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Determinants of peak VO_2 in heart transplant recipients

Determinantes do pico de VO_2 em transplantados cardíacos

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Abstract

Objective: **To establish the determinants of the peak VO_2 in heart transplant recipients.**

Methods: **Patient's assessment was performed in two consecutive days. In the first day, patients performed the heart rate variability assessment followed by a cardiopulmonary exercise test. In the second day, patients performed a resting echocardiography. Heart transplant recipients were eligible if they were in a stable condition and without any evidence of tissue rejection diagnosed by endomyocardial biopsy. Patients with pacemaker, noncardiovascular functional limitations such as osteoarthritis and chronic obstructive pulmonary disease were excluded from this study.**

Results: **Sixty patients (68% male, 48 years and 64 months following heart transplantation) were assessed. Multivariate analysis selected the following variables: receptor's gender (*P*=0.001), receptor age (*P*=0.049), receptor Body Mass Index (*P*=0.005), heart rate reserve (*P*<0.0001), left atrium diameter (*P*=0.016). Multivariate analysis showed r=0.77 and r2=0.6 with *P*<0.001. Equation: peakVO_2=32.851 - 3.708 (receptor gender) - 0.067 (receptor age) - 0.318 (receptor BMI) + 0.145 (heart rate reserve) - 0.111 (left atrium diameter).**

Conclusion: **The determinants of the peak VO_2 in heart transplant recipients were: receptor sex, age, Body Mass Index, heart rate reserve and left atrium diameter. Heart rate reserve was the unique variable positively associated with peak VO_2. This data suggest the importance of the sympathetic reinnervation in peak VO_2 in heart transplant recipients.**

Descriptors: **Heart Transplantation. Exercise. Exercise Tolerance.**

Resumo

Objetivo: **Estabelecer os determinantes do VO_2 pico em transplantados de coração.**

Métodos: **Avaliação do paciente foi realizada em dois dias consecutivos. No primeiro dia, os pacientes realizaram a avaliação da variabilidade da frequência cardíaca seguida de um teste de esforço cardiopulmonar. No segundo dia, os pacientes realizaram ecocardiografia de repouso. Os transplantados foram elegíveis se estivessem em uma condição estável e sem qualquer evidência de rejeição diagnosticada por biópsia endomiocárdica. Pacientes com marca-passo, limitações funcionais não cardiovasculares,**

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Abbreviations, acronyms & symbols	
BMI	Body mass index
BNP	B-type Natriuretic Peptide
DT	Deceleration time
ECA	Angiotensin conversor enzyme inhibitors
IVRT	Isovolumic relaxation time
LF/HF	Low/high frequency domain in heart rate variability
RRi	R-R intervals
VO_2	Oxygen consumption

tais como osteoartrite e doença pulmonar obstrutiva crônica foram excluídos deste estudo.

Resultados: **Sessenta pacientes (68% do sexo masculino, 48 anos e 64 meses após o transplante cardíaco) foram avaliados. A análise multivariada selecionou as seguintes variáveis: sexo (*P*=0,001), idade (*P*=0,049), Índice de Massa Corporal (*P*=0,005), frequência cardíaca de reserva (*P*<0,0001), diâmetro do átrio esquerdo (*P*=0,016), variáveis do receptor. A análise multivariada mostrou r=0,77 e r2=0,6, com *P*<0,001. Equação: VO_2=32,851 - 3,708 (sexo receptor) - 0,067 (idade receptor) - 0,318 (IMC receptor) + 0,145 (frequência cardíaca de reserva) - 0,111 (diâmetro de átrio esquerdo).**

Conclusão: **Os determinantes do pico de VO_2 em transplantados de coração foram: sexo receptor, idade, Índice de Massa Corporal, frequência cardíaca de reserva e diâmetro do átrio esquerdo. A frequência cardíaca de reserva foi a única variável positivamente associada com o pico de VO_2. Estes dados sugerem a importância da reinervação simpática no pico de VO_2 em transplantados de coração.**

Descritores: **Transplante de Coração. Exercício. Aptidão Física.**

INTRODUCTION

Heart transplantation is a worldwide procedure indicated to patients with refractory heart failure. It is well known that heart transplant improves patient's survival, quality of life and exercise capacity, when compared to pre-transplant condition[1,2].

Although heart transplant recipients have an exercise capacity greater than before the procedure, it is known that the physical capacity restoration to normal levels does not always occur[1,2]. This is attributed to physical deconditioning resulting from previous heart failure[3], a low chronotropic response (as a result of a cardiac denervation, also accessed by heart rate variability)[4] and, in many cases, impairment in cardiac function after transplantation[2]. The cardiac systolic function of the transplanted heart seems to be normal in most patients, while diastolic dysfunction appears to be present in most of the transplanted heart. Diastolic dysfunction was recently identified as one of the factors that seem to influence negatively the maximal and submaximal exercise capacity in heart transplant recipients[5,6]. Despite this, little is known about the determinants of exercise capacity in heart transplant recipients.

The aim of this study was to establish the determinants of the peak VO_2 in heart transplant recipients.

METHODS

Study design

This study was performed in a tertiary cardiology hospital in Brazil. Patient's assessment was performed in two consecutive days. In the first day, patients performed the heart rate variability assessment followed by a cardiopulmonary exercise test. In the second day, patients performed a resting echocardiography.

Study population

Heart transplant recipients were eligible if they were in a stable condition (for, at least, 3 months) and without any evidence of tissue rejection diagnosed by endomyocardial biopsy. Patients with pacemaker, noncardiovascular functional limitations such as osteoarthritis and chronic obstructive pulmonary disease were excluded from this study. Patients were recruited from a tertiary cardiology hospital from September 2010 to November 2011. Subjects' characteristics are listed in Table 1.

This protocol was approved by the Ethical Committee of our institution. All patients provided informed consent prior to participation.

Variables considered to be potentially associated with peak VO_2

We considered to be potentially associated with peak VO_2 as follows: donor and recipient age and body mass index (BMI), etiology of heart failure before transplantation (Chagas and non-Chagas), recipient heart rate reserve, gender, percentage of age-predicted peak heart rate, percentage of heart rate drop in the second minute of recovery in the cardiopulmonary test, left atrium diameter, cold ischemia time, time following heart transplantation, resting heart rate, VE/VCO_2 slope, right ventricle diameter, left ventricle diastolic diameter, left ventricle ejection fraction, E/E' ratio and low/high frequency domain in heart rate variability (LF/HF).

Table 1. Characterization of study participants.

Variables	Number of patients (%), dose(mg/day)
Etiology:	
Chagas (%)	45%
Non-Chagas (%)	55%
Men (%)	68%
Recipients age (years)	48±15
Donors age (years)	31±11
Donors weight (kg)	76±9
Recipients weight (kg)	68±13
Donors height (cm)	176±7
Recipients height (cm)	166±10
Ischemic time (min)	206±115
Recipients BMI (Kg/m^2)	25±4
Donors BMI (Kg/m^2)	25±2
Time following heart transplant (months)	64±54
Resting heart rate (bpm)	82±12
Recipients heart rate reserve (bpm)	49±17
% of age-predicted peak heart rate	77±12
% of heart rate drop in the second minute of recovery	8±8
Left atrium diameter	44±10
Cold ischemia time (min)	207±115
VE/VCO_2 slope	30±6
Right ventricle diameter (mm)	22±3
Left ventricle diastolic diameter (mm)	48±4
Left ventricle ejection fraction (%)	62±5
E/E' ratio	6.8±2.3
LF/HF	6.9±8.9
Medication:	
Cyclosporine	71%, 174±58 mg/day
Diuretics	8.3%
ACE inhibitors (enalapril)	10%, 23±14 mg/day
Angiotensin receptor antagonist (losartan)	10%, 62±31 mg/day
Corticosteroids (prednisone)	30%, 5.2±3.4 mg/day
Azathioprine	30%, 76±25 mg/day
Mycophenolate	37%, 1096±422 mg/day
Tacrolimus	25%, 7±4 mg/day
Sirolimus	1.6%, 1 mg/day
Everolimus	3.3%, 1±0.35 mg/day
Calcium channel blocker (diltiazem)	58%, 126±71 mg/day
Ezetimibe	1.6%, 10 mg/day
Simvastatin	68.3%,11.4±4.4 mg/day
Hydralazine	6.6%, 144±116 mg/day
Metformin	6.6%,1700±00 mg/day
Fluoxetine	3.3%, 32±11 mg/day
Gabapentin	1.6%, 400 mg/day
Olanzapine	5%, 10 mg/day
Topiramate	3.3%, 125±106 mg/day
Bromazepam	5%, 3 mg/day
Insulin	7.5%, 69±53 mg/day

BMI=Body mass index, ECA=Angiotensin conversor enzyme inhibitors. LF/HF=Low/high frequency domain in heart rate variability

Cardiopulmonary exercise test

All patients were asked to refrain from both strenuous physical activity and the consumption of any stimulants (e.g., coffee, tobacco, alcohol) for 24h prior to the cardiopulmonary exercise test. Patients' last meal was ingested at least 2h before the test. Heart transplant recipients underwent the test on a programmable treadmill (TMX425 Stress Treadmill; TrackMaster, Newton, KS, USA) in a temperature-controlled room (21-23°C) between 10–12am with a standard 12-lead continuous ECG monitor (CardioSoft 6.5; GE Medical Systems IT, Milwaukee, WI, USA). Blood pressure monitoring was performed by an automatic device. Resting heart rate was considered the 20-min average in a supine position. Minute ventilation, oxygen uptake, carbon dioxide output and other cardiopulmonary variables were acquired breath-by-breath by a computerized system (Vmax Encore29; SensorMedics, Yorba Linda, CA, USA).

Metabolic data were computed as the mean of the final 30 s of the resting period, whereas peak of VO_2 and peak heart rate were the mean values of the final 30 s of effort before exhaustion. The respiratory exchange ratios were recorded as the averaged samples obtained during each stage of a modified Naughton protocol. A satisfactory cardiopulmonary exercise test was characterized by a peak of respiratory exchange ratio>1.05 and symptoms of maximum effort. Heart rate reserve [bpm] was defined as maximum heart rate achieved in the cardiopulmonary exercise test — average of 10-min resting heart rate in the supine position. Heart rate recovery was assessed during the first and second minutes after cardiopulmonary exercise test.

Echocardiography

The assessment followed the recommendations of the American Society of Ecocardiography[7]. We used a commercially available equipment, model IE 33, Philips Medical Systems, Andover, MA, USA. The acquired data considered bidimensional echocardiography, pulsed Doppler, continuous wave Doppler, tissue Doppler and color flow mapping. It was obtained at least three measurements of each echocardiographic variable and the average was considered. We analyzed: left ventricle diameters and volumes, left ventricle ejection fraction (Simpson's rule), left ventricle mass index, left ventricle diastolic assessment (pulsed Doppler of mitral inflow and the study of the flow of pulmonary veins and Tissue Doppler). Thus, we analyzed with pulsed Doppler, E and A waves, E/A ratio, deceleration time (DT), isovolumic relaxation time (IVRT), systolic component of the pulmonary venous flows (S wave), diastolic component of the pulmonary venous flow (D wave), S/D ratio. The analysis with tissue Doppler was obtained in apical four and two chambers with sample volume of 1 to 2 mm. It was checked to the maximum rate of myocardial displacement at the beginning and end of the diastole (E' and A' wave respectively) and during systole (S' wave) at the septal ring, side ring, bottom ring, front ring of right ventricle. Measurement of E/E´ratio was performed in the left ventricular annulus, from the basal septal and lateral segments (considered mean values).

Heart rate variability

Experimental protocol: All the heart transplant recipients remained at rest for 10 minutes on the supine position and were instructed to breathe spontaneously. Then, instantaneous R-R intervals (RRi) were recorded for 10 min with a digital telemetry system, consisting of a transmitter placed on the patient's chest and a HR monitor (Polar® RS800CX; Polar Electro Oy, Kempele, Finland) This system detects ventricular depolarization, corresponding to the R wave on the electrocardiogram, at a sampling rate of 500 Hz, which had been previously validated[8]. The signals were transmitted to a receiver and then to a computer for subsequent analysis. Data analysis: The RRi sequence of length n=256 beats was selected for each subject. The length of greatest stability was chosen from the central region of the time series. The mean and variance of the RRi were also calculated. HRV spectral analysis: The HRV frequency domain analysis was performed with an autoregressive model[9,10], on previously selected RRi sequences. Two main spectral components were considered: low frequency (LF - from 0.04 to 0.15 Hz) and high frequency (HF - from 0.15 to 0.50 Hz) that represent the sympathetic and vagal modulations, respectively[11]. The spectral components are reported as normalized units (LFun and HFun) and LF/HF ratio. Normalization consisted of dividing the power of a given spectral component (HF or LF) by the total power minus the power below 0.04 Hz, and multiplying the ratio by 100.9 All patients presented a respiratory rate in the frequency range of HF band of HRV.

Current medication intake

Medication profile is shown in Table 1. Patients took angiotensin conversor enzyme inhibitors, losartan and isosorbide 5-mononitrate two times per day, one half of the daily dose in the morning (9:00 am) and the other half at night (9:00 pm). Diuretics were taken in the morning (9:00 am). All heart transplant recipients were receiving immunosuppressive therapy two times per day, one half of the daily dose in the morning and the other half at night. Antihypertensive drugs were taken, most of the times, in the morning.

Statistical analysis

Data are presented as mean and standard deviation. We evaluated the association of the variables collected in the 60 selected patients. For this, we used univariate analysis to select the variables to be used in the multivariate model. For the univariate analysis, a significance level of less than 20% (P<0.20) was considered. In multivariate analysis, the non-significant variables were excluded from the model (manual-

ly, one at a time) following the criterion of greater "*P*" value. The model was determined when all the variables were presented with a significance level less than 5% (*P*<0.05). The dependent variable used was the peak VO_2[1,2,5]. After the analysis, we established an equation with variables associated with peak VO_2.

For all statistical analyzes, we used SPSS (Chicago IL, USA) version 13.0.

RESULTS

Participants

From 176 heart transplant recipients alive in our service, 109 were not found by phone calls or lived in another city that prevented the realization of the protocol. Seven patients were excluded due to refusal, pacemaker or sequel of stroke (Figure 1). Sixty patients (68% male, 48 years and 64 months following heart transplantation) were assessed (Table 1).

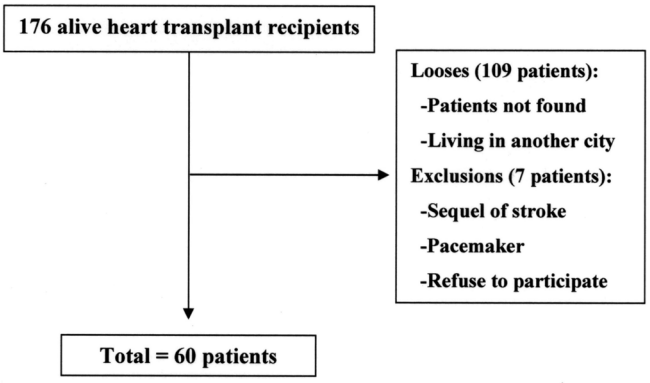

Fig.1 – Patients flow throughout the study.

Outcome data/main results

Univariate analysis selected the following variables: receptor's age (*P*=0.042), receptor's BMI (*P*=0.056), heart rate reserve (*P*<0.0001), percentage of age-predicted peak heart rate (*P*=0.052), percentage of heart rate drop in the second minute of recovery in the cardiopulmonary exercise test (*P*=0.067), slope VE/VCO_2 (0.115), left atrium diameter (*P*=0.028), right ventricular diameter (*P*=0.079), E/E' ratio (0.144), cold ischemia time (*P*=0.15), donor's age (*P*=0.022), LF/HF (*P*=0.18) and receptor's sex (*P*=0.003). The following variables were withdrawn from multivariate analysis model (in order of withdrawal): slope VE/VCO_2 (*P*=0.957), percentage of heart rate drop in the second minute of recovery in the cardiopulmonary exercise test (*P*=0.937), percentage of age-predicted peak heart rate (*P*=0.771), right ventricle diameter (*P*=0.456), LF / HF (*P*=0.434), donor's age (*P*=0.51), cold ischemia time (*P*=0.227) and E/E' ratio (*P*=0.449).

Multivariate analysis selected the following variables: receptor's gender (*P*=0.001), receptor age (*P*=0.049), receptor BMI (*P*=0.005), heart rate reserve (*P*<0.0001), left atrium diameter (*P*=0.016). Multivariate analysis showed r=0.77 and r2=0.6 with *P*<0.001.

Equation derived from the multivariate analysis: peak VO_2=32,851 - receptor gender (3,708) - receptor age (0,067) - receptor BMI (0,318) + heart rate reserve (0,145) - left atrium diameter (0,111)

Considering: peak VO_2 in mL/Kg/min, gender (0=male and 1=female), age in years, BMI in Kg/m^2, heart rate reserve in beats per minute and left atrium diameter in millimeters.

DISCUSSION

The main finding of this study was that peak VO_2 of heart transplant recipients was determined by receptor gender, age, BMI, heart rate reserve and left atrium diameter.

Our study is the first one to investigate the determinants of peak VO_2 in heart transplant recipients using variables that are non-invasive and easy to be collected in clinical practice.

In our study, we observed that the peak VO_2 was negatively associated with gender, BMI and age of the recipient and the diameter of the left atrium of the allograft. Of these, gender and BMI seemed to be the determinants more strongly associated with exercise capacity. Moreover, the heart rate reserve was the unique variable positively associated to peak VO_2.

Our data strongly suggest that the sympathetic reinnervation is the main variable that positively influences peak VO_2 in heart transplant recipients. Nevertheless, the parasympathetic reinnervation does not seem to influence the exercise capacity in heart transplant recipients. Previous studies showed that the parasympathetic reinnervation in adults is not consistent and may occur only from 5 to 10% of cases. Moreover, the sympathetic reinnervation occurs much more frequently and is related to exercise capacity in heart transplant recipients from 50 to 60% of cases in 3 years[1,12,13]. The study by Bernardi et al.[14] showed that exercise training can improve cardiovascular control in heart transplant recipients.

The negative influence of BMI, age and gender in exercise capacity is already well established in exercise physiology field. It is known that women have lower peak VO_2 than men, as well as fatter people compared to skinny and older people compared to younger, when we keep all other variables (such as exercise training levels) constant[15].

A relatively new data appeared in our research: the negative influence of the left atrium diameter in peak VO_2 in heart transplant recipients. The study by Abdul-Waheed et al.[16] showed that the left atrium of adult heart transplant recipients increased in one year of follow-up. Moreover, this study showed an inverse association between left atrium and peak VO_2. The authors hypothesized that the surgical scar could be negatively influ-

encing left atrium pumping. In agreement with Abdul-Waheed et al.[16], our study showed a similar relationship between left atrium and exercise capacity. Unfortunately, our study can not explain the mechanisms involved in this relationship, but the hypothesis raised by Abdul-Waheed at al.[16] seems to be relevant and deserves a deep investigation in future studies.

The lack of influence of the time of transplant and the E/E' ratio in peak VO_2 found in this study is an important information and deserves some discussion. The E/E' ratio is an important echocardiography index in the diagnosis of diastolic dysfunction and has been shown to be related to functional class, cardiac mortality and hospitalization in patients with heart failure[17,18]. The ratio above 15 is a strong indicator of heart failure with preserved left ventricle ejection fraction. The E/E' ratio between 8 and 15 represents a "gray zone" for diagnosis of diastolic dysfunction. In these cases, B-type Natriuretic Peptide (BNP) seem to have a great importance for the differential diagnosis[19].

The prevalence of diastolic dysfunction in our study was 3.4%, which we consider low compared to 33% of the study by Roten et al.[5] We expected that the prevalence of diastolic dysfunction were higher and the E/E' ratio increased along the segment after heart transplantation due to the increased incidence of co-morbidities such as hypertension. There are no data in the literature regarding diastolic function (E/E' ratio) and time of cardiac transplantation. We believe the fact that our patients are well treated and compensated for comorbidities such as hypertension, the E/E' ratio remained constant throughout the follow-up. In a curious way, our study showed no association between peak VO_2 and the time of transplantation, but a positive association between peak VO_2 and cardiac sympathetic reinnervation through heart rate reserve. These data are quite relevant for a deeper understanding of the behavior of exercise capacity over time of transplantation. It seems that the real factor influencing exercise capacity is sympathetic reinnervation and not simply the time of transplantation. This information let us believe that for the same time following heart transplant, we will have more and less reinnervated patients. Consequently we will have patients with higher and lower exercise capacity.

Finally, the study by Roten et al.[5] showed that the diastolic dysfunction was associated with exercise capacity limitation of heart transplant recipients. However, our study found no such association. Because of this conflicting data, some considerations must be taken into account. In our study, the prevalence of diastolic dysfunction was much lower than in the study by Roten et al.[5] Perhaps if our study had shown a higher prevalence of diastolic dysfunction (and consequent higher E/E' ratio), our data would have agreed to the study by Roten et al.[5] Therefore, further studies in this area are necessary for a deeper understanding of the relationship between peak VO_2 and the E/E' ratio.

This study has some limitations. Patients only performed resting echocardiography. Certainly, the assessment of the cardiac function during exercise would bring important information to the understanding of the relationship between E/E' ratio and in exercise capacity of heart transplant recipients. In addition, further investigation of the left atrium would be relevant for a better understanding of the mechanisms involved in the limitation of exercise capacity.

This study was also limited by not assessing the vascular function and peripheral muscle metabolism (oxygen extraction). Tests such as the kinetics of O_2, would be useful in future research to evaluate the influence of the "periphery" in the exercise capacity of transplanted patients.

CONCLUSION

In this study, the determinants of the peak VO_2 in heart transplant recipients were: receptor gender, age, BMI, heart rate reserve and left atrium diameter. Heart rate reserve was the unique variable that was positively associated with peak VO_2. This data suggest the importance of the sympathetic reinnervation in peak VO_2 in heart transplant recipients.

Authors' roles & responsibilities	
VOC	Analysis and/or interpretation of data, statistical analysis, final approval of the manuscript, conception and design of the study, implementation of operations and/or experiments, manuscript writing or critical review of its content
GVG	Analysis and/or interpretation of data, final approval of the manuscript, design and study design, performance of operations and/or experiments
MLCV	Analysis and/or interpretation of data, final approval of the manuscript, current operations and/or experiments, manuscript writing or critical review of its content
AMC	analysis and/or interpretation of data, final approval of the manuscript, current operations and/or experiments, manuscript writing or critical review of its content
VOC	Analysis and/or interpretation of data, final approval of the manuscript, design and study design, performance of operations and/or experiments, manuscript writing or critical review of its content
SMAF	Analysis and/or interpretation of data, final approval of the manuscript, current operations and/or experiments
EAB	Analysis and/or interpretation of data, final approval of the manuscript, design and study design, performance of operations and/or experiments, manuscript writing or critical review of its content.

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Erratum

In the article "Determinants of peak VO_2 in heart transplant recipients", published in the Brazilian Journal of Cardiovascular Surgery/Revista Brasileira de Cirurgia Cardiovascular 30.1, pages 9-15, the correct name of one of the co-authors is Marcelo Luiz Campos Vieira and not Marcelo Luiz Campos-Vieira.