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Letter to the Editor

Prognostic value of VE/VCO_2 and interleukin-6 in chronic heart failure subjects

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Chronic heart failure (CHF) is a complex clinical syndrome with poor prognosis and health conditions that limit quality of life in patients [1]. Cardiopulmonary exercise testing (CPET) has been used to evaluate patients with CHF and can provide useful prognostic information through variables, including peak oxygen consumption (VO_{2peak}) and the minute ventilation/carbon dioxide production slope (VE/VCO_2 slope) [2]. The VE/VCO_2 slope has been shown to have a high prognostic value [2,3]. Besides that, inflammatory activation has grown in importance as a prognostic indicator for CHF subjects. The purpose of this study was to evaluate the prognostic value of VE/VCO_2 slope associated with plasma concentrations of interleukin-6 (IL-6) in CHF subjects.

This longitudinal study was approved by the Ethics Committee of Research (ETIC 489/06 – Ad 01/07). Informed consent was obtained from each subject and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. Subjects with a diagnosis of systolic CHF for at least six months were between 25 and 59 years of age and exhibited symptoms with exertion according to the New York Heart Association functional classes (NYHA) II and III. Also, subjects experienced clinical stability for at least 2 months, had a body mass index (BMI) < 30 kg/m^2, a resting left ventricular ejection fraction (LVEF) $\leq 45\%$ and optimal pharmacological treatment. Subjects performed a symptom-limited, incremental CPET on a treadmill ergometer (ramp protocol) with gas analysis breath-by-breath (CPX Ultima®, Medical Graphics, USA).

On a different day of CPET, 5 mL of blood samples were obtained after 30 min of resting from the antecubital vein into a sterile vacutainer. The IL-6 (pg/mL) was analyzed using ELISA with high sensitivity kits (R & D Systems®, USA). The CHF subjects were monitored for hospitalization and death for 1 year by phone calls conducted every 3 months.

The prognostic value of VE/VCO_2 slope and IL-6 was analyzed using logistic regression and odds ratio (OR) for three, six, nine and 12 months. A univariate analysis for model 1 (VE/VCO_2 slope) and model 2 (IL-6) was used, and a multivariate analysis for model 3 (VE/VCO_2 and IL-6 together) was used. An alpha level of 5% was considered significant.

Thirty CHF subjects (17 NYHA class II, 13 NYHA class III) aged 44.88 ± 9.28 years, with a BMI of 24.58 ± 2.87 KG/m^2, an LVEF of $31.17 \pm 10.16\%$, a VO_{2peak} of 23.34 ± 6.70 mL/kg min^{-1}, a VE/VCO_2 slope of 31.89 ± 4.94 and an IL-6 of 3.21 ± 4.32 pg/mL were assessed. There were four deaths in the follow-up period of the study (one in six months, two in nine months and one after one year). Regression analyses did not show any prognostic indicators for mortality. The VE/VCO_2 slope and IL-6 determined the prognosis of hospitalization ($R^2 = 0{,}91$) at a period of six months (Table 1). The individual values of IL-6 and VE/VCO_2 slope and the presence of hospitalization during the 6-month follow-up are presented in Table 2.

This study is one of the first to evaluate the combination of VE/VCO_2 slope and IL-6 to define prognosis in CHF subjects. The main result was that the combination of VE/VCO_2 slope with IL-6 has been shown to be a more sensitive prognostic indicator in the assessment of hospitalization of CHF subjects after six months than VE/VCO_2 slope alone. In addition, univariate analyses indicated that IL-6 alone was a more sensitive prognostic indicator than VE/VCO_2 slope.

The VE/VCO_2 slope measures ventilatory efficiency and provides robust prognostic information for CHF subjects [4]. This measure is associated with VO_{2peak} and can be used to assess potential candidates for cardiac transplantation and rehabilitation intervention [2]. In this study, we found that VE/VCO_2 slope provided sensitive prognostic information for hospitalization in CHF subjects after six months.

In addition to cardiorespiratory impairment, inflammation may play an important role in the incidence of CHF, and IL-6 has been

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Table 1
Logistic regression analysis to determine prognosis of hospitalization for the period of 6 months.

Model	Independent variable	R^2	p	OR
1	VE/VCO_2 slope	0.31	0.005	1.30
2	IL-6	0.59	0.0001	2.86
3	VE/VCO_2 slope	0.91	0.0001	5.49
	IL-6			24.63

VE/VCO_2 slope - minute ventilation-carbon dioxide production slope; IL-6 - plasma concentrations of IL-6; OR - odds ratio; p - significance level.

Table 2
Individual values of IL-6, VE/VCO_2 slope and hospitalization.

Participants	IL-6	VE/VCO_2 slope	Hospitalization - period of 6 months
1	2.330	26.8	No
2	2.690	33.2	No
3	1.200	33	No
4	0.001	30	No
5	1.036	34.43	No
6	4.910	37.89	Yes
7	1.200	30.75	No
8	0.001	38.5	No
9	0.001	30.86	No
10	0.001	28.43	No
11	1.868	28.83	No
12	1.830	31	No
13	0.001	30.5	No
14	4.401	30.14	Yes
15	6.745	33.5	Yes
16	0.680	30.14	No
17	4.420	38.13	Yes
18	2.170	25.5	Yes
19	1.548	35.57	Yes
20	0.910	27.75	No
21	20.590	24.17	Yes
22	4.367	30.14	Yes
23	1.140	41	Yes
24	3.489	27.57	No
25	9.447	37.17	Yes
26	0.740	42.71	Yes
27	1.804	20.67	No
28	0.668	31.5	No
29	4.601	35	Yes
30	2.080	31.86	No

IL-6 - plasma concentrations of IL-6; VE/VCO_2 slope - minute ventilation-carbon dioxide production slope.

considered a good indicator of deterioration in CHF subjects [5–7]. Furthermore, IL-6 has been described as an independent predictor of poor prognosis and mortality in CHF subjects [4,5]. Deswal et al. found 44% higher levels of IL-6 in non-survivors with CHF [8]. In our study, IL-6 was not a prognostic indicator for mortality, but it was a more sensitive prognostic index for hospitalization at six months than VE/VCO_2 slope.

Despite therapeutic advances, CHF continues to induce high morbidity and mortality [9]. In terms of clinical applicability, the discovery and understanding of prognostic factors are important for the development of treatment strategies and the ability to thoroughly follow patients during the cardiac rehabilitation program. Even with a limited sample size consisting of subjects with mild CHF severity ($VE/VCO_2 < 34$ and most NYHA II), VE/VCO_2 slope and IL-6 were prognostic indicators for hospitalization. Other studies should be conducted using larger samples to better understand the predictive ability of these combined variables in the evaluation of CHF subjects.

The VE/VCO_2 slope and IL-6 proved to be sensitive prognostic indicators in the assessment of hospitalization in CHF subjects NYHA II and III in a six-month period. IL-6 was a more sensitive indicator than the VE/VCO_2 slope when evaluated separately, but the best risk stratification of this sample included both variables.

Conflict of interest

The authors declare no conflict of interest.

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