ORIGINAL ARTICLE

CME

Cardiopulmonary Exercise Testing in Healthy Children

Prueba de ejercicio cardiopulmonar en niños sanos

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ABSTRACT

Background: Cardiopulmonary exercise testing is a valuable tool for assessing the clinical condition and prognosis of patients with cardiovascular disease; it is therefore essential to have normal reference values in healthy children.
Objective: The aim of this study was to perform cardiopulmonary exercise testing in healthy children to obtain reference values in our laboratories.
Methods: Cardiopulmonary exercise testing was performed in 215 healthy children divided into 2 Groups: A, Prepubertal and B, Pubertal. These Groups were in turn divided into male and female. The test was performed on a treadmill with O_2 saturation and breath-by-breath expired gas analysis with a COSMED system. Statistical analysis was performed with SPSS 17 software package.
Results: The A and B Groups are significantly different in age, weight, height, and body surface area. Significant differences were found between the two Groups in VO_2 ml/min ($p < 0.0000$), respiratory exchange ratio ($p < 0.01$), O_2 pulse in ml/bpm ($p < 0.0000$) and VE/VCO_2 slope ($p < 0.0000$). In the analysis by gender there were significant differences in peak VO_2 ml/kg/min, peak VO_2 ml/min, MET, VE/VCO_2 slope and VO_2 ml/kg/min in ventilatory anaerobic threshold. Group A also showed significant gender difference in peak heart rate. VO_2 ml/min and peak O_2 pulse (VO_2 ml/heart rate) increased with age and body surface area. The VE/VCO_2 slope decreases with age.
Conclusions: The data obtained in this study allow analysis of cardiopulmonary exercise testing variables in healthy children according to age and gender. These values can be used as reference data to evaluate patients with cardiovascular disease in Argentina.

Key words: Exercise Testing – Child - Oxygen consumption

RESUMEN

Introducción: La prueba de ejercicio cardiopulmonar es una valiosa herramienta para evaluar la condición clínica y el pronóstico en pacientes con patología cardiovascular, por lo que resulta fundamental contar con valores normales de referencia en niños sanos.
Objetivo: Realizar la prueba de ejercicio cardiopulmonar en niños sanos para obtener valores referenciales en nuestros laboratorios.
Material y métodos: Se incluyeron 215 niños sanos, que realizaron la prueba de ejercicio cardiopulmonar. Se dividieron en dos grupos: A, prepuberal y B, puberal. Estos grupos, a su vez, se dividieron en varones y mujeres. La prueba se realizó en cinta ergométrica, con saturación de O_2 y análisis de gases espirados respiración por respiración con un equipo marca COSMED. Para el análisis estadístico se utilizó el programa SPSS 17.
Resultados: Los grupos A y B son significativamente diferentes en edad, peso, talla y superficie corporal. Se encontraron diferencias significativas entre los dos grupos en VO_2 ml/min ($p < 0,0000$), cociente de intercambio respiratorio ($p < 0,01$), pulso de O_2 ml/lpm ($p < 0,0000$) y pendiente VE/VCO_2 ($p < 0,0000$). En el análisis por sexo se encontraron diferencias significativas en VO_2 ml/kg/min pico, VO_2 ml/min pico, MET, pendiente VE/VCO_2 y VO_2 ml/kg/min en umbral anaeróbico ventilatorio. En el grupo A se observó además una diferencia significativa por sexo en la frecuencia cardíaca pico. El VO_2 ml/min y el pulso de O_2 pico (VO_2 ml/frecuencia cardíaca) aumentaron con la superficie corporal y con la edad. La pendiente VE/VCO_2 disminuye con la edad.
Conclusiones: Los datos obtenidos en este estudio permiten el análisis de variables de la prueba de ejercicio cardiopulmonar en niños sanos de acuerdo con edad y sexo. Estos valores se podrán utilizar como datos referenciales para evaluar pacientes con enfermedad cardiovascular en la Argentina.

Palabras clave: Prueba de esfuerzo - Niños - Consumo de oxígeno

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Abbreviations

AT	Anaerobic threshold	**MET**	Metabolic rate measurement unit
CABA	Autonomous City of Buenos Aires	**O_2**	Oxygen
CO_2	Carbon dioxide	**VE/VCO_2**	Pulmonary ventilation/carbon dioxide production
CPET	Cardiopulmonary exercise testing	**RER**	Respiratory exchange ratio
HR	Heart rate	**VO_2**	Oxygen consumption

INTRODUCTION

The function of the cardiopulmonary system is to provide the tissues with blood flow and consequently with enough oxygen (O_2) to meet the metabolic needs of the organism. Cardiopulmonary exercise testing (CPET) evaluates these functions during exercise when metabolism is maximized (1-3). With physical exercise, the body experiences changes to adapt to the new energy requirements; in normal individuals the resting heart rate undergoes a threefold increase, pulmonary vascular resistance is reduced, and both systolic volume and blood pressure increase. These changes may result in a fivefold increase of cardiac output with maximum exercise. (2, 4, 5) Cardiopulmonary exercise testing is widely used in the evaluation of patients with chronic heart disease such as heart failure, cardiomyopathy, pre- and post-cardiac transplantation, with valve disease and with pulmonary disease in the adult population (1, 5, 6). In pediatrics it is used for the evaluation of congenital heart disease, in which O_2 consumption, pulmonary ventilation/carbon dioxide production (VE/VCO_2) slope and O_2 pulse are early risk markers. As shown in numerous publications, functional capacity is reduced in congenital heart disease. Cardiopulmonary variables that contribute to reduce exercise tolerance include systolic and diastolic dysfunction of both ventricles, absence of venous ventricle in the total bypass, valvular stenosis or regurgitation, as severe pulmonary insufficiency in repaired Tetralogy of Fallot, sinus node dysfunction, as that observed in patients with transposition of the great arteries operated on with atrial techniques, arrhythmias, pulmonary hypertension, residual cyanosis, etc. (7-15) The values obtained in CPET provide data that help to understand the different pathophysiological mechanisms that reduce the functional capacity of these patients and are used as risk markers.

It is therefore essential to have normal values of these parameters in healthy children, obtained in our laboratory, to compare them with congenital heart disease patients. This study attempts to provide an evaluation methodology not previously used in our country in the pediatric population and of which there are limited publications worldwide.

METHODS

Retrospective study between december 2012 and october 2015 was performed in two centers, one public and the other private in the Autonomous City of Buenos Aires (CABA), including 215 healthy children, (191 and 24, respectively), untrained or performing only recreational sport, between 6 and 17 years old, of whom 138 were male and 77 female. The children were divided into two groups, according to age: Group A, from 6 to 11 years and Group B, from 12 to 17 years.

The average age of puberty onset in the Argentine population (16, 17) was taken into account to divide the groups. This is 11 years in girls and 11.8 years in boys. Therefore, in Group A children are prepubertal and in Group B most have already entered puberty.

The test was performed on a treadmill, following the Bruce protocol, until exhaustion, with continuous 12-lead electrocardiographic monitoring, blood pressure recording, O_2% saturation and breath -by-breath expired gas analysis with a COSMED Quark CPET system (Rome, Italy).

The following variables were analyzed:

a. Peak VO_2 ml/min: Average between the last 10 to 60 seconds of exercise. It represents the highest O_2 consumption obtained in the exercise. (6)
b. Peak VO_2 ml/kg/min: Peak O_2 consumption per kilogram of body weight. It varies with age; it tends to increase and peaks in adolescence and young adulthood and then declines progressively. It differs between men and women and is directly proportional to the increase in body surface area, greater muscle mass and more physical training. It is a universal prognostic marker. (6)
c. R coefficient: Ratio between CO_2 production and VO_2. When the ratio is 1:1, it can be assumed that the patient is working close to the anaerobic threshold (AT); once 1:1 is exceeded, R continues to rise. A value of 1.09 reflects an acceptable exercise level. For younger children a value of 1.01 is accepted. (2-18) Assessment of results allows differentiating a low VO_2 value due to poor exercise from that due to pathological causes.
d. MET: Metabolic equivalent; 1 MET=3.5 ml/kg/min O_2 consumption.
e. Peak HR: Maximum HR achieved during physical exercise. It is also evaluated with respect to 100% of predicted value.
f. Peak O_2 pulse: Ratio between VO_2 ml/min and HR bpm. Peak O_2 pulse is related to stroke volume at peak exercise and is therefore one of the available clinical indices most commonly used in the exercise laboratory. $VO_2/HR = O_2$ pulse = (cardiac output/HR) x (A-V dif.). It is also evaluated with respect to 100% % of predicted value. (1, 6, 18)
g. Ventilatory AT VO_2 ml/kg/min: Submaximal VO_2 when there is a nonlinear VE and VCO_2 increase. It is usually between 50% and 65% of peak VO_2. (6) It is often difficult to detect in children due to their immature metabolic system. The direct way to measure it is through the analysis of blood lactate. It expresses an area where the balance between production and removal of lactic acid is upset, leading to its accumulation and to metabolic acidosis and activation of buffering systems.
h. VE/VCO_2 slope: It is the relationship between pulmonary ventilation (VE) and the production of carbon di-

oxide (CO_2). It is an index of gas exchange efficiency during exercise and an important risk marker. It indicates mismatching between ventilation and perfusion. It is a parameter assessed at submaximal exercise and is therefore not affected by the patient's self-control or exercise intensity. Ventilation/perfusion disorders are associated with pathological VE/VCO_2. It is also higher in cyanotic patients who have an increased CO_2 at rest which is more enhanced during exercise. (3, 2, 6)

i. O_2% saturation: It is a variable used in cardiopulmonary disease.

Statistical analysis

Statistical analysis was performed using SPSS 17 software package (Chicago, USA). Student`s t test for two independent samples was used to compare means of normal continuous variables, and the Mann-Whitney U-Test, for non-normal continuous variables. A p value <0.05 value was considered statistically significant. A linear regression analysis was also performed by gender in both Groups.

Ethical considerations

Since this is a retrospective study, no informed consent (CABA Law 3301) was required. According to the Argentine Personal Data Protection Law Nº 25.326, all information will remain confidential.

RESULTS

The population of 215 children was divided into two groups. Mean and standard deviation of anthropometric data are summarized in Table I. The t-test showed significant differences between mean age, weight, height, body surface area and body mass index.

All participants underwent CPET without complications and could complete the protocol until exhaustion. Continuous electrocardiogram monitoring was normal, with no arrhythmias or electrocardiographic disorders. Blood pressure increased within normal limits in all children. O_2 saturation remained within normal limits during the test. Peak HR was maximal in all cases, with no significant difference between mean values of both groups. Mean peak VO_2 ml/kg/min, peak VO_2 ml/min, R coefficient, MET, peak HR, peak O_2 pulse, ventilatory AT % peak VO_2 ml/kg/min, ventilatory AT VO_2 ml/kg/min, VE/VCO_2 slope and % O_2 saturation and their statistical significance are also shown in Table I.

Table II shows that in both Group A and B there was statistically significant difference between boys and girls in peak VO_2 ml/kg/min, peak VO_2 L/min, MET, peak O_2 pulse and AT VO_2 ml/kg/min. Peak HR was higher in girls in Group A, whereas a non-significant difference between boys and girls was found in Group B. The VE/VCO_2 slope was higher in Group B girls, with no significant difference between boys and girls in Group A. No significant differences were observed between boys and girls in both groups in the respiratory exchange ratio (RER) and in the AT % VO_2 ml/kg/min.

Linear regression analysis showed that peak VO_2 ml/min increases with age (R2=0.57) (Figure 1) and with body surface area (R2=0.706) (Figure. 2). It was also observed that O_2 ml/bpm increases with age (R2=0.532) and with body surface area (R2=0.658), as has already been shown in other studies, and that VE/VCO_2 slope decreases with age (R2=0.336) (Figure 3) and body surface area (R2=0.337), which also agrees with other authors. If we consider VO_2 ml/kg/min, the increase of this variable is not significant with age (R2=0.014) because weight acts as a correction factor. It is also noted that there is no correlation between peak HR and age (R2=4.831E-6).

The AT % peak VO_2 ml/kg/min and AT VO_2 ml/kg/min could be detected in 54.4% of children in Group

Table 1. Mean and standard deviation of anthropometric data and of the variables analyzed in the cardiopulmonary exercise test and their statistical significance

	Group A (n=85)	Group B (n=130)	p
Age	9.45±1.36	14.06±1.56	0.0000
Weight	35.09±9.19	54.64±11.78	0.0000
Size	137.40±18.35	132.58±10.34	0.0000
Body surface area.	1.15±0.20	1.54±0.19	0.0000
BMI	17.79±2.8	20.58±3.12	0.0000
Peak VO_2 ml/kg/min	43.28±7.40	43.93±7.87	0.000
Peak VO_2 L/min	1.488 ±348	2388.7±640.54	0.000
Peak RER	1.14±0.08	1.17±0.08	0.011
MET	12.07±2.34	12.39±2.37	ns
Peak HR	191.81±8.76	192.18±8.53	ns
Peak O_2 pulse	7.97±1.83	9.7±2.12	0.000
VE/VCO_2 slope	33.40±4.09	28.39±4.35	0.000
AT % VO_2 ml/kg/min	74.20±12.41	71.49±11.04	ns
AT VO_2 ml/kg/min	30.90±7.28	30.65±6.82	ns

BMI: Body mass index. VO_2: Oxygen consumption. RER: Respiratory exchange ratio. MET: Metabolic rate measurement unit. HF: Heart rate. O_2: Oxygen. VE/VCO_2: Pulmonary ventilation/carbon dioxide production. AT: Anaerobic threshold.

Table 2. Results by gender of the variables analyzed in the cardiopulmonary exercise test and their statistical significance

	Group A(m) (n=55)	Group A(f) (n=30)	p	Group B(m) (n=83)	Group B(f) (n=47)	p
Peak VO_2 ml/kg/min	45.78±7.09	45.78±7.09	0.000	4805±5.82	36.66±5.38	0.0000
Peak VO_2 L/min	1535.41 ±326.72	1535.41 ±326.72	0.000	2663±581.81	19033±412.32	0.0000
Peak RER	1.14±0.08	1.14±0.08	ns	1.16±0.08	1.19±0.08	ns
MET	12.67±2.48	12.67±2.48	0.000	13.59±1.83	10.26±1.62	0.0000
Peak HR	190.16±8.07	190.16±8.07	0.018	191.86±9.2	192.74±7.27	ns
Peak O_2 pulse	7.97±1.83	7.97±1.83	0.05	13.73±3.25	9.69±2.11	0.0000
VE/VCO_2 slope	33.43±409	33.43±409	ns	27.78±4.08	29.48±4.65	0.033
AT % VO_2 ml/kg/min	75.87±10.17	75.87±10.17	ns	70.9±10.95	72.5±11.26	ns
AT VO_2 ml/kg/min	33.31±6.64	33.31±6.64	0001	33.12±6.35	26.33±5.32	0.0000

m: Male. f: Female. VO_2: Oxygen consumption. RER: Respiratory exchange ratio. MET: Metabolic rate measurement unit. HF: Heart rate. O_2: Oxygen. VE/VCO_2: Pulmonary ventilation/carbon dioxide production. AT: Anaerobic threshold.

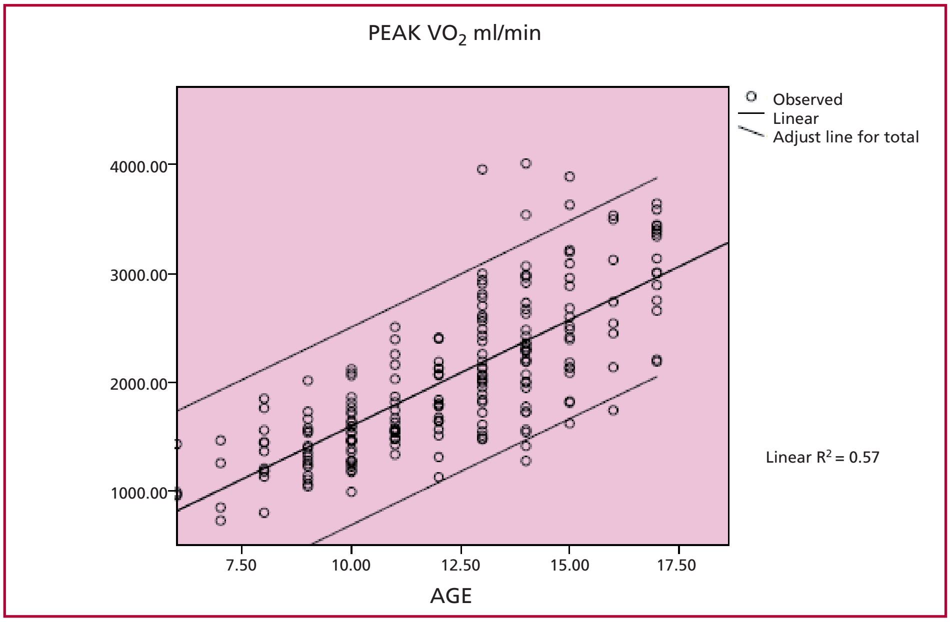


Fig. 1. Relationship between age and peak VO_2 ml/min; mean value and 95% CI.

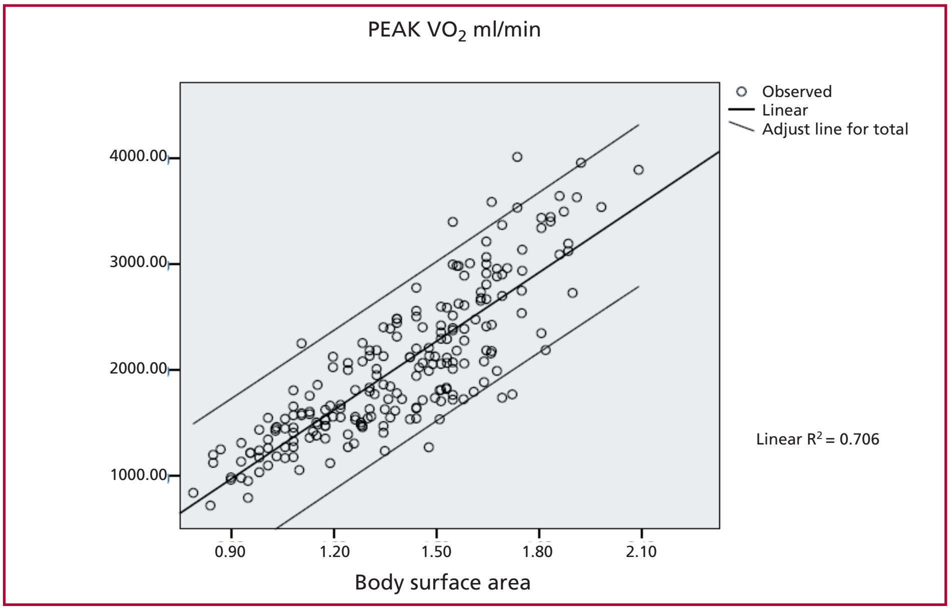


Fig. 2. Relationship between body surface area and peak VO_2 ml/min; mean value and 95% CI.

A and in 82.2% in Group B without significant differences between both groups.

DISCUSSION

The cardiology service of Hospital Ricardo Gutierrez in Buenos Aires has pioneered the use of Pediatric Exercise Test and the reference values in healthy children published in 1990 are used as standards in our setting. (19) Although conventional exercise testing has its indications and is very useful in the evaluation of patients with different pathologies, the inclusion of ventilatory gas measurements to conventional exercise testing is a contribution of great interest for the pathophysiological understanding, diagnosis and prognosis of our patients with congenital heart diseases, since the direct measurement of VO_2 is much more accurate than the indirect measurement, as the latter overestimates its value and this is more evident in patients with heart disease. (18)

The analysis of the data found in the children studied in this work shows that VO_2 ml/min values increase with age, with significant differences observed between Group A (prepubertal) and Group B (pubertal) and between boys and girls, as already observed by other authors. Regarding the differences between boys and girls, we find that boys have higher peak VO_2 ml/kg/min and also peak VO_2 ml/min. This difference is greater in Group B (pubertal), as it begins to decline in girls due to increased body fat that remains in adulthood, while boys develop more muscle mass (2, 3, 21) When peak VO_2 ml/kg/min values are considered, the differences between both groups are not so significant, since weight acts as a correction factor. The VO_2ml/kg/min values in our population are similar to those in the literature (3, 20-24).

In the case of peak O_2 pulse which relates peak VO_2 in ml/min with HR, Group B shows a significantly higher value, since with equal maximum HR it has higher O_2 consumption, demonstrating a better efficiency of the cardiovascular system in older children compared to younger ones. (2)

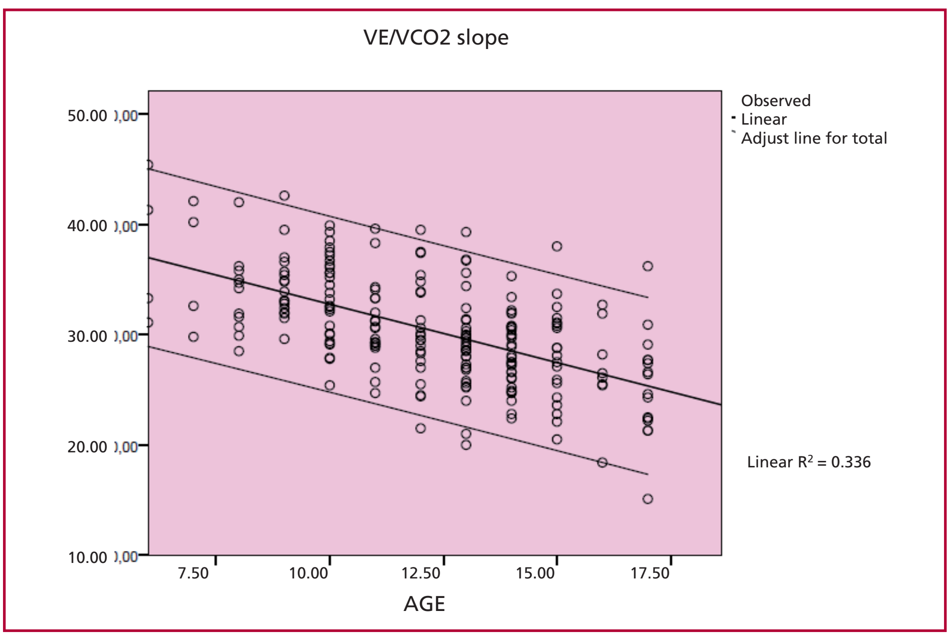
Heart rate between Groups A and B shows no significant difference as already demonstrated in the literature and in our own experience. (19) A higher peak HR was observed in girls of the prepubertal group.

The VE/VCO_2 slope decreases with age: it was significantly higher in Group A than in Group B, a fact that has been observed by other authors and has been attributed to a poor distribution of pulmonary blood flow with slightly lower increased CO_2 pressure in younger children and increased ventilatory efficiency in older children (higher tidal volume and relatively lower respiratory rate). This value is an index of gas exchange equivalent to the amount of liters of air needed to remove 1L of CO_2. The increase of VE/VCO_2 slope has been linked to increased risk of mortality by numerous authors. (25-27)

The AT is an area where energy requirements cannot be supplied only by aerobic metabolism, setting off anaerobic metabolism. This increases blood lactate levels, generating metabolic acidosis, which is buffered producing excess CO_2, enhanced VCO_2 above VO_2 which continues increasing, although to a lesser extent leading to a non-linear VE increase. Accordingly, it is an index of the cardiovascular system capacity to maintain the hemodynamic demands of intense exercise. The AT is usually expressed as percent of predicted peak VO_2 and it rarely decreases by more than 40% in the absence of cardiovascular disease. (2, 6, 18)

Concerning MET, metabolic equivalent where 1 METs is equal to 3.5 ml/kg/min O2 consumption, the values referred in our population are real, because

Fig. 3. Relationship between age and VE/VCO_2 slope; mean value and 95% CI.



they are estimated on VO_2 ml/kg/min measured directly, so they are fairly lower than those estimated indirectly as in a conventional stress test, and this is more evident when evaluating patients with congenital heart disease.

Although CPET provides more data to better understand the pathophysiology of our patients than the variables analyzed in this work, we consider these are the most frequently reported by other authors; however, we will continue researching other variables in subsequent reports.

CONCLUSIONS

The data obtained in this study analyze by age and gender CPET variables in healthy children. According to previous publications, peak VO_2 L/min and O_2 pulse increase with age and body surface area and the VE/VCO_2 slope decreases with age. Group B girls have higher VE/VCO_2 slope than boys. Group B presents higher RER than Group A. Peak VO_2 (ml/min and ml/kg/min), MET and O_2 pulse are higher in boys than in girls. No differences in RER by gender were found. The AT % peak VO_2 was over 70% in both groups with no gender difference. These data may be used as reference values to evaluate patients with cardiovascular disease in Argentina.

Conflicts of interest

None declared. (See authors' conflicts of interest forms in the website/Supplementary material).

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