Profile of plasma N-terminal proBNP following acute myocardial infarction

Correlation with left ventricular systolic dysfunction

S. Talwar, I. B. Squire, P. F. Downie, A. M. McCullough, M. C. Campton, J. E. Davies, D. B. Barnett and L. L. Ng

Aims The aims of this study were to describe the temporal pattern of plasma N-terminal pro-brain natriuretic peptide, to examine the optimum time of sampling and to compare plasma N-terminal pro-brain natriuretic peptide to clinical criteria in terms of identification of impaired left ventricular systolic function following acute myocardial infarction.

Methods and Results Measurements of N-terminal pro-brain natriuretic peptide were made in 60 patients at 14–48 h, 49–72 h, 73–120 h, 121–192 h following myocardial infarction and at 6 weeks in survivors. Left ventricular wall motion index was assessed during hospitalization (WMI-1) and at 6 weeks (WMI-2). N-terminal pro-brain natriuretic peptide levels were elevated at all time points, to a greater extent in anterior compared to inferior infarction (P<0.05). A biphasic profile of plasma concentration was observed in anterior infarction with peaks at 14–48 h and 121–192 h. This was sustained at 6 weeks. N-terminal pro-brain natriuretic peptide at 73–120 h was the best independent predictor of WMI-1 (P<0.005). N-terminal pro-brain natriuretic peptide was higher at all times in patients who received ACE inhibitor therapy compared to those who did not (P<0.005). N-terminal pro-brain natriuretic peptide at 73–120 h (R²=17.7%, P=0.005) and previous myocardial infarction (R²=5.3%, P<0.05) were independent predictors of poor outcome (WMI-2 ≤1.2 or death by 6 weeks).

Conclusions A biphasic pattern of plasma N-terminal pro-brain natriuretic peptide is seen after anterior myocardial infarction. Plasma level is strongly correlated to wall motion index soon after and remote from acute myocardial infarction. Plasma N-terminal pro-brain natriuretic peptide measured later in hospitalization better predicts poor outcome following myocardial infarction than when it is measured in the immediate post infarction period.

Key Words: Brain natriuretic peptide, neurohormones, acute myocardial infarction, left ventricular systolic dysfunction.

See page 1490 for the Editorial comment on this article

Introduction

Recent interest has focused on the use of neurohormonal markers such as B-type natriuretic peptide (BNP), atrial natriuretic peptide (ANP), N-terminal pro-ANP (N-ANP) and N-terminal proBNP (N-BNP) as indices of left ventricular systolic dysfunction and prognosis following acute myocardial infarction[1–3]. Plasma level of N-BNP measured 2 to 4 days after acute myocardial infarction independently predicts left ventricular ejection fraction and 2-year survival[3]. The predictive value of N-BNP for both reduced left ventricular ejection fraction and death following acute myocardial infarction is superior to that of either BNP or N-ANP[3]. Following acute myocardial infarction, increased synthesis of the natriuretic peptides occurs in both the infarcted and non-infarcted myocardium[4]. Plasma levels of these neurohormones may thus reflect not only existing left ventricular systolic dysfunction but may in addition be a sensitive index of abnormal wall stress preceding the process of ventricular remodelling[5,6].

After acute myocardial infarction, temporal profiles of plasma N-BNP may differ in those with and without left ventricular systolic dysfunction, as has been
demonstrated for BNP[8]. In terms of the predicting left ventricular systolic dysfunction, the optimum time of sampling for N-BNP following acute myocardial infarction has not previously been investigated. The aims of this prospective study were to identify the optimum time of sampling for N-BNP following acute myocardial infarction and to compare N-BNP to clinical and echocardiographic assessment of left ventricular systolic dysfunction. We utilized a novel immunoluminometric assay for N-BNP[9].

**Methods**

**Subjects**

We studied 60 patients admitted to the Coronary Care Unit of Leicester Royal Infirmary with a diagnosis of Q wave acute myocardial infarction. Serial blood samples were taken from each subject in each of the following periods: 14–48 h, 49–72 h, 73–120 h, 121–192 h following acute myocardial infarction and at a clinic visit in survivors. In all cases clinical and radiological evidence of left ventricular systolic dysfunction or heart failure at any time during hospitalization was recorded. The study was approved by the local ethical and research committee and all subjects gave written informed consent.

**Echocardiography**

Echocardiographic assessment of wall motion index (WMI), a measure of left ventricular systolic dysfunction, was made in 58 of the 60 patients during admission (WMI-1; median day 4–5, range 2–6) and at the clinic visit (WMI-2; median day 50, range 20–73) in 52/56 survivors. Echocardiography was performed using a Hewlett Packard Sonos 1500 imaging system. Wall motion index was calculated using a nine-segment model, and four-chamber, subxiphoid four-chamber and cross sectional views were obtained. Systolic motion of individual segments was quantitated thus: hyperkinetic +3; normal +2; hypokinetic +1; akinetic 0; paradoxical motion −1. The mean of the nine segment scores was taken as wall motion index, a score of 1–2 corresponding to a left ventricular ejection fraction of 35%. All echocardiographic images were analysed by a single investigator (S.T.) blind to patient details and N-BNP results.

**Blood sampling**

Twenty millilitres of venous blood was taken at each of five different time periods (as above) following the index acute myocardial infarction. Blood was transferred into pre-chilled EDTA (1·5 mg . ml⁻¹ blood) tubes containing 500 IU . ml⁻¹ of aprotenin. Samples were immediately centrifuged at 4 °C and plasma separated and then stored at −70 °C until assayed.

**Assay for N-BNP**

The methodology for assay of N-BNP has been described previously[7]. Briefly, we used an in-house rabbit anti-human N-BNP polyclonal antibody directed against N-BNP (amino acids 65–76 of the C-terminal domain). Plasma N-BNP was extracted on C₁₆ columns. The N-BNP tracer was labelled with the methyl acridinium 9-carboxylate fluorosulfonate[7]. Assays were performed on a Berthold Autolumat LB953 luminometer. N-BNP levels were determined blind to patient details. Each N-BNP value represents the mean of duplicate measurements. The normal range for N-BNP in our laboratory is <200 fmol . ml⁻¹.

**Statistical analysis**

Assessment was made of the strength of the relationship between left ventricular systolic function (wall motion index) during and after hospitalization and N-BNP measured at each time interval. The relationship with wall motion index of a number of additional clinical and laboratory variables was investigated. Predictive models for the response variable (wall motion index) were developed using multiple linear regression analysis and stepwise logistic regression analysis.

Concentrations of N-BNP, age, plasma creatinine, plasma glucose, peak creatine kinase, and wall motion index scores were not normally distributed and were log transformed before analysis. Comparisons of N-BNP levels at different time points was by analysis of variance (ANOVA) with correction for multiple measures. Other comparisons were by Student’s t-test. Comparisons with P<0·05 were considered significant. All statistical analyses were carried out using the software package Minitab (Minitab Inc., PA, U.S.A.). All results are expressed as means ± 1 SD. N-BNP levels are expressed in fmol . ml⁻¹.

**Results**

We studied 60 patients (45 males, median age 63·5 years, range 36–87, 39 anterior acute myocardial infarction). Biochemical and echocardiographic data are in Table 1. A past history of myocardial infarction, angina, hypertension and diabetes mellitus was obtained in four (6·7%), 10 (16·7%), 16 (26·6%) and 4 (6·7%), respectively. None had a previous history of heart failure. Twenty four (40%) and 35 (58%) patients had radiological and/or clinical evidence of heart failure during...
hospitalization. In terms of treatment, 52 (86-7%) received thrombolyis, 33 (55%) diuretic, 38 (63-3%) angiotensin converting enzyme (ACE) inhibitor, 33 (55%) beta-blocker and two (3-3%) digoxin. By 6 weeks, four (6-7%) had died. At this point 35/54 (64-8%) had a wall motion index ≤1-2. At 6 weeks an echo could not be obtained in 2/56 survivors.

**Profile of plasma N-BNP**

Plasma N-BNP levels (f mol . ml⁻¹) were elevated at 14-48 h (748 ± 170), 49-72 h (579 ± 138), 73-120 h (450 ± 124), 121-192 h (823 ± 257) and at the clinic visit (807 ± 176). Plasma N-BNP fell between 14-48 h and 73-120 h (P=0.007) and rose between 73-120 h and the clinic visit (P=0.01, ANOVA). This biphasic response was seen only following anterior acute myocardial infarction. N-BNP levels did not differ among time points following inferior acute myocardial infarction in whom plasma levels were similar at all times (P=0.6, ANOVA) (Fig. 1).

**Table 1 Biochemical and echocardiographic indices of study population**

<table>
<thead>
<tr>
<th></th>
<th>Mean (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biochemistry</td>
<td></td>
</tr>
<tr>
<td>Plasma sodium</td>
<td>137.2 (127-146)</td>
</tr>
<tr>
<td>Plasma urea</td>
<td>6.3 (2.9-11)</td>
</tr>
<tr>
<td>Plasma creatinine</td>
<td>104.7 (46-177)</td>
</tr>
<tr>
<td>Plasma glucose</td>
<td>9.3 (5.7-30.9)</td>
</tr>
<tr>
<td>Peak CK (IUL; NR &lt;200)</td>
<td>2153 (487-8922)</td>
</tr>
<tr>
<td>Echocardiographic indices</td>
<td></td>
</tr>
<tr>
<td>WMI-1</td>
<td>1.2 (0.2-2)</td>
</tr>
<tr>
<td>WMI-2</td>
<td>1.5 (0.2-2)</td>
</tr>
<tr>
<td>NR = normal range.</td>
<td></td>
</tr>
</tbody>
</table>

NR = normal range.

**Figure 1** Profile of plasma N-BNP (mean ± 1 SD) following anterior (■) or inferior (○) myocardial infarction.

**Figure 2** Correlation of wall motion index during hospitalization and N-BNP measured at 73–120 h following myocardial infarction.

At all time points, N-BNP levels (f mol . ml⁻¹) were higher in anterior compared to inferior myocardial infarction (1000 ± 255 vs 292.8 ± 41.1, P<0.005 at 14-48 h; 732 ± 199 vs 261.4 ± 44.6, P<0.05 at 49-72 h; 595 ± 196 vs 214.1 ± 29.5, P<0.005 at 73–120 h; 1140 ± 374 vs 187.4 ± 22.3, P<0.005 at 121–192 h and 1162 ± 268 vs 246.4 ± 40.9, P<0.005 at the clinic visit). N-BNP levels did not differ between those patients with clinical or radiological evidence of heart failure and those without (785 ± 383 vs 485 ± 238, P=0.15 at 14–48 h; 693 ± 467 vs 505 ± 761, P=0.55 at 49–72 h; 686 ± 758 vs 317 ± 314, P=0.28 at 73–120 h; 1091 ± 794 vs 674 ± 1698, P=0.45 at 121–192 h and 597 ± 836 vs 908 ± 385, P=0.33 at the clinic visit).

**N-BNP and wall motion index score**

There was a strong correlation between WMI-1 and WMI-2 (r=0.756, P<0.0001). WMI-2 was significantly higher than WMI-1 (P<0.0001, Table 1). N-BNP at 14–48 h correlated with N-BNP at 49–72 h (r=0.68, P<0.0001), 73–120 h (r=0.68, P<0.0001), 121–192 h (r=0.56, P<0.0001) and at the outpatient visit (r=0.31, P<0.05). There was a consistent correlation between WMI-1 and N-BNP: 14–48 h (r=–0.52, P<0.005), 49–72 h (r=–0.57, P<0.005), 73–120 h (r=–0.64, P<0.005) (Fig. 2) and 121–192 h (r=–0.57, P<0.005). The correlation of WMI-2 with N-BNP was less strong and only significant for N-BNP measured at 14–48 h (r=–0.29, P<0.05) and at 73–120 h (r=–0.41, P<0.005). There was no correlation between N-BNP measured at the clinic visit and WMI-2 (r=–0.098, P=0.526). There was no significant correlation between N-BNP levels at any time and either peak creatinine kinase or plasma creatinine.

**Influence of treatment**

Both WMI-1 (1.1 ± 0.3 vs 1.6 ± 0.4, P=0.0002) and WMI-2 (1.4 ± 0.4 vs 1.8 ± 0.3, P=0.0002) were lower in
patients who received ACE inhibitor therapy. N-BNP was higher in patients who received ACE inhibitor therapy compared to those who did not (997±752 vs 280±195 at 14–48 h; 626±761 vs 194±75 at 49–72 h; 403±304 vs 170±82 at 73–120 h, 962±875 vs 214±123 at 121–192 h; 1158±1078 vs 353±450 at the clinic visit; all P<0.005).

Predictors of wall motion index

**WMI-1**
We considered N-BNP at 14–48 h, 49–72 h, 73–120 h, 121–192 h, together with age, gender, past history of acute myocardial infarction, history of hypertension, history of diabetes mellitus, ECG site of infarct, plasma creatinine, peak creatine kinase, clinical heart failure and radiological heart failure in multivariate models for the predictors of WMI-1. On best subsets analysis, the strongest independent predictor of WMI-1 was N-BNP at 73–120 h (R²=39%, P<0.005). The addition of an anterior site of infarct improved the diagnostic accuracy (R²=49%, P<0.005) of the model. Other significant predictors of WMI-1 were a history of diabetes mellitus (P<0.05) and a history of previous acute myocardial infarction (P<0.05), which when combined with N-BNP at 73–120 h and anterior site of infarct increased the accountable variance in WMI-1 (R²=58%, P<0.005). When only anterior site, N-BNP at 73–120 h, history of myocardial infarction and history of diabetes were included in the analysis, both anterior site of infarct (P=0.002) and N-BNP at 73–120 h (P=0.005) remained independent predictors of WMI-1. In those patients without clinical or radiological evidence of heart failure, the correlation of N-BNP at 72–120 h with WMI-1 remained strong (r=−0.494, P=0.005).

In addition to comparing the relative predictive value of N-BNP measured at all time points, we analysed the predictive value of N-BNP at each individual time. When added as before to the variables age, gender, past history of acute myocardial infarction, history of hypertension, history of diabetes mellitus, ECG site of infarct, plasma creatinine, peak creatine kinase, clinical heart failure and radiological heart failure, N-BNP was superior to all other variables at 49–72 h (R²=32.5%), 73–120 h (R²=40.5%) and 121–192 h (R²=32.9%) (all P<0.005). At 14–48 h the predictive value of N-BNP was lower than at other times (R²=27.4%) and less than that of anterior site of infarction (R²=32.2%). The combination of anterior site of infarction and N-BNP at 14–48 h increased the predictive value of the model (R²=42.4%).

**WMI-2**
We considered the same variables in a model for the predictors of WMI-2. The strongest independent predictor of WMI-2 was again N-BNP at 73–120 h (R²=15%). The addition of anterior site of infarct (R²=20%, P<0.05) and past history of acute myocardial infarction (R²=26%, P<0.005) improved diagnostic accuracy. When analysis was restricted to the variables anterior site, N-BNP at 73–120 h, history of myocardial infarction and history of diabetes, anterior site of infarction (P=0.008) displaced N-BNP at 73–120 h (P=0.03) as the strongest predictor of WMI-2, although both retained independent value.

**Predictors of outcome**
N-BNP level at 73–120 h (R²=17.7%, P=0.005) and history of previous myocardial infarction (R²=5.3%, P<0.05) were the only independent predictors of poor outcome (WMI-2 ≤1:2 or death by 6 weeks), the combination accounting for 25% of the variation in response. The only independent predictors of death alone were plasma N-BNP at 73–120 h (R²=35%, P<0.005) and at 121–192 h (R²=14%, P=0.05). The addition of anterior site of infarction to plasma N-BNP at 73–120 h improved the accuracy of the model in predicting death (R²=40%, P<0.05).

Patients with poor outcome (left ventricular systolic dysfunction or death) had higher N-BNP levels compared to the rest at all times (Fig. 3). N-BNP >240 fmol. ml⁻¹ at 73–120 h had a positive predictive value of 74% and a negative predictive value of 61% in predicting WMI-1 ≤1:2, and a positive predictive value of 41% and a negative predictive value of 91% in predicting death or WMI-2 ≤1:2 (Table 2). The corresponding values using N-BNP at 14–48 h were 78% and 58% for WMI-1 ≤1:2 and 37% and 75% for death or WMI-2 ≤1:2.

N-BNP >500 fmol. ml⁻¹ at any time point during the hospital stay had a positive predictive value of 47% and a negative predictive value of 100% in predicting death or WMI-2 of ≤1:2.

**Discussion**
This study is the first to report the optimum time for measurement of N-BNP following acute myocardial infarction. Our results indicate that N-BNP measured later in hospitalization is superior to measurement at earlier times as regards identifying patients with significant left ventricular systolic dysfunction soon after acute myocardial infarction and with poor echocardiographic or clinical outcome in the 6 weeks following acute myocardial infarction. N-BNP measured during the first 2 days after acute myocardial infarction had similar predictive values for WMI-1 but was less useful than the later measurement in predicting death or left ventricular systolic dysfunction in the weeks after discharge. N-BNP at 72–120 h was superior to clinical, radiological or electrocardiographic parameters in the identification of impaired left ventricular systolic function.

**Profile of plasma N-BNP**
Our study confirms that plasma levels of N-BNP are elevated in the early stages following acute myocardial
infarction, peaking within 48 h before declining over the next 48 h. This is followed, after anterior infarction, by a secondary rise in plasma N-BNP at around day 5, maintained 6 weeks later. The biphasic pattern of plasma N-BNP is, not surprisingly, analogous to the pattern of secretion observed for BNP-32 following acute myocardial infarction[5]. This supports the assertion that the initial rise corresponds to release of stored N-BNP following tissue necrosis in the early phase of acute myocardial infarction, with a secondary rise paralleling the ensuing development of infarct expansion and evolution of left ventricular systolic dysfunction. The strongest correlation with impairment of left ventricular function was with N-BNP at 72–120 h, i.e. at the trough of the biphasic response. While this may appear surprising, we suggest that this time point identifies those in whom N-BNP shows the least fall from the initial peak. This may indicate either large amounts of myocardial necrosis, early initiation of the process of ventricular remodelling, or both. Thus not only the absolute magnitude but also the pattern of N-BNP response is related to the size of infarct and development of left ventricular systolic dysfunction subsequent to acute myocardial infarction.

Both BNP[10] and N-BNP[3] predict left ventricular ejection fraction during and some months following acute myocardial infarction, each of these studies assessing the value of a single peptide level measured in the early post infarct period. Our study suggests that N-BNP measured later rather than earlier in the acute phase is a stronger predictor of poor clinical outcome as measured by death or left ventricular systolic dysfunction. This finding has implications for the potential use of N-BNP as a marker for left ventricular dysfunction following acute myocardial infarction.

**Table 2** Sensitivity, specificity, positive predictive value and negative predictive values of clinical heart failure, radiological heart failure and plasma N-BNP at 73–120 h following myocardial infarction for the prediction of death or WMI-2 ≤1.2

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive predictive value (%)</th>
<th>Negative predictive value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical heart failure</td>
<td>63</td>
<td>70</td>
<td>45</td>
<td>82</td>
</tr>
<tr>
<td>Radiological heart failure</td>
<td>63</td>
<td>48</td>
<td>48</td>
<td>76</td>
</tr>
<tr>
<td>Both clinical and radiological heart failure</td>
<td>75</td>
<td>42</td>
<td>34</td>
<td>81</td>
</tr>
<tr>
<td>N-BNP &gt;240 (fmol . ml⁻¹)</td>
<td>85</td>
<td>56</td>
<td>41</td>
<td>91</td>
</tr>
</tbody>
</table>

**Figure 3** Individual plasma N-BNP in patients with poor outcome (WMI ≤1.2 or death) (□) and others (○) following myocardial infarction. Horizontal bars indicate group mean value.
**N-BNP and assessment of left ventricular function**

Impaired left ventricular function is associated with a markedly worse prognosis after acute myocardial infarction. Improvements in outcome are conferred in this situation by the use of appropriate therapies, in particular ACE inhibitors. While the current ‘gold standard’ for the presence of left ventricular dysfunction is the echocardiogram, provision of this investigation is by no means routine after acute myocardial infarction and adequate images may not be obtained in a proportion of patients. Many physicians routinely use validated clinical criteria, as used in major trials[8], to identify high risk patients.

We found a strong correlation between levels of N-BNP and wall motion index during hospitalization, observed despite wide variation in clinical characteristics and patterns of acute management of patients. Our data have also demonstrated a correlation between N-BNP measured 4–5 days after acute myocardial infarction and wall motion index 6 weeks later, in agreement with previous studies[3]. Although the correlation was statistically significant, the absolute strength of association was only moderate ($r = -0.41$, $P=0.005$). Again this is similar to previous findings with N-BNP[3] and BNP[10].

The predictive value of a test in confirming or excluding the presence of a condition is of more clinical relevance. In this context, our finding that N-BNP better identifies left ventricular systolic dysfunction than does radiological or clinical evidence of heart failure or the combination of these is perhaps the most important finding of this study. Previous studies have reported positive and negative predictive values of 39% and 97%[3] and 32–47% and 100%[10], respectively, for identification of impaired left ventricular function using natriuretic peptides. Other studies have questioned the clinical applicability of natriuretic peptides in the identification of patients with left ventricular dysfunction soon after[11] or remote from[12] acute myocardial infarction.

The clinical usefulness of a test depends not only on the strength of association between the marker being assayed and the condition being sought but also on the robustness of the test in comparison to currently applied criteria. Our data indicate that for the prediction of death or WMI-2 $\leq$ 1.2 measurement of N-BNP better identifies patients at high risk (and who might benefit from appropriate early pharmacological therapy) than do clinical or radiological assessment. The strength of N-BNP is emphasized by our demonstration of its superiority to the anterior site of infarction in multivariate models of factors determining wall motion index. Our data confirm the high negative predictive value of N-BNP, allowing identification of patients at low risk. However, we do not suggest that patients with clinical evidence of heart failure but ‘normal’ N-BNP following acute myocardial infarction should be denied appropriate, i.e. ACE inhibitor, therapy.

Our data may be interpreted as showing that measurement of N-BNP, which of currently available neuropeptides best identifies left ventricular systolic dysfunction, remains inferior to echocardiographic assessment. This is once again in agreement with previous studies with BNP, N-ANP and cGMP[10], with N-BNP[3] and with adrenomedullin[9]. However the most appropriate measure of left ventricular dysfunction upon which to base therapeutic intervention is not clear. To date no study has assessed the relative predictive value of the natriuretic peptides or other peptides when compared to quantitative echocardiographic or radionuclide assessment of left ventricular function for risk stratification following acute myocardial infarction. In other words we do not as yet know whether routine provision of echocardiography after acute myocardial infarction is of more clinical value than routine assay of N-BNP or other peptides. Moreover the value of measurement of the natriuretic peptides may provide information not only on an individual patient’s requirement for therapy but also their response to treatment. Indeed much higher doses of ACE inhibitor than those used in the relevant clinical trials are required to normalize plasma BNP levels in patients with chronic heart failure[13]. Our study shows that N-BNP levels were higher in patients receiving ACE inhibitor therapy. This perhaps simply confirms that ACE inhibitors were prescribed to those patients at highest risk and lends further support to the assertion that N-BNP accurately identifies these individuals.

**Assay of N-BNP**

The choice of antibody and the method of peptide measurement may have important implications for the development of a clinically useful assay. Levels of N-BNP recorded in our study, utilizing an antibody against the C-terminal of N-BNP, are considerably higher than the values determined in a previous study using an antibody directed against the N-terminal of N-BNP[3]. The N-terminal domains of preproBNP have been demonstrated to oligomerise through leucine ‘zipper-like coiled-coil’ motifs[14], a short bundle of peptide $\alpha$-helices wound into a superhelix. It is possible that an antibody directed against N-terminal domains of N-BNP is potentially hindered from binding to its equivalent amino acid sequence. C-terminal domains may be more readily accessible and detectable by immunoassay. Such differences in the immunoreactivities of the N- and C-terminals of N-BNP are likely to account for the disparity between the concentrations of N-BNP observed in previous work[3] and the current study. Furthermore, other studies that have employed antibodies towards the mid-section of N-BNP have failed to demonstrate any diagnostic value for detection of left ventricular systolic dysfunction[15–17], further emphasizing the diagnostic utility of the C-terminal N-BNP epitope.

The antibody used in our work is specific for N-BNP, as demonstrated by the immunoreactivity of the anti-
body on SDS-page gels and the insignificant cross-reactivity of the assay with ANP, BNP-32 and γ-BNP[7]. The chemiluminescent assay is simple and inexpensive to perform, does not require the extensive safety measures of conventional radioimmunoassay, and allows rapid processing of a large number of samples. However, until assays for N-BNP or other neurohormones become routinely available, the use of a biochemical marker is unlikely to replace established methods of assessment of ventricular function such as echocardiography. Nevertheless, assays of N-BNP are highly cost-effective, each test costing under £1, compared to the cost of echocardiography ($60–$80).

Limitations of current study

The main limitation of our study is the relatively small number of patients studied. We deliberately chose to study a high risk population with a high prior probability for left ventricular dysfunction. Sixty-five percent of our population suffered anterior acute myocardial infarction, a figure which may in fact have reduced the discriminatory value of N-BNP as compared to previous studies with BNP[10,12] and N-BNP[3] in which the proportion of patients with anterior site of infarction, 39%, 24% and 40%, respectively, was much lower. In addition, our study was not designed to assess the effect of treatment such as thrombolysis and ACE inhibition on N-BNP levels. While we have shown high levels of N-BNP in patients receiving ACE inhibitor therapy, we cannot comment on what levels may have been expected in these patients had they not received this therapy. Finally our study would be strengthened by longer term follow-up of patients.

Our study may be criticized on the grounds of not having compared N-BNP to alternative neuropeptides and cytokines. We chose to assess the value of N-BNP as this is superior to alternative peptides in the identification of left ventricular dysfunction[9]. Moreover we specifically sought to compare the value of this peptide when compared to clinical, radiological, and electrocardiographic criteria. However, further studies comparing N-BNP with alternative markers of left ventricular systolic dysfunction such as N-ANP[2] and troponin T[18], are required to further explore the significance of each and the possible relationship between circulating peptides in the development and progression of left ventricular dysfunction. Finally it may be suggested that elevated N-BNP may represent reduced clearance rather than increased secretion. While we are unable to exclude this possibility, our data relating the magnitude of elevation in N-BNP to the degree of left ventricular dysfunction and the absence of a correlation with plasma creatinine favour increase secretion as the primary explanation for increased plasma levels.

Conclusions

We have shown that N-BNP demonstrates a biphasic pattern of plasma concentration following acute myocardial infarction. N-BNP measured prior to hospital discharge following acute myocardial infarction better predicts patients with significant impairment of left ventricular systolic dysfunction and at risk of poor outcome than either N-BNP measured soon after admission or clinical and radiological parameters. N-BNP has a high negative predictive value for the identification of patients with left ventricular dysfunction following acute myocardial infarction.

The appropriate parameter for the identification of left ventricular dysfunction upon which therapeutic decisions should be made following acute myocardial infarction is unclear. The ultimate aim of studies such as ours is to enable the clinician to better identify patients for whom specific well-tried therapies are appropriate, including those individuals without clinical manifestations of the condition in question. Our study adds to the evidence supporting a useful role for the natriuretic peptides in the identification of patients with left ventricular systolic dysfunction. Large, prospective studies are required to assess the predictive value of N-BNP and other neurohormones, as well as echocardiographic and clinical criteria for the maximum identification of patients at both high and low risk of left ventricular dysfunction following acute myocardial infarction.

We thank the Leicester Royal Infirmary for S.T.’s support.

References


