Peer reviewed article

Heart rate response determines long term exercise capacity after heart transplantation

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Summary

Background: Exercise capacity after heart transplantation (HTx) remains limited despite normal left ventricular systolic function of the allograft. Various clinical and haemodynamic parameters are predictive of exercise capacity following HTx. However, the predictive significance of chronotropic competence has not been demonstrated unequivocally despite its immediate relevance for cardiac output.

Aims: This study assesses the predictive value of various clinical and haemodynamic parameters for exercise capacity in HTx recipients with complete chronotropic competence evolving within the first 6 postoperative months.

Methods: 51 patients were enrolled in this exercise study. Patients were included when at least >6 months after HTx and without negative chronotropic medication or factors limiting exercise capacity such as significant transplant vasculopathy or allograft rejection. Clinical parameters were obtained by chart review, haemodynamic parameters from current cardiac catheterisation, and exercise capacity was assessed by treadmill stress testing. A stepwise multiple regression model analysed the proportion of the variance explained by the predictive parameters.

Results: The mean age of these 51 HTx recipients was 55.4 ± 13.2 yrs on inclusion, 42 pts were male and the mean time interval after cardiac transplantation was 5.1 ± 2.8 yrs. Five independent predictors explained 47.5% of the variance observed for peak exercise capacity (adjusted $R^2 = 0.475$). In detail, heart rate response explained 31.6%, male gender 5.2%, age 4.1%, pulmonary vascular resistance 3.7%, and body-mass index 2.9%.

Conclusion: Heart rate response is one of the most important predictors of exercise capacity in HTx recipients with complete chronotropic competence and without relevant transplant vasculopathy or acute allograft rejection.

Key words: heart transplantation; heart rate; exercise capacity

Introduction

Long-term outcome following cardiac transplantation has substantially improved since the first successful transplantation in 1967 at the Groote Schuur Hospital in Cape Town [1]. Careful recipient and donor selection, advances in immunosuppressive medication and treatment tailored to the individual recipient provided the basis for a 10-year survival of 72% in HTx recipients in Bern [2]. Quality of life is the most important clinical parameter after cardiac transplantation [3], and for many HTx recipients it is closely related to postoperative improvement in physical performance [4]. However, exercise capacity after HTx often remains reduced to levels seen in stable heart failure patients [5, 6, 9, 11], and considerably lower when compared with matched healthy controls [12, and ref. there]. Nevertheless, some HTx recipients achieve more than 90% of their age-predicted exercise capacity level [7, 13], and even ascent of the Matterhorn (4,478 m above sea level) is reported [14].

Factors related to impaired exercise capacity after HTx are chronotropic incompetence due to cardiac denervation [8, 12, 15–20], diastolic dysfunction of the cardiac allograft [10, 19] or muscular deconditioning and metabolism of the skeletal muscle posttransplant [20–23]. Identified predictive variables for exercise performance after HTx are age, gender, body mass index (BMI), duration of intensive care unit treatment after HTx, pulmonary vascular resistance and maximum systolic blood pressure [13, 24–26]. The predictive value of exercise-induced heart rate increase, however, has not been demonstrated unequivocally [13, 24–27] despite its direct relevance for cardiac output [28]. Chronotropic competence evolves in the cardiac allograft within the first 6 postoperative months [29],

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suggesting that patients with a shorter posttransplant time interval may present with incomplete chronotropic competence. This study tests the predictive significance of heart rate increase for exercise capacity in stable HTx recipients more than 6 months posttransplant.

Methods

Study design, setting and participants

The present study enrolled orthotopic heart transplantation (HTx) recipients followed at the HTx outpatient clinic of Bern University Hospital. Patients were screened when hospitalised for their annual posttransplant follow-up, which includes right and left heart catheterization, histological monitoring of allograft rejection and treadmill exercise testing. Patients were screened when >6 months posttransplant, and after informed consent had been obtained. Exclusion criteria were (1) current allograft rejection ≥4/II (Texas score / ISHLT) within the last 4 weeks, and (2) relevant macroscopic coronary artery disease with >50% stenosis in the most recent coronary angiogram because both may affect exercise capacity; (3) physical inability to perform treadmill exercise; (4) systolic left ventricular pump function <50%; (5) current treatment with negative chronotropic medication.

Study patients received immunosuppressive medication (cyclosporine, tacrolimus, azathioprine, mycophenolate acid, sirolimus, and prednisone) guided by side effects and regular histological monitoring of RV endomyocardial biopsies (postoperative week 1–4: every week; months 2–6: every 2–4 weeks; months 7–12: every 4–6 weeks; 2nd year: every 2–3 months; 3rd year: every 4 months; 4th / 5th year: every 6 months; thereafter: once annually). The study was approved by the local Ethics Committee (study number 120/2002).

Demographic and clinical data

These were obtained from chart review and included in the multiple regression model which is described below.

Exercise testing

All patients were familiar with the test procedure and underwent symptoms-limited exercise stress testing on a computer-controlled, rotational speed-independent bicycle (Ergometrics 800S, Ergoline® GmbH, Bitz, Germany). Each test started with baseline measurements at rest during 1 minute, followed by a 3-minute reference phase of cycling without workload. Thereafter, workload was increased in a stepwise protocol with 10, 15 or 20 watts workload increase per minute. The rate of workload increase was chosen on the basis of age- and gender-predicted values. Study participants were monitored continuously, using a 12-lead ECG, and blood pressure was obtained every other minute.

Exercise capacity was measured in metabolic equivalents (MET [kcal/kg/h]). One MET is defined as 1 kilocalorie per kilogram per hour and is the caloric consumption of a human subject while at complete rest. Heart rate at rest, peak heart rate and blood pressure were recorded. Heart rate response was calculated by subtracting heart rate at rest from peak heart rate.

Statistical analysis

All analyses were done in STATA (version 10.0, STATA Corporation, College Station, TX, USA). Measurements and clinical parameters were expressed as mean values ± one standard deviation (SD), or numbers and percentages, as appropriate. A stepwise multiple regression model was used to identify the predictive strength of every clinical or haemodynamic parameter (= independent variable) for peak exercise measured in METs (= dependent variable). The outcome of interest in this stepwise multiple regression analysis was the adjusted R^2 (= variance observed) which is the proportion of difference observed in the peak exercise capacity predicted by the independent variables. If the independent variables perfectly predict maximal exercise capacity, the adjusted R^2 value is 100% or, in other terms, all of the variance in the maximal exercise capacity can be explained by the total of the respective variance of the independent variables. Every other recorded parameter was added separately as an independent variable into the regression model, together with the a priori variables (age, sex, body mass index and heart rate response). Parameters increasing the adjusted R^2 (= predictors) were kept in our regression model. The final multiple regression model included the clinical and haemodynamic parameters which increased the total adjusted R^2. Statistical significance was set at a p-value of <0.05.

Results

Participants

87 HTx recipients were screened. A total of 36 patients were excluded due to a postoperative time interval shorter than 6 months after HTx (n = 19), inability to perform treadmill exercise (n = 7), or treatment with negative chronotropic agents (n = 10). 51 HTx recipients met the inclusion criteria and entered the final analysis.

Clinical data

Clinical characteristics are shown in table 1. Of the participants 42 were males and 9 females. End-stage heart failure resulted from ischaemic cardiomyopathy (51%), dilated cardiomyopathy (31%), or some other aetiology (18%).

Exercise capacity and invasive haemodynamic measurements

Treadmill exercise data are presented in table 2. The mean peak exercise level was 8.5 MET (range 2.2 to 20.0). The peak exercise level achieved in men was higher but without statistical significance (8.8 ± 3.3 vs 7.1 ± 2.2 MET, p = 0.16). Systolic left ventricular ejection fraction (EF) was normal in all study participants (table 3). Pulmonary vascular resistance (PVR), left ventricular enddiastolic pressure (LVEDP), and cardiac output (CO) were normal (table 3).

Table 1

Demographic and clinical characteristics of study group. ACE-I: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor type II blocker. The binary variables ischaemic cardiomyopathy, diabetes, BMI, dyslipidaemia and hypertension are provided in percent of patients affected or treated with either medication (%).

Number of patients	51
Demographics	
Male/female	42/9
Age at treadmill exercise test, years	55.4 ± 13.2
Age at HTx, years	50.3 ± 12.8
Time posttransplant, years (mean)	5.1 ± 2.8
(range in years)	(0.9–16.8)
Etiology of CHF	
Ischaemic cardiomyopathy (%)	51
Measurements at HTx	
Recipient body weight, kg	75.3 ± 12.3
Donor body weight at transplantation, kg	73.6 ± 10.4
Ischaemic donor time (minutes)	110 ± 45
Risk factors	
Diabetes (%)	23
Body mass index (BMI)	25.5 ± 3.9
Dyslipidaemia (%)	15
Hypertension (%)	0
Mean Texas allograft rejection score (ISHLT)	1.4 ± 0.6
Non-immunosuppressive medication	
Diuretic (%)	48
β-blocker (%)	0
Amlodipine (%)	69
ACE-I / ARB (%)	67

Table 2

Exercise parameters (values = mean ± S.D.).
MET: metabolic equivalent.

	Rest	Submaximal exercise level	Maximal exercise level
MET [kcal/kg/h]	1	6.1 ± 2.6	8.5 ± 3.2
Heart rate [beats/min]	95 ± 12	125 ± 18	137 ± 20
Systolic blood pressure [mm Hg]	128 ± 14	156 ± 19	167 ± 22
Diastolic blood pressure [mm Hg]	86 ± 9	83 ± 11	84 ± 13

Table 3

Haemodynamic parameters.
TEF: ejection fraction; LVEDP: left ventricular enddiastolic pressure; PVR: pulmonary vascular resistance; CO: cardiac output.

	Range	Mean ± S.D.
EF [%]	49 – 78	62.4 ± 6.8
LVEDP [mm Hg]	2 – 18	8.7 ± 4.1
PVR [dyn·s/cm^5]	0 – 289	118 ± 54
CO [litres/min]	3.9 – 11.0	6.5 ± 1.5

Predictors of exercise capacity

Univariate analysis demonstrated peak exercise was significantly related to heart rate response ($p = 0.001$), peak heart rate ($p = 0.005$), recipient age $p = 0.009$), diuretic treatment ($p = 0.011$), PVR ($p = 0.018$), the presence of diabetes ($p = 0.021$), and the number of episodes with postoperative right ventricular heart failure ($p = 0.038$). BMI ($p = 0.09$), left ventricular output ($p = 0.147$) and gender ($p = 0.163$) were not significantly related. The significance level was greater than 0.20 for amlodipine medication, peak systolic blood pressure, time posttransplant, left ventricular enddiastolic pressure, number of rejection episodes, aetiology of CHF, dyslipidaemia, donor weight, left ventricular ejection fraction, medication with angiotensin converting enzyme inhibitors or blockers of the angiotensin type I receptor, immunosuppressive medication, peak diastolic blood pressure and ischaemic donor time.

Stepwise multivariate linear regression identified in declining order heart rate response, gender, age, pulmonary vascular resistance, and BMI as predictive variables of exercise capacity after HTx (table 4). Fig. 1 depicts the correlation of the numeric predictors with peak exercise in METs. Altogether, these 5 independent predictors explain 47.5% of variance observed for maximal exercise. In detail, heart rate response explains 31.6%, while all other variables are less relevant (gender 5.2%, age 4.1%, PVR 3.7%, and BMI 2.9%).

Table 4

Predictors of maximal exercise capacity in 51 heart transplant recipients.
PVR: pulmonary vascular resistance; BMI: body mass index.

Independent variable	Added variance explained	Total adjusted R^2
Heart rate response	31.6%	0.316
Gender	5.2%	0.368
Age	4.1%	0.409
PVR	3.7%	0.446
BMI	2.9%	0.475

Discussion

Exercise capacity after heart transplantation remains limited for a multiplicity of reasons. This study identified exercise-induced heart rate increase as one of the most relevant cardiac predictors of exercise capacity in HTx recipients who are more than 6 months posttransplant.

The predictive relevance of chronotropic competence has not been demonstrated unequivocally in the literature. For instance, peak heart rate was not predictive of maximal exercise capacity in a larger study enrolling 174 patients with a postoperative time interval ranging from 0.3 to many years after HTx [13]. In contrast, chronotropic reserve was predictive of maximal oxygen uptake in 85 HTx recipients enrolled 1–100 months after transplantation [27], and in 95 patients studied after the first postoperative year [24]. Subsumption of these results is difficult because some patients were on negative chronotropic medication at the time of exercise testing [24, 27], or were included before chronotropic competence evolved [13, 27, 29]. This study did not include such HTx recipients, and in

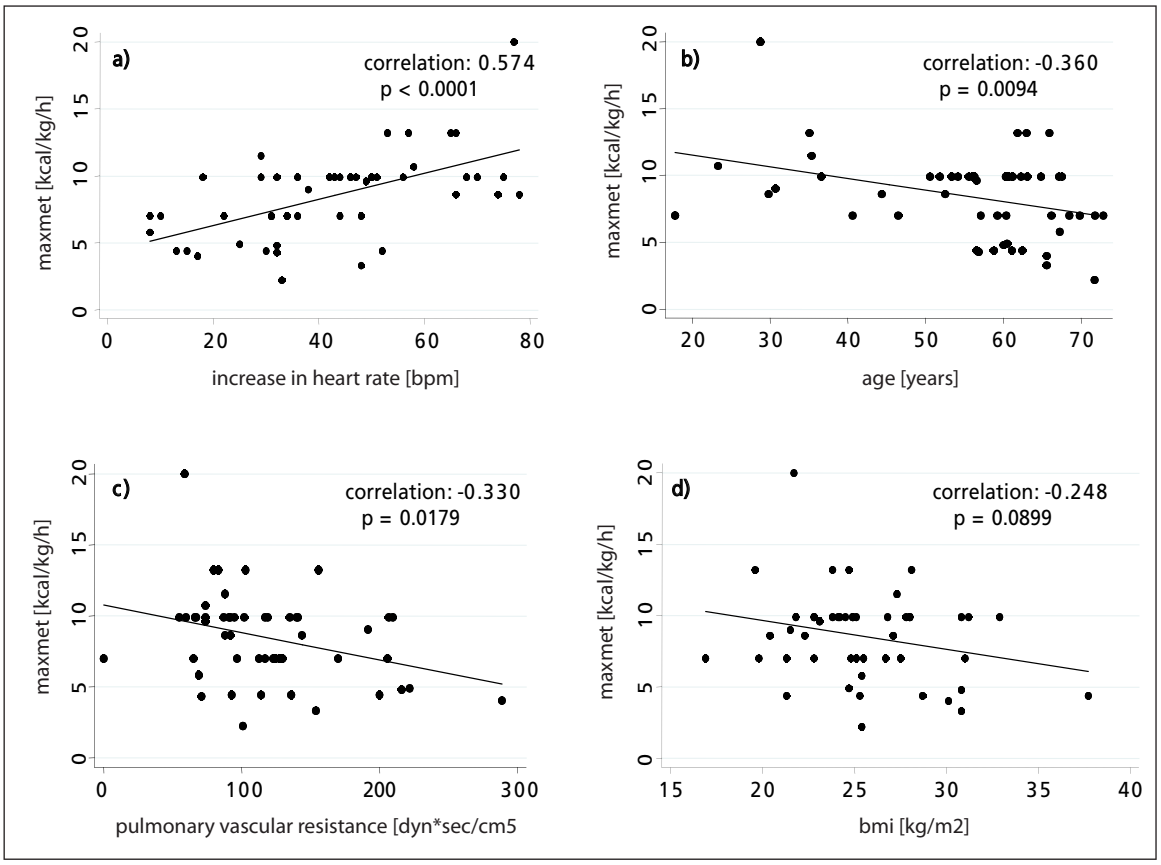

Figure 1

Linear regression between maximal exercise (maxmet) and increase in heart rate (a), age (b) , pulmonary vascular resistance (c), and BMI (d) in the 51 HTx recipients included. Correlations of predictive variables of exercise capacity with exercise capacity. Maxmet: maximal exercise capacity measured in metabolic equivalents.

addition, patients with significant transplant vasculopathy or clinically relevant allograft rejection were excluded from the outset because these factors may affect exercise heart rate and capacity [23].

In fact, exercise-induced heart rate increase explained the largest part (31.6%) of the variance observed for peak exercise in this study, thus underlining the significance of chronotropic competence for exercise capacity after HTx. This observation is in accordance with the relevance of heart rate for the output of the cardiac allograft as demonstrated in haemodynamic studies [28]. A finding of note is that peak heart rate was not predictive in this study, despite its correlation with peak exercise in the univariate analysis. Similar observations are reported from other studies [13, 24], but peak exercise was measured in this study by treadmill exercise testing and therefore we cannot rule out that patients did not exercise to their maximal peak heart rate.

Multivariate analysis identified four additional predictors of peak exercise which contribute another 15.9% to explaining the variance observed. Thus, the five predictors explained together almost half of the variance ($R^2 = 0.475$) observed in peak exercise in this study, in agreement with a result of the same magnitude ($R^2 = 0.51$) reported from another exercise study in 174 HTx recipients [13]. The consistency of these results suggests that both studies may have missed measurement of further variables important for exercise capacity after HTx, such as deconditioning of the skeletal muscle, dysfunctional metabolism of the skeletal muscle posttransplant [20–23], or peripheral blood flow dysregulation. Nevertheless, even if one of the latter variables is of considerable predictive significance, heart rate response should remain important since in this study it explained almost one third of the variance observed.

The other four variables predictive of peak exercise in this study were male gender, explaining 5.2%, age 4.1%, PVR 3.7%, and BMI 2.9%. The minor relevance of PVR and BMI for exercise capacity are in accordance with previous reports [13, 24], although age was only of minor relevance in this study whereas it explained 34% of the variance observed in the study of Gullestad et al. There is no complete explanation for this discrepancy, although differences in the selection criteria or the distribution of the recipient age within the two study collectives may play a role. In addition, the mean postoperative time interval of patients enrolled in this study was longer, and this may have rendered complete chronotropic competence more likely.

Other postoperative variables such as the presence of diabetes, diuretic treatment and the number of episodes of acute right ventricular dysfunction correlated with exercise capacity in univariate analysis but did not remain significant in the stepwise multiple linear regression analysis. Ischaemic donor time, the number of acute allograft rejection episodes or the aetiology of pretransplant heart disease were not related to exercise capacity in this study. These parameters are relevant for short-term morbidity and mortality after HTx [30], and their insignificance indirectly suggests the clinical stability of the patients included into this study.

Limitations of the study

The smaller number of HTx recipients is a limitation which may have prevented identification of other predictive variables. Furthermore, peak exercise capacity was not measured by cardiopulmonary exercise testing, which allows identification of patients not exercising beyond the anaerobic threshold. Because exercise capacity was assessed by treadmill exercise in this study, we cannot rule out that some patients did not exercise to their individual maximum.

Conclusions

This study shows that heart rate response is the most important predictor of exercise capacity in patients without relevant macroscopic coronary angiopathy a long time after HTx. On the basis of our results, monitoring of exercise capacity is recommended in HTx recipients who are started on negative chronotropic medication such as b-blockers or certain calcium antagonists. In addition, heart rate adaptive pacing should be considered, i.e. when chronotropic incompetence in combination with reduced exercise capacity persists more than 6 months after HTx.

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