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PRE-EXISTING COGNITIVE IMPAIRMENT IN WOMEN PRIOR TO CARDIAC SURGERY AND ITS RELATION WITH C-REACTIVE PROTEIN CONCENTRATIONS

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Abstract

Preoperative cognitive state is seldom considered when investigating the effects of cardiac surgery on cognition. The purpose of this study was to determine the prevalence of cognitive impairment in women scheduled for cardiac surgery using non-hospitalized volunteers as a reference group, and to examine the relationship between C-reactive protein levels and cognitive impairment. Psychometric testing was performed in 108 postmenopausal women scheduled for cardiac surgery and in 58 control women of similar age. High sensitivity C-reactive protein levels were measured in the surgical patients. Cognitive impairment in surgical patients was defined as > 2 SD lower scores on ≥ 2 tests compared with the controls. Elevated C-reactive protein level was defined as $> 95\%$ confidence interval for the surgical cohort. Cognitive impairment was present in 49 of 108 (35%) patients. C-reactive protein levels were higher for patients with compared to those without cognitive impairment

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Implication Statement: Cognitive impairment was found in 35% of women prior to cardiac surgery. C-reactive protein levels are elevated in women with this condition but the relationship between this inflammatory marker and pre-existing cognitive impairment is likely secondary to the acute phase reactant serving as a marker for other conditions including widespread cardiovascular disease.

(23.2 ± 37.5 mg/L vs 14.3 ± 14.3 mg/L, $p=0.04$). Based on multivariate logistic regression analysis, patient age, lower attained level of education, type 2 diabetes mellitus, and prior myocardial infarction identified risk for cognitive impairment ($p < 0.05$) but not C-reactive protein levels ($p=0.09$). In conclusion, cognitive impairment is prevalent in women undergoing cardiac surgery. C-reactive protein levels are elevated in women with this condition but the relationship between this inflammatory marker and pre-existing cognitive impairment is likely secondary to the acute phase reactant serving as a marker for other conditions including widespread cardiovascular disease.

Keywords

Cognition; Cardiac Surgery; complications; Inflammation; C-reactive protein

Introduction

Subtle neurologic complications manifest as cognitive dysfunction are reported in over 35% of patients one month after cardiac surgery (1-6). Postoperative cognitive decline is an increasing focus of investigation due in part to its relation with higher hospital costs, diminished quality of life, and long-term cognitive deterioration (1-7). A limitation of many investigations, though, is the failure to include a control group for assessing baseline cognitive level. Rather, each patient often serves as their own control for comparing postoperative psychometric data. Pre-existing cognitive impairment is likely to be prevalent in patients scheduled for cardiac surgery on the basis of extensive cardiovascular disease (6,8-11). Assessing longitudinal change in cognitive end-points is difficult when there is baseline cognitive impairment since a low level of performance on the psychometric tests before surgery make it difficult to demonstrate further reduction after surgery particularly of a magnitude that would meet a dichotomous definition of cognitive dysfunction (i.e. "basement effect") (12). Failure to consider baseline cognitive state may result in erroneous conclusions about the neurologic consequences of cardiac surgery if the methods of detection (cognitive testing) are insensitive for detecting further deterioration in some patients.

Women undergoing cardiac surgery are typically older than men and more often have diabetes and hypertension, predisposing to operative complications (13). In a series of studies our group has found that women are at higher risk for neurologic complications from cardiac surgery than men (14-16). We have also demonstrated gender differences in the cognitive domains affected by cardiac surgery (6). Due to the differences in age and co-morbidities, preoperative cognitive impairment might also be more prevalent among women than men. However, investigations of cognitive state in patients before cardiac surgery compared with control patients have included mostly men and younger patients (5,8-11).

There is a growing appreciation of the importance of inflammatory processes in the pathogenesis of cardiovascular disease including in the transformation from its stable to unstable disease manifestations. C-reactive protein is a non-specific marker of inflammation whose blood levels have been shown to identify risk for cardiac events and stroke (17,18). Underlying inflammatory processes are suggested to contribute to cognitive impairment in the general population but whether this relationship applies to patients with advanced cardiovascular disease such as those undergoing cardiac surgery is not clear (19,20). Understanding the relationship between inflammatory processes and cognitive state in cardiac surgical patients would provide insight into the pathogenesis of these disorders and could also provide a potential means of risk stratification or therapeutic intervention.

The purpose of the study was to assess for the prevalence of baseline cognitive impairment in women scheduled for cardiac surgery compared with a group of non-hospitalized control

individuals. We further sought to test the hypothesis that there is an association between baseline C-reactive protein levels and cognitive impairment.

Methods

All procedures were approved by Washington University's Human Studies Committee and received individual written informed consent. The patients consisted of 138 females scheduled for elective cardiac surgery. Women were either ≥ 55 years of age or had undergone hysterectomy with oophorectomy > 6 months before surgery. Participants were part of a prospectively randomized, double-blind, placebo-controlled study of perioperative 17β -estradiol replacement for women undergoing cardiac surgery. All data were obtained prior to receiving study treatment. Exclusion criteria included: estrogen use within the past 6 months, re-operations or cardiac surgery combined with carotid endarterectomy, renal failure requiring dialysis, emergency surgery, clinically evident cognitive impairment before surgery, inability to attend outpatient visits, and inability to speak or read English. Controls consisted of 58 female non-hospitalized volunteers ≥ 55 years of age not receiving estrogen replacement. Control patients were identified through several sources including a University registry of individuals who might consider participation in clinical research protocols, advertising within our hospital, and personal contacts within the community. Volunteers were paid \$25 for participation.

A standard neuropsychological test battery was administered to the patients 1 to 2 days prior to surgery. The same cognitive testing battery was administered to the controls. The battery is in accordance with Consensus Conference recommendations and provides an assessment of a broad array of cognitive domains including memory, psychomotor speed, mental flexibility, fine motor skill and visual perception (12,21). Specific tests included the *Rey Auditory Verbal Learning Test*, in which a 15-word-list is presented over multiple trials and recall is tested after 30 minutes; the *Digit Symbol* subtest of the Wechsler Adult Intelligence Scale, in which participants transcribe number-symbol pairs under timed conditions; *Trail Making Test A and B*, in which participants connect numbered and then alternately numbered and lettered dots in order, under timed conditions; the *Grooved Peg Board Test*, in which notched pegs are rapidly placed into fitted holes on a shallow box; and the *Benton Visual Form Discrimination Test*, in which subjects match target shapes visually (22-28). The Beck Anxiety Inventory and the Beck Depression Inventory were used to assess depressed and anxious mood states (29,30). For the former tests, scores of 10 to 15 and > 16 are considered mild and severe anxiety, respectively. For the Beck Depression Inventory, scores of 10 to 15, 16 to 23, and 24 to 63 are considered as mild, moderate, and severe depression, respectively. The *Short Blessed Test* was used as a screening test for dementia in order to ensure that patients could provide a truly informed consent (31). The latter is a brief test of cognitive functioning that correlates with clinical dementia staging and with post-mortem pathological findings (32). Healthy, neurological normal subjects average 13 (range 0-13) on the Short Blessed Test, compared to 15.4 (range 2-28) for mildly demented and 18.5 for moderately demented patients. The standard cutoff score of 10 is highly sensitive to clinical dementia, but it is also moderately sensitive to sub-clinical cognitive impairment. Furthermore, presurgical anxiety may affect test scores in some cases. Thus, a slightly higher cutoff score of > 12 was used to exclude patient from further study. Patients scoring between 10 to 12 on the Short Blessed Test were asked to explain the consent form back to the recruiter to ensure that they were capable of providing fully informed consent.

Clinical data were collected by research nurses. Data that were not available from the medical record were obtained by direct contact with attending medical staff or family. Venous blood specimens were obtained the day before surgery and immediately placed in glass tubes devoid of anticoagulants or preservatives. Serum was separated by centrifugation, placed in plastic

tubes, and frozen at -70°C until the time of analysis. C-reactive protein concentrations were measured using a high sensitivity immunonephelometry technique (Dade Behring, Newark, DE). The lower detection limit of the assay is 0.175 mg/L.

Statistical Analysis

Pre-existing cognitive impairment in surgical patients was defined as > 2 SD lower test scores on 2 or more tests, compared with cognitive test data obtained in controls. For timed test (e.g., Peg Board and Trails tests) where a longer time indicates decrement in performance, a score $> \text{SD}$ higher than control patients was considered as “lower test score”. Patients with missing data on one or more tests were not included in the analysis. Categorical data were compared using Chi-2 or Fishers Exact test. Continuous data were compared using t-tests. Data that were not normally distributed were compared with the Wilcoxon test. C-reactive protein levels were highly skewed so the data were log transformed for analysis. Patient were categorized as having elevated C-reactive protein concentrations when their levels were $> 95\%$ confidence interval for the entire surgical cohort. Spearman correlation coefficients were calculated between C-reactive protein levels and scores for each cognitive test. Multivariate logistic regression analysis was performed to assess for variables independently associated with cognitive impairment. Variables with a p value of < 0.2 were included in the model.

Results

Twenty patients had missing data on one or more cognitive test that precluded correct classification as having or not having cognitive impairment. Of the remaining 108 patients, 49 (35%) were categorized as having pre-existing cognitive impairment. Descriptive data for the control volunteers and for surgical patients are listed in Table 1. Patients with cognitive impairment tended to have higher scores (i.e., lower performance) on the Short Blessed Test, compared with those without cognitive impairment. Four patients with cognitive impairment had Short Blessed Test scores between 10 and 12.

Neuropsychological test results for controls and for surgical patients are listed in Table 2. Differences were noted in all psychometric test results between volunteers and patients with cognitive impairment. Compared with volunteers, surgical patients without cognitive impairment had lower scores on some but not all of the psychometric tests. Of note, the grooved pegboard test and Trails A and B are timed tests on which higher score indicates poorer performance.

The mean C-reactive protein concentrations for surgical patients was 12.5 ± 15.6 mg/L and upper 95% confidence interval 19 mg/L. Seventy-four percent of surgical patients had C-reactive protein levels > 3 mg/L. C-reactive protein concentrations were higher for patients with cognitive impairment compared with patients without cognitive impairment (23.2 ± 37.5 mg/L vs 14.3 ± 14.3 mg/L, $p=0.04$). The percentage of patients with elevated C-reactive protein levels and > 2 SD lower score on each cognitive test compared with controls is listed in Table 3. A higher percentage of patients with elevated C-reactive protein levels had poorer performance on Trails A compared to those without high C-reactive protein levels. There was a trend for worse scores on Trails B and for the Digit Symbol test between those with and those without elevated C-reactive protein levels. Sixty-two percent of patients with elevated C-reactive protein levels were classified as having cognitive impairment compared with 40% of patients without elevated C-reactive protein levels ($p=0.0773$). C-reactive protein concentrations were correlated with Digit Symbol Test ($r=-0.186$, $p=0.042$) and Trail Making A test results ($r=0.259$, $p=0.004$). The combination of patient age, C-reactive protein concentrations, and level of education accounted for 27% of the variability on the Trailmaking A test.

Results from the multivariate logistic regression analysis are listed in Table 4. Variables independently associated with pre-existing cognitive impairment include patient age, level of education, type 2 diabetes, and prior MI. A trend was noted for the relation between C-reactive protein concentrations and cognitive impairment ($p=0.09$). This model identified 80% of patients with cognitive impairment. Removing the variable MI from the multivariate model resulted in C-reactive protein becoming a significant independent predictor of pre-existing cognitive impairment ($p=0.04$). The latter model correctly identified 77% of cases of cognitive impairment.

Discussion

Cognitive decline is frequently reported after cardiac surgery (1-7). This complication is believed to primarily result from some combination of cerebral embolism and cerebral hypoperfusion occurring during surgery particularly when cardiopulmonary bypass is employed. While some studies of the effects of cardiac surgery on cognitive outcomes have included control groups undergoing non-thoracic surgery, many investigations assess change in psychometric tests results from the preoperative period with patients serving as their own controls (1-5,7). Patients undergoing cardiac surgery suffer from widespread cardiovascular disease that predispose to cognitive impairment irrespective of surgery (5,8-11). Failure to consider preoperative cognitive state might confound analysis of the effects of cardiac surgery on cognitive function since patients with low baseline psychometric test scores might fail to demonstrate significant subsequent decline after surgery. Failure to include a control group for assessing baseline cognitive state might further fail to account for the natural history of cognitive decline in patients with widespread cardiovascular disease. The importance of the latter has been recently emphasized by the findings of no differences in cognitive function for patients with coronary artery disease after either CABG surgery or percutaneous myocardial revascularization (9,10).

Women represent a minority of patient undergoing cardiac surgery; they are usually older than men, and they have different risk profiles for operative morbidity and mortality (13). Other investigations have reported cognitive deficits in candidates for cardiac surgery when compared with healthy controls. Millar et al (5) reported that 16% of patients had cognitive impairment before CABG surgery using the Stroop screening test and published age-adjusted normative data for comparison. Employing a more extensive psychometric battery, Vingerhoets et al (11) found cognitive and motor impairment in patients before cardiac surgery compared with non-hospitalized controls. In these latter studies the data from both sexes were combined in the analysis, which limits extrapolating the results to women who comprised 18% to 21% of studied patients. Our results thus suggest that the rate of cognitive impairment is exceedingly high for women before cardiac surgery.

The findings of this study that patient age, level of education, diabetes, and prior MI were independently associated with cognitive impairment are consistent with other reports (3,6, 11). The frequency of prior stroke was higher in patients with compared with those without cognitive impairment (23% vs 5%, $p=0.0086$) but history of stroke was not an independent predictor of cognitive impairment. Studies employing MRI report brain infarctions in 40-70% of patients *before* cardiac surgery (33,34). Most patients with these lesions do not provide a clinical history of stroke. It is likely, thus, that relying on clinical history will underestimated the frequency of prior brain infarction.

In the general population elevated plasma levels of C-reactive protein and other inflammatory markers identify risk for stroke and cognitive decline (17-20). Since heightened inflammation is associated with advanced cardiovascular disease, the relation between C-reactive protein and cognitive impairment might merely identify individuals prone to cognitive decline due

cardiovascular disease. Elevated C-reactive protein and interleukin-6, though, appear to have added value in identifying risk for cognitive decline for community dwelling individuals with risk factors for coronary artery disease (19,20). In this study C-reactive protein concentrations were significantly associated with cognitive impairment in the multivariate model only when eliminating prior MI. These results suggest that any relation between C-reactive protein and cognitive impairment in our cohort are related to this acute phase reactant serving as a marker for cardiovascular disease.

A limitation of any study using psychometric testing is selection bias of subjects consenting to the rigors of such testing. Others have reported no differences in cognitive performance in patients with coronary artery disease prior to either CABG surgery or percutaneous coronary interventions (9,10). We chose a control group consisting of community dwelling women without acute illness. Thus, our results provide an estimate of cognitive performance for women undergoing cardiac surgery compared with women free of acute illnesses. While volunteers were tested either in a clinic or in their homes, surgical patients underwent psychometric testing mostly on the hospital ward which might influence the results particularly for timed test (9). Patients but not volunteers would be further exposed to emotional stressors associated with pending major surgery that are difficult to measure. We did find that indicators of anxiety and depression were higher between surgical patients and volunteers. C-reactive protein concentrations were not obtained in the volunteers but data on normative values for this inflammatory marker are available for community dwelling adults. The Centers for Disease Control and the American Heart Association have issued clinical guidelines suggesting that high sensitive C-reactive protein concentrations of > 3 mg/L represent high vascular risk (35). In this study 74% of women had C-reactive protein levels > 3 mg/L most likely reflecting disease processes leading to cardiac surgery. This high level of baseline inflammation might limit the ability of this marker to distinguish women with cognitive impairment from those without.

In summary, these data suggest that pre-existing cognitive impairment is prevalent in women about to undergo cardiac surgery. Our results further suggest that to some extent C-reactive protein levels are associated with susceptibility to this condition but probably only as a marker of cardiovascular disease. Since pre-existing cognitive impairment is an important determinant of risk for cognitive decline after cardiac surgery, preoperative identification of susceptible patients might provide a means for risk stratification and/or focused implementation of neuroprotective strategies.

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Table 1

Volunteer and patient demographics and medical history. Values represent percentage of patients unless otherwise noted. The p-values are for comparisons between surgical patients with or without cognitive impairment.

Variable	Volunteer n=58	All Surgical Patients (n=154)	Patients No Cognitive Impairment n=59	Patients with Cognitive Impairment n=49	p-value
Age (mean±SD, yrs)	64.7±7.7	70.4±8.7	67.8±8.2 [†]	73.1±9.1 [*]	0.0016
Attained education (mean±SD, yrs)	14.7±2.6	11.8±2.4	12.4±2.1 [*]	11.0±2.4 [*]	0.0010
Short Blessed Score (mean±SD)	—	3.5±3.8	2.9±3.4	4.1±3.7	0.0552
Prior Stroke	0	16%	5%	23%	0.0086
Diabetes Type 1	2%	16%	13%	15%	0.7513
Diabetes Type 2	5%	27%	24%	43%	0.0418
Hypertension	26%	86%	84%	89%	0.4023
COPD	0	15%	7%	19%	0.0730
PVD	0	17%	15%	26%	0.1636
Prior MI	4%	43%	33%	57%	0.0464
History CHF	0	26%	20%	40%	0.0240
Impaired left ventricular function	—	42%	38%	51%	0.2111
Coronary stenosis > 70% (mean±SD)	—	87%	2.24±1.35	2.72±0.88	0.1081
Tobacco use - None	46%	53%	52.7%	53.2%	0.9627
- Prior	14%	28%	36%	23%	0.1561
- Current	40%	19%	11%	23%	0.0914
Planned Surgery	—	75%	71%	79%	0.3959
CABG	—	5%	1.8%	8.5%	0.1753
CABG/AVR	—	7%	7.1%	6.4%	0.9999
CABG/MVR	—	7%	8.9%	4.3%	0.4499
AVR	—	6%	10.7%	2.1%	0.1222
MVR	—	65%	61%	70%	0.3633
Medication	14%	56%	55%	56%	0.9294
Beta-blockers	21%	63%	65%	63%	0.8473
ACE inhibitors	12%	70%	71%	65%	0.5707
Statins	32%	20%	20%	19%	0.9020
Aspirin	9%	36%	35%	51%	0.1211
Ca++ channel blockers	0	—	—	—	—
Diuretics	—	—	—	—	—

Note: COPD=chronic obstructive pulmonary disease; PVD=peripheral vascular disease; CHF=congestive heart failure; CABG=coronary artery bypass graft surgery; MVR=mitral valve surgery; AVR=aortic valve surgery.

* p < 0.001 vs Volunteers

[†] p < 0.05 vs Volunteers

Neuropsychological test results for volunteers and for surgical patients with and without pre-existing cognitive impairment. Data are presented as mean±SD. Grooved Peg Board and Trails A and B are timed test, higher score (time in minutes) denotes worse performance while lower scores on other psychometric test indicate worse performance. The listed p-values are for comparison between patients with and without cognitive impairment.

Table 2

Cognitive Domain	Instrument	Volunteers	No Cognitive Impairment	Cognitive Impairment	p-Value
Visual Spatial Processing Complex Attention/ Psychomotor Speed Fine Motor Speed	Benton VFD Test	14.4±2.0	14.0±1.9	11.1±3.0 *	< 0.0001
	Digit Symbol Test	65.2±17.9	51.2±11.4 *	33.2±12.4 *	< 0.0001
	Trailmaking A	37.6±14.1	40.5±10.1	79.2±34.7 *	< 0.0001
	Pegboard Test Dominant hand Non-dominant hand	86.9±32.9	101.4±31.8 †	177.5±66.6 *	< 0.0001
Verbal Memory Executive Function Mood	Rey AVLT (1-7)	99.3±34.0	107.8±35.5 †	182.4±68.6 *	< 0.0001
	Trailmaking B	78.7±14.0	70.1±15.6 †	50.9±18.8 *	< 0.0001
	Beck Anxiety Score	83.6±33.6	103.6±53.8 †	189.8±71.7 *	< 0.0001
	Beck Depression Score	5.4±4.9	12.4±8.7 *	11.6±10.3 †	0.28480
		6.1±3.9	9.0±5.9 †	8.0±4.7 †	0.7981

Note: VFD refers to visual form discrimination. Note:

* p < 0.001 vs Volunteers
† p < 0.05 vs Volunteers.

Table 3

Percentage of patients with elevated C-reactive protein concentrations with scores that were two standard deviations or lower on each respective psychometric test. Those percentage of patients meeting the definition of pre-existing cognitive impairment (> 2 standard deviation lower score on ≥ 2 psychometric tests) is also listed. Elevated C-reactive protein was defined as a level > 19 mg/L or the upper 95% confidence interval for the surgical patients.

Psychometric Test	Elevated CRP	CRP not elevated	p-Value
Benton VFD Test	33%	22%	0.3655
Digit Symbol Test	32%	12%	0.0736
Pegboard Test			
Dominant hand	7%	26%	0.1741
Non-dominant hand	27%	23%	0.7462
Rey AVLT (1-7)	35%	27%	0.4483
Trailmaking A	48%	23%	0.0240
Trailmaking B	50%	28%	0.0672
Cognitive Impairment	62%	40%	0.0773

Note: VFD refers to visual form discrimination.

Table 4

Variables independently associated with pre-existing cognitive impairment.

Variable	Odds Ratio	95% CI	p-value
Age	1.10	1.05 to 1.17	0.0003
Level of Education	0.81	0.68 to 0.96	0.0174
Type 2 Diabetes Mellitus	2.75	1.10 to 6.86	0.0306
Prior Myocardial Infarction	2.48	1.05 to 5.83	0.0372
C-reactive protein concentration	1.02	0.99 to 1.035	0.0907