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Ability of B-Type Natriuretic Peptide in Predicting Postoperative Atrial Fibrillation in Patients Undergoing Coronary Artery Bypass Grafting

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ABSTRACT

Objectives: Atrial fibrillation (AF) is still the most frequent rhythm disturbance after coronary artery surgery. Our aim was to evaluate the predictive value of preoperative brain natriuretic peptide (BNP) levels for determining postoperative new-onset AF in patients undergoing isolated first-time coronary artery bypass grafting (CABG) using cardiopulmonary bypass (CPB).

Methods: We recruited 144 consecutive patients (51 women and 93 men) who underwent isolated CABG. Preoperative and postoperative data were collected. Preoperative BNP levels were measured the day before surgery.

Results: The median preoperative BNP level was 68 pg/mL. Postoperative AF occurred in 36 (25%) of the patients. Univariate analyses showed that both advanced age and median preoperative BNP levels were associated with postoperative AF (63.9 ± 8 years versus 57.3 ± 9.8 years, $P < .001$; 226 pg/mL versus 65.2 pg/mL, $P < .001$). Both variables remained independent predictors of postoperative AF after multivariate logistic regression analyses. For advanced age, the odds ratio was 1.074 (95% confidence interval [CI], 1.019-1.131; $P = .008$); for preoperative BNP level, the odds ratio was 1.004 (95% CI, 1.001-1.006; P = .002). A receiver operating characteristic (ROC) curve demonstrated that preoperative BNP level was a predictor of postoperative AF, with an area under the ROC curve of 0.750. A cutoff value of 135 pg/mL for AF demonstrated a 72.2% sensitivity, a 71.2% specificity, a 45.6% positive predictive value, a 88.5% negative predictive value, and a 71.5% accuracy for predicting postoperative AF.

Conclusions: Elevated preoperative BNP levels and advanced age together are significant predictors for the development of postoperative AF in patients undergoing isolated CABG with CPB.

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INTRODUCTION

Coronary artery bypass grafting (CABG) is associated with significant risk for adverse postoperative cardiac outcomes, and atrial fibrillation (AF) is the most frequent rhythm disturbance, occurring in 10% to 40% of patients who undergo CABG [Leitch 1990; Creswell 1993; Aranki 1996; Mathew 1996]. Although AF is usually benign, it can occasionally cause severe complications [Creswell 1993; Aranki 1996; Mathew 1996]. Because of the loss of the contribution of normal atrial contraction to cardiac output, AF may produce hemodynamic deterioration during the postoperative period. The pathophysiological mechanism of AF after cardiac surgery is unclear.

Lately, there has been substantial interest in the use of new biomarkers for identifying patients who are at risk for adverse outcomes after CABG. Brain natriuretic peptide (BNP) is released by ventricular myocytes and has natriuretic, diuretic, and vasodilator properties [Yasue 1994]. Plasma BNP levels are a marker for prognosis and risk stratification in congestive heart failure, myocardial infarction (MI), and acute coronary syndromes [Morita 1993; Dao 2001; McCullough 2002; Omland 2002]. In our recent report, we evaluated the ability of the baseline BNP concentration to predict postoperative adverse outcomes in 85 patients [Turk 2008]. After these first results, we decided to further evaluate the predictive value of the baseline BNP concentration with more patients with respect to new-onset postoperative AF. The present study evaluates the value of preoperative BNP levels for predicting the development of postoperative AF in patients undergoing isolated first-time CABG using cardiopulmonary bypass (CPB).

METHODS

Patients

For this study, we recruited 144 consecutive patients scheduled for elective first-time isolated CABG at our institution. The study protocol was approved by the institutional ethics committee, and informed consent was obtained from all patients. The criteria for exclusion were urgent operation, off-pump surgery, renal insufficiency (creatinine >1.5 mg/dL), acute MI less than 1 month before surgery, mitral valve insufficiency (>+1), and a history of AF. The left ventricular ejection fraction (EF) was assessed preoperatively via transthoracic echocardiography by the attending cardiologist.

Postoperative Monitoring

Intraoperative and postoperative data, including adverse outcomes and complications, were recorded. After the operation, patient heart rates and rhythms were continuously monitored by individual bedside monitors (Datex-Ohmeda Instrumentarium, Helsinki, Finland) during the first 72 hours. Twelve-lead electrocardiography (ECG) recordings were performed before surgery, 2 hours after surgery, and then daily until hospital discharge. All persistent arrhythmias were confirmed with 12-lead ECG. After 72 hours, clinical observations were carried out every 4 hours until the patient was discharged from the hospital. If there was any clinical suspicion of arrhythmia, an ECG was recorded, and continuous monitoring was restarted. Episodes of AF lasting longer than 10 minutes were included in the study.

β-Blockers, calcium channel blockers, and antihypertensive medications were stopped on the day of surgery and were restarted on the first postoperative day, depending on the clinical situation. Sixty-two patients were on β-blockers preoperatively, 56 of these patients received β-blocker treatment postoperatively, and 75 patients received angiotensin-converting enzyme inhibitors preoperatively.

Potassium deficiency was promptly treated when necessary to maintain electrolyte balance within the normal range.

Clinical diagnostic criteria for perioperative MI were new Q waves, a reduction in R waves of >25% in at least 2 leads, and a significant increase in cardiac-specific enzymes.

Blood Sampling

Blood samples were obtained from patients on the day before surgery after 30 minutes of rest. Blood was collected into EDTA-containing tubes. Samples were analyzed for BNP by means of a fluorescence immunoassay kit (Triage; Biosite, San Diego, CA, USA).

Statistical Analysis

Statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS, Chicago, IL, USA). Comparisons of categorical variables were analyzed by the χ^2 test, and the Fisher exact test was used if the expected frequency in a contingency table cell was <5. Because BNP values were not normally distributed, BNP plasma levels are presented as the median (range). Median BNP levels were compared with the nonparametric Mann–Whitney *U* test. The relationships between the presence of postoperative AF and perioperative variables were investigated with univariate analysis. Independent predictors of AF were then determined by multivariate logistic regression analysis of the variables found in the univariate analysis to be associated with postoperative AF with a *P* value <.10.

Receiver operating characteristic (ROC) curve analyses were performed to identify the best cutoff level for BNP and to ascertain the utility of BNP as a prognostic indicator of postoperative new-onset AF. A *P* value of <.05 was considered statistically significant.

Operative Technique

A conventional median sternotomy was performed in all patients. Anesthesia was induced with midazolam, propofol, and fentanyl. Anesthesia was maintained with sevoflurane before CPB and with propofol and remifentanil on CPB in accordance with the anesthetist's criteria. Anticoagulation was achieved with sufficient heparin (3-4 mg/kg) to maintain an activated clotting time >450 seconds. CPB was achieved with a roller pump and a membrane oxygenator. The pump flow rate was kept between 2.0 and 2.4 L/min per m2 body surface area to maintain a mean arterial pressure of 60 to 70 mm Hg. The systemic temperature was maintained between 30°C and 32°C. Myocardial protection was achieved by an initial antegrade infusion of St. Thomas' crystalloid cardioplegia and then continued with intermittent antegrade cold blood cardioplegia. Distal and proximal anastomoses were constructed during a single period of aortic cross-clamping. "Warm induction" was applied just before the removal of the cross-clamp. Reversal of heparin was achieved with protamine.

RESULTS

The study group consisted of 93 male and 51 female patients with a mean age (±SD) of 58.9 ± 9.8 years. Patients required a mean of 3.3 ± 0.8 distal anastomoses, with a mean cross-clamp time of 83.2 ± 25.6 minutes and a mean perfusion time of 103.6 ± 31.2 minutes. Thirty-eight (26.3%) of the patients required the use of inotropic support, and 10 patients (6.9%) required the support of an intra-aortic balloon pump. Four patients (2.7%) experienced perioperative MI, and 4 patients (2.7%) experienced a cerebrovascular accident. The mean length of hospital stay was 8.4 ± 2.4 days. There were 4 deaths overall, the causes of death being low cardiac output syndrome in 3 patients and multiorgan failure in 1 patient. Postoperative AF occurred in 36 (25%) of the 144 patients. The median preoperative BNP level was 68 pg/mL (range, 5-896 pg/mL). The patients were divided into 2 groups according to whether they developed postoperative AF (Table). Patients who developed postoperative AF were significantly older (63.9 ± 8 years versus 57.3 ± 9.8 years; *P* < .001) and had significantly higher preoperative median BNP levels (226 pg/mL versus 65 pg/mL; *P* < .001). Patients with AF had slightly more distal grafts (3.2 ± 0.8 versus 3.4 ± 0.8; *P* = .148). Univariate analyses for association with the development of postoperative AF are shown in the Table. Variables found to be associated with AF by univariate analysis with *P* values <.10 were analyzed by multivariate logistic regression. This analysis identified 2 significant independent predictors of postoperative AF: advanced age (*P* = .008; odds ratio, 1.074; 95% confidence interval [CI], 1.019-1.131) and elevated preoperative BNP level (*P* = .002; odds ratio, 1.004; 95% CI, 1.001-1.006) (Table).

Using ROC curve analyses, we found that the best cutoff value for predicting development of postoperative AF was 135 pg/mL. A preoperative BNP value of 135 pg/mL had a

Univariate and Multivariate Analyses for Occurrence of Postoperative Atrial Fibrillation (AF)*

	Univariate Analyses			Multivariate Analyses		
	Without AF	With AF	*P*	OR	95% CI	*P*
No. of patients	108	36				
Age, y	63.9 ± 8	57.3 ± 9.8	<.001	1.074	1.019-1.1131	.008†
Male/female sex, n	68/40	25/11	.481			
Hypertension, n	58	20	.847			
Hypercholesterolemia, n	52	13	.209			
COPD, n	18	7	.703			
Previous MI, n	27	10	.741			
LMCA stenosis, n	4	2	.630			
LA diameter, cm	4.1 ± 0.6	4.2 ± 0.8	.547			
EF (<40%/>40%), n	16/92	6/30	.789			
BNP, pg/mL‡	65 (5.7-896)	226 (5-804)	<.001	1.004	1.001-1.006	.002†
No. of distal bypasses	3.2 ± 0.8	3.4 ± 0.8	.148			
Cross-clamp time, min	82.6 ± 23.9	85 ± 30.5	.631			
Perfusion time, min	105.2 ± 35	105.1 ± 35	.740			
Inotropic support, n	26	12	.275			
IABP, n	6	4	.256			
Wound infection, n	11	4	.875			
CVA, n	2	2	.260			
LOS, d	8.2 ± 2.2	8.9 ± 3	.171			
Mortality, n	2	2	.260			

*Data are presented as the mean ± SD where indicated. OR indicates odds ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; LMCA, left main coronary artery; LA, left atrium; EF, ejection fraction; BNP, brain natriuretic peptide; IABP, intra-aortic balloon pump; CVA, cerebrovascular accident; LOS, length of hospital stay.

†Significant predictive factors in a multivariate analysis.

‡Data are presented as the median (range).

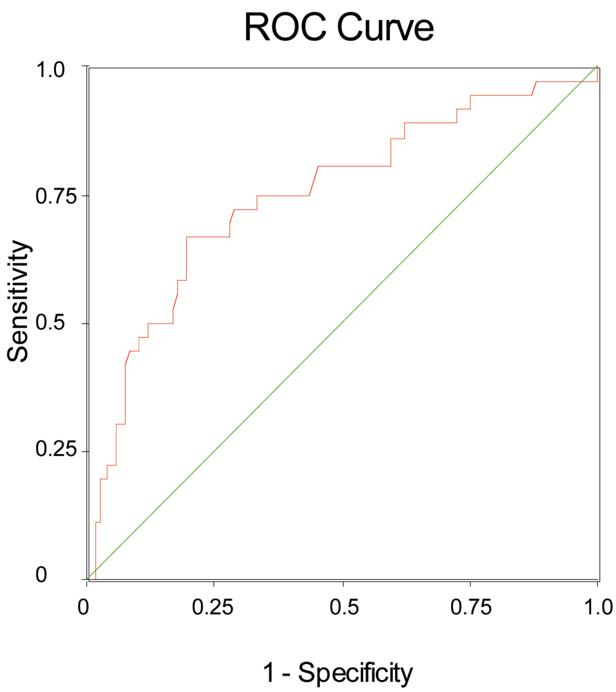
sensitivity of 72.2%, a specificity of 71.2%, a positive predictive value of 45.6%, a negative predictive value of 88.5%, and an accuracy of 71.5% for predicting postoperative new-onset AF with an area under the ROC curve of 0.750. The Figure shows the ROC curve that relates preoperative BNP level to the development of postoperative AF.

DISCUSSION

CABG is associated with significant risk for adverse postoperative cardiac outcomes. Early diagnosis and risk stratification are important for patients who develop adverse outcomes. Quantitative biochemical markers capable of predicting postoperative adverse outcomes are thought to be valuable for the preoperative evaluation of patients undergoing cardiac surgery. Endothelin 1, tumor necrosis factor α, atrial natriuretic factor, plasma norepinephrine, and, recently, BNP have all been studied for this purpose [Gottlieb 1989; Francis 1990; Nozaki 1997; Maeda 1998; Maisel 2001]. BNP levels have been related to coronary disease, diastolic dysfunction, ventricle hypertrophy, and the patient's age [Richards 2003; Wendelboe Nielsen 2004].

Despite advances in cardiac surgery, postoperative AF remains a common arrhythmia developing after CABG and may be due to the increased age and sickness of patients who undergo CABG and advances in continuous monitoring technology [Yasue 1994; Kalman 1995; Pfisterer 1997].

Preoperative and operative factors, such as increased age, hypertension, chronic obstructive pulmonary disease, a greater number of grafts, poor left ventricular function, preoperative β-blocker withdrawal, myocardial ischemia, cardioplegic arrest, systemic and cardiac hypothermia, mechanical manipulation of the atrium, and atrial ischemia have all been reported to increase the incidence of postoperative AF [Rousou 1985; Ferguson 1987; Yasue 1994; Ducceschi 1999; Dorge 2000]. Although thought to be transient and benign,



Receiver operating characteristic (ROC) curve for preoperative brain natriuretic peptide (BNP) level for predicting postoperative atrial fibrillation. The area under the ROC curve for BNP was 0.750 (95% confidence interval, 0.652-0.848). For a cutoff value of 135 pg/mL, the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were 72.2%, 71.2%, 45.6%, 88.5%, and 71.5%, respectively.

AF increases the risk of stroke, heart failure, thromboembolic events, and bleeding from the anticoagulation treatment and lengthens the duration of hospitalization [Creswell 1993; Aranki 1996; Mathew 1996].

Therefore, the use of a quantitative biomarker for predicting the development of postoperative AF would be valuable for every cardiac surgeon and would allow one to use prophylactic medical or surgical treatment strategies that have been proved effective for preventing postoperative AF.

Advanced age is a well-documented risk factor for postoperative AF, and structural changes that are mostly seen in the elderly, such as myofibril hypertrophy, decreased conduction tissue, and progressive fibrosis, seem to contribute to AF [Kitzman 1990]. In our previous report comparing the incidences of postoperative AF after off-pump and on-pump CABG, we demonstrated that advanced age was the major predictor of developing postoperative AF [Turk 2007]. In agreement with the literature, the present study again has demonstrated that advanced age is a strong predictor for the development of postoperative AF.

The present study has shown that elevated preoperative BNP levels are associated with postoperative AF and that a preoperative BNP level >135 pg/mL has an accuracy of 71.5% for predicting the development of postoperative AF. In addition to these findings, our study failed to show a relationship between postoperative AF and male sex, hypertension, the number of grafts, and chest drainage, which previously have been reported to be associated with postoperative AF [White 1984; Mathew 1996; Moulton 1996]. The previous studies of Cosgrave et al [2006] and Hakala et al [2002] failed to find significantly higher baseline plasma BNP levels in patients who underwent isolated CABG with CPB and developed postoperative AF. Both of these studies reported numerically higher baseline BNP levels in AF patients that did not reach statistical significance. The main difference between these 2 studies and the present study was their selection criterion of a preserved left ventricular function (EF >40% and >50%, respectively), which was not an exclusion criterion for our study. Additionally, we found no difference in risk for the development of postoperative AF between patients with an EF <40% and those with an EF >40%. This finding strengthens the idea that an increased risk for the development of postoperative AF might be attributed to an elevated preoperative BNP level itself, not to left ventricular dysfunction. Wazni et al [2004] found an elevated preoperative BNP level to be a stronger independent predictor of the development of postoperative AF than advanced age in patients undergoing cardiac surgery, including valve surgery. Similarly, we also found an elevated preoperative BNP level to be a stronger predictor for the development of postoperative AF than advanced age, although to have a homogenous study group, we included only patients undergoing first-time elective isolated CABG with the help of CPB.

In agreement with the literature, the computer-generated preoperative BNP cutoff level of 135 pg/mL for predicting the development of postoperative AF is within the range of prognostic cutoff values (100-500 pg/mL) found in previous studies [Cheng 2001; Bettencourt 2002; Maisel 2002; Hutfless 2004]. On the other hand, one should keep in mind that our preoperative BNP level of 135 pg/mL has a sensitivity of 72.2%, a specificity of 71.2%, a negative predictive value of 88.5%, and an accuracy of 71.5%. Despite these higher results, the positive predictive value (45.6%) was relatively lower in our study group, suggesting that the preoperative BNP level is best used in conjunction with a risk-stratification index for evaluating the development of postoperative AF. Age especially should be a part of this index because the evidence for age as a risk factor for postoperative AF is well documented. Besides, the high negative predictive value of 88.5% indicates that the absence of an elevated preoperative BNP level is more predictive of the freedom from development of postoperative AF. These results raise the question of whether preoperative intervention to reduce the preoperative BNP level will lower the risk for development of postoperative AF. The answer to this question requires further evaluation.

The main drawback of the present study is the small size of the study group. A second drawback is the absence of continuous Holter monitoring after the first 72 hours, which may have caused us to miss short and asymptomatic episodes of AF. In the present study, AF episodes thought to be clinically important for patients undergoing CABG and needing medical treatment are all included in our approach to assess patients every 4 hours and to promptly record an ECG when there was a suspicion of an arrhythmia.

The identification of patients who are at risk for the development of postoperative AF remains difficult. According to the present study, the predictors of AF after CABG include age and an elevated preoperative BNP level. The ability to accurately predict a group at increased risk for the development of postoperative AF would help in the targeting of prophylactic medical or surgical therapies, such as amiodarone or surgical ablation.

In conclusion, this study suggests that advanced age and an elevated preoperative BNP level are predictors for the development of postoperative AF in patients undergoing isolated CABG using CPB. Therefore, patients with an advanced age and a high preoperative BNP level should be managed aggressively and monitored carefully for development of postoperative AF.

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