

# B-type natriuretic peptide for diagnosis and treatment of congestive heart failure

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## Summary

**Background:** Prognostic classification of congestive heart failure (CHF) is difficult and only possible with the help of additional diagnostic tools. B-type natriuretic peptide (BNP) has been used as a diagnostic and prognostic marker for patients (pts) with CHF. In this study, the clinical value of BNP for stratification and treatment of pts with CHF was evaluated.

**Patients and methods:** 33 out-pts with CHF (age  $57 \pm 12$  years) were included. Left-ventricular (LV) ejection fraction (EF) was  $27 \pm 8\%$  (mean  $\pm$  SD) and NYHA-class  $2.4 \pm 0.7$ . Following parameters were measured: BNP and sodium from blood samples, exercise performance from 6-minute walking test (6MWT, meters) ( $n = 18$ ), LV end-diastolic diameter (LVEDD) and LV mass (LVM) from 2D-echocardiography ( $n = 33$ ), as well as LV end-diastolic pressure (LVEDP,  $n = 23$ ) and systemic vascular resistance (SVR,  $n = 20$ ) from heart-catheterisation. Ten pts were hospitalised in the preceding 6 months because of worsening CHF or for optimisation of medical therapy. BNP was measured at the beginning and end of the hospital-stay. Follow-up was for 1 year.

**Results:** Pts with a high NYHA-class had a higher BNP (pg/ml) than those with a low NYHA-

class: NYHA I  $51 \pm 20$ , II  $281 \pm 223$ , III  $562 \pm 346$  and IV  $1061 \pm 126$  pg/ml ( $p = 0.002$ ). BNP correlated with LVEDP ( $r = 0.50$ ,  $p < 0.02$ ), SVR ( $r = 0.49$ ,  $p < 0.03$ ) and inversely with 6MWT ( $r = -0.60$ ,  $p < 0.009$ ), LVEF ( $r = -0.49$ ,  $p < 0.004$ ) and sodium ( $r = -0.36$ ,  $p = 0.04$ ). In the hospitalised pts, mean BNP (pg/ml) was  $881 \pm 695$  at admission, and  $532 \pm 435$  at discharge (n.s.). Decrease in BNP during hospitalisation paralleled weight-loss and was significantly greater in patients with  $>1000$  pg/ml BNP at admission ( $n = 5$ ) as compared to the 5 patients with BNP  $<1000$  ( $p < 0.03$ ). Patients with an adverse event during 1-year follow-up had significantly higher BNP both at steady-state ( $603 \pm 359$  pg/ml) and at time of decompensation than patients with a favourable outcome ( $227 \pm 218$  pg/ml,  $p < 0.001$ ).

**Conclusions:** BNP correlates well with the clinical severity of CHF (NYHA-class) and is directly related to filling pressure (LVEDP), LV function (LVEF) and exercise performance (6 MWT). Furthermore, BNP has prognostic impact with regard to adverse clinical events.

**Key words:** congestive heart failure; neurohumoral stimulation; natriuretic peptides

## Introduction

B-type natriuretic peptide (BNP) is a cardiac neurohormone that has recently been described as a diagnostic and prognostic marker for patients with congestive heart failure [1-3]. In several studies, BNP has turned out to be superior to the clinically used atrial natriuretic peptide (ANP) in terms of sensitivity as well as specificity [4]. The mRNA of BNP contains four repetitive AUUUA sequences, which lead to its destabilisation and enable the synthesis of BNP in bursts [5, 6]. BNP therefore reflects haemodynamic changes more accurately than ANP.

BNP is synthesised and stored mainly in cardiac ventricles. Increased synthesis and release of BNP occur in response to ventricular volume ex-

pansion and pressure overload [7-9]. Adequate therapy of congestive heart failure decreases wall stress and, thus, leads to a decrease of BNP plasma levels. In end-stage heart failure, medical therapy may be ineffective in reducing haemodynamic overload and diminishing consecutively neurohumoral stimulation. Thus, changes in plasma BNP reflect treatment-responsiveness of heart failure. Patients with persistently high plasma BNP despite adequate heart failure treatment are likely to have a worse prognosis than patients with a significant decrease in plasma BNP under therapy [3].

Current standard criteria for the diagnosis of heart failure include the presence of symptoms of heart failure, objective evidence of cardiac dys-

function and appropriate response to heart failure treatment [10]. Whereas cardiac function is mainly assessed by echocardiography, estimation of treatment-responsiveness is usually based on clinical judgement. BNP may provide an additional tool for estimation of treatment-responsiveness as well as for triage of patients with heart failure-like symptoms who need further investigation by echocardiography.

In the present study, a small cohort with stable or decompensated heart failure patients were evaluated to assess clinical benefit of bedside BNP measurements for risk stratification of patients with congestive heart failure in every-day clinical practice.

## Patients and methods

### Study population

Thirty-three consecutive outpatients presenting in the heart-failure out-patient department of our university hospital with chronic heart failure NYHA I-IV and a left-ventricular ejection fraction  $\leq 45\%$  at echocardiography were included in the study. Patients with isolated diastolic dysfunction, right-heart failure, primary pulmonary hypertension or congenital heart disease were excluded from the present analysis. Treatment consisted of standard heart failure therapy including RAAS antagonists, beta-adrenergic blockers and diuretics. Medication was stable for at least two weeks before blood sampling (most for  $>3$  months). Furthermore, patients had to be clinically stable and on constant doses of diuretics. The following laboratory parameters were determined at baseline: BNP, plasma sodium and potassium, exercise performance from 6-minute walking test (6MWT, meters,  $n = 18$ ), left ventricular end-diastolic diameter (LVEDD) and left ventricular mass (LVM) from 2D-echocardiography ( $n = 33$ ), as well as left ventricular end-diastolic pressure (LVEDP,  $n = 23$ ) and systemic vascular resistance (SVR,  $n = 20$ ) from heart-catheterisation.

Ten of the 33 patients presenting with dyspnoea NYHA class III or IV were hospitalised within the preceding six months before steady state blood sampling because of worsening heart failure or need for optimisation of medical therapy. Diuretic therapy had to be intensified in all patients, either by an increase in the orally administered drug, or by addition of an IV-diuretic. Furthermore, transient vasodilator treatment was established in three patients, and three other patients had to be treated with IV-catecholamines. Duration of the hospital stay was between five and 14 days. BNP was measured at the beginning and the end of the hospital stay. Clinical follow-up was 1 year for all 33 patients.

### Ethics

Informed consent was obtained from all patients for blood sampling and inclusion into the study. Echocardiogram, heart catheterisation, and six minute walking test were based on clinical indications.

### Measurement of BNP plasma levels

Four millilitre of blood was drawn from an antecubital vein into an ethylen-diamine-tetra-actetate containing tube. During blood collection, the patient remained in a sitting position. No exercise was allowed for one hour before blood sampling. Plasma B-type natriuretic peptide was measured using the Triage B-Type Natriuretic Peptide test (Biosite Diagnostics Inc., San Diego, California), as described elsewhere [1]. The Triage BNP test is a fluorescence immunoassay for quantification of the biologically active BNP-32 in whole blood or plasma samples. BNP-32 levels as determined by the Triage kit have demonstrated excellent correlations with the more recently described amino-terminal pro BNP plasma levels with a longer half-life time [11].

### Statistical analysis

In tables and figures, mean values  $\pm 1$  standard deviation are given. Correlations were determined with the Spearman-rank test, statistical differences between groups with the Kruskal-Wallis or the Mann-Whitney U-test. A  $p$  value  $<0.05$  was considered statistically significant. For assessment of the accuracy of the steady-state BNP value to predict an adverse event during 1-year follow-up, a receiver operating characteristic curve (ROC) was computed. A multivariate analysis was not performed due to the small sample size. However, a univariate analysis was carried out. For statistical analyses, the SPSS package and "analyse-it" statistical programs were used.

## Results

Patient characteristics including aetiology of heart failure and medication at the time of blood sampling are given in table 1. With increasing NYHA-class, BNP levels (mean  $\pm$  SD) increased: from  $51 \pm 20$  pg/ml in patients with NYHA-class I to  $281 \pm 223$  pg/ml in patients with NYHA-class II,  $562 \pm 346$  pg/ml in patients with NYHA-class III, and  $1061 \pm 126$  pg/ml in patients with NYHA-class IV ( $p = 0.002$ , fig. 1).

### Correlations

Significant positive correlations were found between BNP and left ventricular end-diastolic

pressure ( $r = 0.50$ ,  $p < 0.02$ ) and systemic vascular resistance ( $r = 0.49$ ,  $p < 0.03$ , Fig. 2). Furthermore, there were significant inverse correlations between BNP and left ventricular ejection fraction ( $r = -0.49$ ,  $p < 0.004$ ) and physical performance (walking distance, m) assessed by the six minute walking test ( $r = -0.60$ ,  $p < 0.009$ , Fig. 3). According to the natriuretic effect of BNP, plasma BNP levels were significantly inverse correlated to sodium ( $r = -0.36$ ,  $p = 0.04$ ). No correlation existed between BNP and age, left ventricular end-diastolic diameter, left ventricular mass, and body mass index (mean  $\pm$  SD  $25.8 \pm 4.3$  kg/m<sup>2</sup>).

**Table 1**

Patient characteristics of outpatients (n = 33).

		range
Gender (m:f)	26:7	
Age (years, mean ± SD, [range])	57 ± 12	(31-80)
NYHA-class		2.4 ± 0.7
Left ventricular ejection fraction (%)	27 ± 8	(15-45*)
<b>Etiology of heart failure</b>		
dilated cardiomyopathy*	17	
coronary artery disease	11	
valvular heart disease	3	
anthracycline-induced cardiomyopathy	1	
myocarditis	1	
<b>Medication at index visit</b>		
	n	
Diuretics	30	91%
Angiotensin-converting-enzyme inhibitors	30	91%
Angiotensin receptor blockers	3	9%
Beta-adrenergic blockers	22	67%
Spironolactone	23	70%
Digitalis	12	36%
Nitrates	6	18%
Amiodarone	11	33%
Salicylic Acid	5	15%
Coumadine	27	82%

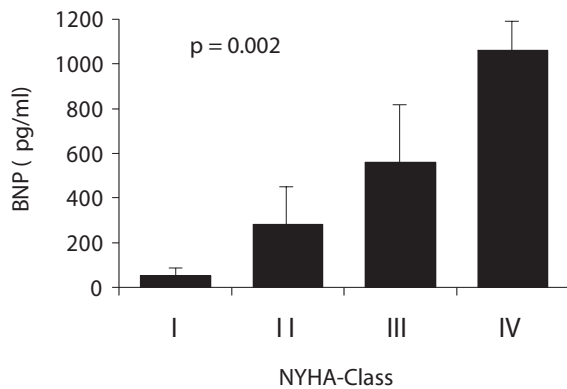
\* including one patient with left-ventricular ejection fraction of 45% and diagnosis of an intracardiac tumour

**Subgroups**

Table 2 shows patient characteristics of the hospitalised patients (n = 10) including aetiology of heart failure and medication at hospital admis-

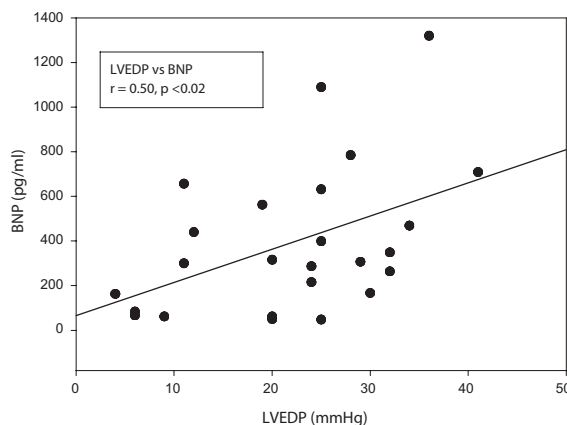
**Figure 1**

Relationship between BNP levels (mean ± SD) and NYHA-class.



**Figure 2**

Correlation between BNP and LVEDP (left) as well as BNP and SVR (right).



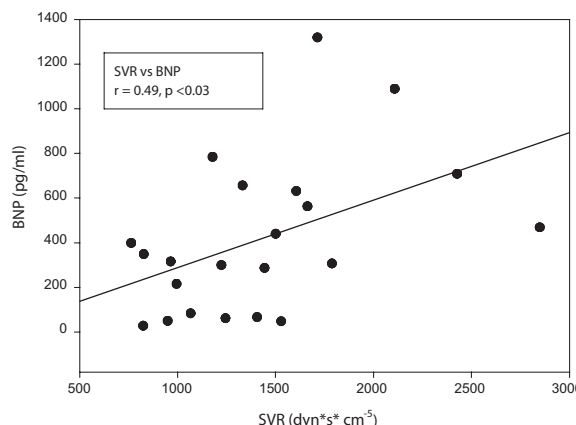
sion. Mean BNP (pg/ml) was 881 ± 695 at admission, and 532 ± 435 at discharge (n.s.). Five patients (group 1) had a BNP >1000 pg/ml (1465 ± 472) at admission, and five (group 2) <1000 (299 ± 109). Left ventricular ejection fraction was significantly lower in group 1 than 2 (19 ± 3 vs. 31 ± 9%, p = 0.012). BNP decreased in both groups with therapy, but significantly more in group 1 than 2: -582 ± 385 vs. -117 ± 78, p = 0.028. The decrease in BNP paralleled weight loss in the two groups, which also was significantly more pronounced in group 1 than 2: -5.1 ± 3.3 kg vs. -0.3 ± 1.2 kg (p = 0.009, fig. 4).

**Follow-up**

During a twelve-month follow-up period two of the ten hospitalised patients died in group 1, but none in group 2. One other group 1 patient was successfully transplanted. In group 2, three patients had to be re-hospitalised, one each for worsening heart failure, atrial flutter, and evaluation of a cardiac tumour, respectively. Two patients in each group remained clinically stable with no need for re-hospitalisation throughout follow-up.

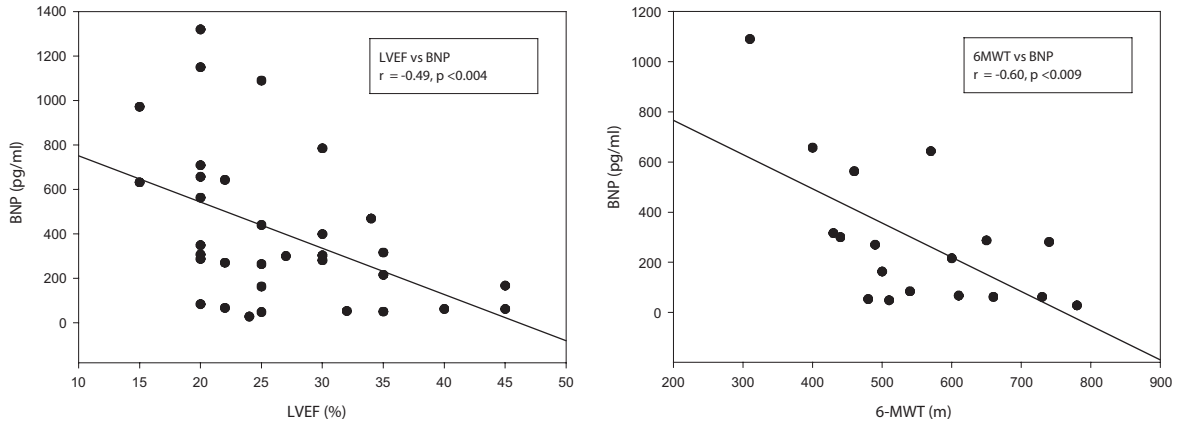
Overall, 16/33 patients exhibited a major adverse clinical event (MACE) such as death (n = 5), heart transplantation (n = 4), or re-hospitalisation for worsening heart failure (n = 4), arrhythmia (n = 1), or surgery (n = 2) in case of coronary, valvular or other heart disease (cardiac tumour), respectively. Patients with MACE had significantly higher steady-state BNP levels than patients without MACE (603 ± 359 vs. 227 ± 218 pg/ml, p = 0.0003). Furthermore, BNP levels of patients who underwent heart transplantation or died were significantly higher (782 ± 376 pg/ml) than those of patients re-hospitalised for other cardiac reasons (373 ± 152, p = 0.023). BNP values in patients with minor clinical events were also significantly higher than in patients without re-hospitalisation (373 ± 152 vs. 227 ± 218 pg/ml, p = 0.033).

The receiver operator curve, shown in figure 5, depicts the sensitivity and specificity of BNP steady-state values in discriminating patients who will have an adverse event (death, heart transplantation or re-hospitalisation) in 1 year of follow-up. The area under the receiver operator curve was 0.868, indicating a high discriminatory power.



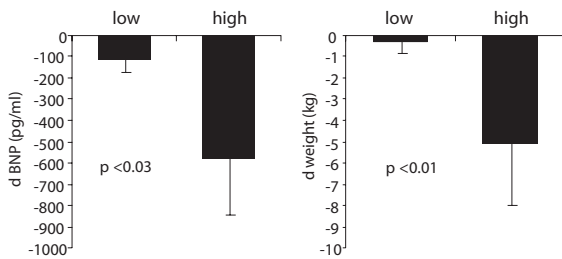
**Figure 3**

Correlation between BNP and LVEF (left) as well as physical exercise performance as estimated by the walking distance (right).



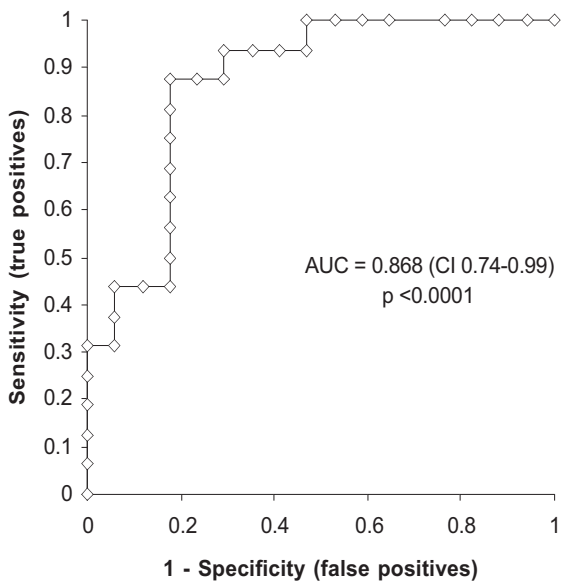
**Figure 4**

Decrease of BNP (left panel) and body weight (right panel) under treatment in patients with high (>1000 pg/ml) and low (<1000 pg/ml) BNP.



**Figure 5**

Receiver Operator Characteristic (ROC) curve for BNP versus adverse cardiac events (death, rehospitalization, cardiac transplantation). For BNP >300 pg/ml the negative predictive value is 87.5% and the positive predictive value 82.3%.



**Table 2**

Patient characteristics of hospitalised patients (n = 10).

	range
Gender (m:f)	9:1
Age (years, mean ± SD)	62 ± 14 (36–66)
Left ventricular ejection fraction (%)	25 ± 9 (20–45*)
<b>Etiology of heart failure</b>	
dilated cardiomyopathy*	7
coronary artery disease	3
<b>Medication at admission</b>	
Diuretics	10 100%
Angiotensin-converting-enzyme inhibitors	7 70%
Angiotensin receptor blockers	2 20%
Beta-adrenergic blockers	4 40%
Spironolactone	9 90%
Digitalis	2 20%
Nitrates	2 20%
Amiodarone	5 50%
Salicylic Acid	2 20%
Coumadine	5 50%

\* including one patient with left-ventricular ejection fraction of 45% and diagnosis of an intracardiac tumor

## Discussion

A significant correlation between BNP and clinical severity of CHF in terms of NYHA-class was found in 33 clinically stable outpatients. Furthermore, BNP was significantly correlated with filling pressure (LVEDP), left ventricular ejection fraction (LVEF) and exercise performance (6 MWT), but correlation between BNP and walking distance in the 6 MWT was stronger than with ejection fraction. Hospitalised patients with a high BNP at admission had a worse clinical outcome during 1 year follow-up than those with a low BNP. The same holds true for steady-state BNP, which was significantly higher in the 16 patients suffer-

ing a major cardiac event within 1 year of follow-up as compared to 17 patients with an uncomplicated clinical course.

### BNP and severity of CHF

In the 33 clinically stable outpatients without signs of water retention, a significant correlation was found between BNP and NYHA-class as already described in other studies [9, 12]. The stimulus for increased BNP synthesis is the stretch of cardiomyocytes by an increased wall stress [13]. Thus, BNP levels can be expected to increase with diastolic filling pressures and peripheral vascular

resistance, which both are the case in the present study. Since elevated filling pressures directly correlate with worsening heart failure symptoms, the correlation of BNP with NYHA-class can be anticipated as well.

NYHA-classification is still one of the major means for describing clinical presentation and severity of CHF, yet it is a subjective measure confounded by personal judgement. The wide overlap of BNP levels observed in our study population especially between NYHA-class II and III patients is characteristic for the varying degree in cardiac haemodynamics and neurohumoral stimulation in patients presenting with a similar functional status. Thus, BNP allows a more precise and objective assessment of the severity of CHF than NYHA-classification alone. This could be important in the long-term follow-up of CHF patients especially in the out-patient setting.

### **BNP in decompensated CHF**

In hospitalised patients, BNP was >1000 pg/ml at admission in half of them, and <1000 pg/ml in the others. In both subgroups, BNP levels could be lowered under intensified therapy, whereby the decrease in BNP paralleled weight loss and clinical improvement in terms of NYHA-class. Fatal outcome in terms of death or heart transplantation occurred in three patients with persistently high BNP despite adequate therapy. Thus, BNP levels at discharge and the course of BNP under treatment reflect treatment-responsiveness of CHF patients and may be a predictor for clinical course and outcome. Although the change in BNP levels under treatment goes parallel with clinical improvement, recent studies indicated that adjustment of medical therapy with dose increases results in a further decrease of BNP despite stable clinical findings (NYHA-class, signs of congestion), indicating a higher degree of neurohumoral adaptation and probably better long-term stabilisation [14, 15].

### **BNP and risk-stratification of CHF**

Several recent studies suggested BNP as important prognostic marker for CHF patients [2, 3, 16]. The worse outcome during 1 year follow-up of our hospitalised patients with high BNP levels at admission and insufficient response to adequate therapy indicates the possible usefulness of BNP for risk stratification in decompensated CHF patients. Consistently, Cheng and co-workers demonstrated in a group of 72 patients with decompensated heart failure, that BNP at admission as well as at discharge, and the change of BNP under treatment are predictors for an adverse outcome in terms of re-hospitalisation, death and worsening heart failure within 30 days after dis-

charge [3]. Furthermore, 16 of our 33 clinically stable out-patients experienced an adverse cardiac event within 1 year after steady-state blood sampling. Steady-state BNP values were significantly higher in those 16 patients as compared to the 17 patients with a favourable clinical outcome, whereby BNP was highest in patients who died or underwent cardiac transplantation. These data are in agreement with the findings of Tsutamoto et al., who described BNP as a significant independent predictor of mortality in a cohort of 85 patients with chronic CHF followed for 2 years [16].

In the clinically stable outpatients, a significant negative correlation between BNP and LVEF was found on the one hand, and physical performance as assessed by the 6 MWT on the other. Interestingly, BNP seemed to be more strongly correlated to the walking distance (6 MWT) than to LVEF. Since resting LVEF only modestly reflects LVEF under exercise, and does not provide any information about diastolic function and wall stress, it is obvious that LVEF can be only a poor indicator for exercise tolerance and functional capacity in patients with CHF [17, 18]. Assessment of functional aerobic capacity is associated with great prognostic impact in CHF patients, where peak oxygen consumption (peak  $\text{VO}_2$ ) represents the gold standard. However, the walking distance assessed by the 6 MWT has been shown to be closely related to peak  $\text{VO}_2$  [19, 20] and to represent an independent predictor of morbidity and mortality [21].

### **Clinical implications**

Our study adds to the increasing evidence that BNP significantly contributes not only to the assessment of clinical severity but also of long-term prognosis in CHF patients and, thus, might be used as a "bed-side test" in every-day clinical practice. The receiver operator curve indicated a high discriminating power (area under the curve 0.868) for identifying patients at high risk for adverse cardiac events during 1 year follow-up. However, the number of patients included in this study is relatively small. Certainly, more and larger studies are needed to confirm these data and to provide enough evidence to allow routine application of BNP for the assessment of CHF patients in the in- and out-patient CHF clinic.

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