**Difference in Elevation of N-Terminal Pro-BNP and Conventional Cardiac Markers Between Patients With ST Elevation vs Non-ST Elevation Acute Coronary Syndrome**

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**Background** N-terminal pro-B-type natriuretic peptide (NT-proBNP) is elevated in patients with acute coronary syndrome (ACS), and is a powerful predictor of long-term mortality. Differences in the clinical utility and pathophysiological implication of NT-proBNP and conventional cardiac markers in patients with ST elevation (STE) vs non-STE (NSTE) ACS were investigated in the present study.

**Methods and Results** Ninety consecutive patients admitted with acute chest pain and a diagnosis of unstable angina or acute myocardial infarction were analyzed. Patients with ≥Killip class II were excluded to focus on the effect of myocardial ischemia on the release of cardiac markers. The markers were measured on admission and analyzed according to the time from onset. Conventional cytosolic marker (creatine kinase-MB) and myofibril marker (troponin T; TnT) were both significantly higher in STE-ACS patients compared with NSTE-ACS patients. Conversely, NT-proBNP was significantly higher in NSTE-ACS patients than STE-ACS especially within 3 h of onset, suggesting a larger ischemic insult despite the smaller extent of myocardial necrosis compared with STE-ACS patients. There was no significant correlation between NT-proBNP level and left ventricular ejection fraction (LVEF) obtained at acute-phase echocardiography in either NSTE-ACS patients (LVEF 57.7±11.2%) or STE-ACS patients (LVEF 55.1±12.7%). Comparison between NT-proBNP and TnT levels revealed a marked difference of elevations, with significantly augmented elevation of NT-proBNP (p<0.001) in NSTE-ACS patients as compared with prominent elevation of TnT in STE-ACS patients.

**Conclusions** NT-proBNP is an early sensitive marker of myocardial ischemia that rises much higher in the earlier phase as compared with conventional markers of myocardial damage, especially in NSTE-ACS patients.

(Circ J 2006; 70: 1372–1378)

**Key Words:** Acute coronary syndrome; Myocardial infarction; Myocardial ischemia; Natriuretic peptides; Troponin

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B-type natriuretic peptide (BNP) is a cardiac neurohormone predominantly secreted by the ventricles in response to increased myocardial stretch or wall tension. Pro-BNP is synthesized as a pro-hormone by cardiac myocytes, and undergoes enzymatic cleavage to produce N-terminal pro-BNP (NT-proBNP) and BNP. It has been reported that the serum level of NT-proBNP is elevated in patients with left ventricular (LV) dysfunction and shows a close correlation with the BNP level. We recently reported that the absolute increment of NT-proBNP exceeds that of BNP, and that NT-proBNP would be a more discerning marker for the detection and evaluation of cardiac dysfunction than BNP. Furthermore, recent clinical trials have shown that NT-proBNP is elevated in patients with acute coronary syndrome (ACS), and is a powerful predictor of both short and long-term mortality.

The pathophysiology of ACS involves disruption of vulnerable plaque and thrombus formation, which produces severe myocardial ischemia and downstream embolization in the coronary vascular bed, leading to subendocardial or transmural necrosis. The clinical spectrum of ACS consists of ST elevation (STE) myocardial infarction (MI) (STEMI) and non-STE (NSTE) MI (NSTEMI) or unstable angina (UA), which are classified from the acute phase electrocardiography (ECG) changes and the development of myocardial necrosis. STEMI is caused by acute total coronary occlusion, whereas NSTEMI is associated with vulnerable plaque and subocclusive thrombosis. Novel cardiac markers, such as troponin T (TnT), and creatine kinase (CK)-MB isozyme, detect the development of minor myocardial necrosis, and have emerged as powerful predictors of risk in patients with ACS. The present study investigated differences in the secretion of NT-proBNP and conventional cardiac markers in patients with STE-ACS vs NSTE-ACS.

**Methods**

**Patients**

One hundred and sixty-five consecutive patients admitted to the coronary care unit of Nippon Medical School Hospital...
(Tokyo, Japan) from April 1999 to September 1999 because of acute chest pain or dyspnea were eligible for the present study. The inclusion criteria were a diagnosis of ACS, defined as UA according to Braunwald’s classification or acute MI (AMI) according to the redefined ESC/ACC Committee criteria. The exclusion criteria were patients who had cardiopulmonary resuscitation before admission, presence of overt pump failure (≥Killip class II) in order to focus on the effect of myocardial ischemia per se on the release kinetics of NT-pro-BNP, or a serum creatinine level >2.0 mg/dl. All patients underwent standard 12-lead ECG immediately after admission, and blood samples were taken for biochemical measurements. The patients were classified into STE and NSTE groups based on the ECG findings on admission.

As demographic data, the history of hypertension, hyperlipidemia, diabetes mellitus (DM), and previous MI were investigated on admission. Echocardiography was performed within 24 h of admission to assess LV function. Undergoing percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) during hospitalization was investigated in all patients.

Of the 165 patients, 62 were excluded because they had non-ACS etiology (pneumonia, chronic obstructive pulmonary disease, esophageal or gastric disorders, congestive heart failure, acute aortic dissection, or stable angina) and another 13 patients fulfilled one or more of the exclusion criteria, thus 90 patients were analyzed in the present study.

**Diagnostic Criteria for STE-ACS and NSTE-ACS**

Patients with ST segment elevation at the J point in 2 or more consecutive leads (with the cut-off point being >0.2 mV in leads V1, V2, or V3, and >0.1 mV in the other leads) were defined as having STE-ACS. Patients with bundle-branch block were included in this group. Patients with ST segment depression, T wave inversion, or no ECG abnormalities were defined as having NSTE-ACS.

**Blood Sampling**

After informed consent was obtained, blood was collected on admission by direct venipuncture of an antecubital vein while the patient was supine. Blood samples were collected into tubes containing EDTA and centrifuged within 30 min, after which plasma CK-MB was measured by an immuno-inhibition assay (NAC, Merck, Darmstadt, Germany), and cardiac TnT levels were measured by an electrochemiluminescence assay (Elecsys 2010, Roche Diagnostics, Germany). Simultaneously obtained plasma was stored at −80°C until analysis of NT-proBNP. Plasma levels of NT-proBNP were measured by an electrochemiluminescence assay (Elecsys 2010) within 2 years of sample collection.

**Echocardiography**

Transthoracic 2-dimensional echocardiography was performed within 24 h of admission by an experienced cardiologist. The LV end-diastolic and end-systolic diameters were measured according to the guidelines of the American Society of Echocardiography. The LV ejection fraction (LVEF) was calculated by the modified Simpson’s method in all 38 STE-ACS patients and 12 of the 52 NSTE-ACS patients, and by the Teichholz’s method in other NSTE-ACS patients with a homogeneous contraction pattern.

**Statistical Analysis**

The NSTE-ACS and STE-ACS groups were compared by the Mann-Whitney U test. The cardiac markers were expressed as medians with interquartile ranges, and other continuous variables were expressed as mean±standard deviation. Differences of percentages were compared by the chi-square test. The cardiac marker and NT-proBNP levels on admission were grouped according to the time from onset of chest pain to presentation at hospital, after which the values were compared between NSTE-ACS and STE-ACS patients. Linear regression analysis was done and correlation coefficients were calculated to assess the relationships between NT-proBNP and CK-MB, TnT, or LVEF. Comparison of 2 regression lines, slopes and intercepts, was performed to reveal the difference in NT-proBNP and TnT elevations between NSTE-ACS and STE-ACS patients. A p-value less than 0.05 was considered statistically significant.

**Results**

**Demographic Data**

The profiles of the NSTE-ACS and STE-ACS groups are shown in Table 1. The mean age was 63.3±10.7 years and 65 patients (72.2%) were men. Of the 90 patients, 52 (57.8%) had NSTE-ACS and 38 (42.2%) had STE-ACS. There were no differences in age, gender, hyperlipidemia, DM or previous MI between the 2 groups, but the prevalence of hypertension was significantly higher in NSTE-ACS patients compared with STE-ACS patients (p<0.01).

Seventy-one patients had a final diagnosis of AMI according to the redefined ESC/ACC criteria and 19 patients had UA. In the NSTE-ACS group, 35 patients (67.3%) had AMI and 17 patients (32.7%) had UA. In the STE-ACS group, 36 patients (94.7%) had AMI and 2 patients (5.3%) had UA (Table 2). There was no significant difference in the LVEF between NSTE-ACS patients (57.7±11.2%) and STE-ACS patients (55.1±12.7%) because we excluded patients with pump failure (≥Killip class II) in the present study to focus on the effect of myocardial ischemia per se.
Emergency coronary angiography was performed within 24 h of admission in 43 patients (82.7%) from the NSTE-ACS group and 35 patients (92.1%) from the STE-ACS group. There was no significant difference in the severity of coronary artery disease between the 2 groups. PCI was performed within 48 h of coronary angiography in 26 patients (50.0%) of NSTE-ACS and in 28 patients (73.7%) of STE-ACS, so the proportion of PCI was significantly higher in the STE-ACS group (p<0.05). CABG was performed in 9 patients with NSTE-ACS vs 5 patients with STE-ACS, and there was no significant difference.

Cardiac Markers

Conventional Cardiac Markers (CK-MB, TnT) The CK-MB levels on admission were significantly higher in the STE-ACS patients than the NSTE-ACS patients (median level 18.5 IU/L [10.0–61.0 IU/L] vs 10.5 IU/L [interquartile range, 6.0–20.5 IU/L], p=0.0032) (Fig 1a). Similarly, TnT levels on admission were also significantly higher in the STE-ACS patients compared with NSTE-ACS patients (0.499 ng/ml [0.07–2.89] vs 0.147 ng/ml [0.01–0.68], p=0.0268) (Fig 1b). When the time from onset to presentation was divided into 3-h intervals, the median CK-MB level was 10.5 IU/L [7.5–13.0 IU/L] at 0–3 h, 9.5 IU/L [6.0–20.0 IU/L] at 3–6 h, 9.0 IU/L [6.5–19.3 IU/L] at 6–9 h, and 15.0 IU/L [10.5–23.3 IU/L] at 9–12 h in the NSTE-ACS group, while the median TnT level was 0.01 ng/ml [0.01–0.14 ng/ml], 0.07 ng/ml [0.01–0.18 ng/ml], 0.13 ng/ml [0.05–0.90 ng/ml], and 0.30 ng/ml [0.10–1.04 ng/ml], respectively. In the STE-ACS group, the median CK-MB level was 15.0 IU/L [8.5–27.5 IU/L], 18.0 IU/L [9.5–49.0 IU/L], 32.0 IU/L [12.0–135.7 IU/L], and 32.0 IU/L [7.5–75.0 IU/L], respectively, while the median TnT level was 0.44 ng/ml [0.03–1.35 ng/ml], 0.09 ng/ml [0.03–0.98 ng/ml], 3.35 ng/ml [0.13–6.11 ng/ml], and 0.75 ng/ml [0.03–2.87 ng/ml], respectively. The conventional cardiac markers tended to be higher in the STE-ACS patients compared with NSTE-ACS patients at any time; however this did not reach statistical significance (Figs 2a,b).

NT-ProBNP Unlike the conventional cardiac markers, the NT-proBNP level on admission was significantly higher in the NSTE-ACS patients compared with STE-ACS pa-

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Table 2  Demographic Data of Patients With NSTE-ACS and STE-ACS

<table>
<thead>
<tr>
<th></th>
<th>NSTE-ACS (n=52)</th>
<th>STE-ACS (n=38)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unstable angina, n (%)</td>
<td>17 (32.7)</td>
<td>2 (5.3)</td>
<td></td>
</tr>
<tr>
<td>Acute myocardial infarction, n (%)</td>
<td>35 (67.3)</td>
<td>36 (94.7)</td>
<td></td>
</tr>
<tr>
<td>Anterior</td>
<td></td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Inferior/lateral</td>
<td></td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>57.7±11.2</td>
<td>55.1±12.7</td>
<td>NS</td>
</tr>
<tr>
<td>ECG findings</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>ST elevation, n</td>
<td>0</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>ST depression, n</td>
<td>25</td>
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</tr>
<tr>
<td>T wave inversion, n</td>
<td>29</td>
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<tr>
<td>No abnormal findings on ECG</td>
<td>4</td>
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<tr>
<td>Bundle branch block, n</td>
<td>0</td>
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</tr>
<tr>
<td>Q wave, n</td>
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<td>4</td>
<td></td>
</tr>
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<td>Coronary angiography, n (%)</td>
<td>43 (82.7)</td>
<td>35 (92.1)</td>
<td>NS</td>
</tr>
<tr>
<td>RCA, n</td>
<td>19</td>
<td>20</td>
<td>NS</td>
</tr>
<tr>
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<td>23</td>
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<td>2-vessel disease, n</td>
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<td>10</td>
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<tr>
<td>3-vessel disease, n</td>
<td>11</td>
<td>7</td>
<td>NS</td>
</tr>
<tr>
<td>Early PCI, n (%)</td>
<td>26 (50.0)</td>
<td>28 (73.7)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>CABG, n (%)</td>
<td>9 (17.3)</td>
<td>5 (13.2)</td>
<td>NS</td>
</tr>
</tbody>
</table>

ECG, electrocardiogram; RCA, right coronary artery; LAD, left anterior descending artery; LCX, left circumflex artery; PCI, percutaneous intervention; CABG, coronary artery bypass grafting. Other abbreviations see in Table 1.
patients (median level 758 pg/ml [interquartile range, 206–2,158 pg/ml] vs 208 pg/ml [94–699 pg/ml], p=0.0031) (Fig 1c). When NT-proBNP levels were assessed according to the time from onset to presentation, the median plasma level was 1,976 pg/ml [489–3,097 pg/ml] at 0–3 h, 488 pg/ml [193–1,410 pg/ml] at 3–6 h, 816 pg/ml [207–1,663 pg/ml] at 6–9h and 838 pg/ml [74.4–2,207 pg/ml] at 9–12 h in the NSTE-ACS group, while the respective values were 98 pg/ml [40.2–216 pg/ml], 161 pg/ml [99–246 pg/ml], 540 pg/ml [99–1,460 pg/ml], and 699 pg/ml [187–1,440 pg/ml], in the STE-ACS group (Fig 2c). When the values for each time period were compared, NT-proBNP levels were significantly higher in the NSTE-ACS patients within 3 h of onset (0–3 h: NSTE-ACS vs STE-ACS, p=0.0132), and showed a tendency to be higher in patients admitted between 3 to 6 h of onset (p=0.0587), whereas there were no significant differences between the 2 groups after this time.

Correlations Between NT-ProBNP and Conventional Markers or LVEF

When the relationships between NT-proBNP and conventional markers were examined in the NSTE-ACS group, no significant correlation was found between NT-proBNP and CK-MB, but a significant positive correlation was observed between NT-proBNP and TnT (r=0.363, p=0.008) (Table 3). Similarly, there was no correlation between NT-proBNP and CK-MB levels in the STE-ACS group, but a significant positive correlation was observed between NT-proBNP and TnT (r=0.474, p=0.003). When both groups were combined, a significant correlation was observed between NT-proBNP and TnT (r=0.273, p=0.010). There was no significant correlation between NT-proBNP and the

![Fig2. Comparison of cardiac markers in patients with (\^) non-ST elevation acute coronary syndrome (NSTE-ACS) and (\._) ST elevation acute coronary syndrome (STE-ACS) according to the time from onset to presentation divided into 3-h intervals. (a) CK-MB, creatine kinase-MB isozyme; (b) TnT, troponin T; (c) NT-proBNP, N-terminal pro-B-type natriuretic peptide.](image)
LVEF obtained at acute-phase echocardiography in either the NSTE-ACS or STE-ACS groups.

When the correlation between NT-proBNP and TnT was analysed (Fig 3), values for NSTE-ACS patients were distributed in the upper left region ($y = 717x + 837; r^2 = 0.340$), whereas the values for STE-ACS patients were clustered in the lower right region ($y = 253x + 247; r^2 = 0.225$). Comparison of the 2 regression lines revealed statistically significant difference in the slopes ($t = 2.846, p < 0.001$). The intercepts did not show significant difference.

**Discussion**

**Differences Between NSTE-ACS and STE-ACS Patients**

In the present study, CK-MB and TnT levels were higher in STE-ACS patients than in NSTE-ACS patients, whereas NT-proBNP was significantly higher during the early acute phase in the NSTE-ACS group than in the STE-ACS group. CK-MB is a marker of cytosolic damage that reflects the area at risk and the resultant size of the infarct.$^{28}$ Whereas TnT is a marker of myofibril damage and is elevated in proportion to infarct size per se.$^{29,30}$ Thus, the STE-ACS group with transmural infarction had a larger infarct size than the NSTE-ACS group. In contrast, NT-proBNP was higher in NSTE-ACS patients than in STE-ACS patients despite lower values of the conventional cardiac markers. We excluded patients with pump failure greater than Killip class II, which suggests that factors other than infarct size or pump failure had a fundamental influence on the elevation of NT-proBNP. In NSTE-ACS patients, the NT-proBNP values were significantly higher than would be expected from the TnT levels in the STE-ACS patients; NT-proBNP levels were clustered in the upper left region of the graph, unlike the TnT levels (Fig 3). The 2 regression lines revealed a marked difference in the elevations, with a significantly augmented elevation of NT-proBNP ($p < 0.001$) in NSTE-ACS patients as compared with prominent elevation of TnT in STE-ACS patients, again indicating the possibility that factors other than infarct size were more influential in NSTE-ACS patients.

**Ischemic Insult and NT-ProBNP Elevation**

The analyses according to the time-windows clarified this finding more obviously; that is, in NSTE-ACS patients the NT-proBNP level was significantly higher (almost 20-fold higher) than in the STE-ACS patients within 3 h of onset, and showed a tendency to be higher between 3 to 6 h of onset. Although the present study did not analyze sequential changes in the markers in each patient, these findings suggest the possibility of there being a larger ischemic insult in the earlier phase in NSTE-ACS patients regardless of the degree of myocardial necrosis, compared with that in STE-ACS patients.

Galvani et al reported similar findings in their multicenter study of patients with ACS.$^{31}$ The elevation of NT-proBNP was much higher in the NSTE-ACS patients than in the STE-ACS patients (506 pg/ml vs 201 pg/ml) in their study as well. Interestingly those values are almost consistent with our data: 758 pg/ml vs 258 pg/ml, respectively. Such early increases would reflect the amount of ischemic insult to the myocardium rather than the actual extent of myocardial damage or degree of heart failure.$^{32,33}$ Thus, myocardial ischemia per se could be another mechanism leading to elevation of NT-proBNP, besides the presence of ventricular dysfunction. It could be also possible that early NT-proBNP elevation in NSTE-ACS patients may reflect the consequences of repeated episodes of myocardial ischemia, both symptomatic and asymptomatic, occurring in the past several hours or days.

Goez et al$^{34}$ analyzed the effect of acute myocardial hypoxia on cardiac BNP gene expression and peptide release using a porcine model with low oxygen delivery to the LV myocardium. They found a robust increase in the BNP mRNA content and an augmented increase in the immature BNP pre-mRNA content in the hypoxic myocardium after 2 h of hypoxia. Furthermore, they confirmed the increase in premature BNP mRNA in freshly harvested ventricular myocytes kept in oxygen-deprived culture flasks, and accumulation of proBNP peptide in the culture medium. Their study results strongly suggest that acute myocardial hypoxia/ischemia per se stimulates BNP expression and release of newly synthesized proBNP peptide.

In the present study, NT-proBNP levels were markedly elevated in ACS patients, especially in the NSTE-ACS group. Taken together with the previous results, NT-proBNP could be an early sensitive marker of myocardial ischemia that rises much higher than be expected than the TnT levels in NSTE-ACS patients, and even in the absence of heart failure.

**Relationship Between Cardiac Function and TnT or NT-ProBNP**

We previously reported a significant correlation between the TnT level and the wall motion score during the acute phase of AMI$^{35}$ and a correlation between the TnT level and LVEF was also found in the present study ($R = –0.268, p = 0.02$). However, there was no correlation between NT-proBNP and LVEF. In patients with heart failure, we have reported that NT-proBNP and BNP show a progressive increase in proportion to the New York Heart Association.
Clinical Implications and Study Limitations

The present study demonstrated that NT-proBNP is significantly higher during the hyper acute phase in NSTE-ACS patients, and is not raised by the process of myocardial necrosis but by the ischemic insult per se. Our results suggest that the release kinetics of cardiac markers, especially NT-proBNP, in patients with NSTE-ACS differ from those in STE-ACS patients. It is conceivable that the ischemic area or the area at risk show a different spectrum in these 2 groups. To elucidate the difference, comparison by radioisotope or positron emission tomography assessment during the acute phase would be necessary. As another possibility, it must be taken into consideration that patients with pump failure (2Killip class II) were excluded from the present study, and analysis was confined to uncomplicated ACS (Killip class I). Thus, the present study did not assess the dynamic changes of NT-proBNP synthesis/secretion during the process from the onset of ischemia to the development of pump failure. Further studies are needed to elucidate the possible differences in the prognostic implication of NT-proBNP between NSTE-ACS and STE-ACS patients.

Acknowledgement

The authors thank Dr Masahiro Yasatake for his kind support of statistical analyses.

References

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