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Plasma Brain Natriuretic Peptide after Isolated On-Pump Coronary Artery Bypass Grafting: Prediction of Postoperative Adverse Outcomes

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ABSTRACT

Background. The heart is an endocrine organ that synthesizes 2 different natriuretic peptides: atrial natriuretic peptide and brain natriuretic peptide (BNP). We assessed the relationship between preoperative BNP levels and postoperative complications and outcomes in patients who undergo isolated coronary artery bypass grafting (CABG).

Method and Results. The study consisted of 85 patients undergoing first-time elective CABG. Preoperative BNP levels were significantly correlated with the preoperative ejection fraction (P = .004), the number of vessels grafted (P = .016), cross-clamp time (P = .041), and perfusion time (P = .032). Preoperative BNP levels were higher in patients who developed postoperative new-onset atrial fibrillation (AF) (median BNP, 197 pg/mL versus 65 pg/mL; P = .006), in patients requiring inotropic support (189 pg/mL versus 65 pg/mL; P = .004), and in patients who required an intra-aortic balloon pump (IABP) (325 pg/mL versus 68 pg/mL; P = .021). Analysis of receiver operating characteristic curves demonstrated the preoperative BNP level to be a predictor of new-onset AF, a need for inotropic support, and a requirement for an IABP (areas under the curve, 0.70, 0.70, and 0.79, respectively). BNP cutoff values of 100 pg/mL for AF, 185 pg/mL for inotropic support, and 235 pg/mL for requiring an IABP predicted these postoperative adverse outcomes with 65%, 73%, and 84% accuracy, respectively.

Conclusion. This study suggests that a higher baseline plasma BNP concentration is associated with postoperative new-onset AF, a need for inotropic support, and an IABP requirement in patients who undergo first-time isolated CABG.

INTRODUCTION

Coronary artery bypass grafting (CABG) is associated with a significant risk for postoperative cardiac adverse outcomes. Early diagnosis and risk stratification are important for identifying patients who will develop adverse outcomes. Many different risk indices have been described to help in preoperative risk assessment of patients who undergo cardiac surgery [Parsonnet 1989; Higgins 1992; Tuman 1992; Tu 1995; Dupuis 2001]. The ability of these risk indices to predict postoperative adverse outcomes is uncertain, however, and no gold standard exists [Weightman 1997; Pons 1998; Martinez-Alario 1999]. A biological marker in the serum that could be used to predict such outcomes would be a valuable addition to the preoperative evaluation of patients undergoing CABG.

The heart is an endocrine organ that synthesizes and secretes 2 different natriuretic peptides: atrial natriuretic peptide and brain natriuretic peptide (BNP). BNP is released by ventricular myocytes in response to increased wall tension and stretch and has natriuretic, diuretic, and vasodilator properties [Yasue 1994]. The plasma BNP level is 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].

BNP has been demonstrated to be correlated with creatine kinase–MB and troponin I, markers of myocardial ischemia [Shirasawa 2000; Provenchere 2006]. The ejection fraction (EF) is a widely used major factor in calculating risk in most of the multifactorial risk-stratification indices for preoperative assessment, and several studies have shown EF to be an independent predictor of postoperative morbidity. BNP concentration has also been demonstrated to correlate with EF and ventricular dysfunction [Krishnaswamy 2001]. Therefore, the purpose of the present study was to evaluate the relationship between BNP level and baseline characteristics of patients and whether preoperative and postoperative serum BNP levels can be used as predictors of postoperative adverse outcomes for patients who undergo isolated CABG with the use of cardiopulmonary bypass (CPB).

MATERIALS AND METHODS

Patients

During a 6-month period we prospectively recruited 85 consecutive patients scheduled for elective first-time isolated CABG at our institution and followed up the patients

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for 30 postoperative days for the occurrence of adverse outcomes. The study protocol was approved by the institutional ethics committee, and informed consent was obtained from all patients for participation in the study. The exclusion criteria were as follows: urgent operation, off-pump surgery, renal insufficiency (creatinine >1.5 mg/dL), acute MI within less than 1 month, mitral valve insufficiency (greater than +1), and a preoperative history of atrial fibrillation (AF). The left ventricular EF was assessed preoperatively with the aid of transthoracic echocardiography. We recorded intraoperative and postoperative data, including adverse outcomes and complications. After the operation, we continuously monitored the patients' heart rate and rhythm with individual bedside monitors (Datex-Ohmeda Instrumentarium Corporation, Helsinki, Finland) during the first 72 hours. Twelve-lead electrocardiograph recordings were performed before surgery, 2 hours after surgery, and daily until hospital discharge. All persistent arrhythmias were confirmed with 12-lead electrocardiography evaluations. After 72 hours, trained nurses performed clinical observations every 4 hours, and an electrocardiograph was recorded if there was any clinical suspicion of arrhythmia. In this study, we included AF episodes lasting longer than 10 minutes.

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

The clinical diagnostic criteria for perioperative MI were new Q waves and a reduction in R waves greater than 25% in at least 2 leads, and a significant rise in cardiac-specific enzymes.

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 during CPB in accordance with the anesthetist's criteria. Anticoagulation was achieved with heparin at 3 to 4 mg/kg to maintain an activated clotting time of >450 s. 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 m^2 body surface area to maintain a mean arterial pressure of 60 to 70 mm Hg. A systemic temperature between 30°C and 32°C was induced. Myocardial protection was achieved by cardioplegia via an initial antegrade infusion of St. Thomas' crystalloid solution and continued with intermittent antegrade cold blood cardioplegia. Distal and proximal anastomoses were constructed during one period of aortic cross-clamping. "Warm induction" was applied just before removal of the cross-clamp. Reversal of heparin was achieved with protamine. Preoperative and postoperative data were collected.

Blood Sampling

Blood samples were obtained from the patients preoperatively (BNP1), at the 24th postoperative hour (BNP2), and on the fifth postoperative day (BNP3). Blood was collected into a tube containing EDTA. A fluorescence immunoassay kit (Triage; Biosite Diagnostics, San Diego, CA, USA) was used to analyze BNP levels in clinical samples.

Statistical Analysis

Data were analyzed with the Statistical Package for the Social Sciences (SPSS, Chicago, IL, USA). Correlations of BNP levels with other variables were analyzed by Pearson correlation analysis. Categorical variables were compared with the χ^2 test, and the Fisher exact test was used if the expected cell frequency in the contingency table was less than 5. The nonparametric Mann-Whitney *U* test was used to compare median BNP levels. We analyzed receiver operating characteristic (ROC) curves to identify the best BNP cutoff values and to determine the utility of BNP as a prognostic indicator of intraoperative and postoperative complications and adverse outcomes (inotropic support, intra-aortic balloon pump [IABP] support, and postoperative new-onset AF). A *P* value of <.05 was considered statistically significant.

RESULTS

All of the patients' clinical characteristics are summarized in Table 1. Forty-nine men and 36 women (mean age, 58 ± 10 years) underwent first-time isolated CABG.

Table 2 summarizes the intraoperative data, postoperative data, and adverse outcomes. The mean (±SD) number of bypass grafts was 3 ± 1 per patient, and the mean cross-clamp time was 84 ± 29 minutes. Nearly one third of the patients required

Table 1. Baseline Characteristics of the Patients and Preoperative Levels of Brain Natriuretic Peptide (BNP)

	Patients, n	Median BNP Level, pg/mL	*P*
Sex			
Male	50	70	.872
Female	35	87	
Diabetes mellitus			
Yes	27	68	.925
No	58	70	
Hypertension			
Yes	41	70	.676
No	44	78	
Hypercholesterolemia			
Yes	36	77	.993
No	49	70	
Chronic obstructive pulmonary disease			
Yes	12	106	.289
No	73	68	
Previous myocardial infarction			
Yes	17	83	.416
No	68	68	
Ejection fraction			
<40%	15	189	.024
≥40%	70	67	
Left main coronary artery disease			
Yes	3	70	.973
No	82	69	

Table 2. Operative Data and Postoperative Adverse Outcomes*

		Median BNP Level, pg/mL	*P*
No. of vessels grafted	3 ± 1		
Cross-clamp time, min	84 ± 29		
Bypass time, min	106 ± 33		
Inotropic support, n			
Yes	25	189	.004
No	60	65	
Intra-aortic balloon pump, n			
Yes	6	325	.021
No	79	68	
Atrial fibrillation, n			
Yes	22	197	.006
No	63	65	
Perioperative myocardial infarction, n	2		
Chest drainage, mL	494 ± 201		
Cerebrovascular accident, n	2		
Postoperative hospitalization, d	8 ± 3		
Mortality, n	3		

*Data are presented as the mean ± SD where indicated.

inotropic support (infusion of dobutamine at 5-15 μg/kg per minute and noradrenaline in case of refractory low cardiac output), and 6 patients required the use of IABP support. Postoperative new-onset AF occurred in 22 patients (26%). Two patients experienced perioperative MI. The average postoperative hospital stay was 8 ± 3 days. There were 3 deaths (4%) overall in the study group within 30 days (Table 2).

Table 3 summarizes the correlations between the baseline BNP level and the patients' perioperative characteristics. The preoperative EF was significantly inversely correlated with the median BNP1 level ($r = -0.307$; $P = .004$), and the number of grafted vessels, the cross-clamp time, and the perfusion time were significantly positively correlated with the median BNP1 level ($P < .016$, $P = .041$, and $P = .032$, respectively; Table 3). BNP1 level was not significantly correlated with age or with the number of postoperative days in the hospital.

The median BNP levels obtained for the 3 measurement periods were as follows: BNP1, 70 pg/mL; BNP2, 206 pg/mL; BNP3, 288 pg/mL. Table 4 displays the correlations between BNP level and different measurements. There were positive correlations between BNP1 and BNP2 levels, BNP1 and BNP3 levels, and BNP2 and BNP3 levels (Table 4).

Table 3. Correlations with Preoperative Brain Natriuretic Peptide Level

	Pearson *r*	*P*
Preoperative ejection fraction	−0.307	.004
No. of grafted vessels	0.262	<.016
Cross-clamp time	0.222	.041
Bypass time	0.233	.032

Table 4. Correlations of Different Brain Natriuretic Peptide (BNP) Measurements*

	BNP2		BNP3	
	r	*P*	*r*	*P*
BNP1	0.634	<.001	0.625	<.001
BNP2	–	–	0.929	<.001

*For sample measurements taken preoperatively (BNP1), at the 24th postoperative hour (BNP2), and on the fifth postoperative day (BNP3).

The relationships of BNP1 levels with perioperative clinical parameters and postoperative adverse outcomes are summarized in Tables 1 and 2. Median BNP1 levels were significantly higher for patients with an EF <40% (189 pg/mL versus 67 pg/mL; $P = .024$, Table 1), patients needing inotropic support (189 pg/mL versus 65 pg/mL; $P = .004$, Table 2), patients requiring the use of an IABP (325 pg/mL versus 68 pg/mL; $P = .021$, Table 2), and patients who developed new-onset postoperative AF (197 pg/mL versus 65 pg/mL; $P = .006$, Table 2). There were no other significant differences in median BNP1 level with respect to other perioperative characteristics and adverse outcomes.

Figure 1 displays the ROC curve for the relationship of preoperative BNP1 level to postoperative new-onset AF. The area under the curve (AUC) was 0.70. A preoperative value of 100 pg/mL had a sensitivity of 68%, a specificity of 64%, an accuracy of 65%, and a negative predictive value of 85% for predicting postoperative new-onset AF. Figure 2 displays the ROC curve for patients who required postoperative

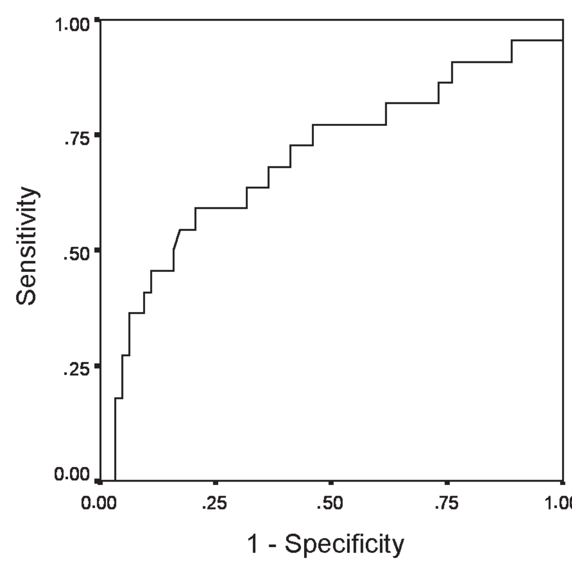

Figure 1. Receiver operating characteristic curve of preoperative brain natriuretic peptide (BNP) level for predicting postoperative atrial fibrillation. The area under the curve for BNP was 0.70 (95% confidence interval, 0.559-0.837). For a cutoff value of 100 pg/mL, the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were 68%, 64%, 40%, 85%, and 65%, respectively.

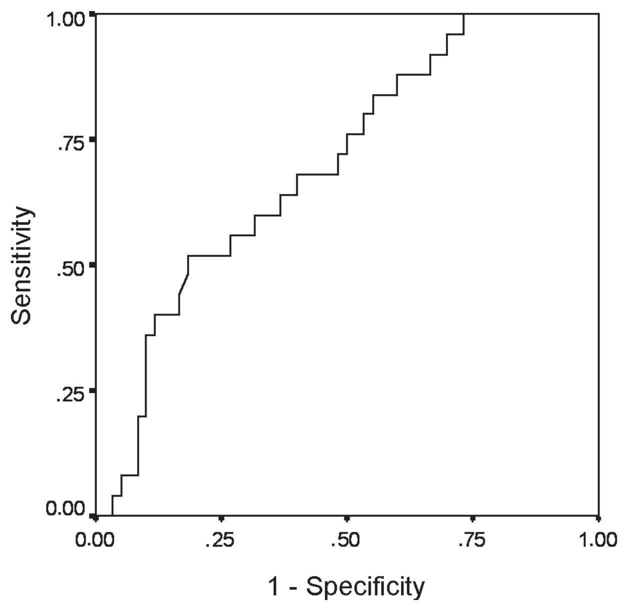

Figure 2. Receiver operating characteristic curve of preoperative BNP level for predicting a postoperative inotropic requirement. The area under the curve for BNP was 0.70 (95% confidence interval, 0.584-0.816). For a cutoff value of 185 pg/mL, the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were 52%, 82%, 54%, 80%, and 73%, respectively.

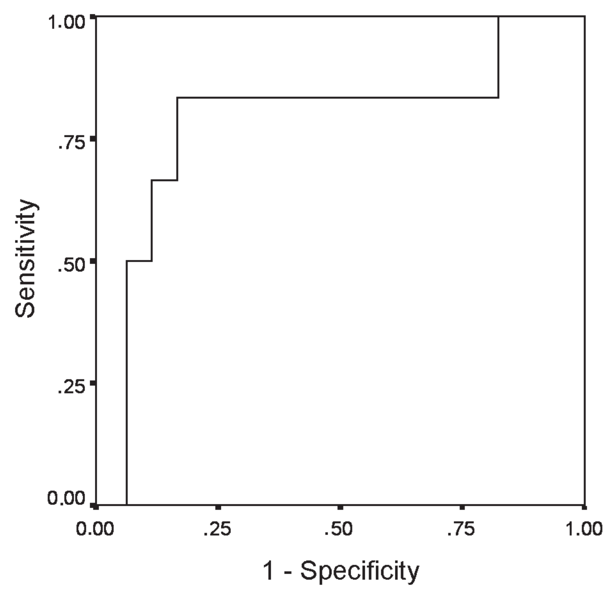

Figure 3. Receiver operating characteristic curve of preoperative BNP level for predicting a requirement for a postoperative intra-aortic balloon pump. The area under the curve for BNP was 0.79 (95% confidence interval, 0.559-1.011). For a cutoff value of 235 pg/mL, the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were 83%, 84%, 28%, 99%, and 84%, respectively.

inotropic support. The AUC for this group was 0.70. A BNP cutoff value of 185 pg/mL had a sensitivity of 52%, a specificity of 82%, an accuracy of 73%, and a negative predictive value of 80% for predicting a postoperative inotropic requirement. Figure 3 displays the ROC curve for patients who required the use of an IABP. The AUC for this group was 0.79. A BNP cutoff value of 235 pg/mL had a sensitivity of 83%, a specificity of 84%, an accuracy of 84%, and a negative predictive value of 99% for predicting postoperative use of an IABP.

DISCUSSION

A variety of risk indices have been developed to attempt to predict postoperative adverse outcomes and cardiac complications in patients undergoing open heart surgery. Although these indices have been studied extensively, there is no gold standard for preoperative risk assessment in patients undergoing open heart surgery. Quantitative biochemical markers capable of predicting postoperative adverse outcomes are thought to be valuable for the preoperative evaluation of patients undergoing cardiac surgery. For this purpose endothelin 1, tumor necrosis factor α, atrial natriuretic factor, plasma norepinephrine, and, recently, BNP have all been studied as markers of cardiac performance [Gottlieb 1989; Francis 1990; Nozaki 1997; Maeda 1998]. None of the risk-assessment indices have included preoperative BNP levels in their calculations, although BNP level has been demonstrated to be correlated with ventricular dysfunction and to be useful in diagnosing heart failure.

BNP is found in brain and atrial tissue and is produced mainly by the ventricle myocardium [Yasue 1994]. Since its original description, BNP has mainly been used in the field of cardiology. BNP produces different effects on the organism, such as stimulating glomerular filtration and decreasing sodium reabsorption, thereby increasing natriuresis. Natriuretic peptides relax vascular smooth muscle and have important central and peripheral sympathoinhibitory effects that lead to reduced blood pressure and ventricle preload. In addition, BNP has a positive lusitropic effect in the myocardium. The usefulness of natriuretic peptides as biomarkers has already been proved in the management of patients in heart failure with respect to diagnosis and prognosis, and as a control in monitoring the effectiveness of medical treatment [Maisel 2001; Richards 2003]. Similarly, BNP levels have been related to coronary disease, diastolic dysfunction, ventricle hypertrophy, and patient age [Richards 2003; Wendelboe 2004].

We report a significant increase in plasma BNP levels after CABG. Of the patients who underwent first-time isolated CABG, we included in the study only those patients who underwent coronary revascularization with the aid of CPB to have a homogeneous population. High postoperative BNP levels such as those commonly found in patients with acute heart failure suggest that specific factors are involved in CABG with aortic clamping and CPB. These significant increases in postoperative BNP levels raise concerns about the mechanisms of BNP secretion after cardiac surgery, because BNP levels have been shown to be elevated after acute MI, even in the absence of ventricular dysfunction [Morita 1993]. The first hypothesis that comes to mind is MI- or ischemia-induced BNP secretion, which might be triggered by the unavoidable ischemia induced by aortic clamping and cardioplegic arrest, even in the absence of myocardial necrosis. We found that preoperative BNP level was correlated with the aortic clamping time, the perfusion time, and the number of distal grafts (which in a way demonstrates the extent of the atherosclerotic coronary disease).

In agreement with the literature [Krishnaswamy 2001], preoperative BNP level was correlated with EF in our group of patients. The ROC curve for preoperative BNP concentration and preoperative EF generated a 100-pg/mL cutoff value for an EF <40% and ≥40%. A plasma BNP concentration of 100 pg/mL was also the cutoff value in the Breathing Not Properly Multinational Study for the diagnosis of congestive heart failure [McCullough 2002].

In the present study, we demonstrated the preoperative BNP level to be a predictor of postoperative new-onset AF, a postoperative inotropic requirement, and postoperative use of an IABP. All of these findings are supported by findings described in previous reports [Saribulbul 2003; Hutfless 2004; Wazni 2004]. The BNP cutoff values for predicting AF, a need for inotropic support, and an IABP requirement were 100 pg/mL, 185 pg/mL, and 235 pg/mL, respectively. All of these cutoff values were within the ranges (100-500 pg/mL) of the prognostic cutoff values found in other studies [Cheng 2001; Bettencourt 2002; Maisel 2002; Hutfless 2004]. Further prospective studies are needed to validate preoperative BNP cutoff ranges. It should be kept in mind that the preoperative BNP levels for predicting these adverse outcomes have sensitivities between 52% and 83%, specificities between 64% and 84%, and accuracies between 65% and 84%, but they had higher negative predictive values, between 80% and 99%. Despite these higher results, the relatively lower positive predictive values in our patient group suggest that preoperative BNP levels are best used in conjunction with existing risk indices.

The first limitation of our study was the small size of our study population. Further studies on larger populations are needed to compare the predictive ability of preoperative BNP level with the frequently used risk indices and to evaluate the integration of this biochemical marker into preoperative risk analysis. Another limitation of our study was that we did not find a preoperative BNP cutoff value for predicting mortality, because only 3 of the patients died. Because of our short follow-up period of 30 days, we were not able to determine how the BNP level correlated with patient outcomes after discharge and over longer terms. Hutfless et al [2004] reported that preoperative BNP levels were higher in patients who died within 1 year. In contrast to Hutfless et al, Provenchere et al failed to show this finding in their study after a multivariate analysis [Hutfless 2004; Provenchere 2006].

In conclusion, we found that higher preoperative BNP levels are associated with postoperative new-onset AF, a need for inotropic support, and a requirement of IABP support. BNP-guided therapy has been shown to be beneficial in outpatient follow-up [Troughton 2000]; therefore, patients with a high preoperative BNP level should be managed aggressively and monitored carefully for postoperative new-onset AF and requirements for inotropic support and an IABP. Alternatively, further prospective studies are needed to demonstrate the prognostic implications of the use of the BNP level in combination with the currently used risk indices and whether it can be a part of these indices.

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