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Evaluation of the prognostic value of selected ergospirometric parameters in patients with chronic systolic heart failure pre-qualified for heart transplantation in the 12-month follow-up

Ocena wartości rokowniczej wybranych parametrów ergospirometrycznych u chorych z przewlekłą skurczową niewydolnością serca kwalifikowanych wstępnie do transplantacji serca, w obserwacji 12-miesięcznej

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Abstract

Introduction. Despite recent advances in diagnosis and pharmacological treatment of cardiovascular diseases, chronic heart failure (HF) carries a poor prognosis. The identification of patients at highest risk for early death from HF is of special importance. Ergospirometric test is known to be useful in predicting survival and oxygen consumption (maximal/ /peak VO2) and minute ventilation-carbon dioxide production relationship ($VE/VCO2_{slope}$) are the most frequently analyzed cardiopulmonary exercise test parameters. The aim of this study was to assess the ability of peak VO2 and $VE/VCO2_{slope}$ to predict cardiac-related mortality and cardiac-related hospitalization (MACE, major adverse cardiac event) in patients with chronic systolic HF, pre-qualified for heart transplantation.

Material and methods. Forty-five patients (38 men; age 50 ± 8 years) with stable chronic HF (21 coronary artery disease, 24 dilated cardiomyopathy), in New York Heart Association functional class II (n. 16)–III (n. 29), with left ventricular ejection fraction (LVEF) below 35% (mean LVEF = 22.7 ± 5.1%), underwent cardiopulmonary exercise testing between 2006 and 2012 year.

Results. At the end of follow-up, 5 (11%) patients had died and 17 (38%) had a hospitalization due to CHF exacerbation. Peak VO2 was 14.5 ± 5.7 mL/kg/min, VE/VCO2 slope was 35.1 ± 6.1. MACE(+) group had a lower peak VO2 (13.9 ± ± 6.9 mL/kg/min vs 15.1 ± 4.3, p = NS) and higher $VE/VCO2_{slope}$ (37.2 + 6.0 vs. 33.1 ± 5.6, p = 0.021) than MACE(–) group. MACE(+) death group had a lower peak VO2 than MACE(–) group (10.9 ± 1.3 vs. 15.1 ± 4.3, p = 0.045). The areas under the receiver operating characteristic curves for predicting MACE at 1 year were 0.68 for peak VO2 and 0.70 for $VE/VCO2_{slope}$. The results of Kaplan-Meier analysis revealed a 1-year MACE free survival of 33% in patients with $VE/VCO2_{slope}$ > 34.9 and 67% in those with $VE/VCO2_{slope}$ < 34.9 (p = 0.0562) and 20% in patients with peak VO2 < 11.6 mL/kg/min and 67% in those with peak VO2 > 11.9 mL/kg/min (p = 0.0085).

Conclusions. Both VO2 and $VE/VCO2_{slope}$, are good prognostic parameters for serious cardiovascular events and improve the risk stratification of chronic HF patients.

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

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Introduction

Despite considerable progress in the diagnosis and treatment of cardiovascular diseases, heart failure (HF) remains one of the biggest problems of modern medicine and the entire health care system. Patients with advanced HF are characterized by a high risk of cardiovascular death; therefore, a very important role is played by prognostic factors, which allow identification of the subgroup of patients requiring the most intensive treatment, including the preparation for heart transplantation. The aim of the study was to prospectively assess the prognostic value of ergospirometric parameters (peak/maximum oxygen consumption [$VO2_{peak}/VO2_{max}$] and the ventilatory equivalent for carbon dioxide, i.e. the relationship between minute ventilation and carbon dioxide production [$VE/VCO2_{slope}$]) in the group of patients pre-qualified for heart transplantation with chronic systolic HF caused by ischemic heart disease or non-ischemic dilated cardiomyopathy.

Material and methods

Forty-five patients (7 women and 38 men aged 27–63 years) with advanced systolic HF (mean left ventricular ejection fraction assessed by echocardiography = 22.7 ± ± 5.1%) in a stable clinical state were prospectively analyzed: 16 patients (35%) in New York Heart Association (NYHA) functional class II and 29 patients (65%) in NYHA class III, hospitalized to consider the pre-qualification to heart transplantation. The diagnosis of chronic HF was based on the criteria of the European Society of Cardiology (ESC): HF symptoms with objectively confirmed impairment of cardiac systolic function at rest. The patients were cardiopulmonary stable and received fixed doses of medication at least 2 weeks prior to the study. The treatment was modified depending on the clinical condition during further outpatient follow-up. The patients were taking the following medications: beta-blockers — 100%, angiotensin-converting enzyme (ACEI) inhibitors — 78.3%, angiotensin receptor blockers (ARB) — 32.6%, spironolactone or eplerenone — 91.3%, and loop diuretics — 82.6%. All patients previously underwent coronary angiography. Ischemic cardiomyopathy was diagnosed in 21 patients and non-ischemic cardiomyopathy — in 24 patients. Coexisting atrial fibrillation was found in 17 patients (37.7%), diabetes in 11 (24.4%), and arterial hypertension in 11 (24.4%). Twenty-six patients (57.7%) were smokers. At the time of inclusion, 16 patients (35.6%) had implantable cardioverter-defibrillators; none of the patients had cardiac resynchronization therapy defibrillator.

Inclusion criteria were also: poor prognosis for survival (assessed on the basis of clinical data, echocardiographic [LVEF < 35%] and/or ergospirometric [$VO2_{peak}$ < 12 mL/kg/min, $VE/VCO2_{slope}$ > 34] parameters), age above 18 years, written consent for participation in the study.

Exclusion criteria were: contraindications to cardiac catheterization, pregnancy or breastfeeding, symptoms of active infection, contraindications to heart transplantation (in addition to hemodynamic contraindications, which were assessed during cardiac catheterization). The major accident cardiac event (MACE) was defined as cardiovascular death or hospitalization due to exacerbation of HF. After reviewing the conditions of participation in the study and signing the informed consent patients underwent ergospirometric test which was repeated every six months (visit 0, after 6 and 12 months).

Statistical analysis

The obtained results were subjected to statistical analysis. The normality of the distribution of variables was checked based on the Shapiro-Wilk test. To compare variables with a near-normal distribution, Student's *t*-test for independent variables and dependent variables was used. For non-normally distributed variables, the results were presented as median and range, and the significance of between-groups differences was checked using the non-parametric U Mann-Whitney test and the Wilcoxon test. Proportions in groups were evaluated with the chi-square test (χ^2). The survival function was estimated according to the Kaplan-Meier method. A log-rank test was used to compare two survival curves. The degree of relationship between the two variables was assessed using Pearson's correlation coefficient, and in the case of non-normally distributed variables — with Spearman's correlation coefficient. In order to find the best parameters and the optimal cut-off value to predict the occurrence of MACE, ROC curves were plotted and the area under the curve (AUC) was determined. The sensitivity, specificity, positive and negative predictive value, accuracy and likelihood ratio (LR) were calculated to assess the prognostic value of the obtained cut-off values. P-value threshold for statistical significance was 0.05. Results close to this level, which may be the inspiration for further research, are presented as being at the level of statistical trend. P-value of 0.1 was assumed to be the threshold of statistical trend. The calculations were performed using the STATISTICA v. 10.0 PL software (StatSoft, Inc.).

Results

Of the 45 patients enrolled in the study, 22 (49.0%) had a composite end-point — MACE(+) — over a 12-month period, with 17 (38.0%) patients experiencing HF exacerbation and 5 (11.0%) patients died. No patient had a heart transplant at that time. Table 1 presents the initial results of the evaluated parameters in the MACE(–) and MACE(+) groups.

Table 1. Baseline values of the evaluated parameters in the MACE(–) and MACE(+) groups

	MACE(+)	N = 22	MACE(–) N = 23	p
VO2	MACE(+) total	13.9 ± 6.9	15.1 ± 4.3	NS
	MACE(+) HF exacerbation	14.7 ± 7.6	15.1 ± 4.3	NS
	MACE(+) death	10.9 ± 1.3	15.1 ± 4.3	0.045
$VE/VCO2_{slope}$	MACE(+) total	37.2 ± 6.0	33.1 ± 5.6	0,021
	MACE(+) HF exacerbation	36.5 ± 5.5	33.1 ± 5.6	NS
	MACE(+) death	139.8 ± 7.8	33.1 ± 5.6	0,032

MACE — major adverse cardiac event; NS — not significant; VO2 — peak/maximum oxygen consumption; $VE/VCO2_{slope}$ — minute ventilation-carbon dioxide production relationship

Table 2. Predictive value of the determined cut-off points of the evaluated parameters

Parameter	Cut-off value	AUC	Sensitivity	Specificity	Accuracy	Positive predictive value	Negative predictive value	LR
VO2	11.6	0.678	0.591	0.870	0.733	0.813	0.690	4.5
$VE/VCO2_{slope}$	34.9	0.696	0.636	0.696	0.667	0.667	0.667	2.1

VO2 — peak/maximum oxygen consumption; $VE/VCO2_{slope}$ — minute ventilation-carbon dioxide production relationship; AUC — area under curve; LR — likelihood ratio

The mean baseline VO2 values were not significantly different (p = 0.473) between the MACE(–) and MACE(+) patients, but in the MACE(+) death subgroup mean VO2 value was statistically significantly lower compared with the MACE(–) group (p = 0.045). The mean baseline VE/VCO2 value in the MACE(–) group was statistically significantly lower than the mean VE/VCO2 value in the MACE(+) group (p = 0.021).

In order to assess the usefulness of VO2 and VE/CO2 measurements in determining the probability of MACE occurrence, receiver operating characteristics (ROC) curves were plotted. They are created based on the determined sensitivity and specificity for different cut-off points. The area under the curve (AUC) above the diagonal shows the classification quality of the diagnostic variable. The analysis of ROC curves makes it possible to determine the optimal values of the analyzed parameters (cut-off points) that best divide the studied group into a subgroup in which the risk of MACE is higher and a subgroup in which the risk of MACE is lower. Table 1 presents baseline values of the parameters evaluated in the MACE(–) and MACE(+) groups and Table 2 presents the ROC curve analysis results in which the area under the curve, specificity, accuracy, positive and negative predictive value and likelihood ratio (LR) were calculated for individual parameters and their cut-off values (Tables 1, 2).

In the presented work, the AUC values for the evaluated parameters indicate the mean value of the decision-making models based on them. The slightly higher AUC was associated with the $VE/VCO2_{slope}$ measurement than with VO2 (0.70 vs 0.68, respectively). On the basis of the determined cut-off points, the studied group was

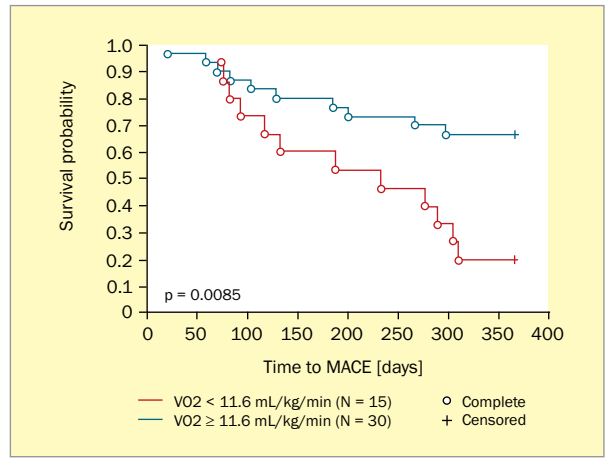

Figure 1. Kaplan-Meier survival functions for groups distinguished based on the determined cut-off value of peak/maximum oxygen consumption (VO2); MACE — major adverse cardiac event

divided and the survival function was estimated using the Kaplan-Meier method. There was a statistically significant difference between the survival curves for patients in the VO2 subgroups (p = 0.0085) (Figure 1).

The calculated relative risk of RR = 2.4 indicates that the risk of MACE in the group of patients with VO2 below 11.6 mL/kg/min is 2.4 times higher than in the group with VO2 over 11.6 mL/kg/min (95% CI 1.36–4.23; p = 0.0024). There was a difference between the survival curves for patients in the $VE/VCO2_{slope}$ subgroups showing a trend towards statistical significance (p = 0.0562) (Figure 2).

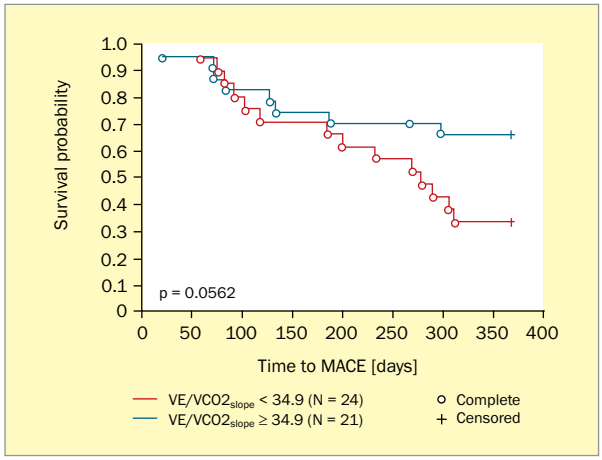

Figure 2. Kaplan-Meier survival functions for groups distinguished based on the determined cut-off value of the ventilatory equivalent for carbon dioxide ($VE/VCO2_{slope}$); MACE — major adverse cardiac event

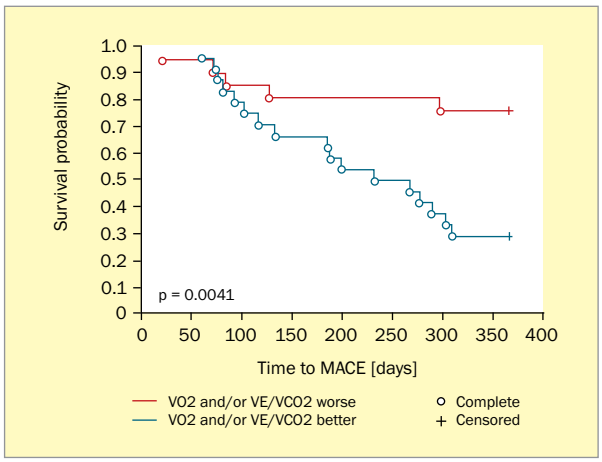

Figure 3. Kaplan-Meier survival functions for groups distinguished based on the determined cut-off values of peak/maximum oxygen consumption (VO2) and ventilatory equivalent for carbon dioxide (VE/VCO2) ("better" VO2 and VE/VCO2 result vs other results); MACE — major adverse cardiac event

The calculated relative risk of RR = 2.0 indicates that the risk of MACE in the group of patients with VE/VCO2 over 34.9 is 2 times higher than in the group of patients with VE/VCO2 below 34.9 (95% CI 1.05–3.80; p = 0.0342). In addition, in our study, the prognostic value of the combined ergospirometric parameters was evaluated; the analysis was carried out in two ways — the first one compared the subgroup of patients with VO2 results over 11.6 mL/kg/min + $VE/VCO2_{slope}$ below 34.9 vs other patients (i.e. "better" VO2 and VE/VCO2 result vs other results). The calculated risk of MACE in the group of patients with a worse result was 2.5 times higher than in the group of patients with a better result (95% CI 1.31–4.90; p = 0.0055) (Figure 3).

The second way was to divide the patients into a subgroup with "the worst" results: VO2 below 11.4 mL/kg/min + $VE/VCO2_{slope}$ over 34.9, and the subgroup with "the best" results: VO2 over 11.4 mL/kg/min + VE/VCO2 below 34.9 (i.e. the comparison of two extreme groups). The risk of MACE in the group of patients with the worst results turned out to be 4.1 times higher than in the group of patients with the best results (95% CI 1.34–12.35; p = 0.0131) (Figure 4).

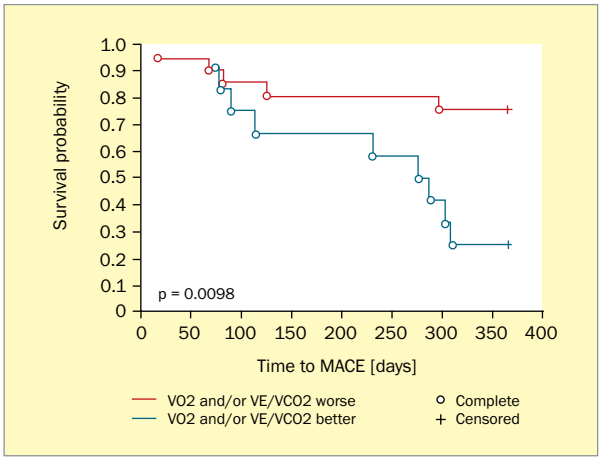

Figure 4. Kaplan-Meier survival functions for groups distinguished based on the determined cut-off values of peak/maximum oxygen consumption (VO2) and ventilatory equivalent for carbon dioxide (VE/VCO2) (2 extreme groups); MACE — major adverse cardiac event

Discussion

The most frequent causes of HF are ischemic heart disease and hypertension [1], while in the younger population the dominating factor is dilated cardiomyopathy (DCM), the third most frequent cause of HF in Western populations [2]. In the presented study, a selected group of patients with chronic systolic HF in the course of coronary disease and non-ischemic cardiomyopathy was observed. The occurrence of adverse cardiac events in the study group during the 12-month follow-up was found in 49% of patients: 17 patients (38.0%) had HF exacerbation and 6 patients (11.0%) died. Minute ventilation-carbon dioxide production relationship proved to be a significant risk factor for the endpoint — a significantly higher mean $VE/VCO2_{slope}$ value was found in MACE patients (+) compared with the MACE(–) group (p = 0.02). Similar results were obtained by Mejhert et al. [3] who found that in patients with HF (n = 67, NYHA class II and III, mean LVEF = 36%) VE/VCO2 and peak VO2 were mortality predictors. According to the authors, $VE/VCO2_{slope}$ with a cut-off value of 45 may be the most

useful tool in determining the risk of death (better than LVEF). However, this is a rather isolated opinion, because the acknowledged predictive cut-off value of VE/VCO2 is 34 (or 35) and it seems that the value exceeding 45 is of little clinical significance. In the authors' own study, the differential value between the MACE(+) and MACE(–) groups was VE/VCO2 equal to 34.9, which is almost identical to the abovementioned most frequently cited cut-off point [4]. Similar results were obtained by Arena [5] and Sarullo [6] who proposed cut-off points slightly higher for VO2 and lower for $VE/VCO2_{slope}$, which probably results from milder echocardiographic criteria of inclusion (LVEF < 45%). Also in a study conducted in the Asian population, assessing the prognostic value of $VE/VCO2_{slope}$, almost identical AUCs were obtained as in our study — 0.67 for mortality and 0.68 for hospitalization due to exacerbation of HF. The cut-off values for differentiating between MACE(+) and MACE(–) groups were also similar, namely: not less than 39.3 for mortality and at least 32.9 for hospitalization due to HF exacerbation [7]. Poggio et al. [8] performed a meta-analysis summarizing available data on the assessment of the prognostic value of VE/VCO2. MACE was defined as death, the need for transplantation or implantation of a left ventricular assist device. In the final analysis, the AUC for VE/VCO2 was 0.75, which is similar to the result obtained in our study. In addition, the prognostic value of $VE/VCO2_{slope}$ was slightly higher than that of VO2, which is also concordant with our observations.

The prognostic value of VO2 in patients with HF has been confirmed in many observations [9–11], and the VO2 below 14 mL/kg/minute was considered an acceptable criterion for cardiac transplantation in outpatient patients already in 1991 [12]. The analysis of peak oxygen consumption in our study showed a statistically significant relationship only to the MACE(–) and MACE(+) death groups (15.1 vs. 10.9, $p < 0.05$), and the AUC value for VO2 was 0.70.

Similar results were obtained by Meyer [13] — in a group of 244 patients with congestive HF (LVEF = 22 ± ± 10%) peak oxygen consumption in survivors vs fatal outcome was 15.1 vs. 12.9 ($p < 0.05$), while AUC for $VO2_{peak}$ was 0.73 [13].

Studies by Gitt [14] and Arena [15] assessed the prognostic value of the combined ergospirometric parameters. According to expectations and the results of our own observations, the largest number of incidents was observed in the subgroup with the lowest oxygen consumption and at the same time the highest $VE/VCO2_{slope}$. The cut-off value for VO2 estimated in our study based on ROC curves was 11.6 mL/kg/min, which has been confirmed by the guidelines of the International Society for Heart and Lung Transplantation (ISHLT), where the VO2 value of less than or equal to 12 mL/kg/min is considered as the indication for cardiac transplantation in patients with chronic heart failure treated with beta-blockers [16]. Our study showed that $VE/VCO2_{slope}$ and VO2 in the MACE(+) death subgroup of patients were statistically significant risk factors for MACE.

Conclusions

Both peak/maximum oxygen consumption and minute ventilation-carbon dioxide production relationship are important predictors of cardiovascular death or hospitalization due to exacerbation of HF. The prognostic value of both parameters proved to be comparable, with a slight advantage of $VE/VCO2_{slope}$. The combined assessment of VO2 and $VE/VCO2_{slope}$ can be considered as an additional valuable tool in determining prognosis in patients with heart failure.

Conflict of interest

The authors do not have any conflict of interests.

Streszczenie

Wstęp. Mimo ostatnich osiągnięć w diagnostyce i terapii chorób układu sercowo-naczyniowego rokowanie w niewydolności serca (HF) pozostaje niezadowalające, dlatego identyfikacja chorych z grupy najwyższego ryzyka wczesnego zgonu ma szczególne znaczenie. Wysiłkowy test ergospirometryczny jest uznanym badaniem w diagnostyce HF, a szczytowe/maksymalne zużycie tlenu ($VO2_{peak}/VO2_{max}$) oraz ekwiwalent wentylacyjny dwutlenku węgla ($VE/VCO2_{slope}$) to najczęściej oceniane parametry.

Celem pracy była prospektywna, roczna ocena wpływu parametrów ergospirometrycznych ($VO2_{peak/max}$ oraz $VE/VCO2_{slope}$) na wystąpienie punktu końcowego (MACE), definiowanego jako zgon z przyczyn sercowo-naczyniowych lub hospitalizacja z powodu zaostrzenia HF u chorych z przewlekłą skurczową HF, kwalifikowanych wstępnie do transplantacji serca.

Materiał i metody. Prospektywnej obserwacji poddano 45 pacjentów (38 mężczyzn, średni wiek 50 ± 8 lat) z rozpoznaną skurczową niewydolnością serca (u 21 osób etiologia niedokrwienna, u 24 osób nieniedokrwienna) w II (n = 16) i III (n = 29) klasie według *New York Heart Association*, ze zredukowaną frakcją wyrzutową lewej komory (LVEF) poniżej 35% (średnia LVEF = 22,7 ± 5,1%). U każdego pacjenta wyjściowo wykonano badanie ergospirometryczne z oceną VO2 i $VE/VCO2_{slope}$.

Wyniki. W okresie 12 miesięcy u 22 (49,0%) pacjentów obserwowano wystąpienie złożonego punktu końcowego (MACE+), w tym u 17 (38,0%) wystąpiło zaostrzenie HF, a 5 (11,0%) pacjentów zmarło. Szczytowe/maksymalne VO2 wyniosło 14,5 ± 5,7 ml/kg mc./min, zaś $VE/VCO2_{slope}$ 35,1 ± 6,1. W grupie MACE(+) obserwowano niższe wartości VO2 (13,9 ± 6,9 ml/kg mc./min *v.* 15,1 ± 4,3; p = NS) i wyższy $VE/VCO2_{slope}$ (37,2 + 6,0 *v.* 33,1 ± 5,6; p = 0,021) niż w grupie MACE(–). Podgrupa MACE(+) zgon miała istotnie statystycznie niższą wartość VO2 niż MACE(–) (10,9 ± 1,3 *v.* 15,1 ± 4,3; p = 0,045).

Na podstawie analizy krzywych ROC wyznaczono dla VO2 i $VE/VCO2_{slope}$ pole pod krzywą, odpowiednio, 0,68 i 0,70; p < 0,05). Oszacowana metodą Kaplana-Meiera funkcja przeżycia wykazała roczne przeżycie wolne od wystąpienia MACE u 33% pacjentów z $VE/VCO2_{slope}$ ponad 34,9 i 67% u tych z $VE/VCO2_{slope}$ poniżej 34,9 (p = 0,0562) oraz u 20% pacjentów z VO2 poniżej 11,6 ml/kg mc./min i 67% u tych z VO2 ponad 11.9 ml/kg/min (p = 0,0085).

Wnioski. Zarówno VO2 jak i $VE/VCO2_{slope}$ są istotnymi czynnikami rokowniczymi wystąpienia zgonu z przyczyn sercowych bądź hospitalizacji z powodu zaostrzenia HF. Wartość rokownicza obu parametrów okazuje się porównywalna z niewielką przewagą $VE/VCO2_{slope}$. Analiza połączonych parametrów ergospirometrycznych ma większą wartość prognostyczną niż osobna ocena VO2 oraz $VE/VCO2_{slope}$.

Słowa kluczowe: ergospirometria, czynniki rokownicze, niewydolność serca

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