Circ J 2007; **71:** 79–83

N-Terminal ProBNP Levels Can Predict Cardiac Failure After Cardiac Surgery

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Background The aim of this study was to evaluate the relationship between the preoperative N-terminal pro-B-type natriuretic peptide (NT-proBNP) level and the need for the inotropic support in the early postoperative period of patients undergoing coronary artery bypass graft surgery.
Methods and Results The patients were divided into 2 groups: NT-proBNP level <220 pg/ml (group A, n=26) or >220 pg/ml (group B, n=26). The normal value for NT-proBNP level was accepted as <220 pg/ml. The cardiac output was measured on arrival in intensive care and at the 16th hour. The groups were compared with respect to early postoperative hemodynamic measurements, urinary output, use of inotropic agents and requirement for additional cardiac-assist devices. Left ventricular ejection fraction, cardiac output and cardiac index were lower in group B and inotropic agents were used for a longer period of time and at higher doses in this group ($p<0.05$).
Conclusion Measurement of the NT-proBNP level in the period before cardiac surgery can indicate the postoperative prognosis of the patient and may be a predictor of the need for postoperative inotropic treatment. (*Circ J* 2007; **71:** 79–83)

Key Words: Cardiac failure; Coronary artery bypass; NT-proBNP

Cardiac failure has a prevalence of 1% in people aged in their 50s and 10% in their 80s. The presence of cardiac failure symptoms in the preoperative period is known to increase the surgical risk and the postoperative mortality and morbidity. In recent years the introduction of new drugs and the increased use of coronary angioplasty and stent methods have enabled coronary heart operations to be performed in older patients and patients with late-stage disease. Thus determination of patient risk prior to operation has acquired importance.

The plasma B-type natriuretic peptide (BNP) level varies according to the grade of heart failure; that is, it progressively increases from Grade I to Grade IV of the New York Heart Association classification and this increase in the secretion of natriuretic peptides is closely associated with left ventricular (LV) wall tension and ventricular filling pressure[1] BNP, which is secreted because of increased LV wall tension, and its aminoterminal fraction N-terminal (NT)-proBNP, have gained a high value with respect to predicting LV function and its prognosis[2,3] Of the natriuretic peptides, NT-proBNP particularly is accepted as a specific marker of cardiac failure[4] and in cases where the NT-proBNP level has increased above approximately 200 pg/ml, a diagnosis of cardiac failure may be made if there are also concomitant signs of cardiac failure[5] Studies of the relationship between the severity of the heart failure after cardiac surgery and the requirement for inotropic agent, as related to the predictive use of NT-proBNP, are limited in the literature.

(Received July 21, 2006; revised manuscript received September 13, 2006; accepted October 13, 2006)
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In the present study, the association between the preoperative NT-proBNP level and the prevalance and level of cardiac failure in the early postoperative period in patients undergoing coronary artery bypass grafting (CABG) was investigated.

Methods

We enrolled 52 adult patients undergoing elective CABG. In all patients the NT-proBNP level was measured via Elecys ProBNP sandwich immunoassay method on the day before surgery, and the normal value was accepted as <220 pg/ml[6] Based on this we divided the patients into 2 groups: NT-proBNP level <220 pg/ml (Group A, n=26) or >220 pg/ml (Group B, n=26). Patients with renal failure (because a preoperative creatinine level >1.6 would cause an increase in the NT-proBNP level), acute myocardial infarction, or combined valvular disease and severe obstructive pulmonary disease were excluded.

All the patients underwent CABG with standard cardiopulmonary bypass (CPB) techniques. The left internal mammary artery was used for revascularizing the left anterior descending coronary artery or a saphenous vein graft was used for the other coronary arteries. Arterial pressure was monitored via a radial artery cannula and cardiac rhythm was followed by the bedside monitor. The values for cardiac output (CO) and cardiac index (CI), pulmonary capillary wedge pressure (PCWP), pulmonary artery pressure (PAP), central venous pressure (CVP) were measured preoperatively and at 0 and 16th postoperative hours via the Swan-Ganz Thermodilution method.

Inotropic agents were used when the patient's arterial pressure was below 80 mmHg and adequate perfusion could not be achieved. Dobutamine was the first-choice, but combined inotropic therapy was administered if arterial pressure was inadequate. Adrenalin was required in combination

Table 1 Demographic Data of the Groups

	Group A (n=26)	Group B (n=26)	p value
Age (years)	59.50±10.50	60.61±10.39	0.703
Height (F/M)	9/17 (34.6%/65.4%)	9/17 (34.6%/65.4%)	1.0
Height (cm)	165.88±7.85	167.11±8.61	0.593
Weight (kg)	71.69±10.33	72.38±13.06	0.833
Body area (m^2)	1.78±0.14	1.80±0.18	0.769
Smoke (yes/no)	12/14 (46.2%/53.8%)	10/16 (38.5%/61.5%)	0.578
Hypertension (yes/no)	17/9 (65.4%/34.6%)	20/6 (76.9%/23.1%)	0.363
Diabetes mellitus (yes/no)	5/21 (19.2%/80.8%)	4/22 (15.4%/84.6%)	0.717
Hyperlipidemia (yes/no)	12/14 (46.2%/53.8%)	11/15 (42.3%/57.7%)	0.782
Coronary artery failure	2.538±0.811	2.384±0.752	0.482
LVEF	45.96±5.66	40.11±7.47	0.003

Data are mean±SD.
LVEF, left ventricular ejection fraction.

Table 2 Operative Data of the Groups

	Group A (n=26)	Group B (n=26)	p value*
CPB (min)	101±36.41	104.73±35.98	0.712
XClamp (min)	57.23±20.66	60.07±20.33	0.619
No. bypass	2.42±0.80	2.57±0.57	0.434
Drainage (ml)	570.57±308.65	550±188.14	0.773
Fluid balance (ml)	344.80±743.18	677.69±695.17	0.102

**p>0.05.*
Data are mean±SD.
CPB, cardiopulmonary bypass; XClamp, cross-clamp.

with dobutamine and dopamine in rare cases. Noradrenaline was not used in any patient. Intra-aortic balloon pumping (IABP) was needed when inotropic agents were insufficient.

The findings were compared and evaluated by the Student's t-test for the intergroup comparisons and Wilcoxon signed rank test was used for within-group comparisons; p<0.05 was considered as statistically significant (SPSS, Chicago, IL, USA).

Results

The demographic data and risk factors of the 2 groups are shown in Table 1. There were no statistically significant differences between the groups. Mean preoperative LV ejection fraction (LVEF) of Group A was higher than Group B (p<0.05). CPB and cross-clamp times, the number of distal bypasses and the quantity of drainage for both groups were not different (Table 2).

Preoperative and postoperative CO and CI values in Group A were higher than in Group B (p<0.05) (Table 3).

In Group A, systolic arterial pressure decreased significantly at the 0 and 16th postoperative hours compared with the preoperative period (p<0.05). Pulse rate increased significantly (p<0.05). The preoperative CO and the CI values were found to be significantly lower than the postoperative values (p<0.05). No statistically significant differences were observed between the preoperative PCWP, PAP and CVP values, and those obtained postoperatively (p>0.05).

In Group B, systolic arterial pressure increased significantly at the 0 and 16th postoperative hours compared with the preoperative period (p<0.05). Pulse rate decreased significantly (p<0.05). The preoperative CO and the CI values were found to be significantly lower than the postoperative values (p<0.05). No statistically significant difference was observed between the preoperative PCWP, PAP and CVP values, and those obtained postoperatively (p>0.05).

Cardiac inotropes were administered to 21 patients in Group B and 4 patients in Group A during the early postoperative period. The dosage and duration of administration was significantly higher in Group B (p<0.05) (Tables 4–6). There was no patient in Group A who received dopamine alone and required IABP. The number of patients who were given dobutamine, and dobutamine in combination with dopamine, in Group A was significantly less than in Group B (p<0.05).

Table 3 Hemodynamic Data of the Groups

	Group A					Group B					p3
	Preoperative	Hour 0	Hour 16	p1a	p1b	Preoperative	Hour 0	Hour 16	p2a	p2b	
AP	109.03±27.35	94.76±19.16	96.80±16.99	0.004	0.026	99.50±26.80	90.23±21.47	90.92±15.90	0.002	0.096	0.210
Pulse	70.23±12.78	83.42±17.49	84.00±15.39	0.003	0.001	72.15±12.52	87.69±14.49	92.34±12.81	0.000	0.000	0.586
CO	4.35±1.41	5.15±1.04	5.35±1.01	0.002	0.000	3.55±0.97	4.25±1.15	4.74±0.83	0.001	0.000	0.004
CI	2.46±0.75	2.86±0.58	2.99±0.57	0.003	0.000	1.95±0.54	2.43±0.63	2.62±0.45	0.000	0.000	0.008
PCWP	11.26±4.72	11.57±4.13	9.65±4.72	0.289	0.063	12.34±5.77	13.07±6.38	10.50±5.55	0.688	0.082	0.465
PAP	16.61±6.09	18.34±6.22	15.65±6.33	0.067	0.567	19.23±6.33	22.23±8.81	20.00±9.24	0.076	0.676	0.135
CVP	8.30±3.05	8.84±3.08	7.07±2.85	0.132	0.120	9.57±3.82	10.00±4.93	9.03±5.08	0.762	0.465	0.192
LVEF	45.96±5.66					40.11±7.47					0.003

p1a, Group A postoperative 0 h compared with preoperative period; p1b, Group A postoperative 16 h compared with preoperative period; p2a, Group B postoperative 0 h compared with preoperative period; p2b, Group B postoperative 16 h compared with preoperative period; p3, hemodynamic values of both groups, obtained preoperatively and (preop), at postoperative 0 and 16 h.
Data are mean±SD.
AP, systolic arterial pressure; CO, cardiac output; CI, cardiac index; PCWP, pulmonary capillary wedge pressure; PAP, pulmonary artery pressure; CVP, central venous pressure. Other abbreviation see in Table 1.

Table 4 Inotropic Drug Usage

	Group A		Group B	
	n	*ratio*	*n*	*ratio*
Patients receiving inotropes	*4*	*15.4%*	*21*	*80.8%*
Patients not receiving inotropes	*22*	*84.6%*	*5*	*19.2%*

p<0.05.

Table 6 Doses of Inotropic Agents

	Dobutamine ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	*Dopamine* ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	*Adrenalin* (*μg/min*)
Group A	*0.50±1.20*	*0.42±1.20*	*0*
Group B	*3.46±2.94*	*3.51±3.04*	*0.4±0.10*

p<0.05.
Data are mean±SD.

The mean NT-proBNP level was 886.25±655.26 pg/ml in patients who required inotropic agents (n=25) and 183.07± 224.79 pg/ml in the others (n=27), which was a statistically significant difference (p<0.001).

Discussion

It is known that LV systolic dysfunction and increased ventricular filling pressure increases blood levels of BNP and NT-proBNP. The measurement of NT-proBNP is used for the diagnosis of congestive heart failure,[5] because increased pressure in the right chambers of the heart secondary to LV dysfunction and severe pulmonary hypertension goes in parallel with increases in the BNP and NT-proBNP levels. The NT-proBNP level can be measured easily via Elecsys ProBNP sandwich immunoassay method. The proBNP level is reported to rapidly increase at birth and decrease within the first days, remain stable after the first 4 months of birth and not to be affected by gender and increased with age in both sexes. Low NT-proBNP values are associated with a lower risk of death, independent of age, gender, and LVEF.[7] Normal values for the mean NT-proBNP level are less than 220 pg/ml[6,8] and level above 220 pg/ml can be accepted as diagnostic for cardiac failure. This value determined the patient groups in our study.

Both the proBNP and NT-proBNP peptide are able to establish the diagnosis of heart failure, but the NT-proBNP level is more sensitive and specific, and can be used as a simple, highly effective diagnostic test for heart failure.[9] The diagnostic value of NT-proBNP is that it may be more accurate and more reliable than BNP for the detection and evaluation of patients with LV dysfunction, because of the longer half life of NT-proBNP.[10,11] NT-proBNP shows a greater proportional and absolute increase in value in many clinical situations. The high negative predictive value of BNP makes it suitable for population screening, but its low positive predictive value emerges as a problem for diagnostic screening because of the large number of false-positive results.[12] Plasma norepinephrine (NE) concentration has no independent prognostic power for clinical cardiac outcomes, which may reflect the heterogeneous response of NE in the early postinfarction period, during which pain, anxiety, and multiple drugs may acutely modify plasma catecholamine levels in addition to the extent of cardiac injury.[13] For this reason the blood NT-proBNP level may be used for accurate diagnosis and prognosis.

Blood NT-proBNP levels increase in patients with renal failure,[14] so we excluded such patients (creatinine levels >1.6) from the study. Female patients with a high body weight have been found to have a higher NT-proBNP level and the proBNP level decreases as body weight decreases; that is, there is an inverse relation between BNP level and body mass index.[15] The high mean arterial pressure does not affect the NT-proBNP level in patients without LV dysfunction, and NT-proBNP is a useful diagnostic aid for LV systolic dysfunction even in hypertensive patients.[16] There was no statistically significant difference between our study groups in relation to mean body weight or presence of preoperative hypertension.

Postoperatively, elevated peak BNP levels and elevated peak BNP levels have beenassociated with prolonged hospital stay and mortality within 1 year.[17] In chronic cardiac failure of ischemic etiology, systolic dysfunction may be assessed by echocardiography. NT-proBNP levels are reported to be significantly related to LVEF values and increased in patients with LV dysfunction.[18] Plasma NT-proBNP is a useful marker for recovery after a high-risk CABG procedure, and conversely significantly correlated with LVEF, and it increases as the LVEF declines.[19,20] In our study we found the LVEF value was statistically significantly higher in Group A than in Group B. The NT-proBNP level can identify patients with symptoms of heart failure and LVEF ≤40% with a sensitivity of 0.92 and specificity of 0.86.[21] NT-proBNP detects an LVEF ≤40% with good sensitivity and specificity and has a performance that is superior or equivalent to that of BNP.[22] NT-proBNP can be used to detect subclinical cardiac impairment and also has prognostic importance; it can be used by the cardiologist for further diagnostic tests and initiation of cardiac treatment if necessary;[4] however, it is unclear if LVEF is the best indicator of prognosis or an appropriate sole trigger for initiation of treatment. A significant proportion of clinical heart failure occurs in the presence of preserved LVEF and some reports indicating the prognostic value of BNP have not included measurement of LVEF.[13] Likewise, because it has been shown that an increased NT-proBNP

Table 5 Inotropic Agents Used in Both Groups

	Dobutamine		*Dopamine*		*IABP*		*Dobutamine-Dopamine*		*Dobutamine-Dopamine-Adrenalin*	
	n	*ratio*	*n*	*ratio*	*n*	*ratio*	*n*	*ratio*	*n*	*ratio*
Group A	*1*	*3.8%*	*–*	*–*	*–*	*–*	*3*	*11.5%*	*–*	*–*
Group B	*3*	*11.5%*	*3*	*11.5%*	*1*	*3.8%*	*11*	*42.3%*	*3*	*11.5%*

p<0.05.
IABP, intra-aortic balloon pumping.

level almost always corresponds with echocardiographic detection of cardiac pathology;[21] we did not compare the echocardiographic results of these patients with their preoperative levels of NT-proBNP.

The 25 patients who developed cardiac failure and required inotropic agents had a mean NT-proBNP level of 886.25±655.26 pg/ml, whereas the mean NT-proBNP level was 183.07±224.97 pg/ml in the remaining 27 cases without heart failure ($p<0.001$). With comparison of the mean LVEF values the statistical difference is less significant (mean LVEF value 39.92+7.96 in the 25 patients who used inotropic agents; 45.42+5.00 in the others $p<0.002$). Like some studies, this finding indicates that preoperative NT-proBNP levels are at least as valuable as the LVEF in predicting cardiac failure during the early postoperative period![11] The blood NT-proBNP level is inversely proportional with CO and CI and the low values signify cardiac failure with poor CO.[23] In the present study, the CO and CI values were significantly higher in Group A, where the NT-proBNP level was within the normal limits, compared with Group B.

Increased LV filling pressure is closely associated with high NT-proBNP levels in patients with LV systolic dysfunction.[24] Because the increase in PCWP leads to increased intraventricular tension, the NT-proBNP level is also increased. The CVP reflects cardiac filling and hence the cardiac tension. An increase in the CVP also causes an increase in the BNP level![17] In the present study, the PCWP, PAP and the CVP values were within the normal limits in both groups and there was no significant difference between Group A and B with respect to these values. Similarly, in another study in which the NT-proBNP level was evaluated in patients undergoing cardiac surgery, no relation was detected between the NT-proBNP level and the PCWP, PAP and CVP values.[23] In our study, the high NT-proBNP levels observed in Group B were not affected by the PCWP, PAP or CVP values. A raised plasma level of NT-proBNP has adverse prognostic significance even when the LVEF is preserved.

There are various inotropic, vasoactive treatment options for hemodynamic support in cases of severe myocardial dysfunction, so the choice of inotropic treatment for achieving adequate blood pressure and CI is important. The selection is usually made according to the etiology of the cardiac failure and the effect mechanism of the drug. A significant relationship has been detected between the inotropic agent administered and the NT-proBNP level.[23] Comparison with the BNP assay suggests that NT-proBNP could play an additional role in the evaluation of patients with LV systolic dysfunction![18]

The number of patients for whom inotropic agents were required was significantly lower in the group with the low NT-proBNP level than in the group with the high NT-proBNP level ($p<0.05$). The mean duration of inotropic agent usage was 0.46±1.13 h in Group A and 5.92±6.40 h in Group B. We also found a higher use of inotropic agents in combination in Group A then in Group B. The requirement for inotropic agents is higher in patients with a high preoperative NT-proBNP level. Although the patients with a low NT-proBNP level in Group A also required inotropic agents, the dosages were very much lower and administration was of shorter duration than in Group B.

The use of IABP during cardiac surgery increases in patients with a high preoperative NT-proBNP level;[25] and in the present study it was used in 1 patient with a high NT-proBNP level in Group B for 48 h.

In the present study, we found that the inotropic agents were used at higher doses and combined with others and used for a longer time in patients with a high preoperative NT-proBNP level. By measuring the NT-proBNP level in the period before open cardiac surgery, the relationship between the preoperative level and the postoperative prognosis of the patient and postoperative inotropic treatment will be seen. Measurement of the preoperative NT-proBNP level may be a predictor in determining future inotropic treatment.

The present findings led us to conclude that the plasma concentrations of NT-proBNP becomes markedly and acutely elevated after cardiac surgery with CPB, and reflects the state of LV function. The severity of acute heart failure after cardiac surgery can be predicted by the preoperative plasma NT-proBNP concentration. In order to obtain a definite relationship between the preoperative level of NT-proBNP and postoperative outcome, further studies are required.

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