

ORIGINAL ARTICLES

Exercise Responses Following Heart Transplantation: 5 Year Follow-Up

R Carter¹, OA Al-Rawas¹, A Stevenson¹, T Mcdonagh², RD Stevenson¹

¹ Department of Respiratory Medicine, Glasgow Royal Infirmary

² Scottish Cardiopulmonary Transplant Unit, Glasgow Royal Infirmary

Correspondence to:

Dr R Carter, Clinical Respiratory Scientist, Department of Respiratory Medicine, Queen Elizabeth Building, Royal Infirmary, Alexandra Parade, Glasgow, G31 2ER

ABSTRACT

Heart transplantation is an established treatment for end stage heart failure. In addition to increased life expectancy, heart transplant recipients report a remarkable improvement in symptoms and functional capacity. Exercise performance following heart transplantation, however, remains impaired even in the absence of exertional symptoms. We have assessed the response to exercise in 47 patients with cardiac failure prior to and then at yearly intervals to five years post transplantation. All patients performed incremental symptom limited exercise tests during which minute ventilation (\dot{V}_E), oxygen consumption ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$) and heart rate (HR) were measured. Ventilatory response ($\dot{V}_E/\dot{V}CO_2$), anaerobic threshold ($\dot{V}O_2$ AT %predicted) and heart rate response ($HR/\dot{V}O_2$) were calculated. The dead space to tidal volume ratio (V_D/V_T) and alveolar-arterial oxygen gradient (A-aO₂) were computed from transcutaneous monitoring. Despite substantial improvement in subjective functional capacity, heart transplant recipients continue to have limited exercise performance [Maximal $\dot{V}O_2$ % predicted pre-transplant 41.3 (2.2); 1 year 48.6 (1.7), $p < 0.001$: $\dot{V}O_2$ AT% 31.5 (1.1); 1 year 35.6 (1.0); respectively $p < 0.05$]. The maximal oxygen uptake continued to improve at two years post-transplant but, thereafter, there was no further significant change at up to 5 years post transplant [50.9 (1.5)]. At one year post-transplantation peak HR [65.2 (0.9) vs 79.1(1.4)] and the $HR/\dot{V}O_2$ response [24.0(1.8) vs 79.6(4.2)] were significantly reduced compared to pre-transplant values. The heart rate response remained lower compared to predicted at 5 years post-transplant although there was a significant increase compared to one year post-transplant (32.9 vs 24.0mls/bt). There was a weak but significant relationship between maximal $\dot{V}O_2$ and peak HR (0.39, $p < 0.05$) and $HR/\dot{V}O_2$ ($r = 0.37$, $p < 0.05$) at one year post-transplant. Prior to transplantation the ventilatory response to exercise was elevated [$\dot{V}_E/\dot{V}CO_2$ 45.6 (2.5)] and decreased significantly following transplantation [1 yr 34.1 (1.3), respectively $p < 0.001$]. In addition, despite significant improvement in V_D/V_T after transplantation, it remained higher than normal [Pre V_D/V_T at maximum exercise 0.35 (0.02); 1 yr 0.31 (0.02); $p < 0.05$]. There was a further fall in the $\dot{V}_E/\dot{V}CO_2$ and V_D/V_T at two years post-transplantation with no further change at up to 5 years post transplantation [$\dot{V}_E/\dot{V}CO_2$ 32.0 (1.0); V_D/V_T 0.29 (0.01)]. Although cardiac output is markedly improved after transplantation, due to chronotropic incompetence associated with denervation, its response remains subnormal and this may explain the residual abnormalities of ventilatory and gas exchange responses to exercise following transplantation.

Introduction

Heart failure is a serious condition with significant morbidity and high mortality. The reported mortality rates in patients with heart failure range from 24% to 35%, reaching greater than 50% in patients with NYHA functional class IV.¹ Although drug therapy with

angiotensin converting enzyme (ACE) inhibitors and vasodilators has been shown to improve survival in heart failure, patients with NYHA class IV and some patients with class III NYHA continue to have very poor life expectancy.¹ In addition, these patients remain severely limited by dyspnoea and fatigue even when on maximal medical therapy.² For these patients, heart transplantation has become the treatment of choice.³

Since the introduction of cyclosporin immunosuppressive therapy, the reported survival rate has reached 80% to 90% at one year and 60% to 70% at five years after heart transplantation.^{4,5,6,7} In addition to increased life expectancy, heart transplant recipients report an improvement in symptoms and functional capacity.^{7,8}

Exercise performance following heart transplantation, however, remains impaired even in the absence of exertional symptoms.^{7,9,10,11,12,13} The maximum symptom-limited oxygen uptake and the ventilatory anaerobic threshold are in the range of 50% to 70% of predicted.^{12,13}

The cause of exercise intolerance in heart transplant recipients is not clear, but there is increasing evidence that it is multifactorial and is related to cardiac, neurohumoral, vascular muscle and pulmonary changes.^{11,13} In a longitudinal study of 57 patients by Givertz et al,¹³ it was demonstrated that at one year post transplantation, transplant recipients have a subnormal maximal exercise capacity that was associated with a blunted heart rate response and reduced peak heart rate (chronotropic incompetence) on cardiopulmonary exercise testing. This group also showed that the heart rate response to exercise was attenuated despite a normal response to exogenous beta-adrenergic stimulation with infused isoproterenol, indicating that the cause of the abnormality is proximal to the beta-adrenergic receptor. During the subsequent four years there was no further improvement in either, exercise capacity or the heart rate rise and peak heart rate achieved

on exertion. The authors suggest that these findings support the hypothesis that the chronotropic incompetence is due to surgical denervation of the heart and that no re-innervation occurs within the first five years following transplantation.

Heart compliance is also reduced resulting in left ventricular dysfunction with relatively preserved systolic function.¹¹ Several factors have been identified as contributing to myocardial stiffness following heart transplantation including: diastolic dysfunction from myocardial ischaemia due to prolonged donor heart ischaemic time and ischaemia sustained during the operation, ischaemia from cardiac allograft vasculopathy, cyclosporin-induced systemic hypertension, cyclosporin myocardial toxicity and recurrent minor episodes of rejection.^{9,11,12,14}

Efficient pulmonary gas exchange is an essential part of the complex process of exercise.^{15,16} Pulmonary dysfunction following heart transplantation is therefore a potential cause of exercise intolerance in heart transplant recipients.¹⁴ Although central haemodynamic and peripheral circulatory changes have been extensively evaluated in heart transplant recipients,¹¹ there is little information on the possible effects of lung dysfunction on exercise performance.^{17,18,19}

We have recently developed the transcutaneous monitoring of arterial blood gases for the non-invasive measurement of indices of gas exchange at rest and during exercise testing.²⁰ We have used this system to directly assess the impact of gas exchange abnormality on exercise capacity in heart transplant recipients.

Study Design

A prospective longitudinal study consisting of heart transplant patients who were transplanted between January 1992 and June 2001 at the Scottish Cardio-Pulmonary Transplantation Unit (SCPTU) based at the Glasgow Royal Infirmary, North Glasgow University Hospitals Trust.

Study Population and Methods

All transplant patients conforming to SCPTU inclusion criteria performed pulmonary function and cardiopulmonary exercise tests according to the testing protocol. Pulmonary function tests and cardio-pulmonary exercise tests were performed during the assessment for heart transplantation and serially after transplantation. Lung

volumes, forced ventilatory flows (Body Plethysmography SensorMedics V6200) and the single breath transfer factor for carbon monoxide (TL_{CO}) (Transflow, Morgan Medical) were performed during each visit and included forced vital capacity (FVC), forced expiratory volume in the first second (FEV_1), residual volume (RV) and total lung capacity (TLC).

Predicted normal values were determined using the European Community for Steel and Coal equations for all variables.²¹

Measured TL_{CO} was corrected for actual haemoglobin concentration using the equation of Dinakara and associates.²²

$$\text{Haemoglobin-corrected } TL_{CO} = \text{Observed } TL_{CO} / (0.06965 \text{ Hb});$$

Where Hb is the patient's actual haemoglobin and 0.06965 is a correction factor to a standard haemoglobin concentration of 14.4 g.dL⁻¹.

Symptom-limited exercise tests were performed using an electrically braked bicycle ergometer. Throughout each test, minute ventilation ($V'E$), oxygen consumption ($V'O_2$) and carbon dioxide ($V'CO_2$) were measured breath by breath by on-line ventilation and expired gas analysis (MedGraphics CPX-D). The ventilatory anaerobic threshold on exertion was calculated by the curve fitting method using a plot of $V'O_2$ against $V'CO_2$.²³ The dead space to tidal volume ratio (V_D/V_T) and alveolar-arterial oxygen gradient ($A-aO_2$) were computed from transcutaneous monitoring following an in-vivo calibration using a single arterialised ear lobe capillary sample.²⁰ A standard 12-lead electrocardiogram was displayed throughout the procedure.

Study Population

Between January 1992 and June 2000, 289 patients were assessed for transplantation, of these, 142 underwent orthotopic heart transplantation at the Scottish Cardio-Pulmonary Transplantation Unit.

A cohort of the patients who had full pre-operative pulmonary function and cardiopulmonary exercise data (47 patients) also performed resting pulmonary function tests and cardio-pulmonary exercise tests at 1,2,3,4 and 5 years post transplantation. Assessment was performed in stable patients who had not suffered from any respiratory illness

during the preceding two weeks. Patients who received treatment for rejection or systemic infection were not tested until at least 2 weeks after completing treatment. All patients were on standard triple immunosuppression (cyclosporin, azathioprine and prednisolone).

Normal subjects

The findings in cardiac failure patients were compared with data from 30 normal subjects recruited as volunteers from the general population in whom there was no evidence of cardio-pulmonary disease.

Data presentation and analysis

Unless stated otherwise, values are expressed as mean +/- one standard error of the mean (SEM). Lung function and cardio-pulmonary exercise data in heart transplant recipients were compared to those of normal subjects using the one way analysis of variance (ANOVA). The relationship between exercise parameters was assessed using the Pearson correlation and linear regression analysis. A p value of <0.05 was considered significant.

Table I Characteristics of the study groups

	Recipients	Normal
Number of subjects	47	30
Age; mean in years (range)	48.1 (19-60)	40.4 (19-61)
Sex		
Male	39 (83%)	23 (82%)
Female	8 (17%)	7 (18%)
Smoking status		
Non-smokers	10 (21%)	16 (53%)
Ex-smokers	37 (79%)	11 (37%)
Current smokers	0	3 (10%)
Diagnosis		
Ischaemic heart disease	30(64%)	-
Dilated cardiomyopathy	15 (32%)	-
Others	2 (4%)	-
Pre-transplant LVEF, mean (SD)	13.4 (1.8)	-
Post-transplant LVEF, mean (SD)	41.9 (2.5)	-
Pre-transplant transpulmonary gradient		-
Mean (SD)	9.7 (2.4)	-
Pre-transplant functional class		
NYHA III	13 (28%)	-
NYHA IV	34 (72%)	-
Mean (SD)	3.9 (0.6)	-
Post-transplant functional class		
NYHA I	15 (32%)	-
NYHA II	31 (66%)	-
NYHA III	1 (2%)	-
Mean (SD)	1.8 (0.4)	-
Haemoglobin, g.dL ⁻¹ ; mean (SD)	12.6(1.3)	assumed 14.6

LVEF Left ventricular ejection fraction

NYHA New York Heart Association functional classification

Results

Subject Characteristics

Subject characteristics are summarised in Table I. All groups had similar age and sex distribution. All patients were either life-long non-smokers or former smokers. After transplantation, there was a significant improvement in both left ventricular ejection fraction (LVEF) and the NYHA functional status

Resting Pulmonary Function

Table II compares the resting pulmonary function results in the study groups. TLC, VC, FEV₁ and FEV₁/VC were

Table II Resting pulmonary function results (as percentages of predicted) in transplant recipients prior to transplantation compared to normal controls

	Recipients	Normal
FEV ₁	90.1 (1.1)	100.2 (3.2)*
FEV ₁ /VC	93.1 (0.9)	98.6 (1.8)**
VC	89.8 (1.2)	102.4 (2.1)*
RV	103.6 (1.4)	99.4 (2.9)
TLC	96.3 (1.2)	100.2 (3.3)**
TL _{CO}	75.6 (1.4)**	98.6 (2.2)
TL _{CO} (Hb-corrected)	79.8 (1.4)**	-
K _{CO}	74.9 (1.2)**	105.3 (2.3)
K _{CO} (Hb-corrected)	78.8 (1.1)**	-

slightly reduced in heart transplant recipients compared to normal subjects. Although the RV was greater in recipients compared to normal controls this did not reach statistical significance. In contrast TL_{CO} and K_{CO} (before and after correction for haemoglobin) were significantly lower in recipients compared to the normal subjects.

Cardio-pulmonary responses to exercise

Table III displays the cardio-respiratory response to symptom limited exercise in heart transplant recipients compared with normal controls. Maximum symptom-limited oxygen uptake (VO₂) as a percentage of predicted was significantly lower in the transplant recipients compared to normal controls (39.5% vs. 92.9% of predicted, p< 0.001). The ventilatory anaerobic threshold was markedly reduced in recipients compared to controls. The ventilatory and gas exchange responses to exercise (V_E/VCO₂, V_D/V_T) were all higher in recipients compared to normal controls although there was no significant difference between the A-aO₂ gradient at maximum exercise in the transplant recipients compared to normal controls. The heart rate response was markedly elevated in the cardiac transplant recipients prior to

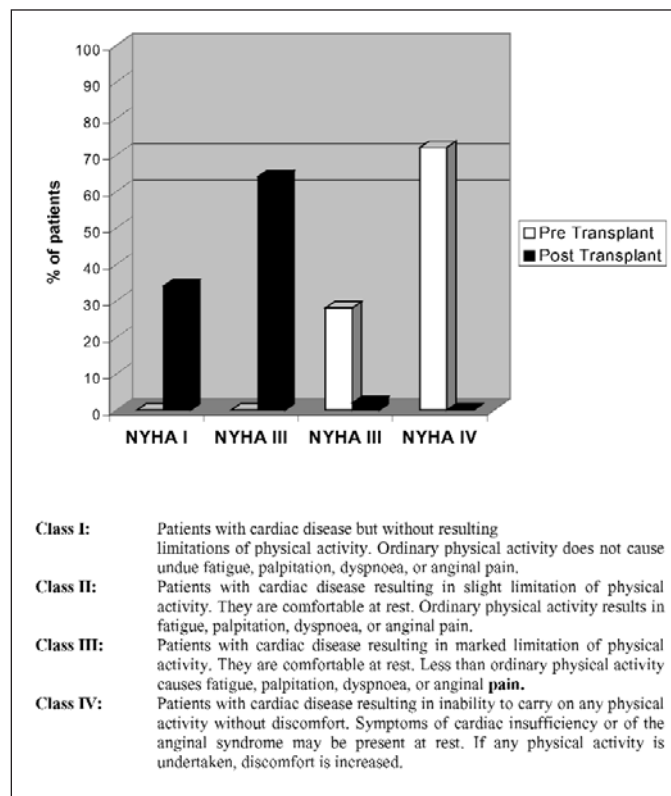
Table III Cardio-respiratory responses to symptom limited exercise in transplant recipients prior to transplantation and normal controls.

	Recipients (N = 113)	Normal Controls (N = 30)
VO ₂ mls.kg ⁻¹ .min ⁻¹	12.5 (0.34)*	28.9 (2.9)
VO ₂ % predicted	39.5 (1.3)*	92.9 (2.5)
VO ₂ AT %	29.6 (0.80)*	52.6 (1.9)
V _E L.min ⁻¹	46.4 (0.76)*	72.4 (4.2)
V _E /MVV	50.0 (1.60)	47.6 (2.6)
V _E % predicted	46.9 (0.81)	57.9 (2.1)
V _E /VCO ₂	46.3 (1.20)*	24.3 (0.1)
V _D /V _T	0.40 (0.01)*	0.19 (0.03)
A-aO ₂ kPa	2.42 (0.06)	1.8 (0.1)
Heart rate (HR) % pred.	79.1 (1.4)	86.4 (1.9)
HR response beats.L ⁻¹	79.6 (4.2)*	35.7 (2.0)
Oxygen pulse, mls beat ⁻¹	8.5 (0.11)*	16.5 (0.6)

transplantation compared with normal controls. The oxygen pulse at maximum symptom limited exercise was significantly lower than in the normal controls.

Figure 1 Functional status of transplant recipients prior to and at one year post transplantation.

KEY : New York Heart Association functional classification (NYHA)



*significant difference between normal controls and patients before and after transplantation

** significant difference between pre- and post-transplant values.

Table IV Resting pulmonary function results in 47 heart transplant recipients prior to and at one year after transplantation compared to normal controls (30 subjects).

	mean % predicted (SEM)		
	Normal Controls	Heart transplant recipients Before	1 year Post
FEV ₁	100.2 (3.9)*	90.1 (1.0)	88.6 (1.1)
VC	102.9 (2.1)*	89.8 (1.2)	94.6 (1.3)
FEV ₁ /FVC	98.6 (1.8)*	93.1 (0.9)	91.0 (0.8)
RV	100.9 (3.3)	103.6 (1.4)	103.2 (1.8)
TLC	100.2 (3.3)*	96.3 (1.2)	93.3 (1.2)
TLCO	98.6 (1.3)*	79.8 (0.9)	59.2 (0.8)**
K _{CO}	105.3 (2.2)*	78.8 (1.1)	54.0(1.0)**

Cardio-pulmonary exercise testing and pulmonary function after cardiac transplantation.

Of the 142 patients who underwent cardiac transplantation 1 and 5 year survival rates were 83 and 69%, respectively. Figure 1 shows the functional status of patients based on the NYHA classification prior to and at one year post transplantation. This shows substantial improvement of subjective functional capacity.

Table IV compares the lung function results in the transplant recipients prior to and at one year post transplantation.

Table V Maximum symptom limited exercise responses in 47 transplant recipients prior to and at 1,2,3,4 and 5 years post transplantation

	Pre	1 year	2 years	3 years	4 years	5 years
VO ₂ %	39.5 (1.3)	49.3* (1.3)	51.3* (1.2)	51.0* (1.3)	50.1* (1.4)	50.9* (1.5)
VO ₂ mls.kg ⁻¹ .min ⁻¹	12.50 (0.34)	15.55* (0.44)	15.96* (0.41)	15.88* (0.51)	15.99* (0.52)	16.09* (0.54)
VO ₂ AT%	29.6 (0.8)	34.5* (0.7)	35.6* (0.6)	36.0* (0.6)	36.4* (0.6)	37.0* (0.7)
HR% pred	79.1 (1.4)	65.2* (0.9)	67.7* (1.04)	70.2* (1.1)	71.1* (1.1)	73.8* (1.0)**
HR response mls/bt	79.6 (4.2)	24.0* (1.8)	26.2* (1.5)	28.8* (1.5)	29.1* (1.6)	32.9* (1.6)**
V _E /MVV	50.0 (1.6)	45.1 (1.3)	40.7* (1.2)**	40.8* (1.2)**	40.0* (1.1)**	39.1* (1.0)**
V _E /VCO ₂	46.3 (1.2)	33.5* (0.7)	32.1* (0.6)	32.2* (0.7)	31.9* (1.0)	32.0* (1.0)
A-aO ₂	2.42 (0.06)	1.81* (0.07)	2.08* (0.06)	1.79* (0.05)	1.81* (0.05)	1.85* (0.06)
V _D /V _T	0.40 (0.01)	0.32* (0.01)	0.29* (0.01)**	0.28* (0.01)**	0.28* (0.01)**	0.29* (0.01)**

Prior to transplantation, FEV₁, VC and TLC were significantly reduced compared to normal predicted values. Although above 80% of predicted, they were all significantly lower than the values in normal controls (P < 0.05). Residual Volume (RV) was slightly elevated, but this was not significantly different from that of normal controls. The greatest impairment, however, was in TL_{CO} and K_{CO}, which were markedly reduced, compared to normal controls. Mean TL_{CO} declined significantly following transplantation (from 79.8% to 59.2% of predicted, p < 0.001), with a similar decline in K_{CO} from 78.8% to 54.0% of predicted (p < 0.001).

Serial cardio-pulmonary exercise testing

Table V shows the maximum symptom-limited exercise responses in heart transplant recipients before and after transplantation. Exercise responses were generally improved at 1 year compared with pre-transplantation. Maximum oxygen uptake corrected for body weight and percent predicted maximal VO₂ was significantly improved compared with before the procedure. The mean maximal oxygen uptake corrected for body weight was 15.55 (SEM 0.44) mls.kg⁻¹.min⁻¹. This represented a percentage-predicted maximum of 49.3 (1.3), matched for age gender and body surface area compared with 12.5 mls.kg⁻¹.min⁻¹; 39.5% predicted (p < 0.05) prior to transplantation, however both were substantially lower than normal controls (28.9 mls.kg⁻¹.min⁻¹; 92.9% predicted; p < 0.001). The ventilatory anaerobic threshold was significantly higher-post transplantation compared to pre-transplant values but was still reduced compared to normal controls. At one year post-transplant, peak heart rate, and the heart rate response (HR/VO₂) were significantly reduced compared to pre-transplant and control values.

The oxygen pulse at maximal exercise was significantly elevated compared to pre-transplantation values but remained lower than normal control subjects. The ventilatory response on exertion (V_E/VCO₂) and the degree of wasted ventilation (V_D/V_T) at maximum exercise were significantly reduced post transplant but remained raised compared to normal control subjects. The ventilatory reserve (V_E/MVV) was similar in all the groups studied.

Maximal oxygen uptake and percent-predicted oxygen uptake increased at 24 months after cardiac transplantation compared with before the procedure but

Figure 2 Regression plot of % predicted maximal oxygen uptake (VO₂) against % predicted peak heart rate achieved at 5 years post-transplantation.

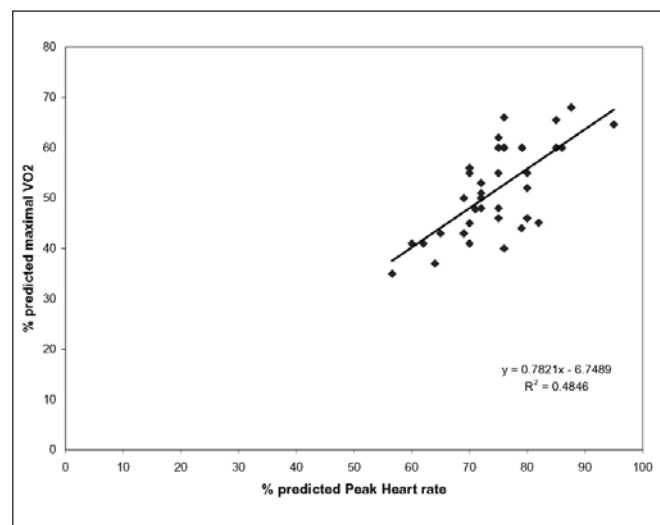
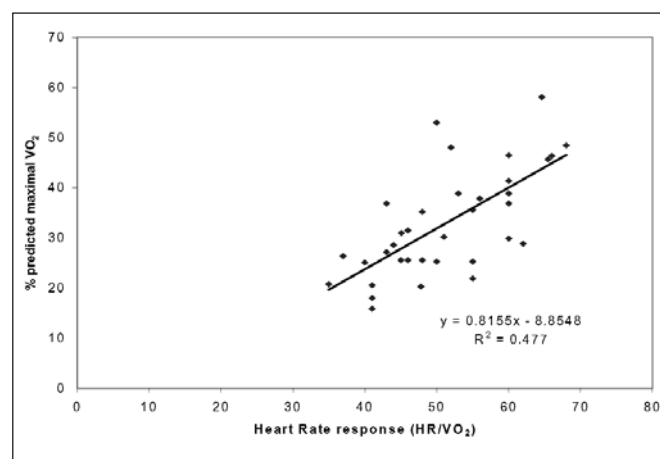


Figure 3 Regression plot of % predicted maximal oxygen uptake (VO₂) against the heart rate response (HR/VO₂) at 5 years post transplantation



did not significantly change thereafter. Compared to pre-transplantation, post-transplantation patients reached a lower peak heart rate (79.1% against 65.2% predicted maximum) and had reduced heart rate response (79.6 against 24.0 mls/bt) at one year. This chronotropic response remained lower compared to predicted normal at 5 years post transplantation although there was a significant increase in the peak heart rate achieved and in the heart rate response compared to one-year post-transplant (32.9 against 24.0 mls/bt). At one year post-transplantation only 6% of patients who performed an exercise test were able to reach >or = 80% of age predicted maximum heart rate compared with 32% at 3 years (p < 0.01) and 45% at 5 years post-transplant (p < 0.01).

There was a weak but significant relationship between the maximal oxygen uptake and peak heart rate achieved (r =

0.39, $p < 0.05$) and the heart rate response (HR/VO_2) on exertion ($r = 0.37$, $p < 0.05$) at one year post-transplantation. At 5 years post-transplantation the correlation was improved between peak heart rate achieved and maximal oxygen uptake ($r = 0.485$, $p < 0.001$) (Figure 2) and the heart rate response on exertion ($r = 0.477$, $p < 0.001$) (Figure 3). The mean resting heart rate preceding the exercise test ranged from 98 to 100 beats/min at the time of the 1-, 3- and 5-year visit after cardiac transplantation.

The ventilatory response on exertion was significantly lower at one-year post-transplantation compared to pre-transplant values but did not significantly change thereafter. The reduced ventilatory response on exercise was associated with a reduction in the degree of wasted ventilation with a significant fall in the V_D/V_T at one-year post-transplantation compared to pre-transplant values. There was a further fall in V_D/V_T at two years compared to one-year post-transplantation with no further change at up to 5 years post-transplant. Ventilatory reserve was also improved post-transplantation with a significant improvement in the V_E/MVV at two years post-transplantation that was maintained at up to 5 years post-transplant.

Discussion

Summary of main results

This study has shown that despite normal or near normal values for lung function parameters and cardiac haemodynamics, the maximal oxygen uptake at one year post transplantation was significantly lower in heart transplant recipients than in normal controls. This abnormal physiological response to exercise was associated with a reduced heart rate response and reduction in peak heart rate post-transplantation. This chronotropic incompetence on exertion is related to cardiac denervation.

In this longitudinal study of 47 patients post transplantation it was shown that the maximal oxygen uptake continued to improve at two years post transplant but, thereafter, there was no further significant change at up to 5 years post-transplant.

Resting pulmonary function

The results of resting pulmonary tests in this study are in agreement with previous reports.^{24, 25}

Pulmonary function after transplantation

Despite improvement in lung volumes, there was a

persistently low transfer factor (TL_{CO}) and transfer coefficient (K_{CO}) after cardiac transplantation (59.2% and 54.0% of predicted, respectively). This confirms the findings of previous studies.^{9, 25, 26, 27, 28} The transfer factor may remain low due to irreversible changes caused by chronic pulmonary congestion, pulmonary oedema or interstitial damage from subclinical infections in immunocompromised patients. The influence of pre-transplant pulmonary function on post transplant lung function is well documented. In the study of Groen et al,²⁵ the percentage reduction in K_{CO} after transplantation was greater in patients with respiratory crackles compared with those without crackles before transplantation. It was suggested that patients with clinical evidence of pulmonary oedema experience a greater reduction in K_{CO} after transplantation. In the same study, the percentage change in K_{CO} was positively correlated with pre-transplant K_{CO} (patients with higher pre-transplant K_{CO} had greater decreases in K_{CO} after transplantation).

In another study of 22 heart transplant patients, Ohar et al²⁸ found no relationship between the change in TL_{CO} and the changes in static and dynamic lung volumes after heart transplantation.

The lack of any significant correlation between the change in TL_{CO} and the pre-transplant static and dynamic lung volumes may be due to the fact that these were only mildly reduced before transplantation. Patients with severe lung function abnormalities and those with significant co-existing primary lung disease are usually excluded in the selection process of heart transplant candidates. This may also explain the absence of any relationship between pre-transplant lung function and outcome after heart transplantation as reported by Brussieres et al.²⁹

Cardio-pulmonary responses to exercise prior to transplantation

The results of the cardio-pulmonary response to exercise in the 47 patients prior to transplantation are in agreement with previous findings which have shown that patients with chronic heart failure exhibit an excessive ventilatory response to exercise.^{30, 31, 32} The results of the present study in stable patients assessed prior to transplantation confirm that excessive ventilatory response to exercise is a characteristic of chronic heart failure. We have previously shown that the ventilatory response to progressive exercise testing and the maximal symptom-limited oxygen uptake as a percentage of predicted are inversely related in the heart transplant recipients.³³ This study has also confirmed that

patients with chronic heart failure have an increased degree of “wasted ventilation” as assessed by V_D/V_T at rest, and this persisted on exertion, confirming the findings of Metra et al.³² and Sullivan et al.³⁰ The relevance of these findings to the reduction in maximal oxygen uptake in patients with cardiac failure has been described previously.³³

Cardio-pulmonary responses to exercise post transplantation

The results of this study of 47 transplant recipients demonstrate a significant improvement in maximal oxygen uptake within one year of the cardiac transplantation. The maximal oxygen uptake then remains stable from 1 to 5 years after cardiac transplantation. The average maximal oxygen uptake one-year after cardiac transplantation was $15.55 \text{ mls min}^{-1} \text{ kg}^{-1}$. This is slightly lower than the range of values reported in previous studies.^{7, 9, 10, 13, 25, 34, 35, 36} One-year maximal oxygen uptake was $17.0 \text{ ml min}^{-1} \text{ kg}^{-1}$ in 60 patients in a study reported by Mandak et al.³⁴ whose mean age was 52 years. In a study by Osada et al.⁷ the maximal oxygen uptake at one-year post transplant in 140 patients, whose mean age was 47 years, was $21 \text{ mls min}^{-1} \text{ kg}^{-1}$. This compares with $15.5 \text{ mls min}^{-1} \text{ kg}^{-1}$ in the 47 patients whose mean age was 50 years in the present study. This finding is similar to the study of Givertz et al.¹³ who showed a maximal oxygen uptake of $16.6 \pm 0.9 \text{ mls min}^{-1} \text{ kg}^{-1}$ at one year post transplantation (57 patients, mean age 45 ± 2 years). This reflected an improvement of 43% compared to pre-transplantation values.

In agreement with these previous reports, the results of this study show that despite substantial improvement of subjective functional capacity, heart transplant recipients continue to have limited exercise performance as assessed by incremental cardio-pulmonary exercise testing. In the present study although most patients had a significant increase in exercise capacity after cardiac transplantation, the average percent predicted maximal oxygen uptake at one-year post transplant was only 49% of predicted. The reasons why peak exercise capacity does not return to normal in most patients after cardiac transplantation are not well understood. Subnormal exercise capacity after transplantation may be due to several factors which include cardiac denervation, which may interfere with the ability to reach age-predicted maximum heart rate response (chronotropic incompetence),¹³ allograft rejection,³⁵ diastolic dysfunction¹⁰ and immunosuppressive therapy, which may result in secondary loss of muscle mass from

steroid induced myopathy, deconditioning and permanent skeletal muscle changes resulting from long standing heart failure prior to cardiac transplantation.^{12, 14, 37, 38, 39, 40}

Similar to previous studies, this study has demonstrated a resting tachycardia and attenuated maximum heart rate response to exercise in patients after transplantation. The maximal oxygen uptake is normally correlated with maximum heart rate, and it is unclear whether the reduced peak heart rate is a consequence of or the cause of the decreased exercise capacity in these patients. The denervated heart causes a chronotropic and inotropic incompetence. The limited ability to increase the heart rate in combination with a subnormal increase of stroke volume diminishes the cardiac output response to exercise^{41,42} and hence reduces the exercise capacity. In heart transplant recipients with their diastolic dysfunction, the ability to augment stroke volume is limited providing a pathophysiological reason for their reduced exercise capacity.⁴³ In the present study a weak but significant correlation was found between the improvement in maximal oxygen uptake at one year post-transplantation and the peak heart rate achieved which supports the theory of a chronotropic incompetence due to a denervated heart contributing to continuing exercise limitation after transplantation. This confirms the findings of Osada et al.⁷ who found a similar relationship between peak heart rate and maximal oxygen uptake at 6 months post transplant ($r = 0.32$; $p = 0.04$). The correlation between these parameters improved at 3 years post transplantation ($r = 0.47$; $p = 0.0002$). Givertz et al.¹³ showed a 43% increase in maximal oxygen uptake at one year post transplantation but that compared with control subjects maximal exercise capacity was subnormal in transplant recipients. This group also showed that the physiological response to exercise remained abnormal in the transplant recipients with a reduced rate of heart rate rise and reductions in peak exercise heart rate. The authors suggested that this reduced exercise capacity compared to control subjects was associated with chronotropic incompetence that is due in large part to cardiac denervation.

The temporal relationship in the ability to achieve age-predicted maximum heart rate was studied. The percentage of patients able to achieve $>$ or $=$ to 80% of age-predicted maximum increased from 6% at one year post transplantation to 32% at 3 years and 45% at 5 years. However the correlation between maximal oxygen uptake

and peak heart rate or heart rate response on exertion, whilst significant, were weak both at one and 5 years post transplantation (highest correlation coefficient $r = 0.48$). These data indicate that the inability of cardiac transplant recipients to achieve normal exercise performance is not completely explained by a limitation of heart rate responsiveness.

Although studies in dogs and monkeys have shown histological and functional evidence of reinnervation with time after cardiac transplantation,^{44, 45, 46, 47, 48, 49} the evidence for reinnervation in humans after transplantation is conflicting. Histological studies in humans have failed to document any evidence of reinnervation. For example, using electron microscopy, Rowan and Billingham⁵⁰ were unable to find evidence of nerve growth in endomyocardial biopsies from 13 long-term heart transplant survivors as late as 12 years after transplantation. Similarly, Regitz et al⁵¹ found that catecholamines were undetectable in endomyocardial biopsies from long-term transplant recipients. In contrast to these histological studies, functional studies have suggested that reinnervation may occur late after transplant in humans. Lord et al⁵² showed that functional sympathetic efferent reinnervation of the sinus node was associated with improved heart rate response during exercise and with recovery after exercise. It is therefore possible that patients with partial reinnervation, causing a positive chronotropic and inotropic status, may be able to do more exercise. In the present study the data suggest that although there is a significant improvement in the number of patients achieving a higher peak heart rate and in the heart rate response at 5 years compared to one year post transplant the responsiveness is less than control subjects. This suggests that functionally significant reinnervation does not occur during the first 5 years post-transplantation. This confirms the findings of Givertz et al¹³ who also showed that at one year post transplantation, peak exercise capacity and chronotropic responsiveness are subnormal and that there was no further improvement in peak exercise capacity or chronotropic responsiveness as late as 5 years after transplantation.

The ventilatory response to exercise in our patients was similar to that reported in previous studies.^{19,53} Before transplantation, V_E/V_{CO_2} was elevated and decreased significantly following transplantation, but remained higher than normal at one-year post transplantation. The ventilatory response remained stable, but higher, than normal up to 5 years post transplant. In addition, the

present study showed that despite significant improvement in V_D/V_T after transplantation, it remained higher than normal. It is not known why ventilatory and gas exchange abnormalities on exercise fail to resolve completely after heart transplantation. One possible explanation is that long standing pre-transplant heart failure leads to irreversible structural damage. Alternatively, these abnormal pulmonary responses may be functional in origin, resulting from a sub-optimal cardiac output response to exercise. Heart failure is characterised by excessive ventilatory response to exercise⁽⁵⁴⁾. Patients with chronic heart failure also have increased "wasted ventilation" as assessed by V_D/V_T .⁵⁴ It has been shown in our previous studies that the ventilatory response and V_D/V_T in heart failure are positively correlated suggesting that they may be causally linked. The observation of a raised degree of "wasted ventilation" or increased V_D/V_T is of great importance. Elevated V_D/V_T values during exercise may be due to a reduction in pulmonary blood flow via a reduced cardiac output. This suggests that pathologically high ventilation/perfusion ratio mismatching occur in patients after transplantation without significantly low ventilation/perfusion mismatching (normal A-aO₂ gradient post transplantation). This places the abnormality on the pulmonary circulation rather than the airway side of the gas exchange unit and suggests perfusion is reduced in well-ventilated lungs.⁵⁵ It is therefore postulated that the failure to increase cardiac output to match ventilation during exercise increases the proportion of lung units with high ventilation/perfusion ratio thereby increasing the V_D/V_T and consequently leading to an excessive ventilatory response to exercise.⁵⁴ Although cardiac output is markedly improved after heart transplantation, due to a chronotropic and inotropic incompetence associated with denervation, its response to exercise remains sub-normal⁴⁴ and this may explain the residual abnormalities of ventilatory and gas exchange responses to exercise following transplantation.

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