Brain Natriuretic Peptide Levels Predict Functional Capacity in Patients With Chronic Heart Failure

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OBJECTIVES
The goal of this study was to determine if brain natriuretic peptide (BNP) levels are associated with exercise capacity in patients with chronic heart failure (HF).

BACKGROUND
Plasma levels of BNP are increased subject to the degree of systolic and diastolic left ventricular dysfunction in patients with chronic HF. Exercise testing is useful to assess functional capacity and prognosis in chronic HF.

METHODS
We prospectively studied 70 consecutive patients with chronic HF (60.3 ± 10.4 years, 51 men) referred for cardiopulmonary exercise testing. Resting BNP was obtained after 10 min of supine rest before symptom-limited bicycle exercise testing.

RESULTS
In patients with chronic HF, BNP levels correlated with oxygen uptake (VO₂), both at anaerobic threshold (VO₂AT: r = −0.54, p < 0.001) and peak exercise (peak VO₂: r = −0.56, p < 0.001). Impairment of ventilatory efficiency (EqCO₂: r = 0.43, p < 0.001) and maximum exercise level (% predicted: r = −0.44, p < 0.05) correlated less well with BNP.

There was a significant inverse correlation between left ventricular ejection fraction and BNP (r = −0.50, p < 0.05). Brain natriuretic peptide discriminated well chronic HF patients with a peak VO₂ <10 ml/min/kg (area under the receiver operating characteristic [ROC] 0.93) or <14 ml/min/kg (area under the ROC 0.72). A BNP >316 pg/ml was associated with a risk ratio of 6.8 (95% confidence interval, 2.3 to 19.8) for a reduced exercise capacity with a peak VO₂ <14 ml/min/kg.

CONCLUSIONS
Brain natriuretic peptide is clearly associated with exercise capacity in chronic HF. Brain natriuretic peptide levels show a significant correlation with the impairment of VO₂ at peak exercise and anaerobic threshold. Brain natriuretic peptide is able to differentiate between chronic HF patients with moderately and severely impaired exercise capacity.

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Manuscript received March 21, 2002; revised manuscript received April 29, 2002, accepted May 23, 2002.
patients. Left ventricular ejection fraction was evaluated with biplane transthoracic echocardiography by the modified Simpson rule using second harmonic imaging (14). Patients with renal failure (defined as a creatinine value >2.0 mg/dl) were excluded from the study.

**Exercise test.** A standard bicycle exercise protocol was used in the postabsorptive state. Exercise began with 10 W after a 2-min unload phase, followed by a ramp protocol with increments of 10 W/min. Oxygen uptake, CO₂ production, and minute ventilation were measured using a breath-by-breath gas analysis (Jäger Oxycon Alpha, Würzburg, Germany). A 12-lead electrocardiogram was continuously registered to exclude significant myocardial ischemia. Blood pressure was recorded every minute by a cuff sphygmomanometer. Peak VO₂ was determined as the highest value in the terminal phase of exercise; the O₂ uptake at the anaerobic threshold (VO₂-AT) was determined as the slope of the VE versus V̇CO₂ relation. Exclusion criteria were exercise-limiting diseases like peripheral vascular disease or degenerative joint disease, relevant primary pulmonary disease, and exercise tests that were not limited by dyspnea or fatigue. All patients reached the AT and a respiratory ratio \( \geq 1.05 \). The physician that performed and analyzed the cardiopulmonary exercise test was unaware of the results of BNP testing.

**Measurement of BNP plasma levels.** In all patients blood was sampled from an antecubital vein after 10 min of supine rest before symptom-limited bicycle exercise. We used a rapid bedside test for determination of BNP (Triage BNP, Biosite Diagnostics, San Diego, California). The Triage BNP test is an immunofluorometric assay for quantitative determination of BNP in ethylenediaminetetraacetic acid-anticoagulated whole blood or plasma (9). The peripheral venous blood was collected into a sampling tube containing EDTA as the anticoagulant. Within 20 min after venipuncture, BNP concentrations were determined by the Triage system by analysts that were blinded to results of ergospirometry and the clinical status of the patients.

**Statistics.** Values are presented as mean values ± SD. All variables were tested for normal distribution by the Kolmogorov-Smirnov test. All data was found normally distributed. Correlations were performed using Pearson’s correlation. Results are presented as coefficient of correlation (r). The area under the receiver operating characteristic curve (AUROC) was utilized for discrimination. The AUROC provides a measure of overall accuracy that is independent of the decision criterion. The criterion value corresponding with the highest accuracy is the value with the minimum false negative and false positive results at the same time. Univariate logistic regression was performed with the BNP criterion value as the explanatory variable and peak VO₂ <14 or <10 ml/min/kg as the response variable. All statistical tests were two-tailed, and a p value <0.05 was considered statistically significant. Data were analyzed using SPSS 10.0 (SPSS Inc., Chicago, Illinois). The AUROC analysis was performed with MedCalc 6.12 (MedCalc software, Mariakerke, Belgium).

## RESULTS

**Patients.** Overall, 70 patients with chronic HF (Table 1) were included in this study.

**BNP levels and exercise parameters.** Table 2 shows the correlation between BNP and exercise variables as well as LVEF. Brain natriuretic peptide levels correlated best with peak VO₂ (Fig. 1a), VO₂-AT and LVEF (Fig. 1b). Compared with BNP levels, LVEF correlated less with peak VO₂ (r = 0.43) and VO₂-AT (r = 0.29). The correlation of

### Table 1. General Patient Characteristics in 70 Patients With Chronic Heart Failure

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patient Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>60.3 ± 10.4</td>
</tr>
<tr>
<td>Men</td>
<td>51 (73%)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>75 ± 14</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>172 ± 7</td>
</tr>
<tr>
<td>NYHA functional class I/II/III</td>
<td>2 (3%)/(44 (63%))/24 (34%)</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>26.4 ± 6.0</td>
</tr>
<tr>
<td>Chronic HF etiology</td>
<td>41 (58.6%)</td>
</tr>
<tr>
<td>Idiopathic dilated CMP</td>
<td>28 (40%)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>1 (1.4%)</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td></td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>57 (81%)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>57 (81%)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>60 (86%)</td>
</tr>
<tr>
<td>Digitalis</td>
<td>55 (79%)</td>
</tr>
</tbody>
</table>

Values are mean ± SD or number of patients (%).

**BNP** = brain natriuretic peptide; **CMP** = cardiomyopathy; **HF** = heart failure; **LVEF** = left ventricular ejection fraction; **NYHA** = New York Heart Association.

**Table 2. Correlation Coefficients Between BNP Levels, Cardiopulmonary Exercise Variables and LVEF**

<table>
<thead>
<tr>
<th></th>
<th>Peak VO₂</th>
<th>VO₂-AT</th>
<th>EqCO₂</th>
<th>W</th>
<th>LVEF</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNP</td>
<td>−0.56</td>
<td>−0.54</td>
<td>0.43</td>
<td>−0.44</td>
<td>−0.50</td>
</tr>
<tr>
<td>p value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

BNP = brain natriuretic peptide; EqCO₂ = ventilatory efficiency; LVEF = left ventricular ejection fraction; VO₂ = oxygen uptake; VO₂-AT = oxygen uptake at the anaerobic threshold; W = maximum exercise level in watts % predicted.
BNP with peak VO₂ was better in patients with dilated cardiomyopathy (r = -0.64) compared with those with ischemic cardiomyopathy (r = -0.41). The correlation of BNP with VO₂-AT was equally good for both etiologies of chronic HF (r = -0.53 vs. -0.57).

Receiver operating characteristic curves illustrate the sensitivity and specificity of BNP in discriminating patients to reach a peak VO₂ <10 or <14 ml/min/kg. The AUROC was 0.93 (95% confidence interval [CI]: 0.85 to 1.0) for peak VO₂ <10 ml/min/kg (Fig. 2a), indicating very good discriminatory power. For peak VO₂ <14 ml/min/kg (Fig. 2b), the area under the curve was 0.72 (95% CI: 0.61 to 0.85), still demonstrating fair to good discriminatory power. The criterion value for BNP to predict a peak VO₂ <10 ml/min/kg was 532 pg/ml with a sensitivity of 100% and a specificity of 78%. A peak VO₂ <14 ml/min/kg was predicted with a BNP criterion value of 316 pg/ml with a sensitivity of 76% and a specificity of 68%. Patients with chronic HF with BNP levels >316 pg/ml had a 6.8-fold higher risk (95% CI: 2.3 to 19.8) to reach a peak VO₂ <14 ml/min/kg compared with patients with BNP levels below this cutoff value.

**DISCUSSION**

Role of BNP in chronic HF. Brain natriuretic peptide is secreted predominantly from cardiac ventricles and is affected by the degree of myocardial stretch, damage, and ischemia in the ventricle (10). Brain natriuretic peptide levels are raised in patients with chronic HF and reflect severity of left ventricular and right ventricular dysfunction (11–13).

Beyond these evidences the present study demonstrated a reliable correlation of BNP levels with exercise parameters.
such as peak VO2, VO2 at the AT, EqCO2, and with LVEF in chronic HF. To the best of our knowledge, this is the first study that systematically examines the correlation of a rapid bedside BNP test with cardiopulmonary exercise testing in patients with mild to severe symptoms of chronic HF.

Brain natriuretic peptide is more useful than atrial natriuretic peptide, endothelin, or norepinephrine as an independent predictor of morbidity and mortality in patients with chronic HF and is independent of other clinical, hemodynamic, and neurohumoral risk factors in chronic HF (6). Endothelin and norepinephrine are closely correlated with exercise capacity in patients with chronic HF (15,16). However, the use of these markers, which give prognostic information in chronic HF, such as norepinephrine, renin, and endothelin, is difficult, impractical, and associated with long-lasting assays (17). For this reason BNP seems to be the most simple, reliable, readily available, and promising laboratory marker of cardiac dysfunction at present.

**Importance of point-of-care testing of BNP in chronic HF.** A rapid bedside BNP test has several advantages compared with the formerly used assay systems to determine BNP (9). The major advantage is its rapid and accurate measurement of BNP from whole blood with 24-h availability in a routine laboratory or at the point-of-care. Additional time-consuming preparation, centrifugation, extraction, and incubation steps can be omitted. Thus, a fast BNP determination is possible, which makes the recently introduced BNP-guided therapy for chronic HF more feasible, especially in an ambulatory setting.

Cardiopulmonary exercise testing as a gold standard is costly, time consuming and has limited availability, so that, with respect to the good correlation of BNP with exercise variables, BNP may be a cost-effective, generally available and reliable tool for the guidance of chronic HF therapy.

**Role of exercise testing in chronic HF.** Exercise testing with gas-exchange analysis has become a routine clinical tool for the evaluation of patients with chronic HF and is predictive of mortality (2,18–22). Therefore, current guidelines recommend exercise testing to select appropriate candidates for heart transplantation (23). Peak VO2 is less valuable in patients with mild symptoms of CHF, although their annual mortality is still high with rates of 8% to 10% (24). In this subset of patients, enhanced ventilatory response to exercise (EqCO2) predicts poor prognosis, whereas peak VO2 is not associated with outcome (25). A significant number of patients with severe chronic HF do not reach maximal exertion. Therefore, some authors assessed the prognostic significance of respiratory data during submaximal exercise. Pardaens et al. (20) found that respiratory data during submaximal exercise are significant predictors of outcome in chronic HF, but inferior to that of peak VO2. Thus, this study examined not only oxygen kinetics at exercise, but also EqCO2.

Many authors concluded that peak VO2 provides superior prognostic information in chronic HF (20). Various cutoff values have been proposed for decision making. Mancini et al. (2) observed that cardiac transplantation could be safely deferred in ambulatory patients with left ventricular dysfunction and peak exercise VO2 of ≥14 ml/min/kg. The highest mortality rate is seen in patients with chronic HF with a peak VO2 of <10 ml/min/kg (21,22). In our study a criterion value for BNP of 532 pg/ml exhibits a very good discriminative power for the prediction of peak VO2 of <10 ml/min/kg, and a criterion value of 316 pg/ml also has good discriminative power for the prediction of peak VO2 of <14 ml/min/kg. A BNP concentration >316 pg/ml constitutes a 6.8-fold higher risk for a reduced exercise capacity with a peak VO2 <14 ml/min/kg. However, peak VO2 is a continuous, rather than a discrete variable, and the evidence of an optimal cutoff point seems questionable (22). Our data underline the importance of peak VO2. The best correlation with BNP as a marker of neuroendocrine activation in chronic HF was seen for peak VO2 and, to a comparable degree, also for VO2-AT. Maximum exercise level, EqCO2 and also LVEF correlated less with BNP. Because there is a good correlation of BNP and exercise capacity, the determination of resting BNP might be a simple and cost-saving alternative in the future to select patients for heart transplantation compared with the more expensive and time-consuming exercise testing, which is not without risk in patients with chronic HF. Moreover, the prognostic power of plasma BNP assessing the mortality in patients with chronic HF has already been shown by Tsutamoto et al. (26).

**Study limitations.** There are several limitations of our study. First, we did not perform invasive hemodynamic tests to evaluate the relation between hemodynamics and BNP. Previous studies have already shown that there is a close correlation between BNP levels and left ventricular end-diastolic pressure. Secondly, we did not study the influence of medications on BNP. All patients were treated according to chronic HF guidelines. Previous studies demonstrated that BNP levels are reduced after treatment with beta-blockers (27), whereas they are increased after treatment with angiotensin-converting enzyme inhibitors (28) or digitals (29). Finally, patients with renal failure were excluded from the study because of potentially marked elevation of plasma BNP (30,31). Thus, it remains unknown whether plasma BNP levels can also be used to predict functional capacity in these patients.

**Conclusions.** Brain natriuretic peptide testing may be an effective way to improve monitoring and therapy of patients with chronic HF, including in-hospital and outpatient management. Brain natriuretic peptide is clearly associated with exercise capacity and LVEF in chronic HF. Brain natriuretic peptide is able to differentiate between patients with chronic HF with moderately and severely impaired exercise capacity. Further studies are needed to compare the prognostic value, outcome, and cost-effectiveness of BNP-guided versus exercise-testing-guided therapy in chronic HF.
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