Preoperative High N-Terminal pro-B-Type Natriuretic Peptide Level Can Predict the Incidence of Postoperative Atrial Fibrillation Following Off-Pump Coronary Artery Bypass Grafting

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Objective: N-terminal pro-B type natriuretic peptide (NT-pro-BNP) is one of the biomarkers, increased by myocardial ischemia or subsequent, burdened wall stress. The aim of this study was to assess if NT-pro-BNP can predict the incidence of atrial fibrillation (AF) after off-pump coronary artery bypass grafting (OPCAB).

Methods: NT-pro-BNP was measured preoperatively in 100 OPCAB patients without preoperative AF. Patients were divided into the AF group (n = 36) of those who developed postoperative AF, and the sinus rhythm (SR) group (n = 64), of those who did not. Odds ratio analysis was carried out with a logistic regression model using the threshold of the high quartile.

Results: Age was more advanced in group AF (70.8 ± 8.7 years old) than in group SR (66.7 ± 8.5 years old), P = 0.025. There were more emergencies in group AF (22.2%) than in group SR (10.9%), P = 0.15. Preoperative NT-pro-BNP was significantly higher in group AF (509.6 ± 641.6 pg/mL) than in group SR (241.1 ± 302.7 pg/mL), P = 0.006. Preoperative administration of statins was relatively greater in group SR (73.4%) than in group AF (58.3%), P = 0.18. Four factors with a P value below 0.2 in the univariate analysis were extracted, which were preoperative administration of statins, emergency, high NT-pro-BNP (>348 pg/mL, high quartile), and advanced age (>75 years old, high quartile). The constructed logistic regression model revealed that high NT-pro-BNP (>348 pg/mL, high quartile) was the only predictor of postoperative AF after OPCAB (P = 0.05; OR, 2.60; 95% CI, 0.96–7.05).

Conclusions: A high preoperative level of NT-pro-BNP could predict the incidence of postoperative AF after OPCAB.

Keywords: coronary artery disease, outcomes, ischemic heart disease

Introduction

Off-pump coronary artery bypass (OPCAB) has become widely accepted in the past decade, especially in Japan.1–8 Many previous studies have shown an equivalent quality of OPCAB to conventional coronary artery bypass grafting (CABG).9,10 Even in the OPCAB...
era, we still encounter several in-hospital postoperative issues, one of which is postoperative new-onset atrial fibrillation (AF). Postoperative new-onset AF is not a life-threatening event but is associated with hemodynamic compromise and thromboembolic events, such as stroke. If we could find a strong preoperative predictor of postoperative, new-onset AF, it could be a very useful solution for an aggressive, intensive prophylactic therapeutic option.

Besides B-type natriuretic peptide (BNP), N-terminal pro-B type natriuretic peptide (NT-pro-BNP) is one of the myocardial stress markers, which are increased by myocardial ischemia or subsequent burdened wall stress caused by an increased left ventricular end-diastolic pressure or decreased cardiac output. NT-pro-BNP has been widely applied for diagnosis and prognosis analysis of patients with heart failure. Recently it is used for cardiac risk stratification tool for noncardiac surgery as well.

The aim of this study was to assess the impact of preoperative increase of serum NT-pro-BNP level on postoperative, new-onset AF after OPCAB.

Patients and Methods

Between the years 2004 and 2011, NT-pro-BNP was measured preoperatively in 100 OPCAB patients, in our institution. We excluded the patients with preoperative AF, chronic renal failure (eGFR; estimated glomerular filtration rate <30 ml/min), and patients who were converted to on pump. Patients were divided into the AF group, those who developed postoperative new-onset AF, and the sinus rhythm (SR) group, those who did not. Preoperative and perioperative characteristics were retrospectively investigated.

Surgical procedures and perioperative management

All preoperative medications, including beta blockers, angiotensin receptor blockers (ARB), angiotensin-converting enzyme (ACE) inhibitors, and calcium antagonists, were continued up to the day of operation, with the exception of non-steroidal anti-inflammatory drugs, which were discontinued one week before surgery, and digoxin, which was discontinued 3 days before surgery.

All operations were performed without CPB. Heparin 1.5 mg/kg was administered, and ACT (anticoagulation time) was maintained above 200 seconds. Anesthetic techniques and medications were similar in all patients. Anesthesia was induced with fentanyl, propofol, and neuromuscular paralytic drugs and maintained with total intravenous anesthesia using the same drugs. We preferred multiple and complete coronary revascularization with composite or sequential grafting and preferred in situ arterial grafts, in particular. For the prevention of arterial spasm, a continuous, intravenous infusion of diltiazem (0.5–1.0 μg/kg) or nicardipine (0.1–0.2 μg) was used intraoperatively and during the first 16 hours after the operation. Diltiazem (100 mg/day) or amlodipine (2.5–5.0 mg/day) was then administered orally, together with aspirin, beginning the following morning. Preoperative medications, shown in Table 1, were basically resumed postoperatively, as long as they were hemodynamically tolerated.

Measurement of plasma NT-pro-BNP

Blood samples were drawn just before surgery. The samples were centrifuged, and plasma was frozen at −80 centigrade degree until assay. An electrochemiluminescence immunoassay kit (Dimension, the Dade Behring, Siemens, Munich, Germany) was used to measure NT-pro-BNP. The method is a sandwich-type quantitative immunoassay based on polyclonal antibodies against epitopes in the N-terminal part of pro-BNP. The lower detection limit was 10 pg/ml. Assays were performed by a laboratory technician blinded to the patients’ clinical data.

Monitoring and follow-up

All medical records, including electrocardiograms and telemetry strips, were reviewed. All patients were monitored with telemetry for at least 1 week, postoperatively. Postoperative AF was defined as an acute and sustained episode (over 10 minutes) requiring intervention. Diagnosis of AF was confirmed by an independent cardiologist. Initial data were collected from the medical records. Institutional approval for this study was obtained, and each patient within the study gave informed consent for serving as a subject.

Statistical analysis

All values are expressed as the mean ± SD or percentages. Differences between patient groups were tested by univariate analysis (χ² test, 2-tailed t-test, Fisher’s exact test, or Mann-Whitney U test as appropriate). Findings of P < 0.05 were considered significant. A logistic
regression model was used to determine predictors of postoperative AF, based on the baseline characteristics. The odds ratio analysis was carried out with Logistic regression model using the threshold of high quartile. Factors that had a P value <0.2 in univariate analysis were proceeded to a logistic regression model. All analyses were performed using SAS statistical software® (version 8.02, SAS Institute Inc., Cary, New Carolina, USA).

**Results**

Thirty six patients developed new-onset AF (36%). Preoperative variables are displayed in Table 2. Age was more advanced in group AF (70.8 ± 8.7) than in group SR (66.7 ± 8.5), P = 0.025. Distribution of age is described in Fig. 1. High quartile of age was 75 years old. Gender distribution was not different between groups (AF 83.3% vs. SR 84.4%, P = 0.99). Number of diseased vessels was not different between groups (SR 2.26 ± 0.78 vs. SR 2.52 ± 0.65, P = 0.22), but there were more emergencies in group AF (22.2%) than in group SR (10.9%), P = 0.15. Preoperative left ventricular ejection fraction (AF 60.9 ± 11.13% vs. SR 57.9 ± 10.6%, P = 0.23), the percentage of left main disease (AF 42% vs. SR 39%, P = 0.84), triple vessel disease (AF 61% vs. SR 48%, P = 0.30) or acute myocardial infarction (AF 2.8% vs. SR 1.7%, P = 0.99) were not different between groups. The prevalence of diabetes mellitus (AF 33% vs. SR 50%, P = 0.26), hypertension (AF 78% vs. SR 78%, P = 0.99), and dyslipidemia (AF 66% vs. SR 66%, P = 0.99) were not different between groups. Preoperative laboratory data are also shown in Table 1. Preoperative NT-pro-BNP was significantly higher in group AF (509.6 ± 641.6 pg/ml) than in group SR (241.1 ± 302.7 pg/ml), P = 0.006. Distribution of NT-pro-BNP is described in Fig. 2. High quartile of NT-pro-BNP was 348 pg/ml. Preoperative serum creatinine level (AF 0.88 ± 0.27 mg/dl vs. SR 0.90 ± 0.23 mg/dl, P = 0.53), e-GFR (AF 69.7 ± 19.5 ml/min vs. SR 66.6 ± 17.5 ml/min, P = 0.43), LDL cholesterol level (AF 106 ± 26 mg/dl vs. SR 110 ± 28 mg/dl, P = 0.53), C-reactive protein level (AF 0.24 ± 0.29 mg/dl vs. SR 0.25 ± 0.61 mg/dl, P = 0.98), and HbAlc level (AF 5.9 ± 1.2 vs. 6.1 ± 1.1, P = 0.42) were not different between groups. Preoperative medications are shown in Table 1. Preoperative administration of statins was relatively greater in group SR (73%) than in group AF (58%) (P = 0.18). Beta blockade (AF 42% vs. SR 50%, P = 0.53), Renin-angiotensin system inhibitors (AF 36% vs. SR 38%, P = 0.99), and Calcium blockade (AF 58% vs. SR 55%, P = 0.83) were not different between groups. Perioperative variables were shown in Table 3. Surgical quality, such as number of anastomosis, blood transfusion rate, or rate of arterial grafting, was not different between groups. Based on these univariate analyses, four factors that

### Table 1 Preoperative medications

<table>
<thead>
<tr>
<th></th>
<th>Group SR (n = 64)</th>
<th>Group AF (n = 36)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>13 (20.3%)</td>
<td>8 (22.2%)</td>
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<tr>
<td>Statin</td>
<td>47 (73.4%)</td>
<td>21 (58.3%)</td>
<td>0.18</td>
</tr>
<tr>
<td>Beta blockade</td>
<td>32 (50%)</td>
<td>15 (41.7%)</td>
<td>0.53</td>
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<tr>
<td>Renin-Angiotensin</td>
<td>24 (37.5%)</td>
<td>13 (36.1%)</td>
<td>0.99</td>
</tr>
<tr>
<td>Calcium channel</td>
<td>35 (54.7%)</td>
<td>21 (58.3%)</td>
<td>0.83</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>45 (70.3%)</td>
<td>26 (72.2%)</td>
<td>0.72</td>
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<tr>
<td>Diuretics</td>
<td>13 (20.3%)</td>
<td>4 (11.1%)</td>
<td>0.28</td>
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</tbody>
</table>

### Table 2 Preoperative variables and laboratory data

<table>
<thead>
<tr>
<th></th>
<th>Group SR (n = 64)</th>
<th>Group AF (n = 36)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>66.7 ± 8.5</td>
<td>70.8 ± 8.7</td>
<td>0.025</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>54 (84.4%)</td>
<td>30 (83.3%)</td>
<td>0.99</td>
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<tr>
<td>Number of</td>
<td></td>
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<tr>
<td>diseased vessels</td>
<td>2.26 ± 0.78</td>
<td>2.52 ± 0.65</td>
<td>0.22</td>
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<td>Emergency</td>
<td>7 (10.9%)</td>
<td>8 (22.2%)</td>
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<tr>
<td>Left ventricular</td>
<td>57.9 ± 10.6</td>
<td>60.9 ± 11.1</td>
<td>0.23</td>
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<tr>
<td>ejection fraction</td>
<td></td>
<td></td>
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<tr>
<td>Left main disease</td>
<td>25 (39.1%)</td>
<td>15 (41.7%)</td>
<td>0.84</td>
</tr>
<tr>
<td>Triple vessel</td>
<td>31 (48.4%)</td>
<td>22 (61.1%)</td>
<td>0.30</td>
</tr>
<tr>
<td>disease</td>
<td>32 (50.0%)</td>
<td>12 (33.3%)</td>
<td>0.26</td>
</tr>
<tr>
<td>Hypertension</td>
<td>14 (21.9%)</td>
<td>8 (22.2%)</td>
<td>0.99</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>20 (31.2%)</td>
<td>12 (33.3%)</td>
<td>0.99</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>3 (4.7%)</td>
<td>0</td>
<td>0.55</td>
</tr>
<tr>
<td>Acute myocardial</td>
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<tr>
<td>infarction (&gt;moderate)</td>
<td>1 (1.7%)</td>
<td>1 (2.8%)</td>
<td>0.99</td>
</tr>
<tr>
<td>Mitral regurgitation</td>
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<tr>
<td>HbA1c (%)</td>
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<tr>
<td>CRP (mg/dl)</td>
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<tr>
<td>LDL cholesterol (mg/dl)</td>
<td>110.8 ± 27.9</td>
<td>106.6 ± 25.6</td>
<td>0.47</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>49.9 ± 14.6</td>
<td>50.0 ± 14.2</td>
<td>0.97</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.90 ± 0.22</td>
<td>0.86 ± 0.26</td>
<td>0.46</td>
</tr>
<tr>
<td>e-GFR (ml/min)</td>
<td>66.6 ± 17.5</td>
<td>69.7 ± 19.5</td>
<td>0.43</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dl)</td>
<td>241.1 ± 302.7</td>
<td>509.6 ± 641.6</td>
<td>0.006</td>
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</table>
had a P value of over 0.2 of in the univariate analysis were extracted. They were preoperative administration of statins, emergency, high NT-pro-BNP (>348 pg/ml, high quartile) and advanced age (>75 years old, high quartile). The result of multivariate analysis was displayed in Table 4. The constructed logistic regression model revealed that high NT-pro-BNP (>348 pg/ml, high quartile) was the only predictor of postoperative AF after OPCAB ($P = 0.05$; OR, 2.60; 95% CI 0.96–7.05).

As an additional study, we compared patients who had high NT-pro-BNP (348 pg/ml, high quartile) with control patients (Table 5). In patients with high NT-pro-BNP (348 pg/ml, high quartile), the preoperative ejection fraction was lower, but other preoperative and postoperative variables were not significantly different.

**Discussion**

For patients with coronary artery diseases, CABG has been the gold standard for several decades. The recent technical improvement in percutaneous coronary intervention (PCI) demands better outcomes and less invasiveness in CABG, as well. Recently, OPCAB has been performed in over 60% of all CABG cases, in Japan. Now, OPCAB has become the standard option for coronary artery disease.

AF is a frequent complication of open heart surgery, with a reported incidence that varies from 10% to 50%. Although it is not a critical complication, it is associated with hemodynamic compromise and thromboembolic events such as stroke and may lead to a longer hospital stay and increased costs, which is very important, when OPCAB is compared with PCI.

Many factors are thought to influence the occurrence of postoperative AF following cardiac surgery. Previous authors have tried to disclose the predictor of postoperative, new-onset AF after cardiac surgery. Predictor analysis of postoperative, new-onset AF is very important because it is very beneficial clinically and economically. If we could find a strong predictor of postoperative new-onset AF, we could figure out who is the high risk patient, and treat them with strong and intensive prophylactic therapy, such as ultra short-acting beta blocker. This process will cause a lower incidence of hemodynamic compromise or stroke, which leads to the decrease of hospital stay and medical costs.
BNP measurement has been used in the medical practice of cardiology and cardiac surgery field. Several precious studies have found that pre- and postoperative BNP levels have some sort of prognostic value of late survival or cardiac event. Besides BNP, NT-pro-BNP is the one of the myocardial stress markers which increase by myocardial ischemia or subsequent burdened wall stress caused by increased left ventricular end-diastolic pressure or decreased cardiac output. It is possible to measure NT-pro-BNP in serum, simultaneously with other components. NT-pro-BNP is more stable in serum or plasma, and more useful to judge the severity because the range of the measured level is wide, but the biggest drawback of NT-pro-BNP is that it is more influenced by renal failure. Particularly in patients with severe renal failure, the reliability of NT-pro-BNP as a screening marker was questioned. In this present study, we excluded patients with eGFR <30 ml/min. Many cardiologists have recently focused on NT-pro-BNP for diagnosis and risk stratification of patients with heart failure. Recently, NT-pro-BNP has become the center of attention for cardiac risk stratification for non-cardiac surgeries, such as vascular or general thoracic surgery, as well. NT-pro-BNP is effective in perioperative risk stratification because of the mechanism of NT-pro-BNP release. Vanderhayden M, et al. revealed that NT-pro-BNP is one of the myocardial stress markers, increased by myocardial ischemia or subsequent, burdened wall stress. We hypothesized that the preoperative NT-pro-BNP level can predict postoperative new-onset AF, which can be influenced by wall stress too. Sabatine, et al. described that in patients with coronary artery ischemia, the level of NT-pro-BNP is correlated with the severity of coronary artery disease, but in our study, the severity of coronary artery disease or quality of CABG was the same in AF and SR groups. So, we still emphasize that NT-pro-BNP can be useful, regardless of the severity of coronary artery disease.

Several authors have described that an advanced age is the strongest predictor of the postoperative new-onset AF after cardiac surgery. Others have described that preoperative statin treatment could reduce the incidence of postoperative AF following CABG. Our study has also shown that advanced age and preoperative statin treatment might be predictors of postoperative new-onset AF, but NT-pro-BNP could be a stronger predictor of postoperative AF.

<table>
<thead>
<tr>
<th>Table 5 Characteristics of patients with high NT-pro-BNP</th>
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<tbody>
<tr>
<td><strong>High NT-pro-BNP (≥348 pg/ml) (n = 25)</strong></td>
</tr>
<tr>
<td><strong>Age</strong></td>
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<td><strong>Gender (% male)</strong></td>
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<tr>
<td><strong>Number of diseased vessels</strong></td>
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<tr>
<td><strong>Emergency</strong></td>
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<tr>
<td><strong>Left ventricular ejection fraction</strong></td>
</tr>
<tr>
<td><strong>Left main disease</strong></td>
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<tr>
<td><strong>Triple vessel disease</strong></td>
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<tr>
<td><strong>Diabetes Mellitus</strong></td>
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<tr>
<td><strong>Hypertension</strong></td>
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<tr>
<td><strong>Dyslipidemia</strong></td>
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<tr>
<td><strong>Peripheral vascular disease</strong></td>
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<tr>
<td><strong>Acute myocardial infarction</strong></td>
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</table>

**Preoperative data**

| **Creatinine (mg/dl)** | 0.88 ± 0.21 | 0.89 ± 0.30 | 0.85 |
| **e-GFR (ml/min)** | 68.3 ± 23.4 | 67.5 ± 16.3 | 0.86 |
| **HDL cholesterol (mg/dl)** | 47.5 ± 11.8 | 50.7 ± 15.1 | 0.42 |
| **LDL cholesterol (mg/dl)** | 104.0 ± 23.7 | 110.9 ± 27.9 | 0.28 |
| **CRP (mg/dl)** | 0.45 ± 0.92 | 0.22 ± 0.23 | 0.07 |
| **HbA1c (%)** | 6.15 ± 1.27 | 5.94 ± 1.08 | 0.43 |
| **Preop left ventricular diastolic diameter (mm)** | 48.7 ± 6.4 | 46.3 ± 6.0 | 0.18 |
| **Preop left ventricular systolic diameter (mm)** | 34.1 ± 8.4 | 30.6 ± 7.2 | 0.12 |
| **Preop left atrial diameter (mm)** | 37.7 ± 1.2 | 36.0 ± 5.4 | 0.53 |
| **Preop trans-tricuspid pressure gradient (mmHg)** | 21.2 ± 4.6 | 22.0 ± 5.5 | 0.69 |

**Preoperative data**

| **Postop CK-MB (ng/ml)** | 36.6 ± 27.6 | 27.4 ± 33.4 | 0.49 |
| **Postop Troponin I (ng/ml)** | 25.6 ± 17.6 | 20.9 ± 33.7 | 0.72 |
predictor than advanced age or preoperative statin treat-
mant as we have proved.

Several previous authors have tried to prove sim-
ilar results. Akazawa, et al. have described that the
preoperative BNP level is an independent predictor of 
postoperative AF, following OPCAB.33) Gasparovic H,
et al. have reported on predictor analysis of postope-
ratve AF following conventional CABG. They concluded 
that preoperative NT-pro-BNP, duration of cardiopul-
monary bypass and advanced age were the independent 
predictors.34) Iskesen I, et al. reported the same situ-
ation and concluded the positive correlation between 
high levels of preoperative NT-pro-BNP and risk of 
new-onset AF after conventional CABG.35) Kerbau F
reported that preoperative and postoperative NT-pro-
BNP levels after OPCAB could predict cardiovascular 
complications.36)

The speculation on the reason why high NT-pro-BNP
is most sensitive, predictive marker for the incidence 
of new-onset AF is still unclear. As we have shown in 
Table 5, other factors related to myocardial stress, such 
as myocardial stress markers, preoperative left atrial 
diameter, and trans tricuspid pressure gradient, were not 
different between high NT-pro-BNP patients and the 
control. Although only NT-pro-BNP level was the 
predictor of AF in this study, these other stress markers 
could be predictors of AF, if large numbers of patients 
were enrolled.

This current study is the first report that NT-pro-BNP 
can predict the postoperative new-onset AF following 
OPCAB, independently. The study result showed that 
NT-pro-BNP levels higher than 348 pg/ml effectively 
stratify patients as high risk, independent of the postope-
ratve new-onset AF. Hence, high NT-pro-BNP might 
be useful as an initial screening tool to identify patients 
who is beneficial by a more extensive, intensive, and 
aggressive prophylactic therapy against AF.

Limitation

There were several limitations in the present study. 
We examined a small number of patients in only 
a single institution in a nonrandomized, retrospective 
fashion. We cannot exclude the possible bias caused by 
institutional standards and the patient population, and 
we used a threshold of high quartile in this present 
study. The ROC (Receiver Operating Characteristic) 
curve should be better employed to make a precise 
threshold, but the distribution of NT-pro-BNP level was 
not equal among patients. We believed that, for the 
clinical feedback, to make a threshold and compare 
the high level group and control group would still be 
informative for this study. So we used the high quartile 
as a threshold.

Conclusions

The high preoperative level of NT-pro-BNP could 
predict the incidence of postoperative new-onset AF 
after OPCAB. Further larger studies are required to 
establish the usefulness and limitations more precisely.

Disclosure Statement

No conflict of interest.

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