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Factors Correlating With Risk of Mortality After Transmyocardial Revascularization

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OBJECTIVES The purpose of this study was to determine factors correlating with the risk of postoperative mortality after transmyocardial laser revascularization (TMR).

BACKGROUND Clinical studies have indicated that TMR reduces angina by an average of two classes in patients with medically refractory symptoms not treatable by coronary artery bypass graft (CABG) or percutaneous transluminal coronary angioplasty. Factors which correlate with mortality after TMR, however, have not been extensively investigated.

METHODS One hundred thirty-two patients with severe angina underwent TMR as sole therapy with a CO_2 laser. Age, gender, ejection fraction, prior CABG, unstable angina and the severity of coronary artery disease (graded on the basis of a newly proposed Anatomic Myocardial Perfusion index, AMP) were each determined. Each vascular territory (left anterior descending artery [LAD] left circumflex artery and posterior descending artery [PDA]) was graded as either having (AMP = 1) or not having (AMP = 0) blood flow through an unobstructed major vessel in the territory. Univariate and multivariate analysis determined which factors correlated with mortality.

RESULTS Patients with at least one AMP = 1 vascular territory (overall AMP = 1) had a 5% (4/82) postoperative mortality rate (POM), compared with 25% (12/49) with overall AMP 0 ($p = 0.002$). Left anterior descending artery AMP ($p = 0.03$) and previous CABG ($p = 0.04$) each correlated with the risk of POM. However, multivariate analysis indicated that no factor improved the correlation obtained with overall AMP by itself. With regard to overall mortality (Kaplan-Meier curves), univariate analysis also revealed correlations with overall AMP ($p < 0.001$), LAD AMP ($p = 0.005$), previous CABG ($p = 0.003$) and PDA AMP ($p = 0.05$) each individually correlated with mortality. Multivariate analysis indicated that overall AMP = 1, female gender and previous CABG together correlated best with lower postoperative mortality.

CONCLUSIONS Patients with good blood flow to at least one region of the heart through a native artery or a patent vascular graft have a markedly reduced risk of perioperative and longer term mortality. (J Am Coll Cardiol 1999;34:55–61) © 1999 by the American College of Cardiology

Transmyocardial laser revascularization (TMR) is currently being evaluated as a therapy for patients with refractory angina who cannot be treated with bypass surgery or angioplasty because of diffuse coronary artery disease (1). From a clinical perspective, most attention has focused on the common finding that this therapy is effective in reducing angina by an average of two classes in these otherwise untreatable patients (2–7). There have also been reports of mild to modest improvements in regional blood flow appearing most consistently between three and six months after the surgery (2–5). Exercise tolerance, when examined, also appears to be improved (8,9).

Despite having now accrued significant clinical experience with this procedure (with reports of up to 4,000 procedures having been performed worldwide), much less attention has focused on understanding factors that may predict which patients benefit most and which are at increased risk of morbidity and mortality from this procedure. Perioperative mortality rates between 3% and 20% have been reported (2–5,7); the reason for this wide range is unknown. Patient eligibility criteria have varied significantly among various ongoing and completed studies and among different investigators, but a generally accepted set of criteria has not emerged. The purpose of this study is to investigate factors that correlate with the risk of mortality after TMR.

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Abbreviations and Acronyms

AMP	=	Anatomic Myocardial Perfusion index
CABG	=	coronary artery bypass graft
EF	=	ejection fraction
LAD	=	left anterior descending artery
TMR	=	transmyocardial revascularization

Physiologic considerations. It was originally proposed that myocardial perfusion could be achieved by the creation of transmyocardial channels which communicate with the left ventricular cavity (1), thus mimicking the physiology of blood flow in reptile hearts (10). However, results of physiologic and anatomic studies in experimental animal models have suggested that blood does not flow through these channels (11–17). This is particularly the case for the acute setting, where it has been demonstrated that TMR channels do not protect myocardial viability in the face of severe acute ischemia (18–20). If applicable to the clinical setting, these findings would suggest that patients undergoing TMR may not derive any perfusion benefit in the days after the procedure. It is therefore possible that patients who are particularly susceptible to ischemia may be at increased risk of perioperative morbidity and mortality because of the stress associated with surgery and the postoperative recovery period. This, in combination with other physiologic considerations (see Discussion), has led to the hypothesis that patients with severe unbypassed three-vessel (or unbypassed left main) disease who lack any areas of myocardium protected by blood flow through patent vessels are at increased risk of perioperative mortality after TMR.

METHODS

Between February 1994 and October 1996, 132 patients with medically refractory class III and IV angina underwent TMR as sole therapy with a CO_2 laser (The Heart Laser, PLC Systems Inc., Franklin, Massachusetts) at the Audubon Heart Center in Louisville, Kentucky by a single operator (A.M.L.). These subjects took part in an investigation of the safety and efficacy of TMR in which the Audubon Heart Center participated. Each patient provided informed consent after being told of the risks and potential benefits of participating in the study. The protocols under which the studies were conducted were approved by the local ethics committee. The present study is a retrospective analysis of the data collected from those patients.

Demographic and medical data were collected on all 132 patients. A preliminary evaluation of many factors and survey of published reports had indicated that the most relevant factors to examine more closely were age, gender, ejection fraction, the presence of prior bypass surgery, the occurrence of unstable angina in the preoperative period and the severity of coronary artery disease. The severity of coronary vascular disease was graded on the basis of angiographic findings as detailed below.

Review and grading of coronary angiograms. The original angiograms of 109 of the patients were retrieved and reviewed by one of the cardiologists participating in this study (D.B. or J.R.R.) who was blinded as to whether the patient did or did not die any time during the follow-up period. For those patients whose angiogram could not be retrieved for review, grading of the extent of vascular disease was based on the report of the most recent angiogram; again, this was also done without knowledge of outcome. The severity of coronary artery disease was graded according to what we have termed the "Angiographic Myocardial Perfusion (AMP) score." The intent of the AMP score is to provide a simple system for designating whether there is or is not an unobstructed path for blood flow to and through the major vessel of a specified region of the heart. In the case that such an unobstructed path exists, the region may be considered to be protected, in the sense that it should not be vulnerable to ischemia during times of stress. Inherent to this grading system is the notion that the path for blood flow may be either entirely through the native vasculature or it may include surgically placed conduits. Each of the three major vascular territories (anterior, lateral and inferior) was graded separately according to the following definitions. A region was considered to have an AMP score of "1" if myocardial perfusion was provided through a major vessel in the region, and the path for blood flow (be it through native vessels or through vascular grafts) was not affected by hemodynamically significant stenoses (i.e., no greater than 50% lumenal narrowings). A region was considered to have an AMP score of "0" if myocardial perfusion in the region was only provided through minor vessels or through vessels with hemodynamically significant stenoses (lumenal narrowings ≥50%). In addition to grading each region individually, an overall AMP score was designated as "1" if there was at least one AMP 1 region on the heart; otherwise the overall AMP score was designated as "0". Guidelines were established to identify "major" vessels in each of the three regions. The left anterior descending artery (LAD) was considered the major vessel for the anterior wall. For the lateral wall, any large caliber marginal branch which reached at least three quarters of the distance from the base to the apex of the heart was considered a major vessel. Similarly, any large caliber posterior descending artery which reached at least three quarters of the distance between the base and the apex of the heart was considered to be a major vessel.

Statistical methods. Data are presented as mean ± SD. The Fisher exact test was used to identify variables which might be related to perioperative mortality (death within 30 days of surgery). Age, gender, ejection fraction, presence of unstable angina, prior coronary artery bypass graft (CABG) experience, anterior AMP, lateral AMP, inferior AMP and overall AMP were also examined using logistic regression. The log-rank test and Cox regression were used to investigate whether any variables or combination of variables were significant predictors of overall survival. Survival curves were estimated using the Kaplan-Meier procedure (21). Hypotheses were tested against two-sided alternatives, and significance levels were set at 0.05.

To test whether there was a "training effect" (i.e., if mortality decreased as the operator gained experience), surgical date was entered as an additional variable. The results of that analysis showed that surgical date did not impact on survival; this factor will not be discussed further.

There were 132 patients in the data set. Complete data were available for 129 patients. Ejection fraction was not available for two patients and AMP scores were not available for one of the patients. For univariate analyses, all available data on the covariate of interest were used. In the multivariate analysis, only data from patients with complete data were used. The SAS (Cary, North Carolina) software system, Release 6.12, was used for all analyses.

RESULTS

Patient characteristics are summarized in Table 1. For the group as a whole, mean age was 61.1 ± 11.3 years. Men constituted 82.6% of the patient population, and most patients suffered from class IV angina (95%). Ejection fraction was generally well preserved, averaging 44 ± 12%. Most patients (84%) had a history of at least one bypass surgery in the past. Nearly half of the patients were classified as having unstable angina requiring intravenous heparin and nitroglycerine before the surgery. Most patients (62%) had an overall AMP score of 1, indicating that they had at least one well perfused region of the heart. The anterior region was protected (i.e., anterior AMP score = 1) in 39% of the cases and was the single most frequently well perfused region; this compares with 24% of patients having a protected lateral wall and only 18% of patients having a protected inferior wall. Table 2 provides further detail concerning the type of vessels providing myocardial protection. Among the 132 patients studied, there were a total of 110 protected regions (Tables 1 and 2). Of these, 30 were protected by native vessels, 50 by saphenous veins and 28 (for the anterior region) by internal mammary arteries as further detailed in Table 2. For the anterior region, the mammary artery was the most frequent means of protection, accounting for more than 50% of the cases.

The degree of angina (graded according to the Canadian Cardiovascular Society Angina Score) was severe before surgery, with approximately 95% of patients suffering with class IV symptoms and the remainder suffering with class III symptoms. At the time of the last available follow-up in the 100 patients who survived and were followed for at least 6 months, 50% were classified with class I angina, 25% had class II angina, 8% had class III angina and 11% had class IV angina; follow-up angina class was unavailable for 6% of these patients. Seventy-two percent of the patients experienced a reduction of angina symptoms of two or more classes, 10% improved by one class, whereas 11% showed no improvement. In 7% of cases, improvement could not be assessed due to missing data. Thus, in surviving patients, there was substantial subjective symptomatic improvement in angina.

Sixteen of the original 132 patients (12.1%) died within the first 30 days after surgery. An additional 13 deaths occurred between 30 days and 1 year after surgery (total one-year mortality 22%). Eight patients died more than one year after surgery, and the remainder were alive at their last

Table 1. Summary of Characteristics of All Patients

Characteristic	All Patients
n	132
Age (yr)*	61.1 ± 11.3 (35–84)
Gender	
Male	109
Female	23
Preoperative angina score	
Class III	7
Class IV	125
Ejection fraction*	44 ± 12 (15–68)
Previous CABG	
Yes	111
No	21
Unstable angina	
Yes	63
No	69
Anterior AMP	
Unknown	1
1	52
0	79
Lateral AMP	
Unknown	1
1	32
0	99
Inferior AMP	
Unknown	1
1	24
0	107
Overall AMP	
Unknown	1
1	82
0	49

*Mean ± standard deviation (range).
AMP = Anatomic Myocardial Perfusion index score; CABG = coronary artery bypass graft.

Table 2. Breakdown of Vessel Type Supplying "Protected" Regions

Protected Region	n	Native Vessel	Saphenous Vein	Mammary Artery
Anterior	52	9	16	27
Lateral	32	12	19	n/a
Inferior	24	9	15	n/a
Total	108	30	50	27

Table 3. Cause of Perioperative and Long-Term Deaths

Cause of Death	Perioperative Death*	Death Between 30 Days and 1 Year
Acute myocardial infarction	7	5
Ventricular fibrillation	3	—
Heart failure	4	3
Cardiac arrest—unspecified cause	—	4
Respiratory arrest	1	—
Pulmonary embolism	1	—
Stroke	1	—
Uncertain	—	1

*One perioperative death was attributed to two factors (stroke and respiratory failure).

follow-up visit. Patients known to be alive at last follow-up had a median follow-up duration of 12.25 months. Overall 1-year survival is estimated to be 75%. The causes of death are summarized in Table 3. Most deaths were attributable to cardiovascular causes.

Results of univariate analysis indicated that perioperative mortality was significantly associated with overall AMP score, anterior AMP score and whether or not the patient had previous CABG (Table 4). Overall AMP score was the strongest predictor of perioperative mortality; patients with an overall AMP score of 1 were over six times less likely to experience perioperative mortality ($p = 0.002$, Fisher exact test). An anterior AMP score of 1 was associated with a five-fold decrease in the likelihood of perioperative mortality ($p = 0.03$). Patients with previous CABG were four times less likely to die in the perioperative period ($p = 0.04$). Although patients with unstable angina were almost twice as likely to die in the perioperative period, this was not statistically significant. Also of note is that none of the 23 women died in the perioperative period, whereas 16 of the 109 men (15%) experienced perioperative mortality. This

Table 4. Results of Univariate Analysis of Factors Correlating With Risk of Perioperative Mortality

Factor	Perioperative Mortality	Odds Ratio (95% Confidence Interval)	p*
Overall AMP			
AMP = 0	12/49 = 25%	0.158	0.002
AMP = 1	4/82 = 5%	(0.048–0.524)	
Anterior AMP			
AMP = 0	14/79 = 18%	0.186	0.03
AMP = 1	2/52 = 4%	(0.40–0.855)	
Previous CABG			
No	6/21 = 29%	0.248	0.04
Yes	10/111 = 9%	(0.079–0.780)	
Unstable angina			
Present	10/63 = 16%	0.505	0.32
Not present	6/69 = 9%	(0.172–1.484)	

*p values are from Fisher exact test. Abbreviations as in Table 1.

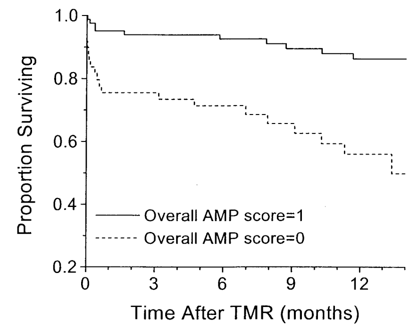

Figure 1. Kaplan-Meier curves depicting survival in patients having (overall anatomic myocardial perfusion index score [AMP] = 1) or not having (overall AMP = 0) unobstructed blood flow to a major vessel in at least one vascular territory. On the basis of univariate analysis, this factor was the strongest single factor which correlated with the risk of mortality after transmyocardial revascularization (TMR) ($p = 0.002$).

difference was not statistically significant. None of the other covariates considered were significantly related to perioperative mortality. When overall AMP score was entered in a multivariate logistic model, no other variables added significantly to the ability to predict perioperative mortality.

With respect to overall mortality, patients with overall AMP scores of 1 had significantly better survival compared with patients with a score of 0 ($p < 0.0.001$, Fig. 1). Anterior AMP score = 1 ($p = 0.005$, Fig. 2), previous CABG ($p = 0.003$, Fig. 3) and inferior AMP score = 1 ($p = 0.05$, Fig. 4) were also predictors of improved survival when considered individually. Multivariate analysis using a backward selection procedure resulted in a model with three covariates: overall AMP score, previous CABG and gender. The risk ratios and 95% confidence intervals for these variables in combination are shown in Table 5. Men with overall AMP score of 0 without previous CABG had the lowest predicted survival curve, with an estimated 1-year mortality exceeding 60%.

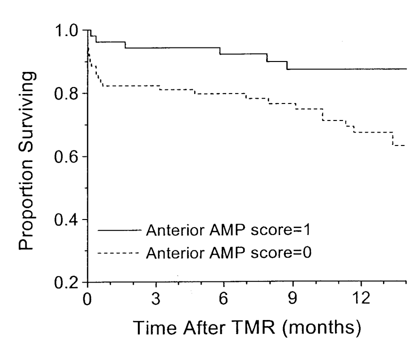

Figure 2. Kaplan-Meier curves depicting survival in patients having (anterior AMP = 1) or not having (anterior AMP = 0) unobstructed blood flow to the left anterior descending artery. On the basis of univariate analysis, this factor also correlated with the risk of mortality after TMR ($p = 0.005$). Abbreviations as in Figure 1.

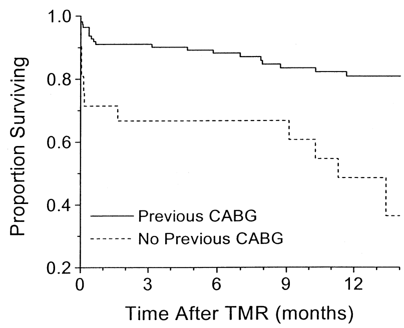

Figure 3. Kaplan-Meier curves depicting survival in patients having had (coronary artery bypass graft [CABG] = 1) or not having had (CABG = 0) previous coronary bypass surgery. On the basis of univariate analysis, prior CABG predicted a better outcome after transmyocardial revascularization (TMR) ($p = 0.003$).

To assess whether differences in overall mortality associated with the various risk factors were mainly due to the risk of postoperative mortality, a separate analysis was performed which included only patients who survived at least 30 days after the surgery. This analysis showed that for patients who survived the 30-day postoperative period, overall AMP score equal to 1 ($p = 0.006$), previous CABG ($p = 0.04$), inferior AMP score equal to 1 ($p = 0.01$) and ejection fractions greater than 45% ($p = 0.02$) were each individually associated with significantly improved survival after the 30-day postoperative period.

For patients with at least one protected region, there were a total of only 9 deaths, 4 in the perioperative period and 5 late deaths. Among this small patient group, 6 patients had only 1 protected region and 3 patients had 2 protected regions. Mammary arteries, saphenous veins and native vessels were roughly equally represented in this small patient group. On the basis of this analysis and the analysis provided in Table 2, there is nothing to indicate that mammary arteries were more protective than saphenous veins or native vessels. An additional factor that was tested was whether older graphs provided less protection. This was tested using univariate analysis by entering the difference between the date of last CABG surgery and the TMR date for subjects who had at least one region of protected myocardium. This analysis showed that time since last CABG surgery did not correlate with mortality in this small patient cohort.

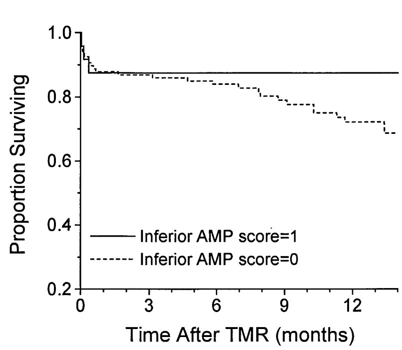

Figure 4. Kaplan-Meier curves depicting survival in patients having (inferior AMP = 1) or not having (inferior AMP = 0) unobstructed blood flow to the posterior descending artery. On the basis of univariate analysis, this exhibited a statistically significant, though weak correlation with the risk of mortality after TMR ($p = 0.05$). Abbreviations as in Figure 1.

Table 5. Risk Ratios for the Three Factors Which Collectively Provide the Strongest Correlation With Risk of Mortality

Characteristic	Risk Ratio	95% Confidence Interval
Overall AMP score = 1	0.270	0.129–0.564
Female gender	0.32	0.108–0.945
Previous CABG	0.307	0.132–0.710

Abbreviations as in Table 1.

DISCUSSION

The results of this retrospective analysis indicate that patients with unprotected three-vessel disease (overall AMP score = 0) are at high risk of perioperative (~25%) and total 1-year (~40%) mortality after TMR. Of the three vascular beds, unobstructed blood flow through the LAD (be it entirely through native vessels or through a patent graft to a patent distal vessel) was the most important vessel for predicting survival. Prior CABG afforded a better outcome. Unstable angina tended to yield a worse outcome, but this was not statistically significant.

Most of the patients who are considered candidates for TMR have severe native three-vessel disease. Most patients, however, have had previous bypass surgery and in many instances, one or more of the grafts are still patent. Thus, despite severe native three-vessel disease, one or more of the major vascular territories is frequently protected by a patent graft and in such a case this predicts decreased mortality. Indeed, vascular grafts (either saphenous veins or a mammary artery) were the most frequent (78/108, Table 2) source of myocardial protection. The age of a vascular graft did not correlate with bad outcome, though there were very few patients with protected regions who died. In the present series, 62% (82/132) of the patients fell into the category of having at least one well protected region; over 39% of patients had a well protected LAD system.

Potential mechanisms of benefit. Several factors may contribute to increased mortality in patients with severe unprotected three-vessel coronary artery disease. First, results of most studies in experimental animal models now suggest that myocardial perfusion is not increased substantially in the acute setting (11,13,14,20,22). Accordingly, it is not expected that patients undergoing TMR surgery would derive an acute perfusion benefit due to the procedure. Yet, patients with severe three-vessel disease are particularly prone to ischemia during periods of physical stress such as would occur during general anesthesia and a thoracotomy, as well as during the postoperative recovery period. In the absence of improved perfusion, these patients would be at increased risk for episodes of myocardial ischemia and possibly even infarction, which appears to be the major cause of mortality seen in the group of patients (Table 2). If this is the primary factor, the risks of this type of therapy might be reduced if the procedure could be performed percutaneously, as is currently being developed (23). It may also be speculated that TMR may disrupt preexistent collateral vessels that developed in the ischemic area, thus interfering with collateral flow in the short run.

The reason for an apparent protective benefit of prior CABG surgery is uncertain. It could reflect a protective effect of previously placed bypass grafts which have remained patent. Alternatively, the poorer outcome in patients without prior bypass may be a reflection of more severe coronary artery disease in subjects who initially present with diffuse unbypassable lesions.

This study has been limited to an analysis of mortality after TMR. We have not addressed other aspects of morbidity because it is not possible to ensure systematic reporting of all adverse events in a retrospective study such as this. Clearly, elucidation of the frequency and factors that predispose to postoperative myocardial infarction, arrhythmias, heart failure, hypotension and other cardiovascular events is an important topic.

In addition, there has been no detailed analysis of the efficacy of TMR, other than to report on the change in angina class in patients who survive the procedure. The patients of the present study were a subset of patients in a larger, multicenter study that had been reported on previously. The authors of those reports suggested that TMR with the CO_2 laser may improve myocardial perfusion (4).

It is also worth specifying that TMR will not alter the AMP score because TMR, a method of indirect revascularization (as compared with CABG, which would be a method of direct revascularization), would not affect the anatomy of the conduit vessels upon which the AMP score is based.

Study limitations. There are several limitations of this study. First, there is no control group derived from the same patient population which received only medical therapy. Therefore, the mortality of patients with the various risk factors identified in the present study treated medically is unknown. However, results of the Coronary Artery Surgery Study provide some guidelines that help put the results of the present study in perspective (24). In patients with preserved ejection fraction (EF $>$50%) the total, all-cause one year mortality for patients with three-vessel coronary artery disease treated medically was ~2%. This increased to only 3% even in patients with EF $<$50%. These quoted mortality rates were slightly better than reported in the European Collaborative Study (25) and in the Veterans Administration Study (26), but in no case were these one-year mortality rates in medically treated patients greater than 5%. Although the patients in the present study deemed to be devoid of any protected region (who generally had preserved EF) may have suffered with more severe angina and may have had more severe coronary artery disease, it is unlikely that mortality in such a group followed medically would approach the approximately 20% perioperative mortality plus the additional ~20% one-year mortality (total 40% one-year mortality). Furthermore, it could be argued based on clinical grounds that these rates of perioperative and one-year mortality identified in the group of patients without any protected regions would be considered excessive when compared with the types and magnitude of symptomatic improvement being provided by TMR (4).

An additional limitation is that this study is a single-center study. This has the disadvantage that there may be some aspects of patient selection, treatment or care that are unique, and therefore, the results may not extrapolate to all centers performing TMR. The potential advantage of a single-center study is in the uniform procedures for patient selection and treatment. Second, this is a retrospective analysis and it is well known that such results may not apply prospectively. Third, there are a relatively small number of patients and a relatively small number of deaths; therefore the study may be underpowered to detect the importance of all factors examined. For example, there was only a small percentage of women, so the effect of gender on outcome may not be accurate. Average ejection fraction was near normal and there were few patients with ejection fractions less than 30%; therefore, we have not determined the risk of mortality in patients with ejection fractions lower than this value. Accordingly, the results of the present study apply to the group of patients with reasonably well preserved ejection fractions. Fourth, there was a significant number of patients who were lost to follow-up after six months. Therefore, the accuracy of the Kaplan-Meier curves diminishes with time due to the reduction in number of available patients. Fifth, patients of this study were treated with a single laser system (CO_2, The Heart Laser). Because the acute tissue effects of various lasers in clinical use (Ho:YAG, excimer) are different, it is possible that the risks of perioperative mortality may differ with other lasers. Finally, there may be other factors that contribute importantly to the risk of postoperative mortality that have not been considered.

Summary. In conclusion, when considering TMR for a patient with severe, unprotected coronary disease in all of the three major vascular territories, the potential benefits should be weighed against the possibility of a relatively high mortality. This study was restricted to an analysis of mortality, which is an indisputable, objective end point. It will be equally important to evaluate other end points of benefit (such as exercise tolerance, myocardial perfusion and quality of life) in large numbers of patients so that a realistic estimate of risks and benefits can be provided to patients. Finally, the results of this retrospective study should not necessarily be considered to be generally applicable prospectively, although they may aid with patient selection in some cases.

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