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MUSCULAR EXERCISE CAPACITY AND BODY FAT PREDICT VO_{2PEAK} IN HEART TRANSPLANT RECIPIENTS

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ABSTRACT

Background: Heart transplant (HTx) recipients usually have reduced exercise capacity, with reported VO_{2peak} levels of 50–70% of predicted values. This study aimed to evaluate central and peripheral factors predictive of VO_{2peak} .

Methods and results: Fifty-one clinically stable HTx recipients >18 years old, and 1–8 years after HTx, underwent maximal exercise testing on a treadmill. Clinical laboratory, hemodynamic and echocardiographic data, lung function and isokinetic muscle strength and muscular exercise capacity were recorded. The mean±SD age was 52±16 years, 71% were male, and time from HTx was 4.1±2.2 years. The patients were assigned to one of two groups: $VO_{2peak} \leq$ or >27.3 mL/kg/min, which was the median value, corresponding to 80% of predicted value. The group with the higher VO_{2peak} had significantly lower body mass index, body fat (%) and triglycerides, and significantly higher body water, muscular exercise capacity, HDL-cholesterol, lung function, mitral annular velocity, peak ventilation, O_2 pulse and VE/ VCO_2 slope. Donor age, recipient age, sex, medication, ischemic time, cardiac dimensions, systolic function and chronotropic responses during exercise were similar. Multiple regression analysis showed that muscular exercise capacity and body fat were the strongest VO_{2peak} predictors.

Conclusions: Chronotropic incompetence is not a limiting factor for exercise capacity in a population of relatively fit HTx patients. The most significant predictors, representing only peripheral factors, are similar to those often determining VO_{2peak} in healthy, non-athletic individuals. Our findings emphasize the importance of a low percentage of body fat and high muscular exercise capacity in order to attain a sufficient VO_{2peak} level after HTx.

Wordcount: 253

Keywords: heart transplant, exercise, exercise test, pulmonary gas exchange, VO_{2peak} , muscle strength, body mass index, body composition, cardiac chronotropy, heart rate.

INTRODUCTION

Physical capacity improves after a heart transplant (HTx) in relation to the recipient's pre-condition, but continues to be subnormal compared with age-matched values in healthy individuals (1;2). The VO_{2peak} levels range from 50% to 70% of predicted values in most studies (1-4), although a few studies have shown very well-trained HTx recipients to achieve normal levels (5;6). Both central hemodynamic and peripheral physiological factors could contribute to the reduced exercise capacity. Central factors could include chronotropic incompetence or reduced stroke volume while peripheral limitations could include reduced muscle strength and oxidative capacity, or abnormal blood supply due to impaired vasodilatory capacity and capillary density (2;4;7). In general, few reports have studied the complicity of reduced physical capacity, and the roles of central and peripheral factors in exercise limitation needs further investigation.

Chronotropic incompetence due to denervation of the heart is usually regarded as one of the most important factors influencing exercise capacity (8-10). However, we have recently demonstrated that the heart rate response improves significantly during the first year after HTx, and that this does not account for all the reduction in exercise capacity (11;12). There is accumulating evidence of structural reinnervation some time after HTx, but the extent of the time frame and the functional significance of possible reinnervation remain unclear. Several studies have documented only sympathetic reinnervation (13), whereas others have described parasympathetic reinnervation (14).

Thus, our hypothesis in the present study was that both central and peripheral factors are involved in exercise limitation in HTx patients, and that common factors determining exercise capacity in healthy, non-athletic individuals may also apply to HTx patients. We therefore evaluated cardiac and pulmonary function, body composition, exercise capacity,

muscle strength and muscular exercise capacity to identify the most strongly predictive variables for $VO_{2\text{ peak}}$ in a group of HTx recipients.

METHODS

Patients and settings

We invited 106 HTx patients to undergo additional exercise testing during their annual follow-up between 2009 and 2010. Forty-nine declined and 57 accepted. The inclusion criteria were: age > 18 years; 1 to 8 years after HTx; optimal medical treatment; stable clinical condition; ability to perform maximal exercise test and provision of written informed consent. Exclusion criteria were: unstable condition; need for revascularization or other intervention; infection; physical disability preventing participation and exercise capacity limited by other disease or illness. The reasons why 49 patients declined to join the study were: did not want to (11); functional disabilities (14); and logistics/other reasons (24). Six of the 57 who agreed to participate were excluded: withdrawal (1); logistics (4); and failed to complete the $VO_{2\text{ peak}}$ test (1). All the 51 participants underwent treadmill exercise testing with gas exchange measurements, isokinetic testing of muscle strength and muscular exercise capacity, blood sampling, measurement of body composition and echocardiography. All participants were treated according to our immunosuppressive protocol with ciclosporin, tacrolimus and/or everolimus, corticosteroids and mycophenolate mofetil or azathioprine, in addition to statins (Table 1).

The study was approved by the South-East Regional Ethics Committee in Norway and by the local ethics committee in our hospital. All procedures were performed in accordance with the recommendations in the Helsinki Declaration. ClinicalTrial.gov identifier: NCT01091194.

Treadmill protocol

We used a modified test protocol from the Working Group on Cardiac Rehabilitation & Exercise Physiology and Working Group on Heart Failure of the European Society of Cardiology (15). Patients started with a warm-up of 10 min on a Runrace Treadmill (Technogym, Cesena, Italy) during which their individual walking speed was determined. After the test was started, the inclination of the treadmill was increased by 2% every 2 min. All patients continued until volitional fatigue. Test termination criteria were a respiratory exchange ratio (RER) > 1.05 and/or rated perceived exertion (Borg 6–20 scale) > 18 (16). Lung function and breath gas exchange were measured using the SensorMedics Vmax (Yorba Linda, CA). ECG and HR were monitored continuously before, during and after exercise. Uptake of O₂, CO₂ production, maximum ventilation (VE_{max}) and RER were calculated online. Blood pressure was measured automatically (Tango, Sun Tech Medical Instruments, NC) before exercise, every 2 min during exercise, and after exercise. After termination of the test, the treadmill was stopped and the patients rested in an upright position for a recovery period of 2 min. VO_{2peak} was calculated as the mean of the three highest 10 s measurements before volitional fatigue was reached. Predicted values were based on the American College of Sports Medicine 2009 guidelines (17). Ventilatory efficiency, described as VE/VCO₂ slope (18;19), was calculated with the slope calculation option of the Vmax software. O₂-pulse is an indirect index of cardiopulmonary oxygen transport; it is strongly correlated with cardiac output and is a surrogate of stroke volume (1;19). It was calculated as the ratio of VO₂ (mL/min) to HR. HR peak was the peak HR during exercise. Age-predicted maximum HR (%HR_{max}) was calculated as: $\text{HR peak} / (220 - \text{age}) \times 100$, with <85% considered pathologically low (20). HR reserve was measured using the difference between HR peak and HR at rest (recorded at rest during echocardiography). Age-predicted HR reserve, or chronotropic response index (CRI), was calculated as $(\text{HR peak} - \text{HR rest}) / (220 - \text{age} - \text{HR rest})$, where a

ratio <0.80 was considered abnormal (20).

Bioelectrical impedance analysis

Compared with the gold-standard in body composition measurement—dual-emission X-ray absorptiometry (DXA)—bioelectrical impedance analysis (BIA) is considered a reliable and more accessible method of body composition screening (21), although BIA may have limited validity in the accurate measurement of very obese individuals and larger fat losses (22).

Body composition data were collected using Tanita 418MA BC-558 systems (Tanita Corporation, Arlington Heights, IL). Several Tanita models have been validated against DXA and measurements have proven to be highly correlated (21;23). The recorded variables included body mass index (BMI), body fat, total body water, muscle mass, visceral fat, bone mass, metabolic age and basal metabolic rate. All participants were screened at the same time of day, with means of three measurements calculated for all patients. No significant differences were calculated when 20% of measurements from the Tanita BC-558 were compared with those from the 418MA.

Muscle strength and muscular exercise capacity

Quadriceps (extension) and hamstrings (flexion) muscle strength and muscular exercise capacity were tested isokinetically (Cybex 6000, Lumex Inc., Ronkonkoma, NY). The participants were in a sitting position, testing one leg at a time. Muscle maximal strength was tested at an angular velocity of 60°/s. Five repetitions were performed, with the mean peak value in Newton meter (Nm) calculated for each patient. Muscular exercise capacity was measured as total work during thirty isokinetic contractions at 240°/s, with total work in Joule (J) calculated as the sum of all repetitions.

Echocardiography

A standard echocardiographic examination was performed with Vivid 7 or E9 (GE Vingmed Ultrasound, Horten, Norway) with the participants in the left lateral position. Three consecutive heart cycles were obtained from three apical projections; images with two-dimensional gray-scale echocardiography and color tissue Doppler imaging (cTDI) were obtained. All data were stored digitally and analyzed offline using an Echopac PC (GE Vingmed Ultrasound). LV ejection fraction (EF) and LV volumes were measured with the modified Simpson method, using the four- and two-chamber views (24). LV mitral annular velocities in early diastole (LVE') were averaged from cTDI measurements at the septal, lateral, anterior and posterior points (25).

Laboratory tests

All participants underwent regular blood screening in the morning, in a fasting state: hemoglobin (Hb), white blood cells, C-reactive protein (CRP), creatinine, urea, estimated glomerular filtration rate (eGFR), uric acid, liver and thyroid function, lipid status, glycemic control and N-terminal prohormone of brain natriuretic peptide (NT-proBNP).

From the 18-mL samples, 6 mL was used to prepare serum and 12 mL was used to prepare plasma. The plasma samples in EDTA-tubes were immediately placed on ice and centrifuged within 30 min. Samples for serum were kept at room temperature for 1-2 hours, centrifuged, and then the supernatant fractions were removed into cryo-tubes and frozen (-80°C) for later analysis.

Statistical analysis

All data were analyzed using SPSS, version 18.0 (Chicago IL, USA). Continuous data are expressed as mean \pm SD or median (range) and categorical data are presented as counts and

percentages. The 51 patients were divided into two groups with respect to median $\text{VO}_{2\text{peak}}$ (mL/kg/min): Group 1 (G1), $\text{VO}_{2\text{peak}} \leq 27.3$; Group 2 (G2), $\text{VO}_{2\text{peak}} > 27.3$. Between-group comparisons were made using unpaired t or Mann–Whitney U tests, as appropriate. For categorical data χ^2 and Fischer’s exact test were used. Bivariate relationships were explored and univariate regression analysis was performed with potential predictors (Table 1). Well-documented predictors and potential predictors with $p < 0.05$ were included in a multiple regression analysis to identify the degree of association with $\text{VO}_{2\text{peak}}$. Hierarchical multiple regression was used to build the final multiple regression model. The model assumptions were thoroughly checked for outliers, normality, homoscedasticity, independence of residuals, possible interactions and multicollinearity.

RESULTS

Clinical characteristics

The mean age was 52 ± 16 (range 19–71) years, 71% were men, and the mean time after transplantation was 4.1 ± 2.2 years. Mean duration of heart failure prior to HTx was 4.3 ± 4.1 years. At the time of study inclusion, 22% were defined as inactive (≤ 30 min exercise once a week), 50% as moderately active (≥ 30 min, two to three times per week) and 28% as very active (≥ 30 min, \geq four times per week). Baseline clinical characteristics are shown by group in Table 1.

While several baseline clinical characteristics, including donor age, recipient age, sex, time after HTx, medication and ischemic time were similar between the groups, body composition showed marked differences.

Exercise responses

The median VO_{2peak} was 27.3 (range 13.9–44.0), corresponding to approximately $80\pm 20\%$ of predicted value. Cardiopulmonary exercise responses, muscle strength and muscular exercise capacity are shown in Table 2. The group with the highest VO_{2peak} walked a longer distance and for a longer time, and had a higher gradient on the treadmill, while maximal effort assessed by peak RER or peak RPE on the Borg 6–20 scale (16) was similar between the two groups.

Body composition and biochemistry

G2 had significantly lower body fat, visceral fat, BMI and metabolic age than G1. The percentage of body water was significantly higher in G2, whereas muscle mass, bone mass and basal metabolic rate were not significantly different, though they were numerically higher in G2. Markers of renal function, HDL-cholesterol, HbA_{1c} and triglycerides, were also in favor of G2 while CRP, Hb and NT-proBNP were similar. The wide NT-proBNP interquartile range in G1 (Table 1) is due to one extreme value, but this did not affect the significance level between groups.

Cardiopulmonary function and hemodynamics

Early diastolic mitral annular velocity (LVE') was significantly higher in G2, while other echocardiographic variables were similar (Table 1). G2 had a significantly higher peak O_2 -pulse (Table 2). Resting HR and diastolic blood pressure were similar, while resting systolic blood pressure was significantly higher in G2 (Table 2). During exercise, however, there were no differences between systolic blood pressure, peak HR or pulse pressure. In fact, $\%HR_{max}$ and CRI were close to normal (Table 2). There were no significant correlations between VO_{2peak} and peak HR, $\%HR_{max}$ or CRI in the total study population. HR reserve and VO_{2peak} had a relatively weak correlation: $r= 0.34$ ($p<0.05$). Pulmonary function variables determined

at rest (FEV₁, PEF) and during exercise (VE_{max}, VE/VCO₂ slope) were all significantly better in G2 ($p < 0.05$).

Muscle strength and muscular exercise capacity

G2 had markedly better maximal muscle strength and muscular exercise capacity in both quadriceps and hamstrings than G1 (Table 2), and both maximal muscle strength and muscular exercise capacity were significantly correlated with all VO_{2peak} variables, although muscular exercise capacity had the highest correlation: VO_{2peak} L/min ($r=0.79$); VO_{2peak} ml/kg^{0.75} ($r=0.63$); VO_{2peak} mL/kg/min ($r=0.51$); VO_{2peak} % of expected ($r=0.31$).

VO_{2peak} determinants

Known central predictors such as peak HR and LV function were not significant contributors in the multiple linear regression analysis with VO_{2peak} (mL/kg/min) as the dependant variable.

The variables age, sex, muscular exercise capacity (quadriceps+hamstrings), body fat (%), blood creatinine and HR reserve accounted for 70.8% of the variance in VO_{2peak} (adjusted $R^2=0.708$, $p < 0.001$). Using the hierarchical 'enter' method we addressed each variable's contribution to the model as a whole, with results presented here as R^2 change (% explained variance), p value: age 0.014 (1.4%), $p=0.414$; sex 0.025 (2.5%), $p=0.265$; muscular exercise capacity 0.209 (20.9%), $p < 0.001$; body fat 0.424 (42.4%), $p < 0.001$; creatinine 0.042 (4.2%), $p=0.014$; and HR reserve 0.029(2.9%), $p=0.031$.

For comparison and verification we forced the same independent variables into a model with % of expected VO_{2peak} as the dependent variable in place of VO_{2peak} (mL/kg/min). As both body fat and expected VO_{2peak} were calculated in %, we exchanged body fat with BMI in this model. Age now explained 8.1% of the VO_{2peak} variance, sex: 2.4%, muscular exercise capacity 16.0%, BMI 37.1%, creatinine 5.3% and HR reserve 1.6%. The second

model as a whole explained 66.5% (adjusted $R^2=0.665$). Both models clearly indicate muscular exercise capacity and body fat as the most important predictive factors in this group of HTx recipients.

DISCUSSION

The main finding in this study is that muscular exercise capacity and body fat (%) were more strongly predictive of VO_{2peak} in a group of HTx recipients than the more common and well-documented central factors such as cardiac dimensions and chronotropic responses. Sex, blood creatinine and HR reserve were less strongly predictive of VO_{2peak} .

Peripheral factors

Muscular exercise capacity and amount of body fat are factors known to influence the physical capacity of healthy, non-athletic individuals. In HTx patients, central factors such as chronotropic incompetence due to denervation and diastolic dysfunction are often more significant (10;26). In our cohort, the chronotropic responses were close to normal and the only apparent limiting central factor was reduced diastolic function (from LVE \dot{V}) in G1 compared to G2, though this was not a significant contributor in the multiple regression analysis. Thus, our findings do not unconditionally support the theory that both central and peripheral factors influence exercise capacity in all HTx patients, but rather suggest that limiting factors are, mainly, peripheral and can be similar to those that determine exercise capacity in healthy, non-athletic individuals. Indeed, peripheral limitations may dominate in the general HTx population, while central limitations may be more apparent in well-trained subjects (6).

The association between VO_{2peak} and muscular exercise capacity (Figure 1) is an important finding. Such results have been observed among athletes (27) and in studies of HTx

patients (28;29). The finding underscores the importance of good peripheral function in order to maintain or improve VO_{2peak} and suggests that resistance training should be an integrated part of rehabilitation programs in this group of patients.

There was a strong negative correlation between BMI and VO_{2peak} , and between body fat and VO_{2peak} (Figure 2). Similar observations have been reported in the general population (30) and in HTx patients (31). Data on body composition and BIA in HTx patients are very limited. We found that full body composition screening not only provided detailed information, but was a valuable tool for motivating patients for further exercise. Although our study demonstrates that HTx patients with normal body fat and BMI have better exercise capacity, it is not clear whether weight reduction is, in itself, sufficient to improve VO_{2peak} . Body water is mainly regulated by hormones, but obesity also decreases the percentage of body water as fat holds a certain amount of fluid. Similarly, a higher percentage of body water indicates a larger amount of muscle and lean tissue (32). This is also reflected in our study, not only by a higher percentage of body water and better muscular exercise capacity in the group with higher VO_{2peak} , but also in the lower amount of body fat and better overall body composition.

In the current study, the blood level of creatinine was a minor, but significant, contributor to the explanation of VO_{2peak} variance. The profile of creatinine level, urea, $eGFR$ and amount of body water which was borderline better in G2 than in G1 supports the role of renal function as a factor limiting physical capacity in HTx recipients. Furthermore, impaired renal function is associated with muscle dysfunction (33) and this supports the importance of resistance training in HTx rehabilitation programs to improve muscular fitness and VO_{2peak} .

Central factors

Previous studies have shown a good correlation between $VO_{2\text{peak}}$ and cardiac output (1), this implies a higher stroke volume in G2 as peak O_2 -pulse was significantly higher in this group and there is a strong correlation between $VO_{2\text{peak}}$ and O_2 -pulse ($p < 0.01$). Stroke volume appears to be of major importance for exercise capacity in HTx patients, although it was not a limiting factor in our study. The importance of stroke volume is supported by Kao et al.(34), who demonstrated, using radionuclide angiography, a marked reduction in stroke volume during peak exercise in HTx patients. Furthermore, the reduction in stroke volume was mainly due to diastolic dysfunction (34), in accordance with our observations of lower LVE' in G1. NT-proBNP values, which reflect myocardial strain and correlate with filling pressures (35), were, however, similar between the groups in the current study.

Chronotropic responses were close to normal (Table 2) in the current study and, thus, were not limiting for exercise capacity. The close-to-normal values probably explain why chronotropic response was of little predictive value in this study. The influence of beta blockers has been thoroughly evaluated, but their use was not significantly different between groups, nor significantly correlated with $VO_{2\text{peak}}$ or significant in the regression analysis.

The number of ex-smokers was numerically higher (Table 1) and lung function lower (Table 2) in G1, but neither of these factors were significant in the multiple regression analysis. The incidence of chronic obstructive pulmonary disease was similar between groups.

Limitations

The study population was relatively fit, with a $VO_{2\text{peak}}$ level corresponding to approximately $80 \pm 20\%$ of predicted, which is higher than in our previous work with unselected HTx patients (3) and most other studies (1;2;4), but not as high as in a few other studies on well-trained HTx recipients (5;6). Although the mean $VO_{2\text{peak}}$ was relatively high, the values were normally distributed, ranging from 13.9 to 44.0, indicating a heterogenous group rather than

solely well-trained subjects. Yet, the inclusion criteria may have led to a selection bias; participants were defined as stable and healthy, and they possibly had a higher-than-average motivation for exercise.

Conclusions

In summary, this study demonstrates that chronotropic incompetence is not a limiting factor for exercise capacity in a population of relatively fit HTx recipients. The most significant predictors are comparable with factors often determining VO_{2peak} in healthy, non-athletic individuals. In this population, the most important predictors, representing only peripheral factors, are body fat and muscular exercise capacity. This suggests that it is important to increase muscle strength and muscular exercise capacity and maintain a low percentage of body fat and normal BMI in order to attain a sufficient VO_{2peak} level after HTx.

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Declaration of conflicting interests

The authors declare that there is no conflict of interest.

Legends for Illustrations

Figure 1

Scatter plot of the correlation between $\text{VO}_{2\text{peak}}$ (mL/kg/min) and muscular exercise capacity

(J). $N=51$

Figure 2

Scatter plot of the correlation between $\text{VO}_{2\text{peak}}$ (mL/kg/min) and percentage of body fat.

$N = 51$

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