N-terminal pro-b-type natriuretic peptide and left atrial function in patients with congestive heart failure and severely reduced ejection fraction†

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Aims
Amino-terminal portion of pro-B-type natriuretic peptide (NT-pro-BNP) is a valuable diagnostic and prognostic marker in congestive heart failure (CHF). In CHF patients, elevation of natriuretic peptide levels correlate with decreased left ventricular (LV) ejection fraction (EF) and increased left atrial (LA) volumes, but a correlation with LA function that is a determinant of haemodynamic and clinical status in CHF with independent prognostic value has never been investigated. Aim of this study was to evaluate the relationship between cardiac neurohormonal activation and LA function in patients with CHF due to dilated cardiomyopathy.

Methods and results
One hundred and one patients (86% males; mean age, 64 ± 11 years) with dilated ischaemic or non-ischaemic cardiomyopathy, LV EF ≤ 45% (mean LV EF, 33 ± 8%), and New York Heart Association class II–IV underwent trans-thoracic echocardiography to evaluate LA fractional active and total emptying from M- and B-Mode images, and, on the same day, venous blood sample collection to dose NT-pro-BNP. By univariate analyses, NT-pro-BNP significantly correlated to age, LA dimensions, LA function indexes, EF, and functional class. At multivariate analysis, LV EF and M- or B-Mode indexes of LA function were the only independent predictors of NT-pro-BNP values. A NT-pro-BNP cut-off of 1480 pg/mL identified LA dysfunction with 89% specificity and 54% sensitivity.

Conclusion
In CHF patients with severely impaired systolic function, NT-pro-BNP levels reflect LA and LV dysfunction. These data should prompt studies to investigate the relationship between changes of LA function and NT-pro-BNP levels and their clinical value as prognostic and therapeutic targets in CHF.

Keywords
Left atrial function • Heart failure • Natriuretic peptides

Introduction
B-type natriuretic peptide (BNP) and amino-terminal portion of pro-BNP (NT-pro-BNP) are established markers of left ventricular (LV) dysfunction and recognized diagnostic and prognostic parameters in patients with congestive heart failure (CHF). Some authors reported that NT-pro-BNP, compared with BNP, would be more accurate for the detection of LV dysfunction and for the prediction of cardiac adverse events, in addition and incrementally to ejection fraction (EF), yet the available literature still remains controversial about any different clinical value of these forms of the natriuretic peptide.
The cardiac hormonal system is activated in response to increased wall stretch due to LV pressure or volume overload, and increased NT-pro-BNP levels correlate with increased LV filling pressures and independently predict elevation of LV end-diastolic pressure in patients with CHF. Augmented LV filling pressure leads, in turn, to progressive dilation and dysfunction of left atrium (LA) and is recognized as independent determinant of LA size and function in patients with coronary artery disease and CHF.

In subjects with normal cardiac function, LA contribution to cardiac filling is limited, but it may account for up to 30% of the stroke volume in CHF patients with elevated end-diastolic pressure. Thus, in CHF patients the occurrence of LA dysfunction further compromises the haemodynamic status, explaining the independent contribution of LA size for predicting adverse prognosis in these patients. Yet, although in CHF patients NT-pro-BNP levels correlate with LA volumes, data investigating the relationship with LA function are lacking. Therefore, the aim of this study was to investigate the relationship between NT-pro-BNP levels and LA function in patients with systolic CHF.

Methods

The study population consisted of 101 consecutive patients referring to the CHF clinic at the Federico II University of Naples, Italy. To be included in the study, patients needed to fulfill the following criteria: (i) LV EF ≤45% in at least two consecutive echocardiographic examinations; (ii) sinus rhythm; (iii) unchanged medical therapy on the last 2 weeks; (iv) coronary angiography within 1 year from enrolment; (v) no acute coronary syndrome in the 6 months before enrolment. In 71 (70%) patients, CHF was of ischaemic aetiology, whereas in 30 (30%) subjects, the aetiology was an idiopathic dilated cardiomyopathy. Patients affected by severe renal failure (glomerular filtration rate ≤30 mL/min, calculated by the Cockcroft–Gault formula), patients with pacemaker rhythm at the electrocardiogram (ECG) examination, and patients with all forms of atrial fibrillation or other supraventricular arrhythmias were excluded from the study. All the patients enrolled in the study were on standard and optimized oral therapy for the treatment of CHF, including the use of angiotensin-converting enzyme-inhibitors or angiotensin II type 1 receptor (AT1) antagonists when not tolerated, beta-blockers, loop diuretics, anti-aldosterone diuretics, and digitalis when necessary in addition to conventional drugs used for secondary prevention of coronary heart disease and for treatment of cardiovascular risk factors (Table 1). On the same day, after recording of clinical data, all patients underwent transthoracic echocardiography and sampling of peripheral venous blood for NT-pro-BNP measurement. The patients gave written informed consent to participate in the study which was approved by the hospital Ethics Committee.

Evaluation of amino-terminal portion of pro-B-type natriuretic peptide

Fasting venous blood samples were collected in ethylenediaminetraacetic acid-containing tubes and centrifuged within 1 h. Amino-terminal portion of pro-B-type natriuretic peptide measurement was then performed using an electrochemiluminescence sandwich immunoassay (ECLIA, Roche Diagnostics) on a Modular analytics Roche Elecsys. The lower analytic sensibility of this method was 5 pg/mL. The analytic range of the NT-pro-BNP assay extended from 5 to 35 × 10^3 pg/mL. The intra-assay and inter-assay imprecision were, respectively, <3 and <5%. The cross reactivity tested on immunologically affine molecules was <0.001%.

Transthoracic echocardiography

A standard transthoracic echocardiography was performed in all patients using a iE33 Philips system with second-harmonic capability and a 3.5 MHz probe. Global and regional LV function was evaluated; in particular, EF was calculated from apical four- and two-chamber views using the Simpson’s biplane method. Measurements of left ventricular diameters were obtained by M-mode technique according to the European Society of Cardiology Recommendations for Chamber Quantification. LA transverse dimensions were assessed in a short-axis view, obtained at the level of the aortic bulb.

Table 1 Oral pharmacological therapy of enrolled congestive heart failure patients and influence on amino-terminal portion of pro-B-type natriuretic peptide

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n (%)</th>
<th>P-value</th>
</tr>
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<tbody>
<tr>
<td>Beta-blockers</td>
<td>83 (82)</td>
<td>ns</td>
</tr>
<tr>
<td>ACE-inhibitors</td>
<td>64 (63)</td>
<td>ns</td>
</tr>
<tr>
<td>AT1 antagonists</td>
<td>34 (33)</td>
<td>ns</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>71 (70)</td>
<td>ns</td>
</tr>
<tr>
<td>Anti-aldosterone</td>
<td>30 (30)</td>
<td>ns</td>
</tr>
<tr>
<td>Digitalis</td>
<td>15 (15)</td>
<td>ns</td>
</tr>
<tr>
<td>Other diuretics</td>
<td>12 (12)</td>
<td>ns</td>
</tr>
<tr>
<td>Calcium-antagonists</td>
<td>14 (14)</td>
<td>ns</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>18 (18)</td>
<td>ns</td>
</tr>
<tr>
<td>Statins</td>
<td>65 (64)</td>
<td>ns</td>
</tr>
<tr>
<td>Antiplatelets</td>
<td>75 (74)</td>
<td>ns</td>
</tr>
</tbody>
</table>

Figure 1 Assessment of M-mode left atrial diameters. Echocardiographic short-axis view at level of the aortic bulb and the relative M-mode imaging with graphic illustration of left atrial maximum, minimum, and pre-contraction diameter. LAMax, left atrial maximum diameter; LAMin, left atrial minimum diameter; LAA, left atrial pre-contraction diameter.
In consideration of the wide range and of the not skewed distribution of NT-pro-BNP levels, the peptide values were log-transformed to reduce the effects of extreme values and to obtain a normal distribution for statistical tests. Accuracy of NT-pro-BNP levels to predict LA dysfunction was assessed by receiver operating characteristics curve (ROC) analysis. A P-value of <0.05 was considered significant.

Results

The study included 101 patients (86% males; mean age, 64 ± 11 years) with a mean LV EF of 33 ± 8% (range 13–45%). Clinical and echocardiographic characteristics of the study population are listed in Table 2. Mean NT-pro-BNP was 2424 ± 5235 pg/mL (range, 6–35,000 pg/mL); mean creatinine was 1.17 ± 0.40 mg/dL, corresponding to mean creatinine clearance of 84 ± 32 mL/min. No patient had significant mitral or aortic stenosis; 66 (65%) patients showed mild mitral regurgitation, 30 (30%) patients showed mild aortic regurgitation, and only 5 (5%) patients had moderate mitral valve regurgitation. Patients with severe mitral regurgitation did not show significant higher NT-pro-BNP values when compared with other subjects (3654 ± 2062 vs. 2444 ± 5524; P = ns). Regarding LV diastolic function, 54 (53%) patients had mild diastolic dysfunction, 23 (23%) patients showed a pseudonormal LV filling pattern, and 13 (13%) patients a restrictive pattern, whereas the other 11 patients (11%) had a normal LV diastolic function. The analysis of variance (ANOVA test) showed significant differences in NT-pro-BNP values between these groups of diastolic dysfunction (P = 0.002); in addition, Bonferroni test demonstrated a statistically significant difference between patients with normal diastolic function vs. subject with restrictive pattern (P = 0.001) and between patients with pseudonormal pattern vs. and subjects with restrictive LV filling pattern (P = 0.02). All, but 8 patients were in stable heart failure status, with 69 (68%) patients in New York Heart Association (NYHA) class II, 24 (24%) in class III, and 8 (8%) in class IV. We performed a linear regression analysis to evaluate the effect of CHF treatment on NT-pro-BNP levels, and no relation was found between NT-pro-BNP and the previously mentioned classes of drugs (Table 1). The two groups of subjects (idiopathic vs. ischaemic CHF) did not differ in terms of LA function, both for M-mode parameters, such as LA FAE M-mode (10.7 ± 5.1 vs. 8.9 ± 4.5, respectively; P = ns) and LA FT M-mode (17.4 ± 7.6 vs. 15.5 ± 6.1, respectively; P = ns), both for biplanar measurements, such as LA FAE B-mode (22.7 ± 6.2 vs. 25.5 ± 6.6, respectively; P = ns) and LA FT B-mode (42.6 ± 10.8 vs. 41.2 ± 8.4, respectively; P = ns); thus
we included these patients together in the statistical analysis and considered them as a single population.

**Determinants of amino-terminal portion of pro-B-type natriuretic peptide**

At linear regression analysis, Log\_NT-pro-BNP significantly correlated with age and LA diameters and volumes, as reported in Table 3. A significant direct correlation was also found between Log\_NT-pro-BNP and NYHA class (Figure 2) and LV diameters and volumes and also with mitral inflow E/A ratio and with E/Ea ratio, whereas a significant inverse correlation was found between Log\_NT-pro-BNP and EF (Figure 2), as listed in Table 3. In addition, a significant correlation was found between Log\_NT-pro-BNP and mono-dimensional and biplanar indexes of LA function. In particular, Log\_NT-pro-BNP was inversely correlated to LA FAE M-mode (r = −0.34, P = 0.001) and to LA FT M-mode (r = −0.36, P < 0.0001), and, similarly, to LA FAE B-mode and to LA FT B-mode (r = −0.28, P = 0.004; r = −0.37, P < 0.0001, respectively; Figure 3). To better assess the relationship between NT-pro-BNP and LA function and dimensions with patients’ haemodynamic status, we performed a multivariate analysis including LA diameters and volumes, LA function measurements, NYHA class, and EF. The analysis showed that only LA function M-mode (LA FAE \( \beta = −0.32, P = 0.02 \); LA FT \( \beta = −0.23, P = 0.01 \)) and B-mode parameters (LA FAE \( \beta = −0.22, P = 0.03; \) LA FT \( \beta = −0.27, P = 0.02 \)) and EF (\( \beta = −0.35, P = 0.02 \)) remained significant predictors of NT-pro-BNP levels, whereas LA diameters and volumes and NYHA did not remain significantly correlated with the natriuretic peptide.

**Amino-terminal portion of pro-B-type natriuretic peptide as predictor of left atrial dysfunction**

Amino-terminal portion of pro-B-type natriuretic peptide levels were then tested to identify patients with abnormal LA function defined by the mean value measured in normal subjects −2.5 SD. By ROC analysis, NT-pro-BNP predicted reduced LA M-mode dysfunction with high specificity. In particular, a cut-off value of 1480 pg/mL predicted reduced LA FAE M-mode with 72% specificity and 57% sensitivity [area under the curve (AUC) = 0.68; \( P = 0.002 \)] and abnormal LA FT M-mode with 89% specificity and 54% sensitivity (AUC = 0.73; \( P < 0.0001 \)). Using biplanar LA function indexes, NT-pro-BNP, for a cut-off of 1000 pg/mL, predicted LA FAE M-mode dysfunction with 72% specificity and 57% sensitivity (AUC = 0.63; \( P = 0.01 \)), and LA FT B-mode dysfunction with 78% specificity and 55% sensitivity (AUC = 0.66; \( P = 0.003 \)) (Figure 4).

**Discussion**

Natriuretic peptides are established diagnostic and prognostic markers of acute \(^1\) and chronic CHF, \(^2\) and NT-pro-BNP also identifies patients with asymptomatic LV dysfunction in populations at risk for CHF. \(^3\) Several studies documented the relationship between NT-pro-BNP and haemodynamic, clinical, and echocardiographic parameters of LV systolic and diastolic function. \(^4\) However, these studies included subjects with heterogeneous degrees of LV dysfunction, whereas determinants of cardiac neurohormonal activation in populations of patients with reduced LV function were less investigated.

In the present study, in which only patients with CHF and reduced EF were enrolled, a significant correlation was found between NT-pro-BNP and LA diameters and volumes, and an inverse significant correlation with single and biplanar parameters of LA dysfunction. Consistent with previous reports, a significant correlation was also found with EF, showing an increase in NT-pro-BNP levels in parallel with the severity of LV dysfunction, \(^4\) and with NYHA class. \(^26\) By multivariate analysis, EF and LA function indexes (measured by either M- or B-Mode) remained the only significant predictors of NT-pro-BNP levels, indicating the incremental contribution of LA function to neurohormonal activation in CHF.

![Table 3](https://academic.oup.com/ehjcimaging/article-abstract/12/7/506/2397102/725622705102?gust&26-January-2019)
Figure 2 Correlation between Log_NT-pro-BNP and New York Heart Association class and between Log_NT-pro-BNP and EF. Scatter plot showing direct correlation between Log_NT-pro-BNP and New York Heart Association class (A). Scatter plot showing inverse correlation between Log_NT-pro-BNP and EF (A). Log_NT-pro-BNP, logarithmic transformation of amino-terminal portion of pro-B-type natriuretic peptide; NYHA, New York Heart Association; EF, ejection fraction; Log_NT-pro-BNP, logarithmic transformation of amino-terminal portion of pro-B-type natriuretic peptide.

Figure 3 Correlation between Log_NT-pro-BNP and left atrial function. Scatter plot showing inverse correlation between Log_NT-pro-BNP and left atrial FAE M-mode (A), left atrial FT M-mode (B), left atrial FAE B-Mode (C), and left atrial FT B-mode (D). Log_NT-pro-BNP, logarithmic transformation of amino-terminal portion of pro-B-type natriuretic peptide; LA FAE, left atrial active emptying fraction; LA FT, left atrial total emptying fraction.
Our findings further expand the reported association between LA dimension, cardiac neurohormonal activation, and prognosis reported in patients with ischaemic and non-ischaemic CHF,11–13,27 and in subjects with pre-clinical cardiac disease.28 In a previous study by D’Andrea et al.,29 lower LA active emptying volume and fraction have been found in patients affected by idiopathic dilated cardiomyopathy when compared with subjects affected by ischaemic dilated cardiomyopathy. In contrast with these results, we found similar LA dysfunction between ischaemic and non-ischaemic patients, both for the evaluation of mono-dimensional LA function and for biplanar parameters.

In CHF patients, increased LA dimensions reflect elevated LV filling pressures and during last years, attention has been focused on the relationship between natriuretic peptides and LA size. Barclay et al.13 found in a series of 52 patients affected by stable chronic heart failure with reduced EF and without significant valvular disease, a significant correlation between BNP and LA volume indexed to body surface area, as an indicator of chronically increased LV filling pressure, and also showed that LA volume was the strongest independent predictor of elevated natriuretic peptide levels. Similar results were reported by Kim et al.14 in patients affected by heart failure with preserved LV EF. In this study, 148 patients with EF ≥50% underwent transthoracic echocardiography to evaluate diastolic dysfunction. The authors could demonstrate only a weak correlation between LA volume and either tissue Doppler-derived diastolic measurements or NT-pro-BNP levels, although they observed that in patients with E/E’ ratio ≥13, that is with diastolic dysfunction, LA volume was the most powerful predictor of elevated NT-pro-BNP levels. The same authors also showed, in patients with non-ischaemic dilated cardiomyopathy, the prognostic independent role of NT-pro-BNP and LA diameter, reporting that patients with both increased NT-pro-BNP and LA dimension index had a 27-fold higher risk of the composite outcome of cardiac death and hospital readmission for worsening of CHF.12 In addition, natriuretic peptides have also been found to correlate with the parameters of diastolic dysfunction providing, in combination with tissue Doppler imaging, high specificity in identifying the presence of isolated LV diastolic dysfunction.30,31 Collectively, these data indicate a relationship between LA size, LV diastolic dysfunction, and increased LV filling pressure with neurohormonal activation in heart failure. Yet, limited data are available on the relationship...
with LA function in CHF. In patients with CHF, LA function plays a relevant contribution to stroke volume increase, and occurrence of LA dilatation and dysfunction compromises the haemodynamic and functional status. In addition, in our study, NT-pro-BNP significantly correlated with mitral inflow indexes, which reflect increased LA pressure, and with E/Ea ratio, which provides an indirect estimate of LV filling pressure. Therefore, our data indicate that both LV and LA dysfunction contribute to increased NT-pro-BNP in patients with CHF, and that NT-pro-BNP increase identifies LA dysfunction with high specificity. This is consistent with the reported observation that LA loss of function due to atrial fibrillation is associated with elevated levels of natriuretic peptides.32,33 In fact, Rienstra et al.32 and Corell et al.33 demonstrated higher values of NT-pro-BNP in patients affected by CHF with atrial fibrillation compared with CHF patients in sinus rhythm. Our data also suggest that NT-pro-BNP changes induced by therapy are not expected to closely parallel changes in EF in patients with persistent LA dysfunction.

Study limitations
In the present study only a single measurement of LA function and NT-pro-BNP was used in each patient. This prevents to evaluate whether changes of LA function during the course of CHF are paralleled by changes in neurohormonal peptides levels and, most importantly, whether they may be useful for therapy optimization and risk stratification. The substantial dispersion of values around correlation lines in Figures 2 and 3, and the reduced sensitivity of BNP measurement to identify LA function abnormally should also caution about the potential use of serial BNP measurement to evaluate therapy and predict the outcome in the single patients. This can only be assessed from prospective observation and cannot be extrapolated from the current findings.

Conclusions
In CHF patients with severely impaired systolic function, NT-pro-BNP levels independently correlate with LV and LA EF. Therefore, NT-pro-BNP levels reflect LA and LV dysfunction in these patients. These data should prompt the follow-up studies to investigate the relationship between changes of LA function and NT-pro-BNP levels and their clinical value as prognostic and therapeutic targets in CHF.

Conflicts of interest: none declared.

References


IMAGE FOCUS

Foetal intrapericardial teratoma

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Clinical message

A healthy 34-year-old woman at 35+0 weeks’ gestation was referred to the Pediatric Cardiology Unit with the diagnosis of a foetal cardiac mass.

A foetal echocardiogram was performed, revealing a 3.5 × 2.7 cm intrapericardial multiloculated cystic mass, with no flow within and mild pericardial effusion associated (Panel A, Supplementary data online, Movie 1). The mass was related to the intrapericardial portion of the aorta and right atrium, without causing compression. No further anomalies were detected. An intrapericardial teratoma was suspected.

Echocardiographic follow-up showed progressive growth of the mass up to 4 × 3.5 cm, with mild pericardial effusion and no haemodynamic repercussion (Supplementary data online, Movie 2).

An elective Caesarean section was performed at 38 weeks of gestation. A male newborn with normal weight and Apgar score was delivered. The transthoracic echocardiogram confirmed the diagnosis of an intrapericardial mass, which seemed to be attached to the right atrium free wall, and extended to the aorta (Panel B, Supplementary data online, Movies 3 and 4). The pericardial effusion remained mild, and no compromise signs were present. Serum alpha-fetoprotein reached 96 756 ng/mL.

Elective off-pump surgery was performed in the third day of life. An intrapericardial mass of 4 × 3.25 cm was excised. The implantation pedicle arose from the aortic root, with an adventitial feeding artery. No adhesion or infiltration of surrounding structures was found. The pathology revealed an encapsulated cystic mature teratoma.

The postoperative course was uneventful. One month later, the patient remains asymptomatic and recurrence-free.

Supplementary data

Supplementary data are available at European Journal of Echocardiography online.

Panel A Foetal short-axis view. Two-dimensional echocardiography demonstrating a multiloculated mass.

Panel B Echocardiographic two-dimensional apical four-chamber view of the newborn. The mass is closely related the right atrium, and associated pericardial effusion is present.