Gender-related differences in morbidity and mortality during combined valve and coronary surgery

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See related articles on pages 929, 932, 936, and 950.

Background: Gender-related differences in morbidity and mortality are well described for coronary artery bypass grafting but are not well understood for combined valve and bypass surgery.

Methods: We reviewed retrospectively the morbidity and mortality of 1570 consecutive patients who underwent combined valve and bypass procedures at the Toronto General Hospital between January 1990 and October 2000.

Results: There were 1073 men (68%) and 497 women (32%). The mean ages ($\pm$ 1 SD) of women and men were 69 ± 9 and 68 ± 9 years, respectively ($P = .02$). Of the 1570 total patients, 973 patients (62%) underwent aortic valve and coronary bypass surgery, 481 patients (31%) had mitral valve and coronary bypass operations, and 116 (7%) patients had double or triple valve and coronary bypass operations. Preoperative hypertension ($P = .002$), diabetes ($P = .001$), and atrial fibrillation ($P = .001$) were seen more frequently in women. Body surface area was significantly lower in women ($P = .0001$). At presentation, more women were in congestive heart failure (69% vs 58%, $P = .001$) and in New York Heart Association functional class III or IV (25% vs 19%, $P = .001$). Although there was no difference in the number of women with three or more diseased vessels (32% vs 38%), only 35% of women received three or more grafts compared with 44% of men ($P = .001$). The use of left internal thoracic grafts, although uncommon in the whole study population (36%), was less common in women than in men (26% vs 41%, $P = .001$). Multivariable logistic analyses for morbidity and mortality showed female gender to be an independent risk factor. Mitral valve replacement, age, left ventricular dysfunction, New York Heart Association classes III and IV, and association of tricuspid valve disease, diabetes, peripheral vascular disease, and preoperative renal failure were found to be independent risk factors for mortality.

Conclusion: Female gender is an independent risk factor for combined morbidity and mortality during and after combined valve and coronary bypass surgery. As with isolated coronary artery bypass grafting, women undergoing combined procedures have more premonitory conditions, are more often in heart failure, had an equal incidence of triple vessel disease but received fewer grafts than men, and, therefore, were more frequently incompletely revascularized.

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Numerous studies have reported the morbidity and mortality results of mitral and/or aortic valve operations in combination with coronary artery bypass grafting (CABG).¹⁻⁷ However, the risk factors influencing the early and late outcomes of valve surgery combined with CABG (V/CABG) are not clearly defined. Additionally, the impact of gender as an independent risk factor for morbidity and mortality after V/CABG is unknown. Most studies examining iso-

lated CABG indicate that morbidity and mortality is higher for women than men.⁸⁻¹¹ Thus, gender may be an independent risk factor for morbidity and mortality after V/CABG surgery. The present study is a retrospective descriptive analysis undertaken to examine gender as a risk factor for morbidity and mortality during and after combined V/CABG.

Materials and Methods

All data were prospectively collected for 1570 consecutive patients undergoing V/CABG at Toronto General Hospital between January 1990 and October 2000. These data are part of a computerized data registry of all cardiac surgical patients at the Toronto General Hospital.

Laboratory Investigations

Cardiac catheterization was performed in all patients over 40 years old to assess ventricular function and the extent of coronary artery disease. The left ventricular (LV) ejection fraction was estimated by a single-plane ventriculogram and graded on a scale of 1 to 4 (1 = > 60%; 2 = 40%-60%; 3 = 20%-40%; and 4 = < 20%). Coronary artery narrowing of > 50% was considered significant.

Operative Technique

Fentanyl citrate was used for induction and maintenance of anesthesia. Cardiopulmonary bypass (CPB) was established in all cases with mild hypothermia (34°C). Myocardial protection was achieved with cold potassium blood cardioplegia (8:1) and a terminal hot shot in all cases. Distal anastomoses were constructed first, followed by replacement or repair of valve(s). The proximal anastomoses were performed after closure of the cardiac chambers. The left internal thoracic artery (LITA) and saphenous veins were used as conduits for CABG. Pharmacologic or mechanical support was initiated during weaning from CPB according to standard clinical practice. All patients were admitted to the intensive care unit postoperatively, and then transferred to the ward when their hemodynamic and respiratory functions were stable.

Preoperative Variables

Preoperative data that were collected included the following: age, gender, associated diseases such as diabetes mellitus, dialysis-dependent and nondependent renal failure, previous cardiac operations, New York Heart Association (NYHA) functional class, extent and symptoms of coronary artery disease, LV ejection fraction, and cardiac rhythm.

Perioperative and In-hospital Postoperative Variables

The type of valve prosthesis or reconstruction, type of conduit, number and site of distal anastomoses, aortic crossclamp time, and duration of CPB were recorded as operative variables. Low cardiac output syndrome was diagnosed when the cardiac index was less than $2 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ and inotropic support (pharmacologic or mechanical) was needed for longer than 20 minutes. Other postoperative complications (death, myocardial infarction [MI], bleeding, cerebrovascular accident, renal failure, sepsis, and wound infection) that occurred during the hospital stay were recorded.

Outcomes

The primary outcome, hospital mortality, was defined as any in-hospital death after surgery. Secondary outcome was defined as combined morbidity and mortality.

Statistical Methods

SAS Statistical Software 6.12 was used for all statistical analyses (SAS Institute, Inc, Cary, NC). Continuous variables are reported as the mean $\pm$ SD in the tables and text. Gender comparisons were made by *t* tests for continuous variables and by χ^2 or the Fisher exact test for categorical variables. The independent, multivariable predictors of outcome were determined by stepwise logistic regression analysis using methods previously reported.¹²

Results

Preoperative clinical characteristics are presented in Table 1. There were a total of 1570 patients in the study population, consisting of 1073 men (68%) and 497 women (32%). The women were older than the men.

Of the total patients, 62% underwent an aortic valve and CABG procedure, 31% a mitral valve and CABG procedure, and 7% a double valve and CABG procedure. Additionally, 13% of both men and women had had previous cardiac operations. Body surface area (BSA) was lower in women than in men ($1.7 \pm 0.2 \text{ m}^2$ vs $1.9 \pm 0.2 \text{ m}^2$, $P = .0001$). Preoperative hypertension and diabetes mellitus were more prevalent in women than in men. Women also more frequently had a history of preoperative thromboembolism in the form of transient ischemic attacks and strokes than men. There was no significant difference in the prevalence of preoperative renal failure, peripheral vascular disease, and chronic obstructive airway disease between men and women.

More women had congestive heart failure. The majority of patients of both sexes (83%) were in NYHA classes III and IV, but there was a gender-related difference with women tending to be more symptomatic. Unstable angina was present in 25% of women and 19% of men. Preoperative atrial fibrillation was more frequent in women. There was no gender-related difference in the number of diseased arteries, the proportion of patients with triple vessel disease, or the incidence of left main coronary artery disease. Similarly, LV ejection fraction was comparable between men and women.

Operative Findings

The operative characteristics of patients are shown in Table 2. There were no differences in CPB or clamp time between women and men. However, more women had urgent or emergency operations than men. Although the number of stenosed coronary arteries was equal between the sexes, and the proportion of patients with triple vessel disease was the same, women received fewer grafts than men. The use of

TABLE 1. Preoperative clinical parameters of patients undergoing combined valve and coronary artery bypass grafting between January 1990 and October 2000 at the Toronto General Hospital

Parameter	Female	Male	Total	P value
Patients	497 (32%)	1073 (68%)	1570 (100%)	
Age (years $\pm$ SD)	69 $\pm$ 9	68 $\pm$ 9		.02
BSA (m ²)	1.68 $\pm$ 0.20	1.93 $\pm$ 0.20		.0001
Hypertension	278 (56%)	509 (48%)	787 (50%)	.002
Diabetes	129 (26%)	188 (18%)	317 (20%)	.001
PVD	71 (14%)	140 (13%)	211 (13%)	NS
Renal failure	13 (2.62%)	37 (3.5%)	50 (3.18%)	NS
TIA/stroke	85 (17%)	124 (12%)	209 (13%)	.003
COPD	22 (4.43%)	49 (4.6%)	71 (4.52%)	NS
AF	109 (22%)	136 (13%)	245 (16%)	.002
CHF	341 (69%)	624 (58%)	965 (62%)	.001
NYHA I	7 (1.4%)	17 (1.59%)	24 (1.5%)	NS
NYHA II	47 (9.5%)	183 (17%)	230 (15%)	.001
NYHA III	231 (46%)	498 (46%)	729 (46%)	NS
NYHA IV	212 (43%)	374 (35%)	586 (37%)	.001
Angina				.001
None	145 (29%)	247 (23%)	392 (25%)	
Stable	225 (45%)	518 (48%)	743 (47%)	
Unstable	127 (25%)	291 (19%)	433 (19%)	.001
MI	39 (7.9%)	73 (7.8%)	112 (7.1%)	NS
Coronary artery disease				NS
$\leq$ 3	299 (67.9%)	652 (62.3%)	867 (63.5%)	
$\geq$ 3	158 (32%)	411 (38%)	569 (36%)	
LMS	53 (11%)	145 (14%)	198 (13%)	NS
Prior operation	70 (14%)	137 (13%)	207 (13%)	NS
AV disease				.001
Stenosis	194 (73%)	466 (67%)	660 (69%)	
Regurgitation	119 (12%)	88 (13%)	119 (12%)	
Mixed	182 (19%)	137 (20%)	182 (19%)	
AV pathology				.001
Rheumatic	15 (6%)	20 (3%)	35 (4%)	
Tricuspid/calc	160 (62%)	389 (60%)	549 (61%)	
Bicuspid	47 (18%)	175 (27%)	222 (25%)	
Other	53 (14%)	114 (10%)	167 (10%)	
MV disease				.001
Stenosis	41 (8.3%)	22 (2.05%)	63 (4.03%)	
Regurgitation	134 (27%)	306 (29%)	440 (28%)	
Mixed	40 (8.1%)	32 (3%)	72 (4.6%)	
MV pathology				.001
Rheumatic	102 (21%)	73 (6.9%)	175 (11%)	
Ischemic	68 (14%)	126 (12%)	194 (13%)	
Myxomatous	27 (5.5%)	117 (11%)	144 (9.3%)	

AF, Atrial fibrillation; AV, aortic valve; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; LMS, left main stem; m, meter; MI, myocardial infarction; MV, mitral valve; NS, not significant; NYHA, New York Heart Association Functional Class; PVD, peripheral vascular disease; SD, standard deviation; TIA, transient ischemic attack.

LITA grafts, although uncommon in the whole study population, was less common in women than in men.

Aortic stenosis, aortic regurgitation, and mixed valvular disease were equally frequent in men and women. Bicuspid aortic valve disease was more common in men. Mechanical aortic valves were used in 23% of men and 17% of women. Biologic aortic valves were used in 75% of men and 79% of women. Aortic valve repair (reimplantation and remodeling) operations were performed in 33 patients.^{13,14}

Mitral stenosis and mixed valve disease as well as rheumatic valve disease were significantly more common in women than in men. Myxomatous mitral disease was more common in men. Mitral valve repair was performed in 44% of men and 18% of women. Mitral valve replacement was more common in women. Biologic mitral valves were used in 40% of women and 28% of men. Mechanical mitral valves were used in the same proportion of men and women.

TABLE 2. Operative variables of patients undergoing combined valve and coronary artery bypass grafting between January 1990 and October 2000 at the Toronto General Hospital

Variable	Female	Male	Total	P value
Patients	497 (32%)	1073 (68%)	1570 (100%)	
Priority of operation				.013
Elective	278 (56%)	680 (63%)	958 (61%)	
Urgent	219 (45%)	393 (36%)	612 (39%)	
CPB ($\bar{x}$ min $\pm$ SD)	129 $\pm$ 3	129 $\pm$ 39		NS
Crossclamp time ($\bar{x}$ min $\pm$ SD)	98 $\pm$ 29	100 $\pm$ 30		NS
Distal grafts				.001
< 3	324 (65%)	591 (56%)	915 (58%)	
$\geq$ 3	655 (35%)	482 (44%)	655 (42%)	
LITA grafts	129 (26%)	436 (41%)	565 (36%)	.001
AV surgery				NS
AV repair	17 (6%)	16 (2%)	33 (3%)	
AV replacement	258 (94%)	681 (98%)	939 (97%)	
MV surgery				.001
MV repair	32 (18%)	129 (44%)	161 (34%)	
MV replacement	150 (82%)	167 (56%)	317 (66%)	

AV, Aortic valve; CPB, cardiopulmonary bypass; LITA, left internal thoracic artery; MV, mitral valve; ns, not significant; SD, standard deviation; $\bar{X}$, mean.

Outcome

Postoperative complications are shown in Table 3. Low cardiac output syndrome, the use of intra-aortic balloon pumping, incidence of leg infection, and requirement for permanent pacing were higher in women than men. There was no difference between the sexes in perioperative MI, postoperative stroke, renal failure, sepsis, or wound infection.

Overall hospital mortality was 7% in women and 4% in men ($P = .02$). Analysis in different subgroups showed that mortality was highest in double and triple valves and CABG (9.8%), followed by mitral valve and CABG (7.3%), and lowest in aortic valve and CABG (3.4%). When mitral valve repairs were excluded, overall hospital mortality was highest in the mitral valve replacement and CABG group (10.62%, $P = .001$).

Over the 10-year period covered by this study, annual hospital mortality for all patients decreased from 6.8% in 1990 to 1.3% in 2000. There was a trend of decreasing mortality in men (6.9% to 0.9%). In women, in-hospital mortality was higher than in men and did not decrease significantly over the 10 years. Combined morbidity and mortality decreased significantly over the 10-year period in men but not in women (32% vs 21%, $P = .002$; 55% vs 38%, $P = .21$).

Multivariable logistic analyses for morbidity and mortality are shown in Table 4. The following risk factors were found to be independent risks of mortality: mitral valve replacement, age, LV dysfunction, NYHA classes III and IV, association of tricuspid valve disease, diabetes, peripheral vascular disease, and preoperative renal failure. Female gender was an independent risk factor for combined mortality and morbidity even when corrected for BSA.

Discussion

More men than women (2:1) underwent combined V/CABG procedures. The difference in rates of procedures is similar to that seen for CABG. This difference may reflect a difference in the incidence of disease and/or a lower rate of referral of women for the procedures. If the latter, fewer women may be referred because of a perceived high risk and poor outcome. Many studies, including those from our own institution, indicate that V/CABG operations are associated with a greater risk for early death than valve or CABG procedures alone.¹³⁻¹⁵ Table 5 gives the gender-specific mortality for isolated aortic, mitral, double valve, and CABG operations at our institution during the study period. Furthermore, our study demonstrates that operative mortality and morbidity after V/CABG is significantly higher in women than in men. In isolated CABG, these differences have been attributed by other investigators to differences in the demographic profile of women at the time of operation¹⁶⁻¹⁸ or to a referral bias.¹⁸⁻²⁰ Women undergoing isolated CABG have more comorbid factors, such as diabetes and hypertension, and a smaller body size than men.²⁰⁻²² In our study, this is also true for women undergoing V/CABG procedures. We found that women were older, smaller, and had more comorbid conditions such as hypertension, diabetes, transient ischemia attacks, and stroke. Similarly, more women than men required urgent or emergency operations with advanced NYHA functional class and congestive heart failure. These latter data suggest that the increase in morbidity and mortality may be related to late presentation, late referral, or both.

We did not see a difference in the number of diseased vessels, proportion of triple vessel disease, and left main

TABLE 3. Postoperative complications of patients undergoing combined valve and coronary artery bypass grafting between January 1990 and October 2000 at the Toronto General Hospital

Complication	Female	Male	Total	P value
MI	13 (2.6%)	19 (1.78%)	32 (2.0%)	NS
LCOS	84 (17%)	110 (10%)	194 (12%)	.001
IABP	45 (9.1%)	56 (5.2%)	101 (6.4%)	.011
Stroke	16 (3.2%)	35 (3.2%)	51 (3.2%)	NS
Renal function	10 (2.0%)	21 (2.0%)	31 (2.0%)	NS
Infection leg	17 (3.4%)	18 (1.7%)	35 (2.2%)	.030
Permanent pacing	45 (9.1%)	67 (6.3%)	112 (7.1%)	.045
Hospital mortality	18 (7%)	45 (4%)	79 (5%)	.026
Combined morbidity and mortality	192 (39%)	314 (29%)	506 (32%)	.001

IABP, Intra-aortic balloon pump; LCOS, low cardiac output syndrome; MI, myocardial infarction; NS, not significant.

TABLE 4. Multivariable analysis for mortality and morbidity of patients undergoing combined valve and coronary artery bypass grafting between January 1990 and October 2000 at the Toronto General Hospital

Variable	Upper confidence limit	Odds ratio	Lower confidence limit
Mitral valve replacement	3.397	2.530	1.884
Age	1.037	1.023	1.009
Female gender	1.819	1.423	1.113
Left ventricular dysfunction	1.689	1.293	0.989
NYHA class	1.769	1.378	1.073
Urgent operation	2.581	1.773	1.218
Number of diseased vessels	1.285	1.142	1.015
Reoperation	4.660	3.032	1.973
Aortic stenosis	1.805	1.374	1.046
Endocarditis	8.444	3.025	1.084
Hypertension	1.574	1.249	0.990
PVD	1.870	1.353	0.979
Renal failure	5.242	2.739	1.431

NYHA, New York Heart Association; PVD, peripheral vascular disease.

stem disease between women and men. Even though there were no differences in the number of diseased vessels between men and women, there were significant differences in the extent and type of revascularization. Only 35% of women had three or more grafts versus 44% of men. This may be incomplete revascularization for women or over-revascularization for men. The increased incidence of low cardiac output syndrome, use of postoperative IABP, and increased hospital mortality suggest it is incomplete revascularization for women.

Use of the LITA in men and women for V/CABG procedures was low for both men and women but more so for women. Other investigators have reported that use of the LITA graft in CABG does not increase morbidity and mortality and in some situations is associated with decreased mortality both in isolated CABG and in combined V/CABG procedures.^{6,23,24} The lower frequency of use of

TABLE 5. Gender-specific mortality for isolated aortic valve replacement, mitral valve replacement double valve replacement, and coronary artery bypass grafting between January 1990 and October 2000 at the Toronto General Hospital

Procedure	Female (%)	Male (%)
AVR	2.3	1.7
MVR	3.3	2.2
DTV	8.8	4.6
CABG	3.6	1.6

AVR, Aortic valve replacement; CABG, coronary artery bypass grafting; DTV, double, triple valve replacement; MVR, mitral valve replacement.

the LITA graft in our study may have contributed to the increased mortality in women and may reflect an institutional bias. Since we intended this study to be a prognostic tool for patients undergoing combined V/CABG, all process of care variables including LITA use were not included in the survival statistical model.

Mitral valve replacement appears to be an independent risk factor for morbidity and mortality in V/CABG operations. Other investigators have reported that mortality in combined mitral valve and CABG surgery is higher for women than men.²⁵ In our study, women underwent mitral valve replacements more often than men. This is most likely related to the etiology of the valve disease. In our study, severe mitral stenosis and mixed valve disease as well as rheumatic valve disease were significantly more common in women than men. Myxomatous mitral disease was more common in men. It is known that rheumatic mitral stenosis is less amenable to repair than myxomatous mitral regurgitation and that operative mortality is lower after mitral valve repair than after replacement.²⁶ These findings may explain why a significantly smaller number of women underwent mitral valve repair as well as some of the differences in mortality.

In our study, female gender was an independent predictor for increased combined morbidity and mortality. Aranki and

coworkers²⁷ also reported that female gender was a significant predictor of operative mortality in the concomitant aortic valve replacement/CABG group but not in the isolated aortic valve replacement group. In previous reports from our unit and others,^{28,29} gender was not found to be an independent risk factor in isolated valve replacement. Unpublished data from our unit suggests that female gender is an independent predictor for isolated CABG. These data suggest that the differences in morbidity and mortality in women and men in V/CABG operation may be related to the coronary artery disease and its associated comorbid conditions.

Conclusions

It is apparent that there are differences in morbidity and mortality after combined V/CABG procedures for men and women.

We found that female gender is an independent risk factor for increased morbidity and mortality. It is not clear whether the differences are due to sex-related differences in the biology of the disease or in gender-related issues of treatment and access to care. Further investigation is merited. In addition, perhaps it is time to acknowledge and embrace the concept that there are differences between the genders and to develop a separate and distinct analysis of mortality and morbidity risks in women. Until this occurs, careful consideration should be given to the true risks and benefits of V/CABG for women.

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