Vigorous response in plasma N-terminal pro-brain natriuretic peptide (NT-BNP) to acute myocardial infarction

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ABSTRACT

Acute myocardial infarction (MI) results in activation of neurohormonal systems and increased plasma concentrations of myocardial enzymes and structural proteins. We hypothesized that plasma levels of N-terminal pro-brain natriuretic peptide (NT-BNP) would respond more vigorously after MI than those of other natriuretic peptides. We also sought to compare this response with that of the established myocardial injury markers troponin T (TnT), myoglobin and creatine kinase MB (CK-MB). We obtained multiple blood samples for measurement of atrial natriuretic peptide (ANP), N-terminal pro-ANP (NT-ANP), brain natriuretic peptide (BNP) and NT-BNP along with CK-MB, TnT and myoglobin in 24 patients presenting to the Coronary Care Unit within 6 h of onset of MI. Multiple samples were obtained in the first 24 h, then at 72 h, 1 week, 6 weeks and 12 weeks. NT-BNP increased rapidly to peak at 24 h and exhibited greater (P < 0.001) absolute increments from baseline compared with BNP and ANP, whereas NT-ANP did not change from baseline. Proportional increments in NT-BNP were also greater than those for the other natriuretic peptides (P < 0.05). Natriuretic peptide levels reached their peak around 24 h, later than peak TnT, CK-MB and myoglobin (peak between 1–10 h), and NT-BNP and ANP remained elevated on average for 12 weeks. Our present results, with detailed sampling of a cohort of acute MI patients, demonstrate greater absolute and proportional increments in NT-BNP than ANP or BNP with sustained elevation of these peptides at 12 weeks.

INTRODUCTION

It is well known that acute myocardial infarction (MI) is associated with activation of neurohormonal systems and increased circulating levels of myocardial enzymes and structural proteins. These have turned out, in some cases, to have diagnostic and prognostic use and also therapeutic implications. It is now clear that plasma levels of atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP), both produced within myocardial cells, also are elevated soon after acute MI [1–7]. Furthermore, reports [8–19] suggest that the level of ANP, N-terminal pro-ANP (NT-ANP) or BNP measured soon after infarction might provide a simple useful biochemical reflection of left ventricular function and/or a prognostic index for subsequent cardiac function and prognosis. Since the N-terminal fragment of pro-BNP (NT-BNP) circulates at similar levels to BNP in healthy volunteers yet increases more steeply as cardiac function deteriorates [20,21], we hypothesized that NT-BNP would exhibit a
more vigorous response after acute MI than BNP, ANP or NT-ANP. If indeed this was so, NT-BNP, assays for which will soon be widely available, might provide a relatively simple, rapid and cheap diagnostic test for, and prognostic index after, acute MI. Detailed comparisons of the response to acute MI of the natriuretic peptides, including NT-BNP, along with the myocardial injury markers troponin T (TnT), myoglobin and creatine kinase MB (CK-MB), have not been carried out previously.

METHODS

The study protocol was approved by the Ethics Committee of the Canterbury District Health Board and patients gave informed consent.

We studied 24 consecutive patients presenting to the Coronary Care Unit at Christchurch Hospital within 6 h of the onset of chest pain and clear evidence of ST-elevation acute MI, together with a rise then fall in plasma TnT. Patients with cardiogenic shock were excluded.

An 18-gauge intravenous cannula was inserted into a forearm vein for blood sampling. Venous samples (10 ml) were drawn on admission to the Coronary Care Unit (time 0) and thereafter at 0.5, 1, 4, 8, 12, 24 and 72 h as in-patients, and at 1, 6 and 12 weeks as out-patients. Samples were taken into tubes on ice and centrifuged at −80°C until analysed. Plasma samples were assayed for TnT, CK-MB and myoglobin using heterogeneous immunoassays on an Elecsys 2010 using ruthenium-labelled biotinylated antibodies. Reagents, consumables and instrumentation were supplied by Roche Diagnostics.

ANP, NT-ANP, BNP and NT-BNP were measured by our well-established and validated RIAs using plasma extracted on C18 Sep Pak cartridges [20,22,23]. All measurements for each analyte were carried out in a single assay to avoid inter-assay variability. Intra-assay variability (coefficient of variation) for the hormone measurements was between 4 and 9%. Cross-reactivity between the individual assays and the other natriuretic peptides was <0.007% for all assays, except the ANP assay, which had a cross-reactivity with BNP of 0.05%.

Comparisons between plasma concentrations and changes in concentrations were made using paired Student’s t tests. Correlations were assessed using Pearson’s correlation coefficients. Statistical significance was taken as P < 0.05. Data are presented as means ± S.E.M.

RESULTS

Twenty-four patients, 19 males, ages 37–82 (mean 65.2) years were studied. Twelve patients had previously documented hyperlipidaemia, nine had hypertension, three had an earlier MI, three were being treated for cardiac failure and four had diabetes mellitus. Medications on admission were diuretics (five patients), angiotensin-converting enzyme inhibitors (six patients), aspirin (15 patients), β-blockers (five patients), calcium channel blockers (two patients) and nitrates (two patients). Three patients had primary percutaneous transluminal coronary angioplasty (PTCA; two with anterior MI and one with anterolateral MI), 21 patients received thrombolysis, two patients subsequently had coronary artery bypass grafting during the admission, and two patients developed left ventricular failure. One patient died from myocardial rupture on the fourth day after admission. One patient developed atrial fibrillation. Seventeen patients had an ECG during the hospital stay, and the average ejection fraction was 54% (range, 24–75%). Average hospital stay for the 23 patients discharged alive was 6.6 days (range, 3–15 days). The time between the onset of chest pain and drawing of the baseline (time 0) venous sample was 3.9 ± 0.3 h.

Baseline NT-BNP (43 ± 6 pmol/l) levels were higher (P < 0.0001) than both concurrent BNP (10 ± 1.5 pmol/l) and ANP (19.5 ± 3.5 pmol/l) levels, but were lower than NT-ANP levels (0.94 ± 0.13 nmol/l; Table 1). Plasma levels of NT-BNP increased rapidly to peak at 12–24 h (Table 1), and exhibited a greater (P < 0.001) absolute increment from baseline than BNP and ANP (123 ± 15 compared with 19 ± 2 and 27 ± 3 pmol/l respectively). Furthermore, NT-BNP showed a greater proportional rise than either plasma BNP or ANP (5.6 ± 0.9-fold compared with 3.4 ± 0.6- and 2.4 ± 0.3-fold respectively; P < 0.05; Figure 1, upper panel). NT-ANP levels were, on average, towards the upper limit of normal at baseline and did not change significantly thereafter (Table 1, and Figure 1, upper panel).

At time 0, the percentage of patients with elevated BNP, NT-BNP, ANP or NT-ANP was identical (29%). The percentage of patients with plasma NT-BNP levels above the upper limit of normal at 8, 12 and 24 h was 95%, 96% and 96% respectively. These percentages were similar for plasma levels of BNP (95%, 92% and 95%), but were considerably higher than for ANP (74%, 79% and 74%) and, particularly, NT-ANP (22%, 29% and 17%).

The temporal pattern of change for NT-BNP, BNP and ANP contrasted sharply with those for plasma levels of TnT, CK-MB and myoglobin (Figure 1, lower panel). Whereas peak levels for NT-BNP, BNP and ANP were achieved generally around 24 h (Figure 1, upper panel), maximum levels of TnT, CK-MB and myoglobin were reached at between 1 and 10 h (Figure 1, lower panel). Furthermore, the elevation in the natriuretic peptide levels was considerably more sustained than TnT, CK-MB or myoglobin, as the latter had normalized by 6 weeks and, in the case of CK-MB and myoglobin had, in general, normalized by 70 h (Figure 1, lower panel, and Table 1), whereas NT-BNP, BNP and ANP remained
Table 1  Levels of natriuretic peptides and myocardial markers in 24 patients after acute myocardial infarction

Values are means ± S.E.M. Time 0 is on average 3.9 ± 0.3 h after the onset of chest pain.

<table>
<thead>
<tr>
<th>Natriuretic peptides</th>
<th>Myocardial markers</th>
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<tbody>
<tr>
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<td>ANP (pmol/l)</td>
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<td>Normal range</td>
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<tr>
<td>0</td>
<td>19.5 ± 3.5</td>
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<td>0.5</td>
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<td>1</td>
<td>16.5 ± 2</td>
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<td>4</td>
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<td>28.5 ± 3</td>
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<td>Time (weeks)</td>
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<td>6</td>
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<td>12</td>
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DISCUSSION

Various biomarkers have been used for the diagnosis of acute MI and as a guide to subsequent prognosis [24–27]. Considerable enthusiasm and experience exists, particularly for the cardiac troponins and, to a lesser extent with, CK-MB and myoglobin. As noted by Hamm [24], the search for new markers will continue, particularly in regard to risk stratification.

It has been known for more than a decade that ANP and BNP are released from cardiac muscle during acute MI [8–19]. The magnitude of the response in ANP and/or BNP has been shown by some authors [8–19] to be predictive of subsequent ventricular dysfunction, morbidity or mortality. As NT-BNP circulates at similar levels to the bioactive BNP itself in healthy volunteers yet shows a proportionally greater rise as ventricular dysfunction deteriorates in patients with heart failure [20,21], we surmized that this 1–76 amino acid peptide might show an exaggerated rise following acute MI compared with ANP or BNP. If so, there might be potential usefulness in measuring this peptide soon after a MI, both from a diagnostic and prognostic viewpoint.

The present study, in a small cohort of patients, demonstrates that NT-BNP exhibits a greater absolute and proportional rise after acute MI than ANP or BNP. Peak levels of the three peptides were observed at approx. 24 h and, in general, remained elevated even at 12 weeks. This pattern of response contrasts with the more standard cardiac biomarkers TnT, CK-MB and myoglobin, whose peak levels were reached between 1 and 10 h and normalizing more rapidly.

In regard to NT-ANP, we found the levels to be elevated in only a minority of our patients after MI with

Figure 1 Proportional change from baseline (time 0) in plasma levels of natriuretic peptides (upper panel) and myocardial markers (lower panel)

Values are means. AMI, acute MI.
little pattern of change thereafter. Accordingly, our results do not raise enthusiasm for measurements of this peptide in diagnosis of acute MI and suggest it may convey less prognostic information than the measurement of NT-BNP.

The mechanisms behind the increase in natriuretic peptides are likely to be numerous and complex, but could involve myocardial hypoxia, intracellular acidosis, stimulation of the renin–angiotensin system and the sympathetic nervous system and, in addition, MI-associated stress of the left ventricle and possibly left atrium [28–32]. As for the differences between the peptide patterns, the plasma half-lives differ, the distribution of ANP and BNP differs in at least some chambers of the human heart and with stretch or hypertrophy gene expression of the peptides differs temporally, at least under experimental circumstances [33–35]. Our present study was not designed to examine this question, and further investigation is required to determine which of these and other factors dictates the patterns observed.

Whether the level of NT-BNP achieved after MI will prove superior as a prognostic indicator to ANP or BNP, or the more standard markers, especially the cardiac troponins, remains to be determined in larger studies. The few studies [36–39] reported previously support the possibility that NT-BNP might prove clinically useful. We observed NT-BNP, measured post-MI, to be predictive of left ventricular function and prognosis [36]. Talwar et al. [37] reported a strong correlation of NT-BNP with left ventricular wall motion index soon after and remote from acute MI. In that study [37], NT-BNP and previous MI were independent predictors of poor outcome [37]. Jernberg and co-workers [38] reported that a combination of NT-BNP, clinical factors, troponins, remains to be determined in larger studies. The few studies [36–39] reported previously support the possibility that NT-BNP might prove clinically useful. We observed NT-BNP, measured post-MI, to be predictive of left ventricular function and prognosis [36]. Talwar et al. [37] reported a strong correlation of NT-BNP with left ventricular wall motion index soon after and remote from acute MI. In that study [37], NT-BNP and previous MI were independent predictors of poor outcome [37]. Jernberg and co-workers [38] reported that a combination of NT-BNP, clinical factors, troponins, remains to be determined in larger studies.

Utilization of NT-BNP as a diagnostic marker of acute MI requires further exploration. It appears most unlikely that it will replace current cardiac biomarkers in the few hours subsequent to the onset of MI. It might, however, find a place when further time has elapsed, particularly beyond 70 h, when CK-MB and myoglobin levels have, by and large, returned to normal. However, it is more likely that NT-BNP might find a place as a prognostic index for subsequent ventricular function or for cardiac morbidity or mortality following acute MI. Whether it will prove more or less successful in this regard than the bioactive peptides ANP or BNP or indeed the more classical biomarkers, particularly TnI, remains to be determined.

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