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ORIGINAL ARTICLE

Comparison of prognostic values of cardiopulmonary and heart rate parameters in exercise testing in men with heart failure

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Abstract

Background: *Cardiopulmonary exercise testing (CPET) is the gold standard in the evaluation of patients with chronic heart failure (CHF). However, this test is relatively expensive, assessment of its results requires experience, and in Poland it is available only in tertiary health care centers. Many heart rate (HR) parameters taken during a standard electrocardiographic (ECG) exercise test also shows prognostic values. Thus, the aim of this study is to compare prognostic values of ventilatory and HR parameters in exercise testing in CHF patients, and to find out if HR parameters can be used instead of ventilatory in the evaluation of a prognosis.*

Methods: *One hundred thirty two men (mean age 49 ± 11 years) with CHF with reduced left ventricular ejection fraction (< 45%) underwent a treadmill CPET using a modified Bruce's protocol, during which both HR and ventilatory parameters were measured. The patients were followed for 27 ± 13 months after CPET.*

Results: *Mortality was 28% (n = 37). Non-survivors demonstrated significantly shorter exercise time (342 ± 167 vs. 525 ± 342 s, p < 0.001), lower maximal HR (122 ± 22 vs. 138 ± 21 bpm, p < 0.001), smaller difference between maximal HR and at rest (36 ± 19 vs. 52 ± 21 bpm, p < 0.001), and lower HR recovery rate (HRR; 16 ± 10 vs. 24 ± 13 bpm, p = 0.002), chronotropic index (CHI; 0.45 ± 0.23 vs. 0.61 ± 0.23, p < 0.001), peak oxygen consumption (13.82 ± 4.62 vs. 18.54 ± 5.68 mL/kg/min, p < 0.001) and oxygen uptake efficiency slope (OUES) value (1.56 ± 0.58 vs. 1.94 ± 0.63, p = 0.001), and higher ventilation to carbon dioxide production (VE/VCO$_2$) slope value (40.56 ± 9.11 vs. 33.33 ± 7.36, p < 0.001). Two parameters that showed good prognostic value and availability in a routine CPET were chosen for receiver operating characteristic analysis, VE/VCO$_2$ slope and CHI, which showed cut-off values of 35 (sensitivity 74%, specificity 71%, p < 0.001) and 64 (sensitivity 74%, specificity 68%, p < 0.001) respectively.*

Conclusions: *Heart rate parameters show significant prognostic values; CHI is the best of them, however, it is weaker than VE/VCO$_2$ slope. HR parameters show somewhat weaker prognostic values in comparison with ventilatory parameters, yet they may be useful in cases of CPET unavailability.* (Cardiol J 2018; 25, 6: 701–708)

Key words: chronotropic index, cardiopulmonary exercise testing, prognosis, chronic heart failure

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Introduction

Chronic heart failure (CHF) is a growing health care issue due to the increasing number of patients, especially those at high-risk of hospitalization and death. It is necessary to evaluate prognosis of CHF patients in order to qualify them for appropriate treatment. Cardiopulmonary exercise testing (CPET) is the gold standard recommended by the European Society of Cardiology and American Heart Association guidelines [1]. It measures ventilatory and heart rate (HR) parameters during exercise; the most important in evaluation of CHF patients are peak VO_2 and VE/VCO_2 slope [2–5]. However, CPET is a time-consuming test, assessment of its results requires experience, and in Poland it is available only in tertiary health care centers. It might be possible to substitute CPET in primary health care with a routine electrocardiographic (ECG) exercise test, which has much greater availability, but measures only HR parameters. Their use in evaluation of CHF patients has not been studied thoroughly, but there is evidence that they also show some prognostic value [6–8].

The aim of the hereby-presented analysis is to compare prognostic values of ventilatory and HR parameters in exercise testing in CHF patients, and to find out if HR parameters can be used instead of ventilatory in evaluation of prognosis.

Methods

This retrospective single-center registry analyzed CPET results of 132 male patients with CHF, 42% (n = 58) of whom had ischemic cardiomyopathy and the rest dilated cardiomyopathy. The CPET was performed in patients considered for heart transplantation. Only male patients were included to eliminate influence of gender on the results. All patients included participated between 1 January 2006 and 31 December 2008, and inclusion criteria consisted of availability of full medical documentation, stable CHF and left ventricular ejection fraction (LVEF) lower than 45%. If a patient underwent multiple CPETs, only the first of them was considered. All the patients underwent a maximal symptom-limited CPET on a treadmill using Bruce's protocol modified for CHF (one stage added at the beginning: 3 min, 1.7 km/h, 5% slope). All tests were terminated because of dyspnea or exhaustion. SensorMedics Vmax 29 device (Becton, Dickinson and Company, US) was used to examine gas exchange during the tests. Each patient underwent spirometry before the test. GE Medical Systems IT Case 4.13 was used to analyze ECG during CPET. HR at rest was evaluated as 1 min average HR of the last minute during few minutes standing before CPET. HR peak was defined as HR at peak exercise calculated with the system.

The following ventilatory parameters were assessed: peak VO_2 (mean value from the last 20–30 s of the test [9]), VE/VCO_2 slope (calculated for VE/VCO_2 graph for the whole test; $y = mx + b$, where b = slope [3]), oxygen uptake efficiency slope (OUES; $VO_2 = a\log VE + b$, where a = OUES [3]), respiratory exchange ratio (RER), and HR parameters: HR at rest (HR rest), peak HR, chronotropic reserve (ΔHR; peak HR – HR rest), chronotropic index (CHI) and HR recovery (HRR; peak HR – HR 1 min after exercise). CHI is shown as percentage of chronotropic reserve using the following formula: $CHI = \Delta HR / [(220 - age) - HR\ rest] \times 100\%$.

Statistical analysis

Statistical analysis was performed using STATISTICA 9, Statsoft. Probability distribution of continuous variables was tested with Shapiro-Wilk test. Most continuous variables had non-normal distribution, and Mann-Whitney U test was used to analyze them. Chi-square tests were used for categorical variables. Univariate regression models, log rank tests and Kaplan-Maier plots were used to assess unadjusted survival. Receiver operating characteristic (ROC) analysis was used to find reference values for chosen parameters (VE/VCO_2 slope and CHI). The data is expressed as mean values with standard deviation for continuous variables and percentages for categorical variables. A p value of < 0.05 was considered statistically significant for all the tests.

Results

Patients were followed for 27 ± 13 months and 28% (n = 37) of them died during this time. Patients who died did not differ significantly as to anthropometric data. However, they demonstrated significantly lower LVEF, higher incidence of coronary artery disease (CAD) and were more likely to be treated with diuretics (Table 1). There were 12 (12.6%) patients with atrial fibrillation in the survivors group vs. 6 (16.6%) in non-survivors, as well as 13 (13.7%) vs. 4 (10.8%) patients respectively with implantable cardioverter-defibrillator, in that 1 patient with cardiac resynchronization therapy in each group. There were 12 patients with implanted

Table 1. General characteristics.

	Alive	Dead	P
Age [years]	49 ± 11	50 ± 11	0.79
Height [cm]	176.8 ± 7.4	173.9 ± 5.9	0.05
Body weight [kg]	86.6 ± 14.9	82.4 ± 17.3	0.19
Body mass index [kg/m^2]	27.6 ± 4.1	27.1 ± 4.9	0.44
Left ventricular ejection fraction [%]	29 ± 7	24 ± 7	**< 0.001**
Dilated cardiomyopathy	62%	40%	**0.030**
Arterial hypertension	32%	43%	0.30
Diabetes mellitus	13%	23%	0.19
ACEI/ARB	87%	80%	0.45
Diuretics	79%	97%	**0.008**
Acetylsalicylic acid	53%	66%	0.23
Statins	57%	63%	0.55
Beta-blockers	92%	86%	0.30

ACEI — angiotensin converting enzyme inhibitor, ARB — angiotensin receptor blocker

Table 2. Cardiopulmonary exercise test results.

	Alive	Dead	P
Exercise duration [s]	525 ± 199	342 ± 167	**< 0.001**
Peak HR	138 ± 21	122 ± 22	**< 0.001**
ΔHR	52 ± 21	36 ± 19	**< 0.001**
CHI [%]	61 ± 23	45 ± 23	**< 0.001**
HRR	24 ± 13	16 ± 10	**0.002**
Peak VO_2 [mL/kg/min]	18.5 ± 5.7	13.8 ± 4.6	**< 0.001**
OUES	1.9 ± 0.6	1.6 ± 0.6	**0.001**
VE/VCO_2 slope	33.3 ± 7.4	40.6 ± 9.1	**< 0.001**
RER	1.06 ± 0.07	1.06 ± 0.08	0.99

HR — heart rate; ΔHR — peak HR – HR at rest; CHI — chronotropic index; HRR — heart rate recovery 1 min after exercise; VO_2 — oxygen uptake; OUES — oxygen uptake efficiency slope; VE/VCO_2 — ventilation to carbon dioxide production; RER — respiratory exchange ratio

pacemakers (9.5% vs. 8.1%, respectively) with no pacemaker related chronotropic incompetence.

The patients who died demonstrated significantly worse CPET results, both ventilatory and chronotropic; all the patients performed a maximal test as shown by RER values above 1.0 (Table 2), which means that all parameters can be used in evaluation of prognosis [10, 11]. There was no significant difference in RER values between groups which underscores that the effort during exercise was similar in both groups. Univariate regression models showed significant prognostic values of all the investigated CPET parameters (Table 3). anaerobic treshold and CHI showed the strongest prognostic values, however, VE/VCO_2 slope and

Table 3. Univariate regression model.

	Hazard ratio	Confidence interval	P
VE/VCO_2 slope	1.08	1.04–1.12	**< 0.001**
Peak VO_2	0.85	0.79–0.92	**< 0.001**
OUES	0.59	0.37–0.93	**0.025**
AT	0.27	0.14–0.54	**< 0.001**
ΔHR	0.97	0.95–0.98	**< 0.001**
CHI	0.24	0.19–0.29	**< 0.001**
Peak HR	0.97	0.96–0.99	**< 0.001**
HRR	0.95	0.92–0.98	**< 0.001**

AT — anaerobic treshold; HR — heart rate; ΔHR — peak HR – HR at rest; CHI — chronotropic index; HRR — heart rate recovery 1 min after exercise; VO_2 — oxygen uptake; OUES — oxygen uptake efficiency slope; VE/VCO_2 — ventilation to carbon dioxide production

CHI were chosen for further analyses. The reason for this choice was that these two parameters do not depend on intensity of exercise as much as the others do. Many patients are not able to perform a maximal exercise and they do not reach peak HR or peak VO_2; it is also estimated that in ca. 30% patients it was not possible to find anaerobic treshold.

ROC analysis of VE/VCO_2 slope and CHI showed the best cut-off values of 35 (specificity 71% and sensitivity 74%, $p < 0.001$) (Fig. 1) and 64 (specificity 68% and sensitivity 74%, $p < 0.001$) (Fig. 2), respectively. VE/VCO_2 slope had a greater area under curve (0.73 vs. 0.71). Survival probability analysis showed 83% 12-month survival probability for patients with CHI ≤ 64% and 98% for those with CHI > 64% ($p < 0.001$) (Fig. 3). Similarly, 12-month survival probability for patients with VE/VCO_2 slope ≥ 35 was 81% and for those with VE/VCO_2 slope < 35 was 93% ($p < 0.001$) (Fig. 4).

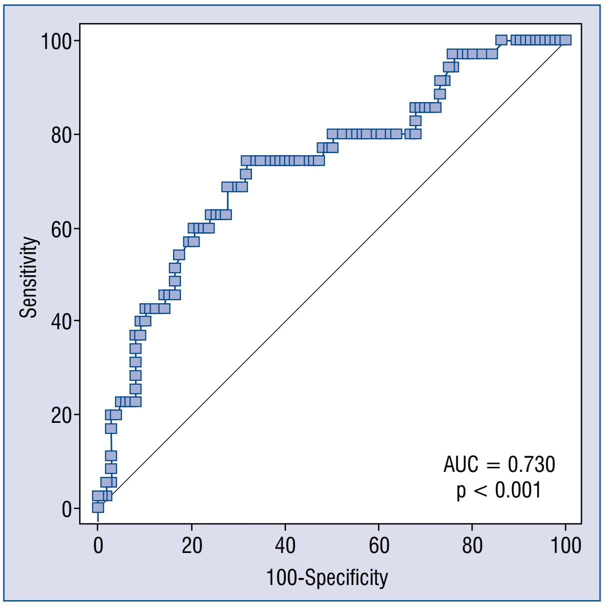

Figure 1. Receiver operating characteristic analysis of ventilation to carbon dioxide production (VE/VCO_2) slope; AUC — area under curve.

Discussion

The main findings of this study are: 1) HR parameters show significant prognostic values in patients with CHF; 2) CHI is the strongest prognostic marker among HR parameters; 3) HR parameters show somewhat weaker prognostic values in comparison with ventilatory parameters; 4)CHI provides a useful cut-off point (64%) similarly to VE/VCO_2 slope (35).

High quality diagnostics are necessary to qualify patients for heart transplantation and implantation of left ventricular assistant devices. The following parameters are most often used in evaluation of CHF patients: LVEF, New York Heart Association classification, peak VO_2, hematocrit, QRS width, tachycardia at rest and lack of reaction to standard treatment [12, 13]. CPET is a gold-standard test used in evaluation of CHF patients, particularly those considered for heart transplantation [3, 14]. In spite of growing number of studies confirming value of CPET in clinical evaluation of various groups of patients, with peak VO_2 as the 'gold standard' in evaluation of physical fitness, this examination is still rarely performed. It is a relatively expensive test and interpretation of its results requires experience [1]. As it is not easily accessible, there is a need for other parameters with prognostic values similar to those of ventilatory parameters, but easier to obtain in e.g. outpatient care [15–17]. A standard ECG exercise test is easily accessible and inexpensive. It is commonly used for clinical evaluation of e.g. patients

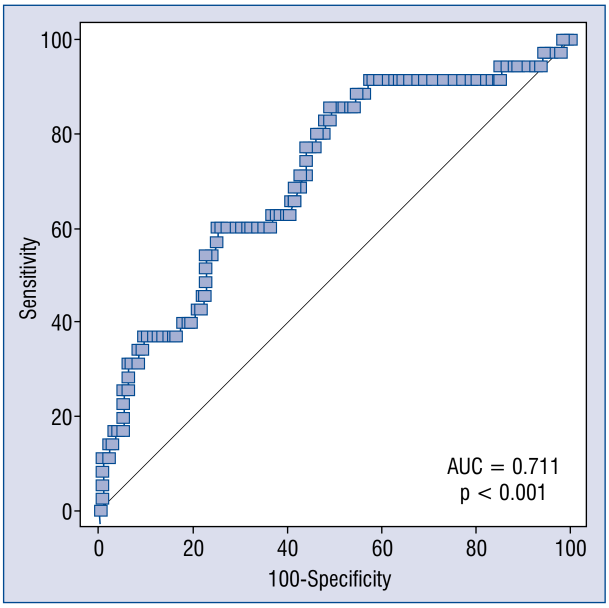

Figure 2. Receiver operating characteristic analysis of chronotropic index; AUC — area under curve.

with CAD and its interpretation is easier. However, physical fitness is only estimated during such a test, as it cannot be measured directly without considering ventilatory parameters.

Peak VO_2, estimated as mean VO_2 in the last 20 s or 30 s of a test was considered the best prognostic marker for a long time [9]. However,

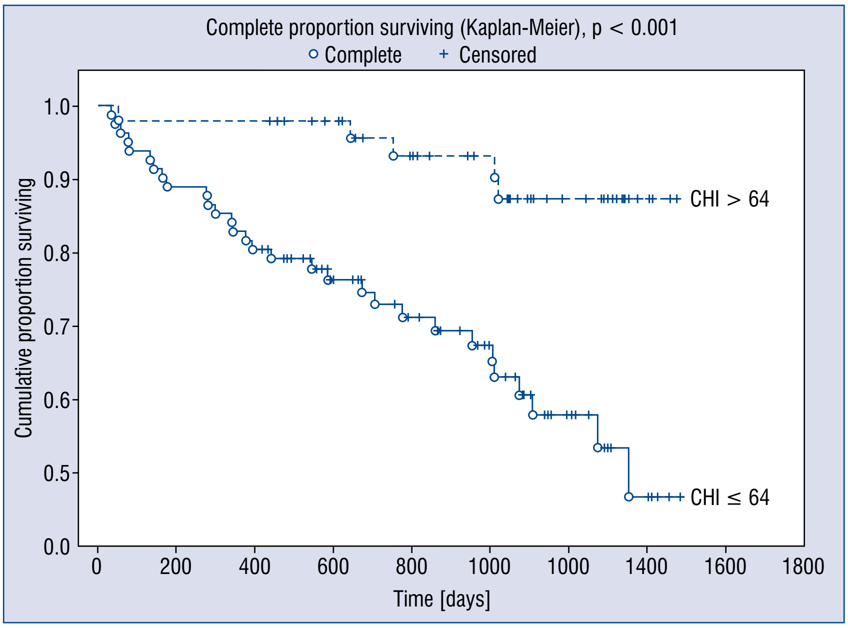

Figure 3. Survival probability curves for patients with chronotropic index (CHI) ≤ 64%.

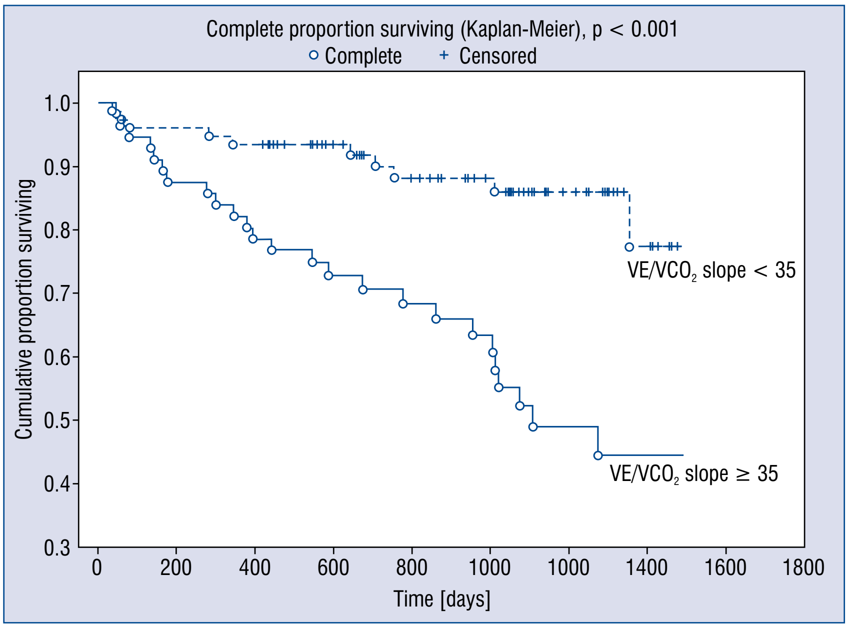

Figure 4. Survival probability curves for patients with ventilation to carbon dioxide production (VE/VCO_2) slope ≥ 35.

many authors showed that this value depends on the intensity of exercise, and it has the greatest prognostic value when RER is higher than 1.0 [10, 11]. In the present study, all the patients performed maximal exercise as shown by mean RER 1.06, and there was no difference between the survivors and the non-survivors. Therefore, the obtained peak VO_2 values could be used in analyses. Recent years have witnessed a growing importance of VE/VCO_2 slope; its small dependence on the intensity of performed exercise made it the most important CPET parameter in evaluation of prognosis in CHF patients [18]. VE/VCO_2 slope above 34 or 36 is considered the best risk marker [2, 13]. Many authors confirm that VE/VCO_2 slope has a better prognostic value than peak VO_2 [19, 20].

This study confirmed the findings of the cited authors in showing that the best cut-off point for VE/VCO$_2$ slope is 35.

Several studies show that a multiple-marker approach to evaluation of CHF patients may have advantages over the traditional approach. These include models such as VE/VCO$_2$ slope, HRR, OUES, PetCO$_2$ and peak VO$_2$ [2]. Each of these may be used as a prognostic marker independently, but combined they show a greater prognostic value [2]. This model does not include CHI because numerous studies show that the only significant HR parameter independent from beta-blocker use is HRR [19, 20]. In this study, univariate regression models showed significant prognostic values of all the investigated parameters, not only ventilatory, but also HR parameters, including CHI, HRR, HRmax and ΔHR. These parameters can also be obtained in a standard ECG exercise test without analysis of gas exchange, and their value in evaluation of patients with CAD was confirmed by numerous authors [21]. There are very few studies investigating usefulness of CHI in CHF patients, and their results are inconsistent [7, 8, 16].

Usefulness of HR parameters remains controversial because of wide use of beta-blockers in CHF patients. Peak HR depends strongly on use of beta-blockers. That is why CHI was developed based on estimated HR reserve [22]. Initially, a cut-off point of 80% was proposed for CHI [6], which however was not confirmed in other studies [7, 12]. Other authors showed a significant cut-off point of 62% for CHI in patients with known or suspected CAD treated with beta-blockers [23] or 65% in patients with CHF [24]. A subanalysis of HF-ACTION trial in patients with CHF with reduced LVEF treated with beta-blockers showed that CHI had no significant prognostic value in a multivariate analysis. However, this study showed that CHI below 60% indicated worse prognosis, i.e. all-cause and cardiac mortality or hospitalizations due to CHF [25]. Al-Najjar et al. [26] have found that patients with CHI had lower exercise time and peak VO$_2$, however CHI was not a significant predictor of mortality.

Chronotropic index is a measure of chronotropic incompetence which is defined as an impairment of normal increase of HR with incremental exercise. In heart failure sympathetic over activity leads to beta-receptor downregulation and reduced myocardial sensitivity to beta-agonists, which may further lead to impaired HR response to exercise. Chronotropic incompetence is related to exercise intolerance, and increases with severity of HF regardless of presence of beta-blocker therapy or beta-blocker daily dose [7]. The controversy exists if CHI contribute to exercise intolerance or merely reflect work performed or the duration of exercise rather than being a discrete pathological entity [8, 26].

The present analysis showed that both the gold-standard ventilatory parameters and the HF parameters of CPET have significant prognostic values in men with CHF. Ventilatory parameters are the best prognostic markers, particularly oxygen uptake at peak exercise (peak VO$_2$) and the marker of increased exertional ventilation (VE/VCO$_2$ slope) as shown in numerous other studies [15, 27–30]. HR parameters demonstrated somewhat weaker prognostic value; CHI, peak HR and HRR are the most important. The strongest HR parameter is CHI, which is however, weaker than VE/VCO$_2$ slope as shown in ROC analysis. Both VE/VCO$_2$ slope and CHI provide cut-off points that clearly distinguish patients with good and poor prognosis. In this study, patients with CHI above 64% demonstrated higher long-term survival probability than those with CHI below 64%. Most of these patients (90%) were treated with beta-blockers, and results are consistent with previously cited works. Similar to the present findings Goda et al. [31] reported, using HR increase (HR difference from rest to peak exercise) and HRR (HR difference from peak to 2 min after exercise) as HR parameters and CEPT parameters, that although HR profiles during exercise are easy to perform and useful prognostic markers in patients with cardiovascular disease (ischemic heart disease, valvular heart disease, cardiomyopathies), they are not superior to respiratory gas analysis [31].

Limitations of the study

This is a single-center retrospective registry including only males with CHF, therefore it does not reflect the whole population of CHF patients. The results need to be confirmed in larger, multicenter studies. A small group of the presented patients had atrial fibrillation, as in other previous studies [7, 26, 31], so generalizing results to patients with atrial fibrillation must be done with caution. This group of patients needs further study.

Conclusions

1. Heart rate parameters show significant prognostic values in patients with CHF.
2. Chronotropic index is the strongest prognostic marker among HR parameters.

3. Heart rate parameters show somewhat weaker prognostic values in comparison with ventilatory parameters, yet they may be useful in cases of CPET unavailability.
4. Chronotropic index provides a useful cut-off point (64%) similarly to VE/VCO_2 slope (35).

Conflict of interest: None declared

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