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Relationship of Resting B-type Natriuretic Peptide Level to Cardiac Work and Total Physical Work Capacity in Heart Failure Patients

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Abstract

PURPOSE—Plasma B-type natriuretic peptide (BNP) levels obtained at rest have been previously shown to be correlated with the global functional capacity measures of peak oxygen uptake ($\dot{V}_{O_{2peak}}$) and the minute ventilation/carbon dioxide ($VE/\dot{V}_{CO_2}$) slope. The purpose of this study was to assess the relationship of the plasma BNP level to the rate-pressure product (RPP) as an indicator of central or cardiac work capacity.

METHODS—Twenty-two subjects (12 men), mean age 57 ± 12 years, diagnosed with heart failure (8 ischemic/14 nonischemic) were recruited. All subjects were stable on optimal medical therapy for at least 1 month. Blood samples for BNP level analysis were obtained at rest. Subjects underwent a symptom-limited treadmill exercise test using a ramping protocol while $\dot{V}_{O_2}$, heart rate (HR), and blood pressure (BP) were monitored. Correlation analyses were conducted to assess the relationship of BNP level to RPP level, $\dot{V}_{O_{2peak}}$, $VE/\dot{V}_{CO_2}$ slope, end-tidal CO_2 pressure ($P_{ET}CO_2$), and left ventricular ejection fraction (LVEF).

RESULTS—Resting BNP levels were significantly correlated with RPP levels ($r = -0.69$). The BNP level and the RPP level were correlated with $\dot{V}_{O_{2peak}}$ ($r = -0.63$ and $r = 0.66$, respectively) and

$VE/\dot{V}_{CO_2}$ slope ($r = 0.53$ and $r = -0.54$, respectively). The RPP level but not the BNP level was correlated with $P_{ET}CO_2$ ($r = 0.57$). Neither BNP nor RPP levels were well correlated with LVEF ($r = -0.26$ and $r = 0.14$, respectively).

DISCUSSION—The results of this study suggest that resting plasma BNP level may be a useful clinical measure for evaluating both global functional capacity and myocardial specific work capacity in individuals with heart failure.

Keywords

BNP; functional capacity; myocardial work

Impaired exercise tolerance is a hallmark clinical manifestation in advancing heart failure. Physiologically, the decrease in exercise tolerance may be attributed to a combination of central (ventricular dysfunction) and peripheral (inadequate oxygen delivery or utilization) factors.¹ In heart failure, the inability of the cardiac pump to adequately meet the increased hemodynamic demands associated with higher levels of physical activity is quite evident. However, the severity of physical impairment, based on exertional symptoms alone, is frequently underestimated by patients and is therefore not the best indicator of functional capacity in heart failure.² The cardiopulmonary exercise test (CPX) rather than the symptoms should be used to evaluate functional capacity in patients with heart failure.²

B-type natriuretic peptide (BNP), a cardiac hormone produced and secreted by the ventricles in response to the increased wall stress, has been shown to be elevated in proportion to the severity of heart failure.^{3–5} Studies have shown a correlation between the plasma BNP level and the established indicators of functional capacity, peak oxygen uptake ($\dot{V}_{O_{2peak}}$), and ventilatory efficiency.^{6–8} $\dot{V}_{O_{2peak}}$, which includes both central (cardiac output) and peripheral (a-v O_2 difference) components, reflects the total body work capacity of an individual and provides 1 objective measure of functional capacity.^{9,10} Ventilatory efficiency, as measured by the minute ventilation/carbon dioxide ($VE/\dot{V}_{CO_2}$) slope, has also been shown to be indicative of functional capacity and severity of heart failure.^{10,11} In addition, plasma BNP level and both the $\dot{V}_{O_{2peak}}$ and the $VE/\dot{V}_{CO_2}$ slope, obtained from CPX, have been shown to have prognostic value for individuals with heart failure.^{4,9,10,12} Recently the exercise end-tidal CO_2 pressures ($P_{ET}CO_2$), another variable obtained during CPX, has been shown to be correlated with functional capacity in individuals with heart failure, demonstrating significant relationships to $\dot{V}_{O_2}$ and $VE/\dot{V}_{CO_2}$ slope.^{12–15}

Historically, the rate-pressure product (RPP) has been used as a surrogate measure of myocardial oxygen uptake, which serves as an indicator of central or cardiac work capacity. The relationship of the plasma BNP level to cardiac work capacity (RPP) in individuals with heart failure has not yet been reported and therefore would provide further insight into the relationship between ventricular dysfunction (ventricular wall stress) and cardiac work capacity (myocardial oxygen utilization). The primary purpose of this study was to assess the relationship of the plasma BNP level to RPP level, and secondarily to compare BNP and

RPP levels with the more established indicators of functional capacity in individuals with heart failure.

METHODS

A subset of 22 subjects (12 men), mean age 57 ± 12 years, who were placed into the randomized intervention arm of the HEART CAMP study, and scheduled for CPX, were included in this analysis. All subjects had been diagnosed with heart failure (8 ischemic/14 nonischemic) and were in the New York Heart Association (NYHA) Classes II–IV (14, 7, and 1 in Classes II, III and IV, respectively). The 1 Class IV subject was recently categorized as Class IV from Class III. The subject had nonischemic heart failure with mild to moderate dyspnea and fatigue at rest. Subjects were stable on optimal medical therapy for at least 1 month. Left ventricular ejection fraction (LVEF) was determined by echocardiography, and the NYHA class was assessed by a heart failure specialist. This protocol was approved by the University Institutional Review Board, and all subjects gave informed consent prior to participation.

Plasma BNP levels were obtained on each subject at rest. Subjects sat quietly at rest for at least 10 minutes before a blood sample was obtained by venipuncture of an antecubital vein for BNP level analysis. The BNP level determination was performed, in duplicate and averaged, using a commercially available immunofluorometric assay (Triage BNP, Biosite Diagnostics, San Diego, California). Plasma BNP levels were reported in pg/mL.

Each subject underwent a symptom-limited CPX using a ramping treadmill protocol.¹⁶ Ventilatory gas analysis was obtained using a metabolic cart (Ultima CARDIO₂, MedGraphics, St Paul, Minnesota), which was gas and flow calibrated prior to each test following manufacturer guidelines. Following 5 minutes of seated rest, heart rate (HR), blood pressure (BP), $\dot{V}_{O_2}$, $\dot{V}_{CO_2}$, and VE were collected for 2 minutes as baseline measurements. Stage 1 of the ramping treadmill protocol began at 1.0 mph and 0% grade with subsequent stages increasing 0.1 mph and 0.5% grade every 30 seconds. HR and rhythm were monitored continuously with a 12-lead electrocardiogram before, during, and following treadmill testing. BP was recorded manually (auscultatory method) pretesting, every 4th stage of the exercise test (2 minute stages), and at peak exercise (all obtained within 5 beats of maximal HR). Rating of perceived exertion (Borg 6–20 scale) was obtained at rest, every 1 to 2 minutes during testing and at peak exercise.

The $\dot{V}_{O_{2peak}}$ and peak exercise P_{ETCO_2} were reported as the highest 10-second averaged value recorded during the final 30 seconds of the exercise test. The RPP level was calculated using HR and systolic BP values obtained at $\dot{V}_{O_{2peak}}$ ($[HR_{peak} \times \text{systolic BP}_{peak}]/100$). The $VE/\dot{V}_{CO_2}$ slope was calculated by least squares linear regression using all exercise data from initiation of exercise to maximal effort. Plasma BNP values were normalized by logarithmic transformation ($\log_{10}$ BNP) prior to correlation analyses. Pearson correlation analyses were performed to assess the relationships between $\log_{10}$ BNP levels and RPP

level, $\dot{V}_{O_{2peak}}$, $\dot{V}_E/\dot{V}_{CO_2}$ slope, exercise $P_{ET} \dot{V}_{CO_2}$, and LVEF. Significance was set at P value .05 or higher.

RESULTS

All subjects exercised to volitional fatigue and none exhibited signs or symptoms of ischemia, significant arrhythmias, or abnormal BP responses that warranted early termination of the exercise test. The mean ($\pm$ SD) of the respiratory exchange ratio at peak effort was 1.05 ($\pm$ 0.1) and that for RPE was 16.3 ($\pm$ 2.2).

Means ($\pm$ SD) of the testing parameters are presented in Table 1. Table 2 shows the correlations between BNP level, RPP level, CPX variables, and LVEF. The BNP level demonstrated a fairly strong correlation with RPP level as an indicator of cardiac work capacity. Both BNP and RPP levels were also well correlated with the more global

functional capacity indicators of $\dot{V}_{O_{2peak}}$ and $\dot{V}_E/\dot{V}_{CO_2}$ slope. The RPP level was correlated with peak exercise $P_{ET}CO_2$ whereas BNP level was not. Both BNP and RPP levels were poorly correlated with LVEF value in this group of subjects.

DISCUSSION

Elevated levels of plasma BNP are positively associated with severity of heart failure and increased dysfunction of the ventricles.^{3–5} Not surprisingly, the results of this study demonstrated that plasma BNP levels obtained at rest were also well correlated with the work capacity of the heart ($r = -0.69$) as indicated by the RPP level calculated at peak effort. In addition, we found that both BNP and RPP levels were correlated with the more established measurements of total functional capacity indicated by $\dot{V}_{O_{2peak}}$ ($r = -0.63$ and $r = 0.66$, respectively) and $\dot{V}_E/\dot{V}_{CO_2}$ slope ($r = 0.53$ and $r = -0.54$, respectively).

The relationship of resting BNP level to $\dot{V}_{O_{2peak}}$ in the present study was similar to that reported by Williams et al⁷ ($r = -0.64$), Krüger et al⁶ ($r = -0.56$), and Passino et al⁸ ($r = -0.53$). Similarly, the relationship of resting BNP level to $\dot{V}_E/\dot{V}_{CO_2}$ slope was consistent with the positive correlations reported by Passino et al⁸ ($r = 0.56$), Krüger et al⁶ ($r = 0.43$), and Scardovi et al¹⁷ ($r = 0.45$). However, the relationship of BNP level to LVEF ($r = -0.26$) was significantly weaker than those reported by Krüger et al⁶ ($r = 0.50$) and Passino et al⁸ ($r = 0.48$). This difference may possibly be a result of our much smaller sample size or the mean LVEF of other subject groups (26% and 30%, respectively) being slightly lower than that of our subject group (33%) at the time of testing.

The ventilatory expired gas variable $P_{ET}CO_2$ has been found to be of potential prognostic value for individuals with heart failure.^{12–14} In studies by Arena et al¹⁴ and Tanabe et al,¹⁵ $P_{ET}CO_2$ measured at peak exercise was also significantly correlated with $\dot{V}_{O_{2peak}}$ ($r = 0.52$ and $r = 0.68$, respectively) and $\dot{V}_E/\dot{V}_{CO_2}$ slope ($r = -0.88$ and $r = -0.84$, respectively). In the present study, we found a similar relationship between peak exercise $P_{ET}CO_2$ and $\dot{V}_{O_{2peak}}$ (r

= 0.62), and $P_{ET}CO_2$ and $V_E/\dot{V}_{CO_2}$ slope ($r = -0.88$). In addition, RPP level was significantly correlated with peak exercise $P_{ET}CO_2$ ($r = 0.57$).

The consistent findings in this study of the relationship between resting BNP level and RPP level at peak exercise suggest that BNP level has potential to serve as a central indicator of cardiac function as well as being a more global indicator of functional capacity in individuals with heart failure. Therefore, resting BNP level appears to be a useful clinical measure for assessing both overall functional capacity and cardiac-specific functional capacity in individuals with heart failure.

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Table 1**KEY TEST VARIABLES**

Variables	<i>M</i> (SD)
Heart rate, bpm	
Resting	74.2 (12.7)
Peak	119.1 (16.9)
$\dot{V}_{O_2}$, mL O ₂ ·kg ⁻¹ ·min ⁻¹	
Resting	3.2 (0.8)
Peak	16.1 (3.1)
$V_E/\dot{V}_{CO_2}$ slope	32.9 (6.9)
Peak exercise P _{ET} CO ₂ , mm Hg	37.3 (4.8)
LVEF, %	33.2 (6.6)
RPP	162.6 (33.8)
Plasma BNP, pg/mL	141.4 (168.0)

Abbreviations: BNP, B-type natriuretic peptide; LVEF, left ventricular ejection fraction; P_{ET}CO₂, end-tidal carbon dioxide pressure; RPP, rate-pressure product; $\dot{V}_E/\dot{V}_{CO_2}$, minute ventilation/carbon dioxide; $\dot{V}_{O_2}$, oxygen uptake.

Table 2

CORRELATION COEFFICIENTS BETWEEN BNP, RPP, AND CPX VARIABLES AND LVEF

Variables	Pearson <i>r</i> (<i>P</i> value)	
	Log ₁₀ BNP	RPP
Peak $\dot{V}_{O_2}$, mL O ₂ ·kg ⁻¹ ·min ⁻¹	-0.63 (.002)	0.66 (<.001)
$V_E/\dot{V}_{CO_2}$ slope	0.53 (.01)	-0.54 (<.01)
Peak exercise P _{ETCO₂} , mm Hg	0.02 (.95)	0.57 (.04)
LVEF, %	-0.26 (.24)	0.14 (.54)
RPP	-0.69 (<.001)	

Abbreviations: BNP, B-type natriuretic peptide; CPX, cardiopulmonary, cardiopulmonary exercise test; LVEF, left ventricular ejection fraction; P_{ETCO₂}, end-tidal carbon dioxide pressure; RPP, rate-pressure product; $V_E/\dot{V}_{CO_2}$ minute ventilation/carbon dioxide; $\dot{V}_{O_2}$ oxygen uptake.