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Oxygen uptake efficiency slope correlates with brain natriuretic peptide in patients with heart failure

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Abstract

Background: *Cardiopulmonary exercise testing is a well-established tool for clinical and prognostic assessment of patients with chronic heart failure (CHF). Recently, a new parameter of this examination — oxygen uptake efficiency slope (OUES) — has been described and proposed as a new prognostic factor in patients with CHF. Brain natriuretic peptide (BNP) is an established prognostic factor in CHF. The purpose of the study was to assess OUES in patients with CHF in relation to other cardiopulmonary parameters and BNP levels.*

Methods: *The study group consisted of 42 patients with CHF and left ventricular ejection fraction (LVEF) < 45% (mean age 50.2 ± 9.3 years, mean ejection fraction 26.1 ± 8.1% and NYHA functional class — 2.5 ± 0.8) and eight healthy controls (age 43.6 ± 14.7 years). Coronary artery disease was diagnosed in 16 patients (38%). All underwent maximal cardiopulmonary exercise treadmill test. BNP level was measured using Abbott AxSYM Immunoassay system.*

Results: *There were significant ($p < 0.001$) differences between the patients and controls in BNP levels (350 ± 520* vs *14 ± 19 pg/mL), OUES (1.7 ± 0.4* vs *2.7 ± 0.5), peak VO_2 (17.1 ± ± 5.1* vs *36.9 ± 4.9 mL/kg/min), O_2 pulse (10.9 ± 3.3* vs *15.9 ± 2.7) and VE/VCO_2 slope (35.7 ± 7.8* vs *25.7 ± 2.7). In patients, OUES was significantly ($p < 0.001$) correlated with LVEF ($r = 0.54$), BNP levels ($r = -0.49$), peak VO_2 ($r = 0.80$), VO_2 AT ($r = 0.65$) and VE/VCO_2 slope ($r = -0.59$). BNP was independently related to OUES in multivariate regression analysis.*

Conclusions: *Oxygen uptake efficiency slope is significantly reduced in patients with CHF and correlates with peak VO_2 and other parameters of cardiopulmonary exercise treadmill test. It is not related to age. BNP is an independent marker of OUES in patients with CHF.* (Cardiol J 2010; 17, 4: 362–366)

Key words: heart failure, oxygen uptake efficiency slope, brain natriuretic peptide

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Introduction

Cardiopulmonary exercise testing (CPX) is a well-established tool for clinical and prognostic assessment of patients with chronic heart failure (CHF), and peak VO_2 is its most commonly used parameter in the assessment of functional status and prognosis [1, 2].

The main concern about the assessment of peak oxygen consumption (VO_2) is the achievement of really maximal effort during exercise test. Many patients are unable to perform maximal exercise as evaluated by reaching the respiratory exchange ratio (RER) just above 1 or even more. During the last decade, many investigators have shown that a ventilatory response to exercise expressed as a minute ventilation (VE)/carbon dioxide production (VCO_2) slope can predict prognosis even better than peak VO_2 [3–5]. It can be used as a prognostic factor also in patients who performed only submaximal effort [5]. Recently, another measure of ventilatory response to exercise, referred to as oxygen uptake efficiency slope (OUES), has been described and proposed as a new prognostic indicator in CHF patients [6]. OUES represents the relationship between O_2 and ventilation during incremental exercise and is the absolute increase in VO_2 associated with a 10-fold rise in ventilation. OUES is described as the regression slope 'a' in equation $VO_2 = a \log VE + b$. It was shown to correlate with peak VO_2 and VE/VCO_2 slope [6, 7].

Brain natriuretic peptide (BNP) secreted by cardiomyocytes in response to ventricular wall stretch is a well-known marker of neurohormonal activation, and is also an important predictor in CHF [8]. It has been shown that plasma BNP is related to the enhanced ventilatory response to exercise expressed as a VE/VCO_2 slope [9]. However, the relationship between abnormal neurohormonal activation and OUES is unknown.

In this study, we have assessed OUES in patients with CHF in relation to other cardiopulmonary parameters and BNP levels.

Study population and design

The study group consisted of 42 consecutive patients with CHF, and left ventricular ejection fraction (LVEF) below 45%, referred for cardiopulmonary exercise testing. The control group consisted of eight healthy subjects. At the time of examination, all patients were in a stable clinical condition and taking optimal medical therapy. Exclusion criteria included: recent myocardial infarction or revascularization (≤ three months), exertional angina or arrhythmias, atrial fibrillation, severe pulmonary disease, severe renal insufficiency or other organ disorders significantly altering physical capacity. Thirty seven patients (88%) were treated with angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, 39 (93%) with beta-blockers, 36 (86%) received furosemid, 27 (64%) aldosteron antagonist, 10 (24%) digoxin, 24 (57%) aspirin, and 10 (24%) antiarrhythmics.

All underwent maximal cardiopulmonary exercise treadmill test performed according to the modified Bruce protocol (adding stage 0: 3 min, 1.7 km/h, 5% grading). The peak VO_2, carbon dioxide production, and minute ventilation were measured with breath by breath technique, using Sensor Medics, model Vmax29. The equipment was calibrated before each test. Patients were encouraged to continue to the limit of their symptoms by the supervising physician. There was continuous electrocardiography (ECG) monitoring and blood pressure was measured at each stage of exercise. Peak VO_2 was defined as the highest 20 s average during the last 60 s of exercise. The predicted VO_2% was calculated using Wasserman's equation [10]. RER > 1.0 was taken to represent adequate effort. VE/VCO_2 slope was calculated for the whole exercise period. Ventilatory anaerobic threshold (VAT) was calculated by the V-slope method. OUES was defined as the gradient of the linear relationship between $\log_{10}VE$ and VO_2 (L/min) [11].

Venous blood was drawn before the exercise test after at least 20 minutes of rest (supine position). BNP levels were measured using the Abbott AxSYM Immunoassay system.

All subjects gave their informed consent to participate and the study protocol was approved by the Ethics Committee of our University of Medical Sciences.

Statistical analysis

The values are given as means and standard deviations. Student t-test, Mann-Whitney and χ^2 analyses were used to evaluate the significance of differences between groups. Correlations between variables were assessed using the Spearman rank test. Multivariate regression analysis was used to assess which of the statistically significant correlations between variables were independently correlated with OUES. A p value of < 0.05 was taken to be statistically significant. All analyses were performed using the Statistica 7.0 package.

Results

The mean age of 42 study patients was 50.2 ± ± 9.3 years and eight (19%) were females. The

Table 1. Clinical characteristics of patients with chronic heart failure (CHF) and controls.

	CHF (n = 42)	Controls (n = 8)	P
Age (years)	50.2 ± 9.3	43.6 ± 14.7	NS
Men (%)	34 (81%)	6 (75%)	NS
LVEF (%)	26.1 ± 8.1	–	–
NYHA class	2.5 ± 0.8	–	–
BMI [kg/m^2]	28.2 ± 4.5	23.7 ± 2.0	0.008
BNP [pg/mL]	350 ± 520	14 ± 19	0.0005

LVEF — left ventricular ejection fraction; NYHA — New York Heart Association; BMI — body mass index; BNP — brain natriuretic peptide; NS — non-significant

Table 2. Cardiopulmonary exercise test results in patients with chronic heart failure (CHF) and controls.

	CHF (n = 42)	Controls (n = 8)	P
Peak VO_2 [mL/kg/min]	17.1 ± 5.1	36.9 ± 4.9	< 0.0001
VO_2 AT [mL/kg/min]	11.9 ± 3.0	21.5 ± 2.7	< 0.0001
AT detected (%)	34 (81%)	8 (100%)	NS
O_2 pulse	10.9 ± 3.3	15.9 ± 2.7	0.0002
VE/VCO_2 slope	35.7 ± 7.8	25.7 ± 2.7	0.0009
OUES	1.7 ± 0.4	2.7 ± 0.5	< 0.0001

VO_2 — oxygen consumption; VCO_2 — carbon dioxide production; VE — minute ventilation; AT — anaerobic threshold; OUES — oxygen uptake efficiency slope

mean LVEF (assessed by ECHO) was 26.1 ± 8.1% and NYHA functional class — 2.5 ± 0.8. Coronary artery disease (CAD) was diagnosed in 16 patients (38%) and dilated cardiomyopathy (DCM) in 26 (62%). The mean age of the eight healthy controls was 43.6 ± 14.7 years, and two of them (25%) were females. Clinical characteristics of the study population are shown in Table 1 and the results of the exercise test in Table 2. We were able to determine ventilatory threshold in 35 patients (83%).

OUES did not correlate with age, body mass index (BMI), or peak heart rate. There was a trend towards men having higher OUES than women (Fig. 1). There were significant correlations between OUES and LVEF ($r = 0.54$; $p = 0.0003$), peak VO_2 ($r = 0.80$; $p = 0.0001$, Fig. 2), VO_2 AT ($r = 0.65$; $p = 0.00003$), O_2 pulse ($r = 0.79$; $p = 0.0001$) and peak systolic blood pressure (SBP) ($r = 0.42$; $p = 0.005$) and inverse correlations between OUES and VE/VCO_2 slope ($r = -0.59$; $p = 0.00003$), and BNP levels ($r = -0.49$; $p = 0.0009$, Fig. 3). In multivariate regression

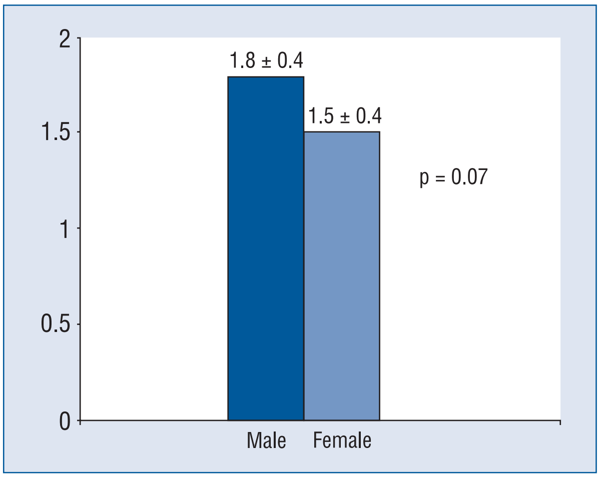

Figure 1. Oxygen uptake efficiency slope in males and females.

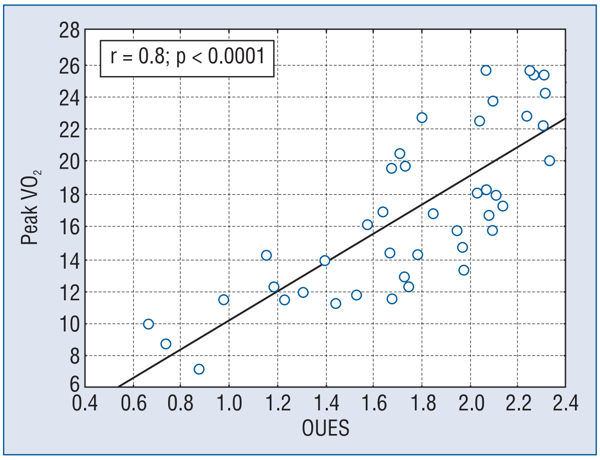

Figure 2. Correlation between oxygen uptake efficiency slope (OUES) and peak oxygen consumption (VO_2) in patients with chronic heart failure.

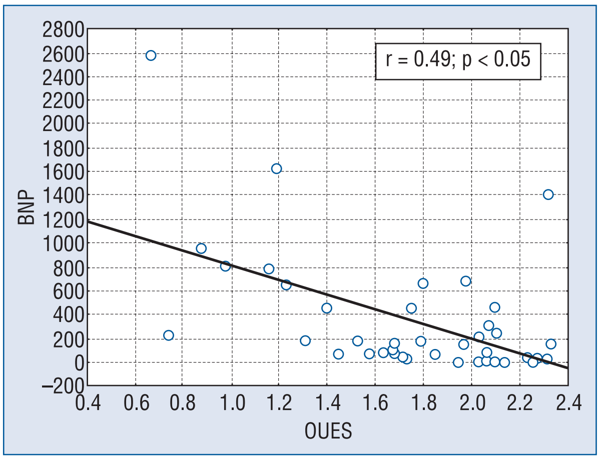

Figure 3. Correlation between oxygen uptake efficiency slope (OUES) and brain natriuretic peptide (BNP) levels in patients with chronic heart failure.

analysis ($R^2 = 0.58$, $p < 0.0001$) with inclusion of LVEF, gender, BNP levels and peak SBP independently associated with OUES were the following: gender ($\beta = 0.27$; $p = 0.02$) LVEF ($\beta = 0.42$; $p = 0.002$), and BNP ($\beta = -0.27$; $p = 0.04$). There were significant correlations between VE/VCO_2 slope and LVEF ($r = -0.58$; $p = 0.00005$), peak VO_2, VO_2 AT, O_2 pulse, peak SBP, and heart rate, and BNP levels. No differences were observed in VE/VCO_2 slope between men and women. VE/VCO_2 slope did not correlate with age or BMI. In multivariate regression analysis ($R^2 = 0.53$, $p < 0.00001$) including LVEF, BNP levels, peak heart rate and peak SBP, independently associated with VE/VCO_2 slope were: LVEF ($\beta = -0.43$; $p = 0.002$), and BNP ($\beta = 0.28$; $p = 0.055$).

Discussion

The available data shows that OUES is significantly reduced in patients with CHF and is correlated with peak VO_2 and other parameters of CPX. It is not related to age. BNP is an independent marker of OUES in patients with CHF.

Cardiopulmonary exercise test is an established method of evaluation of functional status and prognosis in patients with CHF [2, 12]. Despite known limitations (measurement is strongly influenced by the patient's motivation and the tester's subjective choice of test end), peak VO_2 remains the most important parameter of CPX. The ventilatory threshold, which was proposed for assessment and to eliminate the influence of subjective motivation, is unfortunately difficult to obtain in many healthy subjects, and in up to 25% of patients with CHF [13].

We could not determine VAT in 17% of examined patients. Peak VO_2 is widely used as a prognostic index and traditionally remains the most important CPX parameter for the selection of those who may benefit from cardiac transplantation. VE/ /VCO_2 was proposed by Corra et al. [14] to improve the stratification of patients with intermediate peak VO_2 into moderate and high risk groups. Although VE/VCO_2 slope may be derived from the data of submaximal exercise test, the best prognostic significance has the one calculated for the whole exercise [5, 15, 16]. In the European Society of Cardiology guidelines for the diagnosis and treatment of acute and chronic heart failure 2008, VE/VCO_2 is an accepted major prognostic factor, together with peak VO_2 [17]. OUES is a new and promising prognostic marker applicable in cardiac patients unable to perform true maximal exercise [18]. OUES represents, in principle, the absolute rate of increase in VO_2 per 10-fold increase in ventilation. OUES is easily obtained through a simple mathematical calculation, and unlike VAT its determination is not affected by subjective interpretation. OUES, when calculated for the first 75% of the exercise test, differed only by 1.9% from OUES calculated for 100% of exercise time in subjects with peak RER ≥ 1.1 [18]. On serial tests OUES was less variable than exercise duration or peak VO_2. Gademan et al. [19] also did not find significant differences in OUES calculated for the data derived from the first 75%, 90% and 100% of the entire exercise in patients with CHF. OUES, first described by Baba et al. [11], is an index of cardiopulmonary functional reserve integrating cardiovascular, musculoskeletal and respiratory function. The ventilatory response to exercise and OUES are influenced by CO_2 production, arterial pCO_2 and physiological pulmonary dead space ventilation. Thus, OUES depends on mass of working muscle, muscle and pulmonary perfusion, extraction and utilization of oxygen by muscles and the time of appearance of lactic acidosis. Patients with CHF who develop lactic acidosis earlier during exercise, have larger dead space ventilation, and will be expected to have diminished OUES in comparison to healthy subjects, something shown in our analysis that agrees with other work [11, 18]. Hollenberg et al. [18] has shown that OUES was influenced by age, body surface area (to normalize total pulmonary volume) and lean body mass (a surrogate of muscle mass). In addition, they found gender differences in OUES, with higher values in men than women, declining linearly with age, with a steeper rate of decline in men than in women.

In our study, higher values of OUES were found in men than women, but there were no correlations with age in patients with CHF. OUES was strongly correlated with peak VO_2 and ventilation, and less so with VAT, VE/VCO_2 slope, something that tallies with the work of others [6, 7]. Davies et al. [6] found in a retrospective study that OUES had a strong prognostic value, even better than that of standard cardiopulmonary exercise test-derived variables in patients with CHF. They speculated that this may be because its calculation specifically separates the exercise-induced changes in ventilation from any baseline hyperventilation. The best cut-off value for OUES they obtained was 1.47 L/min.

In our analysis, BNP levels were independent markers of OUES, together with gender and peak SBP. Natriuretic peptides are secreted by cardiomyocytes in response to ventricular wall stretch and are markers of neurohormonal activation in CHF. Their levels correlate with functional status, peak

VO_2 and prognosis [8, 20]. Van de Veire et al. [21] found in patients with coronary artery disease (with preserved and with poor left ventricular systolic function; asymptomatic and symptomatic) and intermediate peak VO_2 that OUES was independently predicted by gender, peak heart rate and NT-proBNP. NT-proBNP was also a significant predictor of VE//VCO_2 slope. In our study, BNP was a predictor of VE/VCO_2 slope of borderline significance. Scardovi et al. [9] who examined patients with mild to moderate HF and LVEF < 40% found that BNP was the only independent predictor of the enhanced ventilatory response to CPX (which is defined as VE/VCO_2 slope ≥ 35 and has additive prognostic value in patients with intermediate and preserved exercise capacity).

Probably, OUES in the same way as VE/VCO_2 slope, potentially could also be used to identify a subgroup of patients who might have a worse prognosis. Further studies are needed to confirm its prognostic value in CHF in comparison with BNP and to establish the best cut-off value.

Conclusions

OUES is significantly reduced in patients with CHF and correlates with peak VO_2 and other parameters of CPX. It is not related to age. BNP is an independent marker of OUES in patients with CHF.

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