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The Importance of Prior Stroke for the Adjusted Risk of Neurologic Injury after Cardiac Surgery for Women and Men

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Background: **Women are at higher risk for stroke after cardiac surgery than men. Prior analysis of risk profiles for perioperative stroke that have mostly combined data from women and men may fail to identify gender-specific risks. The purpose of this study was to evaluate whether patient gender impacts adjusted risk for stroke after cardiac surgery.**

Methods: **Demographic and perioperative data were prospectively collected from 2,972 patients undergoing cardiac surgery. Carotid artery ultrasound examination was performed before surgery for patients aged 65 yr or older or when there was a history of transient ischemic attacks or prior stroke. Epiaortic ultrasound was performed at the time of surgery in all patients to assess for atherosclerosis of the ascending aorta.**

Results: **Strokes occurred after surgery in 30 women and 18 men ($P < 0.0001$). Based on multivariate logistic regression analysis, a history of a stroke was the strongest predictor of new stroke for both women and men. Low cardiac output syndrome, atherosclerosis of the ascending aorta, and diabetes mellitus were significantly associated with stroke for women but not for men. Analysis on the data from all patients using a gender-interaction term found that the risk for stroke associated with patient age, atherosclerosis of the aorta, diabetes, and duration of cardiopulmonary bypass was not affected by gender. The prior stroke–gender interaction, however, was significant ($P = 0.017$), suggesting that a prior cerebrovascular event was a more important predictor of stroke for men than women.**

Conclusions: **These data show that prior stroke before surgery is strongly and independently associated with susceptibility for stroke after cardiac surgery, particularly for men. Other risk factors for perioperative stroke, though, do not appear to be influenced by patient gender.**

WHILE mortality from cardiovascular disease is declining for men, the rates of death for women have been increasing during the past decade and have even surpassed the rates for men since the mid-1980s.[1] A rising prevalence of coronary artery disease coupled with higher mortality after myocardial infarction and after nonsurgical and surgical myocardial revascularization procedures for women compared with men may in part explain these mortality trends.[1–14] Together, these observations suggest that there are basic biologic differences in the pathophysiologic responses to coronary artery disease and its treatments between women and men. Understanding the mechanisms for gender differences in outcomes from cardiovascular diseases and related interventions is thus justifiably receiving increasing attention.

Stroke after cardiac surgery is an important cause of mortality, health resource utilization, and impaired quality of life.[4,5,15–26] In an analysis of single-institution and multiinstitutional data, our group has shown that female gender is associated with risk for stroke after cardiac surgery independent of other stroke risk factors and that this higher risk explains a large portion of the excess operative mortality for women.[4,5] Variables identifying risk for perioperative neurologic injury, therefore, could be influenced by patient gender. Prior investigations that have developed predictive risk models for this complication, nonetheless, have mostly combined data from both men and women.[17,19,22–24] If factors that affect stroke risk vary between genders, the latter approach may fail to properly identify those factors that predispose women and men separately for perioperative stroke. The latter would have adverse effects on risk stratifying patients for surgery as well as on the development of stroke preventative strategies or treatments. Accordingly, the purpose of this study was to evaluate whether patient gender impacts adjusted risks for stroke after cardiac surgery.

Materials and Methods

The population consisted of 2,972 patients (out of 3,321 consecutive individuals) aged 50 yr or younger who were undergoing cardiac surgery at a single institution that was part of a previously reported series.[4] There were 1,900 men and 1,072 women. This study was approved by the Human Studies Committee at Washington University (St. Louis, Missouri). Details of the data collection have been reported.[4,5,21,25] Demographics and preoperative patient data were prospectively recorded in an institutional database by trained research nurses. These data included history of a prior stroke that was verified by review of medical records, and the results of computed tomography and/or magnetic resonance imaging when available, or by contacting the patient's primary care physician. Left ventricular function was assessed with angiography at the time of coronary artery angiography using criteria of the Coronary

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Artery Surgery Study.[27] The patients underwent a carotid artery duplex scan if they were aged 65 yr or older, if there was a carotid artery bruits, and/or if there were symptoms or history of strokes, including transient ischemic episodes. Stenosis of the carotid arteries was graded as insignificant or no disease (luminal narrowing $\leq$ 50%), moderate disease (narrowing $>$ 50% but $<$ 70%), or severe disease (narrowing $\geq$ 70%). All patients underwent epiaortic ultrasound of the ascending aorta at the time of surgery to assess for atheromatous disease using methods previously reported.[4,21,25,28–30] Atherosclerosis severity was graded by two blinded investigators as insignificant or no atherosclerosis, mild atherosclerosis (intimal thickening $<$ 3.0 mm without intimal irregularities), or moderate to severe atherosclerosis ($\leq$ 3.0 mm thickening with diffuse irregularities, large mobile or protruding atheromata, ulcerated plaques, and/or thrombi).

Documented complications included perioperative myocardial infarction (new Q wave on 12-lead electrocardiogram or lactate dehydrogenase 1 and 2 ratio $>$ 1), low cardiac output syndrome (cardiac index $<$ 2.0 l $\cdot$ min^{-1} $\cdot$ m^{-2} for $>$ 24 h postoperatively regardless of treatment), renal failure requiring dialysis, and death. The patient's electrocardiogram was continuously monitored after surgery with telemetry to document atrial fibrillation. Patients were evaluated daily by physicians, including intensivists, surgeons, and often cardiologists. A neurologist was consulted when a new neurologic deficit was suspected based on this daily examination or when there was a change in the patient's status noted by the nursing staff. The diagnosis of a stroke was made by a neurologist based on clinical examination and, in the majority of patients, confirmed by computed tomographic scan of the head. The definition of stroke was a new permanent global or focal neurologic deficit not attributable to other neurologic (*e.g.*, dementia) and/or medical (*i.e.*, metabolic abnormalities, hypoxia, or drugs) causes. Transient or reversible neurologic ischemic events (neurologic deficits resolving in $<$ 24 h or $>$ 24 h, respectively) were not included in the analysis because of difficulty consistently documenting such events in the presence of residual anesthetics, analgesics, and sedative drugs.

Statistical Analysis

Data were analyzed using version 8 of SAS (SAS Institute, Cary, NC). Comparisons were made between women and men and separately for members of each gender with and without a perioperative stroke. Univariate comparisons between subjects with and without stroke were performed with chi-square tests for dichotomous variables and *t* tests or Wilcoxon tests for continuous variables. Stepwise logistic regression was used to select a best set of independent predictors of stroke. Variables entered into the initial logistic models were those with a univariate *P* value $<$ 0.2. The final model included all variables with an independent significance level of $P < 0.1$. The quality of the fit of the logistic model was tested with the Hosmer and Lemeshow goodness-of-fit test. Data for continuous variables are presented as mean $\pm$ SD. A significant difference was considered for values of $P < 0.05$.

Results

Demographic and other patient variables are listed for women and men in table 1. Women were significantly older than men, and they more often had coexisting medical conditions, such as diabetes, hypertension, and prior strokes, but a lower frequency of severe carotid stenosis. Single- and two-vessel coronary artery disease were more common in women than men, but there was no difference in the frequency of significant left main coronary artery stenosis between genders. Left ventricular wall motion score was lower in women than in men, indicating better ventricular function. There was no difference in the frequency of moderate or severe atherosclerosis of the ascending aorta between genders. Women more frequently underwent valvular surgery than men, but the duration of cardiopulmonary bypass and aortic cross clamping was no different between women and men. After surgery, women were more likely than men to have low cardiac output syndrome and myocardial infarction. New stroke occurred in 48 patients, of whom 30 patients were women and 18 were men ($P < 0.001$).[4] Operative mortality for women was higher than for men (5.4% *vs.* 2.9%, $P = 0.0008$).

Univariate variables associated with perioperative stroke are separately listed for women and men in table 2. Preoperative history of a stroke, severity of atherosclerosis of the ascending aorta, low cardiac output syndrome, and perioperative myocardial infarction were more frequent in both women and men with stroke when compared with patients of the same sex not having this complication. Other univariate predictors of stroke, however, differed between genders. Compared with women not experiencing a stroke, women with a perioperative stroke were more likely to have diabetes, but diabetes did not impact stroke risk for men. In contrast, hypertension, severe carotid artery stenosis, left main coronary artery stenosis, duration of cardiopulmonary bypass, duration of aortic cross clamping, and postoperative atrial fibrillation ($P = 0.066$) were univariate predictors of stroke for men but not for women.

Independent variables associated with stroke after cardiac surgery are listed separately for women and men in table 3. After adjusting for other risk factors with multivariate logistic regression analysis, history of a stroke before surgery was the strongest predictor of new perioperative stroke for both women and men. For women,

Table 1. Patient Characteristics

	Women (n = 1072)	Men (n = 1900)	*P*
Age, yr	70.0 ± 8.4	67.2 ± 8.7	< 0.0001
History of stroke, %	7.7	5.5	0.061
Diabetes mellitus, %	34.8	23.8	< 0.0001
Hypertension, %	73.3	60.7	< 0.0001
Left ventricular score	9.0 ± 4.0	9.5 ± 4.0	0.002
Pulmonary disease, %	8.2	10.3	0.054
Severe carotid artery stenosis, %*	4.3	6.4	0.031
Coronary stenosis†			
One vessel, %	9.2	6.5	—
Two vessels, %	22.7	20.5	< 0.0001
Three vessels, %	61.7	69.8	—
Left main, %	19.0	21.5	0.100
Ascending aorta atherosclerosis‡			
Normal/mild %	84.3	84.8	—
Moderate, %	10.6	11.1	0.473
Severe, %	5.0	4.1	—
Types of surgery			
CABG, %	64.2	78.5	—
CABG/valvular, %	16.8	8.7	< 0.0001
Valvular, %	19.0	12.8	—
Cardiopulmonary bypass time, min	125 ± 46	126 ± 46	0.673
Cross-clamp time, min	81.7 ± 35	80.6 ± 31	0.380
Postoperative events			
Low cardiac output, %	7.3	3.9	0.0005
Myocardial infarction, %	3.5	1.5	0.002
Atrial fibrillation, %	33.5	35.0	0.414
New stroke, %	2.8	0.9	< 0.0001
Mortality rate, %	5.4	2.9	0.0008

Data are mean ± SD.

* Carotid artery stenosis ≥ 70%. † Coronary stenosis > 70% or > 50% luminal narrowing of left main coronary artery. ‡ Mild ascending aorta atherosclerosis refers to intimal thickening < 3.0 mm without intimal irregularities, moderate and severe refers to intimal thickening ≥ 3.0 mm or diffuse irregularities or with large mobile or protruding atheromata, ulcerated plaques, or thrombi, respectively.

CABG = coronary artery bypass graft.

other variables significantly associated with stroke included low cardiac output syndrome, atherosclerosis of the ascending aorta, and diabetes mellitus. These latter variables were not significantly associated with stroke risk for men, perhaps because of the striking predominance of a prior stroke in men with perioperative stroke. That is, the fact that 15 of 18 men (83%), in contrast to 15 of the 30 women (50%), with a perioperative stroke had a history of a neurologic event before surgery likely precluded adequate assessment of whether other variables might have additional independent significance in identifying risk for stroke for men. To better assess the effect of gender on risk for perioperative stroke, an interaction term that included patient gender was used in a multivariate logistic regression analysis using the entire data set not separated by gender. Based on this analysis (table 4), only the gender–history of stroke interaction term reached significance as an independent predictor of stroke. These latter analyses suggest, at least in this cohort, that gender does not significantly impact the association between stroke risk and atherosclerosis of the aorta, diabetes, and duration of cardiopulmonary bypass. Patient gender does, however, influence the risk for stroke associated with a prior stroke.

Discussion

It is widely reported that women undergoing cardiac surgery have higher operative mortality compared with men, a finding further confirmed by our results.[4,5,6–9] Common explanations for this finding have included that women are of more advanced age at the time of surgery than men, that they have a higher frequency of comorbid conditions, and that they have smaller coronary artery size that compromises the surgical anastomosis. In an analysis of these data, our group has previously reported that, after adjusting for known stroke risk factors including age, diabetes, and atherosclerosis of the ascending aorta and carotid arteries, female gender was independently associated with risk for perioperative stroke and that women with this complication were more likely than men to have mortality.[4] These findings were confirmed in analysis of multiinstitutional data from 416,347 patients (32% women) enrolled in the Society of Thoracic Surgery National Cardiac Surgery database.[5] We have further shown that stroke was second only to low cardiac output states as a cause of mortality after cardiac surgery for women.[31] Taken together, these prior analyses show that women undergoing cardiac surgery are

Table 2. Demographic and Other Characteristics for Women and Men with or without New Perioperative Stroke

	Women without Stroke (n = 1042)	Women with Stroke (n = 30)	*P* (*vs.* Women without Stroke)	Men without Stroke (n = 1882)	Men with Stroke (n = 18)	*P* (*vs.* Men without Stroke)
Age, mean ± SD	70 ± 8	72 ± 7	0.195	67 ± 9	69 ± 9	0.311
History of stroke, %	6.5	50.0	<0.0001	5.6	83.3	< 0.0001
Diabetes mellitus, %	34.2	56.7	0.011	23.8	27.8	0.690
Hypertension, %	73.1	80.0	0.401	60.5	83.3	0.049
Left ventricular score, %	9.0 ± 3.9	10.5 ± 4.5	0.039	9.5 ± 4.0	9.9 ± 4.9	0.629
Pulmonary disease, %	8.1	10.0	0.708	10.3	11.1	0.911
Severe carotid artery stenosis, %*	4.3	3.4	0.826	6.3	21.4	0.021
Coronary stenosis†						
None, %	6.5	0.0	—	3.3	0	—
One vessel, %	9.0	14.3	—	6.5	5.6	—
Two vessels, %	22.7	25.0	0.436	20.4	27.8	0.774
Three vessels, %	61.8	60.7	—	69.8	66.7	—
Left main, %	18.9	20.0	0.882	21.3	44.4	0.017
Ascending aorta atherosclerosis‡						
Normal, %	66.0	40.0	—	67.6	44.4	—
Mild, %	18.9	23.3	0.0008	17.5	16.7	0.001
Moderate/severe, %	15.1	36.7	—	14.9	38.9	—
Types of surgery						
CABG, %	64.6	53.3	—	78.6	72.3	—
CABG/valve, %	18.5	33.3	0.125	12.6	27.8	0.088
Valve, %	16.9	13.3	—	8.8	8.0	—
Cardiopulmonary bypass time, min	124 ± 45	137 ± 52	0.15	125 ± 39	223 ± 34	< 0.0001
Cross-clamp time, min	82 ± 35	86 ± 40	0.528	80 ± 31	109 ± 40	0.002
Postoperative events						
Low cardiac output syndrome, %	6.8	27.3	0.0003	3.7	14.3	0.042
Myocardial infarction, %	3.2	13.0	0.011	1.5	7.1	0.089
Atrial fibrillation, %	33.6	30.0	0.681	34.8	55.6	0.066

* Carotid artery stenosis ≥ 70%. † Coronary stenosis > 70% or > 50% luminal narrowing of left main coronary artery. ‡ Mild ascending aorta atherosclerosis refers to intimal thickening < 3.0 mm without intimal irregularities, moderate and severe refers to intimal thickening ≥ 3.0 mm or diffuse irregularities or with large mobile or protruding atheromata, ulcerated plaques, or thrombi, respectively.

CABG = coronary artery bypass graft.

more likely than men to have a stroke and that this complication contributes to the excessive operative mortality for women compared with men.

In the current study, we extended our previous analysis to evaluate whether patient gender impacted the risks for perioperative stroke. The rationale for this approach is that if susceptibility for stroke differs for each gender, then combining data from men and women (who are a minority of patients) when devising risk profiles could obfuscate important gender-specific risks. Our results showed that many univariate predictors for stroke after cardiac surgery were similar for women and men (table 2), although others differed (*e.g.*, diabetes and perioperative myocardial infarction for women; left ventricular function, severe carotid stenosis, significant left main coronary artery stenosis, duration of cardiopulmonary bypass and aortic cross clamping, and postoperative atrial fibrillation for men). After adjusting for these

Table 3. Independent Predictors of Stroke after Cardiac Surgery by Gender

Variable	Odds ratio (95% confidence interval)	*P*
Women		
History of stroke	44.5 (15.1–130.8)	< 0.0001
Ascending aorta atherosclerosis	2.1 (1.4–3.4) *	0.001
Low cardiac output	6.7 (1.8–24.8)	0.004
Diabetes	2.2 (1.4–3.4)	0.010
Men		
History of stroke	305.8 (38.8–999.0)	< 0.0001
Low cardiac output	1.9 (0.3–11.7)	0.470
Ascending aorta atherosclerosis	1.5 (0.9–2.5) *	0.140
Diabetes mellitus	0.9 (0.3–3.6)	0.944

* Odds ratio reflects risk of stroke with increase in a single level in the aortic scan results. The odds of an increase of two levels (*e.g.*, normal to moderate/severe) is the square of the reported odds ratio.

Table 4. Significance Levels for Gender-interaction Terms for Predictors of Stroke after Cardiac Surgery

Variable	*P*
History of stroke	0.017
Low cardiac output	0.838
Ascending aorta atherosclerosis	0.812
Diabetes mellitus	0.272

variables using multivariate logistic regression analysis, we found that a prior stroke, low cardiac output state, atherosclerosis of the ascending aorta, and diabetes were independently associated with risk for perioperative stroke for women. These variables are similar to those found in prior studies to be associated with risk for stroke using combined data from men and women. Our current analysis did show that a prior stroke was the only variable independently associated with perioperative stroke for men. This latter analysis, though, cannot necessarily say that the other variables found to be independently associated with stroke risk in women are not associated with susceptibility for men because of the predominance of the prior stroke variable relative to the small number of new perioperative strokes in men in this cohort. To better assess the influence of patient gender on stroke risk factors, multivariate logistic regression analysis was performed on the combined data from women and men, and interaction terms were used to evaluate for the influence of gender on the individual variables. These results showed that gender did not influence the impact of ascending aortic atherosclerosis, diabetes, or low cardiac output on the independent risk for stroke. A history of a stroke before surgery, however, was significantly influenced by sex such that this variable was much more of a significant factor for identifying stroke risk for men compared with women.

A neurologic event prior to surgery is a known risk factor for new stroke after cardiac surgery, although some studies have failed to confirm this finding.[4,5,15,16,19,20,22–24,26] An explanation for this observation, however, is not clear. The majority of ischemic strokes after cardiac surgery result from cerebral embolism and/or cerebral hypoperfusion.[4,20,24,26] Atherosclerosis of the ascending aorta is increasingly recognized to be associated with high risk for stroke in the general population as well as after cardiac surgery.[4,21,25,28–30,32–34] During surgery, atheroma may be dislodged during aortic manipulations necessary for cardiopulmonary bypass and during anastomosis of proximal coronary artery bypass grafts, leading to cerebral and systemic embolization. Further, operative injury to atheroma might expose thrombogenic material predisposing to thromboembolism.[35] In a study of 1,200 cardiac surgical patients, our group found that atherosclerosis of the ascending aorta, older age, hypertension, and atrial fibrillation were more frequent ($P < 0.01$) in patients with a prior neurologic event (n = 158) compared with patients without this history.[30] Based on multivariate logistic regression analysis, hypertension (odds ratio 1.81, $P = 0.02$), atherosclerosis of the ascending aorta (odds ratio 1.65, $P = 0.013$), and atrial fibrillation (odds ratio 1.54, $P = 0.06$) were independently associated with a history of prior stroke. A neurologic deficit before surgery, therefore, might merely identify patients with preexisting conditions that increase susceptibility to neurologic injury. In the current study, after adjusting for these risk factors, though, a history of stroke before surgery was independently associated with risk for a new perioperative stroke for men and women. Thus, susceptibility for perioperative stroke can not be solely explained by the confounding effects of a higher prevalence of other stroke risk factors for patients with a history of stroke.

Another explanation for the strong association between a prior cerebrovascular accident and perioperative stroke might be that the latter is an exacerbation or extension of the former event. In a case–control study, new neurologic deficits developed postoperatively in 43.7% of 71 patients with a documented stroke prior to surgery.[26] Of these patients, 26.8% of patients had the reappearance of a previous deficit, and 8.5% of patients had worsening of a previous deficit. Brain computed tomography or magnetic resonance imaging failed to identify new brain lesions, suggesting that many patients with prior stroke appear to have injury to brain areas previously involved with infarction. Brain tissue in the ischemic penumbra of an old infarction and/or compensatory circuitry resulting from cortical somatosensory reorganization that occurs after the initial brain infarction may be more susceptible to perioperative injury than other brain areas.[26,36,37] Impaired autoregulatory control of cerebral blood flow resulting from prior cerebral injury might further increase susceptibility to brain hypoperfusion during cardiopulmonary bypass or with perioperative hemodynamic fluctations.[38]

A strength of this database is the extensive documentation of important stroke risk factors allowing for a more precise statistical adjustment than many other analyses that have focused more on demographic and operative variables. We have previously reported that when adjustments are made for atherosclerosis of the ascending aorta and carotid arteries, many previously reported risk factors for stroke (*e.g.*, patient age and hypertension) were not independently associated with perioperative stroke.[4] That is, some risk factors for perioperative stroke may serve as a surrogate marker for more important risk factors such as atherosclerosis of the ascending aorta and cerebral vasculature. Interestingly, in this study, atrial fibrillation was not independently associated with stroke risk for men or women. Atrial fibrillation, which occurs in more than 30% of patients after cardiac surgery, is reported to increase the risk for perioperative stroke nearly threefold, possibly by increasing the risk for thromboembolism.[39,40] In our previous analysis, we found that atrial fibrillation was independently associ-

ated with postoperative stroke only when associated with low cardiac output syndrome.[4] This suggests the possibility that, at least for some patients, the relation between atrial fibrillation and perioperative stroke is due to an association between this arrhythmia and other stronger stroke risk factors. That is, atrial fibrillation may not necessarily be a direct cause of the neurologic event, but rather an epiphenomenon. There are no data from cardiac surgical populations on whether stroke-preventative strategies for patients with postoperative atrial fibrillation, such as anticoagulation or early cardioversion, can lower the risk of perioperative stroke. Further understanding of the relation between postoperative atrial fibrillation and stroke is necessary to assess the benefits *versus* risks of any therapeutic strategies aimed at reducing the risk for stroke.

A limitation of this study is that our methods for detecting strokes were insensitive. Although the diagnosis of stroke was made by a neurologist, this diagnosis was dependent on detecting new deficits by the patient's primary physicians. The patients did not undergo an extensive preoperative neurologic examination nor was there a systematic neurologic examination made after surgery. A more detailed examination might have detected more subtle neurologic complications such as neurocognitive dysfunction. Thus, the strokes detected in this study most likely represented the most severe form of neurologic complications of surgery, while other lesser severe forms of neurologic injury went undetected. Finally, we acknowledge that in an analysis in which more than one statistical test has been performed, a multiple comparisons issue arises, and some associations may be significant by chance.

In conclusion, these data show that a prior stroke before surgery is strongly and independently associated with susceptibility for stroke after cardiac surgery, particularly for men compared with women. Other risk factors for perioperative stroke, though, do not appear to be influenced by patient gender.

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