Original Research

Chronotropic and Neurohumoral Markers for the Evaluation of Functional Capacity in Patients with Impaired Left Ventricular Function

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Introduction: Brain natriuretic peptide (BNP) levels correlate with functional capacity in patients with heart failure. Autonomic dysfunction and baro-chemo reflex balance play a role in conditioning exercise tolerance and chronotropic competence in heart failure. In this study we examined the relationship between N-terminal pro-brain natriuretic peptide (NT-pro-BNP) and heart rate (HR) response during cardiopulmonary exercise testing and the ability of those two markers to detect low functional class patients.

Methods: We studied 100 patients (age 59 ± 13 yrs) with heart failure and left ventricular ejection fraction 35 ± 9%, who underwent treadmill cardiopulmonary exercise testing using the Dargie protocol. HR response was assessed by the chronotropic response index (CRI), which is calculated using the formula CRI = (peak HR - rest HR) / (220 - age - rest HR) x 100 (%). Blood samples for NT-pro-BNP assessment were taken before exercise.

Results: The overall peak VO_2 achieved was 18 ± 5 ml/kg/min and CRI was 70 ± 26% (normal value >80%). CRI correlated both with peak VO_2 ($r=0.50$, $p<0.001$) and VE/VCO_2 ($r=-0.24$, $p<0.05$). Peak VO_2 correlated strongly with NT-pro-BNP ($r=-0.77$, $p<0.001$). NT-pro-BNP values >335 pg/ml showed 83% sensitivity and 76% specificity for detecting peak VO_2 values <20 ml/kg/min (AUC=86%, $p<0.001$). CRI values >79% showed 70% sensitivity and 60% specificity for detecting peak VO_2 values <20 ml/kg/min (AUC=72%, $p<0.001$). CRI correlated well with NT-pro-BNP at rest ($r=-0.31$, $p<0.001$).

Conclusions: In patients with heart failure, CRI correlates significantly with both functional capacity derived from cardiopulmonary exercise testing and NT-pro-BNP levels. These findings may support the use of CRI as a simple noninvasive marker of heart failure severity.

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Cardiopulmonary exercise testing is widely used to assess functional capacity in chronic heart failure (HF). Previous studies have shown that peak exercise oxygen uptake (peak VO_2) correlates with survival.[1]

Increased sympathetic activity, parasympathetic withdrawal and reduced exercise tolerance are typical features of neuroendocrine activation in heart failure.[2-10] Increased sympathetic drive to the heart results in chronotropic incompetence,[11-13] a decreased contractile response to catecholamines,[13] and a diminished sympathetic reserve during exercise in HF, due more to end organ refractoriness than to inadequate neural stimulation. Reduced baroreflex control has been ascribed to a combination of reduced arterial compliance[14] and impaired central reflex integration.[15]

Increased plasma concentrations of brain natriuretic peptide (BNP) have been found in patients with chronic HF. They are correlated with left ventricular ejection fraction (LVEF) and predict morbidity and mortality in these patients.[16-19] BNP is a circulating cardiac hormone released

mainly from the ventricles in response to increased stretch or wall tension. It is involved in the regulation of blood pressure, blood volume and sodium balance, reflecting its diuretic, natriuretic and vasodilator actions. It is produced as a prohormone pro BNP, which upon secretion is split into BNP and N-terminal pro-brain natriuretic peptide (NT-pro-BNP).

The aims of the current study were: 1. To examine the relationship between chronotropic response index (CRI), NT-pro-BNP, and functional capacity; 2. To evaluate the ability of CRI and NT-pro-BNP to detect the functional class of patients with peak VO_2 <20 ml/kg/min.

Methods

Patient population

We studied prospectively 100 patients (81 men, 19 women), who were diagnosed with left ventricular dysfunction due to coronary artery disease, dilated cardiomyopathy and valvular heart disease, and were being entered in our heart failure program. In the two latter groups coronary artery disease was excluded by coronary arteriography. All patients were in a clinically stable condition for at least six weeks prior to the study and showed no signs of acute cardiac decompensation. Patients were on medical therapy dictated by their physicians.

Mean age was 59 ± 13 (mean ± SD) years. All patients had impaired left ventricular systolic function demonstrated by LVEF <50% (measured by two-dimensional echocardiography). Patients were classified in functional classes I-III according to the New York Heart Association (NYHA). The main exclusion criteria were age <18 or >80 years, treadmill exercise duration <2 min, systolic blood pressure <90 mmHg or >160/100 mmHg, primary pulmonary disease, peripheral vascular or degenerative joint disease which could restrict ability to exercise. The Hospital Institutional Committee approved the present study, and written informed consent was obtained from all subjects.

Cardiopulmonary exercise testing

During treadmill exercise using the Dargie protocol[20] peak VO_2, VE/VO_2 slope, VE/VCO_2 slope were assessed using a standard gas analysis technique with Med Graphics CPX/MAX (Medical Graphics Corp., St. Paul Minnesota, USA). A 12-lead ECG was recorded continuously to rule out significant myocardial ischemia or arrhythmias. Blood pressure was recorded every minute by a cuff sphygmomanometer. Peak VO_2 was determined as the highest value in the terminal phase of exercise. The O_2 uptake at the anaerobic threshold (VO_2-AT) was determined by the V-slope method. Ventilatory efficiency ($EqCO_2$) on exercise was defined as the slope of the VE versus VCO_2 relation. Heart rate (HR) response was assessed by the chronotropic response index (CRI), calculated using the formula CRI = (peak HR - rest HR) / (220 - age - rest HR) x100 (%).[21]

Laboratory analysis

All blood samples were obtained from an antecubital vein at baseline after the patients had been seated for 30 min and were collected in tubes containing ethylene diamine-tetracetic acid (EDTA). The samples were then centrifuged and plasma was stored in aliquots at -20˚C within 30 min. Plasma NT-pro-BNP was determined by Elecsys 1010 Roche Diagnostics Pro BNP sandwich immunoassay. The analytical range extends from 20 to 35000 pg/ml. This automated system has shown the smallest coefficient of analytic variation, just below 2%.[22]

Statistical Analysis

Comparisons of plasma NT-pro-BNP concentrations between cardiac function groups were analyzed using the Statistical Package for Social Sciences (SPSS 10.0) software (SPSS Inc. Chicago Illinois). Based on the Kolmogorov-Smirnov test for normality, we observed that NT-pro-BNP was not normally distributed ($Z=1.99$, $p<0.001$). Thus, we had to log-transform that variable to achieve a normal distribution ($Z=0.75$, $p=0.63$). All analyses were repeated using this log-transformed variable. Receiver operating characteristic (ROC) curves were used for the comparison of the classification accuracy of NT-pro-BNP and CRI for peak VO_2 values <20 ml/kg/min. Logistic regression models were used for NT-pro-BNP and CRI, or both predictors, in order to derive linear predictors and areas under the curve for each model. The comparison of areas under the curve indicates which measure is the best predictor of outcome. In order to examine the independent association of NT-pro-BNP and CRI with peak VO_2 values <20 ml/kg/min multiple logistic regression analysis was conducted. Odds ratios with 95% confidence intervals were generated from the re-

sults of the logistic regression analysis. All p-values reported are two-tailed. Statistical significance was set at 0.05 and analysis was conducted using STATA 7.0 (STATA, College Station TX, USA).

Results

Patients' demographic and clinical characteristics are shown in Table 1.

Cardiopulmonary exercise testing

The mean peak VO_2 achieved was 18 ± 5 ml/kg/min and CRI was 70 ± 26% (normal value >80%). CRI and NT-pro-BNP levels correlated significantly with peak VO_2 (r=0.50, p<0.001; r=-0.77, p<0.001, respectively (Figures 1, 2).

Plasma NT-pro-BNP levels also correlated strongly with VE/VO_2 (r=0.54, p<0.001) and VE/VCO_2 slope (r=0.64, p<0.001) as well as with CRI (r=-0.24, p<0.05).

Resting NT-pro-BNP values >335 pg/ml showed 83% sensitivity and 76% specificity for detecting peak VO_2 values <20 ml/kg/min (p<0.001). CRI values <79% showed 70% sensitivity and 60% specificity for detecting peak VO_2 values <20 ml/kg/min (p<0.001) (Figure 3).

Table 1. Patients' clinical and demographic characteristics

No.	100
Age (years)	59 ± 13
NYHA I	34 (34%)
NYHA II	37 (37%)
NYHA III	29 (29%)
HF aetiology:	
Valvular heart disease	24 (24%)
Coronary artery disease	46 (46%)
Dilated cardiomyopathy	30 (30%)
Medication:	
ACE inhibitors	93 (93%)
Diuretics	84 (84%)
Digitalis	61 (61%)
Beta-blockers	72 (72%)
LVEF (%)	35 ± 9
LVEDD (mm)	63 ± 11
LVESD (mm)	50 ± 12
LA (mm)	45 ± 7
VO_2 peak (ml/kg/min)	18 ± 5
VE/VO_2 slope	38 ± 11
VE/VCO_2 slope	34 ± 8
NT-pro-BNP (pg/ml) baseline	1088 ± 1428
CRI (%)	70 ± 26
Serum creatinine (mg/dl)	1.2 ± 0.3

CRI – chronotropic response index; LA – left atrial diameter; LVEDD – left ventricle end-diastolic diameter; LVEF – left ventricular ejection fraction; LVESD – left ventricle end-systolic diameter; NT-pro-BNP – N-terminal pro-brain natriuretic peptide.

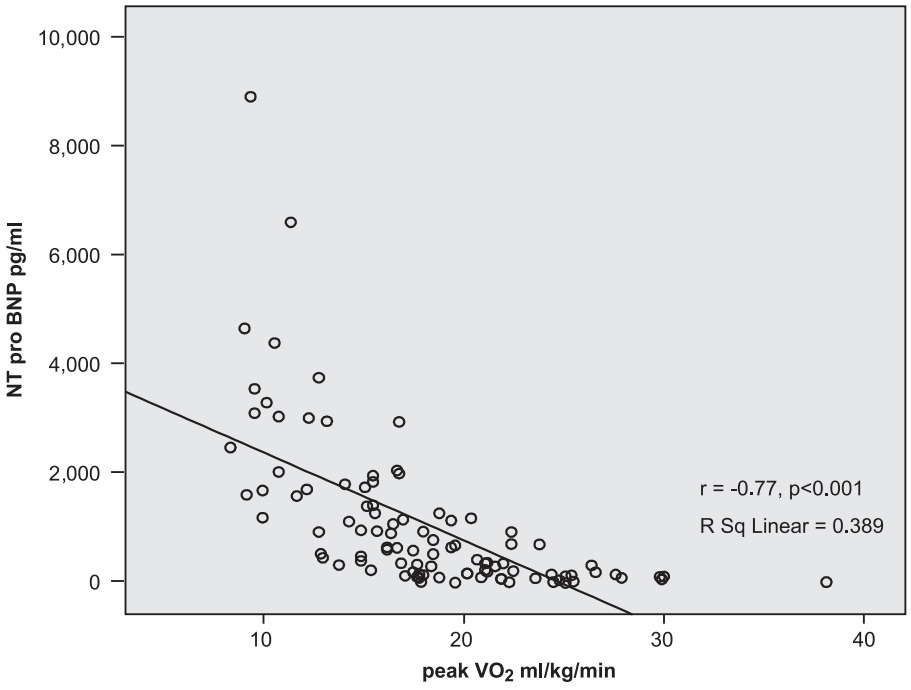

Figure 1. Correlation of peak oxygen uptake (peak VO_2) with plasma levels of N-terminal pro-brain natriuretic peptide.

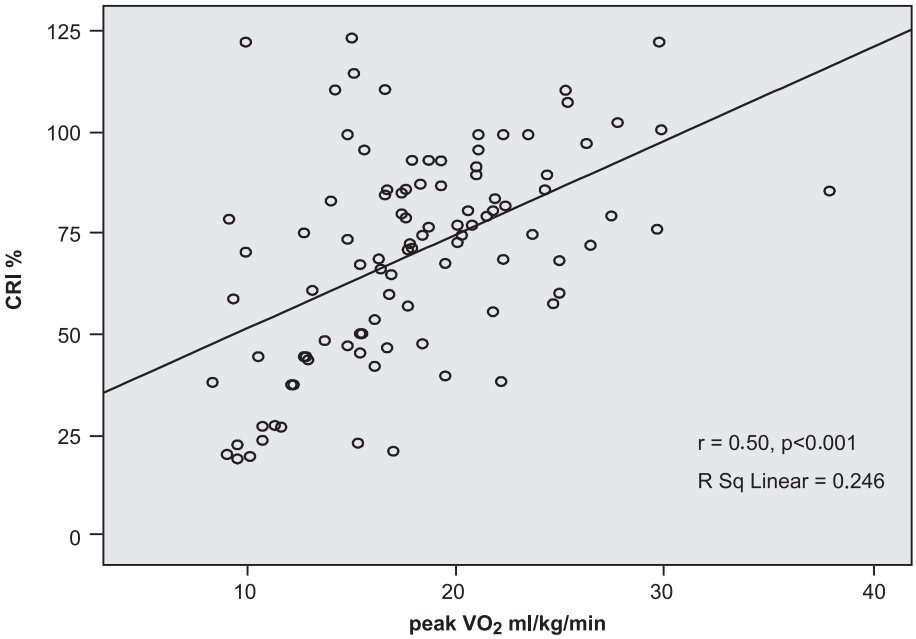

Figure 2. Correlation of peak oxygen uptake (peak VO_2) with chronotropic response index (CRI).

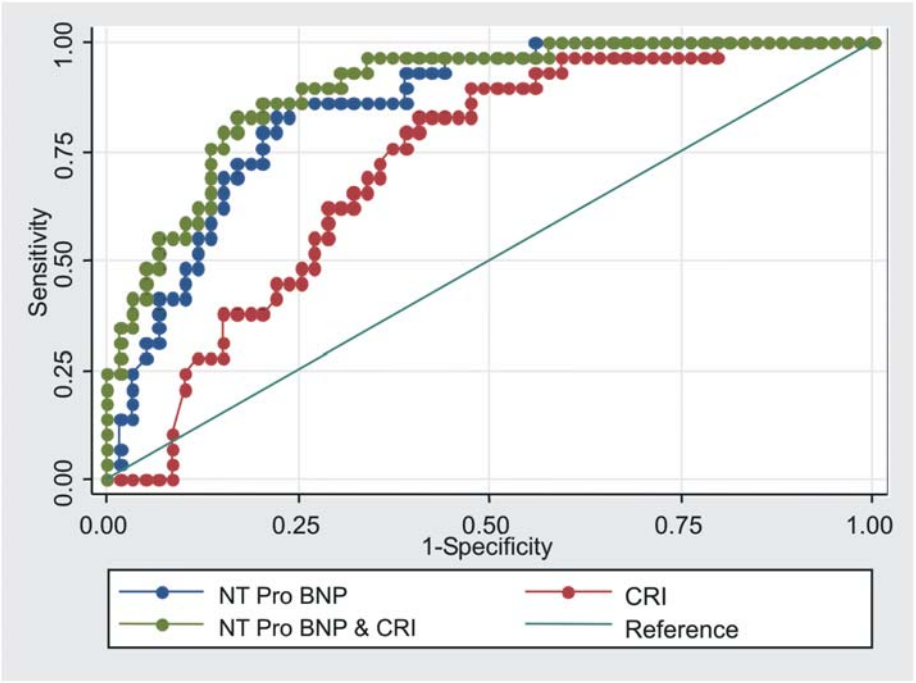

Figure 3. Receiver operator characteristic (ROC) curves of N-terminal pro-brain natriuretic peptide, chronotropic response index (CRI) and their combination for the prediction of peak oxygen uptake values (peak VO_2) <20 ml/kg/ min.

When multiple logistic regression analysis was conducted with dependent variable peak VO_2 values <20 ml/kg/min and independent variables NT-pro-BNP >335 pg/ml and CRI <79.3%, after adjusting for sex, age, medication with β-blockers, LVEF, left atrial diameter, left ventricular end-diastolic and end-systolic diameters, it was found that NT-pro-BNP and CRI were independently associated with peak VO_2 (Table 2). More specifically, subjects with NT-pro-BNP values >335 pg/ml had a 12.98 times greater likelihood of having peak VO_2 values <20 ml/kg/min, while subjects with CRI values less than 79.3% had a 3.78 times greater likelihood of having peak VO_2 values <20 ml/kg/min. NT-pro-BNP had better discrimination than CRI (p=0.046). The discriminatory ability of NT-pro-BNP and CRI together tended to be better than that of NT-

Table 2. Results from multiple logistic regression analysis with dependent variable peak VO_2 values below <20 ml/kg/min. Odds ratios (OR) and 95% confidence intervals (CI).

	OR (95% CI)	p
NT-pro-BNP >335 pg/ml	12.98 (4.23-39.76)	<0.001
CRI <79.3%	3.78 (1.24-11.6)	0.020
Sex, males	1.23 (0.11-14.03)	0.867
Age	1.17 (1.04-1.32)	0.009
Medication with β-blockers	0.25 (0.04-1.59)	0.141
LVEF	1.11 (0.94-1.32)	0.229
LA	1.27 (0.99-1.62)	0.063
LVEDD (mm)	0.90 (0.78-1.04)	0.157
LVESD (mm)	1.15 (0.97-1.36)	0.113
NYHA	*	

*Odds ratio could not be calculated because of no distribution (all subjects with NYHA II or III class had peak VO_2 values <20 ml/kg/min).

Abbreviations as in Table 1.

pro-BNP alone, but the difference did not reach statistical significance (p=0.089) (Table 3). The ROC curves of NT-pro-BNP and CRI are shown in Figure 3.

The mean value of CRI did not differ between those who were under medication with β-blockers and those who were not (71.3 ± 26.6 vs. 67.3 ± 25.4, p=0.490). Age was found to be an additional significant predictor, with odds ratio equal to 1.17 for one year increase.

Echocardiography

LVEF correlated significantly with NT-pro-BNP (r=-0.67, p<0.001). Left ventricular end-diastolic and end-systolic diameters correlated significantly with NT-pro-BNP at rest (r=0.41, p<0.001; r=0.46, p<0.001, respectively). Left atrial diameter also correlated well with NT-pro-BNP (r=0.64, p<0.001). CRI and plasma NT-pro-BNP levels also correlated strongly with NYHA class (r=-0.39, p<0.001; r=0.69, p<0.001, respectively). CRI correlated significantly with NT-pro-BNP (r=-0.31, p<0.001).

Table 3. Areas under the curve (AUC) for the prediction of VO_2 <20 ml/kg/min.

	AUC (95% CI)*	p
NT-pro-BNP	0.86 (0.78-0.94)	-
CRI	0.72 (0.62-0.83)	0.046
NT-pro-BNP & CRI	0.89 (0.83-0.96)	0.089

CI – confidence interval. Other abbreviations as in Table 1.

Discussion

CRI and NT-pro-BNP plasma levels correlated significantly with peak oxygen consumption. NT-pro-BNP circulates at higher levels, has a longer half life, and is less likely to be perturbed by acute stimuli. This may indicate that NT-pro-BNP is a more discriminating marker of cardiac dysfunction and poor outcome.[23]

The direct association between chronotropic response to exercise and peak VO_2 can be explained by the direct relationship between heart rate and cardiac output. In heart failure, cardiac output depends on the increase of heart rate.[24] In our study NT-pro-BNP correlated well with ventricular size and systolic function. We also demonstrated a correlation between NT-pro-BNP and left atrial size, which would be expected to be increased in our patients with left ventricular dysfunction. However, elevated natriuretic peptides have been found by other authors in patients with idiopathic bilateral atrial dilatation and preserved left ventricular function.[25]

Our results suggest that NT-pro-BNP plasma levels increase and CRI decreases with increasing severity of heart failure. In addition, other authors found an inverse correlation between plasma BNP levels and cardiac sympathetic activity.[26] NT-pro-BNP plasma levels were higher in patients with advanced NYHA class.

Peak VO_2 derived from treadmill cardiopulmonary exercise testing is an objective estimator of heart failure severity. Also, a high VE/VCO_2 and VE/VCO_2 slope derived from exercise spirometry demonstrated a similar ability to evaluate HF severity.[27] In our study NT-pro-BNP correlated strongly with peak VO_2, VE/VO_2 and VE/VCO_2 slope, as well as with CRI. To the best of our knowledge, this is the first study to examine the correlation of NT-pro-BNP and CRI with multiple parameters derived from cardiopulmonary exercise testing in patients with impaired left ventricular function. Moreover, we found that levels of NT-pro-BNP and CRI have the ability to identify patients with impaired functional capacity below A class according to the Weber classification system (<20 ml/kg/min).

The relationship between CRI and peak VO_2 supports the hypothesis that the autonomic nervous system has a role in the conditioning of functional capacity and chronotropic incompetence. A low chronotropic response may represent a deterioration of heart failure due to the exhaustion of autonomic compensatory mechanisms and organ refractoriness as a conse-

quence of sustained sympathetic and chemoreflex overactivity.

However, in our study NT-pro-BNP had a better discriminatory ability than CRI. The combination of CRI and NT-pro-BNP plasma levels tended to provide incremental information for the detection of low functional class patients, as expected, but the improvement did not reach statistical significance. Further investigation is necessary to elucidate whether or not the combined information provided by CRI and NT-pro-BNP plasma levels can be useful for the assessment of functional capacity, as well as its possible use in clinical practice.

From a simple objective blood test and the index of CRI, a clinician can deduce the aerobic capacity and indirectly the extent of cardiac dysfunction of patients with chronic HF. In such patients a single NT-pro-BNP assessment can provide extremely useful clinical information. It may well be a simple, noninvasive marker of the severity of heart failure.

Study limitations

Our patients continued their routine HF medication during the study. Previous studies have demonstrated changes of BNP plasma levels following therapy with beta-blockers,[19] angiotensin-converting enzyme inhibitors,[28] or digitalis.[29] According to Costello-Boerrigter, beta-blockers contributed very little to the model after adjustment for age, gender and cardiac condition.[30]

Conclusions

In patients with HF, CRI and NT-pro-BNP correlate significantly with functional capacity derived from cardiopulmonary exercise testing. A reduced CRI represents the progression of autonomic dysfunction and, together with an increase of NT-pro-BNP plasma levels, expresses the worsening of heart failure. These findings may support the use of CRI and NT-pro-BNP plasma levels as a simple noninvasive marker of HF severity.

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