

# Relationship and Clinical Usefulness between Preoperative Levels of Brain Natriuretic Peptide, Other Cardiac Markers and Perioperative Parameters in Patients with Coronary Artery Disease

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Cardiac troponin-I (cTnI), creatine kinase-MB (CK-MB), and C-reactive protein (CRP) are routine cardiac markers for the diagnosis of cardiovascular disease. Recently, brain natriuretic peptide (BNP) has garnered attention as a marker of heart failure. This study was retrospectively designed to investigate the relationships between preoperative BNP, other cardiac markers levels and perioperative parameters in seventy-four adult patients that underwent off-pump coronary artery bypass grafting (OPCAB) and to assess its usefulness for predicting postoperative outcomes. Preoperative levels of BNP, cTnI, CK-MB, and CRP had significantly positive or negative correlations with echocardiographic parameters. There were significantly positive relationships between BNP, cTnI, CK-MB, and CRP concentration. Postoperative mechanical ventilation time had a positive correlation to preoperative levels of cTnI, CK-MB, and CRP, while ICU-staying period had a positive correlation with BNP, cTnI and CK-MB. These results reveal that a preoperative level of BNP is a good predictor and that its combination with cTnI, CK-MB, and CRP might be useful for diagnosis and comprehensive risk stratification of patients with coronary heart diseases, as well as prognosis of perioperative outcomes in OPCAB patients.

**Key words** : Brain natriuretic peptide (BNP), cardiac troponin-I (cTnI), creatine kinase-MB (CK-MB), C-reactive protein (CRP), echocardiography, off-pump coronary artery bypass grafting (OPCAB)

## Introduction

Clinical physicians have utilized a variety of biochemical markers such as creatine kinase isoenzyme 2 (CK-MB), cardiac troponin-T or -I (cTnT and cTnI, respectively), and C-reactive protein (CRP) and electrocardiogram (EKG) for diagnosing and predicting coronary heart disease (CHD). Sensitivity and specificity of CK-MB are <100% despite its usefulness for the diagnosis of acute myocardial infarction (AMI). The laboratory test most utilized for the diagnosis of AMI is creatine kinase (CK, EC 2.7.3.2) and its MB isoenzyme (CK-MB) [20]. Although measurement of CK-MB has been suggested to be the "gold standard" for the diagnosis of myocardial infarction (MI) [9], non-cardiac disorders may also cause increases of CK-MB [24]. Changes on the EKG are the most important tool that should be utilized quickly after presentation of the suspected MI patient.

However, the EKG is not a perfect instrument because its diagnostic sensitivity may be as low as 50% [19]. The troponin complex consists of three subunits referred to as TnT, TnI and TnC. Myocardium contains TnT and TnI isoforms which are not present in skeletal muscles. Even though clinical laboratories are able to determine cTnT quickly and reliably as classical cardiac marker, an increase of cTnT levels have been documented in patients with end-stage renal disease [18]. cTnI has been demonstrated as an excellent marker for the diagnosis of MI.

Nevertheless, there is a difference between cTnT and cTnI in respect to the site of their release. cTnT increases are significantly more prominent in left than in the right ventricles, whereas cTnI isoform transition is significantly more rapid in right than in left ventricles in fetal rabbit [10]. CRP may have a role in identifying patients having unstable coronary plaques. Studies have also investigated the use of CRP for predicting unfavorable outcomes and impairment of left ventricular function, resulting from acute cardiac necrosis or previous MI [23]. However, CRP is an acute phase protein

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that is nonspecific and elevates in non-cardiac disorders (e.g., inflammation).

In recent, clinical physicians have noted brain natriuretic peptide (BNP), which increases in patients with congestive heart failure [6], especially in those with severe hemodynamic impairment [4,21], and is a strong predictor of prognosis in patients with previous MI [11] and congestive heart failure [8].

Patients with coronary syndromes, including coronary stenosis, spasm and MI are dramatically increasing in Korea and their symptoms, types or stratification have been increasingly more diverse. Hence, we need to investigate a combination and comparison between these cardiac markers for accurate and rapid diagnosis and prognosis of CHD.

This study was retrospectively designed and data was postoperatively reviewed to investigate association between preoperative BNP, other cardiac markers levels and perioperative parameters in seventy-four adult patients that underwent off-pump coronary artery bypass grafting (OPCAB).

## Materials and Methods

### Study population

Data for seventy-four patients that underwent off-pump coronary artery bypass grafting (OPCAB) (From 2005, January to 2007, December) were retrospectively reviewed in 'P' hospital. Blood or other samples were never collected from the patients and additional test were not performed for the present study. All patients were discharged from the hospital. We only evaluated the recorded-data for this study. This retrospective study was accepted from the Institutional Review Board for Human Research Inje University Busan Paik Hospital (No. 10-142).

### Analysis of variables

The following variables were preoperatively or postoperatively analyzed and recorded.

### Echocardiography

On the recommendation of the American Society of Echocardiography, M-mode and two-dimensional method were applied for the all patients' echocardiograms.

### Brain natriuretic peptide (BNP)

3-5 ml of blood was injected into EDTA-bottle and plasma

brain natriuretic peptide (BNP) concentration was measured by fluorescence immunoassay with BNP kit (Biosite, San Diego, Triage<sup>®</sup>, USA). Detection ranges of BNP kit are 5-5,000 pg/ml and its reference value is <60 pg/ml.

### Other cardiac markers

Preoperative level of plasma C-reactive protein (CRP) was measured by HITACHI 7600-210 instrument (Hitachi, Tokyo, Japan) with commercial CRP kit (Denka Co., Tokyo, Japan) (reference value; 0-0.5 mg/dl). Preoperative levels of plasma cardiac troponin-I (cTnI) were determined by Access immunoassay system (Sanofi Diagnostic Pasteur, Inc., Toulon, France) with commercial cTnI kit (Boehringer Mannheim, Munich, Germany) (reference value: <0.05 ng/ml). Preoperative levels of plasma creatine kinase-MB (CK-MB) were analyzed by Toshiba instrument (Toshiba Co., Tokyo, Japan) with CK-MB kit (Wako Co., Kyoto, Japan) (reference value; 0-15 U/l).

### Operative procedures

All patients received general anesthesia. After median sternotomy, left internal mammary artery, left radial artery, and great saphenous vein were harvested from all patients for OPCAB. 80-100 mg of heparin was intravenously injected and the heart was exposed. Cardiac apex were lifted for fixing appointed sites of anastomoses using cardiac holding apparatus (Medtronic Inc., Minnesota, Octopus, USA), and one to six vessels were anastomosed by one operator. After the anastomoses, blood flow was reestablished [assessment by HT 107 medical volume flowmeter (Transonic systems Inc., California, USA) (normal flow; >20 ml/min)] and 0.8-1.0-fold protamine of used heparin was administered for neutralizing heparin.

### Perioperative variables

Operation time, vessel grafting-numbers, postoperative mechanical ventilation-time (POMV-time), intensive care unit-staying period (ICU-staying period) and hospitalized-days were recorded.

### Statistical analysis

Data are presented as mean±SD (standard deviation). Pearson's correlation-analysis was applied for the determination of association between preoperative levels of cardiac markers (BNP, cTnI, CK-MB and CRP), echocardiographic parameter and perioperative variables (SAS program).

Statistical significance was accepted with  $p \leq 0.05$ .

## Results and Discussion

### Study population

Study population was seventy-adult patients who had undergone OPCAP for radical treatment of coronary artery disease. There was no case of death (Table 1).

### Echocardiography

Table 2 shows the preoperative results of echocardiography, stenosis degree of coronary vessels and graft flow volume of operative coronary vessels. In the echocardiography, left ventricular internal dimension at systole (LVIDS) was higher, while left ventricular ejection fraction (LVEF) was lower than the each normal range, suggesting that coronary artery disease can cause left ventricular dysfunction and hypertrophy, thereby leading to chronic heart failure and systemic complications.

In the stenosis degree of coronary artery, most patients had severe obstruction, which an obstruction or stenosis of coronary arteries can result in a decreased supply of oxygen

and nutrients into myocardium, contributing to myocardial injury and malfunction.

### Plasma BNP and other cardiac markers

Concentrations of plasma BNP and other cardiac markers were summarized in Table 3.

Concentrations of all variables were values above the normal level. The heart has been recognized as an endocrine organ since a series of experiments done in the mid 1950s [12]. In 1984, the structure of atrial natriuretic peptide (ANP) was identified [17], and in 1988 a compound was isolated from pig brain that caused natriuretic and diuretic responses similar to ANP [32]. Although this peptide was called BNP, the primary site of BNP synthesis is ventricular myocardium [35]. A 32 aminoacid active hormone, BMP is released by the cardiac ventricles in response to volume expansion and pressure load [31]. BNP is a natriuretic, diuretic, and vasodilatory hormone; it offsets the effects of fluid overload, which causes stretching of the cardiac wall and triggers its secretion.

In the kidneys, BNP increases glomerular filtration and renal blood flow via increased efferent arteriolar and decreases the afferent arteriolar tone as well as the renin release and sodium reabsorption, ultimately resulting in both diu-

Table 1. Characteristics in study population

Parameter	Mean	SD	Range
Sample size (no.)	74		
Gender (M : F)	52:22		
Age (year)	61.78	8.33	41.00-79.00
Weight (kg)	65.50	10.38	45.00-86.00
BSA (m <sup>2</sup> )	1.71	0.16	1.35-1.98
OP-time (min)	293.80	47.69	200.00-400.00
POMV-time (hr)	16.60	16.16	2.50-140.00
ICU-period (hr)	68.28	27.13	27.00-216.00
Hospitalization (day)	16.61	5.21	9.00-33.00
Graft-number (no.)	3.82	1.06	1.00-6.00

Abbreviation: BSA, body surface area; OP, operation; POMV, postoperative mechanical ventilation; ICU, intensive care unit. Graft-number, number of vessel for coronary artery bypass surgery.

Table 2. Preoperative level of cardiac markers

Marker	Mean	SD
BNP (pg/ml)	452.74	93.49
cTNI (pg/ml)	2.91	5.63
CK-MB (U/l)	15.74	5.63
CRP (mg/dl)	1.82	1.60

Abbreviation: BNP, brain natriuretic peptide; cTNI, cardiac troponin-I; CK-MB, creatine kinase-MB; CRP, C-reactive protein.

Table 3. Preoperative results of echocardiographic parameters and blood flow in grafting vessels

Parameter	Mean	SD	Normal range
LVIDD (mm)	52.75	7.34	42-54
LVIDS (mm)	37.44	9.32	24-26
PWD (mm)	9.19	1.66	8-11
LA dimension (mm)	40.82	5.74	27-44
LA volume (ml)	62.19	20.43	<60
RVIDD (mm)	19.81	4.86	9-26
LVEF (%)	49.45	14.16	55-76
SLMCA (%)	73.57	21.04	
SLAD (%)	88.19	12.56	
SLCX (%)	88.42	11.63	
SRCA (%)	93.10	12.00	
SBP (mmHg)	126.80	20.87	
DBP (mmHg)	77.24	11.83	

Abbreviation: LVIDD, left ventricular internal dimension at diastole; LVIDS, left ventricular internal dimension at systole; PWD, posterior wall dimension; LA, left atrium; RVIDD, right ventricular internal dimension at diastole; LVEF, left ventricular ejection fraction; SLMCA, stenosis of left main coronary artery; SLAD, stenosis of left descending artery; SLCX, stenosis of left circumflex artery; SRCA, stenosis of right coronary artery; SBP, systolic blood pressure; DBP, diastolic blood pressure.

resis and natriuresis [13]. Because of such characteristics of BNP, earlier studies focused on its elevation following congestive heart failure. However, recent data have demonstrated that left ventricular end-diastolic wall stress and wall stiffness may be the predominate triggers of BNP release [14,34], therefore, clinical physicians are beginning to think it may be a potential predictor for coronary artery disease (CAD). Decreased oxygen and energy supply by obstruction or stenosis of coronary vessels can contribute to left ventricular wall stress and wall stiffness, resulting in heart failure. Recently, Ahn et al. [1] have shown that an increased BNP level was related to event-free survival in patients with low-risk unstable angina. Other studies also demonstrated that BNP is predictive of inducible ischemia in patients with CHD [30]. In the present study, the preoperatively mean level of plasma BNP was 7.55 times of normal value (<60 pg/ml). Previous data and the present study justify a predictive and useful marker of BNP for diagnosis and prognosis of CHD.

The cardiac troponin, including cTNI are regulatory proteins with both cytosolic and structural pools. The best data indicates that cardiac troponin was secreted owing to myocardial necrosis [2]. Our study shows that an increased rate of cTNI was the highest among all cardiac markers (It was 58.20 times of the normal value), meaning that cTNI is a useful marker for diagnosis and prognosis of CAD.

CK-MB is a cytosolic carrier protein for high-energy phosphates. As clinicians become more comfortable with cardiac troponin, it will have a diminishing role in diagnosing of CHD. Some would argue that CK-MB still could be used to define infarct timing or after percutaneous coronary intervention. However, the present data show that a preoperative mean level of CK-MB was similar to the normal value (<15 U/l) (Table 3) even though higher levels were observed in some patients. This result suggests that CK-MB may potentially be an outdated marker.

On the other hand, in the present study CRP level was 3.64 times that of the normal value, indicating a potential usefulness of CRP as a cardiac marker. CRP is an acute-phase reactant protein made in the liver. Its most proximate stimulator is interleukin-6 [7]. There is controversy regarding the variability of CRP levels [26,28]. Some argue that in the absence of acute illness, including myocardial injury, levels of CRP are stable. If one has an elevation and is acutely ill or has evolving infarction, the test should be repeated at least 2 weeks later [26]. Values above 10 mg/l (corresponding

to 1 mg/dl) are likely caused by acute disease [28]. Values >3 mg/l (corresponding to 0.3 mg/dl) are associated with higher risk, and values <1 mg/dl (corresponding to 0.1 mg/dl) are considered intermediate [26]. The mean CRP level in the present study was 1.82±1.60 mg/dl (corresponding to 18.2 mg/l), reflecting that CRP may be elevated in patients with CHD. Moreover, many studies also demonstrate that the CRP level increases in CAD and it was considered to be a predictor of CHD [5].

#### Association between cardiac markers, echocardiographic and other parameters at preoperative period

Table 4 shows the relationships between cardiac markers, echocardiographic and other parameters at the preoperative period. Preoperative BNP, cTNI and CRP level positively related to LVIDD. The correlation coefficient was higher in BNP ( $r=0.39$ ,  $p<0.01$ ) than in cTNI ( $r=0.22$ ,  $p<0.05$ ), suggesting that for functional assessment of left ventricular diastole, BNP and CRP are more powerful than cTNI. Although mean value of LVIDD was normal range, it was near to the upper

Table 4. Association between preoperative concentration of cardiac markers and echocardiographic parameters

Marker Parameter	BNP	cTNI	CK-MB	CRP
LVIDD ( $r$ )	0.31**	0.22*	0.14	0.39*
LVIDS ( $r$ )	0.41**	0.37**	0.28*	0.45**
PWD ( $r$ )	NS	NS	NS	-0.23*
LA dimension ( $r$ )	0.24*	NS	NS	NS
LA volume ( $r$ )	NS	NS	NS	NS
RVIDD ( $r$ )	NS	-0.38*	-0.28	-0.17
LVEF ( $r$ )	-0.52*	-0.47*	-0.33**	-0.51*
SLMCA ( $r$ )	NS	NS	NS	NS
SLAD ( $r$ )	NS	NS	NS	NS
SLCX ( $r$ )	NS	NS	NS	NS
SRCA ( $r$ )	NS	NS	NS	NS
SBP ( $r$ )	-0.30*	-0.22*	NS	-0.31*
DBP ( $r$ )	-0.34**	-0.36**	-0.24*	-0.25*

$r$ , correlation coefficient.

NS, not significant.

\*,  $p<0.05$ ; \*\*,  $p<0.01$ ; +,  $p<0.001$  (significant correlation).

Abbreviation: LVIDD, left ventricular internal dimension at diastole; LVIDS, left ventricular internal dimension at systole; PWD, posterior wall dimension; LA, left atrium; RVIDD, right ventricular internal dimension at diastole; LVEF, left ventricular ejection fraction; SLMCA, stenosis of left main coronary artery; SLAD, stenosis of left descending artery; SLCX, stenosis of left circumflex artery; SRCA, stenosis of right coronary artery; SBP, systolic blood pressure; DBP, diastolic blood pressure. BNP, brain natriuretic peptide; cTNI, cardiac troponin-I; CK-MB, creatine kinase-MB; CRP, C-reactive protein.

limit of the normal value (Table 2), probably suggesting the possibility of heart failure attributable to CHD. In the present study, because abnormally increased LVIDS and left atrial volume and decreased LVEF were observed (Table 2), heart failure and/or LV dysfunction were suggested. Depressed LV contraction can lead to increased LVIDD.

BNP, cTNI, CK-MB and CRP levels were positively associated with LVIDS, where they were negatively correlated with LVEF. The correlation coefficients to LVIDS and LVEF were higher in BNP ( $r=0.41$  and  $r=-0.52$ ) and CRP ( $r=0.45$  and  $r=-0.51$ ) than in cTNI ( $r=0.37$  and  $r=-0.47$ ) and CK-MP ( $r=0.28$  and  $r=-0.33$ ). These data suggest that BNP and CRP may be useful markers or predictors to diagnose and prognose LV dysfunction and heart failure with CHD. LA dimension positively related to BNP level ( $p<0.05$ ). RVIDD had negative correlation with cTNI ( $r=-0.38$ ,  $p<0.05$ ) and CK-MB ( $r=-0.28$ ,  $p<0.05$ ).

On the one hand, SBP had a negative relationship with BNP, cTNI and CRP levels whereas DBP had a negative correlation with CK-MB as well as three cardiac markers ( $p<0.05$  or  $p<0.01$ ). Our data suggest that in addition to cTNI and CK-MB, plasma BNP and CRP levels are very useful markers. Many studies have explained that all cardiac diseases were associated with an increase in the BNP. These included diastolic dysfunction [3,25], cardiac decompensation [33], and acute right heart failure [27]. Acute myocardial infarction (AMI) or historical MI were associated with increased levels of BNP [16,22], suggesting that BNP assay is clinically useful for diagnosing diastolic heart failure. Jung et al. [15] demonstrated that preoperative levels  $>263$  pg/ml predict postoperative complications in patients receiving CABG (coronary artery bypass graft).

Therefore, previous studies and our observations justify that plasma BNP is a very useful marker for diagnosing and prognosing the patients with CHD.

**Association between BNP and other cardiac markers at preoperative period**

Association between BNP concentration and levels of other cardiac markers were summarized in Table 5. BNP had a positive correlation with cTNI, CK-MB or CRP ( $p<0.001$  or  $p<0.05$ ), and it especially had a higher correlation coefficient with cTNI (This is a gold standard marker in diagnosing myocardial injury or CHD) compared with CK-MB or CRP. These results indicate that BNP is a reliable, sensitive and specific marker for diagnosis and prognosis of CHD.

Table 5. Association between plasma BNP concentration and other cardiac markers

Marker	BNP	cTNI	CK-MB	CRP
BNP ( <i>r</i> )	1.0	0.43 <sup>+</sup>	0.22 <sup>+</sup>	0.25 <sup>+</sup>
cTNI ( <i>r</i> )	0.43 <sup>+</sup>	1.0	0.76 <sup>++</sup>	0.52 <sup>+</sup>
CK-MB ( <i>r</i> )	0.22 <sup>+</sup>	0.76 <sup>++</sup>	1.0	0.53 <sup>+</sup>
CRP ( <i>r</i> )	0.25 <sup>+</sup>	0.52 <sup>+</sup>	0.53 <sup>+</sup>	1.0

*r*, correlation coefficient.  
 \*,  $p<0.05$ ; \*\*,  $p<0.01$ ; +,  $p<0.001$ ; ++,  $p<0.0001$  (significant correlation).

BNP, brain natriuretic peptide; cTNI, cardiac troponin-I; CK-MB, creatine kinase-MB; CRP, C-reactive protein.

Table 6. Association between preoperative levels of cardiac markers and operative variables

Variable \ Marker	BNP	cTNI	CK-MB	CRP
OP-time ( <i>r</i> )	NS	NS	NS	NS
POMV-time ( <i>r</i> )	NS	0.30 <sup>**</sup>	0.55 <sup>+</sup>	0.71 <sup>++</sup>
ICU-staying period ( <i>r</i> )	0.31 <sup>**</sup>	0.49 <sup>+</sup>	0.50 <sup>+</sup>	-0.23 <sup>*</sup>
Hospitalization ( <i>r</i> )	NS	NS	NS	NS
Graft-number ( <i>r</i> )	NS	NS	NS	NS

*r*, correlation coefficient.  
 NS, not significant.  
 \*\*,  $p<0.01$ ; +,  $p<0.001$ ; ++,  $p<0.0001$ .

Abbreviation: OP, operation; POMV, postoperative mechanical ventilation; ICU, intensive care unit; Graft-number, number of vessel for coronary artery bypass surgery.  
 BNP, brain natriuretic peptide; cTNI, cardiac troponin-I; CK-MB, creatine kinase-MB; CRP, C-reactive protein.

**Association between preoperative levels of cardiac markers and postoperative parameters**

Table 6 shows association between preoperative levels of cardiac markers and operative variables.

All cardiac markers were not significantly associated with operation time, hospitalization or graft-number ( $p>0.05$ ). POMV-time significantly related to preoperative cTNI, CK-MB or CRP level ( $p<0.01$ ,  $p<0.001$  or  $p<0.0001$ ). ICU-staying period was significantly correlated with preoperative BNP, cTNI, CK-MB or CRP level. Interestingly, correlation coefficients of CRP were the highest, suggesting that preoperative CRP level may be a strong predictor for postoperative outcomes in patients with CHD.

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### 초록 : 관상동맥질환자에 있어 수술 전 brain natriuretic peptide 농도, 심장표지자, 수술전후기 변수들 간의 상관관계와 임상적 유용성

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심혈관질환 진단을 위해 여러 가지 표지자들이 이용되고 있으며 그와 같은 표지자로 cardiac troponin-I (cTNI), creatine kinase-MB (CK-MB), C-reactive protein (CRP)이 있다. 최근, 심장기능부전의 표지자로서 brain natriuretic peptide (BNP)에 대한 관심이 집중되고 있다. 이 연구는 심폐바이패스(cardiopulmonary bypass) 비적용 관상동맥우회수술을 시행한 74명의 성인환자를 대상으로 수술 전 BNP 농도와 다른 심장 표지자들 농도, 그리고 수술 전후 표지자들 간의 상관관계를 규명하기 위해 시행하였다. 수술 전 시기의 BNP, cTNI, CK-MB, CRP 각각의 농도는 수술 전 심초음파 변수와 양 또는 음의 상관성을 보였다. 수술 전 BNP 농도와 수술 전 cTNI, CK-MB, CRP 농도 각각과 높은 양의 상관관계가 있었다. 수술 전 BNP, cTNI, CK-MB, CRP 농도 각각은 수술 후 기계호흡보조시간, 중환자실치료기간과 유의한 양의 상관관계를 보였다. 이 연구의 결과들은 수술 전 BNP, cTNI, CK-MB, CRP와 같은 심장 표지자들의 측정 및 병용은 심혈관질환자들의 진단, 환자들의 등급화, 수술 후 예후평가에 매우 유용한 방법임을 시사하고 있다.