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Appropriate timing of surgical intervention after transmural acute myocardial infarction

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Objective: Recommended timing of coronary revascularization after transmural acute myocardial infarction ranges from immediate surgical intervention to repair 4 weeks after infarction. Such wide variation has created a dilemma in the management of these patients. The objective of this study was to delineate the optimal timing of revascularization after transmural acute myocardial infarction in a large and contemporary patient population.

Methods: We performed a retrospective multicenter analysis of 32,099 patients who underwent coronary artery bypass grafting as the sole procedure after transmural myocardial infarction between 1991 and 1996 by 179 surgeons at 33 hospitals in New York State.

Results: Overall hospital mortality for all patients who underwent coronary revascularization with a history of transmural myocardial infarction was 3.3%. Hospital mortality decreased with increasing time interval between revascularization and transmural acute myocardial infarction: 14.2%, 13.8%, 7.9%, 3.8%, 2.9%, and 2.7% for less than 6 hours, 6 hours to 1 day, 1 to 3 days, 4 to 7 days, 7 to 14 days, and greater than 15 days, respectively. Multivariate analyses of 43 potential risk factors suggests that revascularization within 3 days of transmural acute myocardial infarction is independently associated with mortality.

Conclusions: Coronary revascularization within 3 days of a transmural acute myocardial infarction might be an added risk for mortality. In the absence of absolute indications for emergency surgical intervention, such as structural complications and ongoing ischemia, a 3-day waiting period before surgical revascularization should be considered.

Higher mortality for emergency coronary artery bypass grafting (CABG) after acute myocardial infarction (AMI), ranging from 5% to 30%, has been documented since the early 1970s.¹⁻⁴ Among this patient population, those who had a transmural AMI were more likely to present with cardiogenic shock and to have a worse prognosis.⁵⁻⁹ Many have advocated preoperative support with intra-aortic balloon counterpulsation¹⁰⁻¹² and left ventricular assist device insertion.^{13,14} Another potential strategy to improve outcome has been manipulation of the timing of CABG after AMI.^{3-5,8,15,16} However, recommended timing of surgical

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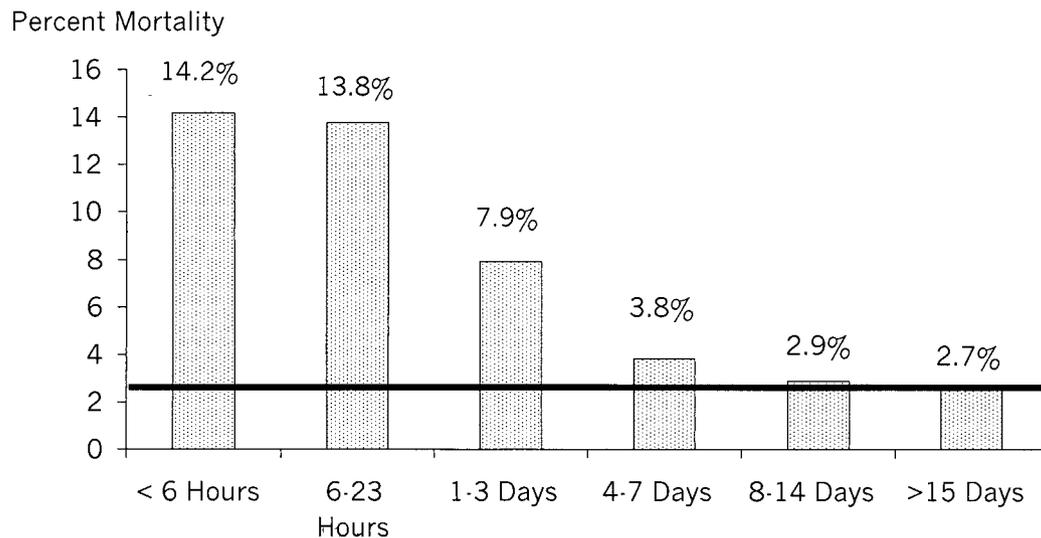


Figure 1. Hospital mortality versus timing of CABG. The horizontal bar represents the baseline mortality rate (2.7%) from the entire patient population.

intervention after a transmural AMI ranges from immediate intervention⁵ to an operation 30 days after the infarction.³ Such wide variation has created a dilemma in the management of these patients. We have previously shown that patients undergoing CABG after transmural and nontransmural AMI have distinctively different patterns of mortality with respect to the timing of operative repair.¹⁷ The objective of this study was to delineate the relationship between mortality and timing of CABG after transmural AMI in a large and contemporary patient population.

Material and Methods

The data for this report are obtained from the Bureau of Health Care Research and Information Services, New York State Department of Health. The New York State Cardiac Surgery Registry is a mandatory outcome reporting system that registers every patient undergoing a cardiac operation, including CABG, within the state. The data of 105,074 patients who underwent CABG as the sole procedure from 1991 to 1996 were identified and selected for analysis. These operations were performed by 179 surgeons at 33 hospitals in New York State. The mean age of the patients was 65 ± 10.2 years (range, 21-95 years). There were 75,829 (72.2%) male patients and 29,245 (27.83%) female patients. The mean left ventricular ejection fraction was $46.3\% \pm 15.8\%$. There were 7640 (7.3%) patients undergoing redo CABG.

Data were analyzed with the SAS statistical analysis software package (SAS Institute, Inc, Cary, NC). Values are expressed as means \pm SD unless otherwise specified. Data were first examined univariately with the Student *t* test for continuous variables and the Fisher exact test for discrete data. Other categorical analysis included use of the χ^2 test for trend and Mantel-Haenszel statistics. For the multivariable analysis, variables with a *P* value of less than .25 were entered into a logistic regression analysis model. The risk factor allowed into the final model with a *P* value of less than .05

is interpreted as an independent risk factor associated with in-hospital mortality and adjusted for other potential risk factors included in the equation.

Results

Among 105,074 patients who underwent CABG as the sole procedure from 1991 to 1996, 32,123 patients had transmural AMI before CABG. The timing designation was missing in 24 patients in this group. Data of the remaining 32,099 patients who had transmural AMI and timing designation were selected for further analysis. The demographics of these patients are similar to those of the patient population as a whole. The mean age of the patients was 64.7 ± 10.3 years (range, 24-95 years). There were 24,146 (75.2%) male patients and 7953 (24.8%) female patients. The mean left ventricular ejection fraction was $40.7\% \pm 14.1\%$. There were 2708 (8.4%) patients undergoing redo CABG.

Overall in-hospital mortality for all patients was 2.7% versus 3.3% and 2.4% ($P < .001$) for patients undergoing CABG with and without a history of transmural AMI, respectively.

Hospital mortality decreased with increasing time interval between CABG and transmural AMI: 14.2%, 13.8%, 7.9%, 3.8%, 2.9%, and 2.7% for less than 6 hours, 6 hours to 1 day, 1 to 3 days, 4 to 7 days, 7 to 14 days, and greater than 15 days, respectively. Mortality is more than double that of the baseline value when operations are performed within 3 days of transmural AMI. The graphic representation of the data is shown in Figure 1. Day 3 appears to be the point of inflection between the steep rise of mortality in early surgical intervention versus the lower mortality at the later time points. Mortality is clearly greater than the base-

line value when surgical intervention is performed within 7 days of transmural AMI.

Table 1 revealed the full list of the 43 potential risk factors for mortality analyzed in this study. About half of the potential risks were found to be independently associated with mortality after multivariate analysis was performed (Table 2). Analysis pertaining to the timing of surgical intervention suggests that CABG within 3 days of transmural AMI is independently associated with mortality, and the odds ratios are 1.6, 2, and 1.5 for less than 6 hours, 6 hours to 1 day, and 1 to 3 days, respectively. Timing of CABG in and of itself after 3 days of transmural AMI no longer influenced outcome (Table 2).

Table 3 showed patient demographics and independent risk factors with the highest odds ratios as a function of timing of surgical intervention. Although more patients undergoing early operations were hemodynamically unstable or in shock, there was no obvious trend with respect to timing of surgical intervention in the distribution of other high odds ratio risk factors listed.

Discussion

The surgical management of AMI has been an issue of ongoing debate. In the setting of AMI and acute coronary occlusion, there are some who have advocated emergency revascularization,^{18,19} but others remained unconvinced and suggested a variable period of waiting before surgical intervention.²⁰⁻²² Our previous report showed a significantly higher mortality among patients undergoing early operations, particularly among those patients with transmural AMI.¹⁷ However, it was not clear precisely at which point the high mortality associated with early operations subsided. The magnitude of the New York State database made it possible to undertake such an analysis on a day-to-day basis after a transmural AMI. With this latest analysis, we found that surgical intervention within 3 days of a transmural AMI is independently associated with mortality. These data provided more support to those who cautioned against CABG as the acute and primary course to revascularization in the absence of ongoing ischemia.

DeWood and colleagues,^{4,5} in Spokane, Washington, have been advocates of early operations after transmural AMI. Their conclusions were derived from a retrospective study of 440 patients with transmural AMI from 1971 to 1981. In that study it was reported that patients started on cardiopulmonary bypass within 6 hours of an AMI had significantly lowered short-term and long-term mortality. Although these results were impressive, the majority of these patients only had 1- or 2-vessel disease, and the mean age of the patients was only 54 years. Their study suggested that surgical revascularization might be performed with an acceptable mortality in the presence of AMI with improved myocardial protection, anesthesia, and surgical techniques.

TABLE 1. Potential risk factors analyzed

Age	Reoperation (1 previous heart operation)
Female sex	Reoperation (2 or more previous operations)
Shock	No thrombolytic therapy
Ejection fraction <30%	Calcified aorta
CCS functional class I	Hypertension
CCS functional class II	Hepatic failure
CCS functional class III	Femoral/popliteal disease
CCS functional class IV	Body surface area
Congestive heart failure	Height
Chronic obstructive pulmonary disease	Weight
Renal failure	Intra-aortic balloon pump implanted preoperatively
CABG <6 h after MI	PTCA before admission
CABG 6-23 h after MI	Left ventricular hypertrophy on ECG
CABG 1-3 d after MI	Immune system deficiency
CABG 4-7 d after MI	Emergency operation after diagnostic catheterization
CABG 8-14 d after MI	Emergency operation after PTCA
Urgent operation	PTCA this admission
Emergency operation	African American
Aortoiliac disease	Hispanic American
Hemodynamically unstable	Malignant ventricular arrhythmia
Intravenous nitroglycerin administered preoperatively	Diabetes requiring medication
Recent smoking history	

However, with the advent of thrombolytic therapy, percutaneous transluminal coronary angioplasty (PTCA), and an aged population, the surgical patient we encounter today bears little resemblance to the patient population represented in the Spokane data.

A more recent prospective randomized study of 302 patients from 1993 to 1998 by Hochman and colleagues^{23,24} showed improved survival in patients undergoing early revascularization after AMI complicated by cardiogenic shock. However, methods of revascularization in this study included either CABG or PTCA. Furthermore, the design of this trial would allow up to 54 hours after onset of AMI for either CABG or PTCA to be performed and still be considered early revascularization.

Many retrospective studies had been undertaken and resulted in a wide range of recommendations regarding the timing of operations and transmural AMI. Dawson and colleagues³ reviewed 1698 patients in the early 1970s and recommended a 30-day waiting period. In the 1980s, Gertler and coworkers¹⁵ studied 26 patients with transmural AMI and proposed a 12-day waiting period. In the 1990s, Deek and associates¹⁶ advocated a 7-day waiting strategy on the basis of comparison of 20 patients undergoing CABG with transmural AMI with patients without AMI. Finally, Braxton and associates⁸ found 48 hours after a transmural AMI to be an acceptable timing for CABG by looking at 58

TABLE 2. Multivariate analysis of risk factors in patients with transmural MI

Risk factor	P value	Odds ratio	95% CI	
			Lower	Upper
Age*	<.0001	1.557	1.447	1.678
Female sex	<.0001	1.466	1.275	1.687
Shock	<.0001	6.204	4.565	8.432
EF <30%	<.0001	1.420	1.221	1.652
CCS functional class IV	.0012	1.345	1.124	1.609
CHF	<.0001	1.630	1.408	1.887
COPD	.0016	1.276	1.097	1.484
Renal failure	<.0001	3.227	2.637	3.949
CABG <6 h after MI†	.0067	1.609	1.141	2.269
CABG 6-23 h after MI†	.0010	1.965	1.315	2.935
CABG 1-3 d after MI†	.0054	1.529	1.134	2.062
CABG 4-7 d after MI†	.7869	1.032	0.819	1.301
CABG 8-14 d after MI†	.5615	0.939	0.760	1.161
Urgent operation‡	.0064	1.315	1.080	1.602
Emergency operation‡	.0020	1.534	1.169	2.013
Aortoiliac disease	<.0001	1.516	1.254	1.835
Hemodynamically unstable	<.0001	2.263	1.846	2.773
Intravenous NTG preoperatively	.0071	1.243	1.061	1.457
Malignant ventricular arrhythmia	.0008	1.465	1.171	1.833
Diabetes requiring medication	<.0001	1.442	1.256	1.657
Reoperation (1 previous heart operation)	<.0001	3.024	2.527	3.618
Reoperation (2 or more previous operations)	.0001	3.180	1.756	5.758
No thrombolytic therapy	.0281	1.356	1.033	1.779
Calcified aorta	<.0001	1.567	1.300	1.888
Hepatic failure	.0255	3.112	1.150	8.427

Hosmer and Lemeshow goodness-of-fit test, $P = .07$. EF, Ejection fraction; CCS, Canadian Cardiovascular Society; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; NTG, nitroglycerin.

*For each additional 10 years of age.

†Compared with CABG greater than 15 days after transmural MI.

‡Compared with elective operations.

TABLE 3. Preoperative risks versus time between CABG and transmural MI

	<6 h (n = 564)	6-23 h (n = 333)	1-3 d (n = 946)	4-7 d (n = 3,021)	8-14 d (n = 4,118)	>15 d (n = 23,117)
Age >70 y	31.7%	33.3%	34.5%	34.0%	35.4%	36.5%
Female sex	27.8%	23.4%	25.9%	26.1%	26.6%	24.2%
Shock	29.6%	16.5%	6.5%	1.9%	0.7%	0.3%
Renal failure	2.5%	6.6%	4.0%	3.1%	3.2%	3.6%
Hemodynamically unstable	37.1%	31.2%	18.8%	9.0%	5.7%	3.1%
Reoperation (1 previous heart operation)	6.6%	6.3%	6.5%	5.2%	4.4%	9.0%
Reoperation (2 or more previous operations)	0.5%	0.3%	0.3%	0.3%	0.1%	0.6%
Hepatic failure	0.0%	0.6%	0.2%	0.1%	0.2%	0.1%

patients in the early 1990s. However, no one to date has reported a study on this topic with a contemporary patient population approximating the size of our patient population.

In this study we have shown that 3 days after a transmural AMI is a clear dividing line after which timing of surgical revascularization is no longer associated with mortality. Although the absolute mortality of CABG does not return to baseline until 7 days after the onset of transmural

AMI, surgical intervention after 3 days shows no trend toward statistical significance as a potential added risk. Statistically, the risk of mortality would be the same whether one waits 3 days or 7 days. Early surgical intervention has the advantage of limiting infarct expansion and adverse ventricular remodeling.²⁵ However, there is a potential risk of ischemia-reperfusion injury, which might lead to hemorrhagic infarct extension, resulting in additional myocardial injury.²⁶

It is unclear why surgical intervention within 3 days of transmural AMI might be an added risk for mortality. It has been reported that serum C-reactive protein (CRP), a marker of acute inflammatory response that increases precipitously after transmural AMI, plateaued on day 3 after the infarction. In addition, this peak level is a strong indicator of prognosis after a first transmural AMI.^{27,28} One might speculate that surgical revascularization within 3 days of an AMI, during the rising phase of CRP, might further augment such a systemic inflammatory response and affect prognosis because CABG is known to cause an increase in serum CRP level with or without cardiopulmonary bypass.²⁹

A multicenter retrospective study on the basis of a large database such as ours certainly has its weaknesses. Each individual surgeon and hospital likely used different protocols and standards relating to surgical techniques, cardiopulmonary bypass, and cardioplegic perfusion. Some might also question the accuracy of data entry. The New York State Department of Health performs periodic data audits to identify irregular reporting patterns to ensure data accuracy.³⁰ Furthermore, many of the important parameters, such as mortality rate, used in this study are objective variables and thus less susceptible to subjective interpretation.

In conclusion, this study revealed that CABG within 3 days of a transmural AMI might be an added risk for mortality. In the absence of absolute indications for emergency surgical intervention, such as structural complications and ongoing ischemia, a 3-day waiting period before CABG should be considered. There are important questions that remained to be answered, such as the role of thrombolytic therapy, early PTCA, and controlled surgical reperfusion in the management of transmural AMI. These questions require the cooperation of our cardiology colleagues in multi-institutional, prospective, randomized clinical trials.

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Discussion

Dr Robert Guyton (Atlanta, Ga). You have answered a question that has generally been answered before, although previous answers have not been as precise nor have they been so firmly based on such a large series. Indeed, 15 months ago, using a smaller portion of the same New York State database, your group

demonstrated that an operation within 24 hours of transmural infarction was an independent predictor, on the basis of multivariate analysis, of mortality for CABG. Today, with a larger series, you have extended that time to 3 days after transmural infarction as an independent predictor of mortality.

My first question is this. Because the mortality for CABG from days 3 to 7 is about 1.3 times the mortality subsequently, is it not feasible that an even larger database—for example, collecting this same data in a national series for 2 or 3 years—might show that an operation within 1 week might be an independent predictor of mortality because we have extended with your larger database from 1 year to the next from 1 day to 3 days? If that is the case and if we even have, as you point out, a 3% to 5% difference in mortality, 1.03, if it were significant, would mean that you have reduced the mortality by 3% by waiting that additional 4 days. Would it not be feasible to think about collecting that data or even at this time waiting the additional 4 days?

My second question is based on a concern that you have not addressed, the more difficult and more penetrating question that we all face. In a patient who begins to have angina or congestive failure or even hemodynamic instability after a transmural infarction in the first few days, when do we advocate medical therapy or even balloon pump insertion to postpone the operation rather than proceeding to the operating room? Can your data help us to answer these questions?

For example, a patient with shock after an AMI has a 60% to 70% mortality with medical therapy. On the basis of your data and other persons' data, the mortality is about 20% to 30% or less with good surgical therapy. Can you use your data to predict mortality

on the basis of multiple preoperative predictors at various times after transmural infarction and compare that with medical mortality so that we can make an evidence-based decision as to the risk and benefit of CABG early after infarction?

We know there is an increased risk of operation in the first few days compared with operation 2 weeks later. What we need to know is the relative risk of surgical therapy in the first few days in a particular patient compared with the medical risk in that same patient.

Dr Lee. Thank you, Dr Guyton. The paper we presented 15 months ago focused on contrasting the difference in the patterns of mortality with respect to timing of surgical intervention in transmural and nontransmural myocardial infarction. In that study the timing of the operation between 1 to 7 days after an AMI was grouped together, as guided by previous publications. With the size of the New York State Database, we were able to break up this subgroup for the first time to analyze mortality on a day-to-day basis and to obtain statistically significant results.

Since the submission of the initial abstract, we added 2 additional years of data and found no change in the conclusions. Statistically, it is unlikely that further extension of the database will produce different results because the *P* values and odds ratios for CABG after 3 days of a transmural AMI showed no trend toward statistical significance in the multivariate analysis.

In this study we addressed the question of when surgical revascularization can be performed safely after a transmural AMI. Surgical intervention after an AMI complicated by congestive heart failure or cardiogenic shock represents a different patient population. We are currently working on the latter question.

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