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Exercise capacity in early and late adult heart transplant recipients

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Abstract

Background: *The aim of this study was to compare peak oxygen consumption (VO_2), heart rate (HR) reserve and HR recovery in early and late heart transplant recipients. Moreover, we also aimed to correlate peak VO_2 and HR reserve.*

Methods: *Fifteen heart transplant recipients (8 early and 7 late), 8 ± 3 and 161 ± 58 months after transplantation, respectively, performed a cardiopulmonary exercise test.*

Results: *Early heart transplant recipients showed lower HR reserve compared to late heart transplant recipients, 39 ± 15 vs. 58 ± 19 bpm ($p = 0.049$), respectively. Peak VO_2(23.4 ± 4 vs. 21.8 ± ± 5 mL/kg/min, $p = 0.56$), VO_2 respiratory compensation point (18.7 ± 2 vs. 18.5 ± 4 mL/ /kg/min, $p = 0.48$) and time of exercise testing (14 ± 3 vs. 13 ± 3 min, $p = 0.95$) %age-predicted peakVO_2 (65 ± 12 vs. 70 ± 10%, $p = 0.24$) were not different between the groups. Moreover, peak VO_2 and %age-predicted peakVO_2 correlated with HR reserve only in early heart transplant recipients ($r = 0.89$, $p = 0.003$ and $r = 0.71$, $p = 0.04$, respectively). Early heart transplant recipients increased HR (2.5 ± 2.0% at first minute and 0.7 ± 2.3% at the second minute), while late recipients decreased HR (–6.0 ± 4.7 at first minute and –15.5 ± 2.4 at the second minute) at the recovery period of cardiopulmonary exercise test.*

Conclusions: *Exercise capacity did not show difference between early and late heart transplant recipients. HR reserve was higher in late compared to early recipients. HR reserve only correlated with peak VO_2 in early recipients. Moreover, only late heart transplant recipients showed decrease in HR during the recovery period of cardiopulmonary exercise test.* (Cardiol J 2013; 20, 2: 178–183)

Key words: peak VO_2, heart rate reserve, transplantation, reinnervation

Introduction

Heart transplantation is worldwide recognized as treatment for end stage of patients with heart failure. Despite of heart transplant recipients show increased exercise capacity when compared to pre-transplantation, it is not restored to normal values considering age-matched health subjects [1].

Too much effort is taken by the scientific community to explain the cardiac and non-cardiac causes of impaired exercise capacity in heart transplant recipients. Diastolic dysfunction [2], chronotropic incompetence, and pre-transplant physical deconditioning [3] have been suggested. It has also been suggested that exercise capacity can increase over the time after heart transplant as

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Table 1. Patient's characteristics.

Characteristics heart transplant recipients	Early	Late	P
Etiology:			—
Non-ischemic [%]	100	71	—
Male [%]	63	86	—
Recipient age [years]	42 ± 11	63 ± 12	0.003
Recipient BMI [kg/m^2]	23 ± 3	27 ± 3	0.049
Donor age [years]	27 ± 12	32 ± 9	0.53
Donor BMI [kg/m^2]	25 ± 3	25 ± 2	0.81
Time posttransplant [months]	8 ± 3	161 ± 58	< 0.0001
Hypertension [%]	37.5	57.1	—
Current medications [%]:			—
Diuretics	12.5	14	—
Angiotensin converting enzyme inhibitor (enalapril)	12.5	28	—
Angiotensin II AT1 receptor antagonists (losartan)	50	0	—
Corticosteroids (prednisone)	87	50	—
Azathioprine	25	28	—
Mycophenolate mofetil			
Tracolimus	50	14	—
Sirolimus	0	14	—
Calcineurin inhibitors (cyclosporine)	50	57	—
Calcium channel blocker (diltiazem)	75	43	—

BMI — body mass index

a consequence of cardiac reinnervation [4]. However no study is available comparing early and late heart transplant recipients.

Considering that cardiac reinnervation is related to exercise capacity and both can increase along the time after transplantation, the aim of this study was to compare peak oxygen consumption (VO_2), heart rate (HR) reserve and HR recovery in early and late heart transplant recipients.

Methods

Study population

A total of 15 heart transplant recipients (8 early and 7 late) in a stable condition (for, at least, 3 months), were recruited from a tertiary cardiology hospital from September 2010 to April 2011 to perform a cardiopulmonary exercise test. Early heart transplant was considered less than 1 year of surgery and late transplant after 10 years. Endomyocardial biopsy did not show any evidence of tissue rejection during the entire study. Patients performed echocardiography before the protocol to assure that they did not have diastolic dysfunction (E/E' ratio < 8). Subjects' characteristics are listed in Table 1.

Patients with diastolic dysfunction, noncardiovascular functional limitations such as osteoarthritis and chronic obstructive pulmonary disease were excluded from this study. Patients with diastolic dysfunction were also excluded.

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

Study design

This cross-sectional study was designed to evaluate exercise capacity and HR reserve in early and late heart transplant recipients. All patients performed a cardiopulmonary exercise test to evaluate HR reserve and submaximal-maximal exercise capacity.

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 24 h prior to the cardiopulmonary exercise test. Patients' last meal was ingested at least 2 h 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

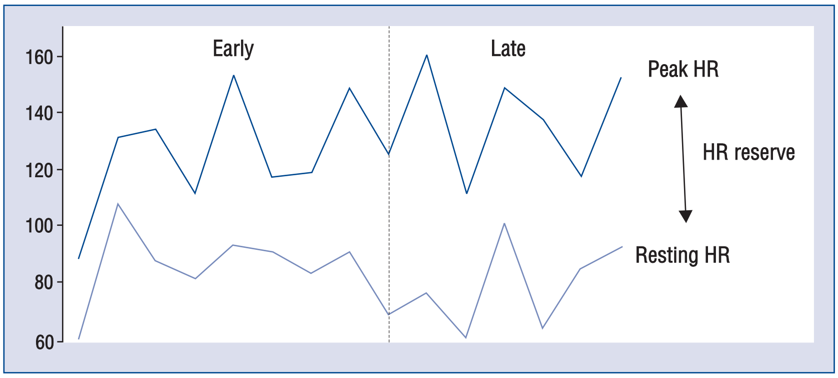

Figure 1. Heart rate (HR) dynamic of early and late heart transplant recipients.

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 HR 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 HR 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. HR reserve [bpm] was defined as maximum HR achieved in the cardiopulmonary exercise test — average of 10-min resting HR in the supine position. HR recovery was assessed during the first and second minutes after cardiopulmonary exercise test.

The anaerobic threshold was determined when the levels of the ratio between VE/VO_2 and the oxygen partial end tidal pressure reached minimum values before rising. The respiratory compensation point was determined when VE/VCO_2 reached their minimum values before rising and the carbon dioxide partial end-tidal pressure reached its maximum level before starting to decrease [5].

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 (9:00am) and the other half at night (9:00pm). Diuretics were taken in the morning (9:00am). 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

The descriptive analysis was presented as the mean and standard deviation. Mann-Whitney test was used to compare HR and VO_2 variables between early and late heart transplant recipients. Spearman test was used for correlation between HR reserve and peak VO_2.

Data were analyzed using the Statistical Package for Social Sciences for Windows, v 11.5 (SPSS Inc, Chicago, IL). Statistical significance was set at $p < 0.05$.

Results

Early heart transplant recipients showed lower HR reserve compared to late heart transplant recipients, 39 ± 15 vs. 58 ± 19 bpm ($p = 0.049$), respectively (Fig. 1). PeakVO_2, VO_2AT, VO_2RCP and time of exercise testing were not different between the groups (Table 2). Peak VO_2 achieved in relation to age-predicted peak VO_2 [6] did not show difference between early and late heart transplant recipients either. Moreover, peak VO_2 and the peak VO_2 achieved in relation to age-predicted peak VO_2 correlated with HR reserve only in early heart transplant recipients (Figs. 2A, B). No patients showed diastolic dysfunction.

Early heart transplant recipients increased HR (2.5 ± 2.0% at first minute and 0.7 ± 2.3% at the second minute), while late recipients decreased HR (–6.0 ± 4.7 at first minute and –15.5 ± 2.4

Table 2. Early versus late exercise variables.

Parameters	Early	Late	P
Peak VO_2 [mL/kg/min]	23.4 ± 4	21.8 ± 5	0.56
VO_2 AT [mL/kg/min]	12.7 ± 2	11.7 ± 3	0.81
VO_2 RCP [mL/kg/min]	18.7 ± 2	18.5 ± 4	0.48
Peak RER	1.17 ± 0.1	1.16 ± 0.1	0.81
Slope VE/VCO_2	28 ± 4	28 ± 4	0.56
Time of CPET [min]	14 ± 3	13 ± 3	0.95
Resting HR [bpm]	87 ± 13	75 ± 15	0.32
Peak HR [bpm]	125 ± 21	133 ± 19	0.41
HR reserve [bpm]	39 ± 15	58 ± 19	0.049
%Age-predicted HR	70 ± 13	84 ± 14	0.132
%Age-predicted peakVO_2	65 ± 12	70 ± 10	0.24
%HR drop 1° minute of recovery	2.5 ± 2.0	–6.0 ± 4.7	< 0.001
%HR drop 2° minute of recovery	0.7 ± 2.3	–15.5 ± 2.4	< 0.001
Resting SBP [mm Hg]	128 ± 19	137 ± 19	0.41
Resting DBP [mm Hg]	92 ± 13	91 ± 13	0.94
Peak SBP [mm Hg]	163 ± 25	167 ± 23	0.99
Peak DBP [mm Hg]	79 ± 15	79 ± 21	0.84

BMI — body mass índex; Tx — transplant; VO_2 — oxygen consumption; AT — anaerobic threshold; RCP — respiratory compensation point; RER — respiratory exchange ratio; CPET — cardiopulmonary exercise test; HR — heart rate; SBP — systolic blood pressure; DBP — diastolic blood pressure

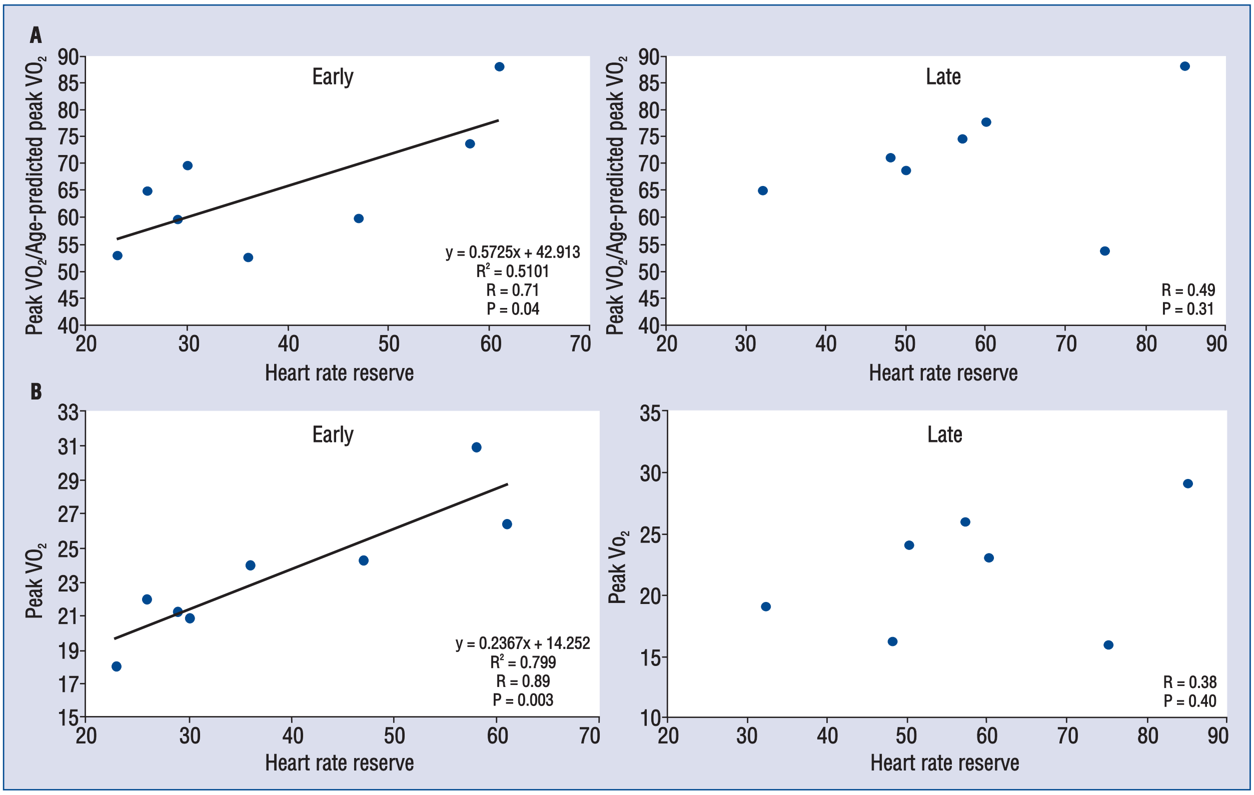

Figure 2A, B. Correlation between peak VO_2 and the peak VO_2 achieved in relation to age-predicted peak VO_2 with heart rate reserve.

at the second minute) at the recovery period of cardiopulmonary exercise test.

Discussion

The main find in this study was the absence of difference in exercise capacity between early and late heart transplant recipients. HR reserve was increased in late recipients and exercise capacity correlated with HR reserve only in early heart transplant recipients. Moreover, early heart transplant recipients showed increase in HR during the recovery period. In the opposite way, late heart transplant recipients showed decrease in HR during the recovery period, what suggests a parasympathetic reinnervation.

During the surgical procedure of heart transplantation, sympathetic nerve fibers that innervate the donor's heart are sectioned causing a complete denervation of the organ. Nevertheless, it has been reported that the process of cardiac innervation can be partially restored over time [7]. Some factors related to the characteristics of the donor and recipient in association with factors related to the perioperative period can also influence the process of reinnervation [8].

Exercise capacity has been proposed to increase along the years following heart transplantation as a consequence of cardiac reinnervation. However, our study did not find differences in exercise capacity between early and late heart transplant recipients. Interestingly, the HR reserve was higher in late recipients. We expected that exercise capacity would increase in late heart transplant recipients due to the reinnervation process and to the improvement in cardiovascular control. It is well known that exercise capacity (in the picture of VO_2) is directly influenced by central (cardiac output or HR × systolic volume) and peripheral (a-vO_2 difference) components. It is also known that, despite of the heart transplant, the neurohormonal activity remains overactivated, what can badly influence the peripheral vasodilation and impair muscle function [9, 10].

Taking into account that HR reserve [11] was higher in late recipients, what might reflect the reinnervation process, and that HR reserve was not correlated to peak VO_2 in late heart transplant recipients, we hypothesized that peripheral components could be playing an important role in the low exercise capacity in late recipients. Cardiac reinnervation does not seem to be the only component involved in exercise capacity over the years following heart transplantation, once late recipients are also chronically taken immunosuppressive drugs that are related to impaired muscle function.

HR recovery in exercise test is a well established and straightforward method of assessing parasympathetic tone. The low drop of HR at the recovery period of exercise test represents a risk factor for cardiovascular disease [12]. Our early heart transplant recipients showed increase in HR during the recovery period, what may reflect the catecholamine pathway of cardiovascular control. After exercise, the body needs some time to "wash" the circulating catecholamine. In the opposite way, the late heart transplant recipients showed decrease in HR during the recovery period, what suggests a parasympathetic reinnervation and less dependence of the catecholamine pathway of cardiovascular control.

Limitations of the study

This study is limited by the small number of patients, however, it represents the larger experience in Brazil. Moreover, peripheral vasodilation and oxygen kinetics were not assessed, what could contribute to a deep understanding in the peripheral components of exercise capacity in heart transplant recipients.

Conclusions

Exercise capacity did not show difference between early and late heart transplant recipients. HR reserve was higher in late compared to early recipients. Only late heart transplant recipients showed decrease in HR during the recovery period of cardiopulmonary exercise test. Moreover, HR reserve only correlated with peak VO_2 in early recipients, what figures that peripheral components could be playing an important role in the low exercise capacity in late recipients.

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Conflict of interest: none declared

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