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Risk Factors for Neurocognitive Dysfunction After Cardiac Surgery in Postmenopausal Women

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Abstract

Background—Women are at higher risk than men for neurologic complications from cardiac operations. This study identified risk factors for neurocognitive dysfunction after cardiac operations in elderly women.

Methods—One hundred thirteen postmenopausal women undergoing primary coronary artery bypass grafting, with or without valve operation, underwent psychometric testing and neurologic evaluation the day before operation and 4 to 6 weeks postoperatively. Risk factors assessed for neurologic complications included atherosclerosis of the ascending aorta and apolipoprotein ε4 genotype. Postoperative neurocognitive dysfunction was defined as the composite end point of a one standard deviation decrement from baseline on two or more psychometric tests or a new neurologic deficit.

Results—Neurocognitive dysfunction was present in 25% of the women 4 to 6 weeks postoperatively. Women with a neurocognitive deficit tended to be older than those without a deficit (72.1 ± 8.1 vs 69.4 ± 8.9 years, $p = 0.144$) and were more likely to have mild atherosclerosis of the ascending aorta, a history of congestive heart failure, longer duration of cardiopulmonary bypass (CPB) and aortic cross-clamping, lower nadir blood pressure during CPB, higher rates of postoperative atrial fibrillation, and longer postoperative hospitalization. Mild atherosclerosis of the ascending aorta, duration of CPB, duration of aortic cross-clamping ($p = 0.051$), and length of postsurgical hospitalization were independently associated with postoperative neurocognitive dysfunction.

Conclusions—Mild atherosclerosis of the ascending aorta, duration of CPB, aortic cross-clamping time, and length of hospitalization, but not apolipoprotein ε4 genotype, identified risk for neurocognitive dysfunction after cardiac operation in postmenopausal women.

Brain injury from cardiac operations is an important source of patient morbidity and mortality [1,2]. Identification of susceptibility for these complications might allow for a focused implementation of neuroprotective practices [1]. Our group has reported that women are more susceptible than men to perioperative neurologic complications, and that this susceptibility explains a large portion of their excess operative mortality compared with men [3–6].

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Because they are a minority of patients, women are underrepresented in most investigations that evaluate perioperative outcomes [2,7,8]. Thus, risk stratification for women is mostly based on data obtained primarily from men, despite the findings that women present for cardiac operation with a different distribution of atherosclerotic and vascular risk factors for brain injury [9–12]. We have previously assessed sex-specific risk factors for stroke after cardiac operation [4,6]. Neurocognitive dysfunction is the most common manifestation of perioperative brain injury [1,2]. Although there is overlap, many risk factors for postoperative neurocognitive dysfunction are distinct from those associated with stroke [2]. Further, despite data suggesting sex differences in the effects of cardiac operation on cognition, data are scarce regarding the predictors of this complication specifically for women [13].

In a prospectively randomized, double-blinded, placebo-controlled trial in elderly women, we evaluated whether the natural neuroprotectant 17β-estradiol given perioperatively would improve neurologic outcomes after cardiac operation [14]. However, no differences were detected in the frequency of the primary outcome—postoperative neurocognitive dysfunction—between 17β-estradiol- and placebo-treated patients. Using that same cohort, here we evaluated the risk factors for neurocognitive dysfunction 4 to 6 weeks postoperatively in elderly women undergoing cardiac operation with cardiopulmonary bypass (CPB).

Patients and Methods

All study procedures were performed after first receiving Institutional Review Board approval and individual informed consent. Our previously described study enrolled 174 women aged 55 years and older undergoing primary coronary artery bypass graft (CABG) or cardiac valve replacement, or both [14]. The patients underwent testing with a psychometric battery 1 to 2 days preoperatively and 4 to 6 weeks postoperatively. The battery conformed with consensus guidelines, was designed to assess a broad array of cognitive domains, and included the following tests:

- the Rey Auditory Verbal Learning Test, a test of verbal memory in which patients recall a 15-word list 30 minutes after initial presentation;
- the Digit Symbol subtest of the Wechsler Adult Intelligence Scale, a measure of psychomotor speed, in which patients transcribe number-symbol pairs under timed pressure;
- Trail Making Tests A and B, in which patients connect numbered and then alternately numbered and lettered dots under timed conditions to assess attention and mental flexibility;
- the Grooved Peg Board Test, which involves inserting notched pegs into fitted holes on a shallow box to test fine motor dexterity; and
- the Benton Visual Form Discrimination Test, which involves visually matching target shapes as a test of visuoperception [15–22], and
- the National Institutes of Health (NIH) Stroke Scale, a standardized and validated neurologic examination that measures neurologic function in 11 categories on a 42-point scale [23], with increases in the score representing worsened neurologic function.

Perioperative Care

We have previously described patient management during and after surgical intervention that included administration of midazolam, opioids, and volatile anesthetics, nonpulsatile CPB with a membrane oxygenator, and maintenance of body temperature between 32° and 34°C [14,

24]. Antifibrinolytic therapy was an exclusion criterion due to unknown interactions between lysine analogs or aprotinin and 17β-estradiol. Epiaortic ultrasound scanning of the ascending aorta was performed in all patients; the images were recorded to enable off-line assessment of atherosclerosis of the ascending aorta by previously described methods [3,25,26]. Atherosclerosis was rated independently by 2 physicians blinded to clinical outcomes as absent, mild, moderate, or severe, depending on the width and irregularity of atheroma.

Apolipoprotein E Genotyping

The apolipoprotein ε4 genotype has been suggested to increase the risk for postoperative neurocognitive dysfunction [27–32]. Therefore, venous blood was obtained from patients before the intervention to determine apolipoprotein E genotype. DNA was extracted from the blood using QIAmp DNA mini-kits (Qiagen Inc, Valencia, CA) following the manufacturer's protocol. APOE genotyping was performed by polymerase chain reaction (PCR) amplification of a 244-bp fragment with primers 5′-TAAGCTTGGCACGGGCTGTCCAAGGA-3′ and 5′-ACAGAATTCGCCCCGGCCTGGTACAC-3′, followed by restriction enzyme *Hha*I digest as described by Hixson and Vernier [33]. The PCR fragments were separated by electrophoresis on a 3% NuSieve (FMC Bioproducts, Rockland, ME) agarose gel containing ethidium bromide and visualized by ultraviolet illumination.

Statistical Analysis

In previous principal components analysis, we found that there was little correlation between cognitive test results, suggesting that our battery evaluated distinct cognitive domains with little overlap [14]. We therefore defined cognitive decline as a decrement from baseline of more than one standard deviation on two or more of the psychometric tests. Neurocognitive dysfunction was a composite outcome that included the presence of a cognitive deficit or an increase in the NIH Stroke Scale score from baseline by more than 2 points. Patients who died before the postoperative visit were classified as having neurocognitive dysfunction.

In initial confirmatory analyses, differences between those with and those without neurocognitive dysfunction in the continuous demographic and clinical variables were statistically assessed using the *t* test for independent samples, and differences in the categoric variables were investigated using the χ^2 goodness-of-fit test. Univariate logistic regression models were created on the binary outcome of dysfunction that included predictors that were close to statistical significance ($p \leq 0.1$) in the confirmatory analyses. In this analysis, apolipoprotein genotype was considered as either the presence of absence of the ε4 variant. A multivariable logistic model was then created using the variables that were close to significance in the univariate models. Age at operation was also included in this model because of its clinical significance, even though age was not associated with dysfunction in the univariate analyses. The goodness-of-fit of the multivariable model to the data was assessed by the Hosmer-Lemeshow test and the area under the receiver operating characteristic curve.

Results

Complete neurologic outcome data and apolipoprotein ε4 genotyping data were available from 113 of the 174 women. Neurocognitive dysfunction was present in 25% of the 113 women 4 to 6 weeks postoperatively. Of the 28 patients with neurocognitive dysfunction, 6 had a neurologic deficit based on NIH Stroke Scale testing results. Demographic and operative data for these women are listed in Table 1 based on the presence or absence of neurocognitive dysfunction. Women with a neurocognitive deficit tended to be older than those without a deficit (72.1 ± 8.1 vs 69.4 ± 8.9 years, $p = 0.14$).

The apolipoprotein ε4 allele was present in 26% of patients: 29.3% of patients without neurocognitive dysfunction and 18.2% of patients with postoperative neurocognitive dysfunction. No patients were homozygous for apolipoprotein ε4. The different distributions of apolipoprotein ε genotypes did vary between patient groups.

Women with postoperative neurocognitive dysfunction were more likely than those without dysfunction to have moderate atherosclerosis of the ascending aorta, longer duration of CPB, and aortic cross-clamping. The nadir perfusion pressure during CPB was lower in women with a neurocognitive dysfunction than in those without a deficit.

The frequencies of major cardiovascular complications were determined after the patients were categorized by the presence or absence of a postoperative neurocognitive dysfunction (Table 2). Patients with neurocognitive dysfunction had a higher rate of postoperative atrial fibrillation compared with women without a deficit. Length of hospitalization in the intensive care unit (ICU) and on the postoperative ward was longer in women with a neurocognitive deficit than in those without a deficit.

Results of logistic regression analysis are listed in Table 3. Variables associated with neurocognitive dysfunction according to the unadjusted analysis included mild atherosclerosis of the ascending aorta, duration of CPB and aortic cross-clamping, and duration of stay in the ICU and postoperative ward. A trend toward a higher frequency of non-Q-wave myocardial infarction (MI) and lower mean arterial pressure during CPB was observed for patients with neurocognitive dysfunction. Of these variables, those that were predictive of neurocognitive dysfunction 4 to 6 weeks after operation according to multivariable logistic regression analysis were mild atherosclerosis of the ascending aorta, duration of CPB, duration of aortic cross-clamping ($p = 0.051$), and length of postoperative hospitalization. The presence of a non-Q-wave MI after operation was associated with a reduced risk for postoperative neurocognitive dysfunction.

Comment

Women are at higher risk than men for neurologic complications after cardiac procedures, independent of known risk factors [3–6]. Furthermore, extensive experimental data have established that 17β-estradiol is a natural neuroprotectant that acts through multiple genomic and nongenomic pathways [34]. Because most women undergoing cardiac operations are postmenopausal, we hypothesized that sex-related vulnerability to perioperative brain injury might be explained by low levels of estrogen. In a prior investigation, however, we did not find that perioperative treatment with 17β-estradiol was beneficial for improving neurologic outcomes in women after cardiac surgical interventions [14]. In that study of prospectively randomized patients, the frequency of neurocognitive dysfunction 4 to 6 weeks after operation was not different between postmenopausal women who received 17β-estradiol (22.4%) and those who received placebo (21.4%, $p = 0.45$).

In the current study we assessed potential risk factors for postoperative neurocognitive dysfunction in this cohort of elderly women. Multivariable logistic regression analysis showed that mild atherosclerosis of the ascending aorta, duration of CPB and aortic cross-clamping, and length of hospitalization were independently associated with risk for neurocognitive dysfunction 4 to 6 weeks after operation. A non-Q-wave MI was associated with a reduced risk for postoperative neurocognitive dysfunction. Our findings largely confirm those of other studies, although in contrast to previous reports, we did not find that age or level of education was associated with risk for neurocognitive dysfunction [2,7,8]. It is not clear whether our observations are related to the focus on women or are due to the narrow range of ages in this predominantly elderly group of patients.

Although significant based on univariate analysis, postoperative atrial fibrillation was not independently associated with risk for neurocognitive dysfunction, a finding that contradicts that of other studies. We are uncertain why a non-Q-wave MI might be associated with a lower risk for neurocognitive dysfunction. The small number of patients in this study does not allow for an analysis of the impact of different medical therapies for non-Q-wave MI, such as antiplatelet drugs or statins, on the frequency of our primary end point.

We found that mild atherosclerosis of the ascending aorta—but not moderate or severe atherosclerosis—was an independent risk factor for postoperative neurocognitive dysfunction. Atherosclerosis of the ascending aorta is an established risk factor for stroke and has been implicated to be associated with neurocognitive dysfunction by some but not all investigations [1,2,7,25,26]. Several lines of evidence suggest that the distribution and plaque characteristics of atherosclerosis differ between sexes [9,11].

Goto and colleagues [9] evaluated the effect of gender on the prevalence of atherosclerosis risk factors for stroke in a study of 720 elderly Japanese patients (31.8% women) undergoing CABG. All patients underwent preoperative brain magnetic resonance imaging and angiography, and intraoperative epiaortic ultrasound imaging. Women were significantly more likely than men to have significant intracranial arterial stenosis, whereas men had significantly higher rates of peripheral vascular disease, abdominal aortic aneurysm, severe carotid artery stenosis, and severe atherosclerosis of the ascending aorta. Our findings and those of Goto and colleagues [9] thus suggest the possibility that cerebral embolism arising from an atherosclerotic aorta is a less important risk factor for perioperative neurologic complications in women than in men.

One explanation for differences in risk for neurologic complications between men and women might be differing frequencies of age-associated vascular stiffness that might occur even in the absence of severe atherosclerosis of the aorta and cerebral arteries [12]. Vascular stiffness leads to increased systolic pressure, elevated pulse pressure, central pressure augmentation, and greater pulse-wave velocity. Loss of the normal dampening effect of a compliant vasculature with vascular stiffening portends higher central pressure leading to arterial remodeling and microcirculatory damage in the brain.

A higher prevalence of vascular disease of the large and small cerebral arteries in women might expose them to cerebral hypoperfusion during CPB, providing one explanation for the relationship between duration of CPB and risk for postoperative neurocognitive dysfunction. We did find that the nadir of mean arterial pressure during CPB tended to be lower in women with postoperative neurocognitive dysfunction than in those without this condition, but this variable was not different after adjustment of the data.

We have previously reported that increased pulse pressure, an indicator of vascular stiffness, was an independent predictor of stroke after CABG [10]. In that study, the prevalence and magnitude of pulse pressure was significantly higher in women than in men. In the current study, pulse pressure was not different between patients with and without postoperative neurocognitive dysfunction. Assessment of pulse-wave velocity and central aortic augmentation index might have provided a more sensitive indication of central vascular stiffness than did brachial artery blood pressure.

The apolipoprotein ε4 genotype has been linked with risk for Alzheimer disease and cognitive decline in the general population, as well as for neurocognitive dysfunction after cardiac operations and after carotid endarterectomy, but this association was not confirmed by other investigations [27–33,35–38]. The mechanism by which apolipoprotein ε4 might confer risk for cognitive impairment is not known, but it may be due in part to its relationship with more advanced atherosclerosis, including cerebral vascular disease, or its role in modulating cellular

processes involved with neuronal injury or reparative processes, or both [37–39]. The number of patients with the ε4 allele (26%) was similar to that reported by other studies of cardiac surgical patients (22% to 39%) [27,30]. Nonetheless, apolipoprotein ε4 did not confer risk for postoperative neurocognitive dysfunction in this cohort of elderly women.

Several explanations could account for the varied results for the role of apolipoprotein ε4 genotype and risk for postoperative neurocognitive dysfunction, including the possibility of either a false-positive or false-negative result for the individual reports, due to the relatively small number of patients studied. It is also likely that the relationship between apolipoprotein ε4 genotype and neurocognitive dysfunction is highly dependent on the population examined, similar to findings for other putative genetic risk factors for cardiovascular disease [40].

In conclusion, many risk factors for neurocognitive dysfunction after cardiac interventions in postmenopausal women mostly overlap with those found in mixed-gender studies. Whether the cause of perioperative brain injury after cardiac procedures differs between women and men requires further investigation.

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Table 1

Demographic Characteristics and Operative Data for Women With and Without Neurocognitive Dysfunction 4 to 6 Weeks After Cardiac Operation

Variable	Neurocognitive Dysfunction		*p* Value
	No (n = 85)	Yes (n = 28)	
Age, mean ± SD, years	69.4 ± 8.9	72.1 ± 8.1	0.144
Race, %			
White	91.80	92.90	0.853
Black	8.20	7.10	
Peri-op 17β-estradiol treatment, %	49.40	57.10	0.478
Comorbidity, %			
Congestive heart failure	22.40	39.30	0.078
Hypertension	84.70	92.90	0.27
Diabetes type I	16.50	21.40	0.551
Diabetes type II	23.50	25.90	0.8
Previous myocardial infarction	35.30	50.00	0.166
Smoking status, %			
Never	57.70	50.00	0.752
Current	16.50	21.40	
Former	25.90	28.60	
Level of education, %			
≤ High school	63.50	71.40	0.446
> High school	36.50	28.60	
Aorta atherosclerosis, %			
Normal	66.20	40.90	0.064
Mild	21.10	45.50	
Moderate/severe	12.70	13.60	
Apolipoprotein ε genotype, %			
ε 3, 2	11.10	25.00	0.023
ε 4, 3	0.00	8.33	
ε 3, 4	63.90	45.80	
ε 4, 5	25.00	20.80	
Pulse pressure,[a] mean ± SD mg Hg	68.9 ± 21.3	73.6 ± 24.6	0.334
Variables during PB, mean ± SD			
Lowest MAP, mm Hg	59.9 ± 7.6	57.1 ± 6.6	0.08
Lowest hematocrit, mean ± SD	21.5 ± 3.8	20.6 ± 3.3	0.276
Lowest temperature, °C	31.8 ± 1.9	31.2 ± 2.3	0.144
Highest glucose, mg/dL	244.0 ± 57.1	252.7 ± 82.0	0.561
CPB duration, mean ± SD min	114.8 ± 42.2	153.7 ± 83.1	0.002
Aortic cross-clamping duration, mean ± SD min	85.1 ± 32.0	106.6 ± 62.4	0.02

CHF = preoperative congestive heart failure

CPB = cardiopulmonary bypass

MAP = mean arterial pressure

SD = standard reaction

[a] Pulse pressure was that recorded during preoperative screening.

Table 2

Perioperative Complications for Women With and Without Neurocognitive Dysfunction After Cardiac Operations

Variable	Neurocognitive Dysfunction		*p* Value
	No (n = 85)	Yes (n = 28)	
Clinical stroke, %	2.1	7.1	0.256
Postoperative MI, %			
Non-Q-wave	10.6	23.1	0.172
Q-wave	7.1	11.5	
Atrial fibrillation, %	35.7	53.6	0.095
LOS, mean ± SD days			
ICU	2.2 ± 2.0	9.0 ± 16.7	<0.001[a]
Hospital	7.2 ± 2.9	14.7 ± 18.8	0.098[a]

LOS = length of stay

MI = myocardial infarction

SD = standard deviation.

[a]Nonparametric Kruskal-Wallis test.

Table 3

Logistic Regression Results in the Univariate (Unadjusted) and Multivariable (Adjusted) Analysis for Neurocognitive Dysfunction 4 to 6 Weeks After Operation in Elderly Women[a,d]

Variable	Unadjusted OR (95% CI)	*p* Value	Adjusted OR (95% CI)	*p* Value
Apolipoprotein ε4	1.25 (0.44–3.46)	0.687		
Age[b]	1.04 (0.99–1.10)	0.145	0.98 (0.90–1.06)	0.591
Race				
Black	0.86 (0.17–4.39)	0.853		
White	Reference			
Education				
> High school	0.70 (0.27–1.77)	0.447		
≤ High school	Reference			
Atherosclerosis				
Normal	Reference		Reference	
Mild	3.48 (1.19–10.17)	0.023	8.52 (1.41–51.44)	0.02
Moderate/severe	1.74 (0.39–7.71)	0.465	1.76 (0.22–15.35)	0.609
Post-op MI				
No MI	Reference		Reference	
Non-Q-wave	2.75 (0.86–8.77)	0.088	0.02 (0.00–0.78)	0.036
Q-wave	2.06 (0.47–9.08)	0.34	0.99 (0.09–11.51)	0.995
CPB duration[c]	1.01 (1.00–1.02)	0.007	1.05 (1.01–1.11)	0.031
Aortic cross-clamp duration[c]	1.01 (1.00–1.02)	0.037	0.94 (0.88–1.00)	0.051
Lowest MAP during CPB[c]	0.95 (0.90–1.01)	0.082	0.97 (0.87–1.07)	0.508
Days in the ICU[e]	1.28 (1.07–1.53)	0.007	0.978 (0.65–1.46)	0.91
Days in the hospital[e]	1.12 (1.02–1.23)	0.017	1.51 (1.17–1.95)	0.001

CPB = cardiopulmonary bypass

CI = confidence interval

ICU = intensive care unit

MAP = mean arterial pressure

MI = myocardial infarction

OR = odds ratio.

[a] Receiver operating characteristic curve = 0.891, Homser-Lemeshow $p = 0.479$.

[b] *or* per year increase.

[c] *or* per minute increase.

[d] *or* per mm Hg increase.

[e] *or* per day increase.

[d] *or* per mm Hg increase.