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Cardiac Allograft Hypertrophy Is Associated With Impaired Exercise Tolerance After Heart Transplantation

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Abstract

Background—Exercise performance, an important aspect of quality of life, remains limited after heart transplantation (HTx). This study examines the effect of cardiac allograft remodeling on functional capacity after HTx.

Methods—The total cohort of 117 HTx recipients based on echocardiographic determination of left ventricle mass and relative wall thickness at 1 year after HTx, was divided into 3 groups: (1) NG - normal geometry (2) CR - concentric remodeling and (3) CH - concentric hypertrophy. Cardiopulmonary exercise testing was performed 5.03±3.08 years after HTx in all patients. Patients with acute rejection or significant graft vasculopathy were excluded.

Results—At 1 year after HTx, 30% patients had CH, 55% had CR and 15% demonstrated NG. Exercise tolerance measured by maximum achieved metabolic equivalents (4.62 ± 1.44 vs. 5.52 ± 0.96 kcal/kg/h), normalized peak VO_2 ($52 \pm 14\%$ vs. $63 \pm 12\%$) and $\text{V}_E/\text{V}_{\text{CO}_2}$ (41 ± 17 vs. 34 ± 6) were impaired in the CH group compared to the NG group. A peak VO_2 14 ml/kg/min was found in 6%, 22% and 48% in the NG, CR and CH groups respectively ($p=0.01$). The CH pattern was associated with a 7.4 – fold increase in relative risk for a peak VO_2 14 ml/kg/min as compared to NG patients (95% CI 1.1 – 51.9, $p=0.001$). After multivariable analysis, a 1-year CH pattern was independently associated with reduced normalized peak VO_2 ($p=0.018$) and an elevated $\text{V}_E/\text{V}_{\text{CO}_2}$ ($p=0.035$).

Conclusion—The presence of CH one year after HTx is independently associated with decreased normalized peak VO_2 and increased ventilatory response in stable heart transplant recipients. The identification of CH, a potentially reversible mechanism of impairment in exercise capacity after HTx, could have important clinical implications.

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Introduction

Heart transplantation (HTx) is an established therapeutic option for patients with end-stage heart failure resulting in improvement in survival and symptoms. However, despite restoration of left ventricular ejection fraction (EF), exercise performance, an important determinant of quality of life(1), remains limited after HTx and reported to be just 50% to 60% level of age-matched healthy controls(2–4) which may not be different from that of medically stable heart failure patients.(5)

There are multiple factors that could affect exercise performance after heart HTx and these include recipient's age, gender, body mass index (BMI),(6) chronotropic incompetence, (5, 7) diastolic dysfunction,(5, 8) defective adrenergic signaling, altered intracellular calcium handling,(9–11) transplant vasculopathy,(12) endothelial dysfunction(13) and skeletal muscle abnormalities.(11, 14, 15)

The implications of left ventricular hypertrophy (LVH) are widely recognized in hypertension(16) and systolic heart failure(17) in terms of cardiovascular events(18) and exercise performance.(19) Only recently has cardiac allograft remodeling after HTx been recognized to be of prognostic importance in the management of HTx recipients. The presence of LVH one year after HTx has been shown to be associated with subsequent mortality in HTx.(20, 21) However, the effect of LVH on exercise performance after HTx remains unclear. This study was therefore undertaken to characterize the significance of cardiac allograft remodeling assessed at one year by echocardiography, on subsequent exercise capacity as assessed by cardiopulmonary exercise testing in HTx recipients.

Methods

The study was performed at Mayo Clinic, Rochester, and approved by the appropriate institutional review board.

Patient characteristics

A total of 151 consecutive subjects who underwent HTx between 1997 and 2005 and survived at least 1 year were analyzed. Patients with history of significant rejection (ISHLT Grade 2R), cardiac allograft vasculopathy (stenosis ≥40% in any major coronary branch) and significant valvular disease at the exercise test were excluded. Although C4d staining was not routinely performed in our program, patients with acute cardiac allograft dysfunction in the absence of significant cellular rejection which responded to antibody-directed therapeutic interventions were defined as antibody-mediated rejection (AMR) and were also excluded from the study.

Finally, 117 patients were enrolled in the study. All subjects were in sinus rhythm without cardiac pacing. The total rejection score (TRS) was calculated as previously described.(21) Heart rate, blood pressure and BMI were recorded at the time of the echocardiogram.

Echocardiographic measures

All echocardiograms were performed at Mayo Clinic, Rochester using a standardized protocol one year after HTx and at the time CPET. Left ventricular end-diastolic dimension (LVDD) and end-systolic dimension (LVSD), posterior wall thickness (EDPWT) and interventricular septum thickness (EDST) were measured by 2-D echocardiography.(22) Relative wall thickness was calculated as $(RWT = EDPWT + EDST / LVDD)$.(23) Left ventricular mass (LVM) was calculated according the formula $0.8 \times (1.04 [(LVDD + EDPWT + EDST)^3] - (LVDD)^3 + 0.6g)$.(24)

Combining RWT with the value of LVM allows determination of the type of geometric pattern.(23) Thus, the sample cohort was divided for analysis into sub-groups based on the echocardiographic determination of left ventricle geometry at 1 year after transplantation: (1) patients with NG, (RWT <0.42 and LVM < 225 gm for men and < 163 gm for women); (2) patients with CR, (RWT ≥ 0.42, LVM < 225 gm (163 gm for women)); (3) patients with EH, (RWT < 0.42, LVM ≥ 225 gm (163 gm for women)) and (4) patients with CH, (RWT ≥ 0.42, LVM ≥ 225 gm (163 gm for women)).(22) Diastolic characteristics were assessed by pulse and tissue Doppler.(25, 26) However, early (E) and late (A) mitral inflow velocities waves were differentiated only in 58% of the patients and non interpretable because of fusion as a result of sinus tachycardia. Therefore, in most patients diastolic function could not be graded. Medial mitral annular velocity (E') as assessed by tissue Doppler and E/E' was used as a marker of diastolic function.

Cardiopulmonary Exercise Testing (CPET)

CPET was performed 5.03±3.08 years after HTx as part of the post-transplantation evaluation. Symptom-limited, treadmill exercise testing with respiratory gas exchange analysis using a modified Naughton protocol (2-min workloads, 2 METs/workload increments in work) was performed.(27) Electrocardiograms were continuously monitored and blood pressure was assessed the last 30 seconds of each 2-min workload. Exercise duration was expressed in minutes and as a percentage of age and gender-predicted values. (28) Breath-by breath minute ventilation (VE), carbon dioxide production (VCO₂), ventilator equivalent for CO₂ (VE/VCO₂), and oxygen consumption (VO₂) were measured using a Medical Graphics metabolic cart (St. Paul, Minnesota). Calibration used gravimetric quality gases before each test and physiologic calibration was performed for weekly quality control. Peak VO₂ was the highest averaged 30 second VO₂ during exercise and was expressed as absolute peak VO₂ or normalized peak VO₂ (percentage of age, gender, and weight predicted).(28) Normalized peak VO₂ was calculated offline. Maximal exercise tolerance was measured in metabolic equivalents (METs). One MET of task is the energy expended by an average individual at rest, defined by convention as a whole-body oxygen consumption of 3.5 mL of oxygen per kilogram of body weight per minute. Quality of exercise effort was assessed by respiratory exchange ratio (RER).(29)

Statistical Analysis

Data were summarized using means ± standard deviation for numeric variables, and percents and counts for categorical variables. Baseline characteristics between the groups were compared using an ordinal logistic regression. Correlations were assessed using linear regression for continuous variables and Spearman regression for categorical variables. Least-square regression analysis models included variables with significance level p ≤ 0.1 in univariate analysis and were used to estimate the relative contributions of the baseline clinical and echocardiographic variables to exercise capacity assessed in metabolic equivalents, absolute and normalized peak VO₂ and VE/VCO₂. Differences in LVM, RWT and LA from baseline to 1 year and 5.03±3.08 years follow-up within groups were compared using a paired t-test. All of the analyses were 2-sided. A p value <0.05 was considered to be statistically significant.

Results

Study Population

Amongst the 117 HTx recipients 34 (30%) patients had CH, 64 (55%) had CR and 18 (15%) demonstrated NG one year after HTx. No patient exhibited EH pattern.

Patients with CH had a higher BMI as compared to patients in the NG and CR groups; and were on a higher mean prednisone dose as compared to the CR group. (Table 1)

Echocardiographic Parameters—There were no differences in systolic or diastolic parameters between the CH, CR and NG groups at the 1 year post HTx echocardiographic study (Table 2A). Stroke volume and LV ejection fraction was preserved in all patients.

The echocardiographic parameters obtained at the time of CPET are listed in Table 2B. LVM at one year after HTx correlated strongly with LVM ($r_s = 0.73$, $p < 0.001$) and RWT ($r_s = 0.52$, $p < 0.001$) measured during the echocardiographic study performed at the time of CPET. There were no significant differences in RWT and LVM (Table 3) in the 3 groups when compared to values obtained during echocardiography one year after HTx suggestive of minimal change in LV mass overall in the 3 groups over time.

LA volume increased in the CR (from 80 ± 29 ml to 94 ± 40 ml, $p = 0.38$) and in the CH group (from 98 ± 46 ml to 105 ± 39 ml, $p = 0.48$) and did not change in the NG group (71 ± 34 ml vs. 73 ± 35 ml, $p = 0.61$) during the follow-up period. However, LA volume measured at the time of CPET was significantly higher in the CR and the CH groups as compared to the NG group.

Exercise Parameters—The exercise data obtained during CPET is outlined in Table 3. The resting heart rate and blood pressure was similar in all 3 groups at the time of CPET. The average exercise duration for the entire cohort was 6.88 ± 2.20 min and did not significantly differ between the 3 groups. Exercise capacity as measured in METs was significantly reduced in the CH group (4.62 ± 1.44 kcal/kg/h) as compared to the NG group (5.52 ± 0.96 kcal/kg/h, $p = 0.03$) with a trend towards reduction noted in the CR (5.14 ± 1.36 kcal/kg/h, $p = 0.09$) group. The primary reason for stopping exercise was fatigue in 61 (53%), dyspnea in 37 (32%) and leg discomfort in 17 (15%) of the patients. The respiratory equivalent ratio (RER) was 1.20 ± 0.11 and did not differ between the groups indicating good exercise effort. There was no significant difference between the 3 groups in changes in heart rate or blood pressure during exercise.

The average peak VO_2 was 18.9 ± 2.9 , 18.2 ± 5.1 and 16.3 ± 5.0 ml/kg/min in the NG, CR and CH groups respectively with a trend towards a reduced peak VO_2 in the CH group as compared to the NG ($p = 0.06$) and CH group (0.07). A peak VO_2 ≤ 14 ml/kg/min was found in 1 (6%) patient with NG, 14 (22%) patients with CR and 14 (48%) patients with CH pattern ($p = 0.01$). The presence of CH pattern one year after transplantation was associated with a 7.4 – fold increase in relative risk for a peak $\text{VO}_2 \leq 14$ ml/kg/min as compared to NG patients (95% CI 1.1 – 51.9, $p = 0.001$) and 1.9 – fold increase in relative risk for peak $\text{VO}_2 \leq 14$ ml/kg/min as compared to CR group (95% CI 1.0 – 3.5, $p = 0.04$).

Normalized peak VO_2 was significantly lower in the CH group (52 ± 14 % predicted) as compared to the NG group (63 ± 12 % predicted, $p = 0.01$) and the CR group (60 ± 16 % predicted, $p = 0.02$).

The ventilatory equivalent for CO_2 ($\text{V}_E/\text{V}_{\text{CO}_2}$) was 41 ± 17 in the CH group and was significantly higher than the CR (36 ± 7 , $p = 0.04$) and NG groups (34 ± 6 , $p = 0.05$). A $\text{V}_E/\text{V}_{\text{CO}_2} \geq 40$ was found in 1 (6%) patient with NG, 14 (22%) patients with CR and 14 (48%) patients with a CH pattern at 1 year ($p = 0.04$). The presence of a CH pattern was associated with a 2.2 – fold increase in relative risk for a peak $\text{V}_E/\text{V}_{\text{CO}_2} \geq 40$ ml/kg/min as compared to NG and CR patients (95% CI 1.02 – 4.58, $p = 0.04$).

Relationship between the Clinical and Echocardiographic Variables and Post-transplant Exercise Capacity

The geometric LV pattern ($p=0.005$), BMI ($p=0.01$) and GFR ($p=0.004$) one year after HTx correlated significantly with exercise intolerance as measured by metabolic equivalents by univariate analysis. However by multivariable analysis, only BMI and GFR remained statistically significant. Importantly the geometric pattern of the LV was, both by univariate and multivariable analysis, a significant correlate of a reduced peak VO_2 , reduced normalized peak VO_2 and elevated VE/VCO_2 . This and other correlates after univariate and multivariable analysis are presented in Tables 4A, 4B, 4C and 4D. A reduction in absolute and normalized peak VO_2 was associated with older recipients' age at HTx, older donors' age and higher BMI in addition to an abnormal LV geometric pattern. Elevated VE/VCO_2 was associated with an increase in heart rate and right ventricular systolic pressure in addition to an abnormal geometric pattern of the LV.

Discussion

The current study is the first to demonstrate that the presence of concentric LVH one year after HTx is one of the strongest correlates of exercise intolerance after HTx. Concentric LVH was independently associated with a reduction in normalized peak VO_2 and a worsening of ventilatory response to exercise as evidenced by an increase in peak VE/VCO_2 . This relationship remained significant after taking into account the resting blood pressure, heart rate and blood pressure response to exercise, immunosuppression, antihypertensive medication use and other echocardiographic parameters.

Normalized peak VO_2 is now recognized as a more reliable and important exercise parameter determining prognosis in heart failure than peak VO_2 alone.(30) In addition, VE/VCO_2 suggested to be the most stable and reproducible marker of ventilatory efficiency,(31) and has been demonstrated to be a powerful predictor of risk for mortality, hospitalization, and other outcomes especially at values greater or equal to 40.(32) Interestingly, in our study approximately 50% of the HTx recipients with CH had peak VO_2 14 ml/kg/min and a VE/VCO_2 40. These values are seen more typically in patients with severe heart failure, and it is not surprising that patients with CH have a poor prognosis as demonstrated in our earlier study.(21)

The reduced normalized peak VO_2 in conjunction with an increased VE/VCO_2 in patients with CH also provides a possible mechanistic insight into the cardiopulmonary limitations to exercise in the patients with CH. LV diastolic function is an important determinant of maximal exercise performance after HTx.(8, 33). The combination of reduced normalized peak VO_2 and increased VE/VCO_2 is suggestive of increased pulmonary congestion likely due to worsening diastolic dysfunction occurring during exercise. (34) Although exercise hemodynamics were not obtained in this study by invasive or non-invasive techniques, an elevated VE/VCO_2 ratio is indicative of pulmonary congestion and in the setting of preserved LVEF may imply diastolic dysfunction as a cause of impaired exercise capacity. In a non-transplant population evidence of concentric LV remodeling is a potential surrogate for diastolic LV dysfunction.(35) Moreover, concentric hypertrophy is considered to be sufficient evidence for the diagnosis of diastolic dysfunction when tissue Doppler yields non-conclusive results.(36) Therefore, the current study suggests that decreased exercise tolerance in heart transplant recipients with concentric hypertrophy of cardiac allograft may result from LV diastolic dysfunction, although we do not have conclusive evidence to prove the same.

Left atrial volume is another useful marker of the severity and duration of diastolic dysfunction in a non-transplant population,(37) After HTx the left atrium is usually

enlarged, and the use of this marker for assessment of cardiac allograft diastolic function has not been validated. However, an increase in left atrial size post heart transplantation correlates inversely with survival and hence is an important echocardiographic parameter for the heart transplant recipient.(38). In the present study LA volume increased in the CR and the CH groups during follow-up and was significantly higher when measured at the time of the CPET in the CH and the CR groups as compared to the NG patients. This increase in left atrial size may reflect the cumulative effect of increased filling pressures over time (39).

Amongst the various echocardiographic parameters, an $E/E' \geq 10$ was the strongest predictor of reduced exercise tolerance in non-transplant population.(40–42) In the present study the mean E/E' was greater than 10 in both the CR and CH groups. Furthermore, a lower E' and higher E/E' ratio was associated with reduced oxygen uptake and increased ventilatory equivalent by univariate analysis (Table 4C and 4D). This association, however, disappeared after multivariable analysis when LV geometry was added to the model demonstrating the independent importance of concentric hypertrophy and its association with cardiopulmonary limitations to exercise. HTx recipients despite having a preserved left ventricular ejection fraction historically have suboptimal exercise performance with a reported 60% reduction in exercise capacity as compared to normal controls.(33) In this study, HTx recipients with NG and CR patterns similarly demonstrated normalized peak $\dot{V}O_2$ of approximately 60% of normal controls. Moreover, normalized peak $\dot{V}O_2$ in recipients with a CH pattern was further reduced at approximately 52% of controls. Clinical factors such as increased BMI, uncontrolled hypertension, oral prednisone and calcium channel blocker use reported to contribute to reduced exercise tolerance in HTx recipients. This study confirms the association of obesity and increased recipient age with impaired exercise capacity as shown in prior studies.(6) Chronotropic incompetence has been reported as a mechanism for reduced exercise tolerance in HTx recipients,(5, 13) however, chronotropic and blood pressure response to exercise was not significantly different amongst the 3 groups in our study. The other variables that were associated with a reduced $\dot{V}O_2$ and increased $\dot{V}E/\dot{V}CO_2$ ratio were higher right ventricular systolic pressure and reduced renal function as measured by GFR. Mean pulmonary arterial pressures can increase by 45% in HTx recipients with exercise(43) and hence increased right ventricular systolic pressures at rest could be associated with exercise intolerance. Chronic kidney disease is common after cardiac transplantation(44) and can be a major source of morbidity and mortality(45). Consistent with previous data(46) we demonstrate that recipients receiving long-term prednisone have decreased exercise capacity: the maintenance dose of prednisone at 1 year inversely correlated with exercise capacity in univariate analysis. However this association disappeared after echocardiographic measurements were added to the multivariate model.

The role of concentric hypertrophy in limiting exercise capacity after HTx has not been previously explored although this phenomenon has been described in other patient populations.(47, 48) Concentric LVH is an independent risk factor for cardiovascular complications and morbidity in essential hypertension(49–51) and it is associated with impaired exercise performance in hypertensive patients.(19) After HTx, adverse left ventricle remodeling at 1 year has been shown to be associated with subsequent development of cardiac allograft vasculopathy and mortality.(20, 21) This process of cardiac allograft remodeling is common and occurs early after HTx. It has been shown previously by our group that most recipients with concentric LVH at 1 year after HTx continue to demonstrate an abnormal LV geometric pattern up to 5 years of follow up.(21) In addition to the 1 year post transplant echocardiogram performed in this study, echocardiography was also performed at the time of CPET. Importantly, there were no significant changes in relative wall thickness, left ventricle mass and geometry in the 3 groups at the time of CPET.

It is now increasingly recognized in the HTx community that there exists a need for a surrogate marker of long term prognosis of HTx recipients and the one year post transplant echocardiogram may help in part fulfill that need.(52) The present study extends our previous findings (20, 21) of the importance of CH and demonstrates that the presence of CH 1 year after HTx could serve as a surrogate marker for subsequent development of exercise intolerance. A change in immunosuppressants from cyclosporine to tacrolimus or sirolimus has been associated with regression of LV mass.(53, 54) Whether such interventions will lead to improved exercise capacity and quality of life in HTx recipients remains to be proven.

Cardiac allograft remodeling and the presence of concentric LVH at one year after HTx in stable heart transplant recipients is associated with decreased exercise capacity, decreased normalized peak VO₂ and increased ventilatory response. The detection, prevention, and reversal of concentric LVH could serve as important goals to improve morbidity and mortality after HTx.

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References

1. Grady KL. Quality of life after heart transplantation: are things really better? *Curr Opin Cardiol.* 2003; 18:129–135. [PubMed: 12652219]
2. Osada N, Chaitman BR, Donohue TJ, Wolford TL, Stelken AM, Miller LW. Long-term cardiopulmonary exercise performance after heart transplantation. *Am J Cardiol.* 1997; 79:451–456. [PubMed: 9052349]
3. Mandak JS, Aaronson KD, Mancini DM. Serial assessment of exercise capacity after heart transplantation. *J Heart Lung Transplant.* 1995; 14:468–478. [PubMed: 7654732]
4. Stevenson LW, Sietsema K, Tillisch JH, et al. Exercise capacity for survivors of cardiac transplantation or sustained medical therapy for stable heart failure. *Circulation.* 1990; 81:78–85. [PubMed: 2297851]
5. Kao AC, Van Trigt P 3rd, Shaeffer-McCall GS, et al. Central and peripheral limitations to upright exercise in untrained cardiac transplant recipients. *Circulation.* 1994; 89:2605–2615. [PubMed: 8205672]
6. Leung TC, Ballman KV, Allison TG, et al. Clinical predictors of exercise capacity 1 year after cardiac transplantation. *J Heart Lung Transplant.* 2003; 22:16–27. [PubMed: 12531409]
7. Savin WM, Haskell WL, Schroeder JS, Stinson EB. Cardiorespiratory responses of cardiac transplant patients to graded, symptom-limited exercise. *Circulation.* 1980; 62:55–60. [PubMed: 6991158]
8. Roten L, Schmid JP, Merz F, et al. Diastolic dysfunction of the cardiac allograft and maximal exercise capacity. *J Heart Lung Transplant.* 2009; 28:434–439. [PubMed: 19416770]
9. Marconi C, Marzorati M, Fiocchi R, et al. Age-related heart rate response to exercise in heart transplant recipients. Functional significance. *Pflugers Arch.* 2002; 443:698–706. [PubMed: 11889566]
10. Andreassen AK. Point: Cardiac denervation does/does not play a major role in exercise limitation after heart transplantation. *J Appl Physiol.* 2008; 104:559–560. [PubMed: 17615275]
11. Stratton JR, Kemp GJ, Daly RC, Yacoub M, Rajagopalan B. Effects of cardiac transplantation on bioenergetic abnormalities of skeletal muscle in congestive heart failure. *Circulation.* 1994; 89:1624–1631. [PubMed: 8149530]
12. Schwaiblmair M, von Scheidt W, Uberfuhr P, Reichart B, Vogelmeier C. Lung function and cardiopulmonary exercise performance after heart transplantation: influence of cardiac allograft vasculopathy. *Chest.* 1999; 116:332–339. [PubMed: 10453859]

13. Patel AR, Kuvin JT, DeNofrio D, et al. Peripheral vascular endothelial function correlates with exercise capacity in cardiac transplant recipients. *Am J Cardiol.* 2003; 91:897–899. [PubMed: 12667585]
14. Lampert E, Mettauer B, Hoppeler H, Charloux A, Charpentier A, Lonsdorfer J. Skeletal muscle response to short endurance training in heart transplant recipients. *J Am Coll Cardiol.* 1998; 32:420–426. [PubMed: 9708470]
15. Schaefelberger M, Eriksson BO, Lonn L, Rundqvist B, Sunnerhagen KS, Swedberg K. Skeletal muscle characteristics, muscle strength and thigh muscle area in patients before and after cardiac transplantation. *Eur J Heart Fail.* 2001; 3:59–67. [PubMed: 11163737]
16. Ganau A, Devereux RB, Roman MJ, et al. Patterns of left ventricular hypertrophy and geometric remodeling in essential hypertension. *J Am Coll Cardiol.* 1992; 19:1550–1558. [PubMed: 1534335]
17. Cohn JN, Ferrari R, Sharpe N. Cardiac remodeling--concepts and clinical implications: a consensus paper from an international forum on cardiac remodeling. Behalf of an International Forum on Cardiac Remodeling. *J Am Coll Cardiol.* 2000; 35:569–582. [PubMed: 10716457]
18. Devereux RB, Dahlof B, Gerds E, et al. Regression of hypertensive left ventricular hypertrophy by losartan compared with atenolol: the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) trial. *Circulation.* 2004; 110:1456–1462. [PubMed: 15326072]
19. Lam CS, Grewal J, Borlaug BA, et al. Size, shape, and stamina: the impact of left ventricular geometry on exercise capacity. *Hypertension.* 1143; 55:1143–1149. [PubMed: 20215563]
20. Goodroe R, Bonnema DD, Lunsford S, et al. Severe left ventricular hypertrophy 1 year after transplant predicts mortality in cardiac transplant recipients. *J Heart Lung Transplant.* 2007; 26:145–151. [PubMed: 17258148]
21. Raichlin E, Villarraga HR, Chandrasekaran K, et al. Cardiac allograft remodeling after heart transplantation is associated with increased graft vasculopathy and mortality. *Am J Transplant.* 2009; 9:132–139. [PubMed: 19067662]
22. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification. *Eur J Echocardiogr.* 2006; 7:79–108. [PubMed: 16458610]
23. de Simone G, Daniels SR, Kimball TR, et al. Evaluation of concentric left ventricular geometry in humans: evidence for age-related systematic underestimation. *Hypertension.* 2005; 45:64–68. [PubMed: 15557389]
24. Devereux RB, Alonso DR, Lutas EM, et al. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. *Am J Cardiol.* 1986; 57:450–458. [PubMed: 2936235]
25. Redfield MM, Jacobsen SJ, Burnett JC Jr, Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. *Jama.* 2003; 289:194–202. [PubMed: 12517230]
26. Nishimura RA, Tajik AJ. Evaluation of diastolic filling of left ventricle in health and disease: Doppler echocardiography is the clinician's Rosetta Stone. *J Am Coll Cardiol.* 1997; 30:8–18. [PubMed: 9207615]
27. Daida H, Allison TG, Johnson BD, Squires RW, Gau GT. Further increase in oxygen uptake during early active recovery following maximal exercise in chronic heart failure. *Chest.* 1996; 109:47–51. [PubMed: 8549215]
28. Wasserman KHJ, Sue D. *Principles of Exercise Testing and Interpretation* (3rd edition). 1999
29. ATS/ACCP Statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med.* 2003; 167:211–277. [PubMed: 12524257]
30. Arena R, Myers J, Abella J, et al. Determining the preferred percent-predicted equation for peak oxygen consumption in patients with heart failure. *Circ Heart Fail.* 2009; 2:113–120. [PubMed: 19808326]
31. Sun XG, Hansen JE, Garatachea N, Storer TW, Wasserman K. Ventilatory efficiency during exercise in healthy subjects. *Am J Respir Crit Care Med.* 2002; 166:1443–1448. [PubMed: 12450934]
32. Myers J, Arena R, Oliveira RB, et al. The Lowest VE/VCO₂ ratio during exercise as a predictor of outcomes in patients with heart failure. *J Card Fail.* 2009; 15:756–762. [PubMed: 19879461]

33. Kao AC, Van Trigt P 3rd, Shaeffer-McCall GS, et al. Allograft diastolic dysfunction and chronotropic incompetence limit cardiac output response to exercise two to six years after heart transplantation. *J Heart Lung Transplant*. 1995; 14:11–22. [PubMed: 7727459]
34. Biasucci LM, Liuzzo G, Grillo RL, et al. Elevated levels of C-reactive protein at discharge in patients with unstable angina predict recurrent instability. *Circulation*. 1999; 99:855–860. [PubMed: 10027805]
35. Yturralde RF, Gaasch WH. Diagnostic criteria for diastolic heart failure. *Prog Cardiovasc Dis*. 2005; 47:314–319. [PubMed: 16003646]
36. Paulus WJ, Tschope C, Sanderson JE, et al. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. *Eur Heart J*. 2007; 28:2539–2550. [PubMed: 17428822]
37. Pritchett AM, Mahoney DW, Jacobsen SJ, Rodeheffer RJ, Karon BL, Redfield MM. Diastolic dysfunction and left atrial volume: a population-based study. *J Am Coll Cardiol*. 2005; 45:87–92. [PubMed: 15629380]
38. Gudmundsson GS, Smull DL, Pisani BA, et al. Increase in atrial size in long-term survivors of heart transplant. *J Am Soc Echocardiogr*. 2003; 16:1043–1048. [PubMed: 14566297]
39. Tsang TS, Barnes ME, Gersh BJ, Bailey KR, Seward JB. Left atrial volume as a morphophysiologic expression of left ventricular diastolic dysfunction and relation to cardiovascular risk burden. *Am J Cardiol*. 2002; 90:1284–1289. [PubMed: 12480035]
40. Guazzi M, Brenner DA, Apstein CS, Saupe KW. Exercise intolerance in rats with hypertensive heart disease is associated with impaired diastolic relaxation. *Hypertension*. 2001; 37:204–208. [PubMed: 11230272]
41. Pichard AD, Smith H, Holt J, Meller J, Gorlin R. Coronary vascular reserve in left ventricular hypertrophy secondary to chronic aortic regurgitation. *Am J Cardiol*. 1983; 51:315–320. [PubMed: 6218741]
42. Skaluba SJ, Litwin SE. Mechanisms of exercise intolerance: insights from tissue Doppler imaging. *Circulation*. 2004; 109:972–977. [PubMed: 14967722]
43. Pflugfelder PW, McKenzie FN, Kostuk WJ. Hemodynamic profiles at rest and during supine exercise after orthotopic cardiac transplantation. *Am J Cardiol*. 1988; 61:1328–1333. [PubMed: 3287883]
44. Stehlik J, Edwards LB, Kucheryavaya AY, et al. The Registry of the International Society for Heart and Lung Transplantation: twenty-seventh official adult heart transplant report–2010. *J Heart Lung Transplant*. 2010; 29:1089–1103. [PubMed: 20870164]
45. Ojo AO, Held PJ, Port FK, et al. Chronic renal failure after transplantation of a nonrenal organ. *N Engl J Med*. 2003; 349:931–940. [PubMed: 12954741]
46. Renlund DG, Taylor DO, Ensley RD, et al. Exercise capacity after heart transplantation: influence of donor and recipient characteristics. *J Heart Lung Transplant*. 1996; 15:16–24. [PubMed: 8820079]
47. Gharavi AG, Diamond JA, Goldman AY, et al. Resting diastolic function and left ventricular mass are related to exercise capacity in hypertensive men but not in women. *Am J Hypertens*. 1998; 11:1252–1257. [PubMed: 9799044]
48. Pierson LM, Bacon SL, Sherwood A, et al. Association between exercise capacity and left ventricular geometry in overweight patients with mild systemic hypertension. *Am J Cardiol*. 2004; 94:1322–1325. [PubMed: 15541259]
49. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. *N Engl J Med*. 1990; 322:1561–1566. [PubMed: 2139921]
50. Koren MJ, Devereux RB, Casale PN, Savage DD, Laragh JH. Relation of left ventricular mass and geometry to morbidity and mortality in uncomplicated essential hypertension. *Ann Intern Med*. 1991; 114:345–352. [PubMed: 1825164]
51. Pierson LM, Bacon SL, Sherwood A, et al. Relationship between exercise systolic blood pressure and left ventricular geometry in overweight, mildly hypertensive patients. *J Hypertens*. 2004; 22:399–405. [PubMed: 15076200]

52. Torre-Amione G. Cardiac allograft hypertrophy: a new target for therapy, a surrogate marker for survival? *Am J Transplant*. 2009; 9:7–8. [PubMed: 19133927]
53. Peura JL, Zile MR, Feldman DS, et al. Effects of conversion from cyclosporine to tacrolimus on left ventricular structure in cardiac allograft recipients. *J Heart Lung Transplant*. 2005; 24:1969–1972. [PubMed: 16297806]
54. Kushwaha SS, Raichlin E, Sheinin Y, et al. Sirolimus affects cardiomyocytes to reduce left ventricular mass in heart transplant recipients. *Eur Heart J*. 2008; 29:2742–2750. [PubMed: 18790727]

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Table 1

Patients' Demographic and Clinical characteristics stratified by LV geometric pattern at 1 year after HTx (n=117)

Variables	NG group N=18	CR group N=64	CH group N=35	P value
Recipient Age, years	49.01 ±11.85	48.86 ±15.31	46.61. ±15.61	0.73
Male gender, n (%)	14(78%)	50(78%)	25(71%)	0.74
Donor Age, years	32.72±14.17	34.93±13.47	30.33±14.50	0.37
Ischemic Time, min	176±536	173±48	149±44 *	0.07
Ischemic Cardiomyopathy, n (%)	(37%)	(30%)	(26%)	0.77
Body Mass Index, g/m ²	24.75±3.26	24.52±5.06	28.87±6.23 *	0.05
Donor/Recipient Weight	0.96±0.20	1.05±0.23	1.04±0.26	0.64
GFR, ml/min	58.07±17.35	54.47±19.32	56.84±23.24	0.76
CMV viremia, n (%)	2(10%)	10(16%)	9 (26%)	0.33
Hypertension, n (%)	14 (78%)	46 (73%)	29 (83%)	0.46
Diabetes Mellitus, n (%)	2(11%)	13 (21%)	10 (29%)	0.34
Rejection Score at 1 year	0.39±0.30	0.32±0.21	0.38±0.22	0.06
ACE inhibitor, n (%)	3 (16%)	16(25%)	10 (29%)	0.55
Beta Blocker, n (%)	1 (5%)	5 (8%)	3 (9%)	0.20
Calcium Channel Blocker, n (%)	5 (28%)	18 (29%)	10 (29%)	0.76
Cyclosporin/Tacrolimus, n (%)	15(83%)/3(17%)	54 (87%)/8(13%)	30(94%)/2(6%)	0.49
Azathioprine / MMF, n (%)	7(41%)/10(59%)	29(48%)/31(52%)	11(39%)/17(61%)	0.69
Prednisone dosage (mg)	8.28±3.53	8.17±3.75	10.27±4.54 †	0.04
Heart Rate, bpm	95±11	91±13	92±13	0.49
Systolic Blood Pressure, mmHg	126±18	129±17	125±24	0.91
Diastolic Blood Pressure, mmHg	80±13	80±12	78±16	0.94

* Difference between the CH/CR and the NG groups, p = 0.05

† Difference between the CH and the CR groups, p = 0.05

Table 2**A Echocardiographic measurements at 1 year following HTx stratified by LV geometric pattern**

Variables	NG group N=18	CR group N=64	CH group N=35	P value
Heart Rate, bpm	95±11	91±13	92±13	0.49
Systolic Blood Pressure, mmHg	126±18	129±17	125±24	0.91
Diastolic blood pressure, mmHg	80±13	80±12	78±16	0.94
RWT	0.38±0.02	0.50±0.05	0.57±0.20 *	<0.0001
LVM, g	167±30	177±35	261±21 *	<0.0001
LVEF, %	62±6	63±5	61±9	0.54
SV, mL	68±12	67±15	71±13	0.68
E', m/s	9±1	8±3	8±3	0.58
E/E'	9.47±3.22	10.88±5.48	10.94±5.02	0.64
Left Atrium Volume, mL	71±34	80±29	98±46	0.64
RVSP, mmHg	37±8	32±8	36±11	0.11

B Echocardiographic measurements at time CPET stratified by LV geometric pattern

Variables	NG group N=18	CR group N=64	CH group N=35	P value
Heart Rate, bpm	91±16	87±13	87±16	0.69
SBP, mmHg	114±14	121±16	123±17	0.86
DBP, mmHg	72±9	74±10	74±11	0.29
RWT	0.38±0.02	0.51±0.07	0.53±0.09 *	<0.0001
LVM, g	142±33	171±37	261±52 *	<0.0001
LVEF, %	62±6	64±7	61±9	0.94
SV, mL	68±14	71±16	82±18	0.26
E', m/s	9±3	9±2	9±4	0.74
E/E'	9.96 ±3.66	10.32 ±3.28	11.36 ±6.65	0.78
LA volume, mL	73±35	94±40 *	105±39 *	0.29
RVSP, mmHg	29±8	34±9	33±8	0.11

* Difference between the CH/CR and the NG groups, p = 0.05

† Difference between the CH and the CR groups, p = 0.05

Table 3

CPET results stratified by LV geometric pattern at 1 year following HTx

Variables	NG group N=18	CR group N=64	CH group N=35	P value
Δ Heart Rate, bpm	46±15	39±21	37±21	0.22
Δ SBP, mmHg	38±16	26±29	28±23	0.23
Δ DBP, mmHg	5±19	7±19	4±11	0.29
Time after transplantation, years	6.29±3.75	4.80±2.56	4.44±2.76	0.20
Exercise duration, min	7.32±2.00	6.94±2.07	6.70±0.38	0.65
Actual METs, kcal/kg/h	5.52±0.96	5.14±1.36	4.62±1.44 [*]	0.03
Peak VO ₂ , ml/kg × min	18.90±2.87	18.16±5.12	16.26±5.07	0.06
Normalized VO ₂ , %	63±12	60±16 [*]	52±14 [*]	0.013
RER	1.21±0.09	1.20±0.11	1.19±0.12	0.81
Peak Ventilation, L/min	58.18±15.79	59.82±16.15	76.11±31.01 ^{*†}	0.017
Breathing Reserve, %	50±12	49±13	48±13	0.79
Anaerobic Threshold, ml/kg × min	1036±242	1076±305	1177±486	0.68
Peak VCO ₂ , L/min	1762±527	1719±513	2078±847 [†]	0.22
V _E /V _{CO2}	34±6	36±7	41±17 ^{*†}	0.15

^{*} Difference between the CH/CR and the NG groups, p = 0.05

[†] Difference between the CH and the CR groups, p = 0.05

Table 4**A Associations of clinical and echocardiographic variables with exercise capacity in metabolic equivalents**

Variables	Univariate Analysis		Multivariate Analysis	
	Estimate	P value	Estimate	P value
Recipient age at Tx	−0.000064	0.011		
BMI	−0.66	0.012	−0.06	0.04
Heart rate	−0.02	0.07		
SBP	−0.01	0.08		
DBP	−0.01	0.04		
LV geometry	−0.25	0.005		
Time after TX	−0.11	0.007		
GFR	0.02	0.004	0.017	0.04
CCB	−0.24	0.09		

B Associations of clinical and echocardiographic variables with peak VO₂

Variables	Univariate Analysis		Multivariate Analysis	
	Estimate	P value	Estimate	P value
Recipient age at Tx	−0.25	0.004	−0.08	0.016
BMI	−0.22	0.039		
Heart rate	−0.16	0.08		
E/E'	−0.20	0.09		
Time after Tx	0.29	0.001		
RVSP	−0.34	0.001		
CCB	0.2	0.018		
Prednisone dosage	−0.24	0.006		
LV geometry	−1.43	0.04	−1.46	0.05

C Associations of clinical and echocardiographic variables with normalized peak VO₂

Variables	Univariate Analysis		Multivariate Analysis	
	Estimate	P value	Estimate	P value
Recipient age at Tx	−0.27	0.004	−0.0009	0.006
Donor age	−0.24	0.02	−0.3	0.006
BMI	−0.63	0.04	−0.7	0.038
LV geometry	−0.06	0.04	−4.5	0.018
E/E'	−5.96	0.005		

D Associations of clinical and echocardiographic variables with V_E/VC_{O_2}

Variables	Univariate Analysis		Multivariate Analysis	
	Estimate	P value	Estimate	P value
Heart rate	0.0002	0.02	0.0003	0.03
LV geometry	0.004	0.036	0.004	0.01
E'	0.094	0.07		
RVSP	0.0002	0.046	0.0003	0.035