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Letter to the Editor

Head-to-head comparison of B-type natriuretic peptide (BNP) and NT-proBNP in daily clinical practice ☆

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Abstract

B-type natriuretic peptide (BNP; Abbott Diagnostics) and N-terminal proBNP (NT-proBNP, Roche Diagnostics) were compared in consecutive samples of 458 patients (mean age 60 years ± 16 years; 159 female, 299 male) sent for NT-proBNP measurement to investigate influences on both markers. BNP and NT-proBNP showed a close correlation with each other ($r = 0.89$, $p < 0.0001$). Using age- and gender-adjusted upper reference values the inter-rater agreement of both parameters was satisfactory (83%, Cohen's kappa coefficient = 0.7). The combination of normal BNP and elevated NT-proBNP was significantly more frequent than vice versa (61 vs. 16 patients), and a calculated glomerular filtration rate < 60 ml/min/1.73 m^2 was found in 39% of these patients. Multiple linear regression analysis revealed a significant influence of a reduced ejection fraction (<50%), renal dysfunction (calculated glomerular filtration rate < 60 ml/min/1.73 m^2), anemia, hypertension, age, and gender on both BNP and NT-proBNP. In conclusion, despite a close correlation and a satisfactory agreement between both markers in classification, frequent discrepancies in individual patients demonstrate that both markers are clinically not completely equivalent.

Keywords: B-type natriuretic peptide; N-terminal proBNP; Direct comparison

B-type natriuretic peptide (BNP) and the amino-terminal fragment of its precursor hormone proBNP (NT-proBNP) have been shown to reflect the severity of heart failure, and there is a growing body of evidence supporting the role of routine BNP and NT-proBNP testing in patients with suspected heart failure [1,2]. As BNP and NT-proBNP can now be easily measured using commercialised, automated assays the performances and the comparison of these markers under routine conditions are of great interest, because the cardiac-specificities of both markers are limited [2]. Despite considerable published data on the comparison of the diagnostic performances and the prognostic values of these markers in preselected patient cohorts [3,4] little data on the agreement of both markers in patient classification as "normal" or "increased" using clinically approved fully automated assays and potential determinants of BNP and NT-proBNP concentrations in daily clinical practice are available. Therefore, we sought to carry out such a clinical study to characterize the factors associated with both markers.

This was a prospective observational study in a university hospital with the aim to compare BNP and NT-proBNP in 500 consecutive samples sent to the hospital's central laboratory for routine NT-proBNP determination. The study is consistent with the Declaration of Helsinki. BNP was measured in ethylenediamine tetraacetic acid (EDTA) plasma

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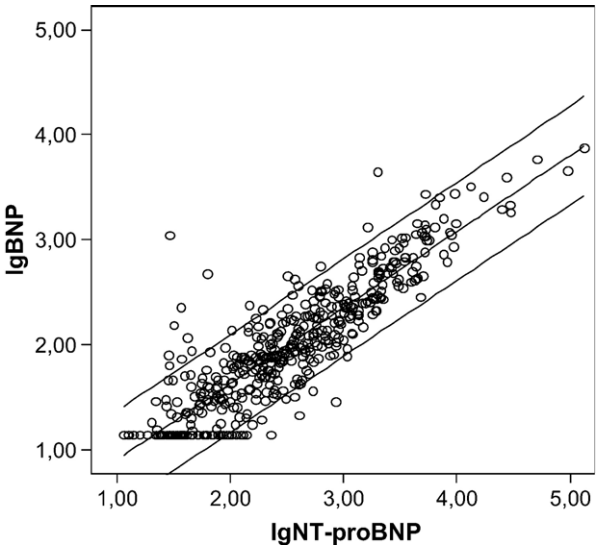

Fig. 1. Linear correlation between BNP and NT-proBNP. There was a close correlation between BNP and NT-proBNP ($r=0.89$, $p<0.0001$), the regression equation was lgBNP=0.8 lgNT-proBNP−0.018. For values < the detection limit the detection limit was used.

sample remnants of patients in whom heparinized blood was sent for NT-proBNP determination. Only one sample from each patient was included in the analysis, and therefore the final study population comprised of only 458 patients (mean age 60 years±16 years; 159 female, 299 male). Patients were classified by careful chart review. Left ventricular systolic dysfunction was defined as an echocardiographically determined left ventricular ejection fraction<50%. Renal dysfunction was defined as from serum creatinine concentrations calculated glomerular filtration rate<60 ml/min/1.73 m^2 using the Modification of Diet in Renal Disease 2 formula [5]. 399 patients had cardiac disease (81 with systolic ventricular dysfunction; 209 coronary artery disease, 31 post-heart transplantation, 50 dilated cardiomyopathy, 34 tachycardia, 10 myocarditis or pericarditis, 65 valvular heart disease), 104 patients renal dysfunction, 226 hypertension and 53 patients suffered from anemia, respectively. Both markers were measured using standard core laboratory assays. BNP was measured by the Abbott assay on the Axsym analyser and NT-proBNP by the Roche assay on the E170 analyser as described previously [6,7].

The statistical analysis was performed with the SPSS 12.0 (SPSS Inc., Chicago, USA) software package. Because of skewed distribution BNP and NT-proBNP values were log-transformed before statistical analysis. Pearson correlation coefficients were calculated. Cohen's kappa coefficient was determined to assess assay agreement in patient classification. Multiple linear regression analyses were calculated to determine independent influences on BNP and NT-proBNP. A p value<0.05 was considered to indicate statistical significance.

BNP and NT-proBNP correlated closely with each other ($r=0.89$, $p<0.0001$; see Fig. 1).

Multiple linear regression analyses revealed significant, independent influence of reduced ejection fraction (higher values), renal dysfunction (higher values), anemia (higher values), hypertension (higher values), age (increase with age), and gender (higher values in females) on both NT-proBNP and BNP concentrations (see Table 1). Because of the significant influence of age and gender we used age- (by decade) and sex-adjusted upper reference limits which have been published ([8]; NT-proBNP) or which are listed in the manufacturer's package insert ([9]; BNP) to evaluate the inter-rater reliability of both markers. Cohen's kappa coefficient revealed a satisfactory agreement in patient classification (kappa=0.7, 83% concordance in patient classification). The group with normal BNP and elevated NT-proBNP ($n=61$) was larger than vice versa ($n=16$). In this group, 56 patients suffered from cardiac diseases, an impaired cardiac function was diagnosed in only 7 patients, but 24 of these patients had renal failure. 14 patients in the group with elevated BNP and normal NT-proBNP ($n=16$) had cardiac diseases. Using the Food and Drug Administration (FDA) approved US decision limits for BNP (<100 ng/l) and NT-proBNP (<125 ng/l if <75 years and <450 ng/l if >75 years) discordant results were more frequent (in 25% of patients). The combination of normal BNP and elevated NT-proBNP was markedly more frequent than vice versa (106 vs. 6 patients).

The main findings of the present study extend the results of previous studies [3,4] in a heterogeneous consecutive large "real world" cohort of patients in whom NT-proBNP determination was ordered by the attending physician for clinical reasons. The correlation between BNP and NT-proBNP was close, and the agreement between both markers in patient classification as "normal" and "increased" was satisfactory using age- and sex-adjusted upper reference limits. Using FDA approved upper reference limits the agreement of both markers was worse, and our results, therefore, endorse the use of age- and sex-adjusted decision limits for BNP and NT-proBNP in clinical practice. By multivariate linear regression analysis we could corroborate that BNP and NT-proBNP increase with age and are higher in women than in men [10]. BNP and NT-proBNP were frequently elevated in the absence of systolic left ventricular

Table 1
Results of multiple linear regression analyses

	NT-proBNP		BNP	
	Standardized β-coefficient	p	Standardized β-coefficient	p
Age	0.259	<0.001	0.314	<0.001
Sex	−0.083	0.049	−0.089	0.045
Reduced LVEF	0.244	<0.001	0.229	<0.001
Renal failure	0.220	<0.001	0.130	0.005
Hypertension	−0.172	<0.001	−0.132	0.003
Anemia	−0.142	0.002	−0.134	0.001

Significant univariate predictors were included into the multivariate models as continuous (age) or binary variables.

dysfunction. NT-proBNP and BNP had similar relationships with age, sex, reduced systolic left ventricular function, anemia, and hypertension. The inverse relationship with renal dysfunction was tendentiously more pronounced for NT-proBNP. Using age- and sex-adjusted upper reference limits renal failure was the most common reason for false positive results, and both markers were affected by renal dysfunction as previously described [11]. In patients with a normal BNP and an increased NT-proBNP a calculated GFR < 60 ml/min/1.73 m^2 was found in 39% of the patients. Below a GFR of 60 ml/min/1.73 m^2 the different clearance of the two markers might become evident and result in a greater relative elevation of NT-proBNP. In conclusion, as a result of this head-to-head comparison it is demonstrated that there are no fundamental differences between both markers, but distinct discrepancies in individual patients emphasize that BNP and NT-proBNP are not completely equivalent in daily clinical practice.

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