CLINICS

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The influence of aerobic fitness status on ventilatory efficiency in patients with coronary artery disease

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OBJECTIVE: To test the hypotheses that 1) coronary artery disease patients with lower aerobic fitness exhibit a lower ventilatory efficiency and 2) coronary artery disease patients with lower initial aerobic fitness exhibit greater improvements in ventilatory efficiency with aerobic exercise training.

METHOD: A total of 123 patients (61.0±0.7 years) with coronary artery disease were divided according to aerobic fitness status into 3 groups: group 1 (n = 34, peak VO_2<17.5 ml/kg/min), group 2 (n = 67, peak VO_2>17.5 and <24.5 ml/kg/min) and group 3 (n = 22, peak VO_2>24.5 ml/kg/min). All patients performed a cardiorespiratory exercise test on a treadmill. Ventilatory efficiency was determined by the lowest VE/VCO_2 ratio observed. The exercise training program comprised moderate-intensity aerobic exercise performed 3 times per week for 3 months. Clinicaltrials.gov: NCT02106533

RESULTS: Before intervention, group 1 exhibited both lower peak VO_2 and lower ventilatory efficiency compared with the other 2 groups (p<0.05). After the exercise training program, group 1 exhibited greater improvements in aerobic fitness and ventilatory efficiency compared with the 2 other groups (group 1: △ = -2.5±0.5 units; group 2: △ = -0.8±0.3 units; and group 3: △ = -1.4±0.6 units, respectively; p<0.05).

CONCLUSIONS: Coronary artery disease patients with lower aerobic fitness status exhibited lower ventilatory efficiency during a graded exercise test. In addition, after 3 months of aerobic exercise training, only the patients with initially lower levels of aerobic fitness exhibited greater improvements in ventilatory efficiency.

KEYWORDS: Coronary Disease; Exercise; Oxygen Consumption; Ventilation.

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INTRODUCTION

Cardiorespiratory exercise testing (CET) is the primary method for quantifying aerobic capacity and, consequently, it is important to target exercise tolerance in patients with cardiovascular disease (1). It is interesting to note that measurements of ventilatory efficiency during CET, which are typically expressed as the minute ventilation/carbon dioxide production ratio, have been validated to be useful in assessing the presence and severity of both heart (1,2) and lung diseases (3,4). In this context, previous studies (5,6) have demonstrated that patients with coronary artery disease (CAD) exhibit ventilatory inefficiency, which suggests the existence of abnormalities in the distribution of ventilation and perfusion in the lungs. Furthermore, a growing body of evidence (7-9) has demonstrated that lower ventilatory efficiency during exercise is considered an important predictor of mortality risk, hospitalization, and other outcomes, in addition to peak oxygen consumption (peak VO_2).

Aerobic exercise training has been recommended as a non-pharmacological treatment for patients with different comorbidities (10-12). In this respect, previous investigations (10,13) have documented numerous physiological adaptations as a result of exercise training programs, such as improvements in maximal cardiac output and muscle oxidative capacity. In addition, previous studies in CAD patients (6,14) have found a strong relationship between an increase in aerobic fitness, defined as the maximal amount of oxygen the body can use during exercise and improvement in ventilatory efficiency after an exercise training program. However, to our knowledge, little is known about whether aerobic fitness status before training is associated with improved ventilatory efficiency after aerobic exercise training in CAD patients.

No potential conflict of interest was reported.

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Thus, the purpose of the present study was to test the hypotheses that 1) CAD patients with lower aerobic fitness exhibit lower ventilatory efficiency and 2) CAD patients with lower levels of aerobic fitness before training exhibit greater improvements in ventilatory efficiency with aerobic exercise training compared with other groups.

METHODS

Study design and population

This retrospective longitudinal study included 123 patients with clinically documented CAD. The patients were admitted to the cardiac rehabilitation program between August 2011 and May 2013 at the Cardiorespiratory Rehabilitation Unit of the Amil Group. The inclusion criterion was stable CAD diagnosed by coronary angiography. The exclusion criteria comprised unstable angina pectoris, complex ventricular arrhythmias, pulmonary congestion and orthopedic or neurological limitations to exercise. The CAD patients were divided into 3 groups according to their aerobic fitness status based on risk stratification criteria for patients with cardiovascular disease by the American College of Sports Medicine (15): group 1 (n = 34, peak VO_2<17.5 ml/kg/min), group 2 (n = 67, peak VO_2>17.5 and <24.5 ml/kg/min) and group 3 (n = 22, peak VO_2> 24.5 ml/kg/min). Patients continued to take their prescribed medications throughout the exercise training program and no changes in medication were reported.

Cardiorespiratory exercise test

A maximal cardiorespiratory exercise test was conducted using a programmable treadmill (Centurion, model 200, Micromed, Brazil). Oxygen consumption and carbon dioxide output were analyzed by means of breath-by-breath gas exchange using an indirect calorimetry system (SensorMedics, model Vmax 229 Pulmonary Function/Cardiopulmonary Exercise Testing Instrument, Yorba Linda, CA, USA). The following variables were obtained breath-by-breath and expressed as 30-s averages: pulmonary oxygen uptake (VO_2 ml/kg/min STPD), the ventilatory equivalent for carbon dioxide (VE/VCO_2) and end-tidal carbon dioxide pressure ($PeTCO_2$ mmHg). Before each test, the gas analyzers used in the test were calibrated using known concentrations of carbon dioxide and oxygen balanced with nitrogen and the flow meter was calibrated using a 3-L syringe. Heart rate was continuously recorded at rest, during the graded exercise testing and during the recovery period using a 12-lead ECG (Ergo PC, Inc., Micromed, Brazil). The blood pressure response during the graded exercise test was obtained by the auscultatory method. Systolic and diastolic blood pressures were recorded at the first appearance (phase I) and at the disappearance (phase V) of Korotkoff sounds.

All tests in this study were performed in the same laboratory and at the same room temperature (20-23℃).

The subjects performed a graded exercise test on treadmill until they were exhausted. The exercise workload (speed and/or slope) was increased every 1 minute with completion of the incremental part of the exercise test between 8 to 12 minutes.

The ventilatory anaerobic threshold (VAT) was determined to occur at the breakpoint between the increase in the carbon dioxide output and VO_2 (V-Slope) or at the point at which the VE/VO_2 reached a minimum value and began to rise without a concomitant rise in the VE/VCO_2 (16). The respiratory compensation point (RCP) was determined to be the point at which the VE/VCO_2 reached a minimum value and began to rise and the $PeTCO_2$ reached its highest value before its progressive fall (17).

The peak oxygen consumption (peak VO_2) was defined as the maximum VO_2 attained at the end of the exercise period when the subject became exhausted (as measured using an analog scale of perceived exertion, according to the Borg scale).

Ventilatory efficiency

Ventilatory efficiency was determined by the VE to VCO_2 ratio and was calculated every minute during exercise. The lowest calculated value was taken to be the lowest VE/VCO_2 ratio (18,19). The change in end-tidal carbon dioxide pressure between rest and the highest value attained during exercise ($\Delta PeTCO_2$ rest-exercise) was also analyzed (1).

Exercise training program

A supervised exercise training program was conducted at the cardiorespiratory rehabilitation unit of the Amil Group. The exercise training program comprised three 60-minute exercise sessions per week over a 3-month period. Each exercise session comprised a 5-minute warm up, 30-50 minutes of aerobic exercise performed on a treadmill and 5 minutes of cool-down exercises. The aerobic exercise intensity was set at the corresponding heart rate between the VAT and the RCP. All patients were able to achieve the set aerobic training intensity.

Statistical analysis

Statistical analyses were performed using SPSS version 16.0 (SPSS Inc., Chicago, IL).

One-way analyses of variance (ANOVA) with repeated measures were performed to test possible inter-group differences in physical characteristics, left ventricular ejection fraction (LVEF) and absolute changes in both aerobic fitness and ventilatory efficiency. Two-way analyses of variance (ANOVA) with repeated measures were performed to test possible within-group and inter-group differences in aerobic fitness, cardiovascular responses and ventilatory efficiency in CAD patients who participated in the exercise training program. When significant differences were found, Tukey's post hoc test was used to compare values.

For all groups, the absolute changes (Δ) between the initial values of both aerobic fitness and ventilatory efficiency and the final values of these variables attained after the exercise training program were calculated.

Data are presented as means$\pm$SEs. A p-value of <0.05 was considered statistically significant.

RESULTS

Baseline measurements

Table 1 summarizes the baseline characteristics of the 3 groups studied. The groups were similar in age and body weight ($p>0.05$, inter-group comparisons). Before interventions, group 1 had lower peak VO_2, peak heart rate, peak oxygen pulse and peak systolic blood pressure values compared with the other groups ($p<0.05$, inter-group comparisons). Moreover, the patients in group 1 exhibited lower ventilatory efficiency compared with the 2 other groups (lowest VE/VCO_2 ratio in group 1: 33.5$\pm$0.5; group

Table 1 - Patient characteristics.

	Group 1	Group 2	Group 3	*p*-value[a]
N	34	67	22	
Age (years)	63.2±1.0	60.4±1.0	59.3±1.3	0.10
Weight (kg)	76.3±2.5	81.4±1.8	75.8±1.9	0.12
Men/women	28/6	62/5	21/1	
Clinical parameters				
AMI	16 (47%)	24 (36%)	6 (27%)	
CABG	16 (47%)	37 (55%)	5 (23%)	
PTCA	18 (53%)	30 (45%)	17 (77%)	
LVEF (%)	52.0±1.9	56.9±1.3	60.3±1.7*	0.04
Drugs				
Beta-blockers	30 (88%)	57 (85%)	17 (77%)	
ACE inhibitors	23 (68%)	40 (60%)	12 (55%)	
Exercise test responses				
Peak VO_2	15.0±0.4	20.2±0.2*	27.4±0.5*	0.001
Peak heart rate, bpm	113.4±3.9	125.0±2.2*	133.3±2.6*	0.001
Peak oxygen pulse, ml/bpm	10.1±0.6	13.2±0.4	15.9±0.4*	0.001
Peak SBP, mmHg	153.6±3.4	163.9±2.7*	160.9±3.5	0.05
Peak DBP, mmHg	80.3±1.3	82.3±1.0	80.7±1.7	0.44
Lowest VE/VCO_2 ratio	33.5±0.5	29.7±0.5*	29.0±0.6*	0.001
Δ $PeTCO_2$ (rest-exercise)	2.4±0.5	4.4±0.6*	5.8±0.7*	0.005

Values are means ± SEs. AMI: acute myocardial infarction; CABG: coronary artery bypass grafting; PTCA: percutaneous transluminal coronary angioplasty; LVEF: left ventricular ejection fraction; SBP: systolic blood pressure; DBP: diastolic blood pressure. * $p \leq 0.05$ *vs.* group 1; the *p*-value[a] represents the main effect among groups by ANOVA.

2: 29.7±0.5; and group 3: 29.0±0.6 units, respectively; $p<0.05$, inter-group comparisons). In addition, group 1 exhibited lower $\Delta PeTCO_2$ (rest-exercise) values compared with the 2 other groups ($p<0.05$, inter-group comparisons). With regard to the LVEF, the patients in group 1 exhibited significantly lower values compared with the other groups ($p<0.05$, inter-group comparisons).

Effects of the intervention

After the exercise training program, all groups exhibited an increase in the peak VO_2 (group 1: PRE: 15.0±0.4 *vs.* POST: 19.4±0.6 ml/kg/min; group 2: PRE: 20.2±0.2 *vs.* POST: 23.3±0.4 ml/kg/min; and group 3: PRE: 27.4±0.5 *vs.* POST: 30.2±0.8 ml/kg/min; $p<0.05$; Table 2). However, only groups 2 and 3 exhibited greater peak heart rate values compared with the values before exercise training. After exercise training, only group 1 exhibited significantly greater peak oxygen pulse values compared with the values before exercise training (Table 2).

Only group 1 exhibited significantly lower VE/VCO_2 values compared with the pre-intervention period (group 1: PRE: 33.5±0.5 *vs.* POST: 31.0±0.4 units; $p<0.05$; Table 2). Further analysis demonstrated that the absolute changes (Δ) in both the peak VO_2 and the lowest VE/VCO_2 ratio were greater in group 1 compared with the other 2 groups ($p<0.05$, inter-group comparisons; Figure 1A and 1B, respectively).

The $PeTCO_2$ response between rest and exercise is shown in Figure 2. Statistical analysis showed that the $\Delta PeTCO_2$ (rest-exercise) only improved in group 1 ($p<0.05$, within-group comparisons).

Table 2 - Cardiorespiratory measurements in coronary artery disease patients who underwent aerobic exercise training.

	Group 1	*p*	Group 2	*p*	Group 3	*p*
N	34		67		22	
Peak VO_2						
Pre	15.0±0.4		20.2±0.2		27.4±0.5	
Post	19.7±0.6	0.001	23.3±0.4	0.001	30.2±0.8	0.001
Peak heart rate, bpm						
Pre	113.4±3.9		125.0±2.2		133.3±2.6	
Post	114.1±4.9	0.99	134.3±1.9	0.002	146.0±2.5	0.01
Peak oxygen pulse, ml/bpm						
Pre	10.1±0.6		13.2±0.4		15.9±0.4	
Post	16.1±3.1	0.008	14.0±0.5	0.99	16.3±0.6	0.99
Peak SBP, mmHg						
Pre	153.6±3.4		163.9±2.7		160.9±3.5	
Post	161.5±3.3	0.35	173.0±2.3	0.03	169.5±4.8	0.49
Peak DBP, mmHg						
Pre	80.3±1.3		82.3±1.0		80.7±1.7	
Post	79.1±0.6	0.99	81.2±1.1	0.91	81.6±2.4	0.99
Lowest VE/VCO_2 ratio						
Pre	33.5±0.5		29.7±0.5		29.0±0.6	
Post	31.0±0.4	0.001	28.9±0.4	0.13	27.6±0.6	0.23

Values are means±SEs. Peak VO_2: peak oxygen consumption; SBP: systolic blood pressure; DBP: diastolic blood pressure.

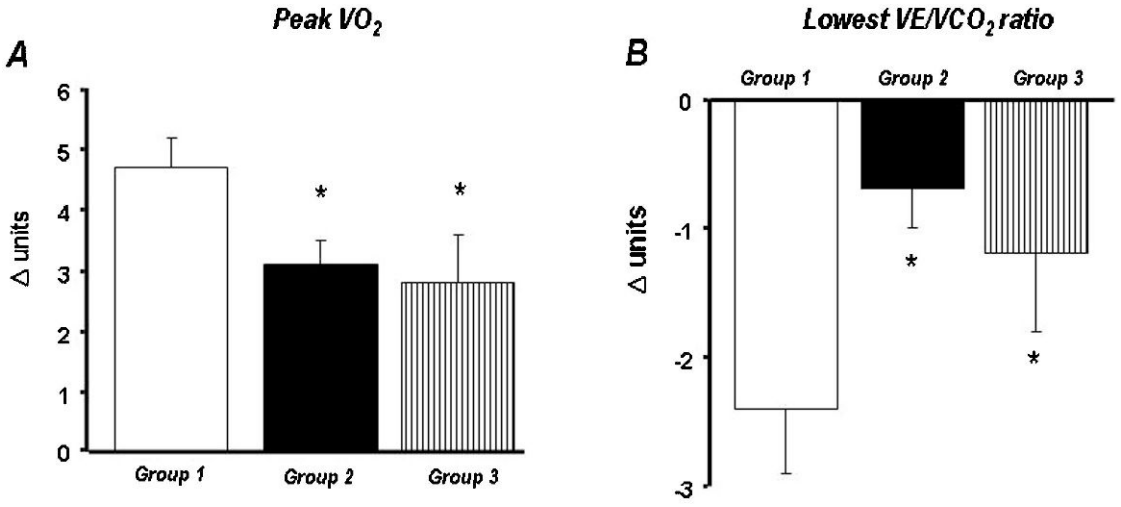

Figure 1 - Absolute changes in aerobic fitness **(Panel A)** and ventilatory efficiency **(Panel B)** in CAD patients who underwent aerobic exercise training. Peak VO_2, peak oxygen consumption; * $p<0.05$ *vs.* group 1.

DISCUSSION

The major findings of the present study were that 1) CAD patients with lower aerobic fitness status exhibited lower ventilatory efficiency and 2) CAD patients with lower initial aerobic fitness exhibited greater improvements in ventilatory efficiency after aerobic exercise training.

Notably, in the current investigation, it was observed that group 1 exhibited lower aerobic fitness compared with the other groups. In this regard, the patients in group 1 exhibited lower peak oxygen pulse values compared with the other 2 groups. In addition, the exercise dyspnea characteristics of patients with cardiovascular disease may also have contributed to their exercise intolerance and reduced aerobic capacity.

An exploration of the mechanisms involved in ventilatory inefficiency in CAD patients with lower aerobic fitness are beyond the scope of the present study. However, we suggest that factors related to ventilation-perfusion (V/Q) mismatch that underlie a limited increase in cardiac output and an increase in pulmonary dead space may be responsible for low ventilatory efficiency in CAD patients. In support of this concept, we found that group 1 exhibited a lower increase in the $\Delta PeTCO_2$ (rest-exercise) compared with the other groups, suggesting that the cardiac output response was attenuated during exercise. In this regard, it has been shown that patients with cardiac disease, especially those with an impaired cardiac output response during exercise, have an abnormally low $PeTCO_2$ during the graded exercise test (20).

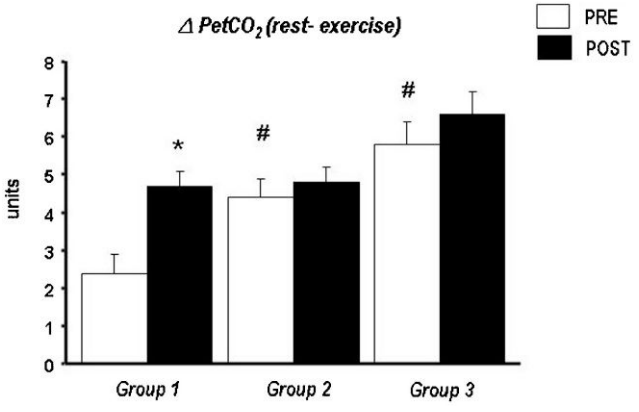

Figure 2 - The change in $PeTCO_2$ from rest to the highest value during exercise in CAD patients who underwent aerobic exercise training; * $p<0.05$ pre-intervention; # $p<0.05$ *vs.* group 1.

Strategies capable of improving ventilatory efficiency and aerobic fitness are of the utmost importance in CAD patients. In this context, aerobic exercise training has been shown to be a potentially useful therapeutic tool for increasing the cardiorespiratory response in patients with different comorbidities (12,14,21). We observed that a three-month aerobic training program effectively improved ventilatory efficiency only in CAD patients with lower initial levels of aerobic fitness (group 1). Similarly, Satoh et al. (5) observed an improvement in ventilatory response in CAD patients with ventilatory inefficiency after 4 months of cardiac rehabilitation. Furthermore, Tomita et al. (6) demonstrated an increase in ventilatory efficiency after 3 months of aerobic exercise training in acute myocardial infarction patients. Importantly, in the same study, the authors observed that ventilatory efficiency improved with exercise training only in patients with lower baseline levels of ventilatory efficiency. It is well-established that physical training ameliorates ventilatory efficiency in patients with chronic heart failure (10,22), whereas ventilatory efficiency has shown to remain unchanged with physical training in healthy subjects (23). These findings suggest that the lowest VE/VCO_2 ratio may be altered with aerobic exercise training only when the baseline levels are elevated.

Elucidating the mechanisms involved in the observed improvement in ventilatory efficiency after exercise training was not the aim of the present investigation. However, we suggest that a possible physiological mechanism responsible for this effect could be related to an improvement in the V/Q mismatch (6). Accordingly, in the present study, only patients in group 1 exhibited a greater increase in the $\Delta PeTCO_2$ (rest-exercise) after the exercise training program. Furthermore, in a previous investigation (14), our group found a negative association between the $PeTCO_2$ and the VE/VCO_2 at the ventilatory anaerobic threshold in CAD

patients after 12 weeks of continuous exercise and interval exercise training. In addition, in the same study, a decrease in the functional estimate of dead space (VD/VT) was observed after the intervention, suggesting that an improvement in the V/Q ratio had occurred.

With respect to functional capacity, we found that CAD patients with a lower initial level of aerobic fitness exhibited greater improvement in the peak VO_2 after aerobic exercise training compared with the other 2 groups. It is widely recognized that exercise training yields an increase in the peak VO_2 among patients who have undergone cardiac rehabilitation (10,24,25). In this context, most studies have shown that exercise training increases aerobic capacity in the range of 15 to 25% (24). We demonstrated that patients with lower initial aerobic fitness levels exhibited an increase of 24% in the peak VO_2. Nevertheless, we observed that patients with greater initial levels of aerobic fitness (groups 2 and 3) exhibited an increase in the peak VO_2 of 13% and 9%, respectively. In addition, Goebbels et al. (24) observed an increase in aerobic fitness only in CAD patients with a reduced ejection fraction compared with an exercise group with normal ventricular function after an 8-week cardiac rehabilitation program. Collectively, these findings suggest that patients with the poorest initial functional capacity are likely to derive the greatest benefit from an exercise training program.

The present findings demonstrate that CAD patients with a lower level of aerobic fitness exhibited a lower ventilatory efficiency during exercise. In addition, after 3 months of aerobic exercise training, the patients with lower initial levels of aerobic fitness exhibited greater improvements in ventilatory efficiency with exercise training.

Collectively, these data suggest that aerobic exercise programs could potentially have clinically significant effects because low ventilatory efficiency observed in patients with CAD is an important predictor of cardiovascular mortality.

There were two main limitations to the present study. The first limitation was that our patients were selected from a database in a retrospective study design. Information about the relationship between our sample and the population is thus limited because our study sample was not selected randomly. Thus, we cannot extrapolate the results of this study to the general population. Second, 35% of the patients with a lower aerobic fitness status had heart failure, which may be associated with the higher ventilatory inefficiency observed in group 1.

AUTHOR CONTRIBUTIONS

Prado DM, Rocco EA and Silva AG conceived and designed the study. Prado DM, Rocco EA, Silva PF, Lazzari JM, Levefre G, Thies SB, Yamada CS, Puig RS and Furlan V acquired the data. Prado DM, Rocco EA and Silva AG analyzed and interpreted the data. All of the authors were involved in manuscript drafting or critically review for important intellectual content and all of the authors approved the manuscript final version for publication. Prado DM had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

REFERENCES

1. Balady GJ, Arena R, Sietsema K, Myers J, Coke L, Fletcher, et al. Clinician's guide to cardiopulmonary exercise testing in adults: A scientific statement from the American heart association. Circulation. 2010;13;122(2):191-225.
2. Wasserman K. Cardiopulmonary exercise testing and cardiovascular health. Armonk, NY: Futura; 2002.
3. Sun XG, Hansen JE, Oudiz RJ, Wasserman K. Exercise pathophysiology in patients with primary pulmonary hypertension. Circulation. 2001;104 (4):429-35, http://dx.doi.org/10.1161/hc2901.093198.
4. Sun XG, Hansen JE, Oudiz RJ, Wasserman K. Gas exchange detection of exercise-induced right-to-left shunt in patients with primary pulmonary hypertension. Circulation. 2002;105(1):54–60, http://dx.doi.org/10.1161/hc0102.101509.
5. Satoh T, Okano Y, Takaki H, Matsumoto T, Yasumura Y, Aihara N, et al. Excessive ventilation after acute myocardial infarction and its improvement in 4 months. Jpn Circ J. 2001;65(5):399-403, http://dx.doi.org/10.1253/jcj.65.399.
6. Tomita T, Takaki H, Hara Y, Sakamaki F, Satoh T, Takagi S, et al. Attenuation of hypercapnic carbon dioxide chemosensitivity after post infarction exercise training: possible contribution to the improvement in exercise hyperventilation. Heart. 2003;89(4):404-10, http://dx.doi.org/10.1136/heart.89.4.404.
7. Arena R, Myers J, Guazzi M. The clinical and research applications of aerobic capacity and ventilatory efficiency in heart failure: an evidence-based review. Heart Failure Rev. 2008;13(2):245-69, http://dx.doi.org/10.1007/s10741-007-9067-5.
8. Gitt AK, Wasserman K, Kilkowski C, Kleemann T, Kilkowski A, Bangert M, et al. Exercise anaerobic threshold and ventilatory efficiency identify heart failure patients for high risk of early death. Circulation. 2002; 106(24):3079-84, http://dx.doi.org/10.1161/01.CIR.0000041428.99427.06.
9. Arena R, Myers J, Abella J, Peberdy MA, Bensimhon D, Chase P, et al. Development of a ventilatory classification system in patients with heart failure. Circulation. 2007;115(18):2410-7, http://dx.doi.org/10.1161/CIRCULATIONAHA.107.686576.
10. Coats AJ, Adamopoulos S, Radaelli A, McCance A, Meyer TE, Bernardi L, et al. Controlled trial of physical training in chronic heart failure-exercise performance, hemodynamics, ventilation, and autonomic function. Circulation. 1992;85(6):2119-31, http://dx.doi.org/10.1161/01.CIR.85.6.2119.
11. Prado DM, Benatti FB, Sá- Pinto AL, Hayashi AP, Gualano B, Pereira RM, et al. Exercise training in childhood-onset systemic lupus erythematosus: a controlled randomized trial. Arthritis Res Ther. 2013;15(2):R46, http://dx.doi.org/10.1186/ar4205.
12. Puente-Maestu L, Sánz ML, Sánz P, Ruiz de Oñã JM, Rodríguez-Hermosa JL, Whipp BJ. Effects of two types of training on pulmonary and cardiac responses to moderate exercise in patients with COPD. Eur Respir J. 2000;15(6):1026-32, http://dx.doi.org/10.1034/j.1399-3003.2000.01509.x.
13. Adamopolous S, Coats AJ, Brunette F, Arnolda L, Meyer T, Thompson CH, et al. Physical training improves skeletal muscle metabolism in patients with chronic heart failure. J Am Coll Cardiol. 1993;21(5):1101-6, http://dx.doi.org/10.1016/0735-1097(93)90231-O.
14. Rocco EA, Prado DML, Silva AG, Lazzari JM, Bortz PC, Rocco DF, et al. Effect of continuous and interval exercise training on the $PETCO_2$ response during a graded exercise test in patients with coronary artery disease. Clinics. 2012;67(6):623-7, http://dx.doi.org/10.6061/clinics/2012(06)13.
15. ACSM Guidelines for Exercise Testing and Prescription, ninth edition: Lippincott Willians & Wilkins; 2013. p.19-34.
16. Wasserman K, Whipp BJ, Koyal SN, Beaver WL. Anaerobic threshold and respiratory gas exchange during exercise. J Appl Physiol. 1973;35 (2):236-43.
17. Prado DML, Dias RG, Matos LDN. Principles of the assessment of cardiorespiratory functional capacity. In: Grave J, Raso V, publishers. Pollock Clinical physiology of the exercise. Barueri: Manole; 2012. p.11-29.
18. Myers J, Arena R, Oliveira RB, Bensimhon D, Hsu L, Chase P, et al. The lowest VE/VCO2 ratio during exercise as a predictor of outcomes in patients with heart failure. J Cardiac Fail. 2009;15(9):756-62, http://dx.doi.org/10.1016/j.cardfail.2009.05.012.
19. Sun XG, Hansen JE, Garatachea N, Storer TW, Wasserman K. Ventilatory efficiency during exercise in healthy subjects. Am J Respir Crit Care Med. 2002;166(11):1443-8, http://dx.doi.org/10.1164/rccm.2202033.
20. Matsumoto A, Itoh H, Eto Y, Kobayashi T, Kato M, Omata M, et al. End-tidal CO_2 pressure decreases during exercise in cardiac patients: association with severity of heart failure and cardiac output reserve. J Am Coll Cardiol. 2000;36(1):242-9, http://dx.doi.org/10.1016/S0735-1097(00)00702-6.
21. Prado DM, Silva AG, Trombetta IC, Ribeiro MM, Nicolau CM, Guazzelli IC, et al. Weight loss associated with exercise training restores ventilatory efficiency in obese children. Int J Sports Med. 2009;30(11): 821-6.
22. Digenio AG, Noakes TD, Joughin H, Daly L. Ventilatory responses to exercise in patients with asymptomatic left ventricular dysfunction. Med Sci Sports Exerc. 1999;31(7):942-8, http://dx.doi.org/10.1097/00005768-199907000-00005.
23. Clark AL, Skypala I, Coats AJ. Ventilatory efficiency is unchanged after physical training in healthy persons despite an increase in exercise tolerance. J Cardiovasc Risk. 1994;1(4):347-51, http://dx.doi.org/10.1097/00043798-199412000-00011.

24. Goebbels U, Myers J, Dziekan G, Muller P, Kuhn M, Ratte R, et al. A randomized comparison of exercise training in patients with normal vs. reduced ventricular function. Chest. 1998;113(5):1387-93.

25. Pashkow FJ. Issues in contemporary cardiac rehabilitation: a historical perspective. J Am Coll Cardiol. 1993;21(3):822-34, http://dx.doi.org/10.1016/0735-1097(93)90116-I.