

Natriuretic peptide system is not exhausted in severe heart failure

Patrícia Lourenço^a, Ana Azevedo^{a,b}, José Paulo Araújo^a and Paulo Bettencourt^a

Objective We aimed to investigate the prognostic value of amino-terminal B-type natriuretic peptide (NT-pro-BNP) in severe heart failure.

Methods We retrospectively assessed 133 patients admitted to the hospital for decompensated heart failure, in New York Heart Association class III or IV, with depressed left ventricular ejection fraction and an NT-pro-BNP measurement within 24 h of admission. Patients were followed up for 6 months.

Results Patients' mean age was 71.2 years; 52.6% were men; 45.9% had severe systolic dysfunction and etiology was ischemic in 56.4%. Thirty- three (24.8%) patients died during follow-up. A forward stepwise Cox regression analysis showed a multivariate-adjusted positive impact of high NT-pro-BNP levels on mortality. Patients in the third NT-pro-BNP tertile (>11378 pg/ml) had a hazard ratio of death of 5.34 [95% confidence interval (CI) 1.65–16.24] when compared with those in the first tertile (<4990 mg/l).

Conclusion We conclude that in patients with severe heart failure, NT-pro-BNP has a powerful prognostic value.

Introduction

The natriuretic peptide system is activated early in heart failure, representing one of the beneficial compensatory mechanisms [1].

Circulating B-type natriuretic peptide (BNP) and amino-terminal B-type natriuretic peptide (NT-pro-BNP) levels play a role in the assessment of prognosis in acute heart failure patients [2–6], with higher levels being associated with poorer outcome. In patients with left ventricular systolic dysfunction, circulating levels of BNP correlate positively with the clinical severity of the disease, as assessed by New York Heart Association (NYHA) classification [7]. A reliable prognostic value of elevated plasma BNP has been consistent in patients with chronic heart failure [4,8–10]. In these patients, each 100 pg/ml increase was associated with a 35% increase in the relative risk of death [4].

Despite these observations, recent reports [11–13] have argued against this general idea and observed a significantly worse prognosis in severe heart failure patients with lower BNP/NT-pro-BNP levels compared with those with higher natriuretic peptide levels. The exhaustion of this

Patients with high NT-pro-BNP had more than five-fold increase in the 6-month risk of death. Our results do not support the hypothesis that ventricular exhaustion with inability to synthesize and secrete natriuretic peptides is the mechanism underlying decompensation. Attenuation mechanisms of compensatory systems ought to be further studied. *J Cardiovasc Med* 10:39–43 © 2009 Italian Federation of Cardiology.

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^aServiço de Medicina Interna—Hospital S. João, Faculdade de Medicina da Universidade do Porto, Unidade I&D Cardiovascular do Porto and ^bServiço de Higiene e Epidemiologia, Faculdade de Medicina da Universidade do Porto, Porto, Portugal

Correspondence Paulo Bettencourt, Serviço de Medicina Interna,
Hospital S. João, Alameda Professor Hernâni Monteiro, 4202-451 Porto,
Portugal
Tel: +351225512200; fax: +351225512332;
e-mail: pbettfer@med.up.pt

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neurohormonal system, with the ventricles being unable to synthesize and release higher amounts of the peptide, or increased degradation or clearance, or both, has been suggested as a possible cause for these observations.

We aimed to study the prognostic value of NT-pro-BNP in patients with severe heart failure in order to evaluate whether severe heart failure patients were unable to produce natriuretic peptides.

Methods

We selected a group of patients admitted to the hospital for severe heart failure between October 2002 and April 2004. Inclusion criteria were: previously established heart failure diagnosis according to the European Society of Cardiology (ESC) guidelines [14]; severely symptomatic decompensated heart failure (NYHA class III and IV at admission); depressed left ventricular function (ejection fraction <40%) and an available NT-pro-BNP measurement in the first 24 h of admission. During the established study period, 177 patients fulfilled the inclusion criteria. Patients with acute coronary syndrome in the previous 3 months, severe renal dysfunction (plasma creatinine > 2.0 mg/dl or in hemodialysis) or chronic liver disease

were excluded. Moderate renal failure was defined by a plasma creatinine of at least 1.5 mg/dl. Nineteen patients were excluded for acute coronary syndrome being the cause of heart failure decompensation, 24 for severe renal dysfunction and one for chronic liver disease with ascitis. One hundred and thirty-three patients were evaluated. During hospitalization, all patients received heart failure treatment according to the discretion of the attending physician. Beta-blocker doses are carvedilol equivalent and angiotensin-converting enzyme inhibitor (ACEi) doses are lisinopril equivalent. Discharge was decided by the attending physician. After discharge, patients were followed for 6 months. Follow-up was made by telephone contact with patients or relatives by an investigator blinded for NT-pro-BNP levels. The primary endpoint was all-cause death. Readmission for decompensated heart failure was considered to be another endpoint.

NT-pro-BNP was measured using a chemiluminescent immunoassay kit (Roche Diagnostics, Indianapolis, Indiana, USA) on an Elecsys 2010 analyzer – measuring range 5–350 000 pg/ml. The intra-assay coefficient of variation was 0.9% at mean value of 474 pg/ml; 1.1% at mean values of 8005 pg/ml and 0.9% at mean values of 13 682 pg/ml.

Statistical analysis

Numerical variables are presented as mean \pm SD or median (interquartile range) if non-normally distributed. Categorical variables are presented as frequencies. NT-pro-BNP was compared between groups by use of a Mann–Whitney *U* test for comparisons between two

groups and a Kruskal–Wallis test when more than two groups were being compared. Univariate Cox regression analysis was performed for all clinical characteristics and heart failure therapies to study their possible prognostic impact on survival and on readmission for worsening heart failure. The prognostic value of natriuretic peptides was evaluated according to NT-pro-BNP tertiles. Forward stepwise Cox regression analysis was used to study the independent prognostic impact of a high-NT-pro-BNP level. All variables shown to have prognostic impact in the univariate analysis entered the multivariate model. Survival curves according to NT-pro-BNP tertiles were estimated by the Kaplan–Meier method. *P* values less than 0.05 were considered to be statistically significant. All the analyses were conducted using SPSS 13.0 (SPSS Inc, Chicago, Illinois, USA).

Results

We assessed 133 patients; the mean age was 71.2 years (range: 33–95 years); 52.6% were men; 61 patients (45.9%) had severe left ventricular dysfunction. Median (interquartile range) NT-pro-BNP levels were 7685 (3882–16 259) pg/ml. The characteristics of the study sample are presented in Table 1 (left).

Eleven patients (8.3%) died during hospital stay and 22 (16.5%) after discharge in a 6-month follow-up period.

NT-pro-BNP was compared between patients who died in hospital and those discharged alive: 29 505 (5646 – 32 336) against 7167 (3438 – 13 183) pg/ml, respectively;

Table 1 Clinical characteristics and heart failure therapies of the sample, and corresponding univariate Cox regression analysis (hazard ratio and 95% confidence intervals)

		HR (95% CI) for readmission with worsening heart failure	HR (95% CI) of all-cause death
Demographic characteristics			
Male sex, <i>n</i> (%)	70 (52.6)	0.65 (0.38–1.11)	0.54 (0.27–1.08)
Age, median (IQR)	73 (65–79)	0.99 (0.97–1.01)	1.03 (1.00–1.07)
Ischemic etiology, <i>n</i> (%)	75 (56.4)	1.03 (0.69–1.55)	0.93 (0.47–1.85)
Arterial hypertension, <i>n</i> (%)	56 (42.1)	0.86 (0.50–1.50)	0.39 (0.18–0.88)
Diabetes mellitus, <i>n</i> (%)	57 (42.9)	0.86 (0.49–1.51)	0.98 (0.49–1.96)
Chronic AF, <i>n</i> (%)	54 (40.6)	1.62 (0.49–2.79)	3.36 (1.63–6.95)
Moderate renal dysfunction, <i>n</i> (%)	28 (21.1)	0.68 (0.33–1.40)	1.42 (0.66–3.05)
Severe LVSD, <i>n</i> (%)	61 (45.9)	1.37 (0.80–2.36)	1.44 (0.73–2.86)
Admission SBP (mmHg), median (IQR)	120 (106–140)	0.99 (0.98–1.00)	0.98 (0.97–1.00)
Admission DBP (mmHg), median (IQR)	80 (70–90)	1.01 (0.99–1.03)	0.98 (0.96–1.01)
Heart rate (bpm), median (IQR)	90 (80–96)	1.00 (0.99–1.02)	1.02 (1.00–1.03)
Laboratory parameters			
Hemoglobin (g/dl), mean (SD)	12.5 (2.3)	1.08 (0.88–1.32)	0.96 (0.72–1.27)
Plasma creatinine (mg/dl), mean (SD)	1.18 (0.36)	0.76 (0.35–1.66)	1.41 (0.55–3.64)
Serum sodium (mEq/l), median (IQR)	140 (5)	0.99 (0.94–1.04)	0.95 (0.90–1.02)
NT-pro-BNP (pg/ml), median (IQR)	7685 (3882–16 209)		
Third vs. first NT-pro-BNP tertile		1.74 (0.89–3.40)	6.95 (2.39–20.23)
Second vs. first NT-pro-BNP tertile		1.09 (0.55–2.15)	1.68 (0.49–5.75)
Medication in use			
ACEi, <i>n</i> (%)	121 (91)	0.54 (0.19–1.50)	0.34 (0.11–0.88)
ACEi dose (mg), median (IQR)	10 (5–10)	1.01 (0.97–1.04)	0.93 (0.85–1.01)
Furosemide dose (mg), median (IQR)	80 (60–100)	1.00 (0.99–1.01)	1.02 (1.01–1.03)
Beta-blocker, <i>n</i> (%)	57 (42.9)	0.77 (0.44–1.33)	0.65 (0.30–1.40)
Beta-blocker dose (mg), median (IQR)	12.5 (6.25–12.5)	1.06 (0.98–1.15)	1.03 (0.90–1.17)
Spironolactone	54 (40.6)	1.17 (0.68–2.01)	0.95 (0.45–1.99)

ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; CI, confidence interval; DBP, diastolic blood pressure; HR, hazard ratio; IQR, interquartile range; LVSD, left ventricular systolic dysfunction; NT-pro-BNP, amino-terminal B-type natriuretic peptide; SBP, systolic blood pressure.

$P=0.01$. Comparison of NT-pro-BNP levels among patients deceased in hospital, those deceased after hospital discharge and survivors is as follows: 29 505 (5646–32 336) vs. 15 394 (7009–33 578) vs. 6582 (2992–11 002) pg/ml, respectively; $P<0.001$. The difference is significant between survivors and each one of the other groups; no significant difference was found between patients dying in hospital and those dying postdischarge.

No significant difference was found in NT-pro-BNP levels between patients with ischemic and nonischemic heart failure: 7363 (3890–16 756) vs. 7260 (4021–11 174) pg/ml, respectively, $P=0.75$.

Patients with severe renal failure were excluded but patients with moderate renal failure were included in the analysis. Twenty-eight patients had plasma creatinine between 1.5 and 2.0 mg/dl. NT-pro-BNP was not different in the two groups: 11 762 (3910–22 701) pg/ml in patients with moderate renal failure against 7074 (3878–12 326) pg/ml in those with creatinine less than 1.5 mg/dl, $P=0.20$.

Also in Table 1, we present the Cox univariate regression for analysis of each variable association with readmission for acute heart failure (middle column) and with the occurrence of death (right column).

None of the variables predicted 6-month readmission for worsening heart failure, basically no difference was found among patients with NT-pro-BNP measurement between extreme tertiles.

Variables found to be crudely associated with death were chronic atrial fibrillation, previous hypertension, admission systolic blood pressure (SBP), admission heart rate, NT-pro-BNP level, ACEi use and diuretic dose during hospitalization. NT-pro-BNP was analyzed according to tertiles; below 4990, between 4990 and 11 378 and above 11 378 pg/ml; and significant differences in terms of death occurrence existed between extreme tertiles, with those with NT-pro-BNP above 11 378 pg/ml having nearly seven-fold higher risk of death in 6 months when compared with those with NT-pro-BNP below 4990 pg/ml.

In the multivariate model, significant differences in terms of mortality persisted between extreme NT-pro-BNP tertiles. Admission SBP and ACEi use lost their prognostic impact; although arterial hypertension (inversely associated with outcome), chronic atrial fibrillation (direct association), admission heart rate (higher rate predicting higher mortality) and furosemide dose (higher doses predicting higher mortality) retained prognostic value (see Table 2). NT-pro-BNP was strongly and independently associated with all-cause death: HR=5.34 (95% CI 1.76–16.24); $P=0.003$ between extreme tertiles.

Table 2 Multivariate model for 6-month risk of death

	HR	95% CI	P value
Arterial hypertension	0.30	0.12–0.83	0.02
Chronic AF	3.35	1.38–8.17	0.008
Admission heart rate	1.03	1.01–1.05	0.002
Diuretic dose	1.02	1.01–1.03	0.001
Extreme NT-pro-BNP tertiles	5.34	1.76–16.24	0.003

AF, atrial fibrillation; CI, confidence interval; HR, hazard ratio; NT-pro-BNP, amino-terminal B-type natriuretic peptide.

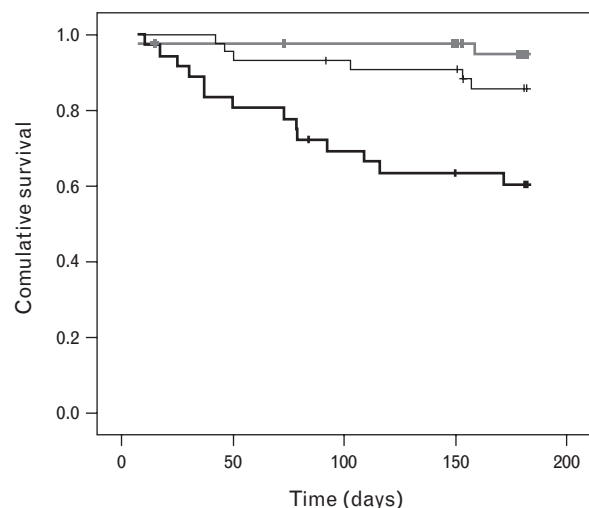
The Kaplan–Meier survival curve according to NT-pro-BNP tertiles is depicted in Fig. 1. Patients with NT-pro-BNP in the third tertile have significantly lower cumulative survival.

Discussion

Our results show that, in severe heart failure, higher levels of NT-pro-BNP have a strong and independent value in mortality prediction, suggesting an upregulation of the natriuretic peptide system even in severe heart failure.

Recent studies have argued against the general idea that high-BNP/NT-pro-BNP levels correlate with higher severity and worse prognosis in heart failure, suggesting that a low BNP level is an adverse prognostic marker in advanced heart failure. Miller *et al.* [11] studied 40 patients with chronic advanced heart failure admitted to hospital and treated with nesiritide and found that patients who died in a 10-month follow-up had significantly lower BNP and NT-pro-BNP levels (before and

Fig. 1



Kaplan–Meier survival curves according to amino-terminal B-type natriuretic peptide tertiles. Black bold line representing those above 11 378 pg/ml (third tertile), grey line representing NT-pro-BNP below 4990 pg/ml (first tertile) and black normal line, patients in the second tertile. Patients in third tertile have significantly worse survival than those in the first tertile. The second tertile represents a grey zone. P value less than 0.001.

after treatment). Sun *et al.* [12] studied 50 patients admitted in NYHA class III/IV and found that the average BNP level in the nonsurvival group was significantly lower than in the survival group. These studies focused on a specific subpopulation of heart failure patients – a subpopulation with severe systolic heart failure. Authors assume that these patients are somewhat different and, in fact, reach the conclusion that, in such patients, low natriuretic peptide levels are predictive of worse prognosis. The suggested mechanism for these observations would be an exhaustion of the natriuretic system. O'Neill *et al.* [13] also questioned the clinical usefulness of BNP measurements at the most severe end of the heart failure spectrum – hospitalized, NYHA class IV patients. In 39 end-stage heart failure patients no correlation was found between BNP and hemodynamic data, and the six patients with relatively low BNP levels (<600 pg/ml) were not significantly different from those with higher BNP levels.

The risk of death in our sample (25% at 6 months) was similar to that observed in the studies with conflicting results (40% at 10 ± 1 months reported by Miller *et al.* [11] and 24% at 12 ± 2 months reported by Sun *et al.* [12]), supporting identical heart failure severity of our patients. However, our sample is rather different in several aspects – patients were slightly older and had less severe systolic dysfunction, in comparison with a mean ejection fraction below 30% in both the populations of Sun *et al.* [12] and Miller *et al.* [11]. Another important difference is that in the latter two studies, patients had more severe renal dysfunction, with mean creatinine levels between 1.8 and 2.2 mg/dl. Interference of such differences on the results obtained is difficult to interpret. As our patients had less severe left ventricular systolic dysfunction, we cannot assure that a more preserved ventricle was not the main factor responsible for the differences found in survivors and nonsurvivors between our study and studies by Miller *et al.* [11] and Sun *et al.* [12].

Our results do not support the suggested exhaustion of the natriuretic peptide system in severe heart failure. Higher natriuretic peptide levels predicted higher mortality and, as Fonarow *et al.* [15] recently reported in their population of 48 629 heart failure patients – the Acute Decompensated Heart Failure National (ADHERE) Registry – an association between elevated natriuretic peptides and in hospital mortality was found.

Our study has several limitations. It is based on a relatively small number of patients and, although all patients had established heart failure and were admitted for decompensation of chronic heart failure, the precise duration of heart failure was not known in many of the study patients. Moreover, it is not a true sample of chronic advanced/end-stage heart failure patients, as defined elsewhere [16–18]. Refractoriness to optimized/maximal

medical therapy was not an inclusion criterion; this was assumed from the beginning to reduce all sources of subjectivity. As known, heart failure therapy is often not increased sufficiently because of assumed rather than actual intolerability [16]. We defined ejection fraction of less than 40% as an inclusion criterion and only 45.9% of the patients had severe left ventricular dysfunction; although this may seem contrary to the idea of ventricular exhaustion, the definition of chronic and advanced heart failure [18] does not need severely compromised left ventricular function.

Despite the limitations described, and although our patient sample is much smaller than recently published studies on the prognostic value of natriuretic peptides in the acute heart failure context [15,19,20], it constitutes a very specific and particular population – those in the most severe end of the heart failure spectrum – patients with established heart failure, hospitalized and with NYHA class III or IV. Even though only applicable to this tail of the heart failure spectrum, it is a contribution addressing specifically this segment of the heart failure population. This end-stage group of heart failure is a very important population for risk stratification, as advanced approaches and heart transplantation must be considered, and we show that the general rule of higher natriuretic peptide levels being associated with higher mortality also applies to this patient subgroup.

We conclude that in patients with severe heart failure, NT-pro-BNP has a powerful prognostic value. Patients with high NT-pro-BNP had a more than five-fold increase in the 6-month risk of death. Our results do not support the hypothesis that ventricular exhaustion with inability to synthesize and secrete natriuretic peptides is the mechanism underlying decompensation. Attenuation mechanisms of compensatory systems ought to be studied further.

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