ORIGINAL ARTICLE

Cardiopulmonary Exercise Test in Heart Transplant Recipients

Prueba de ejercicio cardiopulmonar en receptores de trasplante cardíaco

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ABSTRACT

Background: Exercise capacity of patients with advanced heart failure improves after heart transplantation (HTX). Cardiopulmonary exercise test (CPET) is recognized as the "gold standard" study for the evaluation of aerobic exercise capacity.
Objective: The aim of this study was to analyze the characteristics of CPET in HTX recipients.
Methods: A cross-sectional study was performed in patients over 18 years of age undergoing HTX from November 1, 2013 to June 30, 2019, and with a CPET within the first year after transplantation. Clinical and CPET variables were analyzed.
Results: A total of 122 patients with mean age of 50.1±11.8 years and 77.0% men were included in the study. Peak oxygen consumption (VO2) was 23.3±5.3 mL/min/kg and 45.9% of patients achieved the anaerobic threshold. In 68.0% and 28.7% of cases, the population presented normal oxygen pulse and oxygen uptake efficiency slope (OUES) values, respectively. Mild, moderate, or severe reduced functional capacity was found in 46.7%, 23.0%, and 3.3% of patients, respectively. Oxygen uptake efficiency slope was low in 80.0%, 71.4% and 92.9% of patients with decreased functional capacity of cardiovascular, peripheral, and mixed origin, respectively.
Conclusion: In this population of HTX recipients, a considerable proportion of subjects showed reduced functional capacity or abnormal OUES values. The evaluation of these patients through CPET could favor early referral to cardiovascular rehabilitation centers.

Keywords: Exercise test - Heart transplantation - Oxygen consumption - OUES - Total Lung Capacity.

RESUMEN

Antecedentes: La capacidad de ejercicio de los pacientes con insuficiencia cardíaca avanzada mejora después del trasplante cardíaco (HTX). La prueba de ejercicio cardiopulmonar (PECP) es reconocida como el estudio "estándar de oro" para la evaluación de la capacidad de ejercicio aeróbico. El objetivo del estudio fue analizar las características de la PECP realizada en receptores de HTX.
Métodos: Se realizó un estudio de corte transversal. Se incluyeron pacientes mayores de 18 años receptores de HTX desde el 1 de noviembre de 2013 hasta el 30 de junio de 2019, que hubieran realizado una PECP dentro del primer año posterior al trasplante. Se analizaron variables clínicas y de la PECP.
Resultados: Se incluyeron 122 pacientes (edad media 50,1 ± 11,8 años, 77,0% hombres). El consumo de oxígeno (VO2) pico fue de 23,3 ± 5,3 mL/min/kg y el 45,9% alcanzó el umbral anaeróbico. El 68,0% y el 28,7% de la población mostró valores de pulso de oxígeno y de la pendiente de la eficiencia del VO2 (OUES) normales, respectivamente. El 46,7%, 23,0% y 3,3% presentaron una reducción leve, moderada o grave de la capacidad funcional, respectivamente. El valor de OUES fue bajo en el 80,0%, 71,4% y 92,9% de los pacientes con disminución de la capacidad funcional de origen cardiovascular, periférico y mixto, respectivamente.
Conclusión: En esta población de receptores de HTX, la proporción de sujetos con capacidad funcional reducida o valores de OUES alterados fue considerable. La evaluación de estos pacientes a través de la PECP podría favorecer la derivación temprana a centros de rehabilitación cardiovascular.

Palabras clave: Prueba de ejercicio - Trasplante cardíaco - Consumo de oxígeno -OUES - Capacidad Pulmonar Total.

REV ARGENT CARDIOL 2021;89:397-403. http://dx.doi.org/10.7775/rac.v89.i5.20437

Received: 06/11/2021 – *Accepted:* 09/30/2021

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Sources of support and funding: None

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INTRODUCTION

Cardiopulmonary exercise test (CPET) is recognized as the "gold standard" for the evaluation of aerobic exercise capacity. (1) This test identifies cardiovascular, respiratory or musculoskeletal limitations that may affect physical activity and allows monitoring the behavior of certain variables such as oxygen consumption (VO2), carbon dioxide production (VCO2), ventilation or heart rate (HR). (2) The clinical applicability of CPET has been demonstrated in various clinical scenarios, for example in congestive heart failure (CHF), pulmonary hypertension, respiratory diseases, sports evaluation or dyspnea of unknown origin. (3-5) It has also been recommended in patients with end-stage heart disease that need to be evaluated for heart transplantation (HTX). Despite great progress in the treatment of patients with advanced CHF, there is no intervention that provides a long-term survival rate and quality of life improvement comparable to HTX. During the last decades, more than 120 000 patients with CHF in the world have benefitted with this therapeutic option, prolonging life expectancy by an average of 11.9 years. (6)

Exercise capacity improves after HTX. However, in most cases, the aerobic level observed in healthy individuals of the same age is not attained. (7, 8) Allograft denervation is associated with an elevated HR at rest, a slow increase in the response to exercise and a lower HR at maximum exertion. (9) Systolic dysfunction of the transplanted left ventricle, increased wedge pressure in the pulmonary capillaries during maximum exertion, decreased oxidative capacity of muscle fibers and endothelial dysfunction of peripheral vessels have also been identified as potential associated causes of exercise capacity impairment in these patients. (10)

In this context, CPET emerges as one of the most effective noninvasive methods for risk stratification, the evaluation of the response to treatment or to guide the prescription of physical activity in HTX recipients. Several studies have previously analyzed CPET findings in HTX recipients. However, many of these studies included a reduced number of patients or reported few CPET variables. (11-15) In fact, only a limited number of studies investigated the slope of VO2 efficiency, also known as oxygen uptake efficiency slope (OUES), which has emerged as a submaximal marker of exercise intensity, integrating cardiovascular, musculoskeletal and respiratory functions in a single index that could provide relevant information in these group of patients. Similarly, we do not have local data on CPET variables in HTX recipients.

The aim of this study was thus to analyze CPET characteristics during the first 12 months after HTX.

METHODS

Design and definition of variables: A cross-sectional study using a secondary database (electronic clinical history) was carried out. The population sample was obtained from a private health center of the Autonomous City of Buenos Aires.

Patients over 18 years of age, recipients of HTX between November 1, 2013 and June 30, 2019, and with a CPET within the first year after transplantation, were included in the study. Clinical histories were reviewed and variables obtained were analyzed in the following subgroups: a) gender; b) age ((≥or< 60 years); c) functional capacity (preserved or decreased; and d) OUES (normal or abnormal).

The exercise test was performed in a treadmill (H/P Cosmos, Mercury Med, Germany), with continuous analysis of respiratory gas exchange (Quark CPET of Cosmed, OMNIA 1.6.7 software). A Bruce or modified Bruce protocol was used, selected by the operator according to the clinical condition of the patient. Dynamic electrocardiographic changes (ST-segment depression >1 mm) and arrhythmia occurrence were reported.

The variables recorded included HR, blood pressure, peripheral oxygen saturation (SpO2), VO2, VCO2 and minute ventilation (VE). The respiratory exchange ratio (RER) or VCO2/VO2 relationship was used as maximum exercise indicator. Maximum exertion was considered for RER >1.1. Peak VO2 was defined as average VO2 during the last minute of exercise, and was expressed in milliliters/minute/kilogram of body weight (mL/min/kg) and also as percent of the predicted value (according to prespecified tables that take into account age and body surface area). Functional capacity was defined as normal when peak VO2 was ≥85% of the predicted value. Similarly, functional capacity impairment was classified as mild, moderate or severe, when peak VO2 was between 65% and 84%, 50% and 64% and <50% of the predicted value, respectively. The origin of functional capacity impairment was classified as cardiovascular, respiratory, peripheral (deconditioning) or mixed (cardiovascular and peripheral).

The anaerobic threshold (AT) was identified by observing the ventilatory O2 (VE/VO2) and CO2, (VE/VCO2) equivalents. Oxygen pulse was calculated using the VO2/HR ratio and OUES was defined as the ratio between VO2 and the logarithmic transformation of VE. Oxygen pulse and OUES values were considered normal when so reported by the software based on standardized international formulas. Respiratory reserve was estimated by observing the relationship between VE during exercise and maximum voluntary ventilation (MVV) at rest, both variables expressed in L/min (a value greater than 15 L/min was considered normal).

Statistical analysis

The comparison between two groups with continuous data was performed using Student's t test and the analysis of categorical data with the chi-square test. Continuous variables were expressed as mean ± standard deviation while categorical variables were expressed as percentages.

Pearson's test and the Fleiss kappa index were used to determine the correlation and concordance between peak VO2 and OUES values, respectively. Mild or poor, acceptable or discrete, moderate, significant or almost perfect concordance was defined if the kappa value was <0.20, between 0.21 and 0.40, between 0.41 and 0.60, between 0.61 and 0.80 or between 0.81 and 1, respectively. A value of $p < 0.05$ was considered statistically significant. STATA 13.0 software package was used for statistical analysis.

Ethical considerations

The study was carried out in accordance with the Declaration of Helsinki recommendations for medical research, the standards of Good Clinical Practice and current ethical regulations. The protocol was reviewed and approved by the Institutional Ethics Committee.

RESULTS

A total of 122 patients with mean age of 50.1±11.8 years and 77.0% men were included in the study. The main causes of HTX were idiopathic dilated cardiomyopathy (35.2%), ischemic-necrotic heart disease (30.3%), and Chagas disease (8.2%). The prevalence of type 2 diabetes mellitus was 12.3% and 36.9% of the patients were hypertensive. Table 1 shows population characteristics.

Cardiopulmonary exercise test results presented average peak VO2 of 23.3±5.3 mL/min/kg (73.8%±15.2% of the predicted value) and 45.9% of patients reached the AT (the mean value at which the AT was detected was 55.1%±11.9% of predicted VO2). The VE/VCO2 slope was 33.7±7.1. Moreover, 68.0% and 28.7% of the population showed normal oxygen pulse and OUES values, respectively. In 27.0% of cases, the patients evidenced preserved functional capacity, while 46.7%, 23.0% and 3.3% showed mild, moderate or severe reduction in functional capacity. Total population CPET characteristics can be seen in Table 2.

In the analysis according to gender, women exhibited lower peak VO2 values (20.5±4.2 vs. 24.1±5.3 mL/min/kg, p=0.001), oxygen pulse (10.5±4.8 vs. 14.2±4.0, p <0.001) and OUES (1708.6±526.0 vs. 2221.3±541.1, p <0.001), compared with men. However, the peak VO2 with respect to the predicted (80±15.7% vs. 72±14.6%, p=0.013) and the proportion of HTX recipients with a normal oxygen pulse (89% vs. 62%, p=0.006) was higher in women.

According to age, patients under 60 years of age were able to exercise longer (10.3±2.6 minutes vs. 8.8±2.3 minutes, p=0.008), but reached lower peak VO2 values compared with those predicted (71.5±14.9% vs. 82.3±13.6%, p=0.001) and presented less frequently a preserved functional capacity (23% vs. 42%, p=0.04) compared with subjects 60 years of age or older.

Table 1. Population characteristics

	Total population n = 122
Continuous variables , mean (SD)	
Age, years	50.1 (11.8)
Body mass index, kg/m^2	26.7 (3.9)
Categorical variables, %	
Male gender	77.0
Type 2 diabetes	12.3
Hypertension	36.9
Active smoking	9.8
Dyslipidemia	23.8
Obesity	18.9
Chronic kidney failure	3.3
Chronic obstructive pulmonary disease	2.5
Peripheral vascular disease	0.8

SD: Standard deviation

Subjects with decreased functional capacity were younger and evidenced a higher body mass index with respect to patients with preserved functional capacity. Similarly, patients with decreased OUES values were younger compared with patients with normal OUES values, with no difference in other baseline variables (Table 3).

Peak VO2 and OUES values were moderately correlated (Pearson's r coefficient 0.61). A moderate concordance was found between preserved functional capacity and normal OUES value (kappa 0.51). This concordance was higher in women (kappa 0.62) with respect to men (kappa 0.46). Furthermore, concordance was lower in subjects <60 years (kappa 0.43) compared with patients ≥60 years (kappa 0.68).

Oxygen uptake efficiency slope was low in 80.0%, 71.4% and 92.9% of patients with decreased functional capacity of cardiovascular, peripheral, and mixed origin, respectively. No patient presented respiratory functional capacity impairment. It is interesting to note that one third of patients with preserved functional capacity presented a decreased OUES value (33.3% vs. 85% in subjects with decreased functional capacity, p <0.001). Figure 1 describes the relationship between functional capacity and OUES.

DISCUSSION

This study shows for the first time the analysis of multiple CPET characteristics in the HTX recipient population of our region.

Exercise capacity improves after HTX if we consider the previous physical fitness of patients with advanced CHF. However, it is not possible to reach the levels observed in healthy individuals of the same age group. (16, 17). Most studies report that peak VO2 levels recorded in HTX recipients range between 50% and 70% of the general population, and that this decrease in peak VO2 levels is associated with a worse prognosis. (18) Few studies have reported that HTX recipient populations reach a peak VO2 close to normal levels. (19, 20) Multiple pathophysiological mechanisms of central or peripheral origin could explain the reduction in exercise capacity observed in these patients. (10)

Our study showed, firstly, that a large proportion of HTX recipients exhibited functional capacity impairment during the first year after transplantation; secondly, that in almost half of the cases the cause for this dysfunction was mixed (cardiovascular and peripheral) and, thirdly, that approximately two-thirds of the patients presented low OUES values.

Previous studies have shown that women with CHF have a lower peak VO2 than men and that female gender predicts a lower peak VO2 level after HTX. (21). Differences in peak VO2 values between genders could be explained by several mechanisms, including lower hemoglobin levels, a higher percentage of body fat, and a smaller heart size in women. (22) However, Uithoven et al. showed that women improved their physical fit-

Table 2. Cardiopulmonary exercise test characteristics in the total population

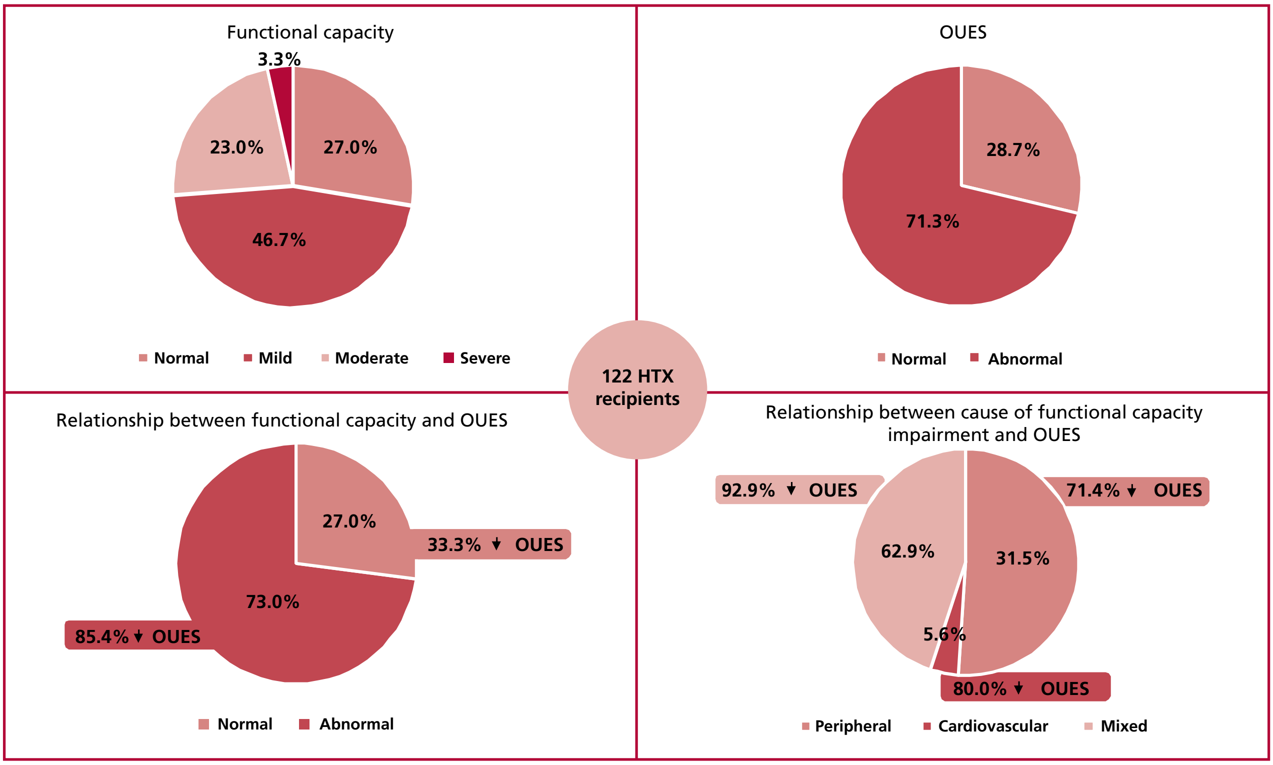
Continuous variables, mean (SD)	
Exercise time, minutes	10.0 (2.6)
METs	6.6 (1.5)
Peak VO_2, mL/min/kg	23.3 (5.3)
% peak VO_2 predicted	73.8 (15.2)
Oxygen pulse	13.4 (4.5)
OUES	2102.7 (577.8)
VE/VO_2 slope	33.7 (7.1)
O_2 saturation at maximal exertion, %	97.0 (1.9)
Categorical variables, %	
Modified Bruce protocol	88.0
Usual Bruce protocol	12.0
RER >1.1	45.5
Dynamic ST changes	0.9
Arrhythmias	38.4
Normal blood pressure behavior	76.8
Normal heart rate behavior	98.2
Symptoms during the study	15.3
Normal oxygen pulse	68.0
Normal OUES	28.7
Anaerobic threshold reached	45.9
Normal ventilatory reserve.	99.2
Preserved functional capacity.	27.0

SD: Standard deviation. METs: Metabolic equivalents. OUES: Oxygen uptake efficiency slope. O_2: Oxygen. RER: Respiratory exchange ratio. VO_2: Oxygen consumption; VE: Minute ventilation.

Table 3. Characteristics of the population according to functional capacity and OUES value

	Preserved functional capacity n=33	Impaired functional capacity n=89	p	Normal OUES n=35	Low OUES n=87	p
Continuous variables, mean (SD)						
Age, years	55.1 (8,3)	48.2 (12.4)	0.004	55.3 (9.2)	48.0 (12.2)	0.002
Body mass index, kg/m²	27.9 (3.9)	23.3 (3.8)	0.04	26.2 (3.6)	26.9 (4.0)	0.35
Categorical variables, %						
Male gender	66.7	80.9	0.09	71.4	79.3	0.35
Type 2 diabetes	13.4	9.1	0.55	17.1	10.3	0.56
Hypertension	33.3	38.2	0.62	31.4	39.1	0.43
Active smoking	3.0	12.4.	0.21	8.6	10.3	0.83
Dyslipidemia	21.1	24.7	0.68	20.0	25,3	0.53
Obesity	24.2	16.9	0.35	11. 4	21.8	0.18
Chronic kidney failure	6.3	2.3	0.28	5.7	2.3	0.34
Chronic obstructive pulmonary disease	0	3.4	0.54	2.9	2.3	0.85
Peripheral vascular disease	0	1.1	0.72	0	1.2	0.52

SD: Standard deviation. OUES: Oxygen uptake efficiency slope



HTX: heart transplant

Fig. 1. Relationship between functional capacity and oxygen uptake efficiency slope (OUES)

ness after HTX in a similar way to men. (23) In contrast to that study, our results showed that women had lower peak VO2, pulse oxygen, and OUES values.

In the general population, there is a decrease in exercise capacity throughout life, that has been growing in recent years. (24) However, in our study, HTX recipients under 60 years of age were able to exercise longer but achieved a lower peak VO2 value with respect to the predicted one, and less frequently showed a preserved functional capacity compared with patients over 60 years.

A limited number of studies have investigated OUES values in HTX recipients. Baba et al. introduced OUES for the first time as an alternative and independent parameter of maximal physical exertion. (25) Later studies suggested that this submaximal parameter could substitute peak VO2. (26) Oxygen output efficiency slope represents the rate of VO2 increase in response to VE during incremental exercise, indicating how efficiently oxygen is removed and delivered to the body. In other populations, such as those with coronary heart disease, CHF, and congenital heart disease, OUES has been identified as a prognostic factor for morbidity and mortality. (27-29) Our study showed that a large proportion of subjects maintained low OUES values. Similarly, Van Laethem et al. reported that OUES values improved significantly after HTX, but, similarly to other parameters, it remained considerably impaired. (30). Our findings showed that although the correlation between OUES and peak VO2 was acceptable, the agreement was moderate. In other words, some patients with preserved functional capacity could have an abnormal OUES value, and vice versa.

The fact that OUES is a submaximal parameter could be useful in HTX recipients who, due to multiple mechanisms, cannot complete a maximal stress test. The proportion of subjects with altered OUES value was similar in patients with decreased functional capacity of different origins and, interestingly, one third of patients with normal functional capacity also showed a decreased OUES value. We cannot establish with certainty the origin of this finding, but we can speculate that it is related to several factors inherent to the pathophysiology of transplanted patients one year after surgery. Given that OUES integrates cardiac and pulmonary function into one variable, its post-transplant alteration could be related to incomplete recovery of static and dynamic lung function after cardiac surgery (31), to residual myopathy of CHF syndrome (32), to inadequate chronotropic response typical of surgical denervation and incomplete postoperative reinnervation (which tends to be completed 2 years after transplantation), (33, 34) or be associated with the characteristics of the hemodynamic response to exercise typical of post HTX patients. (35)

Early identification of subjects with decreased functional capacity and/or low OUES values could favor the indication of a therapy based on cardiovascular rehabilitation. (36) Two randomized studies have shown that training with high intensity intervals improves peak VO2 and muscle exercise capacity in HTX recipients, (37, 38) and a meta-analysis has reported similar findings. (39)

Our study has several limitations. Firstly, as it is a cross-sectional study, the possibility of biases (mainly selection biases) that may influence the results cannot be ruled out. Secondly, this study included a moderate number of patients. Thirdly, our study was not designed to evaluate the prognostic value of the CPET variables. Future studies will have to analyze this aspect. Finally, data on other clinical variables and pharmacological treatments could not be reliably obtained retrospectively, and therefore, could not be included in the analysis. Beyond these limitations, our findings could be relevant since they show that a significant proportion of HTX recipients persist with a decrease in their functional capacity estimated by a maximum parameter (peak VO2) and, in addition, they present a reduced submaximal indicator of exercise (OUES).

CONCLUSION

For the first time in our country, we describe CPET characteristics in HTX recipients. The proportion of subjects with reduced functional capacity was considerable and the measurement of a submaximal parameter such as the OUES was also frequently altered. Submaximal indicators of functional capacity may be useful in HTX recipients, which may be deconditioned by their clinical condition. The evaluation of patients with this method could favor their early inclusion in a cardiovascular rehabilitation program.

Conflicts of interest

None declared.

(See authors' conflict of interests forms on the web/Additional material.)

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