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C-Reactive Protein Levels and Atrial Fibrillation after Cardiac Surgery in Women

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Abstract

Background—The aim of this study was to evaluate whether risk for postoperative atrial fibrillation in women is related to pre-existing inflammation as detected by plasma C-reactive protein (CRP) concentrations. We further sought to assess for the importance of atrial fibrillation for outcome after cardiac surgery in women.

Methods—CRP was measured before coronary artery bypass grafting and/or valvular surgery using cardiopulmonary bypass in 141 women. Univariate and multivariate analysis were used to evaluate for differences in CRP levels between women with and without atrial fibrillation, and to assess for the importance of the arrhythmia and postoperative outcomes.

Results—Atrial fibrillation developed in 46 (33%) women. Neither CRP concentrations (median ±SE, 13.3±2.5 mg/L vs 11.7±1.4 mg/L, p=0.847), nor the frequency of elevated levels (defined as > upper 95% CI or > 19.2 mg/L) (19% vs 21%, p=0.807) differed between women with or without atrial fibrillation. Patient age and previous stroke, but not CRP levels, were independently associated with atrial fibrillation. Women with atrial fibrillation were more likely to have low cardiac output syndrome (p= 0.018), stroke (p=0.031), longer duration of hospitalization in the intensive care unit (p=0.012) and on the postoperative (p=0.0008) ward, and they were more likely to require an extended care facility after surgery (p=0.046).

Conclusions—In contrast to findings from studies that have included mostly men, preoperative CRP concentrations are not associated with risk for atrial fibrillation after cardiac surgery for women. Postoperative atrial fibrillation in women is associated with increased risk for stroke, longer hospitalization, and extended care facility admission.

Keywords

Arrhythmia; Atrial Fibrillation; Gender; Inflammation; On-pump

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Introduction

Women represent a minority of patients undergoing cardiac surgery yet they have been consistently shown to have higher morbidity and mortality than men.(1-4) In several studies our group has found that higher operative mortality in women can be explained in part by perioperative stroke.(2-4) Risk for stroke in these single- and multi-center studies could not be explained by known stroke risk factors. Atrial fibrillation is a common complication after cardiac surgery and a potentially preventable cause of stroke and other adverse events.(5-7) The arrhythmia is believed to result from multiple cardiac perturbations occurring during surgery in the setting of a pre-existing arrhythmogenic substrate.(5,8) Clinical and histological investigations suggest that inflammation may play a role in the initiation and/or maintenance of atrial fibrillation, and that anti-inflammatory agents might reduce its frequency.(7,9,10) Delineating the role of inflammation in postoperative atrial fibrillation, thus, may have both mechanistic and therapeutic implications. Identifying susceptibility before surgery might further provide a means for appropriate targeting of both arrhythmia and stroke preventative medications.

C-reactive protein (CRP) is an acute phase reactant produced in the liver in response to inflammatory cytokines especially interleukin-6.(11) Extensive data have shown that CRP levels provide independent prediction of adverse cardiovascular events such as myocardial infarction and stroke.(11-15) The role of CRP concentrations in identifying risk for complications after cardiac surgery is increasingly under investigation.(16,17) A link between CRP levels and atrial fibrillation supports the notion that inflammation enhances susceptibility to the arrhythmias regardless of whether the surgery is performed with our without cardiopulmonary bypass.(18-22) Patient sex can influence multiple physiologic processes including inflammation and CRP levels.(23) Prior investigations that have evaluated inflammatory mechanisms of atrial fibrillation, though, have included mostly men limiting extrapolation of the findings to women.

The hypothesis of this study is that CRP concentrations measured before surgery are elevated in women who develop atrial fibrillation after cardiac surgery compared with women remaining in sinus rhythm. Since most studies that have investigated postoperative atrial fibrillation have not provided separate analysis based on patient sex, we further sought to assess for the importance of atrial fibrillation and other adverse outcomes after cardiac surgery for women.

Patients and Methods

Study Patients and Investigative Protocol

All procedures of this study met with the approval of the Human Studies Committee of Washington University School of Medicine, St. Louis, MO on May 12, 1999 and were performed only after receiving individual informed consent. Participants were part of a prospectively randomized double-blind outcome study of perioperative 17β-estradiol replacement for postmenopausal women undergoing cardiac surgery. Data for the current report were made available after the first planned interim analysis of that trial. Women > 55 years of age, or those younger with prior oophorectomy, scheduled for elective coronary artery bypass graft (CABG) surgery and/or cardiac valvular surgery were eligible. Exclusion criteria included: 1) surgery not using cardiopulmonary bypass; 2) elevation of liver function tests before surgery or creatinine before surgery (> 2 mg/dl); 3) emergency surgery; 4) severe cognitive impairment before surgery as indicated by clinical history and/or a score >12 on the Short Blessed Dementia Screening Test; 5) inability to attend outpatient visits; 6) history of venous thromboembolism; 7) unexplained vaginal bleeding; 8) history of breast cancer or personal history of endometrial cancer in the absence of hysterectomy; 9) estrogen use within 6 months of the surgery; 10) inability to speak and read English or visual impairment.

Perioperative Care

Patients received an opioid-based anesthetic supplemented with muscle relaxants and volatile anesthetics aimed at early tracheal extubation. Following heparin administration, nonpulsatile cardiopulmonary bypass was instituted using a membrane oxygenator and a 40 μm arterial line filter in the circuit. Blood flow was between 2.0 to 2.4 $L^{-1}min^{-1}m^{-2}$ and urinary bladder temperature ranged between 32°C to 34°C. Alpha-stat pH management was used. Mean arterial blood pressure during cardiopulmonary bypass was maintained between 50 mmHg and 80 mmHg with phenylephrine, sodium nitroprusside or by altering the concentration of volatile anesthetic delivered to the cardiopulmonary bypass circuit. Blood glucose was measured at the onset of cardiopulmonary bypass and every 30 min and regular humulin insulin given when glucose was > 200 mg/dl. Pericardial aspirate was returned to the cardiopulmonary bypass circuit. Protamine dose given at the conclusion of cardiopulmonary bypass was calculated using heparin-protamine titration method (Hepcon, Medtronics, Minneapolis, MN) as previously described.(24)

The patients were evaluated daily after surgery for perioperative complications by a member of the investigative team. All patients had continuous ECG monitoring until hospital discharge using a bedside monitor in the intensive care unit and telemetry on the hospital ward. A 12-lead ECG was obtained before surgery and on the first 4 postoperative days. Troponin I concentrations were measured the day before surgery, immediately after surgery in the intensive care unit and on the first 4 postoperative days.

C-Reactive Protein Measurement

Venous blood specimens were obtained the day before surgery prior to administration of 17β-estradiol. The specimens were 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. CRP 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.

Clinical End Points

Atrial fibrillation was diagnosed when there was an irregularly irregular cardiac rhythm without P-waves lasting > 1 min regardless of treatment. This diagnosis was made by the physicians caring for the patients. Twelve-lead ECGs and troponin I data were independently reviewed by 2 physicians blinded to treatment study assignment. Diagnosis of a Q-wave myocardial infarction was made when there was a new Q-wave > 1/3 the height of the ECG R-wave on the 12 lead ECG and a rise in troponin I concentrations > 6 ng/ml from the preoperative levels. A non-Q wave myocardial infarction was diagnosed in the absence of a new Q-wave when there was an increase in the troponin I concentrations > 13 ng/ml from the preoperative baseline. (25) A diagnosis of myocardial infarction was by consensus. A third cardiologist was consulted when there was disagreement. Low cardiac output syndrome was defined as a cardiac index < 2.0 $L^{-1}min^{-1}m^{-2}$ for > 8 hours regardless of treatment.

Two neurologists blinded to assigned study treatment independently reviewed all cases of clinically diagnosed stroke. Brain imaging results were reviewed when available. The diagnosis of stroke was when there was a new focal or global neurologic deficit that persisted > 1 day and that was not explained by metabolic or pharmacological causes.

Statistical Analysis

Data analysis was performed with a personal computer using Stata Software (Stata Corporation, College Station, Texas). Dichotomous data were analyzed with Chi-2 testing and

continuous data with one-way analysis of variance. Demographics, clinical information, and CRP concentrations were compared between patients with and without postoperative atrial fibrillation. Patients were further categorized as having elevated CRP concentrations when the levels were higher than the 95% confidence interval for the entire patient population. Step-wise multivariate logistic regression analysis was performed to assess for any relation between CRP levels and atrial fibrillation after adjusting for other variables with a $P < 0.2$ on univariate analysis.

Results

Atrial fibrillation developed after surgery in 46 (33%) of 141 women. Demographic and medical data are listed in Table 1. There were no differences in the variables evaluated between women who developed atrial fibrillation compared with those who remained in sinus rhythm. The frequency of atrial fibrillation was not different for the patients receiving perioperative 17β-estradiol replacement compared with placebo.

Baseline CRP concentrations are listed in Table 2. The median CRP concentration prior to surgery was 12.6±1.3 mg/L (95% confidence interval 9.9 mg/L to 19.2 mg/L). There were no differences in CRP concentrations for women who developed postoperative atrial fibrillation compared with women remaining in sinus rhythm (p=0.847). Further, the number of women with elevated CRP concentrations (> 19.2 mg/L) did not differ between the atrial fibrillation and sinus rhythm groups (p=0.807). In total, 76% of women with atrial fibrillation and 73% without atrial fibrillation had CRP concentrations > 3 mg/L (p=0.667).(26) After adjusting for patient age, presence of severely reduced left ventricular (LV) function, prior stroke, and the preoperative use of statindrugs or nitrates before surgery with multivariate logistic regression analysis, CRP was not significantly related to the development of postoperative atrial fibrillation. Predictors of postoperative atrial fibrillation were previous stroke (p=0.04) and patient age (p=0.05). A history of congestive heart failure was the only variable found to correlate with CRP levels (r^2=0.08, p=0.001) based on linear regression that included all demographic variables including aspirin and statin drug use

Adverse postoperative outcomes for women with or without atrial fibrillation are listed in Table 3. Compared with women who remained in sinus rhythm, women with atrial fibrillation were significantly more likely to suffer low cardiac output and to suffer a new stroke. Patients with atrial fibrillation had longer hospitalization in the intensive care unit and on the postoperative ward, and they were more likely to be discharged to an extended care facility. There were no differences in mortality between the patient groups.

Comment

These data show that preoperative CRP concentrations are not associated with the risk of developing atrial fibrillation after cardiac surgery for women. We found that women who developed atrial fibrillation were more likely to have low cardiac output syndrome, stroke, longer hospitalization, and higher likelihood of admission to an extended care facility after hospital discharge.

A mechanistic role of inflammation in the pathogenesis of atrial fibrillation was suggested by the findings of inflammatory cell infiltrates in atrial biopsy specimens from affected patients and the known association between the arrhythmia and pericarditis.(9,10) This speculation was furthered by Bruins et al (18) who reported that CRP mediated complement activation products (C 4b/c) on the 2nd day after CABG surgery were related to the development of supraventricular arrhythmias (p=0.0065). Experimentally, electrophysiological changes conducive to the development of postoperative atrial fibrillation correlate with degree of inflammation measured by tissue myeloperoxidase activity.(27) Treatment with methylprednisolone reduces

both atrial myeloperoxidase activity and the electrophysiologic susbtrate for atrial fibrillation. Elevated CRP might be directly involved in the genesis of atrial arrhyhmias by binding to phosphocholine moieties on cell membranes altering cellular calcium handling, or it may merely serve as a marker for other inflammatory processes more directly related to the development of atrial fibrillation.(11,28-31)

Several investigations have shown a relation between CRP and atrial fibrillation in surgical and non-surgical populations. Chung et al (19) found that CRP concentrations were 2-fold higher in 131 non-surgical patients with atrial fibrillation compared with 71 individuals in sinus rhythm ($p < 0.001$). These results were confirmed in an analysis of data from the Cardiovascular Health Study, a population-based study involving 5806 individuals.(20) In that study, CRP levels predicted baseline and future risk for atrial fibrillation after nearly 7 years of follow-up. Gaudino et al (16) reported that patients with the −174 G/C interleukin-6 promoter genotype had more marked elevations in inflammatory cytokines after CABG surgery using cardiopulmonary bypass and that this accentuated inflammatory response was associated with postoperative atrial fibrillation. More recently Lo et al (22) found a relation between preoperative CRP levels and atrial fibrillation after CABG surgery. For those undergoing surgery on-pump, postoperative atrial fibrillation developed in 55% of patients with high baseline CRP (> 3.0 mg/L,) but in only 21% of patients with low baseline CRP ($p=0.01$). Atrial fibrillation developed after off-pump surgery in 8% of patients with low baseline CRP and in 30% with high baseline CRP ($p=0.002$). In that study CRP remained an independent predictor of atrial fibrillation even after adjusting for other risk factors with multivariate logistic regression analysis.

Studies reporting a relation between elevated CRP and atrial fibrillation susceptibility have included mostly men. The need to separately report clinical trial data for men and women is increasingly recognized since patient sex can modify many pathophysiologic processes including inflammation.(23,32,33) Based on population based assessments, the Center for Disease control and the American Heart Association guidelines suggest that a CRP level of > 3 mg/L represents high risk for vascular disease.(26) Other data, however, suggests that women have higher baseline CRP levels than men. In the Dallas Heart Study, for example, median CRP levels were higher for women compared with men (3.3 mg/L versus 1.8 mg/L, $p < 0.001$). (23) Fifty-one percent of white women and 58% of black women had levels > 3.0 mg/L compared with only 31% and 40% of white and black men, respectively ($p< 0.001$). In the current study, 76% of women with and 73% of women without atrial fibrillation had CRP concentrations > 3 mg/L.

Conceivably, the higher level of inflammatory response to acute cardiovascular disease in women overwhelms the ability to distinguish a true baseline level of inflammation as might be related to risk for atrial fibrillation. Alternativley, inflammatory processes may play a bigger role for determining atrial fibrillation susceptibility for men than women. It is also feasible that the mechanisms of postoperative atrial fibrillation may differ between women and men. Women undergoing cardiac surgery more often than men have preserved left ventricular function, yet more frequently have hypertension and congestive heart failure.(1-4) These findings would be expected to lead to left ventricular diastolic dysfunction that might promote higher atrial pressures and atrial distention. The latter could activate atrial stretch receptors promoting electrophysiologic conditions for atrial fibrillation.(34,35) We are unable to assess these potential mechanisms for atrial fibrillation for women in this small cohort.

In this study we only report CRP concentrations before surgery. Our intent was to evaluate for evidence of pre-existing inflammation as a means to identify individuals with the substrate for atrial fibrillation before surgery. Measurements in the postoperative period may have identified a link between inflammation and atrial fibrillation. Others have shown though that the

concentrations of this inflammatory marker peak on postoperative days 3 to 4, a time frame similar to the onset of atrial fibrillation.(16-18) To avoid the confounding influence of inflammation resulting *from* atrial fibrillation and/or its treatments, postoperative specimens would have to be collected before the onset of the arrhythmia. Not only would this be difficult to ensure clinically, but these specimens would likely be obtained prior to peak CRP levels are achieved. Baseline CRP concentrations have been found to be the strongest predictor of postoperative levels suggesting that "high" responders to the well described inflammatory effects of cardiac surgery with cardiopulmonary bypass would be identified by measurements before surgery.(16-18,36)

Multiple investigations have reported the frequency and importance of atrial fibrillation for patient outcomes following cardiac surgery.(5,7,8) These reports have not separately evaluated whether this relationship specifically applies to women, who represent a minority of the studied patients. Our findings, though, are similar to the reports composed mostly of men. In this study, women developing atrial fibrillation were more likely than those remaining in sinus rhythm to have other cardiac and neurologic complications. We did not determine the temporal relationship between the onset of atrial fibrillation and these complications.(7) Thus, we cannot distinguish whether these associations were causally related or secondarily related to these events (i.e., stroke or low cardiac output occurred because of atrial fibrillation or vice versa). Our findings that women with atrial fibrillation were hospitalized nearly 3 days longer than those without atrial fibrillation, and that they were nearly twice as likely to be discharged from the hospital to an extended care facility are consistent with prior reports. Although the limitations of the small sample size of this study must be acknowledged, our data appears to confirm that the association between atrial fibrillaiton after cardiac surgery and other complications and health resource utilization applies to women.

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