ORIGINAL ARTICLE

Cardiopulmonary Exercise Testing: Reference Values in Adolescent and Adult Patients with Congenital Heart Diseases

Prueba de ejercicio cardiopulmonar: valores de referencia en pacientes adolescentes y adultos con cardiopatías congénitas

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ABSTRACT

Background: The interpretation of cardiopulmonary exercise testing (CPET) in congenital heart diseases represents a challenge, since they constitute a large group of anomalies with different degrees of severity.
Objectives: The aim of this study was to obtain reference values of CPET variables in adolescents and adults with congenital heart diseases in our center, to compare between peers the expected results of CPET according to age, gender and the same pathology.
Methods: A total of 799 tests were performed in 473 patients older than 17 years with different congenital heart diseases. Variables studied were peak VO2 (ml/kg/min), percent-predicted peak VO2, test duration in seconds (discriminated by gender), VE/VCO2 slope and R coefficient for all the tests. Statistical analyses were conducted using mean and standard deviation for each variable and Student's t test for those studied by gender.
Results: Peak VO2 (ml/kg/min), percent-predicted peak VO2, and test duration decreased as the severity of heart diseases increased. The percent-predicted peak VO2 corrects VO2 ml/kg/min values for age and sex, so it becomes a more useful variable for evaluation. An R coefficient greater than 1.1 indicates that patients performed a maximal test. The VE/VCO2 slope is increased in severe heart diseases.
Conclusions: Reference CPET values for the different congenital heart diseases are essential, since they allow us to compare patients with the same pathology. The percent-predicted peak VO2 seems to be the most useful variable for this purpose.

Key words: Exercise Test - Oxygen Consumption - Heart Defect, Congenital

RESUMEN

Introducción: La interpretación de la prueba de esfuerzo cardiopulmonar (PECP) en cardiopatías congénitas representa un desafío, ya que estas constituyen un grupo amplio con diferentes grados de gravedad.
Objetivos: Obtener en nuestro centro valores de referencia para las variables medidas mediante la PECP en adolescentes y adultos con cardiopatías congénitas, con el objetivo de poder comparar entre pares los resultados esperados de la PECP según edad, sexo e igual patología.
Material y Métodos: Se realizaron 799 PECP en 473 pacientes mayores de 17 años con distintas cardiopatías. Variables estudiadas: VO2 pico (ml/kg/min), % predicho de VO2 pico, duración en segundos de la prueba (discriminada por sexo), VE/VCO2 slope y coeficiente R para el total de las pruebas. Análisis estadístico: media y desvío estándar para cada variable, T test para las estudiadas por sexo.
Resultados: El VO2 pico (ml/kg/min), el % predicho del VO2 pico y la duración de la prueba disminuyeron conforme aumentó la gravedad de la cardiopatía. El % predicho de VO2 pico corrige los valores de VO2 (ml/kg/min) por edad y sexo, por lo que constituye un dato más útil para la evaluación. El coeficiente R mayor que 1,1 indica que los pacientes realizaron una prueba máxima. El VE/VCO2 slope está aumentado en las cardiopatías graves.
Conclusiones: Los valores de referencia de la PECP para las distintas cardiopatías congénitas son fundamentales, pues nos permiten comparar pacientes con igual patología. El % predicho de VO2 pico parece ser el dato más útil para este fin.

Palabras clave: Prueba de esfuerzo – Consumo de oxígeno – Cardiopatías congénitas

INTRODUCTION

At present, most patients born with congenital heart diseases reach adulthood. In their evolution, many of them present late complications. Among the tools used in periodic monitoring, cardiopulmonary exercise testing (CPET) has become one of the most valuable. (1) This non-invasive test is accessible, reproducible, and allows risk stratification of morbidity and mortality. It also allows a better evaluation of the need for therapeutic or interventional therapeutic changes, as well as the adaptation of physical and sports activities and cardiovascular rehabilitation. (1, 2)

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In most clinical studies, patients with congenital heart diseases are evaluated at rest; however, the first signs of cardiac dysfunction may appear during an exercise test, and its first manifestation is decreased aerobic capacity. (3)

Interpreting the results of CPET in these patients is a real challenge, since they cover a wide and varied range of heart lesions, often with two or more associated abnormalities. Yet, the classification of severity has not achieved full acceptance among the top experts in the field. (4)

Although there has been a continuous effort to train human resources capable of understanding the multiplicity of factors involved in monitoring these patients, as well as a huge progress in new surgical techniques, interventional catheterization, postoperative recovery, conventional, 3D, transesophageal, intraoperative, fetal and stress echocardiography, cardiac magnetic resonance imaging, myocardial perfusion studies and electrophysiological procedures (from ablations of severe arrhythmias to placement of pacemakers and cardioverter-defibrillators), the great complexity of variables that affect these patients indicate the need for studies that allow us to evaluate them as accurately as possible.

Exercise tolerance has been investigated through numerous studies both in adults and children with congenital heart diseases. Given that the protocols and methodologies differ between centers, it is important that they have their own reference values. (1)

Relating CPET values between patients and healthy individuals is insufficient, since it is well known that they are generally decreased in patients with congenital heart diseases. (1, 3). The same occurs when we compare CPET results of patients with different pathologies, for example, tetralogy of Fallot operated with venous ventricle or sub-pulmonary bypass. Therefore, the main purpose of this work was to find reference CPET values for our center, and to compare patient's results with those expected according to age, gender and congenital heart disease, in order to decide therapeutic or surgical behaviors, since the parameters determined by this test are considered important risk factors.

METHODS

A retrospective study was conducted from June 2012 to July 2019 in 473 patients over 17 years of age in whom 799 cardiopulmonary exercise tests were performed for the following diseases: ventricular septal defect (VSD) (n=31), coarctation of the aorta (CoAo.) (n=91), atrial septal defect (ASD) (n=29), pulmonary stenosis (PS) (n=19), aortic stenosis (AoS) (25), tetralogy of Fallot (293), Ebstein's anomaly (31), dextro-transposition of the great arteries (D-TGA) corrected with arterial switch (n=5), D-TGA corrected with atrial switch (n=36), levo-transposition of the great arteries (L-TGA) (n=21), venous ventricle bypass (n=163) and pulmonary hypertension (PHT) (n=55)

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

The following variables were analyzed:

- VO_2 max (ml/kg/min): peak O_2 consumption per kilogram of body weight. Its normal value is 20-90 ml/kg/min and it has its highest average between the last 10-60 seconds of the test. It depends on age and gender and is directly proportional to body surface area, body mass and physical training. (2, 5, 6) It can also be expressed as percent-predicted peak VO_2 calculated with Wasserman et al.'s equations. (2), which includes age and differs according to gender; a value greater than 85% is accepted as normal. (7) Both parameters are considered level of evidence I/A. (8)
- Exercise duration, in seconds.
- R coefficient: is the quotient between the production of CO_2 and VO_2. When the ratio is 1:1, it can be assumed that the patient is working near the anaerobic threshold; once the 1:1 ratio is exceeded, R continues to rise. A value of 1.10 is widely accepted as excellent physical effort. (5)
- VE/VCO_2 slope: is the relationship between pulmonary ventilation (VE) and carbon dioxide (CO_2) production. 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 determined in submaximal exercise, so it is not affected by the patient's will or by the intensity of physical activity. Ventilation/perfusion disorders are associated with pathological VE/VCO_2. In adolescent and adult patients, a value <30 is accepted as normal. (5) It is considered level of evidence I/A. (8)

Statistical analysis

Mean and standard deviation were calculated for each variable and Student's t test was used to analyze values according to gender using SPSS 21 statistical package. A p value <0.05 was considered statistically significant. Graphs were plotted with the R free software license.

Ethical considerations

As it was a retrospective study, informed consent was not required (Law 3301, CABA). In accordance with Argentine Law No. 25.326 on the protection of personal data, all information will remain confidential.

RESULTS

Table 1 shows that the decrease in peak VO2 is related to disease severity, and, therefore, was lower in the most severe cases. For this variable, significant differences were observed between men and women for most congenital heart diseases (coarctation of the aorta, atrial defect, pulmonary stenosis, tetralogy of Fallot, Ebstein's anomaly, venous ventricle bypass and pulmonary hypertension), which justifies their division by gender. Dextro-transposition of the great vessels corrected with arterial switch data were insufficient for their statistical analysis.

The percent-predicted peak VO2 corrects peak VO2 (ml/lg/min) by gender and age; thus no significant differences were observed between the two genders for any congenital heart disease. This variable seems to be more useful, since it infers what is the average decrease in peak VO2 expected for each of the heart diseases studied (Table 1).

In the case of the R coefficient, in all diseases except pulmonary hypertension, patients reached an average value greater than 1.1, so we can establish that they performed a maximum test (Table 2).

The VE/VCO2 slope increased according to the severity of the heart disease and on average was higher than 30 (maximum value for this variable) (5) in the most serious diseases: Ebstein's anomaly, D-TGA, L-TGA, venous ventricle bypass and pulmonary hypertension (Table 2).

Figure 1 shows different histograms for the percent-predicted peak VO_2 according to each congenital heart disease.

DISCUSSION

Fitness for physical exercise is related to the ability of the cardiovascular system to supply O_2 to the muscles and the ability of the lung system to remove CO_2 from the blood through the lungs. (2, 6, 9, 10)

Exercise testing with direct measurement of O_2 consumption or CPET integrates the electrocardiographic criteria (evolution of heart rate, presence of arrhythmias, ST-T changes, conduction disorders), blood pressure and symptoms with the assessment of gas exchange, which contributes to a more complete

Table 1. Cardiopulmonary exercise testing in adolescents and adults with different congenital heart diseases: peak VO_2 and percent-predicted peak VO_2

Variable	AGE (years)		PEAK VO_2 (ml/kg/min)			%-PREDICTED VO_2 (ml/kg/min)		
	Male	Female	Male	Female	p	Male	Female	p
VSD (31)	27.5 + 10.1	27.2 + 8.5	35.8 + 9.7	28.6 + 6.2	NS	80 + 19.3	85+ 15.5	NS
AoCo. (91)	23.2 +8	26 + 7	37.3 + 8.3	28.2 + 5.5	0.0000	81.4 + 17	81 + 14	NS
AD (29)	22.7 + 11	32.1 + 13.6	39 + 8	27.3 + 6.1	0.0007	80 + 10	84.4 + 16	NS
PS. (19)	22.2 + 4,5	34 + 13.6	37.2 + 8	28 + 3.1	0.01	74.1+ 9	82.2 + 6.4	0.01
AoS. (25)	24.6 + 9.4	24.6 + 4.6	33.6 + 9.6	35.9 + 3.7	NS	71.6 + 15	74.2 + 10	NS
Fallot (293)	25.5 + 8.1	31 + 10.9	32 + 7	23 + 4.8	0.0000	73.6 + 14	70.5 + 16.9	NS
Ebstein (31)	26.1 + 12.5	26 + 7.1	31.7 + 7	20.6 + 5.3	0.0000	68.2 + 11.6	65.1 + 19	NS
TGA (art.) (5)	19.5 + 2.1	17	31.41 + 6.8	29.4		62 + 15	62	
TGA (atr) (36)	28.2 + 7.2	23.7 + 4.1	26.5 + 6.9	24.2 + 4.6	NS	64.3 + 12.5	69 + 10	NS
L-TGA (21)	29 + 12.9	23.6 + 4.4	25.1 + 7.4	22 + 4	NS	61 + 18	64 + 17	NS
By pass (163)	23 + 5.5	25.9 + 5.7	27.2 + 5.8	21.9 + 3.8	0.0000	56.8 + 11.6	60.2 + 11.3	NS
PHT (55)	22.1 + 8.2	29.1 + 13.5	24.6 + 6.4	18.8 + 5.2	0.002	53 .2+ 12.1	54.7 + 13	NS

The percent-predicted peak VO_2 for mild, moderate and severe congenital heart disease is highlighted in deep red, red and light red, respectively. VSD: Ventricular septal defect. AoCo: Aortic coarctation. AD: Atrial defect. PS: Pulmonary stenosis. AoS: Aortic stenosis. Fallot: Tetralogy of Fallot. Ebstein: Ebstein's anomaly. TGA (art): Transposition of the great arteries corrected with arterial switch. TGA (atr): Transposition of the great arteries corrected with atrial switch. L-TGA: Levo-transposition of the great arteries. PHT: pulmonary hypertension.

Table 2. Cardiopulmonary exercise testing in adolescents and adults with different congenital heart diseases: exercise duration, R ratio and slope.

Variable	EXERCISE DURATION (seconds))			R	VE/VCO_2
	Male	Female	p	M and F	M and F
VSD (31)	718.6 + 183	672.6 + 126.2	NS	1.15 + 0.1	29 + 5.1
AoCo. (91)	766 + 147	650.9 + 134.8	0.0000	1.16 + 0.1	29.8 + 5.5
CIA (29)	789.8 + 140	559.9 + 161	0.02	1.14 + 0.1	29.5 + 5
PS. (19)	793.5 + 92.9	640.8 + 108.9	0.002	1.12 + 0.08	30.7 + 4.4
AoS. (25)	726.9 + 142	621 + 40	NS	1.1 + 0.1	28.2 + 4.6
Fallot (293)	692.9 + 144.4	531.8 + 131.9	0.0000	1.11 + 0.12	29.6 + 5.2
Ebstein (31)	722.8 + 114.8	484 + 170.3	0.0004	1.15 + 0.08	35.6 + 9.6
TGA (art.) (5)	706 + 147.2	660		1.12 + 0.1	36.1 + 7.2
TGA (atr) (36)	580.8 + 170.2	540.7 + 63.8	NS	1.12 + 0.1	32.6 + 5.5
L-TGA (21)	604.2 + 173.9	525.8 + 97.1	NS	1.1 + 0.1	33.5 + 6.2
By pass (163)	598.9 + 149	522.8 + 114.8	0.0002	1.1 + 0.1	36.9 + 10.4
HTP (55)	534.9 + 168.3	376.6 + 160	0.01	1.06 + 0.12	38.8 + 12.3

VE/VCO_2 >31 is highlighted in red. Abbreviations as in Table 1.

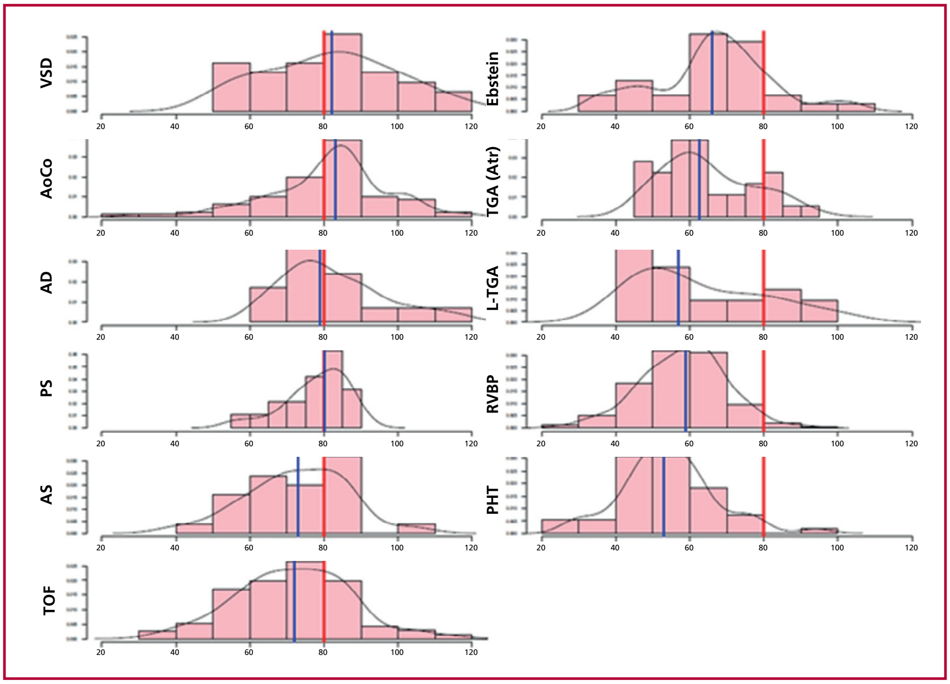

Fig. 1. Percent-predicted peak VO^2 according to the congenital heart disease Pictogram with density curve for each heart disease, where the red line indicates 80% of percent-predicted peak VO^2 and the blue line its median value.

VSD: Ventricular septal defect. AoCo: Aortic coarctation. AD: Atrial defect. PS: Pulmonary stenosis. AoS: Aortic stenosis. TOF: Tetralogy of Fallot. Ebstein: Ebstein's anomaly. TGA (atr): Transposition of the great arteries corrected with atrial switch. L-TGA: Levo-transposition of the great arteries. EVBP: Right ventricular bypass. PHT: pulmonary hypertension.

evaluation of the patient. Direct measurement of O_2 consumption is the most accurate way of evaluating functional capacity, since conventional exercise testing infers O_2 consumption through the work done. (2, 6, 10, 11).

VO_2 and VE/VCO_2 slope values have been correlated with long-term risk of mortality in adults with congenital heart diseases. In this sense, increased risk has been found with low VO_2, low HR reserve and high VE/VCO_2 in non-cyanotic heart diseases. (12)

According to the work of Guazzi et al., patients with heart failure who have peak VO_2 greater than 20 ml/kg/min and VE/VCO_2 slope less than 30 are considered to be >90% free of events between 1 to 4 years. (5) We apply these limit values to patients with congenital heart diseases, since, according to Diller et al. (13), the peak VO_2 in patients with isolated heart failure and in carriers of congenital heart diseases correspond to the same NYHA functional class.

Having reference values for the most significant CPET variables is very important, since the physiology of each heart disease is different and the limit of 20 ml/kg/min suggested for heart failure is insufficient to interpret a CPET in congenital heart diseases. We estimate that the percent-predicted peak VO_2 is a more specific variable, since 25 ml/kg/min is not the same for a 45-year-old woman as for a 25-year-old man.

In tetralogy of Fallot (the most frequent cyanotic heart disease), it is relevant to be able to determine when the pulmonary valve has to be changed and to evaluate functional capacity after its replacement. The exercise tolerance of these patients is quite good (12, 14, 15), but it decreases according to right ventricular function impairment, which dilates, mainly, in severe pulmonary valve insufficiency. (16) Several works have correlated the values obtained in CPET with the risk of morbidity and mortality, and have pointed out peak VO_2, percent-predicted peak VO_2 and VE/VCO_2 slope as the best risk indicators. (12, 14, 15)

In the venous ventricle or subpulmonary bypass, a lower peak VO2 is observed than in most heart diseases, on average 27±7 ml/kg/min (61±15% of predicted value), according to Ohuchi et al (17), since patients must maintain cardiac output without a right pump (10, 17, 18, 19). A high VE/VCO_2 is also observed (17, 18, 19), which, in principle, is justified by the decrease in O_2 % saturation during exercise these patients have due to a right to left shunt through the fenestration, in addition to presenting altered ventilation/perfusion at rest (10). However, it may also indicate system dysfunction and the probability of associated pulmonary hypertension, considering these two variables (VO_2 and VE/VCO_2) as risk predictors.

Congenital heart diseases in which the right ventricle serves as systemic pump, i.e. D-TGA corrected with atrial switch (20) and L-TGA, have low peak VO_2 and high VE/VCO_2 compared with other pathologies. For this reason, it is important to be able to confront them with the results obtained from their peers.

Regarding D-TGA operated with arterial switch, our casuistry is scarce (for this age group) because it is a more recent technique, and the results of CPET are low; however, it was included for being a relevant pathology. It has been studied by other authors with dissimilar results, in some cases with excellent values (21) and in others with a decrease in VO_2 (22, 23), generally attributed to residual obstructive pathology of the right ventricular outflow tract.

Pulmonary hypertension is clearly the pathology in which the poorest peak VO_2 and the highest VE/VCO_2 slope results are obtained. In this case, CPET is essential for diagnosis and a requirement for treatment evaluation at follow-up. (24, 25)

Coarctation of the aorta has very good functional capacity, one of the best in the spectrum of congenital heart diseases, according to some articles. (1, 12, 13, 26) Regarding simpler heart defects, we have a higher proportion of complex patients in our laboratory, but with a lower average age compared with other centers.

These and other important differences observed in the population of patients with congenital heart diseases further highlight the need for their own reference values, to optimize the adequate interpretation of these valuable data obtained by performing a cardiopulmonary exercise test.

Study limitations

It was decided to randomly include all the studies performed for each heart disease, as we assumed that this would improve the work. The studies were carried out over the years, and since in patients with congenital heart diseases functional capacity deteriorates, if we had only included the last exercise test, the one with the best results, when the patient was younger, would have been lost. That was the criteria, pathology and age,

CONCLUSION

Reference CPET values for the different congenital heart diseases are essential, since they allow us to compare patients with the same pathology.

The percent-predicted peak VO_2 seems to be the most useful variable for this purpose.

Conflicts of interest

None declared.

(See authors' conflicts of interest forms on the website/ Supplementary material)

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