Comparison of peak oxygen uptake and VE/VCO$_2$ slope, between children with and without heart failure

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Abstract

Heart failure is a health problem associated with disability and mortality. Physicians may stratify the risk of adult patients with heart failure using a cardiopulmonary exercise testing. Until now, in childhood this evaluation has been poorly used. The purpose of this study is to compare the peak oxygen uptake and minute ventilation/carbon dioxide production slope among children with heart failure versus children without heart disease (control). **Methods:** *Thirty-eight children with heart failure were compared with 194 children without heart disease. All of them performed cardiopulmonary exercise testing using a symptom-limited ramp protocol. Differences between groups were compared using Chi-squared test, Student's t test, or ANOVA. Any value of p < 0.05 was considered significant.* **Results:** *Children with heart failure were older, taller, and with a higher prevalence of male gender. This group had also a lower peak oxygen uptake (27 ± 10 ml O$_2$/kg/min) compared to the control group (37 ± 10 ml O$_2$/kg/min); p < 0.001. The minute ventilation/carbon dioxide production was higher in the heart failure group (31 ± 4) than in controls (28 ± 6); p < 0.001.* **Conclusion:** *Children with heart failure showed lower peak oxygen uptake and higher minute ventilation/carbon dioxide production slope than the control group.* (Gac Med Mex. 2016;152:656-61)

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Introduction

Heart failure (HF) is a clinical syndrome that is accompanied by left ventricular dysfunction, usually progressive, and is the final stage of most heart diseases. HF has elevated mid- and short-term mortality, and is closely associated with poor quality of life[1]. HF clinical presentation often varies with regard to age group and is the result of pathophysiological imbalances between circulatory, neuro-hormonal and molecular phenomena[2]. All this ends up in the heart being unable to satisfy tissue metabolic oxygen demand[3].

Currently, patients can benefit from different treatment options, which may include electrotherapy devices, ventricular support or heart transplantation[4]. The limited number of heart donors makes for risk stratification in probable graft receptors to be imperative[5]. To that end, new tools have been generated that can assess these patients either from an anatomical-functional

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point of view by imaging methods, or from a biochemical-metabolic perspective by using different techniques, such as cardiopulmonary exercise test (CPET)[6]. In adults, this test is widely used for HF risk stratification, and the variables with higher prognostic power[7-9] are low peak oxygen uptake (VO_2) and elevated minute ventilation/carbon dioxide production (VE/VCO_2) slope.

Since its origins, the study of children with HF has fallen behind of that in the adult population. Although HF first clinical description was published by Francesco Ippolito Albertini in his work *Affectionibus cordis* in 1726[10], it was until 100 years later when HF symptoms were described in children[4]. Clinical practice guidelines for diagnosis and management of the child with HF mention that, in contrast with adults, CPET is an underused tool. This is due, in part, to its application in this age group being relatively recent, and evidence on its prognostic capacity is still limited[4-6,11]. We didn't find any study in the literature comparing CPETs of children with HF with those of children without heart disease.

The purpose of this study was to compare cardiopulmonary performance, as objectively measured with the VO_2 peak and VE/VCO_2 values in children with HF and children without heart disease (controls).

Material and methods

A group of children with HF and low left ventricular ejection fraction (LVEF < 50%) was referred from the pediatric cardiology department to the cardiac rehabilitation department for the performance of a CPET. For each case, informed consent was obtained from the parents or legal guardians of each child, who were present during the tests.

A Schiller CS200® equipment and a treadmill (Trackmaster®) were used with a ramp-type incremental workload effort protocol, the characteristics of which have already been published in detail[10]. Prior to the test, a standard 12-lead electrocardiogram was obtained and a spirometry at rest was performed. The leads for the electrocardiographic record were placed according to the Mason Likar scheme and the skin was initially prepared by rubbing it with an alcohol swab, to subsequently carry out a fine desquamation of the superficial skin layer by means of sandpaper. Skin electric impedance was corroborated to be lower than 5,000 Ω prior to performing each test. Heart rate (HR) and blood pressure were recorded at rest, every minute during the effort test and at 1, 3, 5 and 8 minutes of recovery. A calibrated aneroid sphygmomanometer

was used and the size of the cuff was adequate to the circumference of the child's arm[12]. The presence of arrhythmias, abnormalities of the ST segment or conduction alterations was recorded.

For the CPET, a gas analysis automated equipment (PowerCube®) was used, which measured the volume, expired air flow and oxygen and carbon dioxide fractioned concentration. The equipment was calibrated before each test according to the manufacturer's specifications. The gas measurement was carried out ventilation to ventilation, with an average being recorded every 30 seconds. A face mask was used for the collection of expired air, with adequate size for each patient, making sure for leaks not to occur during the test. The CPET started with a 3-minute period of rest, where cardiopulmonary variables baseline measurements were recorded. Subsequently, all children underwent the same effort protocol, with an estimated increase of 1 MET per minute[7,10,13]. Parents were asked to encourage their children to put forth the maximum physical effort. Once maximum effort was reached, the children continued walking for 3 minutes at a velocity of 2 km/h and with no inclination. Subsequently, all children rested in the supine position for 5 additional minutes. In all cases, there was a defibrillator and full cardiopulmonary resuscitation equipment available in the room.

HR was directly obtained from the electrocardiographic signal and its value at rest was recorded after the child remained seated for 3 minutes. Peak HR was the highest value observed during exercise. Reserve HR was calculated by subtracting rest HR from peak HR. HR recovery was obtained by subtracting HR during the first minute of recovery from peak HR. Predicted maximum HR (theoretical) was calculated according to an adequate formula for pediatric population[10]. The exercise systolic blood pressure index was calculated by dividing systolic blood pressure (SBP) during maximum effort by SBP at rest. SBP recovery was obtained by dividing third-minute SBP by SBP at first minute of recovery. Myocardial oxygen consumption was indirectly calculated based on the double product (HR x SBP).

During the CPET, the following variables were recorded: minute volume (VE), respiratory quotient, VO_2 peak, aerobic-anaerobic threshold, VE/VCO_2 slope, time for VO_2 recovery and cardiac power during exercise[14].

Statistical analysis

Data obtained in the cases with HF were compared with those corresponding to the control group of children

Table 1. Demographic characteristics of patients with HF and children without heart disease

Variables	All	HF	No heart disease	p
Patients (n)	232	38	194	–
Age (years)	11.7 ± 4	13.7 ± 4	11.3 ± 4	< 0.01
Males (n, %)	135 (58%)	15 (40%)	120 (62%)	< 0.05
Weight (kg)	45 ± 20	46.8 ± 18	44.7 ± 20	ns
Height (m)	1.47 ± 0.22	1.54 ± 0.2	1.46 ± 0.22	< 0.05
BMI (kg/m^2)	19.7 ± 4	18.8 ± 4	19.8 ± 4	NS
LVEF (%)	53 ± 17	35 ± 12	64 ± 6	< 0.001

Variables expressed as the mean ± standard deviation or as frequency and percentage, as appropriate.
The p-value corresponds to the comparison between patients with heart failure and children without heart disease.
HF: heart failure; BMI: body mass index: LVEF: left ventricular ejection fraction; NS: not significant.

without heart disease[10]. Nominal and categorical variables were presented as frequencies and percentages, and compared using the chi-square test or Fisher's exact test. Continuous variables with normal distribution were presented as the mean and standard deviation. The t-test was used for independent samples and one-way ANOVA was used to compare those continuous variables with Gaussian distribution (Kolmogorov-Smirnov test), whereas those without normal distribution were compared with Mann-Whitney's U-test. The variables were studied by means of scatter plots and a bivariate analysis was performed. The r and p values were obtained with Pearson's test. P values < 0.05 were considered to be statistically significant.

Results

A total of 38 patients with HF were compared with a group of 194 children without heart disease. Demographic characteristics of both groups are presented in table 1. Statistically, the children with HF had higher age, height and male gender prevalence. LVEF was significantly lower in the children with HF. Table 2 shows prevalent heart diseases in the group of patients with HR and the medication they received. The most frequently observed underlying heart condition was idiopathic dilated cardiomyopathy (68%), followed by acyanogenic (21%) and cyanogenic congenital heart disease (11%).

When the children's cardiovascular behavior during CPET was assessed (Table 3), patients with HF were observed to experience significant deterioration of exercise time (23%), peak HR (12%), reserve HR (17%), HR recovery (23%), SBP response (24%) and Veterans

Table 2. Patients with HF: associated heart conditions and treatment

Variables	n (%)
Patients	38 (100%)
Associated pathologies	
– Idiopathic dilated cardiomyopathy	26 (68%)
– Acyanogenic congenital heart disease	8 (21%)
– Cyanogenic congenital heart disease	4 (11%)
Medication	
– ACEI	26 (68%)
– Spironolactone	24 (63%)
– Beta-blocker	19 (50%)
– Loop diuretics	16 (42%)
– Digoxin	16 (42%)
– Platelet antiaggregant	13 (34%)
– Antiarrhythmic drugs	5 (13%)
– Nitrates	2 (5%)
– Lipid-lowering agents	1 (3%)

ACEI: angiotensin-converting enzyme inhibitor.

and Duke scores in comparison with the control (CTRL) group. Patients with HF also showed a stochastically significant decrease in VO_2, both in the aerobic-anaerobic threshold (20%) and at maximum effort (27%), as well as higher VE/VCO_2 slope (11%) and more prolonged post-effort VO_2 recovery (43%) (Figures 1 and 2).

Discussion

Heart failure in children is a health problem. Some studies show that heart conditions account for 61% of hospital discharges in the pediatric population, and that 82% of them had a HF diagnosis[15]. Furthermore,

Table 3. Cardiopulmonary behavior comparison between children with HF and controls without heart disease. The observed differences between both groups are statistically significant for most results, particularly in survival prognostic variables such as exercise time, VO_2 peak, VE/VCO_2 slope and Duke and Veterans ergometric scores

Groups	HF	No heart disease	p
Exercise time (min)	8 ± 3	10.5 ± 2	< 0.001
Rest HR (bpm)	85 ± 15	90 ± 17	NS
Peak HR (bpm)	159 ± 24	179 ± 16	< 0.001
Rest SBP (mmHg)	92 ± 11	97 ± 16	< 0.01
Peak SBP (mmHg)	114 ± 25	128 ± 25	< 0.01
Rest DBP (mmHg)	62 ± 8	62 ± 13	NS
Peak DBP (mmHg)	73 ± 13	73 ± 14	NS
Rest DP (bpm*mmHg*1000)	7.8 ± 1.7	8.7 ± 1.9	< 0.01
Peak DP (bpm*mmHg*1000)	18.4 ± 5.5	23.2 ± 5.3	< 0.01
Reserve HR (bpm)	74 ± 24	89 ± 22	< 0.001
HR recovery (bpm)	24 ± 14	31 ± 13	< 0.01
SBP response	1.25 ± 0.2	1.33 ± 0.2	< 0.05
SBP recovery	0.98 ± 0.1	0.92 ± 0.1	< 0.01
VA score	-1.45 ± 4.2	−10.2 ± 4	< 0.001
Duke score	7.6 ± 4	10.4 ± 3	< 0.001
Peak RQ	1.11 ± 0.1	1.12 ± 0.1	NS
VO_2 AAT (ml/kg/min)	21.1 ± 9	26.4 ± 8	< 0.001
VO_2 peak (ml/kg/min)	27 ± 10	37 ± 10	< 0.001
VE/VCO_2 slope	31 ± 4	28 ± 6	< 0.01
MVO_2 (mlO_2/kg/100 g)	19.5 ± 8	26.1 ± 7	< 0.001
RVO_2 (s)	201 ± 86	140 ± 94	< 0.001

HF: heart failure; HR: heart rate; bpm: beats per minute; NS: non-significant; SBP: systolic blood pressure; DBP: diastolic blood pressure; DP: double product; VA: Veterans; RQ: respiratory quotient; VO_2: maximum oxygen uptake; AAT: aerobic-anaerobic threshold; VE/VCO_2: ventilation-carbon dioxide production slope; MVO_2: myocardial oxygen consumption; RVO_2: oxygen uptake recovery.

children with chronic HF are at high risk of mid-term mortality and CPET is a highly useful tool for their stratification. This is the first study to compare CPET results in patients with HF and children without heart disease.

Initially, we demonstrated that maximum and symptom-limited CPETs can be safely and effectively performed in children, even up to 4 years of age. Additionally, we could observe that there is clear cardiopulmonary performance deterioration during exercise in children with HF in comparison with their peers without heart disease.

There are two published studies assessing CPET usefulness in children with HF. The first one was a study conducted by Guimarães et al.[16] where a group of children with HF was assessed by means of CPET, and they were grouped with regard to the incidence or not of any combined clinical outcome (death or heart transplantation). The second study was carried out by Giardini et al.[5], who studied the association of CPET variables with long-term prognosis (32 months). None of these authors compared their results with a control group.

In our study population, patients with HF carried out less workload (treadmill exercise time) than the children in the control group, which was also lower than findings published by Guimarães et al.[16], since they reported up to 19 minutes of exercise, in contrast with 8 minutes observed in our patients. This phenomenon
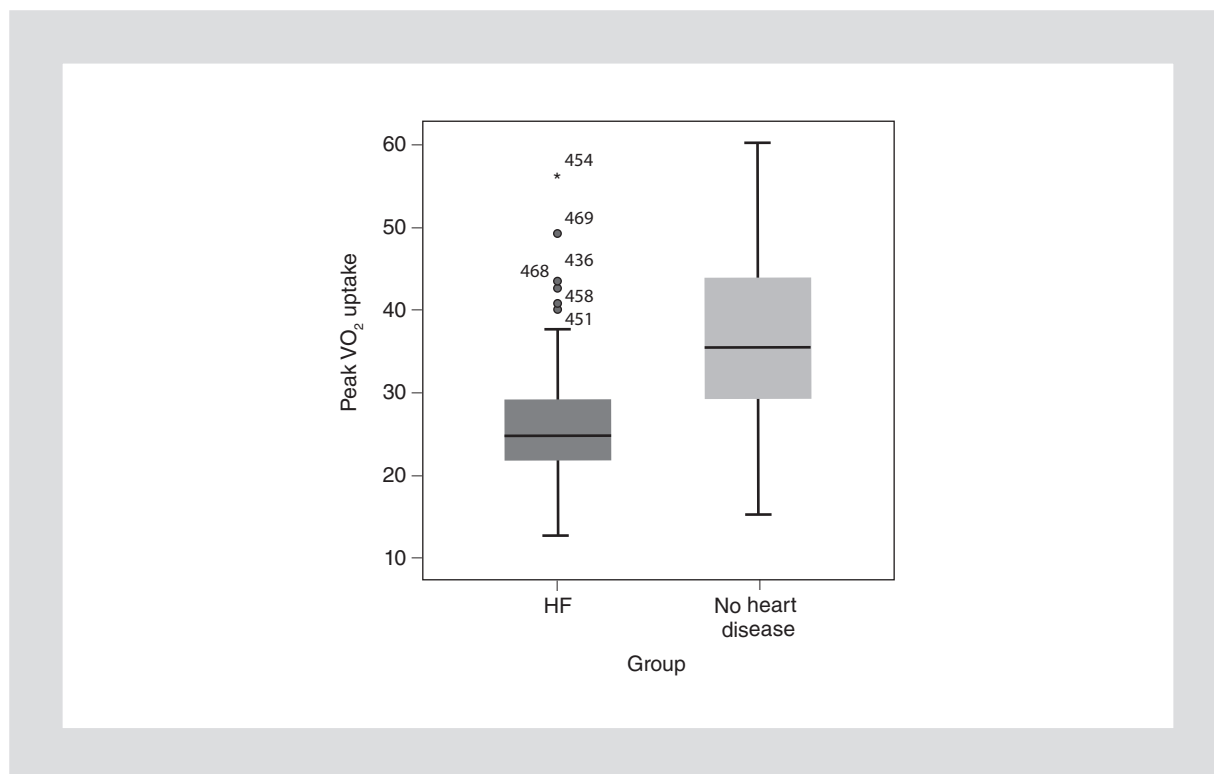
Figure 1. *VO$_2$ peak comparison between children with HF and children without heart disease. Patients with HF showed statistically lower VO$_2$ peak values in comparison with the control group (p < 0.001).*
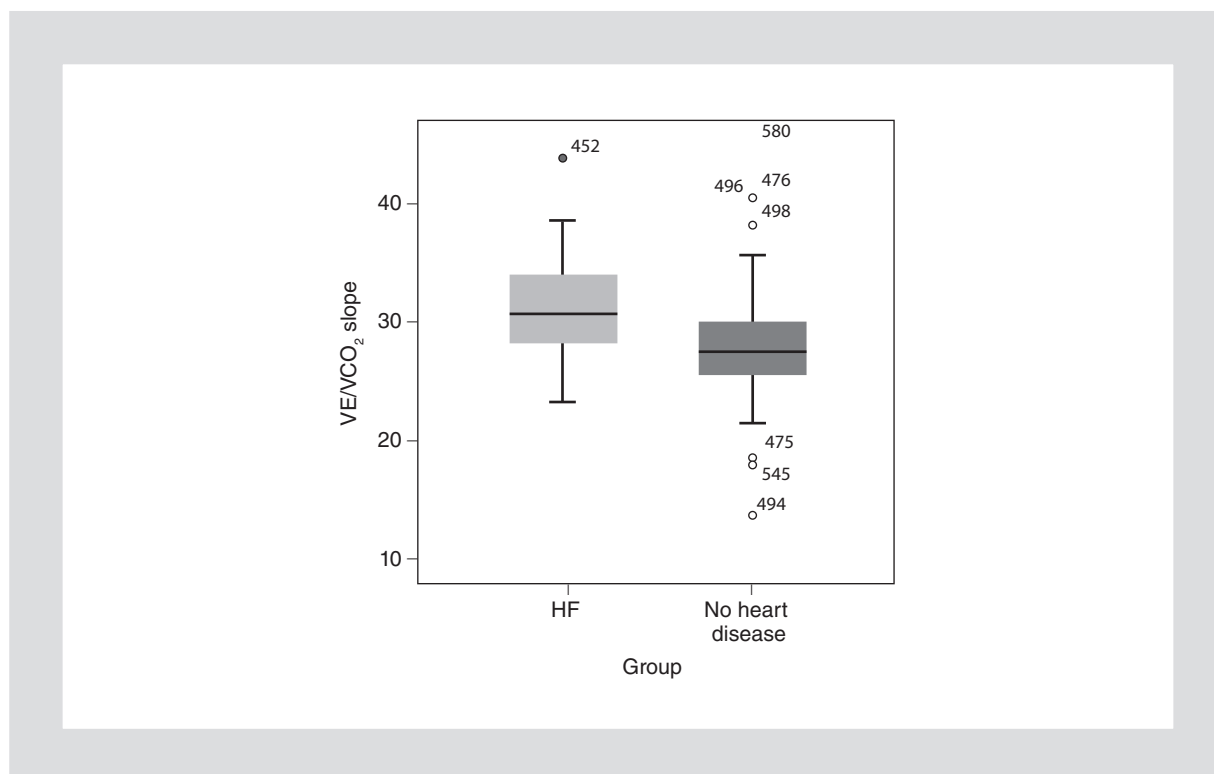
Figure 2. *VE/VCO$_2$ slope comparison between children with HF and children without heart disease. Patients with HR showed more VE/VCO$_2$ elevations than the children without heart disease (p < 0.01). This variable is usually also referred to as ventilatory efficiency.*

may be due to the fact that both the exercise protocol and patients' age were different. On the other hand, Giardini et al.[5] reported that cycle ergometer workload was around 115 watts, which is hardly comparable with the yield in treadmill tests.

With regard to HR behavior, the patients we studied had an inappropriate chronotropic response, reaching a peak HR of 159 bpm, which is intermediate to the values reported by Guimarães et al.[16] (152 bpm) and Giardini et al.[5] (163 bpm). None of the previous investigations reports the behavior of HR recovery, a variable that expresses both autonomous nervous system regulation and changes observed in oxygen debt. In this study, we observed an overt decrease of heart rate recovery (HRR) in patients with HF in comparison with controls.

When maximum exercise tolerance was analyzed, we were able to observe that patients with HF had a clear deterioration of VO_2 peak (27 mlO_2/kg/min) in comparison with controls (37 mlO_2/kg/min), which are similar values to those published by Giardini et al.[5] (28 mlO_2/kg/min), and much higher than those published by Guimarães et al.[16] (19 mlO_2/kg/min).

With regard to the prognostic value of CPET-obtained variables, there is a discrepancy between both these previously mentioned groups of investigators. On one hand, Guimarães et al.[16] showed that variables predictive of long-term outcomes are the accomplished workload (treadmill exercise time) and ejection fraction. Conversely, Giardini et al.[5] observed that VO_2 peak was the variable mortality-associated. In our study, a significant difference was observed in these three variables between the group with HF and the control group.

Thus, in this study we observed that the CPET variables identified with higher prognostic capacity were statistically different between children with HF and children without heart disease. Although variables such as exercise time and VO_2 peak have been associated with higher mortality in this group of patients, reports are still scarce and with a reduced number of cases.

The limitations of the study include its cross-sectional nature. Including more patients and continuing their mid- and long-term follow up is necessary to observe the effect of the observed results on mortality.

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