Biochemical risk assessment and invasive strategies for acute coronary syndromes without ST-segment elevation
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Chapter 4

Dynamics in N-terminal pro-brain natriuretic peptide concentration in patients with non-ST-elevation acute coronary syndrome

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ABSTRACT

Background
Although there is growing evidence that N-terminal pro-brain natriuretic peptide (NT-proBNP) can be used as a powerful tool in risk prediction in patients with non-ST-elevation acute coronary syndrome (NSTE-ACS), the dynamic variation of serum concentrations in time is poorly understood. To gain insight into the dynamics of NT-proBNP, a study was performed using serial serum samples in patients admitted with NSTE-ACS.

Methods
A total of 24 patients admitted with NSTE-ACS was included in this study. Serial samples were taken at baseline, 8 hours, 16 hours, 24 hours, and 36 hours after admittance.

Results
A highly dynamic pattern in serial measurements of NT-proBNP was observed. Although an increase in NT-proBNP serum levels already existed 8 hours after admittance, it did not reach significance as compared with baseline. The samples obtained 16, 24, and 36 hours after admission were all significantly increased as compared with the values at admission (P < .01), generally leading to a >2-fold increase with peak values at 16 to 24 hours after admittance. Furthermore, considerable differences in NT-proBNP concentrations between patients were observed.

Conclusions
It was shown that NT-proBNP is a highly dynamic cardiac peptide. Strategic sampling at 16 to 24 hours after admittance could prove representative regarding the assessment of risk prediction and subsequent clinical decision making.
INTRODUCTION

There is growing evidence that N-terminal pro-brain natriuretic peptide (NT-proBNP) and brain natriuretic peptide (BNP) are powerful predictors of prognosis in patients admitted with acute coronary syndrome (ACS). 1-10 Multiple large cohorts consisting of patients with ACS have shown that BNP and NT-proBNP may reflect in a unique way the integral of different risk markers. 1-4, 6-7, 9

Furthermore, recent data suggest that a subpopulation of patients with high NT-proBNP levels is more likely to benefit from early intervention than patients with low levels of NT-proBNP, indicating clinical importance. 3 However, until now, studies have used a more or less random timing in blood sampling, ranging from within 24 hours after the last episode of chest pain to a median of 3 days after patient admittance. As BNP and NT-proBNP are released into circulation in response to ischemia, it is probable that the production, release, and, therefore, serum concentrations of BNP and NT-proBNP change over time. 11, 12

Although the onset of ischemia in non-ST-elevation acute coronary syndrome (NSTE-ACS) is mostly acute, it was hypothesized that, accordingly, there would be significant dynamic variations in the concentration of NT-proBNP over time. This is of importance because understanding the dynamic variations could provide a better time window for representative measurements and thereby enhance the prognostic and predictive value of NT-proBNP. This could augment the use of NT-proBNP in clinical decision making. The present study evaluated the dynamic variations of NT-proBNP in time in patients admitted with NSTE-ACS.

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 as follows: age >21 years, onset of chest pain within the last 6 hours, and transient
ST deviation >2 mm in 2 contiguous leads and/or elevated troponin T levels upon admission.

The main exclusion criteria were as follows: ischemia suspected not to be caused by coronary artery disease, known history of or presence of congestive heart failure, known or suspected left ventricular hypertrophy, and acute myocardial infarction (AMI) requiring immediate reperfusion therapy and percutaneous coronary intervention (PCI) within 14 days.

The primary aim of the study was to gain insight into the dynamic variations in time for NT-proBNP serum concentrations.

**Blood sampling procedures**

Peripheral blood samples (Li-heparin, BD, Erembodegem-Aalst, Belgium) for plasma NT-proBNP determination were obtained at 0, 8, 16, 24, and 36 hours after admittance. All samples were stored at 2°C to 8°C within 2 hours and transferred to a −20°C freezer within 24 hours after blood withdrawal until measured.

**Assay of NT-proBNP, creatine kinase 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 creatine kinase MB activity was analyzed on a Modular-Analytics (Roche Diagnostics). The specifications, analytic performance, and precision of the NT-proBNP, troponin T, and creatine kinase MB assays have been described previously.

**Statistical analyses**

All the 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, SDs, medians, interquartile ranges, and minimum and maximum values. Categorical variables were described using frequencies and percentages.

Changes in NT-proBNP levels over time were analyzed using analysis of variance for repeated measures. Where the F value was found to be significant, the data were compared with Dunnett’s multiple comparison tests. Comparisons of plasma
concentrations between certain groups were made using unpaired Student’s t tests. A P value of .05 (2 sided) was used to indicate statistically significant difference.

RESULTS

Baseline characteristics
From December 2002 to October 2003, 24 patients admitted with NSTE-ACS were included in the study. During the period of blood sampling, all patients were treated conservatively. Of the samples, 78% (93/120) were found to be valid in quality and timing of sampling. Of the values missing, most occurred at 24 and 36 hours after admittance. Mainly, this was 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 characteristics.

<table>
<thead>
<tr>
<th>Variable</th>
<th>N = 24</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>4 (17)</td>
</tr>
<tr>
<td>Inclusion at admittance by</td>
<td></td>
</tr>
<tr>
<td>&gt;2 mm ST depression (%)</td>
<td>14 (58)</td>
</tr>
<tr>
<td>Elevated troponin T (%)</td>
<td>15 (63)</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 (29)</td>
</tr>
<tr>
<td>Hypercholesterolemia (%)</td>
<td>9 (38)</td>
</tr>
<tr>
<td>Peripheral vascular disease (%)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Myocardial infarction (%)</td>
<td>6 (25)</td>
</tr>
<tr>
<td>PCI (%)</td>
<td>6 (25)</td>
</tr>
<tr>
<td>CABG (%)</td>
<td>2 (8)</td>
</tr>
</tbody>
</table>

CABG, coronary artery bypass grafting.
N-terminal pro-brain natriuretic peptide measurements

A highly dynamic pattern in serial measurements of NT-proBNP was observed. At baseline, the mean concentration of NT-proBNP was 315 (SD 367) ng/L, increasing to 461 (526) ng/L at 8 hours; 650 (578) ng/L at 16 hours; 686 (660) ng/L at 24 hours; and 721 (703) ng/L at 36 hours after admittance (P for trend = .01). The mean values of NT-proBNP in relation to other cardiac markers in time are graphically shown in Figure 1.

**FIGURE 1**
Dynamic variations in cardiac markers in patients admitted with NSTE-ACS.

Values are expressed as mean ± SEM. Asterisk represents P < .01 compared with values on admission.

CK-MB, creatine kinase MB.

Using the known analytic and intraindividual variability, the percentage of change in serial NT-proBNP concentrations considered to be statistically significant was approximately 90% at the 95% bidirectional CIs.16,17
Although an increase in NT-proBNP serum levels 8 hours after admittance was noted (n = 19/24), it did not reach significance as compared with baseline. However, the samples obtained 16, 24, and 36 hours after admission were all significantly increased as compared with the values at admittance (P < .01) (Figure 1).

Another striking observation was the difference between patients in both absolute values and the relative increase of NT-proBNP concentration over time. Figure 2 shows individual curves of NT-proBNP serum concentrations for 15 patients with a complete set of serial samples. The figure suggests that after an initial increase, the NT-proBNP concentration reaches its maximum at approximately 16 to 24 hours after admission. Additional analysis showed that both patients with relatively early NT-proBNP peak values experienced chest pain before the 6-hour time window as stated by protocol, indicating earlier onset of ischemia (Figure 2).

**FIGURE 2**

Variations in NT-proBNP concentration in time - individual curves.

Curves taken from 15 patients with complete blood samples. The thick line represents the mean values. Additional research revealed that the patient represented by an asterisk had another episode of chest pain 1 day before admittance. Additional research revealed that the patient represented by a dagger suffered from recurrent attacks of chest pain during the week before admittance.
Although left ventricular function was not routinely assessed, none of the patients developed clinical symptoms of heart failure.

**Maximum NT-proBNP concentration, troponin T levels, and ST-segment deviation**

To evaluate the relation between NT-proBNP and ischemia, several subanalyses were performed. First, the maximum NT-proBNP concentrations in the group of patients with elevated troponin levels at baseline (cutoff >0.05 ng/L, n = 15) were compared with those in the group of patients without elevated troponin levels (n = 9). No differences in NT-proBNP peak concentrations between the groups were found. Repeated analyses using lower (>0.01 ng/L) or higher (>0.1 ng/L) cutoff points did not alter this finding.

However, a significant relation was observed between NT-proBNP and troponin T peak concentrations, indicating a (partial) relationship between maximum NT-proBNP levels and severity of ischemia (P < .001) (Figure 3).

**FIGURE 3**

Scatterplot of correlation between NT-proBNP and troponin T peak concentrations.

![Scatterplot of correlation between NT-proBNP and troponin T peak concentrations.](image)
Nonetheless, the degree of ST-segment deviation was not correlated to increased NT-proBNP peak levels (data not shown).

Influence of sample time when using cutoff values
To illustrate the importance of sample timing using cutoff values, an analysis was performed regarding the relationship between sample timing and the number of patients above a predefined cutoff value. The Roche package insert for NT-proBNP indicates that the most appropriate decision cutoff for congestive heart failure is 125 ng/L for patients <75 years and 450 ng/L for patients ≥75 years, respectively.\textsuperscript{18} Although an entirely different patient population, these cutoff values were used on the patient population to demonstrate the significance of strategic sampling. At baseline, only 29% of the patients had positive values increasing to 58% and 83% at 8 and 16 hours after admittance, respectively. Unfortunately, the amount of samples at 24 and 36 hours was too small to draw reliable conclusions. Of all patients, 95% reached positive NT-proBNP levels at some point in time using the prementioned criteria.

DISCUSSION

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.\textsuperscript{2,3,6} Reversible ischemia may transiently increase left ventricular wall stress, which could be sufficient enough to cause an elevation in BNP and NT-proBNP levels. It has recently been shown that ventricular BNP gene expression is upregulated by myocardial hypoxia, resulting in augmented plasma concentrations of BNP and NT-proBNP.\textsuperscript{19} Because ischemia probably leads to a transient decrease both in systolic function and in compliance, elevations in BNP may reflect the integral of area at risk and the severity of ischemia in patients with ACS. This could prove to be the pathophysiological substrate for the prementioned strong predictive value of BNP and NT-proBNP in patients with ACS. Whether the considerable interindividual differences in NT-proBNP levels in patients with NSTE-ACS
ACS are associated with the degree of myocardial ischemia, as was recently reported for BNP in patients with stable anginal complaints\textsuperscript{20}, needs to be investigated in future studies. However, given the correlation between NT-proBNP and troponin T peak concentrations, NT-proBNP secretion seems, to a certain degree, to be augmented by the severity of the ischemic event (Figure 3). Furthermore, Heeschen et al\textsuperscript{21} recently reported declining NT-proBNP levels at 48 and 72 hours after admittance in patients with ACS responding to therapy, whereas the NT-proBNP levels remained elevated in patients with refractory ischemia. This finding suggests prolonged secretion of the peptides caused by on-going ischemia.

Although this study has a small patient population and the amount of samples taken at 24 and 36 hours after admittance was limited by clinically driven PCI, the study clearly shows the dynamic behavior of NT-proBNP in patients with NSTE-ACS.

The results of the present study are compatible with the findings of former studies.\textsuperscript{22,23} In patient populations with AMI, peak levels for BNP and, more recently, NT-proBNP are generally achieved 16 to 24 hours after admittance as well. Although these patient populations were clearly different from ours, similar dynamic behavioral patterns are observed.

Multiple studies used sample timing between admittance and 4 days thereafter without taking into account the occurrence of dynamic variations in serum concentration in time of this peptide.\textsuperscript{1-4,6-7} Therefore, it is possible that the mean and median concentrations as well as individual values measured in these studies were biased by the timing of sampling. Although the difference in mean concentration did not significantly decrease after 16 hours post admission, the individual curves demonstrate that a subset of patients already shows declining NT-proBNP serum levels by that time (Figure 2). In addition, former studies in patients with AMI confirm declining BNP and NT-proBNP levels after 24 hours.\textsuperscript{22,23} Furthermore, the results of the present study indicate that with the use of cutoff values, the timing of NT-proBNP sampling is of great importance. Hence, sampling by protocol at 16 to 24 hours after admission could prove important when regarding the assessment of risk prediction and subsequent clinical decision making.
Conclusions
The present study showed that NT-proBNP is a highly dynamic cardiac peptide. After an ischemic event, there appears to be an increase in NT-proBNP concentration with peak concentrations at 16 to 24 hours after admission in a considerable number of patients. In addition, the secretion of NT-proBNP had a strong individual variation that was generally most pronounced in the same time window. Further research is needed to investigate the exact pathophysiological mechanisms of this interindividual variation. Future studies regarding the use of NT-proBNP in patients with ACS may benefit from considering the dynamics of the peptide and thereby increasing its clinical use.
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