Influence of Skeletal Muscle Mass on Ventilatory and Hemodynamic Variables During Exercise in Patients with Chronic Heart Failure

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Objective - *To assess the influence of skeletal muscle mass on ventilatory and hemodynamic variables during exercise in patients with chronic heart failure (CHF).*

Methods - *Twenty-five male patients underwent maximum cardiopulmonary exercise testing on a treadmill with a ramp protocol and measurement of the skeletal muscle mass of their thighs by using magnetic resonance imaging. The clinically stable, noncachectic patients were assessed and compared with 14 healthy individuals (S) paired by age and body mass index, who underwent the same examinations.*

Results - *Similar values of skeletal muscle mass were found in both groups (CHF group: 3863 ± 874 g; S group: 3743 ± 540 g; p = 0.32). Significant correlations of oxygen consumption in the anaerobic threshold (CHF: r = 0.39; P= 0.02 and S: r = 0.14; P = 0.31) and of oxygen pulse also in the anaerobic threshold (CHF: r = 0.49; P = 0.01 and S: r =0.12; P = 0.36) were found only in the group of patients with chronic heart failure.*

Conclusion - *The results obtained indicate that skeletal muscle mass may influence the capacity of patients with CHF to withstand submaximal effort, due to limitations in their physical condition, even maintaining a value similar to that of healthy individuals. This suggests qualitative changes in the musculature.*

Key words: skeletal muscle, chronic heart failure, cardiopulmonary exercise test

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Despite the marked reduction in mortality and morbidity of cardiovascular diseases observed in recent decades, the incidence and prevalence of heart failure (HF) have significantly increased in both developed and developing countries [1].

Heart failure in its chronic form manifests with several signs and symptoms; its most significant clinical characteristic is the incapacity to tolerate progressively milder physical effort, which is an indicator of the severity of heart failure itself [2]. The hemodynamic parameters at rest of patients with heart failure have been shown not to correlate with those during effort [3], the latter having an independent prognostic power for overall and cardiovascular mortality [4]. In addition, the symptoms usually reported by CHF patients underestimate their true physical capacity, which may be better assessed on cardiopulmonary exercise testing [5,6] that provides an assessment of the integrated cardiopulmonary function [7,8].

In the genesis of heart failure syndrome, central hemodynamic abnormalities are present, as are changes in skeletal muscle function, which have been held responsible for fatigue and its consequent exercise limitation [9,10]. These muscle changes reflexly activate the autonomous nervous system, playing an important role not only in the origin of the exercise limiting symptoms, but also in the progression of heart failure [11,12].

Despite the existence of some studies on the influence of the skeletal musculature on the functional capacity of patients with heart failure, no report exists about the relation between skeletal muscle mass and ventilatory and hemodynamic variables, such as anaerobic threshold and oxygen pulse, which have been considered important functional and risk markers in that syndrome. Therefore, the present study aimed at assessing the influence of skeletal muscle mass on different ventilatory and hemodynamic variables in patients with chronic heart failure during exercise.

Methods

This study selected 25 male patients with chronic heart failure in NYHA functional class III with the following etiologies: idiopathic (44%), arterial hypertension (32%), and alcoholism (24%). Patients with the following characteristics were excluded from the study: hospitalization or therapeutic change, or both, within less than 3 months; neurologic or locomotor afflictions, or another disease that could interfere with the tests to be performed; episodes of nonsustained ventricular tachycardia at rest; intracavitary thrombus with emboligenic potential; and cachexia.

All patients were using angiotensin-converting enzyme inhibitors, digoxin, and furosemide, in addition to the following medications: carvedilol (24%), spironolactone (40%), amiodarone (20%), and warfarin sodium (12%).

The resting electrocardiogram showed the following changes: left bundle-branch block (36%), left ventricular hypertrophy (32%), left bundle-branch anterior divisional block (12%), atrial fibrillation (12%), and left atrial hypertrophy (8%).

A control group paired by age and body mass index was recruited for comparison. This group comprised 14 healthy individuals according to the results of a clinical examination, electrocardiography, echocardiography, and cardiopulmonary exercise testing. They were using no medication and were not engaged in a formal physical exercise program. Their characteristics are shown in table I.

This study was approved by the Committee on Ethics for the Analysis of Research Projects of the Hospital das Clínicas of the Medical School of USP and the Committee on Ethics in Research of the Hospital Procardíaco (Rio de Janeiro). All volunteers signed the formal written consent after receiving the necessary explanations.

All patients underwent treadmill testing (ATL10200, Inbramed, Brazil) with simultaneous analysis of pulmonary ventilation and expired gases with a metabolic analyzer (TEEM100, Aerosport, USA), 12-lead electrocardiographic recordings (Mason Likar system), and blood pressure measurement through sphygmomanometry. The ramp protocol was used adjusted to the clinical and biomechanical conditions of the patients, with a progressive increase in the intensity of effort and estimated duration between 8 and 12 minutes, being interrupted by fatigue or dyspnea. Considering the occurrence of natural adaptation to exercise testing, 2 tests were performed at an approximate interval of 1 week, the results of the second test being used for analysis.

The anaerobic threshold, obtained in all cases, was determined by 3 experienced examiners and defined when agreement, at least between 2 of them, occurred. The criteria used for its determination were as follows [13,14]: a nonlinear increase in ventilation, ie, exponentiation of the ventilation curve; point of beginning of the consistent elevation of the curve of the oxygen ventilatory equivalent; and curve elevation referring to the expired oxygen fraction.

The muscle mass of the thigh was determined with magnetic resonance imaging with the patient lying in the dorsal decubitus position. The examinations were performed in a Sigma 1.5 T Horizon LX 8.2 device with torso coil (General Electric, USA). The sequences processed were spin-echo T1 in 5.0-mm thick axial views at 8.0-mm intervals. Topogram was performed in the coronal plane. The skeletal muscle mass (MM) of the right and left thighs was measured in the spin-echo T1 sequence using an irregular cursor around the muscle groups, excluding the fat tissue and bones [15,16]. The anatomic landmark for the first view of the thigh was the hip joint, and the last view was that immediately before the patella. All muscle mass values were added and multiplied by 13 mm and by muscle density (1.05); then, the mean muscle volume was calculated [17].

All variables had a normal distribution and homogeneity of variances. Therefore, parametric procedures were used for all analyses. The Student *t* test for independent samples was used for comparing the results of the patients and controls. The correlation coefficient was used for measuring the association between 2 variables, 0.323 being the critical value for the number of patients studied, and 0.426 for the control group. Linear regression analysis through the least squares method was used to determine the first-degree equation that describes the relation between VE and VCO_2. The correlation coefficient was > 0.95 in all cases. The slope calculated was used for analyzing the correlation with muscle mass. The significance level adopted was 5%.

Table I - Characteristics (mean ± sd) of patients with heart failure (HF) and healthy individuals

	HF n = 25	Healthy n = 14	P
Age (years)	48 ± 12	47 ± 11	0.41
Weight (kg)	73 ± 12	75 ± 11	0.36
Height (metros)	1.71 ± 0.1	1.73 ± 0.1	0.29
BMI (kg/m^2)	25 ± 3	25 ± 3	0.42
VSAQ (METs)	5.5 ± 2	12 ± 3	< 0.001
Ejection fraction (%)	26 ± 8	63 ± 4	< 0.001

BMI - body mass index; VSAQ - veterans specific activity questionnaire; MET - metabolic equivalent: 3.5 ml O_2/kg/min.

Results

The results of the variables obtained in cardiopulmonary exercise testing and magnetic resonance imaging are shown in table II. As expected, the results indicate a lower functional capacity in the CHF patients as compared with that in healthy individuals, although no difference was found in regard to the skeletal muscle mass. Figure 1 depicts the behavior of pulmonary ventilation in relation to CO_2 production in a CHF patient and in a healthy individual.

Table III shows the linear correlations between muscle mass and ventilatory and hemodynamic variables during exercise in patients and control individuals. Significant positive and negative correlations were observed only in the group of patients. Figure 2 depicts the graphs with individual results and the line of linear regression between skeletal muscle mass and oxygen consumption at the anaerobic threshold in patients and control individuals.

Table II - Results (mean ± sd) of patients with heart failure (HF) and healthy individuals

	HF n = 25	Healthy n = 14	P
Metabolic variables			
VO_2 peak (L/min)	1.3 ± 0.5	3.1 ± 0.9	< 0.001
VO_2 anaerobic thresh (L/min)	0.8 ± 0.3	2.1 ± 0.7	< 0.001
Derived variables			
VE/VCO_2 peak	35 ± 8	24.1 ± 4.5	< 0.001
VE/VCO_2 anaerobic thresh	33 ± 7	23.8 ± 4.1	< 0.001
VE x VCO_2 slope	32 ± 9	21 ± 3	< 0.001
VE/VO_2 peak	36 ± 7	25 ± 5	< 0.001
VE/VO_2 anaerobic thresh	29 ± 6	21 ± 5	< 0.001
O_2 pulse peak (mL/beat)	8.6 ± 2.7	18.4 ± 5	< 0.001
O_2 pulse anaerobic thresh (mL/beat)	6.4 ± 2	15.2 ± 3.9	< 0.001
Muscle mass of the thighs (g) (RM)	3863 ± 874	3743 ± 540	0.32
VO_2 anaerobic thresh (% peak)	62 ± 9	66 ± 10	0.10
Borg scale peak	18 ± 2	19 ± 3	0.09
Respiratory quocient	1 ± 0.09	1.1 ± 0.1	0.21

VO_2 peak - oxygen consumption at peak effort; VO_2 thresh - oxygen consumption at the anaerobic threshold; VE / VCO_2 - ventilatory equivalent of carbon dioxide; VE / VO_2 - ventilatory equivalent of oxygen; VE x VCO_2 - linear relation between the volume expired and the ventilatory equivalent of carbon dioxide; O_2 pulse - oxygen pulse.

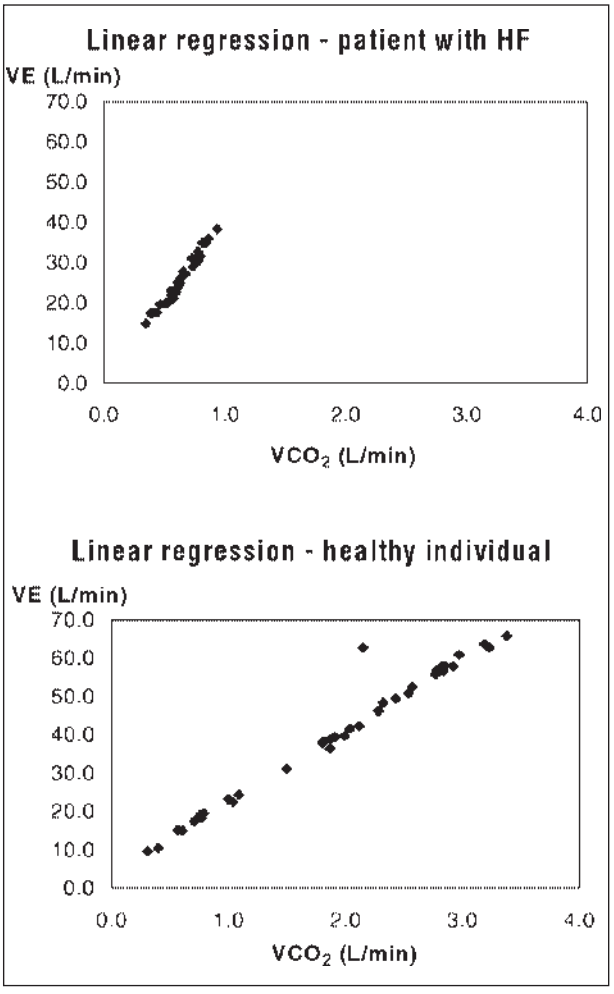

Fig. 1 - Examples of VE x VCO_2 slope. CHF patients = 41; healthy individuals = 19. Relation between ventilation per minute and production of carbon dioxide in a patient with heart failure and in a healthy individual. The ventilation necessary to eliminate carbon dioxide increases earlier in the patient with heart failure as compared with that in the healthy individual.

Tale III - Correlations of the ventilatory hemodynamic variables with muscle mass of the thighs in patients with heart failure (HF) and healthy individuals

	HF n = 25		Healthy n = 14	
	r	P	r	P
Variables				
VO_2 peak x MM	0.36	0.04	0.14	0.32
VO_2 anaerobic threshold x MM	0.39	0.02	-0.14	0.31
VE/VCO_2 peak x MM	-0.33	0.05	-0.15	0.30
VE/VCO_2 anaerobic threshold x MM	-0.36	0.04	-0.08	0.39
VExVCO_2 slope x MM	-0.40	0.02	-0.07	0.40
VE/VO_2 peak x MM	-0.42	0.02	-0.07	0.30
VE/VO_2 anaerobic threshold x MM	-0.38	0.03	-0.11	0.36
O_2 pulse peak x MM	0.47	0.01	0.12	0.36
O_2 pulse anaerobic threshold x MM	0.49	0.01	0.12	0.68

MM - skeletal muscle mass of the thighs.

Discussion

Our study found a correlation between the skeletal muscle mass of the thighs and the variables obtained in the cardiopulmonary exercise test in patients with heart failure. A correlation between muscle mass and the variables was found not only at the peak of effort, but also at the anaerobic threshold.

Quantitative similarity in the muscle mass obtained on magnetic resonance imaging was observed in patients with heart failure and in the control group. This may be explained by the fact that the patients were stable and not cachectic.

The anaerobic threshold was used for the functional assessment of patients, and more elevated values were observed in the control group (P<0.001). This parameter is obtained in submaximal intensities of effort accompanying most of the individuals´ daily activities and is used for programming physical activity [18,19].

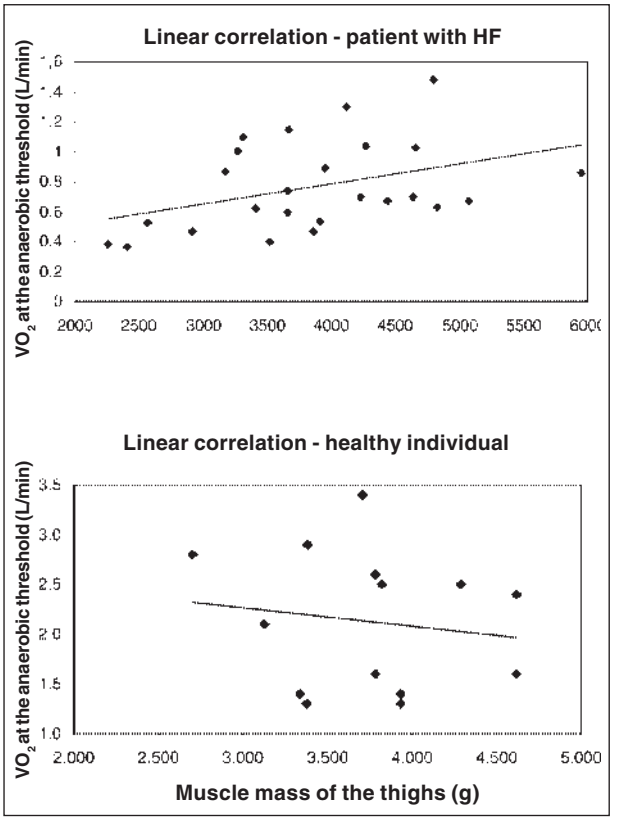

Fig. 2 - Linear correlation between VO_2 at the anaerobic threshold and muscle mass of the thighs. CHF patients: r = 0.39; P = 0.02. Healthy individuals: r = 0.14; P = 0.31.

In our study, the behavior of the VE x VCO_2 slope related to ventilatory inefficiency and intolerance to exercise is worth noting, being an independent variable to estimate the prognosis in patients with heart failure [20]. The mean values of the VE x VCO_2 slope in the patients studied (32±9) are bellow 34, a value confirmed in the study by Chua et al [21] as characterizing severity and a poor prognosis.

Other studies have reported an inverse and significant relation between muscle mass and the VE x VCO_2 slope, confirming the existence of a correlation with the accentuation of the ergoreflex [12,13] with values equivalent to those obtained in this study.

The participation of hemodynamic factors in this study was assessed with oxygen pulse [22,23], which correlates with systolic volume [24]. In the group of patients with heart failure, a direct and significant relation was found between oxygen pulse and muscle mass at the peak of effort and anaerobic threshold. A report on the behavior of this hemodynamic variable related to skeletal muscle has not been found in the literature. One may suppose that the reduced values of oxygen pulse during exercise obtained in all patients cause secondary hemodynamic changes that interfere with muscle mass, with elevation in the arterial-venous oxygen content difference.

A direct and significant relation between skeletal muscle mass and oxygen consumption at the peak of effort was obtained in our study, and these values are similar to those reported by other authors [25,26].

According to the muscle hypothesis [27], the functional limitation of these patients could be attributed to the action of metabolic and structural factors in the skeletal musculature, triggering the ergoreflex, with elevation in the sympathetic activity consequent to peripheral vasoconstriction, leading to ventilatory dysfunctions [28].

Another study on skeletal muscle mass by Toth et al [29] assessed 14 stable and noncachectic patients with NYHA functional class III heart failure and 52 healthy individuals. The values of muscle mass in the heart failure group and in the healthy individuals were, respectively, 3200±400 g and 3300±600 g (NS), and a significant relation to oxygen consumption was found at peak effort. Toth et al [29] used the same methodology used in our study with almost overlapping results. Those authors concluded that qualitative and not quantitative factors of skeletal musculature interfere with the functional condition of these patients; however, the factors were not studied at the anaerobic threshold.

The intrinsic changes in skeletal muscle influencing physical activity have been shown in several studies, such as that by Massie et al [30], who assessed 18 patients in NYHA functional class III and with an inverse and significant correlation between type II ab muscle fibers and peak VO_2. Those authors found a metabolic change in skeletal muscle with a reduction in the oxidative activity of the enzymes.

The study by Okita et al [31] is worth noting. They assessed 12 patients with heart failure and 7 controls and correlated the tolerance to exercise assessed at VO_2 peak to the depletion in phosphocreatine and to the pH reduction in skeletal musculature. The strong relation between oxygen consumption at peak effort and cellular acidosis confirmed that these intrinsic changes are an important limiting factor to exercise.

The relation between muscle mass and oxygen consumption at the anaerobic threshold was a characteristic assessed in our study, but not in other studies published. This relation was direct and significant in patients with heart failure, but nonsignificant in healthy individuals. This shows that the more altered the muscle mass, the lower the tolerance to lactacidemia during exercise, with a reduction in the functional capacity of these patients.

In conclusion, patients with heart failure have a correlation between the skeletal muscle mass of the thighs and the ventilatory and hemodynamic variables at the anaerobic threshold and at the peak effort that participate in the mechanisms that reduce physical capacity.

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