The Society of Thoracic Surgeons Practice Guideline Series: Transmyocardial Laser Revascularization

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Background. Patients with chronic severe angina refractory to medical therapy who cannot be completely revascularized with either percutaneous catheter intervention or coronary artery bypass graft surgery present clinical challenges. Transmyocardial laser revascularization, either as sole therapy or as an adjunct to coronary artery bypass graft surgery, may be appropriate for some of these patients. Although transmyocardial revascularization has consistently been demonstrated as an efficacious means of relieving angina, the mechanism of its effects is still debated, and criteria for the selection of patients for this novel therapy have not been adequately defined.

Methods. We reviewed the available evidence to allow us to make recommendations for the appropriate therapeutic applications of transmyocardial revascularization following the format of the American Heart Association and the American College of Cardiology guidelines for diagnostic and therapeutic procedures. Our recommendations were classified as class I, IIA, IIB, or III. For each recommendation we defined the level of supporting evidence as A, B, or C.

Results. We identified class I indications for transmyocardial revascularization as sole therapy and class IIA indications for transmyocardial revascularization as an adjunct to coronary artery bypass graft surgery with levels of evidence A and B, respectively.

Conclusions. Transmyocardial laser revascularization may be an acceptable form of therapy for selected patients: as sole therapy for a subset of patients with refractory angina and as an adjunct to coronary artery bypass graft surgery for a subset of patients with angina who cannot be completely revascularized surgically.


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IIA. Weight of evidence or opinion is in favor of usefulness or efficacy
IIB. Usefulness or efficacy is less well established by evidence or opinion
Class III. Conditions for which there is evidence or general agreement that the procedure or treatment is not useful and in some cases may be harmful

The level of evidence was assigned using the following criteria:

A. Data derived from multiple randomized clinical trials
B. Data derived from a single randomized trial or from several nonrandomized studies
C. Consensus expert opinion

Process
We reviewed articles obtained through a search of the MedLine database (1966 to present) and the National Center for Biotechnology Information (NCBI) PubMed database using keywords including “TMR,” “laser,” “revascularization,” “transmyocardial,” “TMLR” (transmyocardial laser revascularization), “PMR” (percutaneous myocardial revascularization), and “DMR” (direct myocardial revascularization) as well as subject headings to which these terms were mapped and logical combinations of these sets. Using the same databases, searches were performed by author for investigators active in the field and by direct communication with investigators.

Background
The nature of the connections between the lumina of the ventricles and the coronary arteries has been debated at least since the description by Vieussens in 1706 of ventricles and the coronary arteries has been debated at least since the description by Vieussens in 1706 of “fleshy vessels” thought to represent direct communications between left ventricular myocardium and the left cardiac chambers [1]. These communications are not to be confused with the channels described by Thebesius in 1708 [2]. This debate was reignited by Wearn and colleagues [3] with their classic description of myocardial sinusoids in 1933. These “sinusoids” have evaded detection using modern techniques [4]. Yet some more-primitive vertebrate hearts are supplied, at least in part, by blood from the ventricular cavity [5, 6]. Furthermore, in patients with pulmonary atresia and intact ventricular septum, lumen-dependent myocardial perfusion has been clearly demonstrated [7]. The description of myocardial microanatomy by Wearn and associates [3] stimulated several investigators to develop new techniques for delivering oxygenated blood to the myocardium [8–14].

More than two decades ago, Mirhoseini and Cayton [15] used a 450-W industrial carbon dioxide laser in a canine model of acute ischemia. Mirhoseini and associates [16] were the first to use the technique clinically as an adjunct to CABG. The major limitation of their approach was that the 80-W CO2 laser available for clinical use required a stationary heart during channel creation, requiring ischemic arrest or ventricular fibrillation [17]. Although the original rationale for TMR was the hypothesis that direct channels from the left ventricular lumen could supply the myocardium with oxygenated blood, most have rejected this hypothesis as most experimental and clinical autopsy studies do not demonstrate patent channels [18–30]. Thus, a variety of newer hypotheses of the mechanism of action of TMR have emerged.

Lasers Used for Transmyocardial Revascularization
Since the pioneering efforts of Mirhoseini and associates [15, 16], a variety of laser wavelengths have been investigated for the creation of transmyocardial channels. In contrast to the CO2 laser used by Mirhoseini and coworkers [16], the 800- to 1,000-W PLC laser (PLC Systems, Franklin, MA) was specifically designed with sufficient pulse energy to allow for creation of transmyocardial channels in the left ventricle in approximately 40 ms—fast enough to successfully create transmural channels in a beating heart, heralding the first clinical trial of TMR. Some of the earliest experimental studies were performed by Jeevanandum and associates [31] using a thulium-holmium-chromium (THC):yttrium-aluminum-garnet (YAG) laser and by Yano and coworkers [32] using a holmium:YAG laser. Other laser systems investigated for use in TMR have included the excimer [33], argon, Nd:YAG, and pulsed-dye lasers.

Currently, the only US Food and Drug Administration–approved lasers for TMR are the CO2 laser (PLC Systems) and the holmium:YAG laser (Cardiogenesis, Sunnyvale, CA). The CO2 laser energy (wavelength, 10.6 μm) is more efficiently absorbed by water molecules than the holmium:YAG laser energy (wavelength, 2.1 μm). The energy per pulse of the CO2 system is 20 J to 80 J, and only one pulse is required to create a transmural channel. In contrast, the pulse energy of the holmium:YAG laser used clinically is typically 2 J to 5 J, and multiple pulses during several cardiac cycles are required to generate a transmural channel.

Current Hypotheses for Transmyocardial Revascularization Mechanism of Action
Clinical studies of TMR using a CO2 laser or holmium:YAG laser have consistently demonstrated a reduction in angina symptoms and, in several cases, an improvement in exercise tolerance and quality of life [34–51]. In general, however, these studies are not placebo-controlled, and the degree of angina improvement has varied significantly. The two leading proposed mechanisms of TMR effect include laser-induced angiogenesis with improvement in regional myocardial blood flow and laser-induced denervation of the myocardium resulting in an improvement in angina symptoms without the requirement for any improvement in oxygen delivery.
Table 1. Results of Randomized Clinical Trials of Transmyocardial Revascularization as Sole Therapy

<table>
<thead>
<tr>
<th>Author</th>
<th>Patients</th>
<th>Centers</th>
<th>Laser</th>
<th>Perioperative Mortality (%)</th>
<th>F/U (y)</th>
<th>Channels</th>
<th>Significant Angina Decrease</th>
<th>Significant Hospitalization Decrease</th>
<th>Increase Perfusion</th>
<th>Increase Survival</th>
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<td>18</td>
<td>H-YAG</td>
<td>5</td>
<td>1</td>
<td>39</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>N</td>
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<td>Frazier et al 1999 [47]</td>
<td>192</td>
<td>12</td>
<td>CO₂</td>
<td>3</td>
<td>1</td>
<td>36</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>Burkhoff et al 1999 [46]</td>
<td>182</td>
<td>16</td>
<td>H-YAG</td>
<td>2</td>
<td>1</td>
<td>18</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
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<td>1</td>
<td>CO₂</td>
<td>5</td>
<td>1</td>
<td>30</td>
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<td>Y</td>
<td>...</td>
<td>N</td>
</tr>
<tr>
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<td>1</td>
<td>CO₂</td>
<td>4</td>
<td>3–5</td>
<td>48</td>
<td>Y</td>
<td>Y</td>
<td>...</td>
<td>N</td>
</tr>
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CO₂ = carbon dioxide; F/U = follow-up; H-YAG = holmium:yttrium-aluminum-garnet.

Angiogenesis

A variety of experimental studies in normal and ischemic canine, porcine, and ovine models have demonstrated that myocardial laser injury leads to an increase in the density of arterial vessels [18, 21, 23–27, 29, 30, 52–55]. In a chronically ischemic porcine model, Chiu and associates [52] demonstrated that sufficient needle injury of the myocardium and TMR lead to similar degrees of stimulation of vascular endothelium growth factor expression and angiogenesis. Horvath and colleagues [55] showed that TMR leads to an induction of vascular endothelium growth factor gene expression and elevated tissue levels of vascular endothelium growth factor mRNA. Thus, the bulk of the available evidence demonstrates that there is, indeed, a molecular basis for laser-induced TMR angiogenesis. Several investigators have used mechanical means other than laser to create transmural myocardial channels. The techniques used experimentally have included needle puncture [11–13, 55, 56], a mechanical drill [21], a nonenergized laser fiber [53], and ultrasound [56]. Although some of these mechanical techniques may have theoretical merit, the results have been variable and no mechanical technique is approved by the US Food and Drug Administration.

Denervation

Kwong and associates [57] found evidence that holmium:YAG TMR interrupted subepicardial visceral afferent neural signals. In contrast, Hirsch and colleagues [58] did not find evidence of a reduction in ventricular contractile responses to direct electrical or chemical activation of sympathetic or parasympathetic efferent neurons after holmium:YAG TMR. Al-Sheik and colleagues [59] in a clinical study of 8 patients after holmium:YAG TMR found no increase in resting or stress myocardial perfusion using positron emission tomography imaging with [13N]ammonia but found that most patients had an increase in sympathetic denervation as assessed by positron emission tomography imaging with [11C]hydroxyephedrine. They concluded that the angina relief was caused, at least in part, by cardiac sympathetic denervation.

Outcomes Studies: Symptoms, Function, and Survival

Numerous nonrandomized clinical studies using either the holmium:YAG laser or the CO₂ laser consistently demonstrated a significant improvement in angina class using the Canadian Cardiovascular Society (CCS) scoring system. Many of these studies also demonstrated an increase in exercise capacity after TMR [33, 34, 36–42, 48–50].

Randomized Clinical Trials of Transmymocardial Revascularization as Sole Therapy

These encouraging results stimulated the design and completion of five recently published randomized trials comparing TMR with medical therapy [35, 43–47]. In each randomized trial, TMR patients demonstrated a statistically significant improvement in angina compared with patients treated with medical therapy alone, although none of the trials demonstrated a significant survival benefit. A summary of several of the key results of these trials is presented in Table 1.

The multicenter trial published by Frazier and associates [47] included patients from 12 US centers. Ninety-one patients were prospectively randomized to CO₂ laser TMR and 101 patients to medical therapy. Sixty of the medically treated patients who developed unstable angina crossed over to TMR therapy. Sixty-nine percent of medically treated patients who developed unstable angina decreased from 69% in the medical group to 2% in the
TMR group with a concomitant improvement in quality of life. Each of these differences was highly significant.

Schofield and colleagues [35] reported a single-center, prospective, randomized trial in which 188 patients were randomly assigned to CO2 laser TMR or medical therapy. In contrast to the study by Frazier and coworkers [47], only 27% of the patients enrolled had CCS class IV angina. These authors also found a significant decrease in angina symptoms in the TMR group. Twenty-five percent of the TMR group but only 12% of the medical group had a reduction of two or more CCS classes (p < 0.001). The reduction in angina symptoms was less dramatic than in the study by Frazier and associates [47], although this finding may be a result of the less severe baseline angina symptoms in the patients enrolled. There were no significant improvements in exercise capacity, and the mortality at 12 months was 11% in the TMR group and 4% in the medically treated group, although the difference in mortality was not statistically significant. There was a significant reduction in the number of myocardial segments with reversible perfusion defects in both groups compared with baseline but no significant difference between groups (TMR versus medical therapy) at 12 months of follow-up. There was a disproportionate increase in the number of fixed defects in the medical therapy group, prompting Frazier and colleagues [47] to speculate that the decrease in reversible defects in the TMR group represented improved perfusion whereas in the medical group it was likely the result of progression of some previously ischemic regions to complete infarction. Nonetheless, Schofield and associates [35] concluded that TMR “cannot be advocated.”

Aaberge and colleagues [43] presented the results of the Norwegian randomized, single-center study comparing medical therapy with CO2 laser TMR in patients with refractory angina. One hundred patients were randomized 1:1, and angina symptoms, exercise capacity, and maximal oxygen consumption were evaluated at 1 year. Myocardial perfusion was not assessed postoperatively. Angina severity was assessed using the New York Heart Association (NYHA) functional classification rather than the CCS class used by other investigators. Of the patients randomized to TMR, 24% were in NYHA class IV and 76% in NYHA class III. Of the medically treated patients, 34% were NYHA class IV and 66% NYHA class III. These authors found no improvement in total exercise time and no improvement in maximal oxygen consumption in the patients who underwent TMR. At 1 year 39% of the TMR patients experienced an improvement of two or more NYHA functional classes compared with 0% of the medically treated group. In a more recent study, Aaberge and associates [44] reported 32-month to 60-month follow-up on the same group of patients. At a mean follow-up of 43 months, 60% of the TMR patients were in NYHA class I or II, whereas 16% of the medically treated patients were in class II, and none were in class I. Twenty-four percent of patients in the TMR group had a two or more NYHA functional class improvement compared with 3% of the medically treated patients. Although there was a statistically significant reduction (55%) in hospitalizations for unstable angina, there also was a significant increase in the use of angiotensin-converting enzyme inhibitors and the use of diuretics at 43 months mean follow-up in the TMR group compared with the medically treated group. The authors interpreted these findings to indicate an increase in the incidence of clinical heart failure in the TMR group, although no significant difference in left ventricular ejection fraction was observed.

Allen and coworkers [45] reported the results of a prospective, randomized trial comparing holmium:YAG laser TMR with medical therapy. In this multicenter report, 275 patients, all with medically refractory CCS class IV angina, were randomly assigned to TMR or medical therapy. After 12 months of follow-up, 76% of the patients in the TMR group and only 32% of the patients treated medically had a reduction in angina of two or more CCS classes. Cardiac-related rehospitalization was more common in the medically treated group (61%) than in the TMR group (33%). Both of these differences were highly significant. However, there was no significant difference in myocardial perfusion as assessed using dipyridamole-thallium stress testing at 12 months.

Burkhoff and associates [46] presented the results of a prospective, multicenter, randomized trial also comparing holmium:YAG laser TMR with medical therapy. One hundred eighty-two patients from 16 centers in the United States were randomly assigned to undergo TMR (n = 92) or medical management (n = 90). Thirty-eight percent of the randomized patients were in CCS class III and 62% in CCS class IV. At 12 months, 48% of the TMR patients and 14% of the medically treated patients were in CCS class I or II (p < 0.01). Transmyocardial revascularization significantly increased exercise tolerance and afforded improvement in quality of life as compared with medical therapy. As in the study by Allen and colleagues [45], there was no difference in myocardial perfusion assessed using dipyridamole-thallium stress testing in the two groups at 12 months.

Studies of Transmyocardial Revascularization Combined With Coronary Artery Bypass Grafting

Allen and associates [60] reported the results of a prospective, randomized, multicenter trial of holmium:YAG TMR combined with CABG versus CABG alone for 263 patients with ungraftable myocardial segments. In this study, the ungraftable areas were treated with TMR in the TMR plus CABG arm and were left ungrafted in the CABG alone arm. These authors reported a significant reduction in the perioperative mortality rate (1.5% versus 7.6%) in the patients treated with TMR. It should be noted that the mortality rate in the TMR plus CABG group was substantially lower than the predicted mortality rate for these same patients (8.8%) for CABG alone [60]. At 1 year, the survival for patients in the TMR plus CABG group was 95% but only 89% in the CABG only group (p = 0.05). Although the patients were randomized preoperatively, the precise angiographic criteria used for inclusion in the study were not defined, the angiographic findings of the two groups were not compared, and
Mortality

The largest retrospective study of TMR available is derived from the STS NCD [61]. In an analysis of results obtained from the STS NCD for procedures performed between January 1998 and December 2001, 661 patients underwent TMR alone (holmium:YAG and CO2 laser combined) with a perioperative mortality of 6.4%. As discussed above, for 2,475 patients who underwent TMR with concomitant CABG, the mortality was 4.2%. In the prospective randomized trials of CO2 laser TMR, procedural mortality ranged from 3% to 5% with 1-year survival of 85% to 89% [35, 43, 44, 47]. In the two prospective, randomized trials of holmium:YAG TMR, the procedural mortality ranged from 1% to 5% with 1-year survival of 89% to 96% [45, 46].

In each of the randomized studies, patients with ejection fractions less than 0.20 to 0.30 were excluded [35, 43–47], possibly accounting for the lower perioperative mortality rate observed when compared with several retrospective studies [34, 36, 38–41]. In the study by Peterson and colleagues [61], mortality was significantly higher in patients with unstable angina or myocardial infarction within 21 days. Furthermore, in the 661 patients in the TMR-only group, the 143 patients without unstable angina and with ejection fraction more than 0.50 had an operative mortality of only 2.1%. These authors concluded that appropriate patient selection is the most important factor influencing acute mortality after TMR.

Morbidity

Morbidity from TMR may include myocardial infarction, arrhythmias, left ventricular dysfunction, and cerebral microembolization [34–36, 38, 39, 63–66]. In a study of normal pigs, holmium:YAG but not CO2 laser TMR resulted in an acute decrease in left ventricular systolic function as assessed by preload recruitable stroke work area [67]. Both types of laser TMR resulted in significant increases in myocardial water content and impaired diastolic relaxation [67]. Kadipasaoglu and coworkers [64] compared the results of CO2 laser TMR, holmium:YAG laser TMR, and excimer laser TMR in normal pigs. In their study, 70% of the animals who underwent TMR using the excimer laser and 60% of those with holmium:YAG TMR had ventricular tachycardia compared with only 3% of the animals that underwent CO2 laser TMR. In the study by Peterson and associates [61], using data derived from the STS NCD for patients who underwent TMR as sole therapy, the incidence of major morbidity included reoperation for any reason (2.7%), stroke (0.76%), renal failure (4.8%), and prolonged ventilation (7.7%). In the four randomized trials of TMR as sole therapy published in 1999, the incidence of congestive heart failure ranged from 12% to 32%; myocardial infarction varied from 7% to 18%, and arrhythmias occurred in 8% to 22% [35, 45–47]. In an analysis of 49 patients who underwent CO2 laser TMR enrolled in the Norwegian randomized trial, Tjomsland and colleagues [63] found a transient but significant decrease in cardiac index that was maximal immediately after the procedure. Four patients (8%) suffered a myocardial infarction, 7 patients (14%) had atrial fibrillation, and 2 patients (4%) had ventricular arrhythmias [63]. In a study of 21 patients...
who underwent CO₂ laser TMR by Hughes and coworkers [66], all patients had elevations in creatine kinase and creatine kinase-MB levels, and 54% of patients had ischemic changes on electrocardiogram in the first 48 hours after TMR.

Risk Factors for Morbidity and Mortality After Transmyocardial Revascularization

Unstable Angina

In the randomized trial by Frazier and associates [47], more than 70% of the patients who crossed over to TMR from the medical treatment arm had unstable angina, and these patients had the highest perioperative mortality rate (9%). In the study by Hughes and colleagues [65], the presence of unstable angina was also a significant predictor of postoperative morbidity and mortality. Similarly, in a multicenter study by Hattler and coworkers [68], perioperative mortality was 16% in patients with unstable angina compared with 3% in patients with chronic angina.

Global Myocardial Ischemia

Burkhoff and colleagues [69] investigated the effects of age, sex, ejection fraction, prior CABG, unstable angina, and an index described as the anatomic myocardial perfusion index (AMP) as possible predictors of mortality after CO₂ laser TMR as sole therapy in 132 patients. They graded each vascular territory as AMP = 1 if there was unobstructed blood flow through a major artery to that territory and AMP = 0 if there was not. Patients with at least one territory with AMP = 1 had a mortality of 5% whereas those with AMP = 0 in all territories had a mortality of 25% (p = 0.002) [69]. Only AMP was a significant risk factor for operative mortality in the multivariate analysis. Kraatz and associates [70] found that mortality was highest in patients who underwent TMR alone or TMR plus CABG in whom, after the procedure, there was neither a patent bypass graft nor a native coronary artery perfusing at least one of the three major perfusion zones.

Diminished Left Ventricular Function

Lutter and associates [71] found that higher mortality after TMR has also been observed in patients with impaired left ventricular function or hemodynamic instability and limited reserve. In 7 patients with unstable angina and reduced ejection fraction (<0.35), the combination of CO₂ laser TMR with the use of a preoperative intracorporeal balloon pump resulted in survival of all 7 patients associated with significant improvements in both CCS angina class and NYHA classification [71].

Patients with unstable angina, acute ischemia, and low ejection fraction have the highest risk of perioperative complications from sole therapy TMR. However, when TMR is combined with CABG, the literature provides little information regarding specific risks and benefits of adjunctive TMR.

Recommendations for Transmyocardial Revascularization as Sole Therapy

Class I

1. Patients with an ejection fraction greater than 0.30 and CCS class III or IV angina that is refractory to maximal medical therapy. These patients should have reversible ischemia of the left ventricular free wall and coronary artery disease corresponding to the regions of myocardial ischemia. In all regions of the myocardium, the coronary disease must not be amenable to CABG or percutaneous transluminal angioplasty either as a result of (1) severe diffuse disease, (2) lack of suitable targets for complete revascularization, or (3) lack of suitable conduits for complete revascularization (level of evidence: A).

Class IIB

1. Patients who otherwise have class I indications for TMR but who have either:
   a. Ejection fraction less than 0.30 with or without insertion of an intraaortic balloon pump (level of evidence: C).
   b. Unstable angina or acute ischemia necessitating intravenous antianginal therapy (level of evidence: B).
   c. Patients with class II angina (level of evidence: C).

Class III

1. Patients without angina or with class I angina (level of evidence: C).
2. Acute evolving myocardial infarction or recent transmural or nontransmural myocardial infarction (level of evidence: C).
3. Cardiogenic shock defined as a systolic blood pressure less than 80 mm Hg or a cardiac index of less than 1.8 L · min⁻¹ · m⁻² (level of evidence: C).
4. Uncontrolled ventricular or supraventricular tachyarrhythmias (level of evidence: C).
5. Decompensated congestive heart failure (level of evidence: C).

Recommendations for Transmyocardial Revascularization as an Adjunct to Coronary Artery Bypass Grafting

Class IIA

1. Patients with angina (class I -IV) in whom CABG is the standard of care who also have at least one accessible and viable ischemic region with demonstrable coronary artery disease that cannot be bypassed either because of (1) severe diffuse disease, (2) lack of suitable targets for complete revascularization, or (3) lack of suitable conduits for complete revascularization (level of evidence: B).

Class IIB

1. Patients without angina in whom CABG is the standard of care who also have at least one accessi-
ble and viable ischemic region with demonstrable coronary artery disease that cannot be bypassed either because of (1) severe diffuse disease, (2) lack of suitable targets for complete revascularization, or (3) lack of suitable conduits for complete revascularization (level of evidence: C).

**Class III**

1. Patients in whom CABG is not the standard of care (level of evidence: C).

**Future Applications of Transmyocardial Revascularization**

Additional clinical applications have been suggested for TMR including the treatment of graft vasculopathy after cardiac transplantation [72], although no benefit has been demonstrated. There have also been new approaches proposed for the delivery of TMR. There have been several reports of the performance of TMR using thoracoscopy. These early reports suggest that the technique can be performed safely and adequately using this approach [73]. In contrast, the early results of randomized trials of percutaneous laser myocardial revascularization, also referred to as direct myocardial revascularization, using a holmium:YAG laser catheter-based approach have been less promising [74, 75]. Careful investigation of alternative means for channel creation should continue including the use of ultrasound [56] and radiofrequency ablation techniques [76].

Transmyocardial revascularization appears to stimulate angiogenesis, but this effect may represent a nonspecific phenomenon. The holmium:YAG laser results in a greater degree of myocardial tissue damage than the CO2 laser [27]. A positive correlation between myocardial tissue injury and reduction in contractility after TMR has been demonstrated [77]. Investigation of alternative laser wavelengths may allow for further reduction in the ratio of potentially deleterious laser-induced myocardial tissue injury to the degree of angiogenic stimulus achieved. The combination of TMR with the coadministration of growth factors such as vascular endothelium growth factor and β-fibroblast growth factor or genes encoding these and other growth factors may allow for even greater induction of new vessel growth [78, 79].

**Conclusions**

Transmyocardial revascularization offers consistent amelioration of severe angina in patients having no conventional therapeutic alternative. Surgeons should recognize that the procedure is intended only for the purpose of reducing angina symptoms. There is no statistically conclusive evidence for increased longevity or enhanced myocardial function. Careful patient screening is particularly important because of the unacceptably high operative mortality in patients with acute ischemic syndromes or significant myocardial dysfunction. With proper patient selection and observance of appropriate surgical technique, TMR provides very gratifying symptomatic improvement to desperately ill patients who otherwise would be crippled by unrelenting angina pectoris.

**References**


