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 de 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)
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), levocardia-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 O2% saturation, and breath-by-breath exhaled gas analysis, using the COSMED Quark CPET system (Rome, Italy).

The following variables were analyzed:
- VO2 max (ml/kg/min): peak O2 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 VO2 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 CO2 and VO2. 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/VCO2 slope: is the relationship between pulmonary ventilation (VE) and carbon dioxide (CO2) 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/VCO2. 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/kg/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 VO\textsubscript{2} 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/VCO\textsubscript{2} 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 per- cent-predicted peak VO\textsubscript{2} according to each congenital heart disease.

### DISCUSSION

Fitness for physical exercise is related to the ability of the cardiovascular system to supply O\textsubscript{2} to the muscles and the ability of the lung system to remove CO\textsubscript{2} from the blood through the lungs. (2, 6, 9, 10)

Exercise testing with direct measurement of O\textsubscript{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\textsubscript{2} and percent-predicted peak VO\textsubscript{2}

<table>
<thead>
<tr>
<th>Variable</th>
<th>AGE (years)</th>
<th>PEAK VO\textsubscript{2} (ml/kg/min)</th>
<th>%-PREDICTED VO\textsubscript{2} (ml/kg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VSD (31)</td>
<td>27.5 + 10.1</td>
<td>58.9 + 9.7</td>
<td>NS</td>
</tr>
<tr>
<td>AoCo. (91)</td>
<td>23.2 + 8</td>
<td>58.9 + 9.7</td>
<td>NS</td>
</tr>
<tr>
<td>AD (29)</td>
<td>22.7 + 11</td>
<td>58.9 + 9.7</td>
<td>NS</td>
</tr>
<tr>
<td>PS. (19)</td>
<td>22.2 + 4.5</td>
<td>58.9 + 9.7</td>
<td>NS</td>
</tr>
<tr>
<td>AoS. (25)</td>
<td>24.6 + 9.4</td>
<td>58.9 + 9.7</td>
<td>NS</td>
</tr>
<tr>
<td>Fallot (293)</td>
<td>25.5 + 8.1</td>
<td>58.9 + 9.7</td>
<td>NS</td>
</tr>
<tr>
<td>Ebstein (31)</td>
<td>26.1 + 12.5</td>
<td>58.9 + 9.7</td>
<td>NS</td>
</tr>
<tr>
<td>TGA (art.) (5)</td>
<td>19.5 + 2.1</td>
<td>58.9 + 9.7</td>
<td>NS</td>
</tr>
<tr>
<td>TGA (atrial) (36)</td>
<td>28.2 + 7.2</td>
<td>58.9 + 9.7</td>
<td>NS</td>
</tr>
<tr>
<td>L-TGA (21)</td>
<td>29 + 12.9</td>
<td>58.9 + 9.7</td>
<td>NS</td>
</tr>
<tr>
<td>By pass (163)</td>
<td>23 + 5.5</td>
<td>58.9 + 9.7</td>
<td>NS</td>
</tr>
<tr>
<td>PHT (55)</td>
<td>22.1 + 8.2</td>
<td>58.9 + 9.7</td>
<td>NS</td>
</tr>
</tbody>
</table>

The percent-predicted peak VO\textsubscript{2} for mild, moderate and severe congenital heart disease is highlighted in deep red, red and light red, respectively.


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

<table>
<thead>
<tr>
<th>Variable</th>
<th>EXERCISE DURATION (seconds)</th>
<th>p</th>
<th>R M and F</th>
<th>VE/VCO\textsubscript{2} M and F</th>
</tr>
</thead>
<tbody>
<tr>
<td>VSD (31)</td>
<td>718.6 + 183</td>
<td>NS</td>
<td>1.15 + 0.1</td>
<td>29.5 + 5.1</td>
</tr>
<tr>
<td>AoCo. (91)</td>
<td>766 + 147</td>
<td>0.0000</td>
<td>1.16 + 0.1</td>
<td>29.8 + 5.5</td>
</tr>
<tr>
<td>AD (29)</td>
<td>769.9 + 140</td>
<td>0.02</td>
<td>1.14 + 0.1</td>
<td>29.5 + 5</td>
</tr>
<tr>
<td>PS. (19)</td>
<td>793 + 76</td>
<td>0.002</td>
<td>1.12 + 0.08</td>
<td>30.7 + 4.4</td>
</tr>
<tr>
<td>AoS. (25)</td>
<td>726.4 + 142</td>
<td>NS</td>
<td>1.1 + 0.1</td>
<td>28.2 + 4.6</td>
</tr>
<tr>
<td>Fallot (293)</td>
<td>692.9 + 144.4</td>
<td>0.0000</td>
<td>1.11 + 0.12</td>
<td>29.6 + 5.2</td>
</tr>
<tr>
<td>Ebstein (31)</td>
<td>722.8 + 114.8</td>
<td>0.0004</td>
<td>1.15 + 0.08</td>
<td>35.6 + 9.6</td>
</tr>
<tr>
<td>TGA (atrial) (5)</td>
<td>706 + 147.2</td>
<td>0.01</td>
<td>1.12 + 0.1</td>
<td>36.1 + 7.2</td>
</tr>
<tr>
<td>TGA (atrial) (36)</td>
<td>580.8 + 170.2</td>
<td>NS</td>
<td>1.12 + 0.1</td>
<td>32.6 + 5.5</td>
</tr>
<tr>
<td>L-TGA (21)</td>
<td>604.2 + 173.9</td>
<td>NS</td>
<td>1.1 + 0.1</td>
<td>33.5 + 6.2</td>
</tr>
<tr>
<td>By pass (163)</td>
<td>598.9 + 149</td>
<td>0.0002</td>
<td>1.1 + 0.1</td>
<td>36.9 + 10.4</td>
</tr>
<tr>
<td>HTP (55)</td>
<td>534.9 + 168.3</td>
<td>0.01</td>
<td>1.06 + 0.12</td>
<td>38.8 + 12.3</td>
</tr>
</tbody>
</table>

VE/VCO\textsubscript{2} >31 is highlighted in red. Abbreviations as in Table 1.
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 systemic 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,
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