Original article

Concentration of BNP, endothelin 1, pro-inflammatory cytokines (TNF-α, IL-6) and exercise capacity in patients with heart failure treated with carvedilol

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Abstract

Background: Recent studies on the pathophysiology of heart failure indicate the role of neurohormones and immune and inflammatory processes as potential mechanisms involved in the pathogenesis and clinical course of chronic heart failure (CHF).

Aim: To analyse the relationship between concentrations of brain natriuretic peptide (BNP), endothelin-1 (ET-1), inflammatory cytokines (TNF-α, IL-6) and cardiopulmonary stress test parameters, and to evaluate their changes during carvedilol treatment.

Methods: The study included 86 patients (81 men and 5 women) aged from 35 to 70 years (56.8±9.19) with symptomatic heart failure and left ventricular ejection fraction <40%, receiving an inhibitor of angiotensin II converting enzyme, diuretic and/or digoxin but not beta-blockers. All patients at baseline, and then at 3 and 12 months after treatment, underwent a panel of studies to assess functional capacity according to NYHA, echocardiographic and cardiopulmonary stress test (CPX) parameters, and serum concentrations of BNP, ET-1, TNF-α and IL-6. Before introducing carvedilol we found a weak relationship between concentrations of BNP, ET-1, IL-6 and decreased $VO_{2\ peak}$.

Results: At 12 months exercise tolerance was significantly improved (exercise stress testing prolonged by 143.9 s, p=0.001) and an increase in metabolic equivalent (MET) by 1.41 (p=0.001) was observed. The $VO_{2\ peak}$ was nonsignificantly increased by a mean of 0.9 ml/kg/min. In patients with baseline $VO_{2\ peak}$ <14 ml/kg/min the concentrations of ET-1 and TNF-α were significantly higher than in the remaining ones, and after treatment they were significantly reduced. In these patients $VO_{2\ peak}$%N was also significantly increased (39.5±7.5 vs. 50.1±15,0; p=0.013). The number of patients with $VO_{2\ peak}$ <14 ml/kg/min also significantly decreased from 39 to 21 (p=0.013).

Conclusions: In patients with HF decreased value of $VO_{2\ peak}$ is associated with LV systolic function disorders and increased levels of BNP, ET-1, TNF-α and IL-6. Chronic treatment with carvedilol improves LV systolic function, exercise tolerance and peak oxygen consumption and is associated with significant decrease of BNP, ET-1, TNF-α and IL-6 concentrations.

Key words: heart failure, cardiopulmonary exercise test, exercise test, BNP, endothelin 1, TNF-α, interleukin 6, carvedilol therapy

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Introduction

Contemporary studies dedicated to pathophysiology of chronic heart failure (CHF) stress the role of immunological and inflammatory processes as potential mechanisms involved in CHF pathogenesis [1]. Currently, cytokine activation accompanied by neurohormonal system activation is supposed to be an important factor attributing to CHF progression. An increased level of pro-inflammatory cytokines in CHF patients displays a strong correlation with aggravation of disease symptoms and is of prognostic value. The findings of recently published studies showed a significant role of tumour necrosis factor (TNF-α), interleukin 6 (IL-6) and related cytokines in the regulation of cardiomyocyte hypertrophy and a process of their apoptosis [2]. Activation of pro-inflammatory cytokines such as TNF-α

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and IL-6 correlates closely with CHF symptoms severity. Levels of circulating TNF and IL-6 increase with severity of CHF evaluated according to NYHA functional classification and in the 6-minute walking test [3].

In the course of CHF, activation of the neurohormal system is observed, including a release of brain natriuretic peptide (BNP) and elevated endothelin 1 (ET-1) levels [4-7]. Improved clinical status resulting from treatment with angiotensin converting enzyme inhibitors (ACE-I) and beta-blockers or the use of mechanical circulatory support may lead to alleviation of disturbances of both immunologic and neurohormal responses in CHF patients [8, 9]. The cardiopulmonary stress test (CPX) is employed in daily clinical practice to assess severity of CHF, predict outcomes and establish indications for heart transplantation [6]. Single measurement of peak oxygen consumption ($VO_{2\ peak}$) and other CPX parameters provide important prognostic information. However, these parameters may be changed in the course of disease or as a result of applied treatment [10, 11]. Serial CPX enables objective evaluation of improvement or deterioration of cardiac performance and efficacy assessment of the various medical and surgical management strategies [11, 12]. So far most of the studies evaluating CPX parameters changing in time have involved groups of patients not receiving beta-blockers [13, 14].

The purpose of this study was to analyse the relationship between neurohormones (BNP, ET-1), pro-inflammatory cytokines (TNF-α, IL-6) concentrations and CPX parameters, as well as evaluating their changes over time as a result of employed medical intervention with carvedilol.

Methods

Patients

The study comprised 86 patients (81 men and 5 women) aged 35 to 70 years (mean 56.8±9.19 years) with chronic and symptomatic heart failure, left ventricular ejection fraction (LVEF) <40% assessed by echocardiography who for at least 3 months prior to study enrolment had been treated with ACE-I, diuretics and/or digoxin but without beta-blockers.

In the study group, 30 (34.9%) patients presented heart failure functional NYHA class II and 56 (65.1%) class III. The selected clinical data of patients are presented in Table I. Prior to study recruitment, in 14 (17%) patients percutaneous transluminal coronary angioplasty (PTCA) had been performed, and 7 (8%) had coronary artery bypass grafting (CABG). Three (3%) patients received permanent pacemaker (DDD biventricular pacing) and one cardioverter-defibrillator. All aforementioned procedures were carried out more than 3 months before enrolment in the study.

Studied parameters

Functional status according to NYHA classification, serum concentrations of neurohormones BNP and ET-1, as well as pro-inflammatory cytokines, namely TNF-α and IL-6, were evaluated in all patients at baseline, and at 3 and 12 months after initiation of treatment with carvedilol. Immunoenzymatic method was employed and the following commercially available reagents were used: Immuno-Biological Laboratories (Hamburg) for BNP (normal range up to 100 pg/ml) and TNF-α calculations (up to 5.0 pg/ml), Milenia for interleukin 6 (up to 5 pg/ml) and Cayman for endothelin 1 (up to 3.0 pg/ml).

The efficacy of beta-adrenergic inhibition with carvedilol was assessed by means of resting ECG and based on resting heart rate (HR) and Holter 24-hour ECG monitoring with average heart rate (HR_{mean}) analysis. In the echocardiography, left ventricular end-systolic (LVESd) and end-diastolic (LVEDd) dimensions, left ventricular end-systolic (LVESVI) and end-diastolic volume (LVEDVI) indices as well as left ventricular ejection fraction (LVEF) were calculated.

Exercise capacity was evaluated based on CPX with monitoring of the expiratory gases according to modified Naughton protocol and Working Group on Cardiac Rehabilitation and Exercise Physiology and Working Group on Heart Failure of the European Society of Cardiology recommendations [15]. Cardiopulmonary stress test was performed on a treadmill (Case 16, Marquette Electronics Inc). System VO_2 max 229 was used for measurements of metabolic parameters.

Resting HR, exercise duration (t_{max}) and metabolic equivalent (MET) were evaluated. Peak oxygen consumption expressed in kg/min ($VO_{2\ peak}$) and as

Table I. Clinical data of study patients at baseline (before introduction of carvedilol)

Parameter		Number of patients
CHF aetiology	idiopathic cardiomyopathy	22 (23%)
	ischaemic cardiomyopathy	66 (77%)
Arterial hypertension III period according to WHO		59 (68%)
Hypercholesterolaemia		53 (62%)
Diabetes mellitus type 2		15 (17%)
Previous myocardial infarction	with Q-wave	45 (52%)
	without Q-wave	11 (13%)
Functional NYHA class	II	30 (35%)
	III	56 (65%)
Heart rhythm	sinus	73 (85%)
	atrial fibrillation	13 (15%)
Result of coronary angiography (N=70)	normal coronary arteries	14 (20%)
	one-vessel disease	11 (20%)
	two-vessel disease	15 (27%)
	multi-vessel disease	30 (53%)

a percentage of the calculated normal value ($VO_{2\ peak}$%N) were assessed at the maximal level of exercise. Wasserman's rule involving patient's age, gender and mass was used to calculate percentage of target peak oxygen consumption. Ventilatory carbon dioxide equivalent (VE/VCO_2) was derived from the slope of the curve presenting the relationship of pulmonary ventilation (VE) and volume of produced carbon dioxide (data obtained from CPX device). Moreover, partial pressure of oxygen ($PETO_2$) and carbon dioxide ($PETCO_2$) in the expiratory gas mixture were also entered into the analysis.

Baseline relationships between examined parameters (cross-sectional study) were analysed and then baseline values were compared to those found after medical intervention with carvedilol. Post hoc analysis of the studied neurohormones and inflammatory markers in the patient subsets in relation to either baseline peak oxygen consumption (group with $VO_{2\ peak}$ <14 and group with $VO_{2\ peak}$ >14 ml/kg/min) or an increase in peak oxygen consumption by more or less than 2 ml/kg/min (group with $VO_{2\ peak}$ >2 ml/kg/min and $VO_{2\ peak}$ <2 ml/kg/min, respectively) after medical therapy with carvedilol was also performed.

Statistical analysis

The results of quantitative parameters summarised in the tables are expressed as arithmetic means with standard deviation (SD) and median (ME), lower quartile and upper quartile. Evaluation of differences in examined parameters between analysed groups was done by means of Student's t test for independent variables. If the analysed variable did not meet the criteria of a normal distribution, Mann-Whitney U test was used.

Assessment of differences between measurements of a given variable were done by means of Student's t test if the parameter had a normal distribution; otherwise Wilcoxon test was employed. The course of analysed parameters' variability between measurements in the whole group and in the subgroups in relation to classifying factor was described by means of analysis of variance (ANOVA) with repeated measurements and post hoc Scheffe test. Correlation between two parameters in the analysed subgroups was assessed with Pearson's (r) and Spearman's (r_s) indices of linear correlation. The significance of correlations and differences of qualitative variables between subgroups were verified with χ^2 and Fisher tests.

Statistical tests and p value calculations were carried out using the statistical computer software package STATISTICA. Verifications in all employed tests were performed at the significance level of 0.05.

The study protocol was approved by the Local Bioethical Committee.

Results

Enalapril in the mean dose of 11.9±8.8 mg per day, furosemide at 39.1±19.2 mg per day and spironolactone at 46.3±227 mg per day were used during one-year follow-up in the examined group of patients.

In all patients after baseline examinations, carvedilol was added to previously used medical therapy. The dose of carvedilol was established individually so as to achieve the maximum well tolerated dose. Treatment was initiated with a dose of 3.125 mg twice a day for 2 weeks, then it was increased every 2 weeks. If the first dosing was tolerated well it was increased to 6.25 mg, 12.5 mg and eventually to 25 mg twice a day (in individuals with body mass exceeding 75 kg up to 50 mg twice a day). Maximum tolerable dose was established between weeks 4 and 12, on average after 7.95±2.6 weeks of therapy. Mean dose of carvedilol in the 3rd month was 23.0±13.5 mg/day and after 12 months 25.8±15.2 mg/day, respectively. Mean doses of previously prescribed medications did not change significantly within one-year follow-up.

In the cross-sectional part of the study, the baseline relationships between BNP, ET-1, TNF-α or IL-6 concentrations and examined CPX parameters were analysed. Weak inverse correlations were found between BNP concentrations and $VO_{2\ peak}$ (r=–0.30; p=0.024), BNP and VO_2%N (r=–0.3; p=0.013), ET-1 and $VO_{2\ peak}$ (r=–0.26; p=0.017) and also inverse correlations between IL-6 concentration and $VO_{2\ peak}$ (r=–0.20; p=0.05) as well as between IL-6 level and $PETCO_2$ (r=–0.22; p=0.05).

A positive correlation was observed between IL-6 concentration and VE/VCO_2 value (r=0.19; p=0.015) and between dose of carvedilol and $VO_{2\ peak}$ (r=0.20; p=0.06).

Prior to the initiation of carvedilol treatment, $VO_{2\ peak}$ was found <10 ml/kg/min in 11 (12.8%) patients, between 10 and 16 ml/kg/min in 40 (46.5%) and in 19 (22.1%) subjects ranged from 16 to 20 ml/kg/min. Only 12 (14%) patients had $VO_{2\ peak}$ exceeding 20 ml/kg/min.

A significant decrease in ET-1 concentration was seen after 3 months of treatment with carvedilol. Trends towards a decrease in BNP, TNF-α and IL-6 concentrations were also observed. Significantly slower resting HR by 18 beats/min was noted as well as marked improvement in functional status according to NYHA classification. Echocardiography revealed a significant decrease in LVEDd accompanied by increase in LVEF (Table II).

Moreover, significantly lower HR before exercise, prolonged t_{max} and increased MET were observed (Table III).

Changes in the examined parameters after 12 months of therapy are summarised in Table II. A marked decrease in BNP, TNF-α and IL-6 concentrations was documented. The values of the echocardiographic parameters such as LVESVI, LVEDVI and LVEDd considerably decreased.

Additionally, further significant prolongation of exercise duration and an increase in MET were observed. A significant increase of $VO_{2\ peak}$%N value was found (Table III). Other studied parameters, such as VE/VCO_2, PET O_2 (kPa), and PET CO_2 (kPa), did not show any significant changes in all analysed study periods.

Table II. Changes in the analysed parameters during 12-month follow-up

Variable	Baseline value	Median (lower quartile, upper quartile)	Changes					
			0-12 month		0-3 month		3-12 month	
			total value	p	value	p	value	p
BNP [pg/ml]	464±214	446 (311. 600)	–98.0 (21.10%)	0.001	65.0 (66.4%)	NS	33.0 (33.6%)	NS
ET-1 [pg/ml]	49.3±94.9	24.4 (15.2, 33.9)	–23.3 (47.26%)	0.002	18.6 (81.1%)	0.024	4.7 (18.9%)	NS
TNF-α [pg/ml]	12.2±8.7	14.1 (4.9, 17.3)	–6.9 (56.60%)	0.001	1.5 (21.7%)	NS	5.4 (78.3%)	0.001
IL-6 [pg/ml]	9.4±8.5	8.5 (3.8, 12.1)	–4.1 (43.60%)	0.004	1.9 (46.3%)	NS	2.2 (53.7%)	NS
NYHA class	2.7±0.5	3.0 (2.0, 3.0)	–1.0 (37.00%)	0.0001	0.4 (40%)	0.0001	0.6 (60%)	0.0001
HR [1/min]	87±18	80 (75, 100)	–18.0 (20.6%)	0.0001	15.0 (83.4%)	0.0001	3.0 (16.6%)	NS
LVEDd [mm]	68.8±7.4	69 (63.3, 75.4)	–2.9 (4.20%)	0.002	2.4 (83.3%)	0.014	0.5 (16.7%)	NS
LVEF [%]	28.7±6.2	30.0 (25, 34)	+8.1 (22.00%)	0.0001	5.4 (71.8%)	0.0001	2.7 (28.2%)	NS
LVESVI	67.9±27.4	62.3 (46.9, 84.2)	–12.6 (18.50%)	0.001	4.8 (38.1%)	NS	7.8 (61.9%)	0.002
LVEDVI	96.8±38.8	86.7 (70, 113)	–10.6 (10.90%)	0.009	3.1 (29.2%)	NS	7.5 (70.8%)	NS

Abbreviations: BNP – brain natriuretic peptide concentration, ET-1 – endothelin 1 concentration, TNF-α – tumour necrosis factor concentration, IL-6 – interleukin 6 concentration, HR – heart rate while resting ECG, LVEDd – left ventricular end-diastolic dimension, LVEF – left ventricular ejection fraction, LVESVI – left ventricular end-systolic volume index, LVEDVI – left ventricular end-diastolic volume index

Table III. Changes of selected cardiopulmonary stress test parameters throughout 12-month follow-up

Variable	Baseline value	Median (lower quartile, upper quartile)	Changes					
			0-12 month		0-3 month		3-12 month	
			total value	p	value	p	value	p
HR [l/min]	83±17	81 (69, 92)	–5 (6.0%)	0.029	5 (100.0%)	NS	0	NS
t_{max} [l/min]	589±274	554 (374, 812)	+154 (26.1%)	0.0001	84 (54.5%)	0.007	70 (45.5%)	0.004
MET	4.33±2.29	4.0 (3.0, 6.0)	+1.41 (32.6%)	0.029	0.7 (49.6%)	0.043	0.71 (50.3%)	0.004
$VO_{2\ peak}$ [ml/kg/min]	14.9±4.7	14.5 (12.0, 17.3)	+0.9 (6.0%)	NS	0.3 (33.4%)	NS	0.6 (66.6%)	NS
$VO_{2\ peak}$%N	51.7±15.5	49.5 (41.0, 62.0)	+4.6 (8.8%)	0.016	1.4 (30.4%)	NS	3.2 (69.6%)	NS

Abbreviations: HR – heart rate before exercise, t_{max} – period of physical exercise, MET – metabolic equivalent, $VO_{2\ peak}$ – peak oxygen consumption, $VO_{2\ peak}$%N – peak oxygen consumption as % of valid normal

Post hoc analysis of the examined parameters in relation to the baseline $VO_{2\ peak}$ value was performed. In the baseline examination, $VO_{2\ peak}$ was <14 ml/kg/min in 39 patients and ≥14 ml/kg/min in 47 subjects. Analysis of variance over time showed that concentration of ET-1 and TNF-α differed between those patients (Figures 1 and 2). After introduction of beta-blockers, ET-1 and TNF-α concentrations decreased significantly only in patients with $VO_{2\ peak}$ <14 ml/kg/min.

The BNP concentration was significantly higher in patients with $VO_{2\ peak}$ <14 ml/kg/min than in those with $VO_{2\ peak}$ >14 ml/kg/min (515.2±198 vs. 424.6±204.7 pg/ml, respectively; p=0.04). After 12 months of therapy, a significant increase (p=0.013) in $VO_{2\ peak}$%N from 39.5±7.5 to 50.1±15.0 was noted in the group of patients with baseline $VO_{2\ peak}$ <14 ml/kg/min. After 12 months of treatment with carvedilol, the number of patients with $VO_{2\ peak}$ <14 ml/kg/min decreased from 39 to 21, which was of statistical significance (p=0.04). Exercise capacity improvement was accompanied by a decrease in ET-1 and TNF-α concentrations.

After 12 months of therapy, in 17 (22%) patients an increase of $VO_{2\ peak}$ by at least 2 ml/kg/min was noted, which may be considered as a criterion of improvement in CHF patients treated with beta-blockers. Moreover, in this group of patients a significant drop in IL-6 concentration from 10.6±13.6 to 6.6±5.8 pg/ml (p=0.01) was noted. In patients without increase of $VO_{2\ peak}$ by 2 ml/kg/min, a decrease of IL-6 concentration was not of statistical significance (8.5±5.1 vs. 5.0±4.8; NS). The aforementioned findings indicate a possible association between improvement in exercise capacity and decrease of IL-6 concentration resulting from beta-blockade.

Additional analysis regarding examined parameters with respect to CHF aetiology, concomitant diabetes mellitus and cardiac arrhythmia was carried out. The detailed data regarding these issues will be presented in the ongoing publications.

No differences in echocardiographic parameters and CPX findings with respect to heart failure aetiology were found. In both groups, a significant decrease in ET-1, BNP and inflammatory cytokine concentrations accompanied

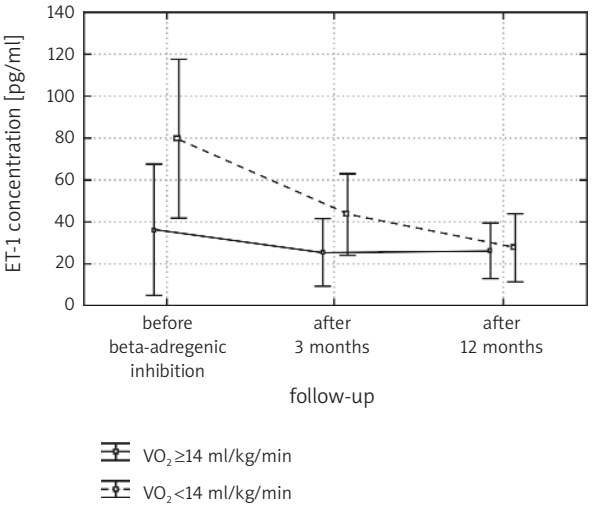

Figure 1. Endothelin 1 (ET-1) concentration in a group of patients with $VO_{2\,peak}$ ≥14 and $VO_{2\,peak}$ <14 ml/kg/min during one-year therapy

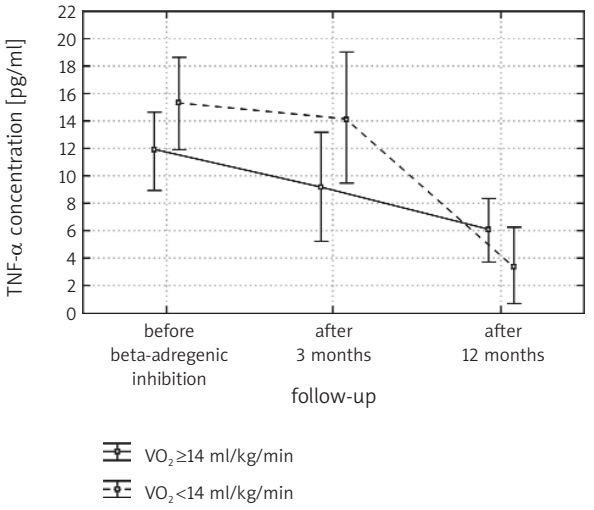

Figure 2. Tumor necrosis factor (TNF-α) concentration in a group of patients with $VO_{2\,peak}$ ≥14 and $VO_{2\,peak}$ <14 m/kg/min during one-year therapy

by marked improvement in echocardiographic parameters was observed in comparison to the baseline findings.

In patients with concomitant diabetes mellitus, higher ET-1 concentrations were observed either at baseline or after 12-month treatment with carvedilol. No significant differences in CPX parameters were noted in patients both with or without diabetes mellitus in the analysed periods. However, one must pay attention to the fact that after 12 months of therapy with carvedilol in patients with diabetes mellitus $VO_{2\,peak}$ increased by a mean of 1.8 ml/kg/min while in the group without diabetes only by 0.6 ml/kg/min.

Prior to initiation of beta-blocker therapy, IL-6 (13.55±10.94 vs. 8.6±7.33; p=0.053) and BNP (582.75±179.35 vs. 442.94±213.75; p=0.036) concentrations were significantly higher in patients with atrial fibrillation (AF) than in those found in sinus rhythm (SR). Marked differences regarding stress test parameters were also observed between examined groups. In patients with AF, higher resting and maximal HR and shorter period of exercise than in individuals with SR were noted. These parameters also differed significantly between groups after 3 and 12 months of treatment. Peak oxygen consumption was significantly lower in patients with AF than in SR in every analysed period of carvedilol therapy.

Discussion

Evaluation of exercise capacity and its changes resulting from therapy was carried out on the basis of serial cardiopulmonary stress tests. There are conflicting data on the impact of beta-blockers on exercise capacity in patients with CHF [14, 16]. According to Florea et al. [14] serial stress testing enables more appropriate assessment of prognosis than single tests. Patients with a good response to the treatment manifest clinical as well as haemodynamic improvement expressed as an increase in $VO_{2\,peak}$ that is also associated with prognosis improvement.

Our observation of patients who underwent serial stress testing comprising analysis of the expiratory gases enables monitoring of the effects of therapy after carvedilol introduction with respect to CPX parameters and changes in either echocardiographic variables or neurohormones, as well as inflammatory cytokine concentrations.

Observation related to time course of the analysed parameters showed that even after 3 months of treatment with carvedilol, a decrease in HR as well as change in some echocardiographic parameters (drop in LVEDd and increase of LVEF) were noted, accompanied by improvement in the functional status and exercise capacity. Carvedilol therapy lasting for many months was associated with an improvement in the majority of echocardiographic parameters that was related to LV remodelling, and with beneficial changes of the parameters evaluated by means of CPX. An interesting finding was to see that these changes were accompanied by a significant decrease in concentrations of the analysed neurohormones or inflammatory markers.

The pathophysiology of impaired exercise tolerance in CHF is enormously complex. Impaired exercise tolerance, additionally to LV dysfunction, may be partially due to a chronic decrease in perfusion of the extremities and a lack of capacity to increase it in response to metabolic stimulation [17]. Limited ability of the failing heart to

increase HR in response to exercise can also play a role. According to Tavazzi [18] it is a result of pathologically high resting HR and abnormal low maximal HR during exercise. Limited cardiac ability to increase HR in response to exercise reflects partially impaired sensitivity of beta-adrenergic receptors resulting from excessive sympathetic tone.

Examining a relationship between parameters of the cardiopulmonary stress test and BNP concentration, an inverse correlation between $VO_{2\ peak}$ or $VO_{2\ peak}$%N and increased BNP levels was noted. This finding may support the correlation between BNP concentration and exercise capacity in CHF patients. So far not many reports regarding this issue have been published [11, 19]. According to some authors [20], BNP concentration reflecting the extent of myocardial injury, stress and ischaemia correlates closely with physical capacity and LVEF in CHF patients. The BNP concentration also correlates with haemodynamic parameters such as right atrial, pulmonary capillary wedge and LV end-diastolic pressures. Brain natriuretic peptide shows a significant association with functional capacity assessed according to NYHA classification [19].

Based on our findings we can conclude that analysis of BNP concentration can help to distinguish patients with various degrees of exercise capacity limitation. The observation that the BNP concentration in patients with $VO_{2\ peak}$ <14 ml/kg/min was significantly higher than in subjects with $VO_{2\ peak}$ >14 ml/kg/min seems to support such an assumption. Our results regarding mean values of BNP concentrations were similar to the findings of Krüger et al. [11].

In our study $VO_{2\ peak}$ was inversely correlated with ET-1 concentration, and an increase of $VO_{2\ peak}$ resulting from treatment with carvedilol caused a significant drop in ET-1 level. According to the results derived from the study of Garlichs et al. [21], reduction of ET-1 concentration was associated with decreased severity of CHF symptoms and improved exercise tolerance.

We found that before introduction of carvedilol an inverse correlation between increased IL-6 concentration and decreased value of either peak oxygen consumption or $VO_{2\ peak}$%N was present. This finding may suggest an association between exercise capacity and pro-inflammatory stimulation in CHF patients. These results are consistent with the findings of other authors [9, 22].

We also found a correlation between IL-6 concentration and both carbon dioxide partial pressure in expiratory gas mixture (PET CO_2) and carbon dioxide ventilatory equivalent (VE/VCO_2), which might indicate indirectly a contribution of the elevated IL-6 concentration to more pronounced respiratory response to exercise.

The true cause of increased respiratory response to exercise in CHF patients is not known. According to Witte et al. [22], pronounced sympathetic activation plays a role, leading to increased response of respiratory receptors to exercise. Although partial pressure of the respiratory gasses in blood of CHF patients is normal, excessive reflexes of baroceptors are seen. It was documented that increased activity of chemoreceptors resulting from pronounced sympathetic tone led to increased ventilatory response to hypercapnia.

In the analysed group of patients higher TNF-α concentration was seen in patients with impaired exercise tolerance compared to individuals with better physical capacity and higher $VO_{2\ peak}$. Impaired exercise tolerance in CHF results not only from deterioration of cardiac performance, but also changes in the peripheral arteries. High TNF-α concentrations induce oxidative stress that causes a decrease in NO level and apoptosis leading to endothelial injury and its dysfunction. Eventually, it causes reduced peripheral vasodilating capacity, muscular fibre atrophy, and a decrease of both skeletal muscle power and their durability. Elevated TNF-α concentration leads to skeletal muscle damage through inhibition of synthesis and simultaneous induction of contractile proteins catabolism [23].

Treatment with carvedilol prolonged duration of exercise and increased metabolic equivalent were seen after 3 and 12 months. After 12 months of treatment, in 58.3% of patients $VO_{2\ peak}$ increased by an average of 0.9 ml/kg/min, although this was not statistically significant. No marked changes were observed with respect to other parameters of gas exchange evaluated by means of CPX examination. Our results confirm previous findings reported by Zugck et al. [16]. However, it was found in the study published by Pohwani et al. [24] that patients with $VO_{2\ peak}$ <12 ml/kg/min receiving beta-blockers manifested prolonged survival compared to subjects with $VO_{2\ peak}$ <14 ml/kg/min but without beta-blockers. Due to the small number of participants in this study no threshold value of $VO_{2\ peak}$ qualifying patients on beta-blockers to heart transplantation was established. However, it was established that the threshold value valid at that time of 14 ml/kg/min should not be applied to patients treated with beta-blockers.

Peterson et al. [25] believe that CHF patients receiving beta-blockers do not have higher one- or three-year survival rate following heart transplantation if preoperative $VO_{2\ peak}$ exceeded or was equal to 12 ml/kg/min. Contemporary progress in the management of CHF is associated with marked reduction of mortality, especially in patients treated with beta-blockers. Their administration in patients with a failing heart improves exercise tolerance; however, in most cases due to reduced chronotropic response to stress it has only a slight impact on $VO_{2\ peak}$ in CHF patients [23]. In the opinion of Kruger et al. [11] $VO_{2\ peak}$ is less relevant in the evaluation of subjects with mild CHF in spite of the high annual mortality rate in this group of patients, ranging from 8 to 10%. Florea et al. [14] reported that calculation of $VO_{2\ peak}$ was of significance with respect to prognosis in

patients with chronic CHF and its serial measurements provided important predictive information.

In the examined group of patients with $VO_{2\ peak}$ <14 ml/kg/min before treatment with carvedilol markedly higher both IL-6 and ET-1 levels and slightly elevated, not significantly, TNF-α concentration were also observed. This may suggest that increased pro-inflammatory cytokine concentration may be associated with markedly depressed exercise performance in CHF patients.

Our study revealed that chronic inhibition of beta--adrenergic receptors did not significantly increase $VO_{2\ peak}$. A favourable result of beta-blockade is improved left ventricular systolic performance and exercise tolerance. Moreover, after introduction of beta-blockers the number of patients with peak oxygen consumption exceeding 14 ml/kg/min did increase. The observed better exercise capacity is likely to be the result not only of improvement in left ventricular systolic performance, but also of the dose of carvedilol used, as well as of a drop in concentrations of neurohormones or pro-inflammatory cytokines.

Based on our results we conclude that CPX parameters should be analysed individually with respect to clinical, echocardiographic parameters, complemented by the assessment of concentrations of both neurohormones and inflammatory cytokines.

Conclusions

In heart failure patients, decreased peak oxygen consumption correlates with increased BNP, ET-1 and IL-6 concentrations.

Chronic treatment with carvedilol significantly improves left ventricular systolic performance, decreases BNP, ET-1, TNF-α and IL-6 concentrations, and increases duration of exercise, metabolic equivalents and peak oxygen consumption expressed in % predicted target values.

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Stężenie mózgowego peptydu natriuretycznego, endoteliny 1 i cytokin (TNF-α, IL-6) a wydolność wysiłkowa u chorych z niewydolnością serca podczas przewlekłego leczenia karwedilolem

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Streszczenie

Wstęp: Współczesne badania nad patofizjologią niewydolności serca (CHF) wskazują na rolę neurohormonów oraz procesów immunologicznych i zapalnych jako potencjalnych mechanizmów biorących udział w patogenezie i przebiegu klinicznym CHF.

Cel: Analiza związku stężenia mózgowego peptydu natriuretycznego (BNP), endoteliny 1 (ET-1) i cytokin zapalnych (TNF-α, IL-6) z parametrami wysiłkowego testu spiroergometrycznego (CPX) oraz ocena ich zmian w czasie pod wpływem leczenia karwedilolem.

Metodyka: Badaniami objęto 86 chorych w wieku 35–70 lat (56,8±9,19) z objawową niewydolnością serca i frakcją wyrzutową lewej komory (LVEF) <40%, którzy otrzymywali inhibitor konwertazy angiotensyny II, diuretyk i/lub digoksynę, ale nie byli leczeni beta-blokerem. Przed leczeniem analizowano wydolność krążenia wg NYHA, parametry echokardiograficzne i CPX oraz stężenie w surowicy BNP, ET-1, TNF-α i IL-6, a następnie analizę powtórzono po 3 i 12 mies. leczenia karwedilolem. Przed interwencją z zastosowaniem karwedilolu stwierdzono słabe korelacje pomiędzy podwyższonymi stężeniami BNP, ET-1, IL-6 a obniżonymi wartościami szczytowego zużycia tlenu ($VO_{2\ peak}$).

Wyniki: Po 12-miesięcznym leczeniu karwedilolem stwierdzono istotną poprawę tolerancji wysiłku [wydłużenie czasu trwania wysiłku o 143,9 s (p=0,001) i zwiększenie ekwiwalentu metabolicznego MET o 1,41 (p=0,001)] oraz nieznamienny wzrost $VO_{2\ peak}$ średnio o 0,9 ml/kg/min. Analiza *post hoc* wykazała, że u chorych z wyjściową wartością $VO_{2\ peak}$ <14 ml/kg/min stężenia BNP, ET-1 i TNF-α były istotnie wyższe niż u pozostałych, a po leczeniu uległy znamiennemu obniżeniu. U tych chorych stwierdzono także istotny wzrost $VO_{2\ peak}$%N (39,5±7,5 *vs* 50,1±15,0; p=0,013). Istotnemu zmniejszeniu uległa także liczba chorych z $VO_{2\ peak}$ <14 ml/kg/min – z 39 do 21 (p=0,013).

Wnioski: U chorych z CHF obniżonym wartościom $VO_{2\ peak}$ towarzyszą zaburzenia czynności skurczowej lewej komory i podwyższone stężenia BNP, ET-1, TNF-α i IL-6. Przewlekłe leczenie karwedilolem poprawia czynność skurczową lewej komory, tolerancję wysiłku i $VO_{2\ peak}$ oraz wiąże się z istotnym obniżeniem stężenia BNP, ET-1, TNF-α i IL-6.

Słowa kluczowe: niewydolność serca, test spiroergometryczny, wydolność wysiłkowa, mózgowy peptyd natriuretyczny, endotelina 1, TNF-α, interleukina 6, terapia karwedilolem

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