Background. Transmyocardial revascularization (TMR) is a form of revascularization technique in which small channels are created between the ischemic myocardium and the left ventricular cavity. The therapeutic value of this technique is derived from studies of reptilian hearts in which blood is delivered to heart muscle via a network of channels directly from the left ventricle. This is supported by findings of Wearn and colleagues. They described “arterio-sinusoidal” communications or vessels that seemed to connect a microcirculatory network from the coronary arteries directly with the left ventricular cavity. Based upon these findings, investigators tried to increase myocardial perfusion “directly” by augmenting blood flow into existing myocardial sinusoids or by creating new sinusoids.

In 1935, Beck grafted vascularized mediastinal fat or parietal pericardium to the heart surface. In the 1940s, Vineburg implanted the distal end of the internal mammary arteries directly into canine myocardium and demonstrated a myocardial “blush” as well as collateralization to the epicardial coronary arteries. In 1954, Vineburg extended this approach by tunneling the internal mammary artery into the myocardium of patients. Both symptoms and survival improved with the implants, and their long-term patency and collateral supply function were documented.

In 1965, Sen and colleagues used blunt instruments to create transmural channels (“transmyocardial acupuncture”) to deliver oxygenated blood directly from the ventricle into sinusoidal channels of the microcirculation or into other vessels perforated by the channels. Unfortunately, channels fibrosed and closed within a few weeks, offering no long-term benefit.

Clinical trials of TMR (Table 1). With the rapid evolution of coronary artery bypass surgery and coronary angioplasty as methods to treat patients with ischemic heart disease, there was reduced interest in investigations designed to evaluate the adequacy of direct myocardial revascularization.

A subgroup of patients has emerged who are not candidates for coronary bypass or coronary angioplasty. This group includes patients with severe diffuse coronary disease, small vessel disease, total coronary occlusions, and those who have had previous revascularization attempts with poor results. Incomplete revascularization in these patients has been associated with a greater likelihood of recurrent angina and subsequent cardiac events, including myocardial infarction and death. TMR using laser energy to revascularize the myocardium is being used as a potential alternative for augmenting
blood flow to ischemic myocardial territories in these patients.

To be a candidate for current TMR procedures, patients must meet the following criteria: 1) severe angina (functional class III or IV) despite optimal medical therapy; 2) poor candidate for catheter-based angioplasty due to high procedural risk or absence of acceptable target sites; and 3) poor candidate for surgical revascularization due to prohibitive risk or absence of acceptable target vessels and/or remaining surgical conduits.

**Surgical TMR.** Surgical TMR, using an 85-W CO₂ laser, was applied in 1983 by Mirhoseini et al.¹¹ to create transmyocardial channels as an adjunct to coronary artery bypass graft surgery in patients who could not be completely revascularized. These investigators reported less angina and greater myocardial perfusion in treated regions.¹²–¹⁴ Later, Frazier and Cooley¹⁵ used a similar surgical TMR approach with an 800-W CO₂ laser as “sole therapy” in 21 patients; they reported reduced angina, increased exercise capacity, and enhanced subendocardial perfusion by positron emission tomographic scans at 12 months.¹⁶ Similar favorable results were reported by Horvath and Cohn¹⁷–¹⁹ using surgical laser TMR techniques. They studied 20 patients with angina refractory to medical therapy and evidence of reversible ischemia who were not candidates for angioplasty, bypass surgery or transplantation. However, a mortality of 10% (2 out of 20 patients) and 3 additional deaths occurred post-discharge. Among survivors, a significant improvement in angina was observed (angina class decreased from 3.7 to 1.0 at 12 months; p < 0.001).

Preliminary results of a recent randomized trial to determine whether surgical CO₂ laser revascularization is superior to medical therapy in patients not amenable to conventional revascularization techniques reported improved symptoms, improved quality of life, and some evidence of enhanced myocardial perfusion in the treated areas.²⁰ Of the patients randomized to surgical TMR, 67% showed reduction of anginal class greater than 2 compared with 6% of the medically treated group, and hospitalization for unstable angina was markedly decreased (13% post-TMR versus 72% with medical therapy). Clinical efficacy in the form of angina threshold was decreased for as long as 2 years after the procedure. Nuclear studies, with analysis limited to the first 3 months, showed a less impressive 15% reduction in reversible defects in the TMR group versus a 7% increase in reversible defects in the control group. In a randomized prospective study, Allen et al.²² performed TMR using the surgical approach and Holmium: YAG laser energy and reported significant improvement in angina class (85% vs. 18%) and decreased hospitalizations for angina compared with maximum medically treated patients at 6 months; clinical benefit was sustained for up to 12 months.

Donovan et al.²¹ used dobutamine stress echocardiography to study 12 patients treated with surgical CO₂ TMR and found significant improvement in the regional contractility in the treated segments.

The physical characteristics of the CO₂ laser allow efficient and precisely localized tissue ablation, but its radiation wavelength does not allow delivery via a flexible fiberoptic system. This limits the use of this device to the open thoracotomy setting. Because of these restraints, TMR investigations began using Holmium: YAG laser energy, which can be effectively transmitted at a much shorter wavelength through flexible fiberoptics.

**Percutaneous approach.** The safety and efficacy of a non-surgical, less invasive, transcatheter approach has been reported in a few observational studies.²³–²⁷ Although clinical trials are in the early stages and randomized trial data are not yet available, preliminary results from these studies appear favorable.

Percutaneous transluminal myocardial revascularization (PTMR) utilizes the percutaneous endoluminal approach adapted from other interventional catheterization procedures and employs catheter/fiber systems.
introduced through the femoral artery and fluoroscopically guided into the left ventricle. Channels (5 mm deep) are created from endocardium to myocardium, not penetrating the epicardium. The goal of catheter-based TMR is to provide channels that are smaller in size but comparable in effect to channels created by the surgical approach, without the need for a thoracotomy or general anesthesia. In addition, the morbidity and mortality should be lower compared to the surgical TMR, where periprocedural death is reported between 9–12% (Table 1).

**PTMR technique.** Patients were eligible for the study, if they: 1) had known coronary artery disease not amenable to percutaneous intervention or coronary artery bypass surgery (as determined by the cardiologist and a cardiovascular surgeon not involved in the direct care of the patient); 2) were in Canadian Cardiovascular Society functional class III or IV; 3) had inducible ischemia on exercise treadmill testing or had unstable angina defined as an ischemic ST-segment depression at rest and requiring intravenous nitroglycerin; and 4) had a preprocedure echocardiogram demonstrating > 9 mm wall thickness of the left ventricular region that was to be lazed and an ejection fraction of > 0.25. A 9 French (Fr) introducer is placed in the femoral artery and an 8 Fr introducer is placed in the femoral vein using standard technique. Heparin 7,000 IU is administered intravenously to achieve an activated clotting time of at least 280 seconds. A 6 Fr pigtail catheter is advanced into the left ventricle and left ventricular end diastolic pressures are recorded. Left ventriculography is performed in the right anterior oblique projection (30°) for the inferior wall, left anterior oblique (45°) for the posterior or lateral wall, and left lateral view for the anterior wall. The pigtail catheter is then exchanged for the 9 Fr PTMR catheter system (Eclipse Surgical Technologies, Inc., Sunnyvale, California; Figure 1) over an 0.038” J Amplatz, Extra Stiff exchange guide wire (Cook, Inc., Bloomington, Indiana). The extra stiff guide wire is looped in the left ventricle and the catheter system carefully positioned in the apex (Figure 2). The guide wire is removed, all air is aspirated, and the catheter system is continuously flushed with heparinized saline. The distal tip of the catheter is positioned in the intended treatment area by gentle torquing and by using the tip deflecting handle (5 or 7 cm). Once positioned, the 1 mm laser fiber (SlimFlex, Eclipse Surgical Technologies) is inserted into the guide system and aligned fluoroscopically with the distal marker band. Laser treatment parameters are preset to produce 3.5 watts at 5 Hertz from the 1 mm diameter optical fiber. Maximum penetration (5 mm) is achieved with 3 consecutive pulses. With the laser in the “ready” mode, the laser fiber is slowly advanced slightly beyond the distal tip marker exiting the guide system contacting the ventricular wall. The foot switch is then depressed and 3 consecutive pulses are delivered to the endocardial surface. Between 15 and 30 laser channels (3 pulses each) are placed approximately one channel per 1 cm², and channels are limited to the lower two-thirds of the left ventricle. Care is taken to avoid the ventricular septum and areas of akinesis. A corresponding premature ventricular couplet is observed during laser pulsing, suggesting energy delivery and creation of a channel.

Once all of the desired channels are created, left ventriculography is repeated in the same projection as pre-PTMR. Patients are discharged the following day after a two-dimensional echocardiogram and sequential creatine phosphokinase are obtained.

**Percutaneous trials (Table 2).** The author has reported procedural and early follow-up data on patients who underwent PTMR using the Eclipse Holmium: YAG system. A recent study focused on 27 patients who were symptomatic before PTMR, with 10 in Canadian Cardiovascular Society functional class III and 17 in class IV. Before PTMR, 15 patients had positive ischemic exercise treadmill test results, and 12 with rest angina did not undergo exercise testing because of inability to wean from intravenous nitroglycerin. The patients were mostly men. A history of myocardial infarction was present in 55% and history of congestive heart failure in 4%. An average of 17 ± 4 channels were created by the laser. Procedural time from creation of

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**Table 2.** Observational studies of percutaneous transluminal myocardial laser revascularization

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of Patients</th>
<th>Laser System</th>
<th>30 day Mortality</th>
<th>Pericardial effusion or Tamponade</th>
<th>Minor CVA</th>
<th>Follow-up Months</th>
<th>Angina Relief</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oesterle²⁸</td>
<td>12</td>
<td>Cardiogenesis</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>6</td>
<td>Improved by &gt; 2 classes in 78%</td>
</tr>
<tr>
<td>Shawl²⁵</td>
<td>27</td>
<td>Eclipse</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>6</td>
<td>Mean angina class reduced from 3.6 to 0.97</td>
</tr>
<tr>
<td>Lauer²⁷</td>
<td>34</td>
<td>Cardiogenesis</td>
<td>1</td>
<td>6</td>
<td>0</td>
<td>6</td>
<td>Mean angina class reduced from 3.1 to 1.3</td>
</tr>
<tr>
<td>Kornowski²⁹</td>
<td>32</td>
<td>Biosense</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>Increase in exercise testing from 440 to 505 seconds</td>
</tr>
</tbody>
</table>

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the first channel to the last channel was 58 ± 26 minutes, with a fluoro time of 15 ± 26 minutes. The energy was constant at 3.5 W for each laser activation. Regional wall motions were unchanged or slightly improved on repeat left ventriculography (Figures 3A and B) or by transesophageal echocardiogram immediately after the procedure. Following the procedure, patients were successfully weaned off intravenous nitroglycerin. The average length of hospital stay for the 27 patients was 1.8 ± 1.5 days. There were no procedure-related deaths, pericardial effusions, or instances of tamponade, and no deaths in the 30 day period after the procedure. One patient had an increase in the total creatine phosphokinase, but the MB fraction was not determined. There was no electrocardiographic evidence of myocardial injury. There were no cerebrovascular accidents or sustained supraventricular or ventricular arrhythmias.

Of the 27 patients (all of whom were in functional class III or IV before the procedure), 15 were in class I, 3 were class II and 9 had no angina at one month. At 30 days, the mean functional class improved from 3.63 ± 0.5 to 0.65 ± 0.8 (p < 0.01). For 12 patients with functional class available at 6 months, mean anginal class was 0.94 ± 0.97.

Follow-up exercise treadmill was available in 12 of the 27 patients at 6 months. Of these, 9 had no electrocardiographic evidence of ischemia or chest pain during exercise. Of the 12 who were originally unstable and unable to be weaned from nitroglycerin, 6 month follow-up was available in 6 patients; 4 out of these 6 had no electrocardiographic evidence of ischemia during exercise testing. The magnitude of ischemia on Tl-201 testing was reduced in 58% (Figures 4A and 4B) and unchanged in 42% of patients. Similar findings were reported by Knopf et al. in a feasibility study of Holmium:YAG PTMR among 18 patients with medically refractory class 3 or 4 angina. No periprocedural deaths occurred and all patients were discharged within 48 hours after the procedure. Mean angina class fell from 3.83 at baseline to 1.07 at the time of hospital discharge and 1.06 at 6 month follow-up. At 6 months, 88% of patients noted improvement by at least two classes in angina severity. Lauer et al. also reported comparable symptomatic improvements in a separate series of 16 patients in a multicenter series. Oesterle and Kornowski recently reported similar results using two other available percutaneous TMR systems (Table 2). Several randomized clinical trials assessing short and long-term procedural success
and clinical benefit are ongoing and results are expected to be reported in the near future.

**Mechanism of benefit.** Despite extensive investigation, the mechanism by which TMR affords clinical benefit is still unknown.\(^3\) Initial studies postulated that patent channels would provide continuous blood flow similar to endocardial perfusion in alligator hearts.\(^1\) However, the long-term patency of the laser channels remains controversial.\(^4,30,31\) Another interesting possibility is the stimulation of angiogenesis by laser-induced injury, leading to increased myocardial perfusion. It is also possible that the dramatic relief of angina as seen in our cases may, in part, be from myocardial sensory nerve damage, resulting in an anesthetic effect.

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**Figure 3.** Left ventriculography (systolic frame) in the right anterior oblique projection pre (A) and post (B) PTMR of the anterior wall. Note the marked improvement in the anterior wall.

**Figure 4.** A 62-year-old male with a history of two previous coronary artery bypass surgeries and inferior myocardial infarction, presents with class III angina due to a diffusely diseased left circumflex and obtuse marginal branches (saphenous vein grafts occluded). Radionuclide Spect Thallium study before (A) and 6 months after (B) PTMR (17 channels) to the posterolateral wall. Note improved perfusion in the left circumflex distribution.
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The reason for the absence of mortality and near absence of significant periprocedural complications with the transcatheter technique may be related to the markedly lower physiologic and structural trauma resulting from the catheter approach. This is particularly important in patients who are not completely revascularized, but who are subjected to major surgical stress. The elevation of creatine phosphokinase in 1 of our patients was likely due to the actual lazing process, although this cannot be determined. However, there were no significant clinical sequelae associated with the enzyme elevation.

Conclusion. Based on early clinical experience, PTMR appears to be a potential palliative treatment for refractory ischemic coronary artery disease not amenable to any form of currently available revascularization techniques. Over the next year or two, data from randomized trials will be available to assess the short- and long-term efficacy. Moreover, further work is required to develop refinement in the catheter technology, improve guidance systems and to better understand the underlying mechanism of this form of revascularization. Recent developments using angiogenic growth factors appear very promising, and the role of growth factors as an adjunct to TMR remains to be seen.

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A P P E N D I X

The second comment I wanted to make had to do with the issue of angiogenesis. As Dr. Zeitler mentioned the other day, angiogenesis probably doesn’t occur in human hearts in a true sense — at least the preponderance of evidence suggests that it doesn’t. Rather, the evidence suggests that we see an opening or a maturation of nascent collaterals or nascent vessels that aren’t being utilized. Robert Schwartz has done some interesting, provocative work in the animal laboratory wherein he has taken pig hearts and mechanically removed a thin layer of tissue from the endoluminal surface; perhaps a millimeter

ALEX ZAPOLANSKI: As a surgeon, I must say I have only been an observer of this technique. It’s been going on for years in my hospital. If I am not mistaken, I think Richard Myler told me that the first human in the United States was done by Dr. John Crew at Seton Medical Center many years ago. I was impressed by the fact that the technique, which has been around for 8–10 years, has not developed more rapidly. In general, when a procedure works, it spreads quickly. It happened with bypass and angioplasty. When you look at procedures like this or cardiomyoplasty, they just don’t come along fast enough. Although the surgical data available to us reflects the fact that the procedure is of some value, I believe it is applicable to a very small number of cases.

FAYAZ SHAWL: I think there are many patients who do not have many options. So I think if you do it percutaneously it would be even more attractive for these patients who have no other options down the road.

JEFFREY WERNER: I think many cardiologists in this group have participated in angina trials for end-stage angina medications. I believe most of us were impressed that at least some patients got better. Why they got better, I don’t know. A lot of it was motivational. A lot of it was having no alternative. A lot of it was just good attention — they came to the office more frequently. So, I have a healthy respect for “just good” care, and I am hopeful that these medications are going to be helpful and that there really is a new technique that will help patients who have very few options. However, I will remain skeptical until I see truly randomized data, with a placebo group if necessary, and extensive, objective patient follow-up. Only at that point can you be certain — or even fairly certain — that your technique is causing the relief that you see. I hope it proves to be the case, but I don’t think we know yet.

DR. SHAWL: We are going to study 200 cases in our randomized trial.

DR. WERNER: Are there some patients that are having their chest opened but not having the holes made?

DR. SHAWL: No, this is all percutaneous.

DR. RODRIGUEZ: Have you found a ck increase?

DR. SHAWL: We have recorded that very carefully.

KIRK GARRATT: I have two comments. First, in our TMR and PMR protocols at Mayo Clinic, we have also been a bit concerned about objective measurements of patient outcomes in the study protocols. There are no sham procedure elements in either the surgical or the percutaneous limb; this raises the question of whether or not there could be some sort of ongoing placebo effect, particularly when your endpoints are measured with such things as a patient’s subjective perception of their angina at some time point down the road.

The second comment I wanted to make had to do with the issue of angiogenesis. As Dr. Zeitler mentioned the other day, angiogenesis probably doesn’t occur in human hearts in a true sense — at least the preponderance of evidence suggests that it doesn’t. Rather, the evidence suggests that we see an opening or a maturation of nascent collaterals or nascent vessels that aren’t being utilized. Robert Schwartz has done some interesting, provocative work in the animal laboratory wherein he has taken pig hearts and mechanically removed a thin layer of tissue from the endoluminal surface; perhaps a millimeter

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of soft tissue is removed in strips. He has found that there is a bit of clot formation that is easily manageable with anti-coagulants to prevent stroke; after a short period of time, you can demonstrate that these nascent collaterals, which are just under the endocardial surface, open and are able to carry blood retrogradely from the left ventricular cavity deep into the myocardium. It raises the question of whether or not we need to be using anything more than some sort of simple mechanical device — not to punch holes deeply into the myocardium and certainly not to approach the myocardium through a sternotomy, but simply to reach into the left ventricular cavity, scrape a few spots and let nature take its course.

CHRISTOPHER CATES: I would like to address Kirk Garratt’s question about objective versus subjective evidence of ischemia. One of the measurements in a lot of these studies is, of course, subjective — in other words, they measure how a person “feels”. But most of the studies also have a very objective measurement, which is flow measurement using tomographic thallium done at 1 and 6 months. I think that data will help us to determine physiologically if there is a correlation to symptom improvement. There has been a lot of talk regarding this technique, particularly in the field of bioscience, about knowing exactly where you are in the ventricle. In Atlanta, we have had both the Eclipse device and the cardiogenic device for a number of months, and have done about 35 cases. We have found that it’s quite easy for experienced angiographers to find their way around by using a single plane lab — without biplane and without bioscience. Our average case time is very short — less than 30 minutes. I think the more time we spend inside the ventricle, the more time there is for problems to arise. The use of biplane, etc., has been emphasized as an important criteria for doing these procedures, but I don’t think that is always practical.

DR. SHAWL: I began doing these procedures in India under TE. Right now, single plane fluoroscopy is sufficient for me. This may change down the road.

WILLIAM O’NEILL: I don’t think that tomographic thallium is the right approach. The patients that we’re doing have had one or two previous total occlusions in some area of fixed defect and I think all of you know how notoriously difficult it is to tell between fixed and reversible ischemia. Also, the technique is not really sensitive enough to look at sub-endocardial blood flow. PET scans perhaps, but I think we are more intrigued by regional wall motion than with echoes. I think that is probably going to be a better tool. I have had a chance to look at the Eclipse surgical data. They’ve randomized 160 patients to medical therapy versus surgery and there was a dramatic difference in the clinical benefits of the surgically treated group at one year. Ninety percent of the medically treated group failed medical therapies, meaning that they would require repeat hospitalization and be put on nitroglycerin again. This only occurred in about 15% of the surgically treated group. This data is going to be published as soon as the 6 month thallium information is available. I think there is really strong surgical data now suggesting that this is an effective technique; in my mind, the only question is whether or not we are going to replicate the surgical results. One protocol was turned down by the FDA, I believe this is because they relied on thallium screening, and I just think that’s the wrong measurement for this technique.