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Perioperative Heart-type Fatty Acid Binding Protein Levels in Atrial Fibrillation after Cardiac Surgery

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Abstract

Background—Postoperative atrial fibrillation (POAF) is common and associated with poor outcomes. Perioperative ischemia can alter arrhythmic substrate.

Objective—To demonstrate an association between perioperative measurement of heart-type fatty acid binding protein (HT-FABP), a sensitive marker of ischemic myocardial injury.

Methods—Blood samples from 63 inpatients undergoing coronary artery bypass surgery (CABG), valve surgery or both were obtained before and up to four days after surgery. Continuous telemetry monitoring was used to detect POAF. 59 patients had at least 3 HT-FABP measurements. The relation of ELISA-measured HT-FABP to POAF was assessed using joint logistic regression adjusted for age and surgery type.

Results—Thirty five patients (55%) developed POAF; these were on average older (69.3 ± 10 vs. 60 ± 11 years, $p=0.0019$), with a higher prevalence of heart failure (43% vs. 17%, $p=0.034$),

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chronic obstructive lung disease (26% vs. 4%, $p=0.017$), preoperative calcium channel blocker use (29% vs. 7%, $p=0.031$) and more likely to undergo combined surgery (21% vs. 11%, $p=0.049$). The joint age- and CABG-adjusted model revealed that postoperative but not preoperative HT-FABP levels predicted POAF (coefficient 1.9 ± 0.87 , $p=0.03$). Longer bypass time, prior infarction and worse renal function were all associated with higher postoperative HT-FABP.

Conclusions—A greater rise of HT-FABP is associated with atrial fibrillation after cardiac surgery, suggesting that ischemic myocardial damage is a contributing underlying mechanism. Interventions that decrease perioperative ischemic injury may also decrease the occurrence of POAF.

Keywords

Atrial Fibrillation; Postoperative; Biomarker; Ischemia; CABG; Valve Surgery

Atrial fibrillation (AF) occurs in up to 60% of patients undergoing coronary artery bypass grafting (CABG) or valve surgery^{1, 2} and is associated with poor outcomes and increased costs.³ The mechanisms underlying postoperative AF (POAF) are poorly understood and current prophylactic medications are empiric and lack reliable efficacy.⁴ Paired with undesirable adverse effects from such medications,^{5–8} routine application is currently not employed. Perioperative ventricular and atrial ischemia changes arrhythmic substrate directly on a cellular level and indirectly via inflammation and myocardial strain. To better elucidate the pathophysiology of POAF, we hypothesized that a greater rise of heart-type fatty acid binding protein (HT-FABP), a sensitive biomarker of ischemic myocardial damage^{9, 10} would be associated with POAF in patients undergoing cardiac surgery.

PATIENTS AND METHODS

Patients

From 11/2009 through 06/2010, 71 inpatients were prospectively enrolled in our study. Three patients died before they went to surgery, one patient refused participation after signing the consent form and 4 patients were treated with percutaneous coronary intervention instead of coronary artery bypass surgery (CABG) after enrollment into the study, leaving 63 patients in sinus rhythm at the time of surgery and without anti-arrhythmic drug therapy, who were prospectively followed until hospital discharge. Only 1 patient had a history of AF. Because we enrolled hospitalized patients only, there was a relatively high prevalence of cardiac and non-cardiac comorbidities, many of which are known risk factors for POAF (Table 1). Patients were predominantly white (94%), male (63%) and underwent isolated CABG ($n=33$). However, isolated valve surgery ($n=14$) and combined CABG plus valve surgery ($n=16$) were represented as well. Among those, 21 patients underwent aortic valve replacement, 5 mitral valve replacement and 6 mitral valve repair.

Patient Data

Epidemiologic, cardiac and non-cardiac clinical and procedural characteristics were prospectively collected. The Cleveland Clinic Institutional Review Board approved the study and informed consent was obtained from all participants.

Definition and Ascertainment of POAF

POAF was prospectively defined as any episode of AF or atrial flutter (there was none) after surgery and before discharge, lasting for at least 5 minutes. AF was detected by continuous telemetry monitoring throughout the hospital stay and presence of AF was confirmed by a Cardiologist.

Blood Sample Processing and Laboratory Testing Methods

Venous blood samples were obtained at prespecified equal intervals in EDTA plasma tubes and serum tubes prior to surgery (mean interval to surgery 1.9 days, 95% confidence interval [CI] 0.99–2.75 days) and on 1st (0.99 ± 0.18 days), 2nd (2.01 ± 0.14 days), 3rd (3.02 ± 0.16 days), and 4th day (4.01 ± 0.16 days) after surgery. Plasma tubes were put on ice immediately after blood draw and together with serum tubes centrifuged at 4° Celsius and 3000 rpm for 20 minutes. Plasma and serum aliquots were obtained immediately after and stored at –80° Celsius. HT-FABP levels were measured by ELISA (Cell Sciences, Canton, MA). Troponin T (TnT) was measured as part of routine care only on postoperative day 1 by our core lab using an electro-chemiluminescence immunoassay performed on a Roche E170 modular analytics immunoassay analyzer.

Statistical Analysis

Because distribution of HT-FABP levels was highly skewed, a logarithmic transformation was used, resulting in a near normal distribution. To account for a variable number of measured data points between patients, we compared biomarker levels of patients with and without AF in 4 groups (E-table 1 in appendix). After exclusion of patients with only 2 data points (n=4, group A in E-Table 1), we created 3 logistic regression models with common regression parameters and different intercepts for each model (a joint shared parameter model), which included patients' age and concomitant CABG. We then maximized the joint likelihood of the 3 models to estimate the parameters in the joint model. HT-FABP levels considered in the joint model were as follows: (1) preoperative HT-FABP levels, (2) 24-hour lagged HT-FABP level, which represented HT-FABP 24 hours before AF in patients with arrhythmia and 24-hours before last measured HT-FABP level in patients without arrhythmia, (3) current HT-FABP level, which was the last HT-FABP measurement before AF occurred in patients with arrhythmia and the last measured HT-FABP level in patients without arrhythmia. This approach was valid, because number of patients with and without AF was similar in all 3 data groups (E-table 2). After evaluating the univariate association of Troponin T level (TnT) obtained on postoperative day 1 with POAF, we forced postoperative day 1 TnT into the multivariable joint model. In secondary analyses, we studied predictors of postoperative HT-FABP levels with longitudinal regression for continuous repeated measurements. Because of the limited capability of this analysis to explore multivariable relations, we initially screened for candidate predictors (E-Table 3) using multivariable linear regression with liberal entry criteria ($p=0.12$) and stay criteria ($p=0.07$) and the assumption of independence of observations. Candidate variables and their transformations, if any, were entered at once into the longitudinal model, and then eliminated one by one until all variables remaining had a p-value of 0.05 or less.^{11–13} We also evaluated the relationship of current HT-FABP levels with POAF in time-to event Cox-Proportional Hazard model, which confirmed our findings of the joint model (results not shown). Finally, we compared baseline characteristics, complication rates and HT-FABP levels in patients with early (within 4 days after surgery) vs. late (after 4 days) occurrence of POAF to investigate possible differences in mechanisms by time of occurrence (supplemental table S1).

All analyses were performed using SAS v. 9.2 statistical software (PROC NLMIXED, PROC MIXED, PROC REG; SAS Inc., Cary, NC).

Presentation

Continuous variables are summarized by means and standard deviations and compared with two-tailed student's t-test or Whitney-Mann-U-test if distribution was skewed. Categorical variables are summarized by frequencies and percentages and compared with appropriate χ^2 statistics (Table 1).

RESULTS

Occurrence of POAF

Among 63 patients who underwent cardiac surgery, 35 (56%) developed POAF. Of those, AF occurred most frequently in patients undergoing combined CABG and valve surgery (11 events, 79%), followed by isolated valve surgery (9 events, 64%), while patients undergoing isolated CABG had the least AF (14 events, 42%). POAF occurred most frequently on day 2 and 3 after surgery (Figure 1).

HT-FABP and POAF

In unadjusted comparisons, patients who developed POAF had similar preoperative, but higher postoperative HT-FABP levels compared to patients who remained in normal sinus rhythm (Figure 2).

In age- and CABG-adjusted joint regression, the last HT-FABP level before development of AF was significantly higher in patients with AF compared to HT-FABP levels in patients without AF. Interestingly, preoperative levels were not associated with POAF, suggesting that ischemic injury during surgery or thereafter and not preoperative ischemia determined arrhythmic risk. HT-FABP levels obtained 24 hours before AF occurred were not associated with development of AF once adjusted for last available HT-FABP levels indicating that levels measured closest to AF occurrence maximized discrimination between patients with vs. without AF (Table 2). In multivariable analysis, creatinine levels were not associated with POAF, indicating that renal function, which can affect clearance of HT-FABP, was not a confounder. Although there was a trend toward higher postoperative day 1 TnT levels in patients who developed POAF compared to patients who remained in sinus rhythm (median 0.56 µg/L (interquartile range 0.29–0.95) vs. 0.78 µg/L (0.37–1.56, $p=0.16$), after multivariable adjustment in the joint model, TnT levels were not associated with POAF ($p=0.7$) and did not confound the association of HT-FABP levels with POAF. However, Troponin T and HT-FABP levels measured on postoperative day 1 correlated significantly (Pearson correlation coefficient 0.62, $p<.0001$).

Predictors of Increased HT-FABP Levels

In longitudinal analyses, we identified variables associated with postoperative HT-FABP levels (Table 3): First, patient variables that were related to myocardial ischemia (prior myocardial infarction and length of cardiopulmonary bypass time), and second, variables that are related to the biomarker dynamics of HT-FABP (higher preoperative HT-FABP levels, shorter time to measurement of HT-FABP, postoperative creatinine levels as surrogate of renal function). Interestingly, a higher grade of mitral valve regurgitation was associated with lower postoperative HT-FABP levels. Supplemental table S1 shows that baseline characteristics, complications rates and HT-FABP levels were similar between early vs. late onset POAF, with the exception of a trend for more CABG in late occurrence and older age in early occurrence POAF.

DISCUSSION

This prospective study of hospitalized patients undergoing CABG, isolated valve surgery or both demonstrated a strong association between postoperative heart-type fatty acid binding protein levels (HT-FABP), a sensitive marker of ischemic myocardial injury, with occurrence of postoperative atrial fibrillation (POAF). These results suggest that ischemic injury during open-heart surgery plays an important role in the development of AF after cardiac surgery and may be a therapeutic target for reducing AF after cardiac surgery.

HT-FABP and Ischemia

HT-FABP binds long chain fatty acids in the cytosol of myocardial cells, and to a lesser extent in skeletal muscle, brain and kidney cells. These proteins protect myocardial cells from the detergent-like properties of fatty acids, which may be of increased importance during ischemia.¹⁴ Ischemia induces intracellular osmolyte and calcium accumulation, leading to mitochondrial edema and disruption of membranes. As a result intracellular constituents are released into the blood, leading to measurable elevations of cardiac enzymes in acute myocardial infarction, and after cardiopulmonary bypass. HT-FABP is released earlier than Troponin, because it is not bound to protein, it is relatively smaller (14kDa compared to 37 kDa of Troponin T (TnT) and 21 kDa of Troponin I) and is less resistant to changes in pH.⁹ Whether release of intracellular myocardial proteins is evidence of irreversible cell death or a controlled property of cell membranes during ischemia is controversial,¹⁵ but elevated HT-FABP is generally accepted as a marker of cell necrosis. HT-FABP levels can estimate infarct size¹⁶ and recently, HT-FABP has been shown to predict subsequent cardiovascular events in TnT-negative patients with acute coronary syndrome.¹⁰ Given these and our findings, we hypothesize that the high sensitivity of the HT-FABP assay for myocardial damage accounts for its predictive power of POAF as opposed to TnT.

Ischemia and POAF

While the link between ischemia and ventricular arrhythmias is well established, relatively few data are available for ischemia-induced atrial arrhythmias. Patients who suffered from myocardial infarction had increased atrial ectopic activity, ranging from 9 to 14 premature atrial complexes (PACs) per hour on day 1 and 1 to 2 PACs per hour on day 10.¹⁷ AF after myocardial infarction however is rare.¹¹ Frequently, the rate of PACs increases in patients with suspected coronary artery disease, who undergo stress testing.¹⁸ Although this suggests that ischemia may increase atrial ectopy, it does not conclusively establish a causal relationship. Secondary effects, such as myocardial stunning followed by increased left ventricular filling pressures and atrial dilatation or pericarditis may also increase PACs post infarction and after surgery, which by itself is a known risk factor for POAF.¹⁹ While this study cannot establish causation, it describes a strong association between postoperative ischemia and AF, and even if the link is indirect, reduction of ischemic injury may attenuate the secondary hemodynamic and electrophysiologic triggers of POAF.

Ischemia during Cardiac Surgery

Because preoperative HT-FABP levels were not predictive of AF, it appears that time of ischemic insult did not occur before surgery, but during or after surgery in our study. We also demonstrate an association between postoperative HT-FABP levels and cardiopulmonary bypass time. Therefore we identified a potential target for reducing POAF. There is evidence that off-pump CABG is somewhat protective from POAF.^{20, 21} This is conceivably related to less ischemic injury during surgery. Malik and colleagues' work is in agreement with this assumption: Patients undergoing off-pump CABG had lower HT-FABP levels when compared to patients who underwent on-pump CABG.²² Patients with prior myocardial infarction, who have greater propensity for perioperative ischemia, had higher postoperative HT-FABP levels. It has been shown that patients with greater perioperative ischemia (evidenced by higher postoperative HT-FABP levels) are at greater risk for LV dysfunction and mortality after CABG.²³ Such patients with high ischemic burden may deserve close monitoring and perhaps should receive prophylactic medications beyond beta-blockers, such as amiodarone. More recently, ranolazine has been shown to suppress POAF more effectively than amiodarone, which also has anti-ischemic properties.²⁴ Although it has been proposed that its antiarrhythmic properties come from sodium channel blockade, ranolazine also increases coronary blood flow, while decreasing ischemia and reperfusion

injury after infarction.^{25, 26} Therefore a drug like ranolazine might specifically target the arrhythmia mechanism proposed by our study.

Limitations

Although the small sample size may limit our study, we had sufficient power to detect a significant difference in biomarker trends and other validated risk factors of POAF (e.g. age). Higher HT-FABP levels were related to renal function, however multivariable analyses demonstrated that renal function was not sufficient to explain higher HT-FABP levels in patients with POAF. While preservation of kidney function after surgery is a worthwhile goal, such efforts may not reduce the occurrence of POAF. Prospective collection of blood samples at standardized intervals and stringent statistical methodology strengthen our results.

CONCLUSIONS

The postoperative rise of heart-type fatty acid binding protein, a sensitive marker of ischemic myocardial injury, is more exaggerated in patients who develop atrial fibrillation after cardiac surgery. Ischemia appears to play a mechanistic role in the development of postoperative arrhythmias. It will be of interest to determine whether drugs that minimize ischemic injury are broadly effective in reducing postoperative atrial fibrillation and in improving surgical outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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List of Abbreviations

AF	Atrial fibrillation
CABG	Coronary artery bypass grafting
CI	Confidence interval
EDTA	Ethylenediaminetetraacetate
ELISA	Enzyme-linked immuno-sorbent assay
HT-FABP	Heart-type fatty acid binding protein
LV	Left ventricle
OR	Odds ratio
POAF	Postoperative atrial fibrillation
TnT	Troponin T

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Figure 1.

Temporal distribution of AF occurrence after cardiac surgery. Most patients developed AF on day 2 and 3 after surgery, while occurrence after day 4 was uncommon.

Figure 2.

HT-FABP levels before and after cardiac surgery. The largest deviation between patients with (red line) and without POAF (black line) was seen on postoperative day 1 and 2. Preoperative levels were similar between groups.

Table 1

Variable	All patients (n=63) No. (%) or Mean $\pm$ SD	POAF (n=35) No. (%) or Mean $\pm$ SD	POAF (n=28) No. (%) or Mean $\pm$ SD	P value
Demographic				
Age (years)	65 $\pm$ 12	69 $\pm$ 11	60 $\pm$ 11	0.0019
Female	23 (37)	14 (40)	9 (32)	0.52
Caucasian race	59 (94)	34 (97)	25 (89)	0.2
Cardiac morbidity				
Heart failure	20 (32)	15 (43)	5 (18)	0.034
Aortic valve stenosis	16 (25)	12 (34)	4 (14)	0.07
LV ejection fraction (%)	46 $\pm$ 13	46 $\pm$ 14	47 $\pm$ 11	0.89
Left atrial volume (mL)	41 $\pm$ 25	41 $\pm$ 23	47 $\pm$ 28	0.3
Noncardiac comorbidity				
COPD	10 (16)	9 (26)	1 (1.6)	0.017
Diabetes mellitus	21 (33)	10 (29)	11 (39)	0.37
Hypertension	51 (81)	30 (86)	21 (75)	0.28
Preoperative Creatinine	1.1 $\pm$ 0.42	1.16 $\pm$ 0.41	1.08 $\pm$ 0.43	0.19
Medication use				
ACE inhibitors	32 (51)	20 (57)	12 (43)	0.26
Angiotensin receptor blocker	11 (17)	7 (20)	4 (14)	0.55
Beta blockers	51 (81)	29 (83)	22 (79)	0.94
Calcium channel blockers	12 (19)	10 (29)	2 (7.1)	0.031
Statins	54 (86)	30 (86)	24 (86)	1
Procedure				
Isolated CABG	33 (52)	14 (40)	19 (68)	0.028
Isolated valve surgery	16 (25)	10 (29)	6 (21)	0.52
CABG & valve surgery	14 (22)	11(31)	3 (11)	0.049

Key: ACE indicates angiotensin converting enzyme; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; POAF, postoperative atrial fibrillation; SD, standard deviation;

Table 2

Adjusted Predictors of POAF	Coefficient	Standard error	P Value
HT-FABP values			
Preoperative	−0.48	0.76	0.5
24 hours before AF occurrence	−0.71	0.72	0.3
Greater last value before AF occurrence	1.9	0.87	0.03
Troponin T on postoperative day 1	0.11	0.33	0.7
Older age	0.0705	0.033	0.04
Isolated CABG	−1.1	0.075	0.14

Key: AF indicates atrial fibrillation; CABG, coronary artery bypass grafting; HT-FABP, heart-type fatty acid binding protein; POAF, postoperative atrial fibrillation;

Table 3

Multivariable-adjusted Predictors of Postoperative HT-FABP	Coefficient	Standard error	P Value
Earlier time to measurement ¹	−0.72	±0.081	<0.0001
Higher preoperative HT-FABP level ²	0.33	±0.14	0.02
Longer cardiopulmonary bypass time ³	0.27	±0.096	0.006
History of myocardial infarction	0.41	±0.15	0.009
Higher grade of mitral regurgitation ⁴	−0.50	±0.24	0.04
Higher postoperative creatinine ⁵	0.94	±0.19	<0.0001

Key: HT-FABP indicates heart-type fatty acid binding protein;

¹Log(interval to FABP measurement)

²Log(pre-op FABP), logarithmic transformation

³Log(CPB time+1), logarithmic transformation

⁴1/(MV regurgitation+1), logarithmic transformation

⁵Log(post-op creatinine), logarithmic transformation