Statement of The Society of Thoracic Surgeons
July 2004

Submitted to the Medicare Coverage Advisory Committee, Centers of Medicare and Medicaid Services, regarding Transmyocardial Revascularization (TMR)

The Society of Thoracic Surgeons (STS) is pleased to provide comment on Medicare coverage of Transmyocardial Laser Revascularization (TMR). The STS was founded over forty years ago to foster and advance the science and practice of cardiothoracic surgery; to provide a forum and publication for scientific presentations and discussions; to promote and support basic standards in the education programs of cardiothoracic surgery; and to represent practicing cardiothoracic surgeons in the United States, as well as cardiothoracic surgeons throughout the world.

There have been remarkable advances in the treatment of heart disease. Cardiothoracic surgeons are performing more complex operations including adjunctive procedures such as repair of valves that were formerly replaced, atrial ablation for treatment of atrial fibrillation, and TMR. Despite the fact that cardiothoracic surgeons are now operating on older, sicker patients, even better outcomes are being achieved [Ferguson 2002], in part, through the careful evaluation and adoption of new technology. Advances in surgical technique and postoperative care have improved the quality of life of millions of Americans, and, in some patient groups, have prolonged life.

The Society of Thoracic Surgeons believes that our organization has a responsibility to be a vigorous participant in the continuous evaluation and monitoring of new techniques and devices in cardiothoracic surgery, with a clear focus on patient benefit. A Workforce on New Technology has been established in conjunction with the American Association for Thoracic Surgery. Our Workforce on Evidence-based Medicine has developed and published a National Practice Guideline on TMR. Continuous monitoring of procedure utilization and perioperative outcomes has been accomplished through the STS National Database. This Database collects data from approximately two-thirds of all cardiac surgeons in the United States. It provides feedback to our surgeons in the form of risk-adjusted perioperative outcomes <u>and</u> promotes best practices by feedback on compliance

with patient-benefit focused practice habits. Because the STS adult cardiac surgical database provides patient characteristics and 30-day outcomes, refinements in patient selection and operative technique are an ongoing process. This accumulation of data on TMR patients is somewhat complicated because the presence of diffuse distal coronary artery disease common to these patients is not currently factored into risk modeling within the STS database or in any other national database or modeling algorithm.

Based on a review of the STS database and the substantially improved health outcomes observed in multiple, prospective randomized trials and five-year follow-up studies, the STS believes that access to TMR is great benefit to selected patients, many of whom have exhausted other options for the relief of disabling angina. We therefore strongly support continued Medicare coverage for the services associated with the TMR procedure for the relief of medically refractory angina due to areas of ischemic myocardium caused by diffuse coronary artery disease that is not suitable for percutaneous intervention or bypass grafting. The STS is prepared to assist CMS and the medical community in a careful, balanced evaluation of this technology and the patient population it affects, and is therefore providing enclosed our recently published practice guideline document for TMR and a current assessment of TMR.

THE SOCIETY OF THORACIC SURGEONS

TECHNOLOGY ASSESSMENT AND REVIEW: TRANSMYOCARDIAL REVASCULARIZATION

Prepared for:

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Centers for Medicare and Medicaid Services

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THE SOCIETY OF THORACIC SURGEONS

TECHNOLOGY ASSESSMENT AND REVIEW: TRANSMYOCARDIAL REVASCULARIZATION

Background. Most patients who experience angina pectoris due to coronary artery disease can be adequately treated with conventional methods such as medical management, percutaneous coronary interventions (PCI), or coronary artery bypass grafting (CABG). However, there are a number of patients with medically refractory angina due to areas of ischemic myocardium caused by diffuse coronary artery disease (CAD) that is not eligible for PCI or CABG. Based on a study of 500 consecutive patients undergoing diagnostic angiography conducted by the Cleveland Clinic Foundation, it is estimated that up to 12% of patients referred for treatment of CAD are ineligible for PCI or CABG due to diffuse disease. [Muhkerjee 1999] In a one year follow-up study of these refractory angina patients managed medically, the authors identified a significant incidence of mortality and morbidity due to their significant diffuse disease.[Muhkerjee 2001] Weintraub and associates, in a study of incomplete revascularization following CABG due to diffuse disease, indicate an incidence rate of up to 25%.[Weintraub 1994] It has been shown that appropriately quantified diffuse coronary artery disease, leading to incomplete revascularization, is a powerful independent predictor of operative mortality and perioperative adverse events.[Weintraub 1994; Graham 1999; Osswald 2001] Others have reported that incomplete revascularization represents a significant risk for late cardiac events. Specifically, the presence of diseased but non-grafted arteries poses a significant negative influence on event-free survival defined as the absence of death, recurrent angina, myocardial infarction, and the need for repeat CABG.[Lawrie 1982; Schaff 1983; Bell 1992]

This clinical problem has served as the basis for developing solutions to the treatment of patients with such late-stage disease. Using a mechanical attempt to surgically mimic blood flow in the reptilian heart (i.e., directly into myocardial tissue from the ventricular cavity), Sen and colleagues first described transmyocardial revascularization using hollow needles in 1965.[Sen 1965] Since this original work, Mirhoseini experimentally and clinically investigated the use of laser energy for channel creation.[Mirhoseini 1981]

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Using both carbon dioxide (CO_2) and holmium:yttrium-aluminum-garnet (Ho:YAG) lasers and delivery systems, feasibility studies and subsequent randomized, controlled clinical trials (RCTs) have been carried out to evaluate the safety and effectiveness of the respective devices for the relief of medically refractory angina in patients having diffuse coronary artery disease in areas of the myocardium that are unsuitable for PCI or CABG. Although initial experimental examinations have been reported for other potential methods, including mechanical devices [Shawl 2000], ultrasound [Smith 1998], cryotherapy [Khairy 2000], and radiofrequency [Yamamoto 2000], no prospective randomized trials using these approaches have been reported.

TMR Laser Systems: The Ho:YAG System. The Ho:YAG laser system uses a pulsed laser with a maximum energy output of 20 Watts. Laser calibrations deliver 6 to 8 Watts per laser pulse at a rate of five pulses per second through a 1mm diameter flexible fiberoptic bundle. When TMR is used as sole therapy, anesthesia includes a short-acting inhalation agent supplemented with low-dose narcotics and propofol. Intravenous fluids are minimized to avoid fluid overloading. The distal two-thirds of the left ventricle is exposed using a limited left anterolateral thoracotomy through the fifth intercostal space. The handpiece allows the surgeon to position and stabilize the embedded fiberoptic against the epicardial surface. Energy delivery of six to 10 pulses is typically required to traverse the myocardium and is controlled with a footswitch. Laser channels are placed every cm^2 in the distal two-thirds of the left ventricle, avoiding obviously scarred areas. After the placement of three to five channels, digital pressure is applied for one to two minutes to obtain hemostasis and allow for myocardial recovery. Epicardial ligation of a laser channel for persistent bleeding is rarely required. Intraoperative arrhythmias are unusual if channels are placed slowly and mechanical manipulation of the heart is minimized. Laser energy, when absorbed by ventricular blood, produces an acoustic image analogous to steam that is readily visible by transesophageal echocardiography (TEE). Initially, TEE can be used to confirm penetration

of the laser into the left ventricle; after several procedures, tactile and auditory feedback enables surgeons to confirm transmural penetration without TEE. **The CO_2 System**. The CO_2 laser system has a maximum energy output of 1000 Watts and is set to deliver 800 Watts in pulses 1 to 99 msec long at energies of 8 to 80 Joules to create 1mm diameter channels. Energy is delivered via an operator-set articulated arm and handpiece. When the CO_2 system is used for sole therapy, patient positioning and surgical approach to the heart are similar to that described above. The CO_2 system uses helium-neon laser guidance for proper epicardial positioning of the handpiece, and electrocardiographic (ECG) synchronization to fire on the R-wave of the ECG cycle when the ventricle is maximally distended and electrically quiescent. TEE is used to confirm transmural penetration. TMR as an adjunct to CABG is performed with or without cardiopulmonary bypass (CPB). If CPB is used, it is preferred to perform adjunctive TMR with the Ho:YAG system on an arrested heart just after initiating CPB. This minimizes intraoperative arrhythmias and may reduce bleeding as compared to placing laser channels at the conclusion of CPB. During off-pump CABG cases, TMR is performed after bypass grafts are completed. Adjunctive TMR using the CO_2 system can be performed either before or after bypass grafts have been placed while the heart is beating.

Approvals, Recommendations, and Alternatives. The TMR technique creates multiple, 1-mm diameter, transmurally ablated channels in ischemic myocardium using laser energy either directly (CO_2) or through fiberoptics (Ho:YAG). The United States Food and Drug Administration has approved two TMR laser systems, with the indication for the "treatment of stable patients with angina (Canadian Cardiovascular Society Class III and/or IV) refractory to medical treatment and secondary to objectively demonstrated coronary artery atherosclerosis and with a region of the myocardium with reversible ischemia not amenable to direct coronary revascularization".[US FDA 1998, 1999] The American College of Cardiology/American Heart Association (ACC/AHA) and the Society of Thoracic

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Surgeons (STS) have published recommendations for the use of TMR in practice guidelines for the treatment of medically refractory angina not amenable to PCI or CABG.[Gibbons 2002; Bridges 2004] TMR is a procedure for which the Centers for Medicare and Medicaid Services (CMS) provide reimbursement, as articulated in national coverage decision memoranda.[US CMS 1999]

Clinical Overview. Reports from five prospective, randomized clinical trials representing 937 patients, designed to evaluate the safety and effectiveness of TMR as sole therapy for the treatment of medically refractory, stable angina have appeared in the literature.[Allen 1999, Burkhoff 1999, Frazier 1999, Schofield 1999, Aaberge 2000]. More recently, three to five year follow-up of these trials has become available.[Horvath 2001, Aaberge 2002, Allen 2004]]. In addition to using TMR in the treatment of stable angina, its use in the management of unstable angina has been reported [March 1997; Allen 1999; Dowling 1998; Frazier 1999; Hattler 1999]. In addition, each laser system has been evaluated in a multi-center, prospective, randomized trial for TMR as an adjunct to CABG in patients who would be incompletely revascularized by CABG alone [Frazier 1999; Allen 2000]. A more detailed review of the clinical data obtained in randomized controlled trials regarding TMR in these patient groups is discussed as follows.

TMR AS SOLE THERAPY IN STABLE PATIENTS

Trial Designs. The safety and effectiveness of Ho:YAG and CO_2 TMR laser systems as sole therapy have been evaluated in five prospective, randomized clinical trials (three multi-centered and two single-centered) for the treatment of patients with medically refractory stable angina whose anatomy was not amenable to CABG or PCI.[Allen 1999, Burkhoff 1999, Frazier 1999, Schofield 1999, Aaberge 2000] Experimental designs and patient selection criteria among the trials were generally similar. Study endpoints included:

operative (in-hospital or to 30 days) mortality and one-year survival, improvement in angina class, myocardial perfusion, exercise tolerance, quality of life, cardiac-related hospitalization and major adverse events. Aside from a variation in the number of patients, certain features made each trial unique **(Table 1)**.

Table 1. Patient Characteristics in RCTs of Sole Therapy TMR

Characteristic	Allen	Frazier	Burkhoff	Schofield	Aaberge
Number of centers	18	12	16	1	1
Patients (N)	275	192	182	188	100
Crossover allowed	Yes	Yes	No	No	No
Age (mean years)	60	61	63	60	61
Male gender	74%	81%	89%	88%	92%
Ejection fraction	0.47	0.50	0.50	0.48	0.49
Class III/IV	0%/100%	31%/69%	37%/63%	73%/27%	66%/34%
CHF	17%	34%	nr	9%	nr
Diabetes	46%	40%	36%	19%	22%
Hyperlipidemia	79%	57%	77%	nr	76%
Hypertension	70%	65%	74%	nr	28%
Prior MI	64%	82%	70%	73%	70%
Prior CABG	86%	92%	90%	95%	80%
Prior PCI	48%	47%	53%	29%	38%
No. of channels (mean)	39	36	18	30	48

Whereas Allen and associates randomized patients with medically refractory class IV angina only, varying proportions of patients with class III and IV angina were enrolled in the remaining trials. Two trial designs [Allen 1999, Frazier 1999] permitted crossover from the medically managed (MM) arm to the TMR arm provided the *a priori* treatment failure criteria were met (hospitalized and unweanable from intravenous antianginals medications [IVAA] for 48 hours). Of the patients initially randomized to the MM arm in

trials reported by Allen and Frazier, 32% (46/143) and 59% (60/101), respectively, met the treatment failure criteria, crossed over and underwent TMR while unstable. In the remaining three trials, crossover from the MM to the TMR arm was not allowed, thus simplifying statistical analyses and data interpretation.

Operative Mortality and Long-Term Survival. Operative mortality following TMR among these five trials ranged from 1% to 5%. The low rate (1%) reported by Burkhoff and colleagues was attributed to strict study enrollment criteria that excluded patients with no region of protected myocardium,[†] left main stenosis >50%, or a change in angina symptoms or medication usage in the preceding 21 days.[Burkhoff 1999] These operative mortality rates are similar to that recently reported by the Society of Thoracic Surgeons for patients undergoing CABG alone (3%).

Kaplan-Meier one-year survival rates for randomized groups within each of the five trials were statistically similar. One-year survival ranged from to 84% to 95% in TMR patients, and from 79% to 96% in medically managed patients. Longer-term survival, which is a key component to establishing the risk/benefit profile of any innovative treatment, has been evaluated in randomized patients in two of these studies. Aaberge and associates, reported similar survival rates among 75 randomized patients with primarily class III angina at a mean of 43 months (78% vs. 76%, TMR vs. MM, p=ns).[Aaberge 2002] In a five-year follow-up of 212 randomized patients, all with class IV angina, Allen and associates reported increased Kaplan-Meier survival for patients randomized to TMR versus MM (65% vs. 52%, p=0.05), with a significantly lower annualized mortality rate beyond one year (8% vs. 13%, TMR vs. MM, p=0.03).[Allen 2004]

[†]Defined as a vascular territory perfused by unobstructed [no lesion with >50% stenosis] blood flow through a major native vessel or bypass graft.
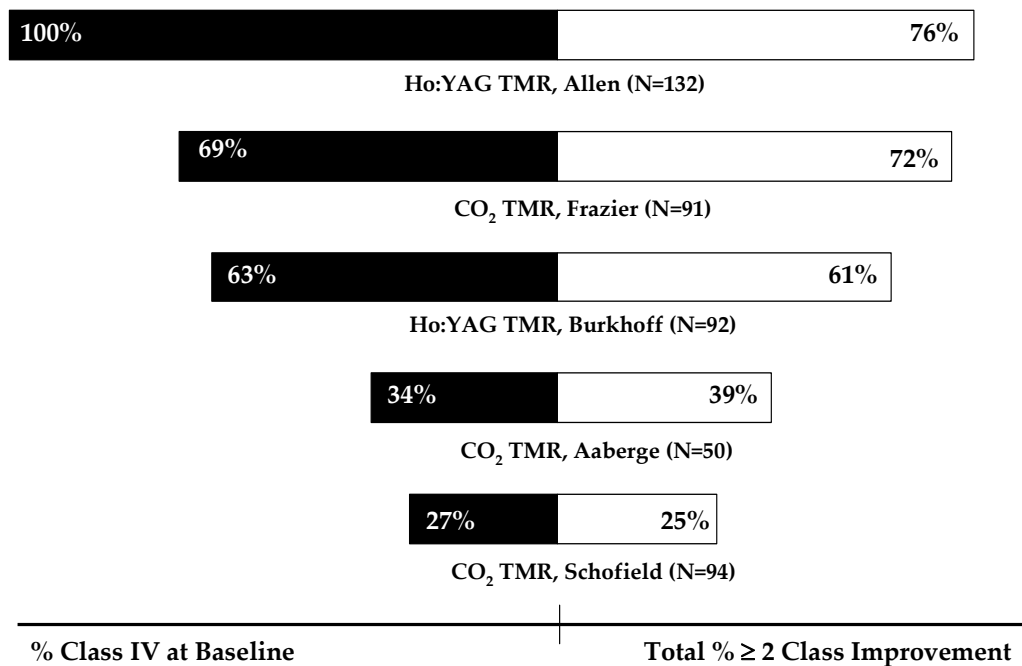
Effectiveness. Angina Improvement at One Year. Significant angina improvement (defined as a reduction of two or more angina classes from baseline) was observed through one year following TMR as compared to MM in each of the five randomized trials (p<0.001). The percentage of TMR-treated patients with at least a two-class improvement in angina at one year varied from 25% to 76%, and appears to be related to the proportion of patients enrolled in each study who had baseline class IV angina [**Figure 1**]. Allen and Frazier, with the highest proportions of patients with baseline class IV angina (100% and 69%, respectively) reported at least two-class angina improvement in 76% and 72% of TMR patients, respectively. Schofield and associates with the lowest proportion of baseline class IV patients (23%), reported angina improvement in only 25% of TMR patients which was still significantly better than the 4% improvement noted in the medical management arm. In each of the five randomized trials, maximal medical therapy was comparable between randomized groups at baseline, although it is recognized that there is not one defined regimen that is constant from patient to patient. In each of these trials, a significant reduction in anti-anginal medication usage at one year was observed in TMR patients versus MM controls. The significant angina relief following TMR is not due to medication, but in fact results in a decrease in requisite anti-anginal drugs.

Figure 1. Angina Improvement One Year Following Sole Therapy TMR By Proportion in Class IV at Baseline.

100%	**76%**	
Ho:YAG TMR, Allen (N=132)		
69%	**72%**	
CO_2 TMR, Frazier (N=91)		
63%	**61%**	
Ho:YAG TMR, Burkhoff (N=92)		
34%	**39%**	
CO_2 TMR, Aaberge (N=50)		
27%	**25%**	
CO_2 TMR, Schofield (N=94)		

% Class IV at Baseline   **Total % ≥ 2 Class Improvement**

N = number of patients randomized to TMR

Effectiveness. Long-Term Angina Improvement. Two reports of long-term follow-up of prospectively randomized patients are available. At a mean of five years, Allen and associates evaluated the effectiveness of TMR in 212 'no option' patients originally randomized to TMR or to MM.[Allen 2004] To eliminate the potential for assessment bias in this long-term follow-up, blinded independent assessors performed angina assessments across centers. Due to the crossover of 26% of MM patients to the TMR arm, analyses were conducted to retain the crossover patients with their randomized arm (intention to treat) as well as to evaluate them as a separate group (three group analyses). Consistent with the

one-year follow-up results, intention to treat analyses determined that significantly more TMR than MM patients continued to experience at least two-class angina improvement from baseline (88% vs. 44%, p<0.001) or were free from angina symptoms altogether (33% vs. 11%, p=0.02) at a mean of five years. In the three-group analysis, improvement in angina among randomized TMR patients was superior to that observed for MM patients excluding crossovers (88% vs. 37%, p<0.001) and was similar to that in patients who failed medical management and crossed over to receive TMR while unstable (88% vs. 67%, p=0.14). Importantly, the investigators found that freedom from angina at one year and angina improvement at one year were significantly predictive of long-term freedom from angina and the survival benefit observed in randomized TMR patients, respectively. No differences between groups in antianginal medication usage were observed. Aaberge and associates, in a single-center follow-up of 75 randomized patients, found that angina symptoms were still significantly improved (24% vs. 3%, TMR vs. MM, p=0.001) and unstable angina hospitalizations were significantly reduced (p<0.05) at a mean follow-up of 43 months.[Aaberge 2002] Results reported by Horvath and colleagues, involving follow-up of a series of 78 nonrandomized patients who received TMR and survived long term, support these findings.[Horvath 2001] At a mean of five years and up to seven years post procedure, 81% of these patients improved to Class II or better, 68% were found to have improved at least two angina classes from baseline, 17% were angina-free, and quality of life remained significantly improved.

Effectiveness. Exercise Tolerance. Exercise tolerance time (ETT) was a primary endpoint in three trials.[Burkhoff 1999, Schofield 1999, Aaberge 2000] Burkhoff reported significantly improved median modified Bruce treadmill exercise tolerance times at one year (+65s, TMR vs. -46s, MM, p<0.0001). Moreover, in a blinded core laboratory analysis at one year, a significant reduction in chest pain at peak exercise with no evidence of an increase in silent ischemia was observed when comparing TMR and MM patients.[Myers 2002]. Unique to

this trial, investigators designed the ETT test to obtain evidence of angina refractory to medical treatment, to account for possible exercise habituation effects, and to ensure test reproducibility (minimum of two tests with durations varying by ≤15%) at baseline. The test could be limited by symptoms or ECG ischemic changes, but typical angina occurring during at least one test was required. In a single-center report, Schofield used a symptom-limited modified Bruce treadmill exercise test and a 12-minute walk test to characterize the effects of TMR versus continued MM on exercise tolerance. At one year, mean adjusted treadmill time was 40s longer in the TMR group than in the MM group (p=0.15), and the test was stopped more frequently for angina among MM than TMR patients (p<0.001). Mean 12-min walk distance was 33m further for TMR than MM patients (p=0.1), and nitrate usage and frequency of angina during or after the walk were significantly lower in TMR than MM patients (p≤0.04). In another single-center report, Aaberge and associates used an electrically braked cycle ergometer held at approximately 60 rpm for exercise testing. Time to chest pain was significantly increased in TMR versus MM patients (p<0.01), and angina was reported as an exercise-limiting factor in significantly fewer TMR than MM patients (62% vs. 76%, p<0.01).

Effectiveness. Quality of Life. Improved clinical status following TMR has been assessed in a variety of ways, including assessment of standardized quality of life measures, calculation of cardiac rehospitalization rates, or determination of event-free survival. Quality of life analyses using the Duke Activity Status Index (DASI) or the Seattle Angina Questionnaire (SAQ) revealed that TMR patients enjoyed significantly improved quality of life at one year compared to MM patients.[Allen 1999; Burkhoff 1999; Frazier 1999; Schofield 1999] Similarly, significantly reduced rates of cardiac-related rehospitalization through one year were reported for patients randomized to TMR versus MM.[Allen 1999; Frazier 1999, Aaberge 2000]. Finally, consistent results have been reported for composite endpoints that strongly favor TMR over MM. Allen observed significantly increased

cardiac event-free survival[†] at one year (54% vs. 31%, TMR vs. MM, p<0.001).[Allen 1999] Using a different composite endpoint, Frazier observed significantly increased event-free survival[‡] at one year (66% vs. 11%, TMR vs. MM, p<0.001).[Frazier 1999]

Effectiveness. Perfusion Studies. The mechanisms explaining the clinical benefit of TMR is a source of ongoing scientific inquiry, with a leading theory attributing results to angiogenesis or redistributed blood flow. Global perfusion studies using thallium scintigraphy did not detect a difference between groups in some studies; nonetheless, objective evidence of improved perfusion following TMR has emerged. Employing technitium sestamibi/thallium scans to determine the areas of scar (fixed defects) and ischemia (reversible defects) at one year, Schofield identified improvement in blood flow to the TMR-treated ischemic areas without a significant increase in the number of fixed defects, with a corresponding doubling of fixed defects or infarcts in MM patients over the same interval. Therefore, TMR led to restoration of normal perfusion in previously ischemic myocardium. Frazier reported a 20% improvement in perfusion in previously ischemic areas in the TMR group and a 27% worsening of perfusion in the ischemic areas of the MM group at 12 months (p=0.02). Non-randomized studies support these findings. Improved perfusion was reported one year following TMR in 59 patients using dual isotope scanning [Horvath 1997] and using N-13 ammonia positron emission tomography (PET), wherein subendocardial perfusion improved significantly compared to the subpericardial perfusion after TMR.[Frazier 1995]

Effectiveness. Placebo Effect. Due to the fact that none of the surgical trials comparing TMR with MM were blinded, although two included blinded validations at one year [Allen 1999; Frazier 1999], it has been suggested that angina relief following TMR may have been

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[†]Defined as freedom from death, Q-wave myocardial infarction, cardiac-related rehospitalization, or subsequent revascularization attempt.

the result of a placebo effect induced by the surgical incision. The scientific validation of a long-term placebo effect from a sham thoracotomy is limited.[Allen 2000] The long-term, persistent benefits of surgical TMR observed in several studies argue strongly against a significant placebo effect. Whereas a placebo effect likely influences early outcomes in any clinical trial involving innovative technology, its persistence is diminished in late follow-up and much less plausible in the long-term, especially in light of the observed survival benefit. The overwhelmingly positive one-year results from multiple prospective randomized trials in which primarily Class IV angina patients were enrolled, as well as the reported persistent significant angina relief beyond three years [Aaberge 2002] and five years [Horvath 2001; Allen 2004] following TMR mitigates the concern of placebo effect as a primary mechanism explaining the clinical benefits of TMR. The other aforementioned body of objective data supports this determination. Furthermore, functional improvement, accompanied by a decrease in myocardial ischemia without an increase in myocardial infarction in TMR treated patients, has been demonstrated using dobutamine stress echocardiography [Donovan 1999] as well as cineangiography and contrast enhanced magnetic resonance imaging.[Horvath 2000; Stamou 2002] This evidence is not subject to placebo effect. Based on an assessment of the cumulative results from multiple randomized trials, the recently updated ACC/AHA practice guideline [Gibbons 2002] and STS practice guideline [Bridges 2004] have determined that the weight of the evidence favors the use of TMR in the treatment of stable, medically refractory, angina patients.

TMR AS SOLE THERAPY IN PATIENTS WITH UNSTABLE ANGINA

In addition to using TMR for the treatment of patients with stable, medically refractory angina, several studies have evaluated it in a limited number of patients with unstable angina [March 1997; Allen 1998; Allen 1999; Dowling 1998; Frazier 1999; Hattler 1999].

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‡Defined as freedom from death, acute myocardial infarction, unstable angina, or class IV angina.

Enrollment criteria included diffuse CAD not amenable to CABG or PCI, inability to be weaned from IVAA after two or more attempts, and a left ventricular ejection fraction ≥25%. March, Allen and Frazier reported results in patients who became unstable after being randomized to medical therapy as part of prospective trials. Hattler and Dowling reported on larger numbers of patients who initially presented with unstable angina and were treated with TMR.

Patients with unstable angina and without conventional interventional options represent a higher risk group for TMR. March, Frazier, and Hattler, using the CO_2 laser system, and Dowling and Allen, using the Ho:YAG laser system, reported operative mortality rates of 27%, 22%, 16%, 12%, and 9%, respectively, following TMR in unstable angina patients.

Hattler, Frazier and Allen compare results following TMR in stable and unstable patients. Hattler compared the effect of sole therapy TMR in medically refractory patients with unstable angina (n=91) and stable angina (n=76). Operative mortality was higher in unstable versus stable patients (16% vs. 3%, p=0.005); however, late mortality from 30 days to one year was similar (13% vs. 11%, p=0.83). Angina improvement at 12 months was significantly improved in both groups from baseline (p<0.001), and was comparable between groups, with approximately 50% of patients able to resume normal activity levels without angina. Frazier and associates compared patients undergoing TMR within 14 days of having an episode of unstable angina (n=49) and patients undergoing TMR at least 15 days after such an episode, who were stabilized at the time of surgery (n=102). Operative mortality was significantly higher in unstable versus stable patients (22% vs. 1%, p<0.001). Allen and colleagues compared TMR in 132 stable patients with 46 unstable 'crossover'

patients.[†] Operative mortality (5% vs. 9%, p=0.48) and one-year survival (84% vs. 91%, p=0.53) were similar. At five years, whereas significant angina improvement persisted similarly in both TMR and crossover patients, survival curves showed a diverging trend.[Allen 2004] Allen reported that histories of myocardial infarction and prior percutaneous coronary intervention were significant predictors of medical therapy treatment failure and subsequent crossover, however these were not predictive of mortality at five years. This suggests that in terms of long-term survival, randomization to the original TMR group is superior to crossing over to receive TMR after becoming unstable.

TMR AS AN ADJUNCT TO CABG

Background. As previously discussed, incomplete revascularization after CABG due to diffuse coronary artery disease occurs in up to 25% of patients and, when appropriately quantified, is a powerful independent predictor of operative mortality.[Weintraub 1994, Graham 199, Osswald 2001] Moreover, it represents a significant risk for late cardiac events.[Lawrie 1982; Schaff 1983; Bell 1992] Thus, owing to its success as sole therapy, TMR has been evaluated in conjunction with CABG in patients afflicted by diffuse coronary artery disease who would be incompletely revascularized by CABG alone. Nonetheless, the safety and effectiveness of adjunctive TMR have been somewhat difficult to assess due to the influence of adjacent bypass grafts and lack of randomized control arms in some studies.[Trehan 1997; Stamou 2002; Wehberg 2003; Peterson 2003]. Specifically, national databases and most commonly used models for predicting surgical risk do not take diffuse or distal coronary artery disease into account, thereby rendering the case-matched

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[†]Crossover patients were initially randomized to medical therapy, met the *a priori* criteria for treatment failure, and crossed over to receive TMR while unstable.

comparisons in these nonrandomized studies inherently flawed and unreliable. To illustrate, two angiograms from demographically similar patients, both with STS predicted operative mortality of 3.1%, are shown in **Figure 2**. The striking difference in the quality of coronary targets (left: good quality, easily visualized; right: poor quality due to diffuse disease) is not accounted for when calculating perioperative morbidity or mortality risk.
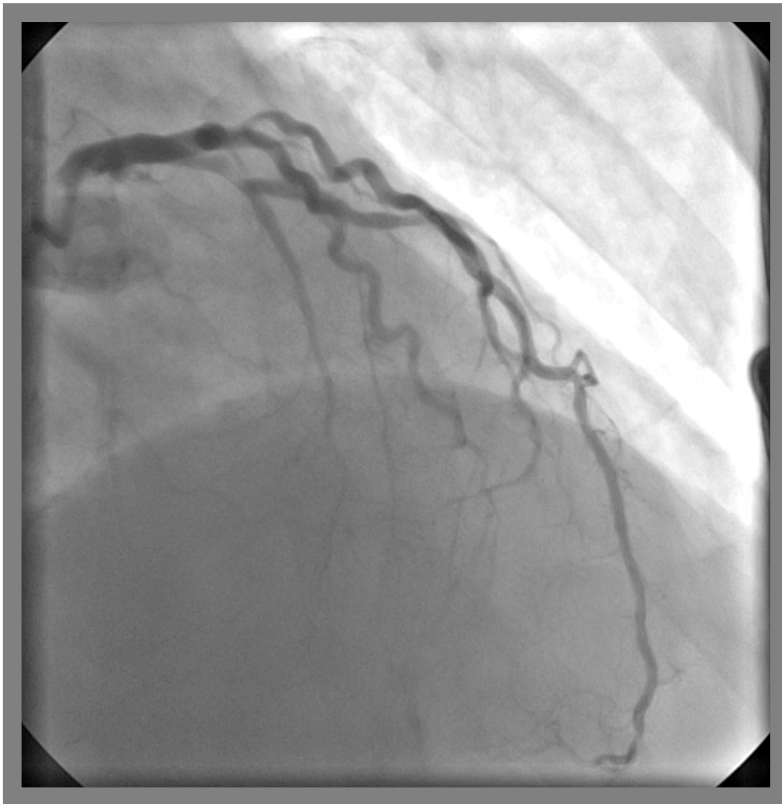
Trial Designs. To date, two prospective, randomized, multi-centered controlled trials have been performed using TMR adjunctively with CABG in patients who would be incompletely revascularized by CABG alone. In a single-blind trial involving 263 patients, Allen and associates randomized patients whose standard of care was CABG but who had one or more viable myocardial target areas served by coronary vessels that were not amenable to bypass grafting to either CABG plus TMR (CABG/TMR, n=132) or CABG alone (n=131).[Allen 2000] Baseline and operative characteristics were similar between groups, including the location and number of bypass grafts placed (3.1 ± 1.2, CABG/TMR; 3.4 ± 1.2, CABG alone, p=0.07). Patients were blinded to their treatment group through one-year follow-up. In a similar study, Frazier and associates randomized 49 high-risk patients having comparable baseline characteristics, including severe, distal, diffuse CAD-induced angina, to CABG/TMR (n=22) or CABG alone (n=27).[Frazier 1999]

Figure 2. **Angiograms from Demographically Similar Patients, Both with STS Predicted Operative Mortality of 3.1%.**

Patient A   Patient B

Operative Events and 1-Year Survival. Allen reported improved outcomes following CABG/TMR versus CABG alone in terms of a reduced operative mortality rate (1.5% vs. 7.6%, p=0.02), reduced postoperative inotropic support requirements (30% vs. 55%, p=0.0001), increased 30-day freedom from major adverse cardiac events (97% vs. 91%, p=0.04), and improved one-year Kaplan-Meier survival (95% vs. 89%, p=0.05). Multivariable predictors of operative mortality were CABG alone (odds ratio 5.3, p=0.04) and increased age (odds ratio 1.1, p=0.03). Frazier and associates reported a similar trend in operative mortality following CABG/TMR versus CABG alone (9% vs. 33%, p=0.09). Early benefits observed in these studies following CABG/TMR must be evaluated in the context of potential study limitations. In both studies, randomization occurred preoperatively, potentially resulting in differences between groups in terms of characterization of bypassable vessels and surgical conduct. In addition, whereas the operative mortality rates observed following CABG alone in both randomized trials (7.6%, 33%) might be viewed as excessive, the evidence in the clinical literature indicates that such incomplete revascularization due to diffuse, distal CAD significantly contributes to this increased risk.

Effectiveness. In terms of operative effectiveness, the use of TMR adjunctively with CABG has been shown to decrease intensive care unit (ICU) times and length of hospitalization stay.[Wehberg 2003]. At one year, Allen and associates reported that the overall angina class distribution and exercise treadmill scores were similar between groups. Frazier and colleagues found a non-significant trend in the incidence of treatment failure[†] favoring CABG/TMR patients at one year (37% vs. 66%, p=0.34). In a multicenter follow-up of the original trial, Allen and associates evaluated the effectiveness of TMR in 218 patients originally randomized to CABG/TMR or to CABG alone. To eliminate the potential for assessment bias in this long-term follow-up, blinded independent assessors performed

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[†]Defined as death, additional revascularization, or failure to improve at least 2 angina classes from baseline.

angina assessments across centers. At a mean of five years, both groups experienced significant angina improvement from baseline, however, the CABG/TMR group had a lower mean angina score (0.4 ± 0.7 versus 0.7 ± 1.1, p=0.05), a significantly lower number of patients with severe angina (class III/IV: 0% vs. 10%, p=0.009), and a trend towards greater number of angina-free patients (78% vs. 63%, p=0.08), compared to CABG alone patients. Although the operative characteristics were similar between groups, non-significant increases in grafting of the circumflex artery and overall number of grafts placed per patient were found in the CABG alone group. Despite this, CABG alone patients still had worse overall angina compared to CABG/TMR patients. Long term survival was similar between randomized groups.

OBSERVATIONAL OPERATIVE SAFETY DATA FROM THE STS NATIONAL DATABASE

A recent report of TMR practice patterns and operative (procedural and through 30 days) mortality and morbidity, based on information collected in the STS National Cardiac Database, was recently made available [Peterson 2003]. This report identified 661 patients that underwent sole therapy TMR and 2,475 patients who received TMR + CABG between January 1998 and December 2001. Over that interval there was an increase in the number of sites that performed TMR from 33 to 131. This increase was due to 1) US FDA approvals in August 1998 and February 1999; and, 2) Medicare coverage of the procedure beginning in July 1999 and clarified to include adjunctive TMR in October 1999.

These initial results from the STS Database are generally similar to previously published results from the RCTs involving sole therapy, operative mortality in the RCTs involving stable patients and unstable patients, respectively, ranged from 1 to 5% and from 9 to 22%. In the STS registry, the overall operative mortality rate in 661 patients was 6.4%. This overall rate initially seems high, but it is similar to the RCTs if separated into stable patients and unstable or low ejection fraction patients: operative mortality was 3.7% in 243

stable[†] patients and 7.9% in 418 sicker patients with unstable angina, recent myocardial infarction, and/or depressed ejection fraction. As adjunctive therapy in patients who could not be completely revascularized by CABG alone, the overall operative mortality was 4.2%; when patients with unstable angina, recent myocardial infarction , and depressed ejection fraction (<30%) were excluded, the mortality rate reduced 2.6%.

A comparison of 390 TMR+CABG patients and 39,000 CABG only patients with triple vessel coronary artery disease who received <3 grafts showed similar unadjusted mortality rates (4.9% vs. 4.1% [p=0.37]). However, the presumption that incomplete revascularization in the CABG only patients was identified accurately and consistently across centers to occur in an area of ischemic viable myocardium supplied by a diffusely diseased, ungraftable coronary artery, cannot be verified through a query of the STS database. This is due to the fact that, unfortunately, the presence of diffuse coronary artery disease is not factored into the STS database or other national database. Thus, it is likely that TMR+CABG patients are not directly comparable to case-matched CABG only patients. This is illustrated in a substantially increased data set that has been collected in the STS Database. From 1998 to 2003, 5,618 patients who underwent TMR+CABG, representing 0.6% of the surgical revascularization population in the STS Database, were compared with 932,715 patients who underwent CABG only operations. Significantly increased baseline comorbidities and risk factors occur in TMR + CABG patients (Table 2). Accordingly, overall operative mortality was higher in TMR+CABG vs. all CABG alone patients (3.8% vs. 2.7%, p<0.001). Again, when comparing a subset of presumed case-matched patients with triple vessel coronary artery disease but who received <3 bypass grafts, operative mortality was similar between TMR+CABG and CABG alone patients (5.2% vs. 4.3%, p=0.13). Although the observed-to-expected mortality ratios for TMR+CABG patients and the 'under-revascularized' CABG patients are similar (1.08 vs. 0.97, odds ratio=1.1, p=0.26), this

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[†]Excluding patients with a recent myocardial infarction, depressed ejection fraction (<30%) and unstable angina.

simplified comparison cannot accurately account for diffuse coronary artery disease in CABG alone patients, which is characteristic of TMR+CABG patients. After excluding unstable angina patients , the operative mortality in TMR+CABG patients was decreased to 2.7% (O/E ratio = 0.87). Moreover, no evidence of overuse of TMR or difference in outcomes were found when comparing sites by volume.

Table 2. Comparison of CABG Only and TMR+CABG Patients in the STS Adult Cardiac Database, 1998-2003

Characteristic	CABG only	TMR+ CABG	P value
N	932,715	5,618	
Body surface area, m2 x (sd)	1.96 (0.24)	1.99 (0.23)	<0.001
Cerebral vascular disease	12%	17%	<0.001
Cerebrovascular accident	7%	9%	<0.001
Chronic lung disease	14%	17%	<0.001
Diabetes (all types)	34%	50%	<0.001
Diabetes (insulin-dependent)	10%	19%	<0.001
Dialysis	1%	2%	<0.001
Hypercholesterolemia	62%	73%	<0.001
Hypertension	72%	80%	<0.001
Myocardial infarction	46%	49%	<0.001
Peripheral vascular disease	16%	20%	<0.001
Prior CABG/reoperation	9%	26%	<0.001
Renal failure	5%	7%	<0.001
Triple vessel CAD	71%	80%	<0.001

The current and ongoing review of the STS Database indicates that TMR+CABG patients have a significantly increased incidence of every surrogate marker of diffuse arterial disease (Table 2), which inherently carry increased operative risk. Nonetheless, through careful patient selection and treatment of patients before they become unstable, superior and ever improving outcomes can be achieved. One of the strengths of surgical intervention for coronary artery disease lies in the ability to provide a more complete revascularization. A method to enhance the completeness of revascularization, when it cannot be accomplished through standard grafting alone due to the presence of diffuse disease, is the adjunctive use of TMR.

THE SOCIETY OF THORACIC SURGEONS

TECHNOLOGY ASSESSMENT AND REVIEW: TRANSMYOCARDIAL REVASCULARIZATION

SUMMARY

Cardiothoracic surgeons are increasingly faced with a more complex patient who has developed a pattern of diffuse coronary artery disease and has exhausted nonsurgical options. Results replicated in multiple randomized, controlled trials augmented by recently available long-term results using Ho:YAG and CO_2 TMR systems have validated the safety, effectiveness, and substantially improved health outcomes through the application of this technology for the treatment of selected patients with severe angina due to diffuse disease, when used alone and as adjunctive therapy. Through the ongoing evaluation of accurate information regarding patient characteristics and outcomes, continued improvement in patient selection, surgical technique, postoperative management, and practitioner education will be achieved.

TECHNOLOGY ASSESSMENT AND REVIEW: TRANSMYOCARDIAL REVASCULARIZATION

References

[1]   Aaberge L, Nordstrand K, Dragsund M, et al. Transmyocardial revascularization with CO_2 laser in patients with refractory angina pectoris. Clinical results from the Norwegian randomized trial. J Am Coll Cardiol 2000;35(5):1170-7.

[2]   Aaberge L, Rootwelt K, Blomhoff S, et al. Continued symptomatic improvement three to five years after transmyocardial revascularization with CO_2 laser: a late clinical follow-up of the Norwegian randomized trial with transmyocardial revascularization. J Am Coll Cardiol 2002;39:1588-93.

[3]   Allen KB, Dowling RD, Heimansohn DA, et al. Transmyocardial revascularization utilizing a holmium:YAG laser. Eur J Cardiothorac Surg 1998;14:Suppl 1:S100-S104.

[4]   Allen KB, Dowling RD, Fudge TL, et al. Comparison of transmyocardial revascularization with medical therapy in patients with refractory angina. N Engl J Med 1999;341:1029-36.

[5]   Allen KB, Dowling R, DelRossi A, et al. Transmyocardial laser revascularization combined with coronary artery bypass grafting: a multicenter, blinded, prospective, randomized, controlled trial. J Thorac Cardiovasc Surg 2000;119:540–9.

[6]   Allen KB, Shaar CJ. Transmyocardial laser revascularization as a clinical procedure. Letter to the editor. N Engl J Med 2000; 342:438.

[7]   Allen KB, Dowling RD, Angell W, et al. Transmyocardial Revascularization: Five-Year Follow-up of a Prospective, Randomized, Multicenter Trial. Ann Thorac Surg 2004;77:1228-34.

[8]   Allen KB, Dowling RD, Richenbacher W. Letter to the editor. J Am Coll Cardiol 2004;43(12):2364-5.

[9]   Allen KB, Dowling RD, Schuch D, et al. Adjunctive transmyocardial revascularization: 5-year follow-up of a prospective, randomized, trial. Ann Thorac Surg 2004 [In Press].

[10]   Al-Sheikh T, Allen KB, Straka SP, et al. Cardiac sympathetic denervation after transmyocardial laser revascularization. Circulation 1999;100(2):135-40.

[11]   Arora RC, Hirsch GM, Hirsch K, et al. Transmyocardial laser revascularization remodels the intrinsic cardiac nervous system in a chronic setting. Circ 2001;104 [suppl I]:115-20.

[12]   Bell, MR, Gersh BJ, Schaff HV, et al. Effect of completeness of revascularization on long-term outcomes of patients with three-vessel disease undergoing coronary artery bypass surgery. Circulation 1992; 86:446-57.

[13]   Bridges CR, Horvath KA, Nugent B, et al. Society of Thoracic Surgeons practice guideline: transmyocardial laser revascularization. Ann Thorac Surg 2004;77:1484-1502.

[14]   Burkhoff D, Schmidt S, Schulman SP, Myers J, Resar J, Becker LC, Weiss J, Jones J. Transmyocardial revascularization compared with continued medical therapy for treatment of refractory angina pectoris: a prospective randomized trial. Lancet 1999;354:885-90.

[15]   Dowling RD, Petracek MR, Selinger SL, Allen KB. Transmyocardial revascularization in patients with refractory, unstable angina. Circulation 1998;98 Suppl II:II73-II76.

[16]   Ferguson TB, Hammill BG, Peterson ED, et al. A decade of change – risk profiles and outcomes for isolated coronary artery bypass grafting procedures, 1990-1999; a report from the STS national database committee and the Duke Clinical Research Institute. Ann Thorac Surg 2002;73(2):480-9.

[17]   Frazier OH, March RJ, Cooley DA, et al. Myocardial revascularization with laser. Circulation 1995;92[Suppl II] 58-65.

[18]   Frazier OH, March RJ, Horvath KA. Transmyocardial revascularization with a carbon dioxide laser in patients with end-stage coronary disease. N Engl J Med 1999;341:1021-28.

[19]   Frazier OH, Boyce SW, Griffith BP, Hattler B, Kadipasaoglu K, March R. Transmyocardial revascularization using a synchronized CO_2 laser as adjunct to coronary artery bypass grafting: results of a prospective, randomized multi-center trial with 12 month follow-up. Circulation 1999; (Suppl I)100:I248.

[20]   Gibbons R, Abrams J, Chatterjee K, et al. ACC/AHA 2002 guideline update for the management of patients with chronic stable angina—summary article: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients with Chronic Stable Angina). Circulation. 2003; 107:149-58.

[21]   Graham MM, Chambers RJ, Davies RF. Angiographic quantification of diffuse coronary artery disease: reliability and prognostic value for bypass operations. J Thorac Cardiovasc Surg 1999; 118:618-627.

[22]   Hardy RI, Bove KE, James FW, et al. A histologic study of laser-induced transmyocardial channels. Lasers Surg Med 1987;6(6):563-73.

[23]   Hattler B, Griffith B, Zenati M, Crew J, Mirohseini M, Cohn L, Aranki S, Frazier O, Cooley D, Lansing A, Horvath K, Fontana G, Landolfo K, Lowe J, Boyce S. Transmyocardial laser revascularization in the patient with unmanageable unstable angina. Ann Thorac Surg 1999;68:1203-09.

[24]   Horvath KA, Kim RJ, Judd RM, et al. Contrast enhanced MRI assessment of microinfarction

after transmyocardial laser revascularization. Circulation 2000;102:II-765-8.

[25]   Horvath KA, Aranki SF, Cohn LH, et al. Sustained angina relief 5 years after transmyocardial laser revascularization with a CO_2 laser. Circulation 2001; 104[Suppl. I]:I81-84.

[26]   Hutchins GD, Schwaiger M, Rosenspire KC, et al. Noninvasive Quantification of Regional Blood Flow in the Human Heart Using N-13 Ammonia and Dynamic Positron Emission Tomographic Imaging. J Am Coll Cardiol 1990; 1032-42.

[27]   Khairy P, Dubuc M, Gallo R. Cryoapplication induces neovascularization: a novel approach to myocardial revascularization. J Am Coll Cardiol 2000;35:5A-6A.

[28]   Lawrie GM, Morris GC, Silvers A, et al. The influence of residual disease after coronary bypass on the 5-year survival rate of 1274 men with coronary artery disease. Circ 1982;66:717-23.

[29]   March RJ, Boyce S, Cooley DA. Improved event free survival following transmyocardial laser revascularization versus medical management in patients with unreconstructed coronary artery disease. The 77th Annual Meeting of the American Association of Thoracic Surgery.1997;94 (abstract).

[30]   Mirhoseini M, Fisher JC, Cayton MM. Myocardial revascularization by laser: a clinical report. Lasers Surg Med 1983;3:241-5.

[31]   Muhkerjee D, Comella K, Bhatt D, et al. Direct myocardial revascularization and angiogenesis-how many patients might be eligible? Am J Cardiol 1999;84(5):598-600.

[32]   Muhkerjee D, Comella K, Bhatt D, et al. Clinical outcome of a cohort of patients eligible for therapeutic angiogenesis or transmyocardial revascularization Am Heart J 2001;142(1):72-4.

[33]   Myers J, Oesterle S, Jones J, Burkhoff D. Do transmyocardial and percutaneous laser revascularization induce silent ischemia? An assessment by exercise testing. Am Heart J 2002; 143:1052-7.

[34]   Osswald B, Blackstone E, Tochtermann U, et al. Does the completeness of revascularization affect early survival after coronary artery bypass grafting in elderly patients? Euro J Cardiothorac Surg 2001; 20:120-6.

[35]   Peterson ED, Kaul P, Kaczmarek RG, et al. From controlled trials to clinical practice: monitoring transmyocardial revascularization use and outcomes. J Am Coll Cardiol 2003;42:1611-16.

[36]   Schaff H, Gersh B, Pluth J, et al. Survival and functional status after coronary artery bypass grafting: results 10 to 12 years after surgery in 500 patients. Circulation 1983;68:(Supp II):200-4.

[37]   Schofield PM, Sharples LD, Caine N, et al. Transmyocardial laser revascularization in patients

with refractory angina: a randomized controlled trial. Lancet 1999;353:519-24.

[38]   Sen PK, Udwadia TE, Kinare SG, et al. Transmyocardial acupuncture. A new approach to myocardial revascularization. J Thorac Cardiovasc Surg 1965;50:181-9.

[39]   Shawl FA, Kaul U, Saadat V. Myocardial revascularization using a myocardial channeling device: first experience using the Angiotrax system. J Am Coll Cardiol 2000;35:61A.

[40]   Shroyer AL, Coombs LP, Peterson ED, et al. The Society of Thoracic Surgeons: 30-Day Operative Mortality and Morbidity Risk Models. Ann Thorac Surg 2003;75:1856-65.

[41]   Smith NB, Hynynen K. The feasibility of using focused ultrasound for transmyocardial revascularization. Ultrasound Med Biol 1998;24:1045-54.

[42]   Stamou SC, Boyce SW, Cooke RH, et al. One-year outcome after combined coronary artery bypass grafting and transmyocardial laser revascularization for refractory angina pectoris. J Am Coll Cardiol 2002;89(12):1365-8.

[43]   Trehan N, Mishra M, Bapna R, Mishra A, Maheshwari P, Karlekar A. Transmyocardial laser revascularization combined with coronary artery bypass grafting without cardiopulmonary bypass. Euro J Cardiothorac Surg 1997; 12: 276-84.

[44]   U.S. Centers for Medicare and Medicaid Services. Transmyocardial revascularization for severe angina (#CAG-00004). Decision memorandum July 1999; addendum October 1999.

[45]   U.S. Food and Drug Administration Summaries of Safety and Effectiveness. PLC Medical Systems, 1998; CardioGenesis, 1999. Available via the internet at www.fda.gov/cdrh/pdf/p950015b.pdf and www.fda.gov/cdrh/pdf/p970029b.pdf.

[46]   Wehberg KE, Julian JS, Todd JC, et al. Improved patient outcomes when transmyocardial revascularization is used as adjunctive revascularization. Heart Surg Forum 2003;6(5):1-3.

[47]   Weintraub WS, Jones EL, Craver JM, Guyton RA. Frequency of repeat coronary bypass or coronary angiogplasty after coronary artery bypass surgery using saphenous venous grafts. Am J Cardiol 1994;73:103-12.

[48]   Yamamoto N, Gu AG, Derosa CM, et al. Radiofrequency transmyocardial revascularization enhances angiogenesis and causes myocardial denervation in a canine model. Lasers Surg Med 2000;27:18-28.