

## N-Terminal Pro-B-type Natriuretic Peptide Is Useful to Predict Cardiac Complications Following Lung Resection Surgery

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**Background:** Cardiovascular complications are major causes of morbidity and mortality following non-cardiac thoracic operations. Recent studies have demonstrated that elevation of N-Terminal Pro-B-type natriuretic peptide (NT-proBNP) levels can predict cardiac complications following non-cardiac major surgery as well as cardiac surgery. However, there is little information on the correlation between lung resection surgery and NT-proBNP levels. We evaluated the role of NT-proBNP as a potential marker for the risk stratification of cardiac complications following lung resection surgery. **Material and Methods:** Prospectively collected data of 98 patients, who underwent elective lung resection from August 2007 to February 2008, were analyzed. Postoperative adverse cardiac events were categorized as myocardial injury, ECG evidence of ischemia or arrhythmia, heart failure, or cardiac death. **Results:** Postoperative cardiac complications were documented in 9 patients (9/98, 9.2%): Atrial fibrillation in 3, ECG-evidenced ischemia in 2 and heart failure in 4. Preoperative median NT-proBNP levels was significantly higher in patients who developed postoperative cardiac complications than in the rest (200.2 ng/L versus 45.0 ng/L,  $p=0.009$ ). NT-proBNP levels predicted adverse cardiac events with an area under the receiver operating characteristic curve of 0.76 [95% confidence interval (CI) 0.545~0.988,  $p=0.01$ ]. A preoperative NT-proBNP value of 160 ng/L was found to be the best cut-off value for detecting postoperative cardiac complication with a positive predictive value of 0.857 and a negative predictive value of 0.978. Other factors related to cardiac complications by univariate analysis were a higher American Society of Anesthesiologists grade, a higher NYHA functional class and a history of hypertension. In multivariate analysis, however, high preoperative NT-proBNP level ( $>160$  ng/L) only remained significant. **Conclusion:** An elevated preoperative NT-proBNP level is identified as an independent predictor of cardiac complications following lung resection surgery.

Key words: 1. Cardiac  
2. Complication  
3. Lung surgery  
4. Prognosis

### INTRODUCTION

Cardiovascular complications are major causes of morbidity

and mortality following non-cardiac thoracic operations [1]. In order to improve risk stratification and predictability of potential postoperative complications, various tools, such as revised

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cardiac risk index (RCRI) or American College of Cardiology/American Heart Association clinical risk factors, have been developed. These tools, however, cannot entirely replace a physician's judgment for individual patients, particularly because of the complexity of these diagnostic tools and the lack of evidentiary support for their usefulness [2].

Therefore, simple and reliable method for identifying high-risk patients is necessary. It would allow a more targeted and more cost-effective application of prophylactic interventions. It would also enable us to detect postoperative cardiac complications earlier through vigilant surveillance over selected high-risk patients.

Cardiac natriuretic peptides including brain natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) have recently emerged as potentially useful biomarkers in the diagnosis and prognostic stratification of heart failure patients as well as patients in other clinical settings such as liver cirrhosis or chronic renal failure [3,4]. More recently, it has been reported that these biomarkers are elevated in patients who experience perioperative cardiac complications following major cardiac and non-cardiac surgery [5-7]. However, there is little information on the correlation between lung resection surgery and NT-proBNP levels.

We evaluated the role of NT-proBNP as a potential marker for the risk stratification of cardiac complications following lung resection surgery.

## MATERIAL AND METHODS

### 1) Study sample

One hundred one consecutive patients, who underwent elective lung resection surgery at our institute from August 2007 to February 2008, were enrolled in this prospective study. Among them, three patients were excluded due to newly developed arrhythmia during anesthesia or significant hypotension related to perioperative bleeding because the objective of this study was to observe the net effect of pulmonary resection on the development of cardiac complications. Thus, 98 patients constituted the study cohort. Twenty-six patients had a history of hypertension and 6 of them had been taking beta-blocker. Five patients out of seven patients who had a history of coronary artery occlusive disease had re-

ceived a percutaneous coronary artery intervention (PCI) or coronary artery bypass graft (CABG). All patients underwent elective lung resection surgery and had been free from major acute clinical events for at least two months before surgery. Patients were assessed prior to surgery by an attending anesthesiologist for American Society of Anesthesiologists (ASA) score. The study protocol was approved by the local Institutional Review Board.

### 2) Data collection

Preoperative data collection encompassed patient demographic data, medical and surgical histories, preoperative medications, 12-lead electrocardiography (ECG), pulmonary function tests, and the data on renal and hepatic function. Preoperative blood samples were also obtained to measure serum NT-proBNP level. The Revised Cardiac Risk Index (RCRI) was calculated from preoperative variables [8]. All patients remained under continuous ECG monitoring for at least 24 hours following surgery and underwent daily clinical cardiologic evaluations before discharge. All data was collected prospectively.

### 3) Postoperative cardiac events

The occurrence of cardiac-related death or cardiac complications requiring treatment (myocardial injury, ECG evidence of ischemia or arrhythmia, or heart failure) before discharge was evaluated. Acute postoperative myocardial injury was defined as the evidence of myocardial cell necrosis (Troponin T >0.1 mg/L). ECG evidence of ischemia was defined as the development of T-wave inversion of greater than 2 mm, and ST segment deviation of greater than 2 mm in at least two contiguous chest leads or greater than 1 mm in at least two contiguous limb leads. Arrhythmia was defined as a new sustained abnormal cardiac rhythm. All ECGs were analyzed by a cardiologist. Heart failure was defined as an occurrence of symptoms of congestive heart failure (orthopnea or dyspnea on exertions, venous distention, cardiomegaly, ankle edema, etc.) without the evidence of pneumonia.

### 4) Serum NT-proBNP assays

To measure the serum NT-proBNP levels, blood samples were obtained 12 hours before and after the operation. Before

the preoperative blood sample, patients were asked to lie quietly in the supine position to eliminate any potential effects of posture and exercise on serum NT-proBNP levels. NT-proBNP was assayed by a semiautomated analyzer (Elecsys-1010, Roche Diagnostics, Germany) using an electrochemiluminescence immunoassay kit (Elecsys NT-proBNP Test, Roche Diagnostics, Mannheim, Germany).

### 5) Statistical analysis

Categorical data are presented as absolute values and percentage. Continuous variables are presented as the mean and standard deviation. Fisher's exact test was used to test differences between two independent categorical data. Differences between two independent groups of continuous data were evaluated using Mann-Whitney U-test. To establish a NT-proBNP cut-off value with appropriate sensitivity and specificity, receiver operating characteristic (ROC) curves were plotted and the area under the curve was estimated. Linear logistic regression was used to test the cardiac event predictability of elevated NT-proBNP levels and other selected parameters. A p-value less than 0.05 was considered significant. All statistical analyses were performed with the Statistical Package for Social Science (SPSS 12.0, Chicago, IL, USA).

## RESULTS

There were 60 male and 38 female patients, and their mean age was  $61.1 \pm 12.0$  years. Twenty seven patients (23.5%) suffered from postoperative complications. Eight patients had pulmonary complications such as pneumonia, acute lung injury or bronchopleural fistula, and one patient suffered from chylothorax. Prolonged air leakage (air leakage  $> 5$  days) occurred in 8 patients. Nine patients (9.2%) experienced cardiac complications following lung resection surgery. Atrial fibrillation occurred in 3 patients, ischemic change requiring vasodilator therapy in 2 patients, and heart failure in 3 patients including one patient with simultaneous pneumonia. One patient had simultaneous atrial fibrillation and heart failure.

All cardiac events occurred within a week after the operation. ECG changes were identified in 9 patients (5 with

T-wave or ST segment abnormalities and 4 with new onset atrial fibrillation). All patients with atrial fibrillation were treated with antiarrhythmic agent. Among 5 patients with T wave or ST segment abnormalities, two were treated with vasodilator immediately after the operation. All of these five patients' ECGs recovered to their preoperative state within 7 days. Acute myocardial injury did not occur in any patient.

Postoperative heart failure requiring inotropic agents occurred in 4 patients. All of them suffered from oliguria, leg edema and dyspnea without the evidence of pneumonia on a chest X-ray. Notably, ejection fractions determined with echocardiography decreased over 10% and ejection fractions were below 40% in 2 patients.

The relationship between preoperative and postoperative NT-proBNP levels and postoperative cardiac complications is demonstrated in Table 1.

In patients with cardiac complications, both preoperative and postoperative NT-proBNP median values were significantly higher than in patients not experiencing cardiac complications (Table 1).

The areas under the ROC curve, which signifies the utility of preoperative and postoperative NT-proBNP in predicting cardiac complications following lung resection surgery, were 0.76 [95% confidence interval (CI) 0.545~0.988,  $p=0.01$ ] and 0.82 (95% CI 0.626~1.024,  $p=0.001$ ), respectively (Fig. 1). The value of 160 ng/L was found to be the single best cutoff point for preoperative NT-proBNP in predicting the development of cardiac complications. A preoperative NT-proBNP value of 160 ng/L carried a positive predictive value of 0.857 and a negative predictive value of 0.978 for detecting postoperative cardiac complications.

The univariate predictors for postoperative complications included a poor NYHA functional class ( $\geq 2$ ), a history of hypertension, a higher ASA score ( $\geq 2$ ) and higher NT-proBNP ( $> 160$  ng/L). In the multivariate analysis, only the preoperative NT-proBNP remained significant as a predictor for postoperative cardiac complications (Table 2).

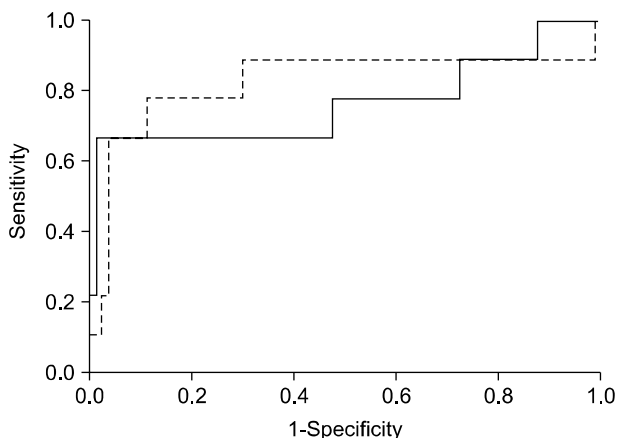
## DISCUSSION

In this study, preoperative serum NT-proBNP was indicated as an independent predictor for cardiac complications follow-

**Table 1.** Clinical and demographic characteristics of patients with or without postoperative cardiac complications

Patient characteristics	Patients with postoperative cardiac complications (n=9)	Patients without postoperative cardiac complications (n=89)	p-value
Male	7 (77.8%)	53 (59.6%)	0.287
Age median	69 (57~78)	65 (15~77)	0.012
Smoking status			0.253
Never	2 (22.2%)	35 (39.3%)	
Former	6 (66.6%)	20 (22.5%)	
Current	1 (11.1%)	34 (38.2%)	
History of hypertension	6 (66.7%)	20 (22.5%)	0.004
Use of beta-blocker	1 (11.1%)	8 (9.0%)	0.448
CAD	2 (22.2%)	5 (5.6%)	0.067
Prior CABG or PCI	1 (11.1%)	4 (4.5%)	0.390
Creatinine	0.9 (0.6~1.9)	0.8 (0.6~1.8)	0.226
RCRI $\geq$ 3	2 (22.2%)	5 (5.6%)	0.067
NYHA class $\geq$ 2	6 (66.7%)	5 (5.6%)	0.001
ASA grade $\geq$ 2	8 (89%)	46 (52%)	0.039
LVEF, % median	60.0 (31.0~69.0)	65.0 (28.0~73.0)	0.227
FEV1, % predicted	81.7 (44.7~89.8)	81.9 (51.4~96.8)	0.874
Type of operation			
Pneumonectomy	2 (22.2%)	6 (6.7%)	0.108
Bilobectomy	2 (22.2%)	12 (13.5%)	0.477
Lobectomy	4 (44.4%)	66 (74.2%)	0.061
Segmentectomy	1 (11.1%)	5 (5.6%)	0.515
VATS	3 (33.3%)	36 (40.4%)	0.679
Estimated blood loss (mL), median	150 (0~900)	200 (50~1,500)	0.042
NT-pro BNP (ng/L)			
Preoperative, median	200.2 (21.6~1,722.0)	45.0 (10.6~355.4)	0.009
Postoperative, median	674.6 (45.2~1,932.0)	190.2 (40.1~1,397.0)	0.001

CAD=Coronary artery disease; CABG=Coronary artery bypass graft; PCI=Percutaneous coronary intervention; RCRI=Revised Cardiac Risk; Index=NYHA, New York heart association; ASA=American society of anesthesiologists; LVEF=Left ventricular ejection fraction; FEV1=Forced expiratory ventilation in 1 second; VATS=Video assisted thoracoscopic surgery.



**Fig. 1.** ROC curve for preoperative NT-proBNP (solid line) and postoperative NT-proBNP (dashed line). ROC=Receiver operating characteristic.

ing lung resection surgery by a multivariate analysis.

Cardiac complications occur frequently after lung resection surgery. Atrial fibrillation is the most common cardiovascular complications after thoracic surgery, with a reported incidence of 8% to 20% after lobectomy and up to 40% after pneumonectomy [8,9]. These events contribute significantly to morbidity, mortality and the increased cost of medical care. Hence, a proactive approach for identifying patients with a higher risk for these complications is necessary.

Various tools have been developed to improve risk stratification and predictability for postoperative complications. The most widely used risk assessment tool for predicting major cardiac complications after non cardiac surgery is the revised cardiac risk index (RCRI) [2]. The six independent risk

**Table 2.** Univariate and multivariate analysis for predictors of adverse cardiac outcome using logistic regression

Patient characteristics	Odds ratio (95% CI) univariate	p-value	Odds ratio (95%CI) multivariate	p-value
NT-proBNP > 160 ng/L	2.28 (1.95~2.66)	<0.001	1.88 (1.21~2.90)	0.008
Age (> 65 years)	1.09 (0.96~1.24)	0.195	0.98 (0.89~1.08)	0.195
Hypertension	1.21 (1.06~1.37)	0.004	1.12 (0.85~1.46)	0.389
Beta-blocker use	1.08 (0.85~1.38)	0.517	0.94 (0.66~1.32)	0.690
NYHA class $\geq$ 2	1.67 (1.43~1.94)	<0.001	1.21 (0.77~1.90)	0.384
RCRI $\geq$ 3	1.23 (0.98~1.54)	0.066	1.18 (0.83~1.67)	0.338
ASA score $\geq$ 2	1.13 (1.01~1.27)	0.033	0.87 (0.61~1.25)	0.427
Ejection fraction	0.98 (0.97~1.01)	0.135	1.00 (0.99~1.01)	0.937
Estimated blood loss $\geq$ 500 mL	1.06 (0.90~1.25)	0.475	1.11 (0.74~1.66)	0.592

NYHA=New York heart association; RCRI=Revised cardiac risk index; ASA=American society of anesthesiologists.

predictors in the index include ischemic heart disease, heart failure, cerebrovascular disease, chronic renal insufficiency (serum creatinine level > 2 mg/dL), insulin-dependent diabetes mellitus, and high-risk surgery. Patients can be classified as low (zero or one risk factor), intermediate (two factors), or high (three or more factors) risk groups with corresponding postoperative cardiac complication rates of approximately 1%, 5%, and 10%, respectively. However, RCRI may not always be precise in predicting postoperative cardiac complications. In our study, a high RCRI score (RCRI  $\geq$  3) was not associated with postoperative cardiac complications (Table 2).

Many surgeons utilize various preoperative imaging studies for cardiac function (including i.e. echocardiography, magnetic resonance imaging, and radionuclide studies) to evaluate left ventricular (LV) function [10-13]. It is generally agreed that depressed LV function is associated with a higher risk of postoperative cardiac complications, but it remains debatable whether these tests provide additional information to routine clinical evaluation [14]. Halm et al. [10] reported that an LV ejection fraction of less than 40% was associated with postoperative cardiac complications, particularly heart failure. However, our study demonstrated that the LV ejection fraction did not correlate with the risk of postoperative cardiac complications after lung resection surgery (Table 2).

It has been suggested that NT-proBNP levels could be a useful markers of left ventricular dysfunction in both symptomatic and asymptomatic patients. Plasma levels of atrial natriuretic peptides have been reported to be elevated not only in patients with advanced heart failure or acute myocardial in-

farction, but also in other clinical settings such as liver cirrhosis or chronic renal failure. Recently, several reports regarding the correlation between NT-proBNP and cardiac complications following major cardiac and non-cardiac surgery have been published. However, there is little information on the correlation between lung resection surgery and NT-proBNP levels. Cardinale et al. [15] recently demonstrated that NT-proBNP is a strong independent predictor of postoperative atrial fibrillation in patients undergoing thoracic surgery for lung cancer. However, other cardiac complications were not evaluated in that study, and the comparison of the predictability of adverse cardiac outcomes between NT-proBNP and other risk factors was not elucidated.

Our study took into account various cardiac complications (including atrial fibrillation), and demonstrated that preoperative NT-proBNP levels were an independent predictor of the adverse outcomes by a multivariate analysis, after adjusting other risk factors such as revised cardiac risk index which is most widely used for predicting major cardiac complications. This finding carries important clinical implications, and may enable us to accurately stratify patients according to their risk of adverse outcomes. Awareness of preoperative NT-proBNP levels in patients who are undergoing lung resection surgery may help preventing the occurrence of cardiac complications after surgery. Assessment of NT-proBNP levels may offer a simple and cost-effective means of identifying high-risk patients, and may benefit the patients by getting around invasive and costly preoperative work-up.

There is no consensus on the cut-off value for abnormal NT-proBNP concentrations. When using the chemiluminescent kit from Roche Diagnostics, the upper 97.5 percentile level is identified as 155 ng/L for men and 84 ng/L for women under 50 years of age. Between 50 and 65 years, the upper limit comes up to 222 ng/L for men and 194 ng/L for women. According to the studies in different clinical settings, the suggested cut-off values of NT-proBNP ranged from lower than 100 ng/L to higher than 1,000 ng/L [16-19]. We suggested a cut-off value of 160 ng/L for NT-proBNP, but this value may need further evaluation before clinical application.

As mentioned above, NT-proBNP level increases in various clinical conditions such as left ventricular hypertrophy (LVH), left atrial enlargement or compensated heart failure. Lung resection, which may be a precipitating factor in patients with increased NT-proBNP level, brings a transient, but a significant extent of, pressure load to the heart. We assume that this abrupt hemodynamic change may bring about ischemic change on ECG in patient with LVH, atrial fibrillation in patient with left atrial enlargement, and symptomatic heart failure in patient with compensated heart failure.

In addition to preoperative measurements, we also checked NT-proBNP levels 12 hours after surgery. Postoperative NT-proBNP levels were also useful to identify the high-risk patients. When both preoperative and postoperative NT-proBNP levels were integrated, the sensitivity of NT-proBNP increased from 0.667 to 0.778. These findings suggest that both preoperative and postoperative elevation of NT-proBNP levels can predict cardiac complications for patients undergoing lung resection surgery.

Our study had several limitations. Firstly, although NT-proBNP and other preoperative parameters were collected prospectively, the occurrence of cardiac complications was analyzed retrospectively. Thus, it is possible that some patients may have had very transient episodes of arrhythmia which went unnoticed. Secondly, only a small number of patients in a single center was enrolled in this study. Thirdly, we examined only one biologic marker. Presumably, further studies on other preoperative biologic markers may be necessary in patients with low NT-proBNP levels to improve sensitivity and positive predictive value of the preoperative assessment for the delineation of the patients with a higher risk of post-

operative cardiac events.

## CONCLUSION

Elevated preoperative NT-proBNP level is identified as an independent predictor for cardiac complications following lung resection surgery. This correlation may enable us to plan adequate treatments in advance, and to detect cardiac complications as early as possible through the monitoring of postoperative NT-proBNP levels in selected high-risk patients. Further studies are necessary to support our observation, and to clarify the relationship between NT-proBNP levels and existing methods of risk stratification.

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