Plasminogen Activator Inhibitor-1 as a Predictor of Postoperative Atrial Fibrillation After Cardiopulmonary Bypass

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**Background**—Postoperative atrial fibrillation (AF), leading to significant morbidity and prolongation of hospital stay, complicates 20% to 40% of surgical procedures requiring cardiopulmonary bypass (CPB). This study tests the hypothesis that biomarkers predict the development of postoperative AF.

**Methods and Results**—We enrolled 253 adult patients undergoing elective cardiac surgery requiring CPB and who were in sinus rhythm at the time of surgery. Blood samples were obtained for measurement of 21 biomarkers immediately after separation from CPB and administration of protamine. Patients who developed postoperative AF (67 subjects, 26.5%) were significantly older (P<0.001), more likely to have a remote history of AF (P<0.001), and tended to be more likely to have had valve surgery (P=0.082). Plasminogen activator inhibitor-1 (PAI-1) (P=0.014), interleukin (IL)-6 (P=0.019), and N-terminal prohormone brain natriuretic peptide (P=0.028) concentrations were significantly higher in the blood of patients who developed postoperative AF. Logistic regression identified age (P<0.001), remote history of AF (P=0.001), and postoperative PAI-1 (P=0.036) as independent predictors of postoperative AF. When preoperative PAI-1 antigen concentrations were included in the model age (P<0.001), remote history of AF (P<0.001) and preoperative PAI-1 (P=0.015) were identified as independent predictors of postoperative AF. The Chi-squared Automatic Interaction Detection (CHAID) model indicated that age was the primary determinant for the development of postoperative AF (17% in age ≤67.3 years versus 49% in age >67.3 years). Within younger patients (age ≤67.3 years) without remote history of AF, postoperative PAI-1 antigen concentration next determined risk of AF (13% if PAI-1=28.5 ng/mL versus 46% if PAI-1>28.5 ng/mL).

**Conclusion**—An elevated preoperative or postoperative PAI-1 antigen concentration is an independent predictor for development of AF after CPB. Studies are needed to determine whether drugs that reduce PAI-1 concentrations can also reduce the risk of postoperative AF. *(Circulation. 2007;116[suppl I]:I-1–I-7.)*

**Key Words:** atrial fibrillation ■ plasminogen activator inhibitor ■ inflammation ■ cardiopulmonary bypass
Methods

Patient Enrollment
This study was approved by the Vanderbilt University Institutional Review Board for Research on Human Subjects and conducted according to the Declaration of Helsinki. All patients provided written informed consent. We prospectively enrolled unselected cardiac surgery patients from November 1999 until November 2004 into the Vanderbilt Cardiac Surgery Registry, a repository of clinical and laboratory data for use in outcome studies. For this study, we excluded patients who: (1) were in AF at the time of surgery or at the time of their preoperative evaluation within a week before surgery (n = 32), (2) underwent heart or lung transplant, ventricular assist device placement, or off-pump procedures (n = 37), and (3) did not have a post-CPB blood sample available (n = 200). The final data set consisted of 253 adult subjects in sinus rhythm at the time of surgery, undergoing procedures involving CPB.

Patient Treatment
Anesthetic and surgical management were conducted according to institutional protocols. Briefly, patients received general endotracheal anesthesia, consisting of induction with a combination of thiopental, midazolam, fentanyl, or etomidate and maintenance with isoflurane, pancuronium, and fentanyl. Monitoring included standard modalities (ECG, temperature, invasive blood pressure, pulse oximetry, and gas monitoring) plus central venous pressure or pulmonary artery catheter monitoring and transesophageal echocardiography. Aprotinin was used for repeat sternotomy procedures and those involving more than 1 open chamber procedure. E-aminocaproic acid (E-ACA) was used for first-time sternotomy operations for patients without a history of venous thrombosis or unstable coronary syndromes. Anticoagulation for CPB consisted of 400 U/kg unfractionated porcine heparin. Temperature management involved cooling to 28°C to 30°C, temperature uncorrected blood gas management (α stat), and cold anterograde and retrograde cardioplegia techniques. At the conclusion of CPB, anticoagulation was reversed with 250 mg protamine, with an additional 50 mg administered in the following 10 minutes in the presence of ongoing microvascular bleeding. Metoprolol 12.5 mg twice a day was given if heart rate was greater than 60 and systolic blood pressure greater than 100 mm Hg starting on postoperative day 1. All patients were monitored with continuous telemetry until discharge from hospital.

Clinical Parameters
We determined prospectively-defined preoperative, intraoperative, and postoperative variables by chart review. Preoperative medication variables were defined as those medications the patient was receiving on a regular basis at the time of preoperative evaluation. Preoperative medical history was defined as those conditions listed on the patient’s preoperative evaluation. Postoperative AF was defined as AF occurring within 2 weeks after surgery with ECG evidence from telemetry tracing or 12-lead ECG (n = 50), or evidence in the chart for postoperative AF (n = 17), consisting of at least 2 of the following: (1) AF in nurses notes, (2) AF in daily physicians progress notes, (3) AF documented in the discharge summary, (4) change in medications consistent with AF (β-blockers, diuretics, verapamil, amiodarone, coumadin, etc), or (5) consultation of the cardiology service for AF management.

Blood Sampling and Biochemical Assays
Blood was collected on ice in vacutainer tubes containing 0.105 mol/L sodium citrate (BD Vacutainer Systems) and centrifuged immediately at 0°C for 20 minutes. Plasma was then separated and stored at −70°C until the time of assay. All blood samples were taken from an indwelling arterial line. Blood samples obtained immediately after separation from CPB and administration of protamine were analyzed for biomarkers. These included C-reactive protein (CRP), serum amyloid A (SAA), serum amyloid protein P (SAP), fibrinogen, haptoglobin, E-selectin, vascular cell adhesion molecule 1 (VCAM-1), intercellular adhesion molecule 1 (ICAM-1), matrix metalloproteinase-9 (MMP-9), myeloperoxidase (MPO), adiponectin, plasminogen activator inhibitor-1 (PAI-1), interleukin (IL)-1β, IL-6, IL-8, IL-10, interferon-γ, tumor necrosis factor-α, monocyte chemoattractant protein 1 (MCP-1), N-terminal prohormone brain natriuretic peptide (NT-proBNP), and vascular endothelial growth factor (VEGF). Samples were analyzed using multiplex LINCOplex Biomarker immunoassays (LINCO Research, Inc.).

Based on the results of these analyses a preoperative blood sample obtained on the morning of surgery was analyzed for PAI-1 antigen using ELISA (Biopool AB) and for IL-6 using ELISA (GE Healthcare).

Statistical Analysis
Data are presented as means ± SEM. Categorical data were compared between groups using χ² or Fischer exact tests, as appropriate. Continuous data with a nonparametric distribution were log transformed and then compared using Student t test. Correlation between variables was determined by the Spearman rho test. A 2-tailed probability value less than 0.05 was considered statistically significant. Risk for developing AF was evaluated by both logistic regression and Chi-squared Automatic Interaction Detector (CHAID), whereby patients were classified as either having developed AF or not between arrival to the operating room and postoperative day 14.

Logistic-Regression Models
Backward stepwise logistic regression was performed to identify independent predictors of postoperative AF. In an initial analysis, variables with a P<0.1 by univariate analysis as well as risk factors commonly reported in the literature (age, history of AF, valve surgery, BMI, and CRP) were included in the model. Age was categorized in 10-year intervals assuming that the risk increased in a linear fashion from category to category. Variables were entered and maintained in the model if their contribution was significant at the level of P<0.1.

CHAID
CHAID modeling identifies variables that delineate subgroups of patients with distinct patterns of postoperative AF. The CHAID model provides a way to identify major factors and their interactions associated with an outcome, whereas logistic regression allows the joint effects of multiple characteristics to be evaluated simultaneously. Using as a criterion the significance of a statistical test, CHAID evaluates all of the values of a potential predictor variable. It merges values that are judged to be statistically similar with respect to the target variable and maintains all other values that are dissimilar. It then selects the best predictor variable to form the first branch in the decision tree, such that each node is made of a group of homogenous values of the selected variable. This process continues recursively until the tree is fully grown. The following variables were included in the CHAID model: age, BMI, history of CHF, remote history of AF, valve surgery, postoperative CRP, PAI-1, IL-6, MCP-1, NT-proBNP, and preoperative PAI-1. We set the criteria to grow the tree as minimum size for parent node and child node of 20 and 10, respectively, and maximum level below root of 3. A Bonferroni adjustment was used to correct for the number of different ways a single predictor variable can be split. All analyses were performed with the statistical package SPSS for Windows (Version 11.0.1, SPSS) and Answer Tree (Version 3.1 SPSS).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Demographic Characteristics
The patient population, classified by occurrence of postoperative AF, is represented in Table 1. Postoperative AF was observed in 67 subjects (26.5%) with a peak incidence of AF occurring on postoperative day 2. Patients who developed...
postoperative AF were significantly older ($P<0.001$) and were more likely to have had a remote history of AF ($P<0.001$). Left atrial diameter was increased among patients who developed postoperative AF (45.7 $\pm$ 1.4 mm in 29 patients in whom it was measured) compared with those who did not (41.1 $\pm$ 1.2 mm in 64 patients, $P=0.024$). Patients with postoperative AF also tended to be more likely to have had valve surgery ($P=0.082$) and a prior medical history of congestive heart failure ($P=0.065$) compared with patients who did not develop postoperative AF, but these trends were not significant. There were no statistically significant differences in the use of preoperative medications between the 2 groups. $\beta$-blocker administration in the postoperative period was not significantly different between patients who developed postoperative AF compared with patients with no postoperative AF (85.1% versus 82.3% respectively, $P=0.748$).

### Postoperative Biomarkers

Patients who developed postoperative AF (Table 2) had significantly higher concentrations of PAI-1, IL-6, and NT-proBNP immediately after CPB compared with patients who did not develop AF. There were significant correlations of postoperative PAI-1 antigen concentration with age ($r^2=0.035$, $P=0.005$), BMI ($r^2=0.020$, $P<0.001$), CPB time ($r^2=0.060$, $P=0.008$), and IL-6 ($r^2=0.020$, $P=0.001$). In addition, postoperative PAI-1 concentrations were significantly higher in patients with a history of hypertension ($P=0.001$), preoperative statin use ($P=0.007$), preoperative $\beta$-blocker use ($P=0.036$), and preoperative ACE inhibitor use ($P=0.031$). Postoperative PAI-1 concentrations were significantly higher in patients that received aminocaproic acid compared with patients that received aprotinin (16.8 $\pm$ 0.7 ng/mL versus 12.0 $\pm$ 1.5 ng/mL, $P<0.001$). Among patients undergoing coronary revascularization those who developed AF had significantly higher concentrations of PAI-1 (18.4 $\pm$ 1.8 ng/mL versus 15.0 $\pm$ 0.8 ng/mL, $P=0.046$) and tended to have higher CRP concentration (17.7 $\pm$ 6.0 $\mu$g/mL versus 14.7 $\pm$ 3.3 $\mu$g/mL, $P=0.075$). Among patients undergoing valvular surgery only, those who developed postoperative AF had significantly higher concentrations of PAI-1 (16.5 $\pm$ 2.4 ng/mL versus 10.5 $\pm$ 0.9 ng/mL, $P=0.006$) and NT-proBNP (357.3 $\pm$ 109.2 pg/mL versus 181.2 $\pm$ 59.6 pg/mL, $P=0.019$).

### Logistic Regression Models

Binary logistic regression identified 3 independent predictors for the development of postoperative AF among the 253 patients.
patients: age ($P<0.001$), remote history of AF ($P<0.001$), and postoperative PAI-1 antigen concentration ($P=0.036$). Other predictors of postoperative AF that were included in the regression model but did not reach a level of statistical significance were valve surgery, history of CHF, BMI, and the postoperative biomarkers CRP, IL-6, MCP-1, and NT-proBNP.

**Preoperative Biomarkers**

Based on the finding that postoperative PAI-1 predicted postoperative AF, we next assessed the predictive value of preoperative PAI-1 concentrations. Preoperative PAI-1 concentrations correlated significantly with postoperative PAI-1 concentrations ($r^2=0.214$, $P<0.001$) as well as with BMI ($r^2=0.131$, $P<0.001$) and were significantly higher in subjects who developed AF compared with those who did not (29.0±2.1 ng/mL versus 24.3±0.9 ng/mL, $P=0.044$). In addition, increased preoperative PAI-1 concentrations were associated with a history of hypertension ($P<0.001$), preoperative statin use ($P=0.017$), preoperative ACE inhibitor use ($P=0.033$), preoperative diuretic use ($P<0.001$), and intraoperative use of aminocaproic acid ($P=0.034$). Preoperative IL-6 concentrations were not significantly different between patients who developed postoperative AF compared with patients who did not develop postoperative AF (2.7±0.5 versus 3.3±0.9 pg/mL respectively, $P=0.098$).

In binary logistic regression analysis that included both preoperative and postoperative PAI-1 antigen concentrations, age, remote history of atrial fibrillation, and valve surgery, preoperative PAI-1 concentration was a stronger predictor of postoperative AF than postoperative PAI-1 concentration (Table 3). The Hosmer and Lemeshow Goodness-of-Fit test for the final model was 12.656 ($P=0.124$ with DF=8). Because valvular surgery per se is a strong risk factor for developing postoperative AF we repeated the logistic regression excluding patients who had valvular operations. In this model age (OR 2.08, 95% CI 1.36 to 3.19, $P=0.001$), remote history of AF (OR 4.72, 95% CI 1.04 to 21.32, $P=0.044$), and preoperative PAI-1 antigen concentrations (OR 1.05, 95% CI 1.02 to 1.09, $P=0.003$) remained independent predictors of postoperative AF. Because increased PAI-1 antigen concentrations are associated with a history of hypertension, preoperative use of statins, β-blockers, ACE inhibitors, diuretics, and intraoperative use of aminocaproic acid we evaluated the possible confounding by these variables in a logistic regression model that included these variables plus age, remote history of AF, preoperative PAI-1 antigen, and valve surgery. In this model none of the possible confounders was significant and age (OR 1.75, 95% CI 1.33 to 2.29, $P<0.001$), remote history of AF (OR 5.70, 95% CI 2.14 to 15.15, $P<0.001$) and preoperative PAI-1 antigen concentrations (OR 4.72, 95% CI 1.04 to 21.32, $P=0.044$) remained as independent predictors of postoperative AF. Forcing possible confounders into the model did not change the results.

**CHAIAD Model**

Using CHAIAD analysis, we successively partitioned our study population into subgroups, using the most significant predic-
tor variables. The CHAID model indicated that age was the primary determinant for the development of postoperative AF (Figure). Among patients older than 67.3 years of age (the age cutoff chosen by the CHAID algorithm) 49% developed postoperative AF, whereas only 17% of those 67.3 years or younger developed AF. Among the patients 67.3 years or younger, the next most important determinant of postoperative AF was remote history of AF: patients with a remote history of AF had a 42% risk for developing AF, whereas those with no remote history of AF had a 15% risk. Among the patients younger than 67.3 years with no remote history of AF, the next division was postoperative PAI-1 concentration. In this group, a PAI-1 concentration less than 28.5 ng/mL was associated with a 13% risk for developing AF, whereas patients with a PAI-1 concentration greater than 28.5 ng/mL had a 46% risk. Preoperative PAI-1 concentration was not a significant predictor in this analysis. Among patients older than 67.3 years, the next division was remote history of AF: patients with a remote history of AF had an 83% risk for developing AF, whereas those with no remote history of AF had a 42% risk.

**Discussion**

AF complicates 20% to 40% of cardiac surgical procedures requiring CPB. Although off-pump coronary artery bypass graft (CABG) surgery has been associated with a reduction in AF, the incidence of postoperative AF is still 22% suggesting that not only CPB, but surgery itself, contributes to the development of postoperative AF. This study examined which biomarkers, measured immediately after cardiac sur-

### TABLE 3. Multivariate Logistic Regression Model for Postoperative Atrial Fibrillation

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Incidence of postoperative AF n/Total (%)</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>0/10 (0)</td>
<td>1.75 (1.35–2.26)*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>30–39</td>
<td>2/15 (13.3)</td>
<td></td>
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<tr>
<td>40–49</td>
<td>6/35 (17.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50–59</td>
<td>11/61 (18.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60–69</td>
<td>17/72 (23.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>70–79</td>
<td>24/48 (50.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;80</td>
<td>7/12 (58.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remote history of Atrial Fibrillation</td>
<td>15/24 (62.5)</td>
<td>5.87 (2.23–15.47)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Preoperative PAI-1 antigen, ng/mL</td>
<td></td>
<td>1.03 (1.01–1.05)</td>
<td>0.015</td>
</tr>
<tr>
<td>Valve Surgery</td>
<td></td>
<td>1.81 (0.95–3.44)</td>
<td>0.070</td>
</tr>
</tbody>
</table>

OR indicates odds ratio; CI, confidence interval. Variables included in the analysis were age, remote history of atrial fibrillation, valve surgery, preoperative and postoperative plasminogen activator inhibitor-1 (PAI-1). *The OR is for a 10-year change.
gery, best predicted the development of postoperative AF. We confirmed previously reported clinical risk factors for AF that included age and history of AF. In addition, higher PAI-1 antigen concentration was an independent predictor for postoperative AF.

The pathophysiology of AF is complex with increasing evidence suggesting that inflammation and fibrosis contribute to the pathogenesis of AF. Histology of atrial biopsies has demonstrated inflammatory infiltrates within atrial tissue in patients with lone or nonvalvular AF. In addition, several studies have found an association between the inflammatory markers (IL-6 and CRP) and AF. Cardiac surgery is associated with an acute-phase response marked by an increase in inflammatory markers throughout the postoperative period. The peak incidence of postoperative AF occurs on the second and third postoperative day which coincides with the peak elevation in CRP concentrations. Both IL-6 and CRP have been reported to be independent predictors of postoperative AF after cardiac surgery. Although IL-6 concentrations were significantly higher in individuals who developed postoperative AF in our study population, neither IL-6 nor CRP independently predicted the development of postoperative AF after controlling for other risk factors. The lack of association between IL-6 and postoperative AF in our study may be explained by the fact that we measured concentrations of inflammatory makers immediately after CPB and protamine administration, whereas in the other study, IL-6 concentrations were measured repeatedly over several days.

In this regard, the measurement of biomarkers at a single time point represents a potential limitation of the study. Because the concentration of many cytokines and inflammatory markers, including PAI-1, peak later in the postoperative period we may have missed important associations with postoperative AF. For example, IL-6 concentrations increase at the end of CPB and peak at 4 to 6 hours after surgery. PAI-1 antigen concentrations transiently decrease during CPB and then begin to rise by separation from CPB, peaking on postoperative day 1. On the other hand, we found that preoperative PAI-1 concentrations predicted postoperative AF suggesting that the underlying inflammatory and fibrotic state rather than the acute inflammatory response, may determine risk of this event. Moreover, the selection of the postprotamine time point enabled us to assay blood when many biomarkers are starting to rise, but early enough to direct future preventive strategies.

In addition to functioning as an acute phase reactant, PAI-1 serves as the primary inhibitor of tissue-type plasminogen activator (t-PA). As a consequence of reduced t-PA activity, less plasmin is formed from plasminogen. Plasmin, a proteolytic enzyme, plays an important role in extracellular matrix turnover. Increased PAI-1 reduces extracellular matrix turnover and promotes fibrosis. Increased fibrosis can modify the atrial substrate and potentially lead to postoperative AF given a trigger event such as cardiac surgery. Cardiac PAI-1 expression is increased in animal models of AF and PAI-1 concentrations have been reported to be increased in patients with chronic AF. In our study population both preoperative and postoperative PAI-1 antigen concentrations were significantly higher in patients who developed postoperative AF. Whether measured preoperatively or postoperatively, PAI-1 was the only biomarker that independently predicted postoperative AF in the multivariate analysis. For example, the odds of postoperative AF increased 3% with every 1 ng/mL increase in preoperative PAI-1 antigen concentrations. As reported previously, PAI-1 antigen concentrations correlated with age, BMI, and IL-6. In addition, postoperative PAI-1 antigen concentrations correlated with CPB time, which may indicate that postoperative PAI-1 concentrations reflect not only the basal fibrinolytic and inflammatory state but also the acute inflammatory response to surgery. In the CHAID model the additional predictive value of PAI-1 was primarily among those age <67.3 and no history of AF. Measuring postoperative PAI-1 in this group may be potentially useful as a screening tool for postoperative AF.

That PAI-1 antigen concentration predicts the risk of postoperative AF suggests the hypothesis that drugs that decrease PAI-1 antigen could influence the risk of AF. Statins reduce both inflammation and PAI-1 and have recently been shown to reduce the risk of postoperative AF. Another such class of drugs is the ACE inhibitors. ACE inhibitors decrease the development of AF in patients with left ventricular dysfunction. In a study of patients treated preoperatively with an ACE inhibitor and randomized to continue or discontinue ACE inhibition, continued ACE inhibition decreased plasma PAI-1 antigen concentrations after CPB.

Study Limitations
In the current study, preoperative ACE inhibitor use, as well as statin use, was associated with increased pre- and postoperative PAI-1 antigen concentrations. In addition, ACE inhibitor use did not affect the risk of AF. Because neither ACE inhibitor use nor statin use was randomized, these observations may well reflect confounding by indication. For example, individuals treated with ACE inhibitors preoperatively were older and more likely to be diabetic, to have hypertension, and to have a history of congestive heart failure. In addition, ACE inhibitor use was generally discontinued preoperatively, and Mathew et al have reported that withdrawal of ACE inhibitors, in contrast to continued ACE inhibitor administration, increases the risk of postoperative AF. We did not detect an effect of preoperative β-blocker use on the risk of postoperative AF in this study. However, because more than 83% of patients received β-blockers in the postoperative period this confounded any interpretation of the effect of preoperative β-blocker use. Although aminocaproic acid treatment has been shown to blunt the postoperative PAI-1 response, both pre- and postoperative PAI-1 concentrations were significantly higher in patients that received aminocaproic acid compared with patients that received aprotinin suggesting that drug treatment did not affect PAI-1 response in our nonrandomized study population. Also, aminocaproic acid was not a significant predictor of postoperative AF when included in a logistic regression model with other potential confounders of PAI-1. One potential limitation of the CHAID model is that the best cut-off points are more likely to be occurred in the extreme values. This will lead to groups with extremely small sample size and thus make the
group less representative. However, despite these limitations, the CHAID model provides additional information regarding subsets of patients in which PAI-1 antigen is a predictor of postoperative AF.

In conclusion, our study demonstrates that increased PAI-1 antigen, in addition to age and remote history of AF, acts as an independent predictor for postoperative AF. This study supports the hypothesis that postoperative AF occurs secondary to fibrosis and inflammation. Future clinical trials are needed to evaluate if drugs that attenuate PAI-1 can reduce the incidence of postoperative AF.

Acknowledgments
We thank Lisa L. Rush BS, MEd, for database management.

Sources of Funding
This research was funded by NIH grants HL085740, HL065193, HL060906, HL077398, U01 HL065962, RR00095 and K23 HL004476. Sample analysis was provided through a generous gift from LINCO Research Inc.

Disclosures
None.

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Circulation. 2007;116:I-1-I-7
doi: 10.1161/CIRCULATIONAHA.106.677906

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