SURGERY FOR ACQUIRED HEART DISEASE

PREDICTORS OF LOW CARDIAC OUTPUT SYNDROME AFTER CORONARY ARTERY BYPASS

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The purpose of this study was to identify patients at risk for the development of low cardiac output syndrome after coronary artery bypass. Low cardiac output syndrome was defined as the need for postoperative intraaortic balloon pump or inotropic support for longer than 30 minutes in the intensive care unit to maintain the systolic blood pressure greater than 90 mm Hg and the cardiac index greater than 2.2 L/min per square meter. The preoperative patient characteristics that were independent predictors of low cardiac output syndrome were identified among 4558 consecutive patients who underwent isolated coronary artery bypass at The Toronto Hospital between July 1, 1990, and December 31, 1993. The overall prevalence of low cardiac output syndrome was 9.1% ($n = 412$). The operative mortality rate was higher in patients in whom low cardiac output syndrome developed than in those in whom it did not develop (16.9% versus 0.9%, $p < 0.001$). Stepwise logistic regression analyses identified nine independent predictors of low output syndrome (percent frequency in parentheses) and calculated the factor-adjusted odds ratios associated with each predictor: (1) left ventricular ejection fraction less than 20% (27%, odds ratio 5.7); (2) repeat operation (25%, odds ratio 4.4); (3) emergency operation (27%, odds ratio 3.7); (4) female gender (16%, odds ratio 2.5); (5) diabetes (13%, odds ratio 1.6); (6) age older than 70 years (13%, odds ratio 1.5); (7) left main coronary artery stenosis (12%, odds ratio 1.4); (8) recent myocardial infarction (16%, odds ratio 1.4); and (9) triple-vessel disease (10%, odds ratio 1.3). Low cardiac output syndrome is a clinical outcome that may result from inadequate myocardial protection or perioperative ischemic injury. Patients at high risk for the development of low cardiac output syndrome should be the focus of trials of new techniques of myocardial protection to resuscitate the ischemic myocardium. (*J Thorac Cardiovasc Surg* 1996;112:38-51)

The contemporary results of coronary artery bypass grafting are excellent. A recent review from our institution indicated that despite an increased frequency of high-risk patients, operative mortality

did not change.¹ Since that publication in 1989, the operative mortality rate after isolated coronary artery bypass grafting at The Toronto Hospital has decreased to 2.4%; however, in higher risk groups the operative mortality rate is still two to four times greater. This study was intended to identify the independent predictors of low cardiac output syndrome. We defined low cardiac output syndrome as the requirement for intraaortic balloon counterpulsation or inotropic support for longer than 30 minutes after the patient was returned to the intensive care unit to maintain the systolic blood pressure higher than 90 mm Hg and the cardiac index greater than 2.2 L/min per square meter.

The development of low cardiac output syndrome

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may represent a failure of myocardial protection or difficulty with bypass grafting and is often associated with a higher mortality and prolonged hospital stay. A recent randomized clinical trial done at the University of Toronto by The Warm Heart Investigators showed no difference in operative mortality or perioperative myocardial infarction (MI) between patients who received warm blood or cold blood cardioplegic solution.² However, the occurrence of low cardiac output syndrome was significantly lower in the warm group. Similarly, a large clinical trial that evaluated acadesine as a myocardial protective agent failed to show any difference in the prevalence of perioperative infarction except in a subgroup of patients with high-risk conditions.³ Because of the low rates of operative mortality and perioperative MI, studies aimed at developing improved strategies of myocardial protection are unlikely to show a benefit unless they include a large number of patients or limit their focus to subgroups of patients at high risk. Both operative mortality and a new perioperative MI occur infrequently and these outcome measures are difficult to use in a trial of alternate myocardial protective strategies even in patients at high risk.

Low cardiac output syndrome is a more frequent event and may be modified by improved methods of myocardial protection in high-risk subgroups. However, the syndrome must be carefully defined and its pathophysiologic components may be better understood by assessment of the predisposing risk factors. To make comparisons between studies, the definition of low cardiac output syndrome must become standardized. This study presents the independent preoperative risk factors for the development of low cardiac output syndrome in 4558 consecutive patients undergoing isolated coronary artery bypass grafting at The Toronto Hospital.

Methods

Patient population. Preoperative, perioperative, and postoperative data were collected prospectively on all patients undergoing isolated coronary artery bypass grafting between July 1, 1990, and December 31, 1993, at The Toronto Hospital. The preoperative characteristics of the 4558 consecutive patients are shown in Table I.

Operative technique. After median sternotomy and heparinization, cardiopulmonary bypass was established with a single two-stage right atrial cannula and an ascending aortic cannula. During bypass, the hematocrit was maintained between 20% and 25%, pump flow rates between 2.0 and 2.5 L/min per square meter, and mean arterial pressures between 50 and 60 mm Hg by use of sodium nitroprusside or phenylephrine hydrochloride as required. In elderly patients or in patients with carotid

Table I. Patient population

	N	%
N	4558	
Sex		
Male	3673	81
Female	885	19
Age (yr)	61.5 ± 9.6	
Timing		
Elective	2620	57
Semielective	1130	25
Urgent	657	14
Emergency	151	4
Recent MI	692	15
LVEF		
>60%	1530	34
40%–60%	1926	42
20%–40%	956	21
<20%	146	3
NYHA class		
I	76	2
II	654	14
III	1861	41
IV	1967	43
CAD		
1 vessel	308	7
2 vessel	1083	24
3 vessel	3159	69
Left main CAD	808	18
Repeat operation	335	7
Diabetes	1086	24
Hypertension	2337	51
PVD	591	13

LVEF, Left ventricular ejection fraction; NYHA, New York Heart Association; CAD, coronary artery disease; PVD, Peripheral vascular disease.

artery stenoses, the mean arterial pressure was maintained higher than 70 mm Hg in an attempt to improve cerebral perfusion. Blood cardioplegic solutions were delivered after oxygenated blood from the bypass circuit was mixed with a crystalloid solution in a 4:1 ratio. Blood cardioplegic solution was administered either in an antegrade fashion via the aortic root or in a retrograde fashion via the coronary sinus.

In all patients, the heart was arrested with an aortic root infusion of high potassium (27 mEq/L) blood cardioplegic solution. Cardioplegia was maintained with a low potassium formulation (15 mEq/L). Proximal and distal anastomoses were constructed during a single prolonged cross-clamp period.⁴ A left internal thoracic artery graft was used in 3789 (83%) patients. Cardiac output was measured with a thermodilution catheter placed percutaneously via the internal jugular vein into the pulmonary artery.⁵

Patients in whom weaning from cardiopulmonary bypass was difficult or in whom inadequate cardiac performance developed in the intensive care unit had an intraaortic balloon pump (Datascope Corporation, Paramus, N.J.) inserted percutaneously via the common femoral artery. Patients with less severe hemodynamic compromise received inotropic medication.

Study design. This study represents a retrospective analysis on data gathered in a prospective fashion and included in a database registry. Multivariable analyses were used to determine the independent predictors of outcomes. Comparisons of baseline, operative, and postoperative data were made between patients in whom the outcome of interest occurred and patients in whom it did not.

Definitions of variables. Appendix A gives a definition of all preoperative variables.

Study outcomes. Low cardiac output syndrome was diagnosed if the patient required an intraaortic balloon pump either in the operating room or in the intensive care unit because of hemodynamic compromise. Patients who had a balloon pump inserted preoperatively because of either ischemic chest pain or hemodynamic dysfunction were believed to have a postoperative low cardiac output syndrome if, in addition to the balloon pump, they also required inotropic medication. Low cardiac output syndrome was also diagnosed if the patient required inotropic medication to maintain the systolic blood pressure greater than 90 mm Hg and the cardiac output greater than 2.2 L/min per square meter for at least 30 minutes in the intensive care unit after correction of all electrolyte or blood gas abnormalities and after adjusting the preload to its optimal value.⁶ Afterload reduction was also attempted when possible. Patients received either dopamine hydrochloride, dobutamine hydrochloride, amrinone, or epinephrine. We believe that prolonged treatment with inotropic medication may augment perioperative ischemic injury.^{7,8} Therefore inotropic medication was avoided when possible and was used only in patients who had mild and transient hemodynamic compromise. An intraaortic balloon pump was inserted in patients who had moderate or severe hemodynamic compromise. Patients who received less than 4 μ g/kg of dopamine to increase renal perfusion were not considered to have low cardiac output syndrome. Patients who received vasoconstricting medication because of a high cardiac output (≥ 2.5 L/min per square meter) and low peripheral resistance were not considered to have low cardiac output syndrome.

Operative mortality and MI. Operative mortality was defined as any death that occurred within 30 days of operation or during the same hospital admission. A perioperative MI was documented when a new Q wave was found on the postoperative electrocardiogram. An MI was also diagnosed if the postoperative electrocardiogram had a new left bundle branch block, loss of R wave progression, or new ST and T wave changes if accompanied by a rise in the level of the MB isoenzyme of creatine kinase (CK-MB) greater than 50 U/L and if the CK-MB/CK ratio was greater than 5%. An antibody inhibition technique was used to measure the CK-MB level. The highest postoperative CK-MB value was recorded and expressed as a fraction of total CK if a perioperative ischemic event was suspected clinically. This definition of perioperative MI requires electrocardiographic changes and therefore may underestimate this outcome.

Statistical analysis. Statistical analysis was done with the SAS program (SAS Institute, Cary, N.C.). Categorical data were analyzed by a χ^2 or Fisher's exact test where appropriate. Continuous data were analyzed by two-tailed

t tests. Logistic models for each outcome variable were constructed with the use of methods described by Hosmer and Lemeshow.⁹ Each prognostic variable was carefully evaluated by the appropriate univariate test. Variables were selected for inclusion in a multivariable model if their univariate *p* value was less than 0.25 or if the variable was of known clinical importance but failed, univariately, to achieve the critical alpha level.

Models were fit and the best model for each outcome variable was determined by (1) an examination of the Wald statistic for each variable⁹ and (2) a comparison of each estimated coefficient with the coefficient from the univariate model that contained only that variable. Coefficients that changed markedly in magnitude indicated that one or more of the excluded variables were important in the adjustment of the effect of the remaining variables in the model and an effort was made to refit the model.⁷

The next step in determining the best multivariable model was to examine the goodness-of-fit statistic. Goodness of fit assessed the effectiveness of the model in describing the outcome variable. In addition, differences between the observed data and the estimated values (the residual) for each covariate pattern were calculated by the Pearson or Hosmer-Lemeshow χ^2 statistic.⁹ The null hypothesis for goodness of fit claims that there are no significant differences between the predicted outcomes and the observed data. Therefore a probability greater than 0.05 indicates acceptance of the null hypothesis and a valid model.

The final approach to determining the best model for each outcome variable was to examine the receiver operator characteristic (ROC) curve for each model. ROC curves are usually used to evaluate and compare an operator or diagnostic test with a "gold standard" and to explore the trade-offs between sensitivity and specificity for a test.^{10,11} Tests that discriminate well will crowd the curve toward the upper left corner. The overall accuracy of a test can be described as the area under the curve; increasing the area under the curve corresponds to a better test because it optimizes the sensitivity and specificity.^{12,13} When calculated in the BMDP LR program (BMDP Statistical Software Inc., Los Angeles, Calif.),¹¹ the ROC curve is independent of both the cut-point criteria (predicted probabilities) and the prevalence of the outcomes. This independence allows comparison of the ROC area of different study populations where sensitivity and specificity would be distorted by differences in the prevalence of the outcomes of interest. Therefore we used these curves to provide an additional "diagnostic" tool to determine the optimum model for our binary outcome variables.

The internal validity of the model was assessed by use of a bootstrap method in which the regression coefficients for the entire data set were correlated with the regression coefficients of a test data set. The test data set was derived as a subpopulation of the entire data set.

Results

The preoperative characteristics of the entire patient population are listed in Table I. The overall mortality rate was 2.4% (*n* = 109). Low cardiac

output syndrome developed in 412 patients (9.1%). Table II compares the operative data for patients in whom low cardiac output syndrome developed with data for those patients in whom it did not. Patients in whom low cardiac output syndrome developed were older (64 versus 61 years, $p < 0.001$) and had more extensive coronary artery disease ($p < 0.001$). There were no significant differences in the number of bypass grafts constructed between the two groups. Complete revascularization was accomplished in 4193 (92%) patients. The operative mortality rate in patients in whom complete revascularization was achieved was 2.3% compared with 3.9% in patients in whom revascularization was not complete ($p = 0.068$). The prevalence of low cardiac output syndrome was 8.1% in patients in whom revascularization was complete versus 14.6% in patients in whom it was not ($p < 0.001$).

The left anterior descending artery (LAD) territory was revascularized in 99.6% of the patients with LAD disease. Similarly, the territories of the circumflex and right coronary arteries were revascularized in 96.2% and 94.7% of the respective patients with disease in those territories.

Patients in whom low cardiac output syndrome developed had longer cardiopulmonary bypass times, longer aortic crossclamp times, a longer postoperative intensive care unit stay, more days of ventilatory support, a longer hospital stay, and a higher postoperative CKMB level. Patients in whom low cardiac output syndrome developed had a higher mortality rate (17%) than patients in whom it did not develop (1%, $p < 0.001$). Patients in whom low cardiac output syndrome developed were more likely to have a perioperative MI (14.3% versus 1.8%, $p < 0.001$).

Predictors of low cardiac output syndrome. Figs. 1 and 2 and Table III illustrate the univariate results for the multivariable predictors of low cardiac output syndrome. Stepwise logistic regression analyses identified nine independent predictors of postoperative low cardiac output syndrome (percentage in whom low cardiac output syndrome developed in parentheses) and the factor-adjusted odds ratio (OR) associated with each predictor: (1) left ventricular ejection fraction less than 20% (27%, OR 5.7); (2) repeat operation (25%, OR 4.4); (3) emergency operation (27%, OR 3.7); (4) female gender (16%, OR 2.5); (5) diabetes (13%, OR 1.6); (6) age older than 70 years (13%, OR 1.5); (7) left main coronary artery disease (12%, OR 1.4); (8) recent MI (16%, OR 1.4); and (9) triple-vessel disease

Table II. Operative data

	No LOS	LOS	<i>p</i> Value
No. of patients	4146 (91%)	412 (9%)	
Age (yr)	61.3 ± 9.6	63.6 ± 9.6	<0.001
Diseased vessels			
1	286 (7%)	22 (5%)	0.0012
2	1011 (24%)	72 (18%)	
3	2844 (69%)	315 (77%)	
Grafts			
1	72 (2%)	10 (2%)	0.660
2	482 (12%)	51 (12%)	
3	1440 (35%)	138 (33%)	
4	1778 (43%)	177 (43%)	
5	374 (9%)	36 (9%)	
Pump time (min)	85 ± 24	110 ± 39	<0.001
Crossclamp time (min)	60 ± 18	67 ± 27	<0.001
Days of ventilator support	1.1 ± 2.5	2.9 ± 5.0	<0.001
Days in ICU	2.2 ± 3.3	5.0 ± 6.3	<0.001
Days in hospital	9.9 ± 9.2	13.8 ± 12.4	<0.001
CK (units)	897 ± 769	1429 ± 1309	<0.001
CK-MB (units)	41 ± 37	83 ± 102	<0.001
Percent CK-MB	5.9 ± 9.9	6.7 ± 6.4	<0.001
Periop. MI	74 (1.8%)	59 (14.3%)	<0.001
Stroke	47 (1.1%)	14 (3.4%)	<0.001
Mortality	39 (0.9%)	70 (16.9%)	<0.001

LOS, Low cardiac output syndrome; ICU, intensive care unit.

(10%, OR 1.3). Table IV presents the regression coefficients, their standard errors derived from the logistic regression analysis, the ORs, the 95% confidence intervals (95% CIs) for the ORs, the improvement χ^2 p value, and the goodness-of-fit p value for the nine independent predictors. The predictive probability of the development of low cardiac output syndrome can be calculated by the formula $P = e^x / (1 + e^x)$, where x is the sum of the regression coefficients (see Appendix B). Fig. 3 depicts the predicted probability of low cardiac output syndrome (abscissa) versus the logit score (ordinate) for several combinations of covariate patterns for low cardiac output syndrome. This figure can be used to determine the probability of low cardiac output syndrome for an individual patient.

There were 133 patients (2.9%) who had a perioperative MI. The operative mortality rate was 21.8% in this group of patients compared with 1.8% in patients who did not have an infarct. Patients with low cardiac output syndrome had a significantly higher prevalence of perioperative MI (14.3% versus 1.8%, $p < 0.001$). Conversely, patients who had a perioperative MI had a 44% prevalence of low

Fig. 1. Univariate results of multivariable predictors of low cardiac output syndrome (LOS) and operative mortality (OM). Left ventricular grade (LV GRADE) designated by 1, ejection fraction 60%; 2, ejection fraction 40% to 59%; 3, ejection fraction 21% to 39%; or 4, ejection fraction 20%. Repeat operation (REDO), that is, previous aorta-coronary bypass, noted as yes (Y) or no (N). Timing of operation designated by 1, elective operation; 2, operation during same hospitalization as cardiac catheterization or cardiac event (semielective); or 3, urgent operation within 72 hours of cardiac event. Gender noted as male (M) or female (F). Diabetes; age younger than 70 years; and left main coronary artery disease (LEFT MAIN), that is, significant (greater than 50%) stenosis of left main coronary artery, noted as yes or no.

Fig. 2. Univariate results of multivariable predictors of low cardiac output syndrome (LOS) and operative mortality (OM). Recent MI, that is, MI within 30 days before operation; triple-vessel disease; and hypertension noted as yes (Y) or no (N).

cardiac output syndrome compared with 8% in patients who did not have an infarct.

Operative mortality. There were 109 operative deaths in this population. Among patients in whom low cardiac output syndrome developed ($n = 412$) there were 70 deaths (17%) compared with 39 deaths (9.5%) in those in whom low cardiac output syndrome did not develop ($n = 414$). The mean postoperative length of stay for patients who died after the development of low cardiac output syndrome was 7.4 ± 11.3 days (median 3.5 days, range 0 to 53 days). The mean postoperative length of stay for patients who died without having the development of low cardiac output syndrome was 23.1 ± 26.6 days (median 12.5 days, range 0 to 84 days).

The operative mortality rate was significantly higher by univariate analysis in patients with a left ventricular ejection fraction less than 20% (10.9% versus 1.2% with left ventricular ejection fraction greater than 60%, $p < 0.001$); in patients undergoing repeat operation (7.5% versus 2.0%, $p < 0.001$); in patients with peripheral vascular disease (6.6% versus 1.8%, $p < 0.001$); in patients older than age 70 (5.0% versus 1.1% in patients younger than age 50, $p < 0.001$); in patients undergoing emergency operation (6.6% versus 1.7% in elective operation,

$p < 0.001$); in patients with diabetes (3.8% versus 2.0%, $p = 0.001$); in female patients (3.8% versus 2.0%, $p = 0.002$); in patients with left main coronary artery disease (3.6% versus 2.1%, $p = 0.014$); in patients with hypertension (3.0% versus 1.8%, $p = 0.006$); in patients who had an MI less than 30 days before operation (4.0% versus 2.1%, $p = 0.002$); in patients with chronic obstructive pulmonary disease (3.4% versus 2.2%, $p = 0.036$); and in patients with New York Heart Association class IV disease (3.6% versus 1.3% in New York Heart Association class I, $p = 0.002$).

The multivariable predictors of operative mortality were (1) left ventricular ejection fraction less than 20% (OR 8.1); (2) repeat operation (OR 4.9); (3) peripheral vascular disease (OR 2.8); (4) age older than 70 (OR 2.8); (5) emergency operation (OR 2.7); (6) diabetes (OR 1.7); (7) female gender (OR 1.7); (8) left main coronary artery stenosis (OR 1.5); and (9) hypertension (OR 1.4). Table V presents the regression coefficients, their standard errors derived from the logistic regression analysis, the ORs, the 95% CIs for the ORs, the improvement χ^2 p value, and the goodness-of-fit p value for the nine independent predictors. The 95% CIs for left main coronary artery stenosis and hypertension both in-

Table III. Univariate analysis for low cardiac output syndrome and operative mortality

	LOS		No LOS		P Value (LOS)	Mortality		p Value (OM)
	N	%	N	%		N	%	
No. of patients	412	9	4146	91				
LVEF								
>60%	87	6	1443	94	<0.001	19	1	<0.001
40%-60%	146	8	1780	92		44	2	
20%-40%	139	15	817	85		30	3	
<20%	40	27	106	73		16	11	
Repeat operation	82	25	253	75	<0.001	25	8	<0.001
No Repeat	330	8	3893	92		84	2	
Timing					<0.001			<0.001
Elective	169	6	2451	94		45	2	
Semielective	112	10	1018	90		35	3	
Urgent	90	14	567	86		19	3	
Emergency	41	27	110	73		10	7	
Sex								
Male	271	7	3402	93	<0.001	75	2	0.002
Female	141	16	744	84		34	4	
Diabetes	137	13	949	87	<0.001	41	4	0.001
No diabetes	275	8	3197	92		68	2	
Age								
<70	283	8	3261	92	<0.001	58	2	<0.001
≥70	129	13	885	87		51	5	
Left main CAD								
Y	94	12	714	88	0.005	29	4	0.014
N	318	9	3432	91		80	2	
Recent MI								
Y	112	16	580	84	<0.001	28	4	0.002
N	300	8	3566	92		81	2	
Triple-vessel CAD								
Y	315	10	2759	90	0.002	80	3	0.651
N	94	7	1391	93		29	2	
Hypertension	230	10	2107	90	0.053	70	3	0.006
No hypertension	182	8	2039	92		39	2	

LOS, Low cardiac output syndrome; OM, operative mortality; LVEF, left ventricular ejection fraction; Y, yes; N, no; recent MI, MI within 30 days before operation; CAD, coronary artery disease.

Table IV. Multivariable analysis for low cardiac output syndrome

Variable	Regression coefficient	SE	OR	95% CI	Improvement χ^2 p value	GOF p value
Constant	-3.866	0.166				
LVEF						
40%-60%	0.1777	0.146	1.19	0.89-1.59		
20%-40%	0.8614	0.153	2.37	1.75-3.19		
<20%	1.7410	0.232	5.70	3.62-8.99	<0.001	0.031
Repeat operation	1.4770	0.151	4.38	3.26-5.89	<0.001	0.277
Timing of operation						
Urgent	0.2451	0.128	1.28	0.99-1.64		
Emergency	1.3120	0.237	3.72	2.34-5.91	<0.001	0.966
Female gender	0.9287	0.122	2.53	1.99-3.22	<0.001	0.825
Diabetes	0.4644	0.119	1.59	1.26-2.01	<0.001	0.983
AGE ≥70	0.3691	0.122	1.45	1.14-1.84	0.001	0.990
Left main CAD	0.3500	0.133	1.42	1.09-1.84	0.011	0.993
Recent MI	0.3241	0.148	1.38	1.04-1.85	0.023	0.994
Triple-vessel disease	0.2841	0.130	1.33	1.03-1.71	0.026	0.996

SE, Standard error; GOF, goodness of fit; LVEF, left ventricular ejection fraction; CAD, coronary artery disease; Recent MI, MI within 30 days before operation.

Fig. 3. Predictive probability of low cardiac output syndrome after coronary artery bypass grafting. Left ventricular grade (*LV GRADE*) scored from 1 to 4. Repeat aorta-coronary bypass (*ACB REDO*), diabetes, age older than 70 years, left main coronary artery disease (*L MAIN DISEASE*), recent MI, and triple-vessel disease (*TVD*) scored 0 for no, 1 for yes. *M*, Male; *F*, female; *E*, elective; *S*, semielective; *U*, urgent.

Table V. Multivariable analysis for operative mortality

Variable	Regression coefficient	SE	OR	95% CI	Improvement χ^2 p value	GOF p value
Constant	-5.760	0.316				
PVD	1.0330	0.215	2.81	1.84-4.28	<0.001	1.000
LVEF						
40%-60%	0.4847	0.284	1.62	0.93-2.83		
20%-40%	0.7036	0.306	2.02	1.11-3.68		
<20%	2.0920	0.371	8.10	3.91-16.80	<0.001	0.448
Repeat operation	1.5810	0.251	4.86	2.97-7.95	<0.001	0.357
Age ≥70	1.0250	0.208	2.79	1.85-4.19	<0.001	0.439
Female gender	0.5178	0.227	1.68	1.08-2.62	0.004	0.214
Diabetes	0.5560	0.212	1.74	1.15-2.64	0.009	0.637
Timing of operation						
Urgent	0.1317	0.217	1.14	0.75-1.75		
Emergency	0.9907	0.390	2.69	1.25-5.79	0.039	0.230
Left main CAD	0.4341	0.232	1.54	0.98-2.43	0.059	0.660
Hypertension	0.3542	0.212	1.43	0.94-2.16	0.091	0.682

SE, Standard error; GOF, goodness of fit; PVD, peripheral vascular disease; LVEF, left ventricular ejection fraction; CAD, coronary artery disease.

clude unity, which indicates that they are weak predictors of operative mortality.

Fig. 4 illustrates the predicted operative mortality for all combinations of the nine independent predictors. Fig. 5 depicts the ROC curves for both low cardiac output syndrome and operative mortality.

The area under the ROC curve for low cardiac output syndrome is similar to that for operative mortality (74% versus 76%), which indicates that both models are similar in terms of their sensitivity and specificity to detect their respective outcomes.

Fig. 4. Predictive probability of operative mortality after coronary artery bypass grafting. Peripheral vascular disease (*PVD*), repeat aorto-coronary bypass (*ACB REDO*), age older than 70 years, diabetes, left main coronary artery disease (*L MAIN DISEASE*), and hypertension scored 0 for no, 1 for yes. Left ventricular grade (*LV GRADE*) scored from 1 to 4. *M*, Male; *F*, female; *E*, elective; *S*, semielective; *U*, urgent.

Discussion

An increasing number of patients with high-risk conditions are undergoing coronary artery bypass grafting.¹ The extension of cardiac operation to patients at higher risk is a result of improved operative techniques and perioperative myocardial protection. Cardiologists and surgeons have extended the benefits of coronary artery bypass to patients at higher risk as the risks of operation have decreased.¹⁴ To continue to reduce perioperative morbidity and mortality, cardiac surgeons must devise strategies to improve myocardial protection in patients at high risk.

Traditionally, the results of coronary artery bypass have been evaluated by operative mortality and perioperative MI.¹⁴⁻¹⁶ Low cardiac output syndrome is another clinical outcome that can be used to assess the efficacy of perioperative myocardial protection. Two large randomized clinical trials failed to show any difference in perioperative mortality or MI between the treatment groups.^{2,3} The low rates of operative mortality and the problems inherent in uniformly defining and identifying perioperative infarction have made the use of these outcome mea-

sures impractical in modern studies of myocardial protection.

For example, to detect a 20% reduction in the operative mortality rate from 2% to 1.6%, one would need to study 8504 patients to achieve a 5% level of significance with a power of 80%. To detect a 20% reduction in the prevalence of perioperative MI from 3% to 2.4%, one would require 5618 patients. A similar 20% decrease in the prevalence of low cardiac output syndrome from 10% to 8% would require 1577 patients to achieve a 5% level of significance. Patients in whom low cardiac output syndrome develop have a significantly higher prevalence of perioperative MI and a higher operative mortality. Thus the development of low cardiac output syndrome represents either inadequate revascularization or inadequate myocardial protection and may act as a marker of intraoperative myocardial injury. Our results indicate that the territory supplied by the LAD was revascularized in more than 99% of patients with disease in that distribution. Revascularization was incomplete in the territory of the right coronary artery in 5% of the patients with right coronary artery disease. These

Fig. 5. ROC curves of predictive models for low cardiac output syndrome (*left*) and operative mortality (*right*).

patients likely represent a subpopulation with a previous inferior MI and an occluded coronary artery. Despite having preserved left ventricular function, these patients were still at risk for the development of postoperative low cardiac output syndrome.

Diagnosis. A diagnosis of low cardiac output syndrome required the active intervention of the cardiac surgeon, and at our institution this intervention represented a failure of our usual perioperative strategy. Thus the diagnosis of low cardiac output syndrome was a reproducible clinical outcome. The Warm Heart Investigators established an independent committee to evaluate postoperative low cardiac output syndrome.² Their criteria for diagnosis were similar to ours and again support the concept that this syndrome can be used as an objective measurement of perioperative myocardial injury.

This study identified nine independent preoperative predictors of low cardiac output syndrome after coronary artery bypass grafting (Figs. 1 and 2). The potential causes for inadequate postoperative cardiac performance are not well established.

Poor ventricular function. Poor left ventricular function continues to be the most important predictor of postoperative morbidity and mortality. Patients with poor ventricular function have a limited margin for myocardial protection.¹⁶ However, the dysfunctional myocardium may not be irreversibly damaged and may be "stunned" or "hibernating." Revascularization of the reversibly injured heart may result in improved left ventricular performance. Cold injury or inhomogeneous cardioplegic delivery may exacerbate perioperative ischemic injury and result in inadequate early postoperative ventricular function.¹⁷ Prolonged reperfusion with a terminal "hot shot" of cardioplegic solution may restore function in patients with poor ventricular function.¹⁸ Warm cardioplegia may improve postoperative left ventricular function in patients with high-risk conditions, inasmuch as we have previously shown that warm cardioplegia improves ventricular function in patients at low risk undergoing elective operations.¹⁷ Unfortunately, some patients will continue to have poor ventricular function after operation and the role of myocardial protection in these

patients may be to limit the extent of perioperative injury.

Reoperation. Patients undergoing repeat operations represent a challenge for intraoperative management. Patients undergoing reoperation have more diffuse disease and are at risk of having a shower of emboli from their previous bypass grafts. The management of patent grafts is difficult. The study by Lytle and associates¹⁹ from the Cleveland Clinic revealed that the operative mortality rate in patients undergoing repeat coronary artery bypass was 4.3%. They found that patients with stenoses in vein grafts to the LAD region had decreased survival. However, there were no in-hospital deaths among patients with totally occluded vein grafts or patent internal thoracic artery grafts to the LAD region. The authors speculated that the retrograde introduction of cardioplegic solution significantly lowered the operative mortality rate of repeat operation as a direct consequence of reducing atherosclerotic emboli from previous vein grafts.¹⁹

Urgent operation. Patients who require urgent operation because of unstable angina may benefit most from improved strategies of myocardial protection. Prolonged preoperative ischemia may deplete metabolic reserves. Substrate enhancement with Krebs cycle intermediates^{20, 21} may benefit these patients. Rousou and associates²¹ showed that cardioplegic enhancement with Krebs cycle intermediates such as glutamate, malate, succinate, and fumarate preserved high-energy phosphates during ischemic arrest but that this preservation did not extend to the reperfusion period. To date the effectiveness of substrate-enhanced cardioplegia remains controversial. The use of warm rather than cold cardioplegia may help to resuscitate the ischemic myocardium. Cold cardioplegia reduces myocardial oxygen consumption and lactate production, but delays the recovery of oxidative metabolism and ventricular function. Cold cardioplegia has the advantage of improved protection to areas that are difficult to perfuse because of coronary obstructions. Warm cardioplegia may resuscitate the ischemic myocardium if it can be delivered uniformly and continuously. Discontinuation of normothermic blood cardioplegic solution delivery to permit visualization of the distal anastomosis may result in ischemic anaerobic metabolism. Perhaps the ideal cardioplegic temperature lies between the two extremes. We have recently reported the use of "tepid" (29° C) cardioplegia.²² Tepid cardioplegia reduced lactate and acid production compared with

warm (37° C) cardioplegia and improved left ventricular function compared with cold (10° C) blood cardioplegia.²²

Female gender. The Coronary Artery Surgery Study investigators reported female gender to be associated with higher perioperative morbidity and mortality.¹⁵ The authors postulated that this increased morbidity was a result of the smaller size of the coronary vessels and the higher risk of graft thrombosis. A recent review from our institution^{22a} revealed that female patients had a higher prevalence of operative mortality and postoperative low cardiac output syndrome. The predictors of operative mortality and postoperative low cardiac output syndrome were similar for both men and women. Small body size was an independent risk factor for postoperative morbidity. In patients of similar body size, female gender was an independent risk factor for low cardiac output syndrome and operative mortality.

Diabetes mellitus. Patients with diabetes may have more diffuse atherosclerotic disease, which may limit complete revascularization. In addition, patients with diabetes may have silent ischemia and be seen for operation after extensive MI or may have diffuse coronary artery disease. Cardioplegic protection may pose a problem in patients with diffuse coronary disease. Proximal coronary lesions may impair antegrade delivery of cardioplegic solution and venovenous and thebesian shunting may reduce the retrograde delivery of cardioplegic solution. Homogeneous distribution of cardioplegic solution may improve intraoperative myocardial protection in these patients. A recent study by Hayashida and associates²³ showed that a combination of antegrade and retrograde cardioplegic solution delivery may provide the best protection by improving the distribution of cardioplegic solution. Intermittent antegrade infusions after each period of continuous retrograde cardioplegic solution delivery resulted in the washout of accumulated lactate. This finding suggested that the two directions of cardioplegic solution delivery perfuse different myocardial territories. Combining the two techniques may result in a more homogeneous distribution of cardioplegic solution.

Advanced age. Elderly patients continue to be at high risk for postoperative complications (Fig. 2). At our institution an increasing proportion of patients older than age 70 are presenting for surgical treatment, but the prevalences of perioperative infarction and operative mortality have decreased during

the past decade.²⁴ The elderly are at increased risk not only because of the obvious effects of aging but also because of the increased prevalence of comorbid conditions in this population. Misare, Krukenkamp, and Levitsky²⁵ showed an age-dependent sensitivity to myocardial ischemia in an ovine model. These authors termed this phenomenon the *senescent myocardium*. Thus, independent of other comorbid conditions, elderly patients may be at increased risk for perioperative myocardial injury because of their senescent myocardium.

Left main coronary artery disease. The presence of left main coronary artery disease is no longer as important a predictor of operative mortality as it was previously.¹ Although left main stenosis was selected as an independent predictor of operative mortality, the confidence interval for the OR includes one, which indicates that left main disease may not be a major predictor of operative mortality. However, in this study, left main coronary artery disease was still an independent risk factor for the development of low cardiac output syndrome. Improvements in myocardial protection may have compensated for the increased risk in left main coronary artery disease. The use of retrograde or combination cardioplegic techniques may further reduce the importance of left main disease on the outcome of low cardiac output syndrome.

Recent MI and triple-vessel disease. Patients with an MI within 30 days of operation were at slightly higher risk for the development of low cardiac output syndrome. Similarly, patients with triple-vessel disease were at higher risk for the development of low cardiac output syndrome. Although both of these risk factors were selected as independent risk factors for the development of low cardiac output syndrome, the confidence interval of their ORs approached one. Thus, although statistically significant, these risk factors are weak predictors of low cardiac output syndrome.

Hypertension and peripheral vascular disease. Hypertension and peripheral vascular disease were independent predictors of mortality but not of low cardiac output syndrome. These risk factors predispose patients to stroke and mortality may have been a result of noncardiac causes. Therefore these variables did not predict postoperative low cardiac output syndrome. Strategies to minimize the impact of these variables include improved management of perioperative blood pressure and minimal manipulation of the aorta during operation. The use of intraoperative ultra-

sonography to detect atherosclerotic plaques to aid aortic cannulation has been advocated by Barzilai and colleagues.²⁶

Models. Fig. 3 illustrates the predictive probability of the development of low cardiac output syndrome on the basis of data from our patient population. Fig. 4 illustrates the predictive probability of operative mortality after aorta-coronary bypass.

Greenland²⁷ concluded that both stratified (populations stratified on the basis of risk) and modeling (predictive models derived from multivariable analyses) techniques to analyze populations have limitations based on the control of variable selection and the size and quality of data sets. Neither approach can compensate for fundamental methodologic errors such as misclassifications, selection bias, or lack of statistical power to address the questions of interest. Greenland²⁷ therefore concluded that more effort should be put into correctly interpreting and intelligibly presenting modeling results to reflect these underlying errors. An evaluation of the ability of a model to correctly represent the underlying data set is mandatory when presenting regression analyses. The Pearson or Hosmer-Lemeshow statistics yield a measure of the goodness of fit for a particular model and can be used to compare models derived from the same underlying data. The goodness-of-fit p values for our final models of low cardiac output syndrome and operative mortality were greater than 0.99 and 0.65, respectively, and suggested an excellent agreement between observed and predicted values. The internal validity of our models was evaluated with use of a bootstrap method. The regression coefficients between the whole data set and the test data set correlated for both operative mortality ($r^2 = 0.981, p < 0.001$) and low cardiac output syndrome ($r^2 = 0.987, p < 0.001$). These results lend further support to the validity of these models.

The ROC curves are another tool to evaluate the ability of a model to accurately represent the underlying data. The advantage of the ROC curve is that it is independent of the prevalence of the outcome of interest and thus can be used to compare logistic models derived from different data sets with varying levels of incidence and prevalence. The areas under the ROC curve for the low cardiac output syndrome and operative mortality models were 74% and 76%, respectively (Fig. 5). These figures can be used to compare our logistic models with other models derived from a different patient population. The

larger the area under the ROC curve, the more accurate the model is in predicting outcomes in the underlying data set. With use of these objective criteria, one can determine whether differences in predictive models are true differences in the underlying data or a result of inaccuracies in a poorly fit model. Similarly, these objective criteria can be used to compare models derived from different data sets and patient populations. Thus differences in predictive variables between patient populations can once again be ascribed to either true differences between the populations or to inaccuracies in poorly fit models. The use of such objective criteria will alleviate the problem of different multivariable equations arising from the same data set.^{28, 29}

This study presents the independent predictors of low cardiac output syndrome in 4558 consecutive patients who underwent isolated coronary artery bypass grafting at The Toronto Hospital. Our definition of low cardiac output syndrome is objective and reproducible and can be used as an alternative clinical outcome of interest when the efficacy of new myocardial protective strategies is evaluated.

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Appendixes

Appendix A: Definitions of perioperative variables

Elderly. Patients older than age 70 years.

Diabetes. A preoperative diagnosis of diabetes mellitus treated with insulin, oral hypoglycemic agents, or diet.

Triple-vessel disease. Critical lesions (greater than 50% luminal narrowing) affecting the territories supplied by the right, LAD, and left circumflex coronary arteries.

Left main coronary artery disease. Greater than 50% stenosis of the left main coronary artery.

Peripheral vascular disease. Known carotid, aortoiliac, or femoropopliteal disease or cases in which the patient had a previous carotid endarterectomy or peripheral vascular operation.

Transient ischemic attacks. A preoperative history of transient ischemic attacks, reversible ischemic neurologic deficits, or stroke.

Normothermia. Systemic temperature higher than 35° C during cardiopulmonary bypass.

Timing. Elective, same hospitalization, urgent (within

72 hours of an event), or emergency (within 12 hours of an event). An event is either cardiac catheterization or an ischemic event after cardiac catheterization. Timing of operation is dependent on the symptomatic status of the patient.

Recent MI. MI within 30 days before operation (Q wave or non-Q wave with an elevation of CK-MB level).

Hypertension. Preoperative systemic hypertension necessitating medical treatment.

Smoking. A history of smoking or current smoking.

Left ventricular grade. Ejection fraction greater than 60% (grade 1), ejection fraction between 40% and 60% (grade 2), ejection fraction between 20% and 40% (grade 3), ejection fraction less than 20% (grade 4), as assessed by a single-plane contrast ventriculogram or by echocardiography or nuclear ventriculography if a contrast ventriculogram was not done.

Appendix B. To calculate the predicted probability of low cardiac output syndrome or operative mortality for a given patient, start with the *constant* and then add the regression coefficients that describe the patient's characteristics for a coefficient total (x). Then use the formula $p = e^x / (1 + e^x)$. For example, from Table IV the predicted probability of low cardiac output syndrome for a 72-year-old male patient with a left ventricular ejection fraction of 35% and left main coronary artery disease but no diabetes, no previous coronary artery bypass grafting, and no recent MI undergoing urgent operation would be $x = -3.866 + 0.3691 + 0.8614 + 0.350 + 0 + 0 + 0 + 0 + 0.2451 - 2.0404$; $p = e^{2.0404} / (1 + e^{2.0404}) = 0.115$ (or 11.5%).