

Cardiopulmonary Exercise Testing in Heart Transplant Candidates

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Abstract

Introduction: We evaluated the results of patients with congestive heart failure (CHF) who underwent cardiopulmonary exercise testing (CPET) as part of their assessment for heart transplantation in order to examine the relationship between exercise capacity and resting indices of left ventricular function in these patients. **Materials and Methods:** Twenty-seven ambulatory heart transplant candidates underwent CPET using a cycle ergometer and an incremental work-rate protocol till symptom-limitation. These patients included 24 men and 3 women with a mean age of 42.3 years. The aetiology of CHF was coronary artery disease in 14 patients, dilated cardiomyopathy in 11 patients, and congenital heart disease in 2 patients. Mean resting left ventricular ejection fraction (LVEF) was 19% (range 7% to 36%). **Results:** Thirteen of the 27 tests performed were maximal studies and all except 2 subjects attained a measurable anaerobic threshold during CPET. Of the 13 maximal tests, the causes of exercise limitation were cardiomyopathy in 3 patients, ischaemic heart disease in 2 patients, significant oxygen desaturation in 2 patients, ventilatory limitation due to obstructive lung disease in 1 patient, ventilatory limitation secondary to a restrictive lung disease in 3 patients, and combined obstructive ventilatory and cardiovascular limitation in 2 patients. There was no significant correlation between resting LVEF and peak VO_2 percent predicted ($r = 0.14$, $P = 0.49$). **Conclusions:** Exercise intolerance in patients with CHF may not be related to limited cardiac reserve and non-cardiac causes of exertional symptoms should also be considered. CPET is useful for the evaluation of functional capacity and mechanisms of exercise intolerance in patients with CHF.

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Introduction

Congestive heart failure (CHF) is a leading cause of cardiovascular morbidity and mortality. This syndrome tends to run a chronic course with a wide spectrum of compensatory physiological and neurohormonal mechanisms that may be maladaptive in the terminal phase of the illness. Despite recent advances in the therapy of heart failure, the quality of life and prognosis of patients with severe heart failure remain poor.¹⁻⁴

Heart transplantation has emerged as an important adjunct to medical therapy for CHF and has been considered the treatment of choice for patients with end-stage heart disease.^{5,6} The shortage of donors for cardiac transplantation and the expanding list of potential candidates, however, have made it imperative to restrict the option to those with the greatest need for transplantation. In this regard,

stratification of heart failure patients by objective criteria has improved ability to select appropriate patients for heart transplantation. Previously, clinical and resting haemodynamic determinants of survival in patients with CHF were emphasised.^{2,5} Recent consensus reports, however, have recommended that peak exercise oxygen consumption (VO_2) be used to help determine the timing of heart transplantation in ambulatory patients with heart failure.⁶

Direct measurement of VO_2 with exercise can be obtained with cardiopulmonary exercise testing (CPET). A cardiopulmonary exercise test is an integrative evaluation with gas exchange and ventilatory measurements added to monitoring of the electrocardiogram and blood pressure during exercise. It can provide essential information in the assessment of the functional capacity of patients with

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cardiac and pulmonary disorders. It also assists the clinician in differentiating between cardiovascular and respiratory causes of exercise limitation.

We evaluated the results of patients with CHF who underwent CPET as part of their evaluation for heart transplantation in order to examine the relationship between exercise capacity and resting indices of left ventricular function in these patients. As a secondary objective, we evaluated the exercise and pulmonary function tests of patients who were able to perform maximal tests during CPET in order to determine the factors limiting exercise tolerance in these patients.

Materials and Methods

Between May 1998 and August 1999, ambulatory patients referred to the pulmonary function laboratory of the Singapore General Hospital for CPET as part of their heart transplantation evaluation were included in the study. Resting left ventricular ejection fraction was determined from radionuclide ventriculography or two-dimensional echocardiography. Cardiac output (CO) and pulmonary artery wedge pressure (PAWP) at rest were measured during cardiac catheterisation studies performed during heart transplantation evaluation.

Symptom-limited CPET was performed using an electronically-braked cycle ergometer (JAEGER® ER 900; ERICH JAEGER GmbH, Germany) after informed consent was obtained from all patients prior to exercise testing. CPET was performed under the supervision of a physician with defined criteria for stopping, such as serious cardiac arrhythmias, hypotension and electrocardiographic changes. An incremental protocol was used in which the work rate was increased by 5 watts per minute after an initial 3 minutes of unloaded pedaling. Standard 12-lead electrocardiograms were obtained at rest, every 3 minutes during exercise and for 6 minutes into the recovery phase while blood pressures were measured using a standard cuff sphygmomanometer at similar intervals. Measurements of mixed expired oxygen, mixed expired carbon dioxide and expired volume were determined at rest and every 10 seconds throughout exercise using a metabolic cart (JAEGER® Oxycon Alpha; ERICH JAEGER GmbH, Germany). Oxygen saturation via pulse oximetry and heart rate by electrocardiography were recorded continuously throughout exercise and during recovery. Anaerobic threshold (AT) was defined as:

- 1) the point at which the ventilatory equivalent for O_2 (VE/VO_2) was minimal followed by a progressive increase;
- 2) the point after which the respiratory gas exchange ratio consistently exceeded 1; and
- 3) the VO_2 after which expired carbon dioxide increased nonlinearly relative to oxygen consumption (V-slope). The anaerobic threshold percent (AT%) was defined as

$(VO_2 \text{ at AT/the predicted maximal } VO_2) \times 100$. The peak VO_2 was the highest VO_2 observed during the exercise test. At the end of exercise testing, the reasons for termination of exercise were obtained from the subjects. Predicted maximal VO_2 and predicted maximal work rate (WRmax) were determined using the prediction equations of Hansen et al⁷ and Jones et al,⁸ respectively.

The criteria for a maximal test in this study were:

- 1) peak VO_2 equal to or greater than 85% of the predicted value;
- 2) exercise terminated because of a serious electrocardiogram (ECG) abnormality;
- 3) maximal heart rate attained is greater than 85% predicted (cardiovascular limitation);
- 4) minute ventilation at maximal exercise greater than 85% of maximal voluntary ventilation (ventilatory limitation); and
- 5) significant decrease in oxygen saturation (SaO_2) of greater than 4%.

Exercise tests were considered maximal if subjects achieved one or more of these criteria.

The maximal voluntary ventilation (MVV) was directly measured in all patients using spirometry as previously described.⁹ At least 2 MVV manoeuvres were recorded with the 2 values within 10% of the mean of the measurements. The best MVV measured in each patient was higher than 35 times the patient's forced expiratory volume in 1 second (FEV_1), indicating appropriate effort.¹⁰

All the data of this study were prospectively collected. For statistical analysis, the relationship between two sets of data was analysed using the Pearson correlation test. A $P < 0.05$ was considered to be statistically significant.

Results

During the 16-month study period, 27 ambulatory heart transplant candidates were referred for CPET as part of their heart transplant work-up. These patients included 24 men and 3 women with a mean age of 42.3 years (range 32 to 55 years). The aetiologies of CHF were coronary artery disease in 14 patients, dilated cardiomyopathy in 11 patients, and congenital heart disease (atrial septal defect with pulmonary hypertension) in 2 patients.

The left ventricular function of the patients in this study was severely reduced with a mean LVEF of only 19% (range 7% to 36%). Mean resting cardiac output was 3.4 L/min (range 1.6 to 5.5 L/min) and mean pulmonary artery wedge pressure at rest was 27 mmHg (range 11 to 53 mmHg).

The predominant symptoms limiting exercise were leg fatigue in 18 patients, dyspnoea in 6 patients, chest pain in 2 patients and dizziness in 1 patient. Of the 2 patients who could not continue with the test because of chest pain, 1 had

angina pectoris that was accompanied by typical ECG changes and the other had atypical chest pain not associated with ECG abnormalities.

Thirteen of the 27 studies performed were maximal tests based on the criteria listed above. However, 7 patients were taking both digoxin and beta-blockers and 13 patients were taking digoxin at the time of CPET and this may have affected the chronotropic response in some patients leading to a greater number of submaximal tests. Of the 13 maximal tests, the causes of exercise limitation were cardiomyopathy in 3 patients, ischaemic heart disease in 2 patients, significant oxygen desaturation in 2 patients, ventilatory limitation due to lung disease in 4 patients, and combined obstructive ventilatory and cardiovascular limitation in 2 patients.

Four patients were found to be principally ventilatory limited at peak exercise. One patient with ventilatory limitation as a result of obstructive lung disease was a 52-year-old man with ischaemic cardiomyopathy and a 20-pack year smoking history who stopped cycling because of leg fatigue (patient 1). There was a substantial heart rate reserve at termination but breathing reserve was low (10.3 L). Pre-exercise spirometry revealed a moderate obstructive ventilatory pattern with FEV₁ of only 63% predicted. Two cases with ventilatory limitation secondary to restrictive lung disease (patients 2 and 3) did not have any breathing reserve at exercise termination during CPET. The TLC (total lung capacity) of patients 2 and 3 was 61.3% predicted and 74.3% predicted, respectively. With regard to the cause/s of the pulmonary restriction, both patients did not have any history of lung disease and did not agree to undergo further investigation for the restrictive lung disease so the exact cause/s of the pulmonary restriction could not be ascertained. Nonetheless, patient 2 was an obese man with a body mass index of 33.3 kg/m² and obesity could have accounted for the restrictive lung disease. Patient 4 was a 41-year-old man with atrial septal defect (ASD) and pulmonary hypertension who stopped cycling because of dyspnoea and had no breathing reserve at peak

exercise. Spirometry at rest suggested a restrictive abnormality and TLC was a low normal value of 80.2% predicted. While slightly decreased values for vital capacity, FEV₁ and MVV (ranging from 75% to 85% of normal subjects) have been documented in patients with ASD,¹¹ the exact cause of the ventilatory limitation during exercise in this case is unclear. As the chest X-ray (CXR) of patient 4 showed hyperaemic lung fields and his diffusion capacity was raised (consistent with left-to-right shunting), it is conceivable that the ventilatory limitation may be related to increased pulmonary blood volume during exercise. The results of pulmonary function tests of patients 1 to 4 are shown in Table I.

Significant oxygen desaturation, as defined above by a decrease in SaO₂ during exercise of greater than 4% from baseline, occurred in 2 patients. In both patients, the SaO₂ dropped to lower than 85% for at least 12 seconds during exercise. Both patients stopped exercising within one minute of the SaO₂ falling lower than 85%. There should not have been significant oxygen desaturation during exercise in patients with left ventricular failure *per se*, and there were no evidence to suggest the presence of interstitial or obstructive lung disease in these 2 patients which may have led to oxygen desaturation during exercise. Hence, the most likely explanation for the significant oxygen desaturation during exercise in these 2 patients is the presence of pulmonary vascular disease (pulmonary hypertension). However, invasive exercise testing would have been necessary to further characterise any gas exchange abnormality during exercise.

The mean peak VO₂ in these patients was 14.56 mL/min/kg (range 7.5 to 23 mL/min/kg). Fifteen patients had peak VO₂ >14 mL/min/kg, eleven patients had peak VO₂ ranging from 10.1 to 14 mL/min/kg, and 1 patient had a peak VO₂ ≤10 mL/kg/min. All except 2 patients attained AT during CPET, with the AT ranging from 47% to 93% of the corresponding peak VO₂ in these patients.

Figure 1 depicts the relationship between LVEF and

TABLE I: PULMONARY FUNCTION DATA OF 4 PATIENTS WITH VENTILATORY LIMITATION DURING CPET*

	Patient 1	Patient 2	Patient 3	Patient 4
FEV ₁ (L)	1.55 (63.0)	1.44 (49.4)	1.58 (51.5)	1.77 (57.9)
FVC (L)	2.41 (74.4)	1.78 (46.2)	2.02 (50.1)	2.26 (57.5)
FEV ₁ /FVC (%)	64.3	80.8	78.2	78.0
TLC (L)	4.33 (92.0)	3.33 (61.3)	4.13 (74.3)	4.30 (80.2)
RV (L)	2.19 (142.6)	1.72 (105)	1.36 (83.8)	1.91 (127.0)
RV/TLC (%)	50.57	51.7	32.8	44.3
DLCO (% predicted)				152

* Percent predicted values in parentheses

DLCO: diffusion capacity; FEV₁: forced expiratory volume in 1 second; FVC: forced vital capacity;

RV: residual volume; TLC: total lung capacity

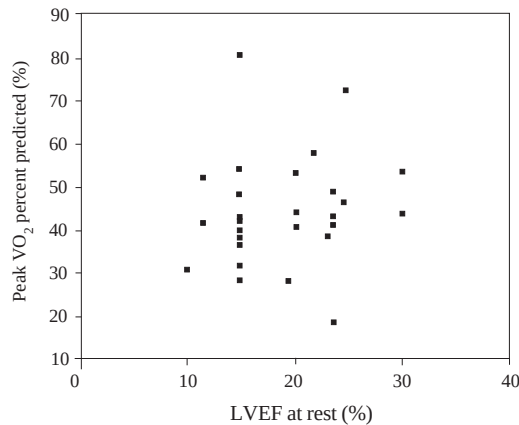


Fig. 1. Scatter plot of LVEF at rest and peak exercise VO_2 percent predicted.

peak VO_2 percent predicted. There is no significant correlation between resting left ventricular function as reflected by the LVEF and peak VO_2 percent predicted ($r = 0.14$, $P = 0.49$). In addition, there is a large variance of peak VO_2 values for each degree of LVEF. For example, in 10 patients with a LVEF of 15%, their corresponding peak VO_2 values were very different. Resting LVEF also did not correlate significantly with and other exercise parameters e.g. WRmax percent predicted ($r = 0.17$, $P = 0.39$), AT% ($r = 0.06$, $P = 0.78$) and peak oxygen pulse ($r = 0.30$, $P = 0.12$).

There is no significant correlation between peak VO_2 percent predicted and resting CO ($r = 0.34$, $P = 0.13$). There is modest negative correlation between peak VO_2 percent predicted and PAWP but this relationship was also not significant ($r = -0.22$, $P = 0.33$).

Termination of exercise by the supervising physician was not required for any patient and there were no complications arising from the conduct of CPET in these patients.

Discussion

Exercise intolerance is one of the most common problems experienced by patients with heart failure. Exercise limitation in CHF is usually attributed to circulatory dysfunction and this assumption has in turn led physicians to treat exertional dyspnoea and fatigue primarily with cardiovascular medications in patients with CHF. There has been increasing evidence, however, that exercise intolerance in CHF is not solely due to circulatory factors¹⁻³ and is probably multifactorial. Although central haemodynamic factors, such as a rise in pulmonary capillary pressure and an attenuated rise in cardiac output, may contribute to exercise symptoms, the magnitude of these haemodynamic abnormalities correlate poorly with the severity of exercise intolerance.² Our findings are consistent

with those of previous studies, which demonstrated that exercise capacity correlates weakly, if at all, with LVEF in CHF patients, indicating that systolic cardiac function is not a key determinant of exercise capacity. Additionally, in the subset of our patients who were able to perform maximal tests, we found diverse causes of exercise limitation. Intolerance to exercise can be the result of limited cardiovascular reserve, ventilatory inadequacy, or failure of some metabolic systems to meet the body's demands at peak activity. Even in this group of patients with severely depressed cardiac function, the main causes of exercise limitation were not all cardiovascular in origin. These observations have major clinical implications. Physicians should not assume that exertional symptoms in patients with CHF indicate pump dysfunction and therefore rely solely on pharmaceutical interventions to treat these symptoms. The possibility that exertional symptoms are related to muscle deconditioning, obesity and other non-cardiac causes should be considered.

Including ventilatory and gas exchange measurements to the monitoring of blood pressure and ECG during exercise can be useful in evaluating the mechanisms limiting exercise tolerance in these patients. The present study has shown that CPET can provide objective information, safely and without the need for invasive measurements, on the primary cause/s of exercise limitation in about half of patients with severe CHF. CPET should be considered for the interpretation of exercise symptoms in patients with stable and chronic CHF whenever the cause of exercise intolerance is in doubt.

Previously, selection criteria for heart transplant were based on the New York Heart Association (NYHA) functional classification and resting haemodynamic data. Examples of the haemodynamic factors that had been used to predict increased mortality include an increased left ventricular end-diastolic pressure (more than 27 mmHg), increased pulmonary capillary wedge pressure (more than 12 mmHg), decreased left ventricular stroke volume (less than 40 mL), reduced cardiac output (less than 2.25 litres/min per m^2), and increased systemic vascular resistance (more than 23 $\text{U} \cdot \text{m}^2$). Furthermore, among patients with coronary artery disease, an ejection fraction of less than 22% was associated with a 3-year survival of less than 10%.⁵ Several recent studies, however, have demonstrated poor correlation between these variables and outcome.^{1,12,13} Currently, focus has shifted to exercise parameters, particularly peak VO_2 , which reflects a reproducible, dynamic and objective variable indicative of cardiac reserve and peripheral adaptation to exercise given the depressed cardiac condition of these individuals.⁶ The landmark study by Mancini et al¹⁴ highlighting peak VO_2 as the best predictor of survival based on univariate and multivariate

analyses, catalysed a barrage of research emphasising the value of direct measurement of peak VO_2 using CPET and revealing the inadequacy of resting haemodynamic data in predicting outcome in CHF patients.^{1-3,13} Based on the results of such studies, the American Heart Association consensus reports⁶ have suggested that a peak exercise VO_2 level of ≤ 14 mL/min/kg be used as a key criterion for the acceptance of ambulatory patients with CHF for transplantation. Patients with preserved exercise capacity based on a peak VO_2 of greater than this value can be safely treated with medical therapy until exercise capacity deteriorates.

It has to be emphasised that, when using CPET for the prioritisation of heart transplant candidates, peak VO_2 should be considered only after the AT is detected, in order to guarantee a nearly maximal exercise performance. A recent study called for caution in the use of peak VO_2 for the selection of heart transplantation candidates in patients with peak VO_2 less than 14 mL/min/kg, as 31% of such patients in that study did not achieve AT.¹⁵ This has not been our observation as all except 2 of the patients in the present study had measurable AT by non-invasive means. Therefore, we are of the opinion that the peak VO_2 of the vast majority of patients in this study (even among those patients whose peak VO_2 is less than 14 mL/min/kg) are of prognostic value. Many other studies have found unmeasurable AT among heart transplant candidates undergoing exercise testing.^{2,5,16,17} Opasich et al¹⁸ studied 653 patients referred for heart transplantation in an effort to clarify the use of peak VO_2 in those who failed to reach AT. Approximately 28% of their patients had this outcome. The authors showed by survival analyses that a peak VO_2 of 10 mL/kg/min or less had a prognostic power that persisted over time, with a mortality rate of 18% within 6 months, 36% within 1 year, and 45% within 2 years even among individuals who did not attain AT. Therefore, it has been recommended that a peak $\text{VO}_2 \leq 10$ mL/min/kg, with or without AT, be used as a definite decisional indicator for transplantation. For patients with a peak $\text{VO}_2 > 10$ mL/kg/min and without a detectable AT, the peak VO_2 value may not provide prognostic information and repeat exercise test is advisable in these patients.

Conclusion

Exercise intolerance in patients with CHF may not be related to limited cardiac reserve and other causes of exertional symptoms should also be considered. Exercise testing provides a unique tool for the evaluation of exercise capacity and the mechanisms limiting activity in CHF patients. CPET currently plays a major role in prognostic assessment and prioritisation of patients for heart transplantation and can be performed safely in patients with stable and chronic CHF.

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