolerance, quality-of-life scores, and dipyridamole-thallium imaging, took place at 3, 6, and 12 months. At the end of the study period, 76% of the TMR treated patients had a two-class or greater decrease in anginal scores, as compared with 32% in the medical therapy group (p < 0.001). Patients randomized to TMR also had a significantly greater exercise tolerance (5.0 vs. 3.9 metabolic equivalents, p = 0.05). A significant improvement was also noted in quality-of-life scores and rates of cardiac-related rehospitalization, but no differences were seen in myocardial perfusion between the two groups.

The second largest trial by Frazier et al. (15) randomized...
192 patients with CCS class III or IV angina to either TMR or continued medical treatment. Crossover was allowed from medical to surgical groups for patients requiring greater than 48 h of intravenous antianginal therapy. The severity of angina, quality of life, and cardiac perfusion by 201T1:SPECT scanning were evaluated at baseline and at 3, 6, and 12 months. At the end of the follow-up period, the investigators found that TMR decreased anginal scores by two or more classes in 72% of patients, compared with 13% of patients treated with medical therapy (p < 0.001). According to the responses on the SF-36 questionnaire, patients in the TMR group had a greater improvement (38%) in their quality of life than patients in the medical treatment arm (6%) at three months (p < 0.001). This difference was also significant at six and 12 months. Furthermore, for each component of the Seattle Angina Questionnaire, TMR was associated with a significantly better result than medical treatment. And finally, in a more objective measure of outcomes, myocardial perfusion improved by 20% in the TMR group and worsened by 27% in the medical treatment group at 12 months (p < 0.002).

How do we explain such apparently impressive results? Does the placebo effect play a role in the response to TMR? Previous trials have compared the surgical treatment of angina with internal mammary artery ligation to a sham operation in which patients received only a skin incision (81,82). With our present knowledge, neither of these procedures would be expected to improve anginal symptoms. Remarkably though, both groups demonstrated a 35% average improvement after a follow-up of six to 12 months. Similarly, Bienenfeld et al. (83) report that both a 30% to 80% improvement in exertional angina and a 90- to 120-s increase in exercise tolerance can be expected with placebo therapy. These numbers are similar to what has been reported for TMR. To desist patients with end-stage CAD, TMR represents highly advanced technology with the potential to ease suffering (74,84). This patient bias in favor of laser therapy is an important confounding variable in unblinded trials (74,84). Unfortunately, blinded, sham-controlled surgical trials are difficult to conduct (84).

A limitation of the two aforementioned trials was the crossover of 32% and 59% of patients from medical therapy to the TMR group. Frazier and colleagues (15) allowed crossover as “an incentive for patients assigned to maximal medical therapy to remain in the study if medical therapy failed” (i.e., when the subjective end point of angina was reached). Allowing such crossovers, however, suggests a bias on the part of the investigators that TMR is more effective than medical therapy (84).

In a European randomized trial of TMR, Schofield et al. (16) separated the two study groups for the whole 12-month observation period without crossover. These investigators found that CCS angina score decreased by at least two classes in 25% of TMR and 4% of control patients (p < 0.001). However, there was no statistically important difference between the two groups in mean treadmill time,

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**Table 2. Published Randomized Clinical Trials of TMR Versus Medical Therapy With 12-Month Follow-Up**

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of Patients</th>
<th>Crossover Allowed?</th>
<th>Laser Used (Modality)</th>
<th>Laser Used (Number of Channels Produced)</th>
<th>% of Patients With Two or More Classes Decrease of CCS</th>
<th>Improvement in Exercise Time (s)</th>
<th>Survival</th>
<th>Perfusion Modality: Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allen et al. (14)</td>
<td>275</td>
<td>Yes</td>
<td>Ho:YAG (39)</td>
<td>76 vs. 32 (p &lt; 0.001)</td>
<td>+5.0 vs. +3.4 MET* (p &lt; 0.001)</td>
<td>84% vs. 89% (p &lt; NS)</td>
<td>201T1:SPECT: no change</td>
<td></td>
</tr>
<tr>
<td>Frazier et al. (15)</td>
<td>192</td>
<td>Yes</td>
<td>CO 2 (30)</td>
<td>72 vs. 13 (p &lt; 0.001)</td>
<td>NA</td>
<td>85% vs. 79% (p &lt; NS)</td>
<td>201T1:SPECT: improved</td>
<td></td>
</tr>
<tr>
<td>Schofield et al. (16)</td>
<td>188</td>
<td>No</td>
<td>CO 2 (30)</td>
<td>25 vs. 4 (p &lt; 0.001)</td>
<td>NA</td>
<td>89% vs. 96% (p &lt; NS)</td>
<td>99mTc:SPECT: no change</td>
<td></td>
</tr>
<tr>
<td>Aaberge et al. (18)</td>
<td>100</td>
<td>No</td>
<td>Ho:YAG (48)</td>
<td>39 vs. 0 (p &lt; 0.001)</td>
<td>+8 vs. +10 (p &lt; 0.01)</td>
<td>88% vs. 92% (p &lt; NS)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Jones et al. (19)</td>
<td>86</td>
<td>No</td>
<td>Ho:YAG (NA)</td>
<td>NA</td>
<td>+119 vs. +85 (p &lt; 0.001)</td>
<td>NA</td>
<td>201T1:SPECT: no change</td>
<td></td>
</tr>
</tbody>
</table>

*Exercise treadmill testing was not part of the original study design, and no treadmill tests were performed at baseline, analysis of total exercise time included only 81 patients who underwent Naughton testing; ‡Exact data not available, however, the difference in exercise times between the two groups was 40 s (in favor of TMR) at 12 months (p < 0.001); †Time to chest pain during exercise increased by 66 s in the TMR group and decreased by 3 s in the control group (p < 0.01); ‡Statistically not significant; SPECT = single-photon emission computed tomography; TMR = transmyocardial laser revascularization.

**References:**
- Allen et al. (14)
- Frazier et al. (15)
- Schofield et al. (16)
- Aaberge et al. (18)
- Jones et al. (19)
OBSERVATIONAL STUDIES OF PMR

In 1997, Kim et al. (86) reported the feasibility of creating myocardial channels from the endocardial surface of the left ventricle using a catheter system introduced through the femoral artery. With PMR, only half the number of myocardial channels is made compared with TMR. A study examining different densities of channel spacing suggests that a dose-response relationship related to channel number might be of significance (87). Nonetheless, early results of PMR indicate that the reduction in angina approaches that reported for TMR (Table 3). As an example, Lauer et al. (12) studied 34 patients with CCS class III or IV angina and severe coronary disease not amenable to either PCI or CABG. The PMR procedure was successfully completed in

12-min walking distance, or in the overall rate of hospital admissions. Furthermore, the number of left ventricular segments with reversible myocardial ischemia fell in both treatment groups, with no significant differences between the two groups.

In contrast, the Angina Treatments–Lasers and Normal Therapies in Comparison (ATLANTIC) trial (17) randomized 182 CCS class III or IV patients to TMR and continued medication or continued medication alone. The patients were also followed for 12 months without crossover. The study investigators found a 65-s increase in total exercise tolerance in the TMR group but a 46-s decrease in the control group (p < 0.0001). Furthermore, an independent, blinded assessment of angina score also showed a significant benefit to TMR, with a CCS score of II or lower in 48% of the TMR group versus 14% in the control group (p < 0.001).

In an editorial on TMR, Lange and Hillis (84) report that there is little objective evidence that the results of TMR are superior to those of medical therapy; in the trial by Allen et al. (17), patients randomized to TMR had greater exercise tolerance 12 months after enrollment. However, exercise treadmill testing was not part of the original study design and was measured in only 29% of patients. Furthermore, no treadmill tests were performed at baseline to establish that the TMR and medical therapy groups were comparable in this respect. In four other trials (16–19) in which exercise tolerance was assessed routinely at baseline and after enrollment, only two (17,19) showed an improvement in effort capacity. Transmyocardial laser revascularization did not improve myocardial perfusion in four of five trials (14,16,17,19) in which perfusion was assessed before and at various times after enrollment. In the remaining trial in which a benefit was seen (15), there was a poor follow-up in the medical arm of the study. Also, the degree of symptomatic improvement was disproportionate to the degree of improvement in perfusion. Finally, in none of these trials was TMR associated with a survival benefit at one year.

Unlike the evidence for TMR as sole therapy for end-stage coronary disease, promising results have been shown when TMR was used as an adjunct to CABG. Allen et al. (85) conducted a blinded, randomized, controlled trial of 263 patients, in which TMR was combined with CABG in patients not amenable to complete revascularization. Twelve-month follow-up data on angina relief and treadmill improvement was no better when compared with incompletely revascularized patients. However, the operative mortality rate was 1.5% after the hybrid procedure and 7.6% after CABG alone. Furthermore, one-year Kaplan-Meier survival (95% vs. 89%, p = 0.05) favored the combination of CABG and TMR. These observed benefits require confirmation by a larger validation study, which is ongoing.

### Table 3. Studies of PMR

<table>
<thead>
<tr>
<th>Author (Reference)</th>
<th>Number of Patients (Months of Follow-Up)</th>
<th>Laser Used*</th>
<th>Mean CCS Class: Baseline vs. Follow-Up (p Value)</th>
<th>Improvement in Exercise Time (s): (p Value)</th>
</tr>
</thead>
<tbody>
<tr>
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*Commercial systems, all based on the holmium:ytrrium-argon-garnet laser; †18-month data in a subgroup of 16 patients showed an average CCS class of 1.4; §Exact data not available, however, the average rate-pressure product improved by 18% at three months (p value not specified); ¶Double-blinded, randomized, sham-controlled trial; §High-dose direct myocardial revascularization (20 to 25 channels per zone); ¶There was no statistically significant difference in exercise time between the two groups, however, the time to chest pain increased by 76 s in the laser group and decreased by 12 s in the control group (p < 0.05). CCS = Canadian Cardiovascular Society; NA = data not available; NS = statistically not significant; PMR = percutaneous myocardial revascularization.
all patients. Follow-up occurred at six months, demonstrating an average reduction of two angina classes and a 130-s increase in exercise capacity, but no improvement in perfusion by thallium scintigraphy. A second smaller study reported similar results (13).

**RANDOMIZED CONTROLLED TRIALS OF PMR**

The Potential Class Improvement From Intramyocardial Channels (PACIFIC) trial investigators assigned 221 patients with refractory CCS class III or IV angina and reversible perfusion defects on thallium stress testing to either PMR with continued medical treatment or to medical treatment alone (20). The primary end point was exercise tolerance at 12 months. In the PMR group, there was a median increase of 89 s in exercise duration as compared with an increase of 12.5 s in the control group (p = 0.008). In addition, the CCS class assigned by the investigators (who were aware of the treatment assignment) decreased by ≥2 classes in 46% of patients assigned to PMR compared with only 11% of control patients. Unfortunately, 11 patients died during the follow-up period (eight PMR, three control; p = 0.21). Higher rates of heart failure, bradycardia, and bundle branch block were also observed in the PMR group than in the control group (31 events versus 15; p value not specified). Another limitation of this study was the lack of blinding. When the investigators’ assessments of angina class were compared with those made by an independent panel without knowledge of treatment assignment, it was shown that the study investigators assigned significantly lower CCS scores to PMR patients than did the blinded panel. However, grades from the blinded panel were still significantly lower with PMR than with medical therapy.

Three recent blinded trials have compared PMR to a sham procedure (Table 3). Two of these trials have not yet been published in peer-reviewed journals but have been presented in abstract form. Interim results of the Direct myocardial revascularization In Regeneration of Endomyocardial Channels Trial (DIRECT) were presented in the fall of 2000 (88). A total of 298 patients underwent left ventricular electromechanical mapping using the Biosense direct myocardial revascularization (DMR) system. The patients were then randomized to either a low-dose DMR (10 to 15 channels per zone), high-dose DMR (20 to 25 channels per zone), or to the sham procedure. For the primary end point of change in exercise duration from baseline to six months, the investigators found a statistically significant improvement in each of the treatment arms including those receiving sham treatment, but there was no statistical difference between the three groups. In fact, the best performance was in the sham treatment group, with 42% of patients improving by two or more functional classes by three months. Other exercise parameters, such as time to symptom onset and time to ST-segment depression, showed no benefit. Furthermore, there were no statistically significant differences in quality-of-life scores between the groups. The trial investigators concluded that the benefits seen in previous studies were secondary to the placebo effect and that all unblinded trials in this field should be viewed with caution.

The results of the Prospective, Multicenter, Randomized trial of PMR in Patients with Nonrecanalizable Chronic Total Occlusions has been recently published (89). A total of 141 patients with class III to IV angina and a nonrecanalizable chronic total occlusion were randomized to either PMR with the Eclipse system (CardioGenesis Corporation, Foothill Ranch, California) or to maximal medical therapy. Randomization took place after an unsuccessful, uncomplicated attempt to cross the chronic occlusion. Blinding was achieved through heavy sedation, dark goggles, and the concurrent performance of PCI in all patients. To assess the adequacy of blinding, patients completed a questionnaire before discharge regarding their belief about treatment assignment. Symptom-limited stress testing was performed at baseline and at six months. The primary end point was the change in total exercise time from baseline to follow-up. Exercise time improved by 62 s in the PMR group and by 54 s in the medical therapy group (p = 0.86), highlighting the importance of blinding and of the placebo effect in these patients.

The third study, the Blinded Evaluation of Laser Intervention Electively for Angina Pectoris (BELIEF) trial, was presented in the spring of 2001 (90). A total of 82 patients were randomized to PMR using the Eclipse system or to a sham procedure, and were followed for improvement in CCS functional class, exercise tolerance, and quality of life. At six months, 41% of patients in the PMR group improved by two or more CCS classes compared with only 13% in the control group (p = 0.006). There was no significant difference in exercise duration between the two groups, although patients in the control group had a faster onset of chest pain. Furthermore, there appeared to be a mild improvement in quality-of-life scores in favor of the PMR group.

The results of the BELIEF trial appear to support the clinical benefit reported with TMR. However, the larger DIRECT and PMR in Chronic Total Occlusions trials argue against such benefit. It has also been suggested that the lack of a positive result in the DIRECT trial might represent a device-specific failure. It was widely believed that the Biosense DMR laser would be advantageous because of the mapping system that allows precise definition of the target ischemic area. However, with the Biosense system, lasing is done with pulses carried out at the endocardial surface, whereas with the Eclipse and CardioGenesis systems, lasing is done within the heart muscle by physical puncture of the endocardial surface (Fig. 1). The clinical implication of this difference in technique is not known. However, the DIRECT trial (using the Biosense DMR laser) and the PMR in Chronic Total Occlusions...
trial (using the Eclipse laser) arrived at similar conclusions with respect to PMR. These results imply that the type of laser instrument is only of secondary importance. Therefore, a review of the PMR literature suggests that the clinical benefits of laser revascularization are largely due to a placebo effect. Before we can arrive at definitive conclusions, however, blinded trials of PMR with greater numbers of patients, and with long-term follow-up, are needed.

Conclusions. A proper balance of procedural risks and benefits remains the most important principal for any new and innovative therapeutic intervention. In this respect, TMR appears to be safe and is currently approved for use in North America and in Europe. However, relatively small numbers of patients have been randomized, and there are methodological problems with many of the studies, including a lack of blinding. Ideally, future trials would employ sham controls in order to avoid observations that may be due to the placebo effect. Such trials, however, are considered unethical. Percutaneous myocardial laser revascularization appears to be associated with less morbidity than TMR. However, the technique is still considered investigational and is not FDA approved. Furthermore, the results of recent well-performed double-blinded trials are conflicting, suggesting a significant placebo effect in the response to PMR. Larger trials are, therefore, needed to examine the value of this technique.

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REFERENCES


64. Hughes GC, Shah AS, Yin B, et al. Transmyocardial laser revascularization: results of a multicenter trial with transmyocardial laser revascularization method after 3 months of chronic myocardial isch
88. Leon MB. DIRECT (DMR In Regeneration of Endomyocardial Channels Trial). Presented at Late-Breaking Trials, Transcatheter Cardiovascular Therapeutics; October 19, 2000, Washington DC.