Biochemical risk assessment and invasive strategies for acute coronary syndromes without ST-segment elevation
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Chapter 5

NT-ProBNP serum levels reflect severity and extent of ischemia in patients admitted with non-ST-elevation acute coronary syndrome

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ABSTRACT

Objective:
To explore the relationship between NT-proBNP elevation and prognosis in patients with NSTE-ACS.

Background:
High NT-proBNP levels are related to a worse prognosis in patients with ACS. The precise mechanism by which is not clear.

Methods:
Serial sampling of NT-proBNP, Troponin T and CK-MB was performed in 23 patients admitted with NSTE-ACS. Using coronary angiography in each patient a culprit lesion was identified. Proximal lesions were located before or at the first major branch of the parent artery. All other lesions localizations were considered distal. To evaluate the influence of left ventricular systolic function on NT-proBNP levels WMSI was measured by echocardiography.

Results:
Proximal culprit lesion localization was associated with significant higher baseline (mean 506 ng/l, SD 440 ng/l) and peak NT-proBNP levels (mean 1055 ng/l; SD 236 ng/l), as compared to patients with a distal lesion localization. (Baseline: 139 ng/l, SD 140 ng/l, peak: 381 ng/l; SD 64 ng/l). (P = 0.01) NT-proBNP levels were highly correlated to Troponin T and CK-MB peak serum levels. Adjustments for left ventricular dysfunction did not alter these associations.

Conclusions
High peak NT-proBNP levels are independently associated with both proximal culprit localization and elevated biochemical markers of myocardial damage. These findings suggest that NT-proBNP levels reflect the amount of jeopardized myocardium and could signify the integral of the extent and severity of an ischemic event.
NT-ProBNP serum levels reflect severity and extent of ischemia in patients with NSTEACS

INTRODUCTION

Risk assessment of patients with non-ST-elevation acute coronary syndrome (NSTEACS) plays an important role in determining prognosis and clinical decision-making. Besides well-known risk predictors as medical history, physical examination findings, ECG changes, cardiac Troponin levels, and inflammation markers such as high sensitive C-reactive protein (HS-CRP), there is growing evidence that N-terminal pro brain natriuretic peptide (NT-ProBNP) and brain natriuretic peptide (BNP) are powerful predictors of prognosis.1–7

Former studies have suggested that myocardial ischemia augments the synthesis and release of B-type natriuretic peptide, even in the absence of myocardial necrosis or pre-existing left ventricular dysfunction.1–2,4 It has recently been shown that ventricular brain natriuretic peptide (BNP) gene expression is upregulated by myocardial hypoxia, providing increased plasma concentrations of BNP and NT-proBNP.8

In patients with NSTE-ACS, this results in an increased NT-proBNP concentration with peak levels at 16–24 h after admission. In addition, the secretion of NT-proBNP has a strong individual variation which is generally most pronounced in the same timeframe.9 It is currently unclear whether the considerable inter-individual differences of NT-proBNP levels in patients with NSTE-ACS are associated with the degree of myocardial ischemia, as was recently reported for BNP in patients with stable anginal complaints.10

A recent sub study of the TACTICS-TIMI-18 (treat angina with Aggrastat and determine cost of therapy with an invasive or conservative strategy – thrombolysis in myocardial infarction – 18) trial showed that elevated BNP levels at admission were associated with tighter culprit stenosis and left anterior descending coronary artery (LAD) involvement.11 However, the dynamic behavior of BNP was not taken into account.

The present study was designed to explore whether NT-ProBNP peak concentrations, measured by serial sampling, are related to the extent and severity of myocardial ischemia.
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METHODS

Study design and patient population
Patients with NSTE-ACS, admitted to the coronary care unit of the Onze Lieve Vrouwe Gasthuis, Amsterdam, the Netherlands, were screened for the study. Informed consent was obtained from all study participants. The inclusion criteria were: age > 21 years; onset of chest pain within the last 6 h and either ST-depression > 2 mm in two contiguous leads and/or elevated Troponin levels upon admission (cut-off 0.05 ng/l).

The main exclusion criteria were, ischemia unrelated to coronary artery disease; a known history of – or existing congestive heart failure; contraindication for coronary angiography, known or suspected left ventricular hypertrophy; acute myocardial infarction requiring immediate reperfusion therapy and percutaneous coronary intervention (PCI) within the past 14 days.

Blood sampling procedures
Peripheral blood samples (Li-heparin, Becton Dickinson) for plasma NT-proBNP, Troponin T and CK/CK-MB determination were obtained at 0, 8, 16, 24 and 36 h after admittance. All samples were stored at 2–8°C within 2 h and transferred to a −20°C freezer within 24 h after blood withdrawal until analyzed.

Assay of NT-proBNP, CK-MB and Troponin T
The immunoassays for NT-proBNP and Troponin T were performed on an Elecsys 1010 chemiluminescence analyzer (Roche Diagnostics, Mannheim, Germany). The creatinine kinase-MB (CK-MB) activity was analyzed on a Modular-Analytics (Roche Diagnostics, Mannheim, Germany). The specifications, analytical performance, and precision of the NT-proBNP12, Troponin T13 and CK-MB14 assays have been described previously.

Coronary angiography
During admission, coronary angiography was performed after obtainment of the last blood sample (36 h after admittance) using standard percutaneous techniques via
the radial or femoral arteries. At least two representative, preferably orthogonal views were made before PCI was performed. The physician performing the procedure was asked to identify one culprit lesion based on clinical, electrocardiographical, and angiographic findings. Localization of the culprit lesion was estimated by the use of predefined anatomic coronary segments. Proximal lesions were located before or at the first major branch of the parent artery. All other lesions were regarded as distal lesions.

**Echocardiography**

Segmental myocardial function was assessed by transthoracic echocardiography using a Vingmed, system five, imaging system (Horten, Norway). Left ventricular wall motion index, a regional measurement of left ventricle systolic dysfunction (which correlates to left ventricular ejection fraction by radionuclide cardiography and invasive ventriculography), were calculated using a sixteen-segment model. Segments were graded semi quantitatively on a 4-point scoring system (1, normal; 2, hypokinesis; 3, akinesis; and 4, dyskinesis). As described previously, left ventricular systolic dysfunction was defined as a left ventricular wall motion index \( \geq 1.2 \).

**Myocardial infarction**

Non ST-elevation myocardial infarction (NSTEMI) was defined as an elevated CK-MB rising 2 times above the upper limit of normal in at least one sample, in the absence of ST-elevation.

**Statistical analyses**

All patients included in the study were included in the analysis. Descriptive statistics and/or patient data listings were used to summarize the data collected. Continuous variables were summarized using means, standard deviations, medians, inter-quartile ranges, minimum and maximum values. Categorical variables were described using frequencies and percentages. Categorical variables were compared by using the \( \chi^2 \) test for proportions and continuous variables by the Student’s t-test. Changes in NT-proBNP levels over time were analyzed using ANOVA for repeated measures. Where the F value was found to be significant, the data were compared with Dunnett’s
multiple comparison tests. Correlations were assessed using Pearson's correlation coefficients or the Spearman-Rank test as appropriate. Furthermore, a multivariate analysis was performed to evaluate the relationships found between different variables and peak NT-proBNP values. A P-value of 0.05 (two-sided) was used to indicate statistical significant difference.

RESULTS

Patients
From December 2002 to October 2003, 23 patients admitted with NSTE-ACS were included in the study. During the period of blood sampling all patients were treated conservatively. Of the samples, 73% (84/115) was found to be valid in quality and timing of sampling. Of the values missing, most occurred at 24 and 36 h after admittance and was mainly because 9 patients were treated by clinically driven PCI before the last samples could be obtained. The baseline characteristics of the studied population are described in Table 1.

TABLE 1
Baseline clinical characteristics.

<table>
<thead>
<tr>
<th>Variable</th>
<th>n = 23</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
</tr>
<tr>
<td>Mean age, y</td>
<td>66 (±11)</td>
</tr>
<tr>
<td>Female sex (%)</td>
<td>3 (13)</td>
</tr>
<tr>
<td>Inclusion at admittance by: &gt;2mm St depression (%)</td>
<td>13 (57)</td>
</tr>
<tr>
<td>Elevated Troponin T (%)</td>
<td>14 (61)</td>
</tr>
<tr>
<td>Previous medical history</td>
<td></td>
</tr>
<tr>
<td>Diabetes Mellitus (%)</td>
<td>3 (13)</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>7 (30)</td>
</tr>
<tr>
<td>Hypercholesterolemia (%)</td>
<td>9 (39)</td>
</tr>
<tr>
<td>Peripheral vascular disease (%)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Myocardial infarction (%)</td>
<td>6 (26)</td>
</tr>
<tr>
<td>PCI (%)</td>
<td>6 (26)</td>
</tr>
<tr>
<td>CABG (%)</td>
<td>2 (9)</td>
</tr>
</tbody>
</table>

PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting.
During in-hospital follow up, none of the patients died and no ST-elevation myocardial infarctions (STEMI) occurred. None of the patients developed clinical symptoms of heart failure. Sixteen (65%) patients developed elevated troponin T levels of which 6 (30%) patients suffered from a NSTEMI, defined as a CK-MB rise above twice the upper limit of normal (ULN). All patients underwent cardiac catheterization where after 16 (70%) patients were treated with PCI, 4 patients (17%) underwent coronary artery bypass grafting (CABG) and 3 (13%) were treated conservatively.

**Dynamics in NT-proBNP concentration**

A highly dynamic pattern in serial measurements of NT-proBNP was observed. Although an increase in NT-proBNP serum levels already existed 8 h after admittance, it did not reach significance as compared to baseline. The samples obtained 16, 24 and 36 h after admission were all significantly increased as compared to the values at admission ($P<0.01$), generally leading to a more than twofold increase showing peak values at 16–24 h after admittance. (Figure 1)

**FIGURE 1**

**Dynamic variation in NT-proBNP serum levels in patients with NSTE-ACS.**

Values are expressed as mean±standard error of the mean (SEM). *$P<0.01$ compared with values on admission.
Localization of the culprit lesion and NT-proBNP values

In 22 of the 23 patients, a culprit lesion could be identified (Table 2). One patient had no significant coronary lesion at the time of catheterization, assumable due to a coronary spasm or transient coronary thrombus.

### TABLE 2

**Angiographical characteristics.**

<table>
<thead>
<tr>
<th>Characteristics NSTE-ACS group (n = 23)</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAD</td>
<td></td>
</tr>
<tr>
<td>0 vessel</td>
<td>1 (4)</td>
</tr>
<tr>
<td>1 vessel</td>
<td>5 (22)</td>
</tr>
<tr>
<td>2 vessel</td>
<td>11 (48)</td>
</tr>
<tr>
<td>3 vessel</td>
<td>6 (26)</td>
</tr>
<tr>
<td>Target vessel</td>
<td></td>
</tr>
<tr>
<td>NA</td>
<td>1 (4)</td>
</tr>
<tr>
<td>LAD</td>
<td>14 (61)</td>
</tr>
<tr>
<td>RCX</td>
<td>5 (22)</td>
</tr>
<tr>
<td>RCA</td>
<td>3 (13)</td>
</tr>
<tr>
<td>Proximal localization of culprit lesion</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>11 (50)</td>
</tr>
<tr>
<td>No</td>
<td>11 (50)</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
</tr>
<tr>
<td>Conservative</td>
<td>3 (13)</td>
</tr>
<tr>
<td>PCI</td>
<td>16 (70)</td>
</tr>
<tr>
<td>CABG</td>
<td>4 (17)</td>
</tr>
</tbody>
</table>

NSTE-ACS, non st elevation acute coronary syndrome; CAD, coronary artery disease; NA, not applicable; LM, left main stem; LAD, left anterior descending; RCX, Ramus circumflex; RCA, right coronary artery; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting.

Using the pre-mentioned discriminating criteria, 11 (50%) patients were considered to have a proximal and 11 (50%) a distal culprit lesion localization. Both baseline and peak NT-proBNP levels were associated with proximal lesion localization. The correlation was equal in strength. For baseline values, patients with proximal lesion site had a mean value of 506 ng/l, SD 440 ng/l whereas patients with distal lesions showed a mean value of 139 ng/l, SD 140 ng/l, (P = 0.01). Regarding NT-proBNP peak values, the group with a proximal culprit lesion showed markedly higher NT-proBNP levels (mean 1055 ng/l; SD 236 ng/l) as compared to the group with a distal lesion localization (mean 381 ng/l; SD 64 ng/l), (P = 0.01), (Figure 2).
NT-ProBNP serum levels reflect severity and extent of ischemia in patients with NSTEACS.

**FIGURE 2**

Proximal localization of the culprit lesion and maximum NT-ProBNP levels.

*One patient was excluded in the analyses because no significant lesion was observed during angiography.

**NT-proBNP levels and left ventricular function.**

It is widely known that BNP and NT-proBNP correlate with left ventricular function. In a stable patient population, high NT-proBNP levels are a powerful predictor for left ventricular dysfunction. The mean wall motion score index (WMSI) of the studied population was 1.15 (minimum 1.0, maximum 1.75, SD 0.20). Eight patients (35%) had left ventricular dysfunction, measured as a WMSI≥1.2. Although patients with left ventricular dysfunction showed higher NT-proBNP peak levels than patients without (1009 ng/l; SD 931 ng/l and 543 ng/l; SD 373 ng/l, respectively) it did not reach significance. (P = 0.2), (Table 3).
**TABLE 3**

<table>
<thead>
<tr>
<th>Clinical subgroup</th>
<th>No. of patients</th>
<th>NT-proBNP peak levels (ng/L)</th>
<th>P-value</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesion site proximal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>11 (50%)</td>
<td>1055, SD 236</td>
<td>$P = 0.01$</td>
<td>$P = 0.005$</td>
</tr>
<tr>
<td>No</td>
<td>11 (50%)</td>
<td>381, SD 64</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSTEMI (CKmb&gt;2×ULN)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>7 (30%)</td>
<td>1240, SD 810</td>
<td>$P = 0.04$</td>
<td>$P = 0.03$</td>
</tr>
<tr>
<td>No</td>
<td>16 (70%)</td>
<td>471, SD 394</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left ventricular dysfunction (WMSI 1.2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>8 (35%)</td>
<td>1009, SD 931</td>
<td>$P = 0.2$</td>
<td>$P = 0.3$</td>
</tr>
<tr>
<td>No</td>
<td>15 (65%)</td>
<td>543, SD 373</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multi-vessel disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>17 (74%)</td>
<td>842, SD 700</td>
<td>$P = 0.01$</td>
<td>$P = 0.1$</td>
</tr>
<tr>
<td>No</td>
<td>6 (26%)</td>
<td>317, SD 140</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Target vessel is LAD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>14 (61%)</td>
<td>756, SD 599</td>
<td>$P = 0.6$</td>
<td>$P = 0.5$</td>
</tr>
<tr>
<td>No</td>
<td>9 (39%)</td>
<td>625, SD 741</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>6 (26%)</td>
<td>846, SD 904</td>
<td>$P = 0.5$</td>
<td>$P = 0.7$</td>
</tr>
<tr>
<td>No</td>
<td>17 (74%)</td>
<td>655, SD 553</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NT-proBNP, N-terminal probrain natriuretic peptide; NSTEMI, non-ST elevation myocardial infarction; CK-mb, Creatinine kinase mb; ULN, upper limit of normal; WMSI, wall motion score index; LAD, left anterior descending; SD, standard deviation.

However, previous myocardial infarction and the occurrence of a proximal culprit lesion were significantly associated with a higher WSMI. Patients with a proximal culprit lesion had a mean WSMI of 1.26 (SD 0.22), while patients with a distal lesion had a WSMI of 1.04 (SD 0.08) ($P<0.005$). Patients with previous AMI showed a mean WMSI of 1.29 (SD 0.27) and those without, a mean WMSI of 1.10 (SD 0.14) ($P = 0.04$).
NT-proBNP values and markers of myocardial necrosis.

Of all the patients, 7 (30%) suffered from NSTEMI. No Q-wave infarctions were observed. The mean concentration of peak levels of CK-MB in this group was 87 U/L (SD 33 U/L). Regarding baseline measurements, there was no significant correlation between NT-proBNP levels and the occurrence of NSTEMI. In patients with NSTEMI, the mean baseline was 429 ng/l; SD 510 ng/l versus 265 ng/l; SD 290 ng/l in the patient group without (P = 0.3). However, the dynamic response in this group was marked, with NT-proBNP peak levels reaching 1240 ng/l; SD 810 ng/l. The group without NSTEMI remained at significantly lower values: 471 ng/l; SD 394 ng/l (P<0.05) (Figure 3). Furthermore, a clear association between peak Troponin T, CK-MB levels and peak NT-proBNP serum levels was detected (Figures 4 and 5).

FIGURE 3
Influence of the occurrence of NSTEMI on NT-proBNP serum concentrations.

*Non ST-elevation myocardial infarction (NSTEMI) was defined as an elevated CK-MB rising above 2 times the upper limit of normal in at least one sample.
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FIGURE 4
Scatterplot of correlation between NT-proBNP and Troponin T peak concentrations.

![Scatterplot of correlation between NT-proBNP and Troponin T peak concentrations.](image)

$n = 23$
$r = 0.715$
$P <0.001$

FIGURE 5
Scatterplot of correlation between NT-proBNP and CK-MB peak concentrations.

![Scatterplot of correlation between NT-proBNP and CK-MB peak concentrations.](image)

$n = 23$
$r = 0.572$
$P <0.01$
Multivariate analyses
Multivariate analyses showed that both proximal localization and occurrence of NSTEMI were independently associated with high NT-proBNP peak serum levels (Table 3). However, neither left ventricular dysfunction, nor the presence of multivessel disease proved to be significant after adjustment for the other variables.

DISCUSSION

The current study showed that both proximal culprit localization and biochemical markers of myocardial damage are associated with high peak NT-proBNP levels. These results are compatible with a recent study in which BNP levels at admission were significantly related to severity of angiographic disease and extent of myocardium at risk.11

Both baseline and peak NT-proBNP levels correlated equally with proximal culprit lesion localization. However, baseline NT-proBNP levels lacked any association with the occurrence of NSTEMI, while peak levels did correlate highly.

The inverse relationship between NT-proBNP and prognosis in patients with acute coronary syndrome (ACS) may be explained as follows. First, proximal culprit lesion location is associated with an increased risk of adverse outcomes in patients admitted with an acute MI.16

Although the patient population used in the current study is clearly different, it is not unreasonable to assume that proximal localization of the culprit lesion in patients with NSTE-ACS is also associated with poor outcome.

Second, it is known that myocardial necrosis in patients with ACS is related to a worse prognosis. However, the threshold at which a CK-MB elevation is associated with increased risk of adverse events remains a controversial issue. A recent meta-analysis, pooling data from 23,230 patients who had undergone PCI, showed that any increase of CK-MB above normal limits was associated with increased mortality.18 Although NT-proBNP levels are known to relate to left ventricular function,17 this relationship is probably the result of the severity and extend of an ischemic event.
As a more proximal culprit lesion and more severe ischemia lead to more myocardial damage, this could likely result in more myocardial dysfunction, both reversible and irreversible. Therefore, it may be argued that the dynamic rise in NT-proBNP does reflect the amount of newly jeopardized myocardium.

While recent research shows that a selective invasive treatment in patients with NSTE-ACS, is not inferior to early invasive management, NT-proBNP measurements could further stratify the patient population pointing to those who could benefit most from and early invasive approach.\textsuperscript{3,19}

Limitations
The study was performed with a limited number of patients and, unfortunately, there were a considerable proportion of intended serum samples missing. Consequently, it is possible that a number of comparisons are underpowered. This may limit the value of the multivariate analysis. Moreover, it could be argued that the proximal versus distal lesion location system is too simplistic. However, this system is very suitable in daily practice and is associated with prognosis, as was shown previously.\textsuperscript{16}

Conclusions
High peak NT-proBNP serum levels were independently associated with a proximal localization of the culprit lesion and high Troponin/CK-mb peak levels in patients with NSTE-ACS.

These findings correlate to the hypothesis that NT-proBNP levels reflect the amount of jeopardized myocardium and may, therefore, signify the integral of the extent and severity of an ischemic event. The exploring nature of the study implicates hypothesis generation. Future studies are needed to evaluate this hypothesis in a more sophisticated manner.
REFERENCES


