Correlation of B type natriuretic peptides with clinical and echocardiographic parameters in heterogeneous population of patients with symptoms suggestive of heart failure

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Abstract

Purpose: NT-proBNP and BNP concentrations in CHF correlate with NYHA class and LVEF. Little research has been conducted to compare the clinical performance of these two natriuretic peptides in heterogeneous CHF population. Purpose: to evaluate and compare the clinical performance of NT-proBNP and BNP in heterogeneous group of CHF patients on the basis of these peptides' correlation with NYHA class, LVEF and WMI measured by echocardiography.

Material and methods: Consecutive patients admitted for suspected of CHF. Blood samples were drawn for NT-proBNP, BNP, creatinine and echocardiography was performed.

Results: 71 patients were included. CHF was diagnosed in 53. Sensitivity of NT-proBNP and BNP in diagnosing CHF was 83% and 94% respectively (P=0.079). Levels of both peptides correlated equally well with NYHA class (R=0.537, p<0.001; R=0.473, P<0.001), LVEF (R=-0.623, p<0.001; R=-0.601, P<0.001) and WMI (R=0.590, P<0.001; R=0.527, P=0.001). Creatinine correlated with both peptides, age correlated with NT-proBNP. No difference between sexes was found in both peptides' concentrations. In multivariate analysis independent determinants of BNP were LVEF, presence of valvular disease and NYHA class. In case of NT-proBNP age and creatinine also displayed independent influence.

Conclusions: NT-proBNP and BNP show good sensitivity in detecting CHF. Levels of both peptides correlate equally well with clinical and echocardiographic parameters of CHF, which makes them equally adequate in biochemical staging of CHF's severity regardless of its underlying cause. Levels of natriutretic peptides reflect contractile dysfunction, valvular disease and clinical condition. Age and creatinine concentration but not patients' sex should additionally be considered when measuring NT-proBNP.

Key words: NT-proBNP, BNP, chronic heart failure, NYHA class, LVEF, valvular heart disease.

Introduction

Tests measuring B type natriuretic peptides (BNP, brain natriuretic peptide and its biologically inactive counterpart – NT-proBNP, N-terminal probrain natriuretic peptide) have established themselves as diagnostic as well as prognostic tools in chronic heart failure and acute coronary syndromes. [1] In heart failure BNP and NT-proBNP are produced in increased quantities from the common precursor, pre-pro-BNP, and released from the ventricles in response to increased myocardial stretch and elevated ventricular pressure. The levels of B type natriuretic peptides depend on the amount of ventricular wall stretch and the severity of cardiac damage. Therefore their concentrations correlate with the clinical condition (NYHA class) and systolic function of the left ventricle (left ventricle ejection fraction, left ventricle end diastolic diameter, left ventricle end diastolic volume) measured by echocardiography, radionuclide scintigraphy or magnetic resonance imaging despite certain discrepancies in the strength of these correlations [2-4].

In establishing diagnosis and prognosis in patients suspected of heart failure tests measuring NT-proBNP and BNP show similar performance [5,6] in spite of some differences between the two analytes in half-life in circulation, *ex vivo* stability, renal clearance, age and sex with NT-proBNP being more stable, having longer half-life and depending more on renal function and age, which may be caused by its renal non-receptor mediated elimination [7,8]. It is not quite clear; however, if levels of both peptides perform equally well in clinical practice in a population with various underlying causes of heart dysfunction since there

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Table 1. **Clinical characteristics of the patients with chronic heart failure (CHF) and without chronic heart failure (non CHF)**

Patient group	n	MI	VD	DCM	CAD non-MI	AH	LVEF* (%)	Crea* (mg/dl)	PE
All	71	25	12	11	9	11	48.1 (25-73)	1.2 (0.6-4.1)	1
CHF (S/D)	53	21 (21/0)	11	11 (11/0)	5 (4/1)	4 (1/3)	43.9 (25-73)	1.3 (0.6-4.1)	1**
Non-CHF	18	4	1	0	4	7	60.2 (46-70)	1.05 (0.7-1.5)	0

AH – arterial hypertension; CAD non-MI – coronary artery disease without myocardial infarction; CHF – chronic heart failure; DCM – dilated cardiomyopathy; MI – myocardial infarction; Non-CHF – no chronic heart failure (heart failure excluded); PE – pulmonary embolism; VD – valvular disease; S/D – systolic (mainly)/diastolic dysfunction; LVEF (%) – left ventricle ejection fraction; Crea – creatinine concentration; * mean and range; ** right-sided heart failure

are only few such head-to-head comparisons of these markers. [9,10].

The aim of the study

The aim of the study was to evaluate and compare the clinical performance of NT-proBNP and BNP in patients with symptoms suggestive of heart failure and various cardiovascular conditions predisposing to it on the basis of correlations of these peptides' levels with clinical condition (NYHA class) and echocardiographic parameters (LVEF, WMI).

Material and methods

We included consecutive patients admitted to the department for symptoms suggestive of heart failure. On the second day of hospitalization all patients underwent physical examination preceded by detailed history taking independently of the first examination performed on admission. On the same day echocardiography was performed and blood sample was obtained for NT-proBNP, BNP and creatinine measurement. Diagnosis of heart failure was made on the basis of clinical evaluation (Framingham criteria) [11] and echocardiography: symptoms of dyspnea in accordance with Framingham criteria and sings of pulmonary and/or peripheral congestion accompanied by relevant echocardiographic findings. All patients received optimal treatment. The patients' clinical condition was evaluated and they were divided into NYHA classes I-IV. The echocardiographic examination was performed with a Vingmed ultrasonograph by a single echocardiographer blinded to peptide values and exact clinical characteristics of patients. LVEF (left ventricle ejection fraction) was evaluated and calculated by the modified Simson's formula. WMI (wall motion index) was calculated according to the 16-segment division of the left ventricle. The anatomy of the valves was evaluated in 2-D mode and flow, gradients and regurgitation with pulsed-wave, continuous wave and color Doppler. The presence of a significant valvular disease was established according to commonly accepted criteria [12,13]. NT-proBNP concentration was measured in serum with Roche Elecsys 2010 analyzer. BNP concentration was measured in plasma with Abbott AxSYM analyzer. Creatinine concentration was measured with Roche Integra 700 analyzer.

Bioethics committee of the Military Medical Institute approved the study.

Table 2. **Concentrations of BNP and NT-proBNP in patients with and without CHF**

	Non-CHF (n=18) (median and range)	**CHF** (n=53) (median and range)	**P**
BNP (pg/mL)	47 (1.5 – 485)	297 (0 – 3353)	<0.001
NT-proBNP (pg/mL)	245 (35 – 1387)	2353 (13 – 42034)	<0.001

Since the distribution of natriuretic peptide concentrations was not normal, results were shown as medians and ranges. The differences in values between groups were estimated with a U Mann-Whitney test. The difference in diagnostic sensitivity of the two peptides was estimated with an index of structure difference. Correlations of natriuretic peptide levels with other parameters were estimated with a non-parametric Spearman method or with Pearson method after logarithmic transformation leading to normalization of value distribution. The latter was especially done to normalize distribution before calculating and comparing differences between correlation coefficients. In order to elicit the independent determinants of B type natriuretic peptides' levels multivariate analysis was performed that included all significant variables and confounding factors.

Results

The study included 71 patients (39 men and 32 women aged between 34 and 94, mean age 67 years). Chronic heart failure diagnosis was confirmed in 53 patients (75%). Three patients were in NYHA class I, 26 in NYHA class II, 18 in class III, and 6 in class IV.

Detailed characteristics of patients including the underlying cause of chronic heart failure or other cardiovascular diseases is presented in *Tab. 1*.

NT-proBNP and BNP concentrations were significantly higher in the CHF group compared with the non-CHF group. Median concentration of BNP was 6.3 times higher and NT-proBNP was 9.6 times higher in the CHF group compared with the non-CHF group (*Tab. 2*).

The roughly estimated diagnostic sensitivity in detecting heart failure was 83% for BNP (cut-off value of 100 pg/ml) and 94% for NT-proBNP (cut-off value of 125 pg/ml) (diagnostic cut-offs recommended by manufacturers). The difference

Table 3. **Correlations of natriuretic peptide concentrations with NYHA class, echocardiographic parameters, creatinine concentration and age in patients with CHF and in all patients (italics)**

	Number of pts	NYHA	LVEF[#]	WMI[&]	Creatinine	Age
BNP	53	0.473***	-0.452***	0.423*	0.332*	0.226
(pg/mL)	71		*-0 .601****	*0.527****	*0.387****	*0.292**
NT-proBNP	53	0.537***	-0.421**	0,443**	0.443***	0.345*
(pg/mL)	71		*-0.623****	*0,590****	*0.473****	*0.384***

[#] LVEF – Left Ventricle Ejection Fraction; [&] WMI – Wall Motion Index; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

between the sensitivities was not statistically significant but it was not far from it (P=0.079).

Concentrations of natriuretic peptides correlated significantly with NYHA class. NT-proBNP tended to correlate with NYHA class better than BNP but correlation coefficients were not significantly different (*Tab. 3*).

NT-proBNP and BNP correlated similarly with echocardiographic parameters (LVEF, WMI). NT-proBNP tended to correlate stronger with creatinine concentration than BNP but this difference was not significant. Correlations of B type natriuretic peptides' levels with echocardiographic parameters were stronger for a wider range of values (i.e. when all, CHF and non-CHF patients were included) than for a narrower range typical of patients with CHF (*Tab. 3*).

Concentrations of NT-proBNP and BNP correlated well with each other for all patients (R=0.899; P=0.001) and for CHF patients (R=0.879; P<0.001).

In patients with CHF BNP levels were not dependent on age and NT-proBNP levels increased with age mildly. We did not observe any significant differences in NT-proBNP and BNP concentrations between men and women in the whole group or in the group with CHF [log NT-proBNP (all men/CHF men)= 3.163 (0.704)/3.322 (0.627), log NT-proBNP (all women/CHF women)=3.010 (0.840)/3.376 (0.753), P=0.41/P=0.78; log BNP (all men/CHF men)=2.320 (0.580)/2.442 (0.539), log BNP (all women/CHF women)=2.211(0.939)/2.687 (0.611) P=0.14/P=0.56]. In our patients creatinine concentrations did not depend on sex and age.

In multivariate analysis the levels of NT-proBNP and BNP were independently determined by LVEF, the presence of significant valvular disease and NYHA class. Furthermore, age and renal function were also independent determinants of NT-proBNP (*Tab. 4 a,b*).

Table 4. **Multiple regression analysis of factors influencing NT-proBNP (4a) and BNP (4b) concentrations**

4a)

	BETA	Standard error	P value
LVEF	-0.391	0.090	<0.001
VD	-0.246	0.010	0.017
NYHA	0.245	0.104	0.022
Age	0.260	0.092	0.007
log10 Crea	0.237	0.096	0.018

4b)

	BETA	Standard error	P value
LVEF	-0.509	0.103	<0.001
VD	-0.411	0.113	<0.001
NYHA	0.237	0.116	0.049
log10 Crea	0.044	0.109	0.686

LVEF – left ventricle ejection fraction; VD – valvular disease, NYHA – New York Heart Association class; Crea – creatinine

Discussion

The concentration of both peptides (NT-proBNP and BNP) were significantly higher in patients who were diagnosed with heart failure. The B type natriuretic peptides detected heart failure with a good sensitivity exceeding 80% at cut-offs recommended by the manufacturers. Such high sensitivity could partially be explained by the fact that almost half of the examined patients were severely ill (NYHA class III and IV). The average increase in NT-proBNP in CHF patients was 50% greater than that of BNP. This could be a basis for a hypothesis, partially supported by other trials, that NT-proBNP could be slightly more sensitive in detecting heart failure and might be a slightly better discriminator among NYHA classes than BNP. Our study showed that NT-proBNP tended to correlate with NYHA class better that BNP and was slightly (but not significantly) more sensitive. This is consistent with findings by other authors [9,10].

Concentrations of NT-proBNP and BNP correlated significantly with NYHA class, LVEF and WMI measured by echocardiography. Correlations of these peptides with echocardiographic parameters were practically identical, which remains consistent with findings by Masson et al. who demonstrated clinical equality of BNP and NT-proBNP [14].

Concentrations of both natriuretic peptides did not depend on sex in our patient group. Apparently mechanisms involved in synthesis and secretion of natriuretic peptides in CHF exert such a strong influence on their levels that difference between the sexes in peptide levels observed in healthy population becomes insignificant [15]. This hints at the possibility of adopting one diagnostic cut-off independent of sex. The levels of both peptides depended on creatinine concentration and this correlation was slightly stronger for NT-proBNP. This observation reflects the results of other studies [16].

This more pronounced dependence of NT-proBNP levels on renal function may result from the fact that NT-proBNP is cleared mainly by kidneys in an unchanged form, whereas there is an additional receptor-dependent path of BNP elimination [17]. It must be stressed; however, that in our patient group only 2 persons had creatinine levels exceeding 2 mg/dl.

NT-proBNP showed a weak correlation with age which was independent of creatinine.

The multivariate analysis showed that left ventricle ejection fraction, the presence of valvular disease and NYHA class were the main independent determinants of NT-proBNP and BNP levels. Moreover, the levels of NT-proBNP were also independently influenced by age and creatinine concentration. This is an important finding demonstrating that contractile dysfunction, valve dysfunction and present clinical status (level of exacerbation) all significantly contribute to the elevated NT-proBNP/BNP levels we measure. Few studies have so far tried to ascribe natriuretic peptides' levels to particular clinical and echocardiographic parameters in heterogeneous group of patients and compare the two commercially available markers in this respect since most trials concentrated on comparative analytical precision and sensitivity analysis [9,10,18,19]. NT-proBNP levels also reflect renal function and aging and these two factors need to be considered when this marker is measured. With this exception the clinical usefulness of both markers is comparable and they can both serve as credible gauges of cardiac performance in HF patients.

The group examined in our study was heterogeneous. The common denominator for all participants was the presence of cardiovascular disease having already caused or predisposing to heart failure in the future. According to the new heart failure classification these patients belong to group A, B, C or D [20]. Clinically symptomatic heart failure in the traditional sense had 53 out of 71 participants (groups C and D of the new classification). Such choice of patients, far from optimal from the methodological standpoint, and their limited number is undoubtedly a limitation to the study. On the other hand it reflects the working conditions of a clinician and falls in line with an accepted method of including consecutive patients in a study.

Conclusions

1. Both B type natriuretic peptides (BNP and NT-proBNP) demonstrate good sensitivity in detecting heart failure which exceeds 80%.

2. Concentrations of NT-proBNP and BNP correlated well both with clinical condition of the heart failure patients (NYHA class) and echocardiographic parameters of left ventricle dysfunction (LVEF, WMI). This makes the two peptides equally adequate for the evaluation of the severity of heart failure regardless of its underlying cause.

3. Contractile left ventricle dysfunction, valve dysfunction and present clinical status all significantly contribute to both NT-proBNP and BNP levels in heterogeneous population of heart failure patients.

4. Levels of B-type natriuretic peptides do not depend significantly on sex in chronic heart failure patients so this factor need not be considered in diagnosing or monitoring heart failure patients with NT-proBNP/BNP. On the other hand age and renal function need to be considered especially when interpreting NT-proBNP results.

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