Value of Cardiopulmonary Exercise Testing and Big Endothelin Plasma Levels to Predict Short-Term Prognosis of Patients With Chronic Heart Failure

MARTIN HÜLSMANN, MD,* BRIGITTE STANEK, MD,* BERNHARD FREY, MD,* BARBARA STURM, MD,* DINAH PUTZ, MD,** THOMAS KOS, MD,* RUDOLF BERGER, MD,* WOLFGANG WOLOSZCZUK, Ph.D,† GERALD MAURER, MD, FACC,* RICHARD PACHER, MD

Vienna, Austria

Objectives. We tested the hypothesis that, in patients with stable heart failure, measuring big endothelin-1 (ET-1) plasma level at rest predicts short-term prognosis better than peak oxygen consumption (VO2max) at exercise.

Background. Cardiopulmonary exercise testing and evaluation of neurohumoral plasma factors are established tools to estimate survival in patients with heart failure. No data, however, exist comparing the prognostic value of both marker categories simultaneously.

Methods. Two hundred twenty-six heart failure patients were studied in regard to a combined end point of death and prioritization for urgent cardiac transplantation within 1 year follow-up.

Results. During the study period 149 patients were without cardiac events (group A), 69 patients died or were urgently transplanted (group B) and 8 patients were alive after a nonurgent heart transplant operation. Norepinephrine (p < 0.0001), atrial natriuretic peptide (p < 0.001), big endothelin plasma levels (p < 0.0001) as well as workload, VO2max and achieved percentage of predicted peak oxygen consumption (pVO2max) (all p < 0.0001) differed significantly between groups A and B. In multivariate stepwise regression analysis, however, only big ET-1 plasma concentration (×2 = 74.4, p < 0.0001), New York Heart Association function class (×2 = 33.9, p < 0.0001), maximal workload (×2 = 7.2, p < 0.01), and plasma atrial natriuretic peptide (ANP) concentration (×2 = 4.6, p < 0.05) were independently related to outcome. Peak oxygen consumption or pVO2max did not reach statistical significance in this model. Event-free survival rates were significantly lower in patients with a big ET-1 level of 4.3 fmol/ml or more than with lower big ET-1 levels (p < 0.0001).

Conclusion. We conclude that in patients with chronic heart failure who are stable on oral therapy measuring big ET-1 and ANP plasma levels may be a valuable noninvasive adjunct to improve the prognostic accuracy of detecting high risk patients compared with exercise testing alone.

(J Am Coll Cardiol 1998;32:1695–700)
©1998 by the American College of Cardiology
exercise limitation of heart failure is likely. Such a relationship was recently confirmed in a small study showing that plasma ET-1 levels during exercise correlated inversely with VO₂max (17).

The objective of the present study was to determine the relative prognostic importance of circulating big ET-1 levels among other neurohormonal factors at rest compared with variables derived from cardiopulmonary exercise testing to enhance the risk stratification of heart failure patients who are stable on a background therapy of digitalis, diuretics and angiotensin converting enzyme (ACE) inhibitors.

Patients and Methods

Two hundred twenty-six patients (199 men, 27 women) who were managed in our heart failure program between 1992 and 1996 were evaluated. All data were obtained within the same day, except for LVEF, which was measured within 2 months prior to entrance. All patients received background therapy consisting of digitalis (digoxin 0.07 mg/day) diuretics and ACE inhibitors for at least 3 months. There were no changes in the therapeutic approach between 1992 and 1996. Except for a flexible diuretic regimen adjusted to daily weight and symptoms, the oral medication was held constant in all patients. Each patient was followed for 12 months after enrollment, and those who were transplanted under priority status were transplanted according to the nonurgent request mode. Such patients were excluded from further analysis, because in these patients HTx did not reflect rapid deterioration of heart failure.

Measurements. The LVEF was determined by radionuclide ventriculography with an Elscint system (Apex 415 gamma camera, Israel) using a standard gated equilibrium blood pool technique (18). All patients underwent an upright bicycle test with gas-exchange analysis. Expired gas was analyzed with a commercially available Sensormedics 2900 metabolic measurement cart that was calibrated before each test. Both the mixing chamber (187 patients) and the breath-by-breath method (39 patients) were used. A 12-lead electrocardiogram (ECG) was monitored continuously and blood pressure was measured at rest and during exercise in 2-min intervals. After warming up, an increment workload rate of 25 W was selected. Workload was increased every 2 min until volitional fatigue, dyspnea, leg pain or a drop in blood pressure occurred. The following parameters were obtained: oxygen consumption at maximal exercise (VO₂max), percentage of age- and gender-adjusted predicted VO₂max (pVO₂max), as calculated according to Wasserman’s equation (19), workload, carbon dioxide production (VCO₂) under maximal exercise, ventilation (VE) and VE/VCO₂.

Blood sampling procedures and hormonal assays. Venous blood samples were obtained after at least 30 min of rest from an indwelling catheter to determine baseline levels of big ET-1, norepinephrine, atrial natriuretic peptide (ANP), and aldosterone. Test tubes were placed on ice and centrifuged immediately. Plasma samples were stored at −70°C until analysis. Big ET-1 was measured as immunoreactive big ET-1 by an extraction-based radioimmunoassay (Biomedica, Vienna, Austria), as described in detail elsewhere (20). Normal range: 0.8 to 1.8 fmol/ml. Plasma norepinephrine (pg/ml) was measured by high pressure liquid chromatography. Normal range: 100–300 pg/ml. The ANP (pg/ml) was measured by a commercial radioimmunoassay purchased from Eiken Chemical (Tokyo, Japan). Normal range: 20–65 pg/ml. Plasma aldosterone (pg/ml) was measured by a commercial radioimmunoassay purchased from Sorin, Biomedica (Saluggia, Italy). Sensitivity: 15 pg/ml. Specificity: 100% for aldosterone and 4.2% for 3 β-5-tetrahydro-aldosterone. Normal range: 35–300 pg/ml.

Statistical analysis. Continuous variables were expressed as mean value ± SD. For comparison of groups, the Student t test was used for analysis of continuous variables and Fisher’s exact test was used to compare categorical data. A stepwise proportional hazards regression Cox model was used to determine the independent predictors of death or HTx under priority status. A p value of <0.05 was used as an entry and exit criterion of the model. Continuous rather than dichotomized

<table>
<thead>
<tr>
<th>Abbreviations and Acronyms</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE = angiotensin converting enzyme</td>
</tr>
<tr>
<td>ANP = atrial natriuretic peptide</td>
</tr>
<tr>
<td>ET-1 = endothelin-1</td>
</tr>
<tr>
<td>HTx = heart transplantation</td>
</tr>
<tr>
<td>LVEF = left ventricular ejection fraction</td>
</tr>
<tr>
<td>NYHA = New York Heart Association</td>
</tr>
<tr>
<td>pVO₂max = percentage of predicted VO₂max</td>
</tr>
<tr>
<td>VCO₂ = carbon dioxide production</td>
</tr>
<tr>
<td>VE = ventilation</td>
</tr>
<tr>
<td>VO₂max = peak oxygen consumption</td>
</tr>
</tbody>
</table>
Patients. A total of 149 patients were 1-year-survivors (group A) and 32 patients died. Of those, 14 died of progressive heart failure, 16 died suddenly, 1 died of pneumonia and 1 patient died following acute myocardial infarction. HTx was performed in 45 patients, 37 of these under priority status. Thus, 69 patients were defined as group B. Nonurgent HTx (group C, 8 patients) was excluded. All patients received therapy with similar doses of ACE inhibitors in addition to digitalis and diuretics, the dose of which was slightly lower in group A than in group B. Also, distribution of NYHA-score and LVEF differed between the groups, with slightly higher values in group A compared to B. Patient characteristics by study group are given in Table 1.

Univariate analysis. Maximal workload, \( V_{O2\text{max}} \) as well as achieved percentage of predicted \( V_{O2\text{max}} \) were all markedly higher in group A than in group B. The anaerobic threshold, as determined in 103 patients in group A and in 71 patients in group B, was also higher. Moreover, ventilation (VE) under maximal exercise was also more pronounced in group A, whereas \( V_{CO2} \) was suppressed in group B, resulting in a different VE/\( V_{CO2} \) slope between the groups (Table 2). Norepinephrine, ANP and big ET-1 were increased above normal in both groups, however, with greater elevations in group B compared to group A (Fig. 1).

Multivariate analysis. A proportional hazards regression model was built with all variables that were found to differ significantly in univariate analysis (NYHA-class, daily furosemide dosage, LVEF, workload, \( V_{O2\text{max}} \), percent predicted \( V_{O2\text{max}} \), \( V_{CO2} \), VE, and VE/\( V_{CO2} \), plasma norepinephrine, ANP and big ET-1). Of these 12 variables, the following provided independent prognostic information: 1) big ET-1 (\( x^2 = 74.4, p < 0.0001 \)); 2) NYHA-class (\( x^2 = 33.9, p < 0.0001 \)); 3) maximal workload (\( x^2 = 7.2, p < 0.01 \)); and 4) ANP (\( x^2 = 4.6, p < 0.05 \)).

Kaplan-Meier lifetime analysis. Event-free survival rates were significantly lower in patients with big ET-1 levels \( \geq 4.3 \) fmol/ml than in patients with big ET-1 levels below this cutpoint (\( p < 0.0001, \) Fig. 2).

Discussion

The results of this study again confirm that big ET-1 is a potent prognostic marker in patients with heart failure. Big ET-1 plasma concentration predicted cardiac death or HTx under priority status within the following year. A cutoff value of 4.3 fmol/ml was useful for the assessment of prognosis regarding imminent need of urgent measures and for identifying low risk patients who can be safely maintained on oral medical therapy. These data confirm our previous findings obtained in a similar patient population, but extends the prognostic import of big ET-1 by the inclusion of cardiopulmonary exercise testing (15,16). In addition to big ET-1,
that big ET-1 plasma levels are moderately increased in various cardiovascular patient populations and in normals showing circulating concentration of this propetide separately in various cells and open an analytic window. We have measured the concentration, integrate the secretory activity of endocrine elements without biologic activity often circulate in higher prohormone big ET-1 (28). It is well known that precursor severe heart failure consists mainly of the 39-amino-acid information for a wide range of disease severity (8–14). It was recognized that ability to exercise depends on cardiac performance, pulmonary function, peripheral muscle mass, blood flow and metabolism (22–24). All these contributing factors are recognized that ability to exercise depends on cardiac performance, pulmonary function, peripheral muscle mass, blood flow and metabolism (22–24). All these contributing factors are adversely affected as heart failure progresses. Interestingly, impaired metabolism of resting skeletal muscle was reported in patients who were judged to be in NYHA-class III, when patients do not perceive symptoms at rest (25). Specifically at this advanced clinical stage increased ET-1 as well as big ET-1 plasma levels are reported (8–12). By pharmacologic inhibition, ET-1 was found to contribute to vasoconstriction in the forearm as well as to total peripheral vascular resistance (26,27).

Measurement of endothelin in heart failure. Endothelin-1 (ET-1) is a 21-amino-acid peptide with potent vascular, cardiac, and renal actions (6). As with other peptides with high biologic activity, ET-1 is rapidly cleared, and in case of abluminal secretion and paracrine action only a fraction of mature ET-1 can reach the circulation. In patients with heart failure circulating levels of ET-1 are increased, reflecting symptoms according to NYHA-class and providing prognostic information for a wide range of disease severity (8–14). It was reported, however, that elevation of “immunoreactive ET-1” in severe heart failure consists mainly of the 39-amino-acid prohormone big ET-1 (28). It is well known that precursor elements without biologic activity often circulate in higher concentration, integrate the secretory activity of endocrine cells and open an analytic window. We have measured the circulating concentration of this propetide separately in various cardiovascular patient populations and in normals showing that big ET-1 plasma levels are moderately increased in hypertension and in mild heart failure, but continue to rise along with further clinical deterioration of heart failure symptoms (11). Moreover, single resting big ET-1 levels were of prognostic significance when LVEF was as low as 20% and less and were superior to hemodynamic data and previously established neurohumoral plasma variables such as norepinephrine and ANP (15,16).

Role of increased endothelin levels. The reason of increased ET-1 production in heart failure is certainly multifactorial. Apart from the classic physiologic stimuli, such as shear stress, thrombin, cytokines, norepinephrine, angiotensin II, and other vasoconstrictors (which are all operative in heart failure), it was reported that experimental hypoxemia furthers ET-1 production in humans. Accordingly, raised ET-1 levels as found in isolated right heart failure correlated inversely with pulmonary artery oxygen saturation (29). The VE/VCO₂ slope (which signifies the deadspace volume) was also found to be related to ET-1 plasma levels (17). Thus, oxygen economy may be an important factor to influence ET-1 metabolism in human heart failure. Interestingly, in the dog ventricular pacing heart failure model ET-1 is expressed particularly in the lungs, while heart and kidney were of minor importance (30). This accorded well with the previous notion that, in heart failure, the heart is a target rather than the source of increased ET-1 levels (28). As a speculation, the activation of ET-1 production in severe chronic heart failure could mirror hidden injury in the pulmonary vascular bed. This theory is based on the finding that both mature ET-1 and big ET-1 plasma concentrations correlate significantly with pulmonary artery pressure (12,15). The close correlation between ET-1 spillover in the lungs and pulmonary vascular resistance suggests that this peptide acts mainly as a local factor rather than as a circulating hormone.

Effect of endothelin receptor blockade. Even more suggestive of a preferential role of ET-1 to narrow the pulmonary circuit is gained from studies using pharmacologic inhibition of the endothelin pathway. In a placebo-controlled study of patients with severe heart failure (LVEF 21% on average) who were off ACE inhibitors at the time of study, bosentan, a mixed ETA/ETB receptor antagonist, increased cardiac index and reduced systemic vascular resistance, suggesting a role of ET-1 in left ventricular afterload (27). However, to an even greater extent, bosentan reversed the elevated pulmonary vascular resistance in these patients. Similar effects of bosentan were seen in a rat heart failure model on top of ACE inhibitors (31). Of these, rats with the highest ET-1 levels had the greatest hemodynamic benefit from ET-1 receptor blockade. Structurally, ET-1’s potent proliferative effects (7) may induce adverse tissue growth in heart failure resulting in an increase in the ventricular mass and cavity enlargement of the ventricle. It was recently reported that in the postinfarct rat model, long-term treatment with BQ123, a selective ETA-receptor antagonist, prevented ventricular remodeling and greatly improved survival in those animals (32). This beneficial effect was accompanied by significant amelioration of left ventricular dysfunction.
Effect of current heart failure treatment. In several recent prospective heart failure trials using ACE inhibitors (33,34) as well as the β-blocker vasodilator carvedilol (35), changes in plasma ET-1 levels reflected both the magnitude and the direction of the response to therapy. Fosinopril in a placebo-controlled study lowered plasma ET-1 levels to normal with alterations in plasma ET-1 being the only covariate explaining the patients’ impression of health status (33). Lisinopril reduced plasma ET-1 concentrations as well, albeit only at a high dose (34). Carvedilol’s beneficial effects were also paralleled by significant falls in ET-1, and the change in ET-1 after treatment was an independent noninvasive predictor of functional and hemodynamic responses to therapy in these patients (35). We have also pursued this question by examining the reaction of circulating big ET-1 in response to enalapril with similar results. In treatment responders, big ET-1 levels fell within 6 months, whereas in patients who deteriorated subsequently big ET-1 levels remained elevated. Moreover, sequential big ET-1 plasma level after 6 months showed a remarkable effect on prognosis (36). Thus, reduction in ET-1 and big ET-1 plasma level during therapy can mirror the beneficial effect of pharmacologic treatment.

Study limitations. A number of noninvasive markers other than ET-1 provide long-term prognostic information in heart failure patients. Although norepinephrine (4) and ANP (5) were among the first to be shown to be associated with a fatal outcome, both do not clearly predict such. In contrast, other newer cardiac natriuretic peptides such as N-terminal ANP and brain natriuretic peptide are also raised in the plasma of patients with left ventricular dysfunction whether symptomatic or asymptomatic and have gained popularity as an index of impending heart failure (37). While ANP is stored in large concentrations in the atria, brain natriuretic peptide is derived to much greater extent from the cardiac ventricles. In cardiac failure, brain natriuretic peptide concentrations increase more than do ANP concentrations, so that in severe heart failure plasma brain natriuretic peptide often exceeds plasma ANP. This differential release rate may make brain natriuretic peptide concentrations a more sensitive indicator of left ventricular dysfunction as ANP concentrations. Our investigation did not include N-terminal ANP and brain natriuretic peptide plasma level measurements. Thus, further studies are necessary to validate the prognostic value of ET-1 or big ET-1 in comparison with these important cardiac hormones.

Clinical implications. The present study demonstrates that the use of 4.3 fmol/ml big ET-1 plasma levels as a cutoff point provides short-term prognostic information in heart failure patients independent of functional capacity. From its objective and noninvasive character on one side, and its stronger informative potency on the other, determination of big ET-1 in plasma at rest appears to be an excellent alternative to VO₂max, or pVO₂max at exercise, in particular in HTx candidates. Measurement of plasma big ET-1 levels can further improve the selection process and prevent adverse outcomes.

References


