IS BODY SIZE THE CAUSE FOR POOR OUTCOMES OF CORONARY ARTERY BYPASS OPERATIONS IN WOMEN?

Although small body size and coronary artery diameter are recognized as major contributors to the increased risk of coronary artery bypass grafting in women, few studies have established the independent influence of body size and gender on outcome. We studied 7025 consecutive patients (5694 men, 1331 women) undergoing isolated coronary artery bypass grafting between 1990 and 1994. Women were older, had higher preoperative prevalences of urgent operation because of unstable angina, diabetes, peripheral vascular disease, hypertension, and single-vessel coronary artery disease ($p < 0.0001$), and a lower prevalence of left ventricular ejection fraction 40% or less ($p < 0.0001$). The prevalences of operative mortality (men, 1.8%; women, 3.5%), low-output syndrome (men, 6.6%; women, 14.8%), and myocardial infarction (men, 2.8%; women, 5.5%) were higher in women ($p < 0.0001$). Patients were divided into quartiles for body surface area, weight, height, and body mass index. For both men and women, there was no difference in operative mortality between the highest and lowest quartiles of body size. Women, however, had a higher prevalence of operative mortality than men in the lower quartiles of body surface area, height, and weight and in the higher quartiles of body mass index. Among men, the prevalence of low-output syndrome increased ($p < 0.0001$) with decreasing body surface area, weight, and body mass index, suggesting that body size did influence the prevalence of low-output syndrome. However, women had a higher prevalence of low-output syndrome than men in every category and quartile of body size ($p < 0.0001$). Multivariable analysis identified gender as a significant determinant of operative mortality (odds ratio 1.83, 95% confidence interval 1.27 to 2.64) and low-output syndrome (odds ratio 2.52, 95% confidence interval 2.05 to 3.11). When multivariable adjustments were made for body size and preoperative risk factors, gender remained a predictor of both operative mortality and low-output syndrome. Multivariable assessment of risk for men and women separately identified that urgent operation was a predictor of operative mortality (odds ratio 2.52, 95% confidence interval 1.32 to 5.61) and low-output syndrome (odds ratio 1.57, 95% confidence interval 1.14 to 2.17) in women but not men. In conclusion, the increased risk of coronary artery bypass grafting in women may be explained in part by dramatic differences in preoperative risk factors between men and women. In both men and women, small body size did not increase the risk of operative mortality, but may have contributed

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to the risk of low-output syndrome. After adjusting for preoperative risk variables and body size, gender remains a significant independent predictor of operative mortality and low-output syndrome. (J THORAC CARDIOVASC SURG 1995;110:1344-58)

The risk of operative mortality and morbidity after coronary artery bypass grafting is significantly higher in women than in men.¹⁻¹¹ The causes for this difference have been variably attributed to the different demographic profile of women at the time of operation,^{3-6, 9, 10} to referral bias,^{10, 12, 13} or to as-yet undefined biologic and chemical differences between men and women.⁶ However, by far the most widely held belief and reported reason for poor outcomes in women suggests that the smaller body size, and hence smaller coronary artery diameter, is responsible.^{4, 5, 9} Fisher and colleagues,⁴ reporting results from the Coronary Artery Surgery Study, concluded that when adjustments were made for clinical presentation and size, gender no longer influenced operative mortality. However, they used the combination of height, coronary artery diameter, and body surface area as a composite size variable. The independent influence of body size on outcome is not well established.

This study was designed to determine the influence of body size and gender on operative mortality and low-output syndrome after isolated coronary artery bypass grafting and to assess whether gender-specific differences exist in the risk factors for bypass operation.

Methods

Patient population. The study population consisted of all patients who underwent isolated coronary artery bypass grafting between January 1, 1990, and June 30, 1994, at the Toronto Hospital and Sunnybrook Health Science Centre. Patients who also required valve operation, aneurysmectomy, operation for congenital heart disease, aortic operation, or other noncoronary heart operations were excluded from analysis.

Surgical and perfusion technique. Cardiopulmonary bypass was instituted with moderate hemodilution as previously described.¹⁴ Cardioplegia techniques consisted of systemic hypothermia (25° to 30° C) and intermittent administration of cold blood cardioplegic solution or systemic mild hypothermia (32° to 35° C) and intermittent normothermic cardioplegia. Proximal anastomoses were done either during a single crossclamp period or during reperfusion with a partial occluding clamp.

Data collection and definitions. Clinical variables previously used to compare men and women,¹⁻¹¹ as well as variables collected in our institutional database, were prospectively collected. Urgent operation was defined as

operation that occurred within 48 hours of coronary catheterization because of unstable symptoms not controlled by medical therapy, hemodynamic instability, or failed angioplasty. Preoperative myocardial infarction was defined as a Q wave or non-Q wave myocardial infarction that occurred within 30 days of operation and was documented by a rise in cardiac isoenzyme values or electrocardiographic changes. Diabetes was determined to be present in patients receiving insulin therapy or oral hypoglycemic medications because of documented elevations of fasting blood sugar values. Hypertension was deemed to be present in those patients with a documented history of hypertension necessitating medical treatment. Peripheral vascular disease was determined to be present in patients with known carotid, aortoiliac, or femoral popliteal disease or in patients with a previous carotid endarterectomy or peripheral vascular operation. Chronic obstructive pulmonary disease was present in those patients who underwent pulmonary function studies and had a forced expiratory volume in 1 second or diffusion capacity less than 75% of predicted. At the time of catheterization biplane cineangiography allowed for measurement of left ventricular ejection fraction by planimetry. At the time of admission to the hospital for operation the patients were weighed and their height measured. Body surface area (BSA) and body mass index (BMI) were calculated by standard formulas¹⁵⁻¹⁷:

$$BSA = \left(\frac{\text{height} \times \text{weight}}{3600} \right)^{1/2}$$

and

$$BMI = \frac{\text{weight}}{\text{height}^2}$$

Operative mortality was defined as any death that occurred during the hospital stay or within the first 30 days of operation if patients died after discharge. Low-output syndrome was diagnosed if the patient required an intra-aortic balloon pump (either in the operating room or in the intensive care unit) because of hemodynamic compromise. Low-output syndrome was also diagnosed if patients required inotropic medication to maintain systolic blood pressure greater than 90 mm Hg and a cardiac index greater than 2.2 L/min per square meter for at least 30 minutes in the intensive care unit. A perioperative myocardial infarction was documented when a new Q wave was identified on the postoperative electrocardiogram. A myocardial infarction was also diagnosed if the postoperative electrocardiogram had a new left bundle branch block or loss of R wave progression or new ST and T wave changes, if accompanied by a rise in creatine kinase MB levels greater than 50 IU/L. A postoperative stroke was

Table I. Gender differences in preoperative characteristics and perioperative outcomes

	Men	Women	<i>p</i> Value
NYHA class (%)			
I	2.4	0.7	
II	18.5	7.8	
III	42.5	38.2	
IV	36.6	53.3	0.0001
Unstable angina (%)	61.3	73.1	0.0001
Preoperative stroke/TIA (%)	6.3	8.9	0.001
Hypertension (%)	46.6	61.8	0.0001
Chronic obstructive pulmonary disease (%)	13.7	12.7	0.58
Elevated cholesterol (%)	51.0	57.3	0.0001
Positive family history for coronary artery disease (%)	65.1	70.8	0.0001
Exercise stress test (%)			
Not done	25.7	38.4	
Negative	2.2	1.8	
Positive	72.1	59.8	0.0001
Single-vessel disease (%)	5.1	8.5	0.0001
Single or double CABG (%)	14.4	24.5	0.0001
LITA with or without RITA	85.4	69.3	0.0001
Coronary endarterectomy (%)	8.7	6.5	0.01
Time in operating room (min)	189 ± 49	182 ± 48	0.001
Crossclamp time (min)	60.3 ± 18.5	55.5 ± 19.8	0.001
Cardiopulmonary bypass time (min)	90.6 ± 27.4	86.2 ± 29.7	0.001
Ventilation time (days)	1.3 ± 3.0	1.6 ± 3.5	0.03
Length of ICU stay (days)	2.4 ± 3.6	2.9 ± 4.7	0.002
Length of hospital stay (days)	7.4 ± 7.8	9.3 ± 14.0	0.0001
Postoperative stroke (%)	1.3	1.7	0.40
Reoperation for bleeding (%)	1.6	2.0	0.10
Sternal infection (%)	1.0	1.4	0.34

Values given plus or minus the standard deviation where appropriate. NYHA, New York Heart Association; TIA, transient ischemic attack; CABG, coronary artery bypass grafting; LITA, left internal thoracic artery; RITA, right internal thoracic artery; ICU, intensive care unit.

defined as a persistent focal neurologic deficit at the time of discharge. Deep sternal infection was diagnosed when patients required sternectomy and muscle flap repair or prolonged (greater than 6 weeks) intravenous antibiotic therapy because of a documented bacterial pathogen.

Study design and statistical analysis. Statistical analysis was done with the SAS program (SAS Institute, Cary, N.C.) and BMDP statistical software (BMDP, Irvine, Calif.). Categorical preoperative and perioperative gender differences were assessed by use of a χ^2 test or Fisher's exact test where appropriate. Continuous data were ana-

lyzed by two-tailed *t* tests. A conventional correction for multiple comparisons was done.¹⁸ Only *p* values <0.01 were considered significant.

Differences in size (body surface area, weight, height, body mass index) between survivors and nonsurvivors and between patients with and without low-output syndrome were analyzed (separately for men and women) using two-tailed *t* tests.

Patients were divided into quartiles on the basis of distributions of size¹⁹ (body surface area, weight, height, body mass index). Differences between men and women (within quartiles of size) for postoperative mortality and low-output syndrome were analyzed by χ^2 tests.

Multivariable logistic models for risk factors for operative mortality and low-output syndrome were constructed (1) for the entire population, (2) for women alone, and (3) for men alone. In the multivariable model determining risk of operative mortality or low-output syndrome for the entire patient population, body surface area or height, or weight, or body mass index were each separately forced into the model to identify what happened to the predictive value of gender. Logistic models for each outcome were constructed with the use of methods described by Hosmer and Lemeshow.²⁰ Each prognostic variable was evaluated by the appropriate univariate test (χ^2 , Fisher's exact, or two-tailed *t* tests). Variables were selected for inclusion in a multivariable model if their univariate *p* value was less than 0.20. Models were fit and the best model for each outcome variable was determined.

The receiver operator characteristic curve²¹ was also used to assess the predictive value of each model. Receiver operator characteristic curves are usually used to evaluate the trade-offs between sensitivity and specificity for a test. 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 sensitivity and specificity. When calculated in the BMDP LR program, the receiver operator characteristic curve is independent of both the cut point criteria (predicted probabilities) and the prevalence of the variables. Standard deviations are used when continuous data are described in the text and tables.

Results

Preoperative and perioperative demographics.

The preoperative and perioperative characteristics of men and women are listed in Table I and in Fig. 1. There were 5694 men (81%) and 1331 women (19%). Women had a significantly different clinical profile from that of men. The internal thoracic artery was used more frequently in men than in women. The internal thoracic artery was used less frequently in men and women with a body surface area less than 1.79 m² (men, 79.8%; women, 67.3%) compared with its use in men and women with a body surface area 1.79 m² or greater (men, 86.7%; women, 73.3%; *p* < 0.01). Female patients received single or double bypass grafts more frequently and spent significantly less time in the operating room than men, with shorter crossclamp and bypass times

Fig. 1. Gender differences in preoperative presentation and risk variables are illustrated. Women had significantly different demographic and risk profile from that of men. *Urgent*, Urgent timing of operation; *TVD*, triple-vessel disease; *Diabetes*, diabetes mellitus; *EF*, left ventricular ejection fraction; *PVD*, peripheral vascular disease; *Preop MI*, preoperative myocardial infarction within 30 days of operation; *LMS*, left main stenosis; *Reop Sx*, reoperation; *CHF*, congestive heart failure; *RI*, renal insufficiency.

(Table I). However, women were at significantly higher risk of poor outcomes, with a higher prevalence of mortality, low-output syndrome, and myocardial infarction (Fig. 2) and received ventilator support longer and stayed in the intensive care unit and hospital for longer periods (Table I). All differences remained significant after adjustments for multiple comparisons were made. The prevalences of stroke, sternal wound infection, and reoperation because of bleeding were similar (Table I).

Body size. Fig. 3 demonstrates that the distributions of body surface area, height, and weight differed significantly between men and women. Men had a significantly larger body surface area ($1.95 \pm 0.17 \text{ m}^2$) than women ($1.73 \pm 0.18 \text{ m}^2$, $p < 0.0001$). Men were also taller ($172 \pm 10 \text{ cm}$) than women ($158 \pm 8 \text{ cm}$, $p < 0.0001$) and heavier ($81.5 \pm 13.7 \text{ kg}$) than women ($69.3 \pm 12.7 \text{ kg}$, $p < 0.0001$). The

distribution of body mass index was similar between men ($28.0 \pm 4.8 \text{ kg/m}^2$) and women ($28.4 \pm 5.7 \text{ kg/m}^2$).

Table II compares the average size of patients who survived with the average size of patients who died (for men and women separately). For both men and women there was no statistically significant difference in body surface area, height, weight, or body mass index between survivors and nonsurvivors.

Table II also compares the average size of patients who had low-output syndrome with that of those patients who did not have this complication (for men and women separately). Among the male population, those who had low-output syndrome had a significantly lower body surface area, weight, and body mass index than those who did not have low-output syndrome. Among the female population, those who had low-output syndrome had a

Fig. 2. After operation, women had significantly higher prevalence of operative mortality (*OM*), low-output syndrome (*LOS*), intraaortic balloon pump assistance (*IABP*), and myocardial infarction (*MI*) than men.

Fig. 3. Distribution of body size for men and women is illustrated. Men had significantly larger body surface area (*BSA*) and were taller and heavier than women ($p < 0.0001$). Body mass index (*BMI*) was more evenly distributed between men and women. *Wt*, Weight; *Ht*, height.

significantly lower body surface area and weight than those without low-output syndrome.

The total patient population was divided into quartiles for body surface area, height, weight, and

body mass index, and male-female differences in the prevalence of operative mortality (Fig. 4) and low-output syndrome (Fig. 5) were compared at each quartile of size. Women with body surface area

Table II. Influence of body size on operative mortality and low-output syndrome for men and women

	Men	<i>p</i> Value	Women	<i>p</i> Value
<i>Mortality</i>				
Body surface area (m ²)				
Survivors	1.95 ± 0.17	0.32	1.73 ± 0.17	0.30
Nonsurvivors	1.93 ± 0.22		1.71 ± 0.19	
Weight (kg)				
Survivors	81.3 ± 12.9	0.19	69.7 ± 12.5	0.28
Nonsurvivors	79.4 ± 15.3		67.7 ± 13.4	
Height (cm)				
Survivors	170.5 ± 8.7	0.61	157.0 ± 8.3	0.47
Nonsurvivors	171.0 ± 10.4		156.1 ± 8.2	
Body mass index (kg/m ²)				
Survivors	28.1 ± 4.8	0.05	28.4 ± 5.7	0.45
Nonsurvivors	27.1 ± 4.8		27.8 ± 5.5	
<i>Low-output syndrome</i>				
Body surface area (m ²)				
No LOS	1.96 ± 0.17	0.0001	1.73 ± 0.17	0.02
LOS	1.92 ± 0.19		1.71 ± 0.17	
Weight (kg)				
No LOS	81.5 ± 12.8	0.0001	69.9 ± 12.5	0.03
LOS	78.4 ± 13.9		67.7 ± 12.1	
Height (cm)				
No LOS	170.6 ± 8.7	0.10	157.0 ± 8.2	0.68
LOS	169.8 ± 8.9		156.7 ± 9.1	
Body mass index (kg/m ²)				
No LOS	28.1 ± 4.8	0.001	28.5 ± 5.6	0.16
LOS	27.2 ± 4.5		27.8 ± 6.4	

Values given plus or minus the standard deviation. LOS, Low-output syndrome.

between 1.79 and 1.90 m², those 162 to 168 cm in height, those weighing 70 to 77 kg, or those with body mass index 27.5 to 30.4 kg/m² had a significantly higher prevalence of operative mortality than men in the same size category (Fig. 4). Women had a significantly higher prevalence of low-output syndrome than men at every quartile of size (Fig. 5).

Operative mortality was not different between highest quartile and lowest quartile of body surface area, height, weight, or body mass index for both men and women (Fig. 4). In women, the prevalence of low-output syndrome was not different between the highest and lowest quartiles of size (Fig. 5). In men, the prevalence of low-output syndrome was significantly higher in patients with body surface area less than 1.79 m² compared with that in those with body surface area 2.04 m² or greater, in patients weighing less than 70 kg compared with 87 kg or greater, and in patients with body mass index less than 25 kg/m² compared with 27.5 to 30.4 kg/m² (Fig. 5).

Multivariable models for operative mortality and low-output syndrome. Table III depicts the multivariable risk factors for operative mortality in the

entire patient population. Female gender was a predictor of operative mortality with an odds ratio of 1.83 and a 95% confidence interval of 1.27 to 2.64. The area under the receiver operator characteristic curve for this model was 77%. Table IV depicts the multivariable risk factors for low-output syndrome in the entire patient population. Gender was a significant predictor of low-output syndrome with an odds ratio of 2.52 and a 95% confidence interval of 2.05 to 3.11. The area under the receiver operator characteristic curve for this model was 75%.

When body surface area, height, weight, and body mass index were each mathematically forced into the multivariable model for operative mortality, gender remained a significant independent determinant of operative mortality (Table III). The area under the receiver operator characteristic curve was 78%. Body surface area, height, weight, and body mass index were not independent predictors of operative mortality (95% confidence intervals included unity).

When body surface area was mathematically forced into the multivariable model for low-output syndrome, gender remained an independent predictor of operative mortality with slightly reduced odds

Fig. 4. This figure depicts gender differences in prevalence of operative mortality (OM) according to quartiles of body size. Women (*W*) had higher prevalence of operative mortality than men (*M*) in same size category. For both men and women, prevalence of operative mortality was not different between highest and lowest quartile of body surface area (*BSA*), height (*Ht*), weight (*Wt*), or body mass index (*BMI*).

ratios (Table IV). Body surface area was a significant negative determinant, with an odds ratio of 0.30 and a 95% confidence interval 0.17 to 0.53. When height or weight was mathematically forced into the multivariable model of low-output syndrome, gender remained an independent predictor with slightly reduced odds ratios. When body mass index was mathematically forced into the model, gender remained an independent predictor with increased odds ratios. Height, weight, and body mass index contributed poorly to the predictive value of the model (95% confidence intervals included unity).

When the male population was assessed, the multivariable determinants for operative mortality were age 70 years or older, left ventricular ejection fraction 40% or less, reoperation, preoperative presence of peripheral vascular disease,

renal failure, a preoperative myocardial infarction within 30 days of operation, and coronary endarterectomy (Table V). The multivariable analysis of operative mortality for women identified left ventricular ejection fraction 40% or less, reoperation, urgent operation, peripheral vascular disease, and age 70 years or older as independent determinants (Table V).

The multivariable determinants of low-output syndrome in the male population were reoperation, left ventricular ejection fraction 40% or less, a myocardial infarction within 30 days of operation, age 70 years or older, preoperative diabetes, the need for a coronary endarterectomy, the presence of preoperative congestive heart failure, and left main stenosis (Table VI). Reoperation, left ventricular ejection fraction 40% or less, coronary endarterectomy, left main stenosis, and urgent op-

Fig. 5. This figure depicts gender differences in prevalence of low-output syndrome (LOS) according to quartiles of body size. Women (W) had significantly higher prevalence of low-output syndrome than men (M) for every category of body size and at every quartile of size. In men, but not women, prevalence of low-output syndrome was significantly higher in lowest quartiles of body surface area (BSA), weight (Wt), and body mass index (BMI) compared with highest quartiles of respective body size. Ht, Height.

eration were multivariable predictors of low-output syndrome among women (Table VI).

Discussion

Since the mid-1970s, studies have consistently reported higher rates of operative mortality and morbidity in women undergoing coronary artery bypass grafting.¹⁻¹¹ The excess mortality in women has been attributed to a higher prevalence of pre-operative risk factors, to referral or treatment bias, and, most frequently of all, to a smaller body habitus and by extension smaller coronary arteries. Although body surface area has been shown to correlate with the diameter of coronary arteries,^{9, 22, 23} this study did not examine coronary artery size, but

rather focused on the independent influence of body size on postoperative outcomes.

Body size. Assessing the influence of body size on postoperative outcomes is difficult when men and women are being compared. We have demonstrated in this study that body surface area, weight, and height do not have similar distributions in men and women. Therefore the extremes of high and low size contain more of one gender than another. These variables may act as a proxy for gender, in addition to providing information about size. Body mass index, however, is a measurement of size that is more evenly distributed between men and women. It has been suggested to be the best measurement for study of obesity.^{15, 16}

Table III. Multivariable analysis for operative mortality: all study patients

Variables in model	No body size variables in model		Body surface area in model	Weight in model	Height in model	Body mass index in model
	Regression coefficient*	Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)
Constant	-5.337 ± 0.178					
Body size variable	Not entered		0.66 (0.25-1.74)	0.99 (0.98-1.01)	1.00 (0.99-1.02)	0.97 (0.94-1.01)
Female gender	0.605 ± 0.186	1.83 (1.27-2.64)	1.68 (1.10-2.55)	1.70 (1.14-2.51)	1.96 (1.25-3.06)	1.85 (1.29-2.67)
Age ≥70 yr	0.941 ± 0.171	2.56 (1.83-3.58)				
LV ejection fraction ≤ 40%	1.032 ± 0.168	2.81 (2.02-3.91)				
Reoperation	1.660 ± 0.207	5.26 (3.50-7.89)				
Left main stenosis	0.517 ± 0.188	1.68 (1.16-2.42)				
Peripheral vascular disease	0.819 ± 0.185	2.27 (1.58-3.26)				
Diabetes	0.532 ± 0.177	1.70 (1.20-2.41)				
Renal insufficiency	0.901 ± 0.271	2.46 (1.45-4.19)				
Coronary endarterectomy	0.683 ± 0.230	1.98 (1.26-3.11)				

CI, Confidence interval; LV, left ventricular.

*Values given plus or minus standard error.

Body surface area is an especially confusing measure of body habitus. Differentiating a short obese patient from a tall thin patient is difficult when body surface area is used as a measure. For example, an 80 kg woman who is 160 cm tall would have the identical body surface area (1.88 m²) as a 71 kg man who is 180 cm tall. Body mass index would be a better measure of body habitus in the above example (woman, 31.3 kg/m²; man, 21.9 kg/m²).

Body size and operative mortality. In this study we demonstrated that body size was not a major determinant of operative mortality. In both male and female patients the average body surface area, height, and weight were not significantly different between patients who died or survived. We also demonstrated that in both men and women, operative mortality was not different between the high and low quartiles of any of the measurements of body size. However, women had a higher operative mortality than men in the lower quartile of body surface area, height, and weight and in the top quartile for body mass index. These data suggest that women have a higher operative mortality irrespective of body habitus. When body surface area, height, weight, and body mass index were mathematically

forced into the multivariable models to account for size, gender did not drop out of the model and continued to be an independent predictor of operative mortality.

Although body size has been implicated as a major cause of increased operative mortality in women, only four previous studies have examined the influence of size and gender on outcome.^{4, 5, 9, 10} Grover and associates²⁴ studied 12,712 mostly male patients (99%) from various Veterans Administration centers and identified height, weight, and body surface area as significant univariate, but not multivariable, predictors of operative mortality. Khan and associates¹⁰ also did not find a significant association between mortality and body surface area. O'Connor and colleagues⁹ demonstrated an inverse quadratic relation between operative mortality and body surface area for both men and women. The population studied by O'Connor and colleagues⁹ was substantially smaller (3055 patients) than that in this study (7025 patients) and the study included data from five centers (19 surgeons) compared with two centers (9 surgeons) in the present study. Fisher⁴ and Loop⁵ and their associates also demonstrated that patients with smaller body surface area

Table IV. Multivariable analysis for low-output syndrome: all study patients

Variables in model	No body size variables in model		Body surface area in model	Weight in model	Height in model	Body mass index in model
	Regression coefficient*	Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)
Constant	-3.880 ± 0.124					
Body size variable	Not entered		0.30 (0.17-0.53)	0.98 (0.97-0.99)	0.99 (0.98-1.00)	0.97 (0.95-0.99)
Female gender	0.925 ± 0.106	2.52 (2.05-3.11)	2.01 (1.59-2.55)	2.16 (1.73-2.70)	2.19 (1.70-2.83)	2.64 (2.15-3.24)
Age ≥70 yr	0.379 ± 0.106	1.46 (1.19-1.80)				
Urgent operation	0.229 ± 0.111	1.26 (1.01-1.56)	Not selected by model	Not selected by model		Not selected by model
LV ejection fraction ≤40%	0.836 ± 0.102	2.31 (1.89-2.82)				
Reoperation	1.687 ± 0.130	5.41 (4.19-6.97)				
Left main stenosis	0.379 ± 0.114	1.46 (1.17-1.83)				
Triple-vessel disease	0.260 ± 0.110	1.30 (1.04-1.61)				
Preoperative MI	0.452 ± 0.128	1.57 (1.22-2.02)				
Diabetes	0.363 ± 0.104	1.44 (1.17-1.76)				
Congestive heart failure	0.599 ± 0.191	1.82 (1.25-2.65)				
Coronary endarterectomy	0.686 ± 0.139	1.99 (1.51-2.61)				

CI, Confidence interval; LV, left ventricular; MI, myocardial infarction.

*Values given plus or minus standard error.

were at higher risk of operative mortality even after adjustment for clinical and angiographic variables. Fisher and associates⁴ demonstrated that as vessel diameter increased, operative mortality decreased significantly for both men ($p = 0.005$) and women ($p = 0.01$) by the χ^2 test for linear trend. However, when they tested the relation between increasing height and operative mortality, they did not demonstrate a statistically significant trend ($p > 0.05$) for either gender. Furthermore, body surface area univariately predicted operative mortality in urgent but not elective cases. The authors used the combination of patient height, coronary artery diameter, and body surface area as a composite "size variable," in a stepwise discriminant analysis. The influence of body size was not assessed separately from coronary size. We performed a logistic regression analysis of the Coronary Artery Surgery Study data reported by Fisher and colleagues⁴ (Appendix A) and identified gender as a significant determinant of outcome after adjusting for coronary artery and body size. Loop and associates⁵ reviewed the

results in 2445 women and 18,079 men. A higher operative mortality was noted in women, which was explained by body size. After adjusting for body surface area they determined that gender was not an important risk factor for operative mortality. They concluded that small people regardless of gender are at increased risk of death even after adjusting for other risk variables. Their study, however, was comprised of patients operated on between 1967 and 1980, and women accounted for only 11.9% of the total patient population.

Body size and low-output syndrome. In this study we demonstrated that the prevalence of postoperative low-output syndrome significantly increased with decreasing body surface area, weight, and body mass index for men, but not for women. The absence of correlation in women may have been related to the small patient population in the higher quartiles of body size. However, even within quartiles of body size, women continued to have a higher prevalence of low-output syndrome than men, which suggests other causes in addition to

Table V. Multivariable analysis for operative mortality: men and women separately

Men only			Women only		
Variables in model	Regression coefficient*	Odds ratio (95% CI)	Variables in model	Regression coefficient*	Odds ratio (95% CI)
Constant	-5.303 ± 0.184		Constant	-4.752 ± 0.334	
Age ≥70 yr	1.074 ± 0.203	2.93 (1.97-4.36)	Age ≥70 yr	0.741 ± 0.289	2.10 (1.19-3.70)
LV ejection fraction ≤40%	0.893 ± 0.201	2.44 (1.65-3.62)	LV ejection fraction ≤40%	1.105 ± 0.295	3.02 (1.69-5.38)
Reoperation	1.650 ± 0.227	5.21 (3.34-8.12)	Reoperation	1.068 ± 0.452	2.91 (1.20-7.07)
Peripheral vascular disease	0.874 ± 0.219	2.40 (1.56-3.69)	Peripheral vascular disease	1.025 ± 0.303	2.79 (1.54-5.05)
Preoperative renal insufficiency	1.010 ± 0.299	2.75 (1.53-4.93)	Urgent operation	0.879 ± 0.333	2.41 (1.25-4.62)
Coronary endarterectomy	0.741 ± 0.259	2.10 (1.26-3.49)	Model evaluation		GOF <i>p</i> value 0.417
Preoperative MI	0.645 ± 0.222	1.91 (1.23 ± 2.95)			Area under ROC curve 75.7%
Model evaluation		GOF <i>p</i> value 0.416 Area under ROC curve 77.7%			

CI, Confidence interval; LV, left ventricular; MI, myocardial infarction; GOF, goodness of fit; ROC, receiver operator characteristic.

*Values given plus or minus standard error.

Table VI. Multivariable analysis for low-output syndrome: men and women separately

Men only			Women only		
Variables in model	Regression coefficient*	Odds ratio (95% CI)	Variables in model	Regression coefficient*	Odds ratio (95% CI)
Constant	-3.638 ± 0.098		Constant	-2.546 ± 0.140	
Age ≥70 yr	0.475 ± 0.126	1.61 (1.26-2.06)	Reoperative surgery	1.426 ± 0.292	4.16 (2.35-7.38)
LV ejection fraction ≤40%	0.796 ± 0.115	2.22 (1.77-2.77)	LV ejection fraction ≤40%	0.899 ± 0.177	2.46 (1.74-3.48)
Reoperation	1.721 ± 0.137	5.59 (4.27-7.30)	Coronary endarterectomy	1.146 ± 0.249	3.15 (1.93-5.12)
Left main stenosis	0.273 ± 0.133	1.31 (1.01-1.71)	Left main stenosis	0.509 ± 0.191	1.66 (1.14-2.42)
Coronary endarterectomy	0.617 ± 0.156	1.85 (1.36-2.52)	Urgent operation	0.451 ± 0.165	1.57 (1.14-2.17)
Diabetes	0.492 ± 0.122	1.64 (1.29-2.08)	Model evaluation		GOF <i>p</i> value 0.408
Congestive heart failure	0.722 ± 0.213	2.06 (1.36-3.12)			Area under ROC curve 70.0%
Preoperative MI	0.674 ± 0.128	1.96 (1.53-2.52)			
Model evaluation		GOF <i>p</i> value 0.774 Area under ROC curve 72.7%			

CI, Confidence interval; LV, left ventricular; MI, myocardial infarction; GOF, goodness of fit; ROC, receiver operator characteristic.

*Values given plus or minus standard error.

size were responsible for the outcomes. When body size was mathematically forced into the multivariable model along with adjustments for other traditional risk factors, body surface area

became a significant negative predictor of outcome (odds ratio 0.302, 95% confidence interval 0.174 to 0.525). However, gender remained a significant predictor of low-output syndrome when adjust-

ments were made for size and other risk factors. Our contemporary results demonstrating that body surface area is a risk factor for low-output syndrome, but not operative mortality, and the results of other studies concluding that body surface area is a significant determinant of operative mortality, may be explained by improvements in the management of postoperative ventricular dysfunction. Patients with small body surface areas who would have previously died of postoperative low-output syndrome may now be surviving because of improvements in the management of low-output syndrome. O'Connor and associates⁹ determined that the major cause of postoperative death in women was heart failure.

Demographic differences between men and women: multivariable risk factors. Women are not only smaller than men, but they also have a distinct clinical picture. We demonstrated statistically significant differences between men and women in many preoperative demographic descriptors. Khan and colleagues¹⁰ demonstrated that women were older and more frequently had unstable angina, postmyocardial infarction angina, and New York Heart Association class IV symptoms. O'Connor and associates⁹ also demonstrated that women were older with more unstable angina, urgent operation, and diabetes mellitus. Weintraub and associates⁶ demonstrated that women were older with a higher prevalence of hypertension, diabetes, congestive heart failure, class III to IV symptoms, urgent operation, and single-vessel disease. These differences have been used by some investigators as evidence of referral bias.^{10, 12} However, others have concluded that the higher prevalence of single-vessel disease and well-maintained left ventricular function do not suggest bias.^{5, 6} Urgent operation for class III to IV symptoms in women has been found to be appropriate and free of referral bias in our institutions.¹³ In this study, we identified that women have a higher frequency of never having smoked and a higher prevalence of hypercholesterolemia and positive family histories for coronary artery disease compared with men. This may suggest that the mechanisms of atherogenesis may also be different between the sexes.

Some of the excess risk of mortality and low-output syndrome may be attributed to the more severe demographic profile in women. However, the multivariable analysis done in this study adjusted for factors such as age, diabetes, congestive heart failure, and urgent

operation. Therefore gender remained a significant and independent predictor of operative mortality after controlling for other risk factors. Furthermore, all risk factors of operative mortality in women, except for urgent operation, were also significant risk factors in the male population. The presence of additional risk factors in the male population may be related to the higher number of male patients studied and therefore the higher statistical power. Interestingly, urgent operation was not a risk factor for mortality in men, but was a significant risk factor in women. When all patients were combined, urgent operation was not a significant determinant of operative mortality, which suggests most of the influence of urgent operation is attributable to women.

The increased risk of mortality and morbidity in women undergoing coronary artery bypass grafting is probably multifactorial. The increased number of risk variables they possess before operation and body and coronary artery size probably contribute to the increased risk. However, female gender is a determinant of outcome and may be a proxy for variables we currently do not measure. Perhaps the mechanism of atherogenesis and the disease progress are different in women. Further studies are necessary to identify the mechanism by which operative mortality and low-output syndrome occur in women after operation.

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Discussion

Dr. Robert A. Guyton (*Atlanta, Ga.*). Our own report from Emory on 13,000 patients presented in 1993 supports your data, but we did not look at the complex issue of body size. I would emphasize one thing that we found and that these authors also found: compared with men, women are seen for coronary artery bypass operation with more advanced symptoms, more congestive heart failure, and more angina, yet they have less advanced ischemic heart disease, with less severe coronary pathologic conditions and less impairment of ejection fraction. We found as the current investigators did that women have more noncardiac comorbid risk factors including: age, emergency operation, hypertension, and diabetes. Finally, we found that the odds ratio for female gender was 1.79, and the authors found an odds ratio of 1.83.

The difficult task comes along as one attempts to insert body size or body habitus into a multivariate analysis. This is because patients in cachexic conditions or very underweight patients may have a high risk and very overweight or massively obese patients may have a high risk. When one uses weight or body surface area or body mass index as a continuous variable or as a noncontinuous quartile variable, therefore, the high risk of low weight may cancel out the high risk of high weight; therefore the variable does not appear as an important variable in the multivariate analysis.

My first question applies to this thought. Do the authors think it might have been more logical to examine small or subnormal body weight as one variable and large or supranormal body weight as a second variable in the analysis?

My second question has to do with the fact that the risk associated with size or weight probably has to do with the extremes of size or weight. Do the authors think they might have seen a different result if they had looked at the bottom and top 5% or 10% of the patients in examining the data rather than the bottom or top 25% as a single group?

Dr. Christakis. We performed a large number of calculations and separate and multiple analyses within this extensive data set. However, there is a distinct compromise one accepts when performing multiple comparisons, that is, positive or significant statistical results may have occurred by chance alone (enhanced by the multiple tests done). To minimize the statistical problems associated with multiple comparisons and to avoid "data dredging" or data-generated hypotheses, we derived a prospective, preanalysis hypothesis, and we prespecified every analysis before this study was begun. The combinations and per-

mutations of statistical analyses possible for the study of body size are truly enormous. We, therefore, carefully and parsimoniously preselected the analyses to address the hypothesis. It is true that when body size is used as a continuous variable, high morbidity associated with extremes of size can cancel out any effect. However, when body size is divided into categoric variables (quartiles), this should minimize the chance of cancellation. The middle categories of the quartiles should be significantly different from the upper and lower quartiles. We could have used subnormal or supernormal size as individual variables in our analysis rather than quartiles as Dr. Guyton suggests, and this may have to be addressed in another study. Interestingly, however, the univariate data do not support the hypothesis that upper quartiles of body size do worse than middle categories.

Dr. Guyton also correctly point out that examining the bottom (or top) 5% to 10% of the population would better answer the question of influence of extremes of body size. We, however, avoided this type of analysis because the number of patients in the top or bottom categories would be insufficient to allow for appropriate statistical power. Furthermore, we believe that extremes of body size may influence outcome differently in men and women. Our data suggest that extremely small men may well have higher morbidity, but very large men do not appear to have poor outcomes frequently. Extremes of size in women, however, may result in higher morbidity and mortality.

Dr. Lynda L. Mickleborough (Toronto, Ontario, Canada). We have recently reported a prospective study on 1487 consecutive patients operated on by a single surgeon at The Toronto Hospital. Twenty-four percent of these patients were women. Our study was undertaken specifically to determine whether there was a difference in operative mortality between men and women and whether this can be related to small vessel size as determined at the time of operation. It has been documented in the literature that vessel size less than 1.5 mm is associated with increased perioperative infarction rate and a decrease in long-term graft patency rate. In our study, distal vessels were sized in a prospective manner with calibrated probes to determine whether the distal vessel was equal to or greater than 1.5 mm or less than 1.5 mm.

In our study, comparing men and women, we found no difference in the percentage of patients who had small vessels at the time of operation (<1.5 mm in size). In this series there was no statistically significant difference in operative mortality between men and women.

We also looked at our data with respect to body size, that is, surface area 1.8 m² or greater versus body surface area 1.8 m² or less. We found no difference in operative mortality between large and small patients but there was an increase in morbidity (perioperative myocardial infarction or low-output syndrome) in smaller patients irrespective of gender.

In our series, in patients with small distal vessels, we used intravenous nitroglycerine perioperatively in a prophylactic manner because we were concerned about the possibility of spasm being more important or more catastrophic in these patients.

My question to the authors is whether in their series there was any attempt to use antispasm agents in the

perioperative period. Do you think that this might influence results in those patients with small vessel size, irrespective of gender?

Dr. Christakis. We did not prospectively collect information on the use of antispasm agents perioperatively, as we can therefore only conjecture. It is well known that women have smaller, more friable coronary vessels that are prone to vasospasm. Antispasm agents may therefore decrease the prevalence of perioperative morbidity. I am not certain what happens to these vessels when administration of antispasm agents is eventually terminated.

Appendixes

Appendix A. We used data from the study by Fisher and associates⁴ (CASS) to assess the multivariable (logistic regression) influence of gender, height, and coronary diameter on operative mortality.

In Figs. 1 and 2 of their article, Fisher and associates⁴ used height and coronary artery diameter to assess the influence of these variables on operative mortality with the use of stepwise discriminant analysis (Table V, Fisher and associates⁴). Height and coronary artery diameter, however, were not used as continuous variables but were entered as categoric data. Three categories of height were used to analyze women (<160 cm, 160 to 169 cm, 170 to 179 cm) and five categories of height for men (<160, 160 to 169, 170 to 179, 180 to 190, >190 cm). Four categories of coronary artery diameter were used to assess both men and women (<1.5, 1.5 to 1.9, 2.0 to 2.4, >2.4 mm).

Categoric data are better assessed by stepwise logistic regression analysis. We used this technique as described in the BMDP statistical software manual, vol. 2 (Dixon WJ, Berkely: University of California Press, 1992:1129).

Because the data were presented in two separate figures we could only assess operative mortality with gender/height and gender/coronary artery diameter separately. We did not have data at our disposal to allow for analysis of gender/height and coronary artery diameter together.

Analysis 1. Determinants of operative mortality using height and gender

Case No.	Data entered			
	Gender*	Height†	OM‡	No.§
1	1	1	5	200
2	1	2	32	1296
3	1	3	49	3093
4	1	4	27	1563
5	1	5	1	96
6	2	1	27	505
7	2	2	22	572
8	2	3	2	95

*Gender 1, male; gender 2, female.

†Height 1, <160 cm; height 2, 160 to 169 cm; height 3, 170 to 179 cm; height 4, 180 to 190 cm; height 5, >190 cm.

‡OM (operative mortality), number of deaths in this category.

§Total number of patients in this category.

Results. Gender was the only significant predictor of operative mortality.

Term	Coefficient ± standard error	Odds ratio (95% confidence interval)	Improvement		Goodness of fit	
			χ^2	P Value	χ^2	P Value
Constant	-3.985 ± 0.094					
Gender	0.895 ± 0.172	2.45 (1.75-3.43)	24.0	0.000	7.58	0.27

Analysis 2. Determinants of operative mortality using coronary artery diameter and gender

Case no.	Data entered			
	Gender*	Diameter†	OM‡	No.§
1	1	1	12	374
2	1	2	58	2605
3	1	3	26	2401
4	1	4	4	594
5	2	1	9	105
6	2	2	28	512
7	2	3	11	406
8	2	4	0	85

*Gender 1, male; gender 2, female.

†Diameter 1, <1.5 mm; diameter 2, 1.5 to 1.9 mm; diameter 3, 2.0 to 2.4 mm; diameter 4, ≥2.5 mm.

‡OM (operative mortality), number of deaths in this category.

§Total number of patients in this category.

Results. Both gender and coronary artery diameter were significant predictors of operative mortality.

Term	Coefficient ± standard error	Odds ratio (95% confidence interval)	Improvement		Goodness of fit	
			χ^2	P Value	χ^2	P Value
Constant	-3.357 ± 0.235					
Gender	0.915 ± 0.180	2.5 (1.76-3.55)	26.28	0.0001	34.64	0.0001
Diameter						
2	-0.420 ± 0.250	0.65 (0.40-1.0)	32.11	0.0001	2.53	0.47
3	-1.153 ± 0.279	0.32 (0.18-0.54)				
4	-1.942 ± 0.550	0.14 (0.04-0.42)				

Conclusions

1. Multivariable assessment of the influence of gender and height on operative mortality demonstrated that only gender was a significant determinant.
2. Multivariable assessment of the influence of gender and coronary artery diameter on operative mortality demonstrated that both terms were significant predictors.

3. Numeric data for preoperative risk factors were not available to differentiate the effect of gender from the influence of risk variables.

Appendix B. The following is a list of variables analyzed:

Preoperative factors

Gender
Age
Height
Weight
Body surface area
Body mass index
New York Heart Association class
Unstable angina
Urgent timing of operation
Reoperation
Left ventricular ejection fraction
Left main coronary artery stenosis
Single-vessel disease
Triple-vessel disease
Myocardial infarction
Stroke or transient ischemic attack
Peripheral vascular disease
Diabetes
Hypertension
Renal insufficiency
Congestive heart failure
Chronic obstructive pulmonary disease
Elevated cholesterol
History of smoking
Family history of coronary artery disease
Exercise stress test

Perioperative factors

Single or double coronary artery bypass grafting
Use of arterial grafts
Coronary endarterectomy
Time in operating room
Crossclamp time
Cardiopulmonary bypass time
Length of time on ventilator
Length of intensive care unit stay
Length of hospital stay

Postoperative factors

Operative mortality
Low-output syndrome
Intraaortic balloon pump
Myocardial infarction
Stroke
Reoperation for bleeding
Sternal infection