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Heart rate dynamics in heart transplantation patients during a treadmill cardiopulmonary exercise test: A pilot study

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Abstract

Background: *One way of defining an individual's heart effort is to calculate the maximum heart rate to be expected given their age, but the reinnervation seen in patients who have received heart transplants makes for different calculations from patients who have suffered heart failure. The purpose of this study is to evaluate heart rate dynamics (rest, peak and percentage of predicted heart rate for age) in heart transplant patients compared to optimized beta-blocked heart failure patients during a treadmill cardiopulmonary exercise test.*

Methods: *Twenty two (81% male, 46 ± 12 years) sedentary heart failure patients and 15 (47% male, 44 ± 13 years) sedentary heart transplant patients performed a treadmill cardiopulmonary exercise test between 10 am and 3 pm. Heart failure optimization was considered 50 mg/day or more of carvedilol, with a resting heart rate of between 50 and 60 bpm.*

Results: *Basal heart rate was lower in heart failure patients (58 ± 5 bpm) compared to heart transplant patients (93 ± 11 bpm; $p < 0.0001$). Similarly, the peak heart rate (percentage of the maximum predicted for age) was lower in heart failure patients (60 ± 13%) compared to heart transplant patients (80 ± 12; $p < 0.0001$). Maximum respiratory exchange ratio did not differ between the groups (1.05 ± 0.06 in heart failure patients and 1.11 ± 0.1 in heart transplant patients; $p = 0.08$). Moreover, the heart rate reserve between heart failure (49 ± 22) and heart transplantation (46 ± 16%) was not different ($p = 0.644$).*

Conclusions: *No patient reached the maximum heart rate predicted for their age during a treadmill cardiopulmonary exercise test. The heart rate reserve was similar between groups. A heart rate increase in heart transplant patients during cardiopulmonary exercise test of more than 80% of the maximum age-adjusted value should be considered an effort near the maximum.* (Cardiol J 2009; 16, 3: 254–258)

Key words: heart failure, heart rate, heart transplantation, exercise

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Table 1. Subject results.

	Heart failure (22)	Heart transplantation (15)	p	95% confidence interval
Age (years)	46 ± 12	30 ± 6	0.626	–6.681 to 10.923
Peak oxygen consumption [ml/kg/min]	19 ± 6	31 ± 4	0.805	–5.283 to 4.130
Body mass index [kg/m^2]	24 ± 3	22 ± 1	0.054	–6.449 to 0.064
Resting heart rate [bpm]	57 ± 3	89 ± 14	< 0.0001	–40.770 to –28.150
Maximum heart rate predicted for age (%)	60 ± 13	80 ± 12	< 0.0001	–27.660 to –10.671
Heart rate reserve [bpm]	49 ± 22	46 ± 16	0.644	–10.000 to 15.973

Introduction

Heart failure is considered the last stage of heart disease and a significant cause of mortality and morbidity worldwide [1]. End-stage heart failure, marked by a lack of response to medical treatment, disabling symptoms and repeated hospitalizations, is associated with high morbidity and mortality [2]. Heart transplantation is an acceptable 'gold standard' treatment for selected patients in the terminal stages [3].

Cardiopulmonary exercise testing is a well-established technique to evaluate peak oxygen consumption in heart transplant patients. Aerobic exercise training is also a well-established non-pharmacological way of increasing oxygen consumption in heart transplant patients. In this population, the prescription of adequate aerobic effort is crucial to obtain both an increase in exercise capacity and a reasonable control of exercise-related risks [4].

The maximum heart rate adjusted for age (220 – age) is commonly used to characterize a maximum effort in normal subjects and prescription of exercise [5]. Although the heart rate dynamics are known in optimized carvedilol heart failure patients [6–8], in heart transplant patients the increased cardiac output is masked by other factors such as the cardiac denervation that impairs an efficient control of heart rate and of cardiac output [9]. The aim of this study is to evaluate heart rate dynamics (basal, reserve, peak and percentage of the predicted heart rate for age) in heart transplant patients compared to optimized beta-blocked heart failure patients during a treadmill cardiopulmonary exercise test.

Material and methods

Study population

Twenty two (81% male, 19% female) sedentary heart failure patients (46 ± 12 years old) having an average left ventricle ejection fraction of 25 ± 11% (determined by echocardiography), and 15 (47% male, 53% female) sedentary heart transplant patients (44 ± 13 years old) were included in the study. Data was collected between May 2007 and September 2008. The characteristics of the subjects studied and their treatments are shown in Tables 1 and 2. All sedentary heart transplant patients were in a clinically stable condition, 5.4 ± 3.3 years having elapsed following transplantation. Endomyocardial biopsy did not show any evidence of tissue rejection during the entire study. Heart transplant and heart failure patients with atrial fibrillation, a pacemaker, non-cardiovascular functional limitations such as osteoarthritis and chronic obstructive pulmonary disease were excluded from this study. Heart failure patients whose drug therapy was not optimized were also excluded. Optimization was considered to be 50 mg/day or more of carvedilol and a resting heart rate of between 50 and 60 beats per minute, maintained for at least three months [10].

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

Cardiopulmonary exercise test

Patients were asked to refrain from strenuous physical activity, and from the consumption of stimulants (coffee, tobacco, alcohol) that could influence heart rate, for 24 hours before the cardiopulmonary exercise test. The patients' last meals were ingested at least two hours before the start of the test. All subjects underwent the cardiopulmonary exercise test on a programmable treadmill (Series 2000, Marquette Electronics, Milwaukee, WI, USA) in a temperature-controlled room (21–23° C) between 10 am and 3 pm with a standard 12 lead continuous electrocardiogram monitor (Max 1, Marquette Electronics). Blood pressure monitoring was performed by the auscultation method. Minute ventilation, oxygen uptake, carbon dioxide output and other cardiopulmonary variables were acquired breath-by-breath by a computerized system (Vmax

Table 2. Characteristics of the patients.

	Number of patients (%); dose [mg/day]	
Etiology:	Heart failure	Heart transplantation
Ischemic	31%	14%
Non ischemic	69%	86%
NYHA class:		
I	50%	–
II	14%	–
III	36%	–
LVEF	25 ± 11%	–
Current medications:		
Diuretics		
Furosemide	64%; 52 ± 30	21%; 33 ± 11
Hydrochloro-thiazide	48%; 43 ± 24	21%; 26 ± 2
ACE inhibitors		
Enalapril	64%; 38 ± 6	42%; 16 ± 5
Captopril	20%; 93 ± 37	–
AII (losartan)	16%; 75 ± 29	7%; 50 ± 0
ARB (carvedilol)	100%; 61 ± 30	–
Spironolactone	30%; 25 ± 0	–
Digoxin	40%; 0.25 ± 0	–
Isosorbide 5-mononitrate	15%; 56 ± 35	–
Immunosupressive drugs:		
Corticosteroids (prednisone)	–	57%; 4,5 ± 1
Antiproliferative agents	–	
Azathioprine	–	21%; 75 ± 35
Mycophenolate mofetil	–	71%; 744 ± 488
TOR inhibitors		
Tracolimus	–	7%; 8 ± 0
Sirolimus	–	7%; 2 ± 0
Calcineurin inhibitors (Cyclosporine)	–	71%; 161 ± 57
Ca (Diltiazem)	–	78%; 78 ± 54
Hydrolazin	–	14%; 25 ± 0
Clonidim	–	28%; 0,1 ± 0,1
Atorvastatin	–	7%; 20 ± 0
Ezetimibe	–	7%; 10 ± 0

LVEF — left ventricular ejection fraction; AII — angiotensin II AT1 receptor antagonists; ARB — beta-adrenergic receptor blocker; Ca — calcium channel blocker

229 model, SensorMedics, Yorba Linda, CA, USA). Resting oxygen consumption and heart rate were computed as the mean of the final 30 s of the resting period, while peak effort (oxygen consumption) and 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 the protocol in both heart failure and heart transplant patients (Modified Naughton protocol). A satisfactory cardiopulmonary exercise test was characterized by respiratory exchange ratio > 1.05 and symptoms of maximum effort. Maximum heart rate predicted for age was calculated by the equation: 220 – age.

Current medication intake

All heart failure patients were receiving a beta-blocker (carvedilol) associated with ACE inhibitors (enalapril) or angiotensin II AT1 receptor antagonists (losartan). The medication profile of the heart failure patient group is shown in Table 2. Patients took beta-blockers, ACE inhibitors, angiotensin II AT1 receptor antagonists and isosorbide 5-mononitrate twice a day: one half of the daily dose in the morning (9 am), the other half at night (9 pm). Diuretics, digoxin and spironolactone were taken in the morning (9 am). All heart transplant recipients were receiving immunosuppressive therapy twice a day, one half of the daily dose in the morning, the other half at night. Antihypertensive drugs were normally taken in the morning.

Statistical analysis

The descriptive analysis was presented as the mean, standard deviation and 95% confidence interval (CI). The basal heart rate, peak heart rate, percentage of the maximum heart rate predicted for age, heart rate reserve, respiratory exchange ratio, VO_2, slope VE/VCO_2 and body mass index for heart failure and heart transplant patients were normally distributed. To compare these variables, we used the unpaired student's *t*-test.

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

Results

All subjects performed a satisfactory cardiopulmonary exercise test (respiratory exchange ratio 1.05 ± 0.06 in heart failure patients and 1.11 ± 0.1 in heart transplant patients; $p = 0.08$). The basal heart rate was lower in optimized beta-blocked

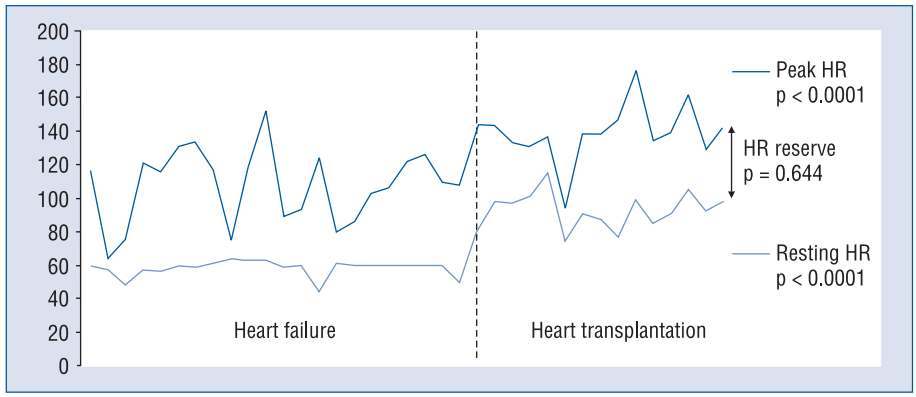

Figure 1. Resting heart rate, peak heart rate and heart rate reserve in heart failure patients and heart transplant patients; HR — heart rate

heart failure patients (58 ± 5 bpm) compared to heart transplant patients (93 ± 11 bpm; $p < 0.0001$; Fig. 1), as also seen with peak heart rate (percentage of maximum heart rate predicted for age; 60 ± ± 13% for heart failure and 80 ± 12 for heart transplantation; $p < 0.0001$; Fig. 2). No patients reached the maximum heart rate predicted for their age. Moreover, heart rate reserve was not different between the groups ($p = 0.644$; Fig. 1).

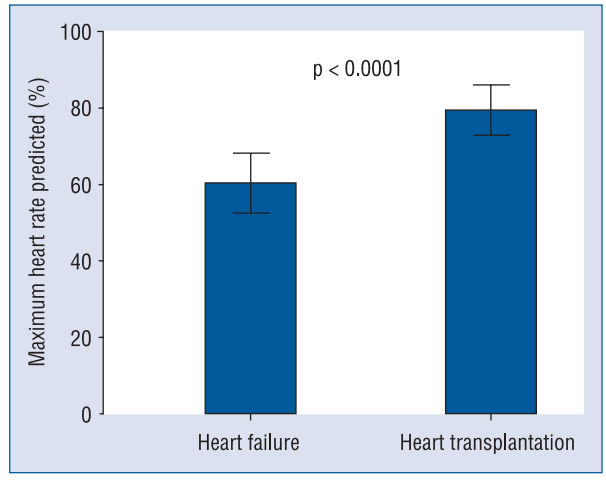

Figure 2. Data is presented as the mean ± 95% confidence interval. Mean peak heart rate (percentage of the maximum heart rate predicted for age).

Discussion

The main finding of this study is that no patient reached the maximum heart rate predicted for their age. The heart transplantation group reached 80% of the predicted heart rate. Moreover, no difference was seen between heart rate reserve between heart failure and heart transplantation groups.

Heart rate variability has been studied as a non-invasive tool to assess cardiac autonomic control of the nervous system, and it is proposed to reflect the interaction of sympathetic and parasympathetic activity [11]. The heart rate dynamics in heart transplant patients during the cardiopulmonary exercise test is unknown. Achievement of age-predicted values for maximal heart rate during exercise is often used as a reflection of maximal or near maximal effort (220 – age) [5]. This method has been questioned by some authors [12], but is currently the most commonly-used one worldwide.

In the first year after heart transplantation, the autonomic nervous system does not normally exert significant effects at heart rate. Reinnervation occurs independently of the exercise training [13]. It is known that heart transplant patients with reinnervation have a greater capacity for exercise than those with denervation [14]. The most prominent clinical finding observed in heart transplant patients is the rapid resting heart rate increase. This is usually 15–25 beats per minute above age and sex-matched controls [15]. This is due to the sinoatrial node free from vagal inhibition.

In rehabilitation programs, the use of the Borg scale is strongly advised for exercise prescription, instead of heart rate, because reinnervation status could impair the heart rate increase during exercise. Despite this, some exercise training protocols with heart transplant patients are prescribed by the heart rate reserve [4]. It is proposed that peak heart rate is reduced approximately 80% of the normal and the heart rate reserve from 30–50 beats

per minute [16]. Our study, which looked at heart transplant patients over a period of more than a year, showed that the heart rate reserve is the same as optimized carvedilol heart failure patients. Perhaps the time of heart transplantation (re-innervation) could explain these different results. Carvalho et al. [6] showed that optimized carvedilol heart failure patients had the same heart rate reserve as healthy subjects. This data leads us to think that heart rate reserve could be an important tool to prescribe exercise in heart transplant patients.

In our study, no patient reached the maximum heart rate predicted for their age during the cardiopulmonary exercise test. Our data suggests that the maximum heart rate predicted for age (220 – age) should not be used to estimate a maximum effort in heart transplant patients. Thus, a peak heart rate of 80% of the maximum heart rate predicted for age should be considered to characterize and estimate a near-maximal effort in heart transplant patients and help with the prescription of exercise. This equation [80% (220 – age)] has never been evaluated previously.

Limitations of the study

This study is limited by the small and different number of patients in each group. We evaluated the heart rate dynamic in heart failure patients with just one kind of beta-blocker drug (carvedilol). We used only one method of cardiopulmonary exercise test (the treadmill). The neurohormones dynamic was not performed in this study.

Conclusions

In the treadmill cardiopulmonary exercise test, optimized beta-blocked heart failure patients had both rest and peak heart rate lower than heart transplant patients. No patient, in either group, reached the maximum heart rate predicted by their age, despite the fact that the heart rate reserve was the same. In heart transplant patients, the maximum heart rate during cardiopulmonary exercise test should be set as 80% of 220 – age to characterize and estimate near-maximal effort during the exercise treadmill test. Based on our results, we propose a new method of exercise prescription for heart transplant patients based on the heart rate.

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