Short-term fluctuations of plasma NT-proBNP levels in patients with new-onset atrial fibrillation: a way to assess time of onset?

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Short-term fluctuations of plasma NT-proBNP levels in patients with new-onset atrial fibrillation: a way to assess time of onset?

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ABSTRACT

Objective The objective of this study was to characterise short-term kinetics of plasma amino-terminal pro-B type natriuretic peptide (NT-proBNP) levels in patients with new-onset atrial fibrillation (AF) without heart failure.

Design Prospective cohort study.

Setting Emergency departments and inpatient services of three large community hospitals.

Patients 31 consecutive patients with new-onset atrial fibrillation (<24 h prior to presentation) persisting at least 48 h, without evidence of heart failure.

Main outcome measures Plasma NT-proBNP levels were obtained at presentation and then 6, 12, 18, and 24 h after presentation. A final sample was obtained 48 h after onset of AF.

Results Mean plasma NT-proBNP levels and 95% CIs (pg/ml) during the 48-h period following onset of AF were: 0–6 h: 636 (395 to 928), 6–12 h: 1364 (951 to 1778), 12–18 h: 1747 (1412 to 2083), 18–24 h: 1901 (1549 to 2253), 24–36 h: 1744 (1423 to 2066) and 36–48 h: 1101 (829 to 1373). Mean time to peak NT-proBNP levels was 16.7 (0.7) h; 29 patients reached their peak levels within 24 h. The mean peak NT-proBNP level was significantly higher than those obtained at 0–6 h and at 36–48 h after onset of AF (p<0.001 for both). There was no correlation between ventricular rate and plasma NT-proBNP levels during any time period after onset of AF.

Conclusion In patients with new-onset AF but no clinical or radiographic evidence of heart failure, plasma NT-proBNP levels rise progressively to a peak during the first 24 h and then rapidly fall. This pattern may serve as an aid to assess the time from AF onset.

Plasma NT-proBNP levels have been reported to be elevated in patients with AF.7–9 Successful cardioversion is followed by a rapid decrease in plasma NT-proBNP levels in such patients. Previous studies assessing the relation of natriuretic peptides and AF did not distinguish between patients with new-onset AF and those with persistent or permanent AF.8 9 Moreover, prior studies have not reported the short-term evolution of plasma natriuretic peptide levels in patients with new-onset AF without overt heart failure who do not revert to sinus rhythm.5 9 This study assesses the short-term kinetics of plasma NT-proBNP in patients with new-onset AF without clinical or radiographic evidence of heart failure, with the aim of potentially identifying patterns which might permit an approximate assessment of the time of onset of the arrhythmia.

METHODS

Patient selection

Consecutive patients presenting to one of three emergency departments with new-onset AF (onset <24 h prior to presentation) without clinical or radiographic evidence of heart failure were considered for inclusion. Only patients who could specify the precise time of onset of AF were considered for entry. Patients with heart failure (Framingham criteria), an echocardiographic left ventricular ejection fraction <40%, a serum creatinine level ≥1.4 mg/dl, moderate to severe valvular heart disease, pulmonary hypertension and hyperthyroidism or hypothyroidism were excluded, as were patients who reverted to sinus rhythm within 48 h of onset of AF.

Protocol

A complete medical history, physical examination, 12-lead electrocardiogram, chest x-ray, and trans-thoracic (M-mode and two-dimensional) echocardiogram were performed on each patient. Venous blood was obtained for a complete blood count, a serum thyroid stimulating hormone level, serum electrolyte, serum creatinine level and a blood urea nitrogen analysis. Echocardiographic measurements were performed in accordance with the American Society of Echocardiography criteria using a Philips iE33 echocardiography system (Philips Medical Systems, Andover, Massachusetts, USA). Left ventricular ejection fraction was measured using Simpson’s rule in the apical four-chamber view. Left atrial volumes were measured in a similar fashion. Right ventricular systolic pressure was assessed by interrogating the tricuspid valve regurgitant jet

B-type natriuretic peptide (BNP) is a polypeptide produced by the cardiac atria and ventricles as the precursor molecule proBNP.1–4 ProBNP is enzymatically cleaved in the plasma to produce an active carboxy-terminal fragment (biologically active BNP) and an inactive amino-terminal fragment (NT-proBNP).1–4 Both of these biomarkers have proven to be valuable in the evaluation of a variety of cardiac conditions, particularly heart failure.3–4 The plasma half-life of BNP is 21 min, while that of NT-proBNP ranges from 60 to 120 min.1–4 Thus, plasma BNP fluctuates more in response to acute haemodynamic alterations than NT-proBNP, which is more stable over time.4

Atrial fibrillation (AF) occurs in 0.5–1.0% of the general population and in up to 8% of octogenarians,5 6 representing an important cause of stroke.3
(using the built-in system software, which applies the Bernoulli equation), according to common laboratory practice. All measurements were performed during six cardiac cycles and averaged, to account for beat-to-beat variation due to the arrhythmia. Echocardiographic values required consensus of two experienced echocardiographers.

Pharmacologic cardioversion was attempted in all patients using oral propafenone, intravenous amiodarone or intravenous ibutilide at the discretion of the attending physician. Only those who failed cardioversion during the 48-h period after onset of AF remained eligible for the study. All patients received subcutaneous enoxaparin, 1 mg/kg twice per day.

Venous blood samples were obtained using a standard venipuncture technique. Specimens were analysed within 1 h of venipuncture whenever possible. When immediate analysis was not possible, blood samples were centrifuged, and the serum was frozen at –80°C for later analysis. Plasma NT-proBNP levels were measured using a commercially available immunofluorescent assay (Elecsys proBNP, Roche Diagnostics, Mannheim, Germany). The assay has a functional sensitivity of 30 pg/ml, with an upper measuring limit of 35 000 pg/ml and a coefficient of variation in the range of 1.0–6.0%. Blood samples were obtained at presentation and then 6, 12, 18 and 24 h after presentation. A final blood sample was obtained 48 h after onset of AF.

The measured values of NT-proBNP at each time point (at presentation and at 6, 12, 18 and 24 h from presentation) were plotted against time from onset of AF, as were the final measurements performed 48 h after onset of AF as identified by each patient. This process resulted in a total of 186 plasma NT-proBNP measurements scattered continuously over the 48-h period after onset of AF; and values were summarised within the following time periods from AF onset: 0–5, 0–6, 6–12, 12–18, 18–24, 24–36 and 36–48 h. In addition, we present data on NT-proBNP levels for 29 of the 31 patients from blood samples collected approximately 2 weeks after discharge (ie, approximately 2 weeks after conversion to sinus rhythm). This is off-protocol data, gathered as part of the standard follow-up of patients in the outpatient departments of the respective institutions and is presented with the sole purpose to indicate that these patients did not have generally elevated “background” NT-proBNP levels.

This study was approved by the human studies committees of all participating hospitals. Informed consent was obtained in accordance with the principles of the Declaration of Helsinki.

Statistical analysis
Continuous variables were expressed as mean values (1 SE of the mean) and compared using the Student t test for paired and unpaired data. Categorical variables were expressed as counts or percentages. Proportions were compared using the χ² test. Goodness of fit to the normal distribution was tested using the Kolmogorov–Smirnov test (in all groups of NT-proBNP measurements, the Kolmogorov–Smirnov test did not show significant deviations from the normal distribution). The independent effect of multiple variables on plasma NT-proBNP levels was tested using multivariate analysis of variance, of which, that is, through the generalised linear model function. The model included all variables showing in the univariate analysis a tendency (p<0.10) to be associated to the NT-proBNP levels (continuous variables were entered as such, and categorical ones were handled automatically by the software procedure via creation of sets of contrast variables). Univariate analysis of variance was applied to test the significance of the differences among plasma NT-proBNP levels over the time periods cited in the Methods section. A p value <0.05 was required to achieve statistical significance. All statistical analyses were performed using SPSS 15.0 software.

RESULTS
Patient characteristics
Thirty-one patients fulfilling the inclusion criteria were studied. There were 16 women and 15 men (mean age: 64.6 (1.6) years). Patient characteristics are shown in table 1.

Plasma NT-proBNP levels at presentation: relation to clinical and echocardiographic variables
The mean time from onset of AF to presentation was 8.7 (1.1) h (range: 1–20 h). There was a weak positive correlation between time from onset of AF to presentation and age (r=0.499, p=0.004).

Thirty of the 31 patients had plasma NT-proBNP levels at presentation that were well above the reference laboratory upper limit of normal (125 pg/ml) (range 105–9628 pg/ml, median 1475 pg/ml, 95th percentile: 3676 pg/ml).

Multivariate analysis of variance showed that plasma NT-proBNP level at presentation was significantly and independently associated with time from onset of AF, age, sex, left ventricular ejection fraction, right ventricular systolic pressure and left atrial diameter (table 2) (NT-proBNP at presentation was higher in men than women: 1868 (297) vs 1259 (291) pg/ml (multivariate p=0.010), an association which became non-significant when peak hospitalisation NT-proBNP levels were used as the dependent variable, as evident from the data presented in table 2; the rest of these associations were positive, with the exception of left ventricular ejection fraction).

Short-term plasma NT-proBNP kinetics after onset of AF
During the 48-h period after the onset of AF, plasma NT-proBNP levels exceeded the upper limits of normal in all patients. In 29

Table 1 Patient characteristics

<table>
<thead>
<tr>
<th>Patients (n)</th>
<th>31</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>64.6±1.6 (45–79)</td>
</tr>
<tr>
<td>Men</td>
<td>15 (48.4%)</td>
</tr>
<tr>
<td>Women</td>
<td>16 (51.6%)</td>
</tr>
<tr>
<td>History of coronary artery disease</td>
<td>3 (9.7%)</td>
</tr>
<tr>
<td>Mild valve disease</td>
<td>4 (12.9%)</td>
</tr>
<tr>
<td>Hypertension*</td>
<td>18 (58.1%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>5 (16.1%)</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>10 (32.3%)</td>
</tr>
<tr>
<td>Dyslipidaemia†</td>
<td>5 (16.1%)</td>
</tr>
<tr>
<td>Ventricular rate at presentation (beats per minute)</td>
<td>118±3 (91–152)</td>
</tr>
<tr>
<td>NT-proBNP level at presentation (pg/ml)</td>
<td>1553±212 (105–3628)</td>
</tr>
<tr>
<td>Peak NT-proBNP level (pg/ml)</td>
<td>2126±170 (621–3628)</td>
</tr>
<tr>
<td>Time from onset of AF to presentation (h)</td>
<td>8.7±1.1 (1.0–20.0)</td>
</tr>
<tr>
<td>Time from onset of AF to peak NT-proBNP (h)</td>
<td>16.7±0.7 (9.0–26.0)</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>58±1.4 (48–65)</td>
</tr>
<tr>
<td>Right ventricular systolic pressure (mmHg)</td>
<td>28.8±1.3 (15.0–41.0)</td>
</tr>
<tr>
<td>Left atrial diameter (mm)</td>
<td>41.1±0.6 (34.0–49.0)</td>
</tr>
<tr>
<td>Left atrial volume (ml)</td>
<td>61.3±1.1 (51.0–72.0)</td>
</tr>
</tbody>
</table>

Continuous variables are expressed as mean±1 SE of the mean and range. Categorical variables are expressed as counts and percentages.

*SYSTOLIC BLOOD PRESSURE >140 mmHg and/or diastolic blood pressure >90 mmHg or receiving antihypertensive therapy.
†Low-density lipoprotein >100 mg/dl in patients with coronary artery disease or equivalent <160 mg with Framingham 10-year risk <10%, <130 mg/dl with Framingham 10-year risk of 10–20%, HDL <40 mg/dl or >triglyceride level >200 mg/dl.

AF, atrial fibrillation; NT-proBNP, amino-terminal pro-B natriuretic peptide.
patients, a pattern of increase—peak—decrease of plasma NT-proBNP levels was observed. Two patients presenting 16 and 19 h after onset of AF demonstrated a peak—decrease pattern. The mean peak plasma NT-proBNP level was 2126 (171) pg/ml (range: 621–3628 pg/ml, median: 2256 pg/ml, 95th percentile: 3626 pg/ml). The mean time from onset of AF to peak plasma NT-proBNP level was 16.7 (0.7) h (range: 9–26 h, median: 17 h). Twenty-nine of the 31 patients (95.5%) reached peak levels within the first 24 h after onset of AF. The remaining two reached peak levels at 25 and 26 h. By 48 h after onset of AF, plasma NT-proBNP levels were decreasing in all patients. At 48 h after the onset of AF, the mean plasma NT-proBNP level was 669 (76) pg/ml (range: 124–1597 pg/ml).

The mean plasma NT-proBNP level at presentation (1553 pg/ml) and the mean plasma NT-proBNP level 48 h after onset of AF (668 pg/ml) were significantly lower than the peak plasma NT-proBNP level (2126 pg/ml, p<0.001 for both).

Plasma NT-proBNP levels rose rapidly after onset of AF. In seven patients presenting within 3 h of onset of AF, the mean plasma NT-proBNP level was 402 (181) pg/ml.

Multivariate analysis of variance showed significant independent associations between peak plasma NT-proBNP levels and increasing age, left ventricular ejection fraction, left atrial diameter and right ventricular systolic pressure (table 2).

Univariate analysis of variance for differences in mean plasma NT-proBNP levels collected during the time periods designated in the Methods section showed significant variation across strata (F statistic 5.626, p<0.001). Figure 1 shows mean NT-proBNP levels during 0–6, 6–12, 12–18, 18–24, 24–36 and 36–48 h after onset of AF. Mean values (pg/ml) during the time periods cited and their 95% CIs (in parentheses) were as follows: 0–6, n=16, 636 (395 to 928); 6–12 h, n=21, 1564 (957 to 178); 12–18 h, n=28, 1747 (1412 to 2083); 18–24 h, n=31, 1901 (1549 to 2253); 24–36 h, n=31, 1744 (1423 to 2066) and 36–48 h, n=31, 1101 (829 to 1373). It is worthy of note that, if the NT-proBNP age-adjusted cutoff levels, determined in the Interna-

cional Collaborative of NT-proBNP Study as highly predictive of acute heart failure,10 were used (over 450 pg/ml in those <50 years of age, over 900 pg/ml in those aged 50–75 years and over 1800 pg/ml in those >75 years), 67.7% (21 of 31) of the patients had NT-proBNP above the cutoff at presentation, and 83.9% (26 of 31) exceeded the respective cutoff at any time during the sampling period.

NT-proBNP levels in blood samples collected approximately 2 weeks post-discharge (ie, with patients in sinus rhythm) were significantly lower than the levels measured at presentation as well as after 48 h in AF (194 (21) pg/ml vs 1571 (226) pg/ml vs 648 (79) pg/ml; p<0.001). The fact that, about 2 weeks after the AF episode, patient NT-proBNP levels had almost returned to normal indicates that these patients had generally “normal” background NT-proBNP values, and the increased levels measured during the study were indeed a result of AF.

Relation of the ventricular rate and blood pressure to plasma NT-proBNP levels

Ventricular rates at presentation ranged from 91 to 152 beats per minute (mean: 118 (3) beats per minute). Only two patients received rate control medication. Mean ventricular rate and blood pressure at various sampling time points are shown in table 3. There was no correlation, after controlling for age and sex, between ventricular rate and plasma NT-proBNP level at presentation (r=0.350; p=0.065) or at 0–6, 6–12, 12–18, 18–24, 24–36 and 36–48 h after onset of AF (p non-significant for all). Blood pressure, as obvious in table 3, did not demonstrate significant variation during the sampling period. The above observations indicate that the observed NT-proBNP pattern cannot be attributed to changes in heart rate and blood pressure.

DISCUSSION

This study confirms previous observations that plasma NT-proBNP levels are frequently elevated in patients with AF without clinical or radiographic evidence of heart failure.8 9 Our findings extend these observations by characterising the kinetics

Table 2

<table>
<thead>
<tr>
<th>Variable</th>
<th>F statistic</th>
<th>Multivariate p Value</th>
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</thead>
<tbody>
<tr>
<td>At presentation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time from onset of AF to presentation*</td>
<td>139.827</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age*</td>
<td>35.361</td>
<td>&lt;0.001</td>
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<tr>
<td>Sex</td>
<td>7.939</td>
<td>0.010</td>
</tr>
<tr>
<td>Left ventricular ejection fraction†</td>
<td>16.077</td>
<td>0.001</td>
</tr>
<tr>
<td>Left atrial diameter*</td>
<td>4.775</td>
<td>0.041</td>
</tr>
<tr>
<td>Left atrial volume*</td>
<td>3.030</td>
<td>0.009</td>
</tr>
<tr>
<td>Right ventricular systolic pressure*</td>
<td>4.806</td>
<td>0.041</td>
</tr>
<tr>
<td>Ventricular rate</td>
<td>2.500</td>
<td>0.128</td>
</tr>
<tr>
<td>At peak levels</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age*</td>
<td>33.698</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex</td>
<td>1.150</td>
<td>0.295</td>
</tr>
<tr>
<td>Left ventricular ejection fraction†</td>
<td>23.432</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left atrial diameter*</td>
<td>26.197</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left atrial volume*</td>
<td>4.783</td>
<td>0.041</td>
</tr>
<tr>
<td>Right ventricular systolic pressure*</td>
<td>7.445</td>
<td>0.012</td>
</tr>
<tr>
<td>Ventricular rate</td>
<td>0.204</td>
<td>0.656</td>
</tr>
</tbody>
</table>

Bold-faced p values indicate statistical significance, ie p<0.05.

*Positive association.

†Negative association.

AF, atrial fibrillation; NT-proBNP, amino terminal pro-B type natriuretic peptide.

<ref>Figure 1</ref> Kinetics of plasma NT-proBNP levels during the 48-h period after onset of atrial fibrillation (AF). Note the progressive increase in mean plasma NT-proBNP levels during the first 24 h after onset of AF, followed by a rapid decrease during the second 24-h period. Bars represent mean values, and the "whiskers" correspond to 1 SE of the mean.
of plasma NT-proBNP levels during the 48-h period after onset of AF. Our results demonstrate that plasma NT-proBNP levels rise to a peak during the 24-h period following onset of AF and then progressively decline over the next 24 h. It was also shown that the majority of studied patients exceeded the age-adjusted NT-proBNP levels considered to be highly predictive of acute heart failure, either at presentation or at any time during the sampling period. This was true despite the fact that no patient had history or clinical/radiography signs of acute heart failure (as these were exclusion criteria), suggesting that NT-proBNP levels may be less specific for acute heart failure in the context of acute onset AF.

Previous studies have reported elevated plasma NT-proBNP levels in patients with AF without heart failure with levels ranging from 900 to 1100 pg/ml. However, these studies are not directly comparable to ours in that they did not confine their study populations to patients with AF of recent onset. Our results indicate that plasma NT-proBNP levels rise rapidly after onset of AF. Plasma NT-proBNP levels were more than three times the upper limit of normal 5 h after onset of AF. The main source of NT-proBNP in this setting is probably the atria.\(^1,1^2\) Proposed mechanisms for stimulation of NT-proBNP production include the high frequency of atrial myocyte contraction and local atrial inflammation.\(^1^2,1^5\) In addition, increased intracardiac pressures, specifically intra-atrial pressures, and altered haemodynamics during AF may stimulate increased natriuretic peptide secretion by the heart.

The key finding in this study is the rapid rise of plasma NT-proBNP levels to peak followed by a rapid decline. The cause of this pattern is uncertain. One explanation is that the precursor peptide proBNP is rapidly produced in the atria following onset of AF only to become depleted as AF persists. Normal atrial myocytes express atrial natriuretic peptide and BNP genes. ProBNP is stored in atrial granules.\(^1,1^2,1^4,1^5\) A possible explanation for our findings is that pre-produced proBNP molecules stored in abundance in atrial myocyte granules are secreted as BNP and NT-proBNP in response to the haemodynamic effects of new-onset AF. The subsequent decline in plasma NT-proBNP levels may reflect depletion of stored proBNP followed by a steady-state lower-level production of NT-proBNP by atrial myocytes as AF persists.\(^1^2\) This hypothesis is conjecture. However, a decline in plasma atrial natriuretic peptide levels in patients with protracted AF induced by surgical atrial damage and the inverse relationship between plasma atrial natriuretic peptide levels and duration of AF observed in such patients have been postulated to occur because of depletion of the precursor to atrial natriuretic peptide.\(^1^9\) This finding is not directly comparable to ours as it involved patients with permanent AF. Nevertheless, that study like our study raises the possibility of atrial myocyte depletion of atrial pro-natriuretic peptide precursors as an explanation for observed variations in plasma natriuretic peptide levels in patients with AF without heart failure. It should additionally be noted that during AF the atria are not the only source of NT-proBNP, since it is highly likely that the ventricles will also respond to altered haemodynamics and intraventricular pressures, releasing natriuretic peptides.

### Study limitations

Study limitations include the small sample size and potential errors in assessing the actual time of AF onset. Although we took care to obtain reliable information concerning time of onset of AF and excluded patients for whom information was questionable or unreliable, there is no infallible way to be certain about the precise time of AF onset, short of direct observation. Accordingly, we are unable to eliminate this potential error with absolute certainty.

### Study implications

Apart from a purely theoretical observation, the pattern of variation noted during the first 48 h after onset of AF may assist clinicians in determining whether or not the onset of AF was recent or more remote. According to our observations, a rising trend is markedly indicative of the fact that AF onset did not happen more than 24–48 h before presentation. As a consequence, obtaining two to three plasma NT-proBNP levels within 24 h of presentation in patients with AF without heart failure who cannot satisfactorily pinpoint the time of onset may assist in determining whether the onset of the arrhythmia was recent. Such information is pertinent to decisions concerning anti-coagulation and cardioversion.

### Competing interests None.

### Patient consent Obtained.

### Ethics approval This study was conducted with the approval of the Review Boards of participating Hospitals.

### Provenance and peer review Not commissioned; externally peer reviewed.

### REFERENCES