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Exercise-Induced Hypoxemia in Heart Transplant Recipients

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Objectives. **The purpose of this study was to determine whether heart transplantation has an adverse effect on pulmonary diffusion and to investigate the potentially deleterious effects of impaired pulmonary diffusion on arterial blood gas dynamics during exercise in heart transplant recipients.**

Background. **Abnormal pulmonary diffusing capacity is reported in patients after orthotopic heart transplantation. Abnormal diffusion may be caused by cyclosporine or by the persistence of preexisting conditions known to adversely affect diffusion, such as congestive heart failure and chronic obstructive pulmonary disease.**

Methods. **Eleven patients (mean age 50 ± 14 years) performed pulmonary function tests 3 ± 1 months before and 18 ± 12 (mean ± SD) months after heart transplantation. Transplant patients were assigned to groups with diffusion >70% (n = 5) or diffusion <70% of predicted values (n = 5). The control group and both subsets of patients performed 10 min of cycle exercise at 40% and 70% of peak power output. Arterial blood gases were drawn every 30 s during the 1st 5 min and at 6, 8 and 10 min.**

Results. **Significant improvements in forced vital capacity (17.4%), forced expiratory volume in 1 s (11.7%) and diffusion capacity (6.6%) occurred in the patients; however, posttransplantation vital capacity, forced expiratory volume and diffusion were lower ($p \leq 0.05$) compared with values in 11 matched control subjects. Changes in blood gases were similar among groups at 40% of peak power output. At 70% of peak power output, arterial blood gases and pH were significantly ($p \leq 0.05$) lower in transplant patients with low diffusion (arterial oxygen pressure 15 to 38 mm Hg below baseline) than in patients with normal diffusion and control subjects. Cardiac index did not differ ($p \geq 0.05$) between transplant patients with normal and low diffusion at rest or during exercise. Posttransplantation mean pulmonary artery pressure was significantly related to exercise-induced hypoxemia ($r = 0.71$; $p = 0.03$).**

Conclusions. **Abnormal pulmonary diffusion observed in patients before heart transplantation persists after transplantation with or without restrictive or obstructive ventilatory defects. Heart transplant recipients experience exercise-induced hypoxemia when diffusion at rest is <70% of predicted. Our data also suggest that abnormal pulmonary gas exchange possibly contributes to diminished peak oxygen consumption in some heart transplant recipients; however, direct testing of this hypothesis was beyond the scope of the present study. This possibility needs to be investigated further.**

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Abnormal pulmonary diffusing capacity is reported in patients after orthotopic heart transplantation (1,2). Immunosuppressive therapy with cyclosporine and the surgical procedure are cited as possible mechanisms responsible for diminished pulmonary diffusion in heart transplant recipients (1); however, pulmonary diffusion is markedly impaired in some patients with congestive heart failure awaiting transplantation (3–5). Abnormal posttransplantation pulmonary diffusing capacity may occur as a consequence of immunosuppressive therapy and the surgical procedure, or the observed diffusion abnormalities may simply be the persistence of preexisting conditions known to adversely affect pulmonary diffusion such as congestive heart failure (3–5) and chronic obstructive pulmonary disease (6,7). Published studies that have measured pulmonary diffusing capacity in the same patient sample before and after heart transplantation and accounted for differences in age, smoking history and months after transplantation are noticeably absent. Furthermore, there is a paucity of data on heart transplant recipients concerning the effects of impaired pulmonary gas exchange on blood gas dynamics during exercise.

The purpose of this study was to determine whether cardiac transplantation has an adverse effect on pulmonary diffusing capacity and to investigate the potentially deleterious effects of impaired pulmonary diffusion on arterial blood gas dynamics during exercise in heart transplant recipients. We hypothesized that heart transplant recipients with impaired pulmonary gas exchange at rest would experience transient arterial hypoxemia during exercise. We further speculated that exercise-induced hypoxemia would be a

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noncardiac factor contributing to the diminished exercise capacity in some of these patients. Accordingly, we measured pulmonary function in a cohort of patients before and after heart transplantation and recorded serial arterial blood gas measurements during moderate and strenuous dynamic exercise.

Methods

Subjects. Eleven patients (10 men, 1 woman) who underwent orthotopic heart transplantation at Shands Hospital at the University of Florida, Gainesville, volunteered to participate in the study. The indications for transplantation were idiopathic cardiomyopathy (seven patients), ischemic cardiomyopathy (three patients) and retransplantation for refractory rejection (one patient). The heart transplant recipients averaged 50 ± 14 (mean ± SD) years of age (range 21 to 63). They were studied 18 ± 12 months (range 7 to 41) after transplantation.

All transplant recipients were clinically stable and free of significant rejection, infection or other major illness. Nine patients received triple-drug immunosuppressive therapy with cyclosporine, prednisone and azathioprine, and two patients were treated with cyclosporine and prednisone. Four heart transplant recipients required furosemide for fluid retention, and all required one or more antihypertensive drugs for mild to moderate hypertension: clonidine (three patients), nifedipine (six patients), captopril (three patients) and enalapril (eight patients). No beta-adrenergic blocking agents or other cardiac medications were used by the transplant recipients at the time of the study. All patients followed their usual protocol of daily medications on the days of experiments. Five transplant recipients had a smoking history (28 ± 4 pack-years for the five patients), but all had stopped smoking a minimum of 4 months before transplantation and none smoked after transplantation.

Eleven control subjects were selected to match the heart transplant recipients, as closely as possible with respect to age, gender and body composition. They were not athletic and had no clinical cardiac or pulmonary disease, as determined by clinical examination, pulmonary screening and exercise testing. None of the control subjects received prescription medication at the time of the study. Four control subjects had a smoking history (27 ± 4 years for the four subjects); however, all had stopped smoking a minimum of 6 months before the study.

The subjects were tested on two different days separated by a minimum of 72 h. All subjects were restricted from strenuous physical activity for 24 h before experiments and reported to the laboratory 2 to 3 h after a meal. The protocol was approved by the Institutional Review Board of the University of Florida College of Medicine, and all subjects provided written informed consent to participate.

Maximal graded exercise test. During the first visit to the laboratory, subjects underwent a physical examination, rest 12-lead electrocardiogram and body composition analysis. After initial screening, they underwent a graded exercise test to symptom-limited maximum on a cycle ergometer. Peak oxygen consumption and plasma levels of vasopressin, norepinephrine, atrial natriuretic peptide, angiotensin II, aldosterone and renin activity were measured during the graded exercise test. Additional information concerning peak oxygen consumption and the neuroendocrine responses during exercise has been reported elsewhere (8).

Submaximal exercise tests. Submaximal exercise tests on day 2 of the experiments were performed at the same time of day (12:00 to 3:00 PM) as the maximal graded exercise test on day 1 to control for a possible effect of circadian rhythms. Environmental conditions within the laboratory were maintained relatively constant at 22 to 23°C, 56% to 62% relative humidity and 760 to 765 mm Hg barometric pressure.

To study arterial blood gases and pH during exercise, each subject performed 10-min periods of constant-load square-wave cycle exercise at 40% and 70% of the peak power output achieved during the maximal graded exercise test. A 20-gauge catheter with a three-way stopcock and 7.5-cm T-connector was placed in the radial artery of the nondominant arm. Before the submaximal exercise tests, the subjects rested for 10 min while seated on the cycle. After collection of a rest blood sample for hematocrit, hemoglobin and arterial blood gases, the subject pedaled at 60 rpm at 40% of peak power output. Arterial blood gas samples were drawn every 30 s during the 1st 5 min of exercise and at 6, 8 and 10 min.

Cardiac output was estimated in duplicate by impedance cardiography technique (9) (Minnesota Impedance Cardiograph and Surcom Cardiographic microcomputer model 7000) at rest and every 30 s during the 1st 5 min of exercise and at 6, 8 and 10 min. At the end of the 1st 10-min cycle test, the subject stopped pedaling and rested quietly in a chair for 10 min. The second submaximal cycle test at 70% of peak power output also began with the subject seated quietly for 10 min on the cycle, providing a total of 20 min of seated recovery between tests. The sample collection described above was repeated during the second ride at 70% of peak power output.

Blood samples were drawn after aspirating and discarding the contents of the catheter and T-connector dead space (≈1 ml). Each arterial blood gas sample was uniformly drawn under anaerobic conditions using a small (3 ml) heparinized plastic syringe. After blood removal, the syringe was immediately capped and stored on ice until analysis. Blood gas determinations were performed within 60 min after sample removal.

Pulmonary function tests. Ten of 11 heart transplant recipients underwent pulmonary function tests within 3 ± 1 months before transplantation as part of the routine pretransplantation evaluation. Pulmonary function tests were repeated 18 ± 12 months after heart transplantation on the same day as the maximal graded exercise test. Pulmonary function reference values were calculated before and after transplantation using the same gender-specific prediction

equations with appropriate corrections for age, height, race and smoking history (10,11). Posttransplantation pulmonary function tests were performed during the same portion of the day (morning or afternoon) as the pretransplantation pulmonary tests in an attempt to control for variations in spirometry that occur over a 24-h period (12). Repeated trials of all tests were performed until results of two trials were in close agreement (≤5%). The mean of these trials served as the criterion value.

A flow-volume loop test was used to generate values for forced vital capacity and forced expiratory volume in 1 s. Single-breath carbon monoxide transfer was used to measure total lung diffusion capacity and the rate of diffusion per unit of lung volume (13). Total lung diffusion capacity and the rate of diffusion per unit of lung volume were measured with appropriate correction for the subject's hemoglobin level on the day of the pulmonary function tests (14). Alveolar volume was also estimated during the diffusion test by using inert and insoluble neon in the diffusion mix. Alveolar volume values were considered estimates of total lung capacity, and they were subsequently used in all calculations requiring total lung capacity values.

Blood gas analysis. Blood gas and pH analyses were performed on a Nova Stat 5 blood gas and acid-base analyzer (Nova Biomedical), with all values normalized to 37°C.

Hematocrit and hemoglobin. Hematocrit and hemoglobin determinations were made with a QBC II Centrifugal Hematology system (Becton Dickinson). Layer measurements were used to compute hemotocrit. Hemoglobin concentration was derived from the hematocrit and measurements of red cell density (15). The percent change in plasma volume during each exercise test was calculated from the preexercise and postexercise hematocrit values (16).

Cyclosporine. The mean of three cyclosporine determinations was used as the criterion cyclosporine value. Cyclosporine was measured at the time of the posttransplantation pulmonary function test and 3 and 6 months before the posttransplantation pulmonary function test for each subject. Cyclosporine concentrations were measured in whole blood specimens by fluorescent polarization using an Abbott TDX Fluorometer (Abbott Laboratories).

Hemodynamics. All patients underwent preoperative and postoperative complete right heart catheterization in the Cardiac Catheterization Laboratory of Shands Hospital at the University of Florida. Pretransplantation catheterization was performed at the time of the preoperative pulmonary function test. Posttransplantation hemodynamic data are from the complete right heart catheterization performed closest to the exercise studies (group mean, 12 months postoperative). Catheterizations were performed with 7F thermodilution Swan-Ganz catheters from femoral, antecubital or right internal jugular percutaneous venous access sites under local anesthesia with minimal sedation in the postabsorptive state. Pressures were recorded on a photographic multichannel recorder (VR-12, Electronics for Medicine). Cardiac output was determined in triplicate using thermodilution technique with 10 ml of room temperature saline solution.

Table 1. Physical Characteristics of the Control and Heart Transplant Groups

Variable	Control Group	Transplant Group
Age (yr)	50.4 ± 13.9	50.1 ± 13.7
Height (cm)	178.2 ± 6.5	176.2 ± 9.7
Weight (kg)	85.5 ± 15.2	85.0 ± 13.8
Body fat (%)	24.7 ± 6.0	27.5 ± 5.6

Values are expressed as mean value ± SD.

Statistical analysis. Descriptive characteristics and pulmonary function test values were compared between groups using analysis of variance. Analysis of variance was also used to compare pretransplantation and posttransplantation pulmonary function test measures in the heart transplant recipients. Pearson product-moment correlation coefficients were calculated to determine the relations among cyclosporine levels, smoking history and pulmonary diffusion capacity and the changes in arterial oxygen pressure during exercise.

Analysis of covariance (ANCOVA) for repeated measures was used to analyze the temporal pattern of cardiac output, arterial blood gases and pH. When a statistically significant time effect or group by time interaction was observed, within-group comparisons between time points or among-group comparisons at each time point, or both, were made using ANCOVA with contrast analysis for obtaining appropriate post hoc custom hypotheses tests. All statistical analyses were completed using the SAS statistical program. An alpha level of $p \leq 0.05$ was required for statistical significance.

Results

Descriptive characteristics (Table 1). The physical characteristics of the heart transplant and control groups are presented in Table 1. The two groups did not differ ($p \geq 0.05$) with respect to age, height, weight and body composition.

Pulmonary function tests (Table 2). Pretransplantation and posttransplantation pulmonary function test data are shown in Table 2. Significant ($p \leq 0.05$) improvements in lung volumes and flow rates occurred after transplantation, with mean increases of 17.4% in forced vital capacity and 11.7% in forced expiratory volume in 1 s. Pulmonary diffusing capacity improved significantly after transplantation ($p \leq 0.05$), with mean increases of 6.6% in whole-lung diffusing capacity and 7.2% in the rate of diffusion per unit of lung volume. Rest arterial oxygen pressure (91.7 before vs. 100.7 mm Hg after) and arterial carbon dioxide pressure (35.6 before vs. 37.0 mm Hg after) showed a trend toward improvement after transplantation, but the changes were not significant ($p = 0.06$). Total lung capacity did not increase significantly ($p \geq 0.05$) from pretransplantation to posttransplantation.

Whole blood cyclosporine concentration in heart trans-

Table 2. Pulmonary Function Test Measurements* and Resting Blood Gas Values of 11 Patients Before and After Orthotopic Heart Transplantation

Pt No.	DLCO (%)		KCO (%)		Pao_2 (mm Hg)		$Paco_2$ (mm Hg)		FVC (%)		FEV_1 (%)		TLC (%)		Smoking History (pack-yr)	Cyclosporine† (ng/ml)
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post		
1	92	96	108	120	98	—	35	—	70	93	84	92	86	90	0	539
2	40	51	51	65	109	105	23	36	74	91	53	71	85	90	59	545
3	99	95	104	96	92	102	38	38	74	93	90	100	84	86	10	555
4	48	59	54	62	96	98	34	36	82	100	91	101	90	92	30	547
5	84	83	81	103	99	101	34	38	81	88	96	97	102	93	0	557
6	78	89	84	91	88	104	43	37	102	100	118	102	100	100	11	507
7	95	89	114	98	102	101	34	36	63	89	67	91	87	89	0	575
8	67	84	75	90	81	99	37	37	60	91	68	95	84	91	0	500
9	35	52	31	49	67	93	44	35	72	87	39	63	97	99	32	584
10	67	68	73	78	92	103	34	40	73	91	81	94	89	90	0	574
11	—	68	—	80	—	104	—	38	—	90	—	99	—	87	0	598
Mean	70	77	78	85	92	101	36	37	75	92	79	91	90	91	13	552
SD	24	18	27	21	14	4	6	2	12	5	23	10	12	7		27
p value	≤ 0.05		≤ 0.05		0.06		0.06		≤ 0.05		< 0.05		0.43			

*Values are expressed as percent of predicted value. †Mean of three whole blood cyclosporine levels determined within 6 months of the posttransplantation pulmonary function test. DLCO = whole-lung diffusion capacity; FEV_1 = forced expiratory volume in 1 s; FVC = forced vital capacity; KCO = diffusion capacity per unit total lung volume; $Paco_2$ = arterial carbon dioxide pressure; Pao_2 = arterial oxygen pressure; Post = after transplantation; Pre = before transplantation; Pt = patient; TLC = total lung capacity.

plant recipients averaged 552 ng/ml during the 6-month period preceding the posttransplantation pulmonary function test (Table 2). For comparison, parent-compound levels by radioimmunoassay would be expected to be in the 200- to 250-ng/ml range. We found no relation between cyclosporine level and changes in whole lung diffusing capacity ($r = 0.18$, $p = 0.82$). Furthermore, the change in diffusing capacity from pretransplantation to posttransplantation was not significantly correlated with either patient age ($r = 0.34$, $p = 0.34$) or the number of months of cyclosporine therapy ($r = 0.10$, $p = 0.79$). A significant inverse relation was present between smoking history (pack-years) and pretransplantation lung diffusing capacity ($r = 0.74$; $p = 0.02$) and posttransplantation lung diffusing capacity ($r = 0.78$, $p = 0.03$).

Although pulmonary function was improved after heart transplantation, posttransplantation pulmonary function measures in the heart transplant recipients were significantly ($p \leq 0.05$) lower than in the control group (Table 3). Absolute and relative (percent of predicted) measures of whole lung diffusing capacity, the rate of diffusion per unit of lung volume, forced vital capacity and forced expiratory volume in 1 s were lower ($p \leq 0.05$) in the heart transplant recipients compared with the control group, but total lung capacity was not different ($p \geq 0.05$) between groups.

Relative exercise intensity. Physiologic variables that were considered valid indicators of differences in relative exercise intensity between the two groups are shown in Table 4. There were nonsignificant ($p \geq 0.05$) differences between the heart transplant and control groups for heart rate (percent of heart rate reserve), rating of perceived exertion and reductions in plasma volume (percent change from rest) at the conclusion of each of the exercise conditions. These data indicate that the relative exercise stimulus during the submaximal exercise tests was comparable between groups.

Arterial blood gas. Satisfactory blood gas comparisons included 10 heart transplant recipients and 10 control subjects (patient 1 in Table 2 was omitted). For statistical analysis of arterial blood gas responses during exercise, the heart transplant recipients were separated into two subsets using posttransplantation whole lung diffusing capacity values as the criterion for group assignments. Five heart transplant recipients had lung diffusing capacity values >70% of predicted, and five heart transplant recipients had lung diffusing capacity values <70% of predicted.

The temporal patterns of arterial blood gases and pH during 10 min of cycle exercise at 40% of peak power output

Table 3. Pulmonary Function Values* of the Control and Heart Transplant Groups After Heart Transplantation

Variable	Control Group	Heart Transplant Group
DLCO ($ml \cdot min^{-1} \cdot mm\ Hg$)	29.20 ± 4.39	20.74 ± 4.21†
% Predicted	106 ± 10	77 ± 18†
KCO	4.51 ± 0.75	3.75 ± 1.13†
% Predicted	100 ± 12.3	85 ± 21†
FVC (liters)	4.75 ± 0.87	4.13 ± 0.66†
% Predicted	97 ± 9	92 ± 5†
FEV_1 (liters)	3.74 ± 0.71	3.03 ± 0.88†
% Predicted	101 ± 12	91 ± 10†
TLC (liters)	6.50 ± 0.64	5.74 ± 1.08
% Predicted	94 ± 9	91 ± 7

*Values are expressed as mean value ± SD. †$p \leq 0.05$, transplant group versus control group. Abbreviations as in Table 1.

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Table 4. Heart Rate*, Rating of Perceived Exertion† and Plasma Volume Changes‡ During Submaximal Exercise Tests

Variable	% Peak Power	
	40%	70%
Heart rate (% HRR)		
Control group	46.4 ± 8.6	81.2 ± 6.4
Heart transplant group	51.9 ± 16.3	81.6 ± 7.9
Perceived exertion		
Control group	12.2 ± 1.2	15.1 ± 1.1
Heart transplant group	12.5 ± 1.2	16.6 ± 1.2
%Δ plasma volume		
Control group	−4.6 ± 3.4	−10.8 ± 2.4
Heart transplant group	−5.7 ± 4.3	−10.1 ± 3.8

*Heart rate expressed as percent of heart rate reserve (HRR). †Borg (1962) scale. ‡Percent loss in plasma volume (rest–exercise). Values are expressed as mean value ± SD.

are shown in Figure 1. Baseline arterial oxygen pressure was not significantly different ($p \geq 0.05$) among the three groups. The group by time interaction for arterial oxygen during exercise at 40% of peak power output was not significant ($p \geq 0.05$), although arterial oxygen pressure returned to baseline by 2.5 min of exercise in the control and normal diffusion groups but continued to decrease in the low diffusion group. Baseline arterial carbon dioxide pressure was significantly ($p \leq 0.05$) lower in the low diffusion group than in the control or normal diffusion groups. The group by time interaction for arterial carbon dioxide pressure during exercise was not significant ($p \geq 0.05$), but carbon dioxide pressure in the low diffusion group was different ($p \leq 0.05$) from baseline by 4 min after the onset of exercise, whereas the control and normal diffusion groups remained isocapnic. Arterial pH was similar in the three groups at rest ($p \geq 0.05$) and during exercise ($p \geq 0.05$), with values decreasing significantly ($p \leq 0.05$) below rest values by min 3 of exercise.

Figure 1. Temporal pattern of arterial oxygen pressure (Pao_2), arterial carbon dioxide pressure ($Paco_2$) and pH during 10 min of constant load cycle exercise at 40% of peak power output in patients with normal (NL-DLCO) and low (LO-DLCO) pulmonary diffusion capacity and the control group. Values are expressed as mean value ± SEM.

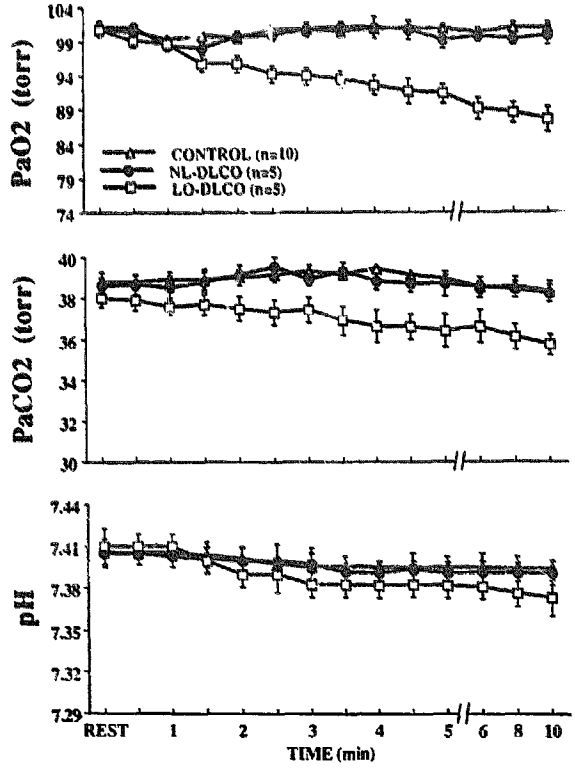

Figure 2. Temporal pattern of arterial oxygen pressure (Pao_2), arterial carbon dioxide pressure ($Paco_2$) and pH during 10 min of constant load cycle exercise at 70% of peak power output in patients with normal (NL-DLCO) and low (LO-DLCO) pulmonary diffusion capacity and the control group. Values are expressed as mean value ± SEM. *$p \leq 0.05$ LO-DLCO versus control group and NL-DLCO during exercise.

During exercise at 70% of peak power output, arterial oxygen pressure in the low diffusion group was significantly ($p \leq 0.05$) lower than in the control and normal diffusion groups by 1.5 min after the onset of exercise (Fig. 2). Arterial oxygen pressure decreased to <70 mm Hg in two patients in the low diffusion group. Arterial carbon dioxide pressure in the low diffusion group also decreased significantly ($p \leq 0.05$) more than in the control and normal diffusion groups by 3.5 min of exercise. Arterial pH decreased more rapidly in the low diffusion group, becoming significantly different ($p \leq 0.05$) from the control and normal diffusion groups by 4.5 min of exercise. Highly significant inverse relations were

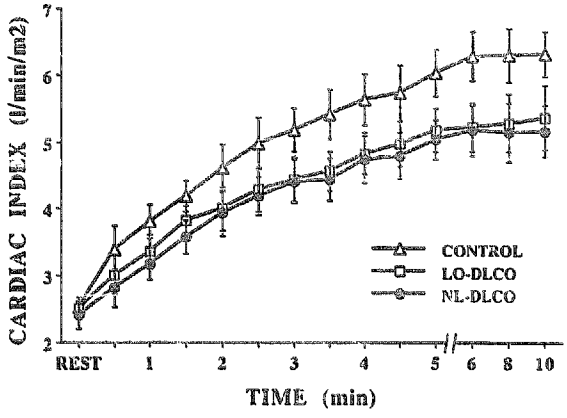

Figure 3. Temporal pattern of cardiac index (liters·min^{-1}·m^2) during 10 min of constant load cycle exercise at 70% of peak power output in patients with normal (NL-DLCO) and low (LO-DLCO) pulmonary diffusion capacity and the control group. Values are expressed as mean value ± SEM.

present between rest whole lung diffusion capacity and the transient hypoxemia experienced during cycle exercise at 40% ($r = -0.94$; $p = 0.01$) and 70% ($r = -0.97$; $p = 0.001$) of peak power output.

Cardiac output. Rest cardiac index was not significantly different ($p \geq 0.05$) among the three groups (2.51, 2.48 and 2.53 liters·min^{-1}·m^2 for the low diffusion, normal diffusion and control group, respectively). Cardiac index was not significantly different ($p \geq 0.05$) between the low diffusion and normal diffusion groups at any measurement period during exercise at 40% or 70% of peak power output. The temporal pattern of cardiac index during exercise at 70% of peak power output is presented in Figure 3. During exercise at 70% of peak power output, cardiac index in the control group was significantly greater ($p \leq 0.05$) than in both the low diffusion and the normal diffusion group at all measurement periods; however, 70% of peak power output represented a greater absolute exercise intensity in the control group and required a greater absolute cardiac output.

Hemoglobin. Pretransplantation hemoglobin was 14.5 ± 1.7 and 14.8 ± 1.4 g/dl in the normal diffusion and low diffusion group, respectively. Posttransplantation hemoglobin was significantly reduced ($p \leq 0.05$) in both the normal diffusion (12.9 ± 1.5) and low diffusion groups (13.1 ± 1.8) compared with pretransplantation hemoglobin values. However, absolute hemoglobin concentration and the relative change in hemoglobin concentration from pretransplantation to posttransplantation did not differ ($p \geq 0.05$) between the low and normal diffusion groups. Therefore, the differences in whole lung diffusion capacity between subsets of heart transplant recipients cannot be explained by differences in hemoglobin. Hemoglobin concentrations were significantly lower ($p \leq 0.05$) in both the normal diffusion and low diffusion groups than in the control group (14.1 ± 1.2).

Pulmonary hypertension and hypoxemia. To evaluate the possible relation between pulmonary hypertension and whole lung diffusion impairment, we reviewed and retrospectively analyzed right heart catheterization data in the heart transplant recipients. Significant decreases ($p \leq 0.05$) in systolic (40%), diastolic (42%) and mean pulmonary artery pressures (43%) and pulmonary vascular resistance (47%) occurred by 1 year after transplantation. One purpose of this analysis was to detect possible differences in hemodynamic factors between the low diffusion and normal diffusion groups. A comparison of right heart catheterization data in the low diffusion and normal diffusion groups is shown in Table 5. Preoperative systolic pulmonary artery pressure was significantly ($p \leq 0.05$) higher in the normal diffusion group than in the low diffusion group. At 1 year after transplantation, systolic, diastolic and mean pulmonary artery pressure and pulmonary vascular resistance were not significantly different in the low and normal diffusion groups. Our second purpose was to determine whether any pretransplantation or posttransplantation hemodynamic variables correlated with exercise-induced hypoxemia. None of the preoperative right heart catheterization variables were significantly ($p \geq 0.05$) correlated with posttransplantation exercise-induced hypoxemia; however, postoperative mean pulmonary artery pressure was significantly related to exercise-induced hypoxemia ($r = 0.71$; $p = 0.03$). Figure 4 illustrates the relation between mean pulmonary artery pressure at approximately 1 year after transplantation and the decline in arterial oxygen pressure during submaximal exercise at 70% of peak power output.

Table 5. Comparisons of Systolic, Diastolic and Mean Pulmonary Artery Pressures and Pulmonary Vascular Resistance in the Normal Lung Diffusion (NL-DLCO) and Abnormal Lung Diffusion (LO-DLCO) Groups Before and After Heart Transplantation

Variable	NL-DLCO (n = 5)	LO-DLCO (n = 5)	p Value
Before			
PA_{syst} (mm Hg)	61 ± 15	38 ± 8	0.03
PA_{dias} (mm Hg)	29 ± 2	27 ± 9	0.59
PA_{mean} (mm Hg)	42 ± 8	31 ± 10	0.10
PVR (Wood U)	3.6 ± 2.5	2.1 ± 0.9	0.29
After			
PA_{syst} (mm Hg)	28 ± 8	31 ± 12	0.72
PA_{dias} (mm Hg)	14 ± 7	17 ± 6	0.46
PA_{mean} (mm Hg)	17 ± 7	24 ± 9	0.19
PVR (Wood U)	1.6 ± 1.1	1.8 ± 0.9	0.86

Values are expressed as mean value ± SD. PA_{dias} = diastolic pulmonary artery pressure; PA_{mean} = mean pulmonary artery pressure; PA_{syst} = systolic pulmonary artery pressure; PVR = pulmonary vascular resistance.

Discussion

Our results show that the impaired pulmonary diffusing capacity observed in some patients before transplantation persists after heart transplantation with or without accompanying restrictive or obstructive ventilatory defects. Our data also suggest that abnormal pulmonary diffusing capacity

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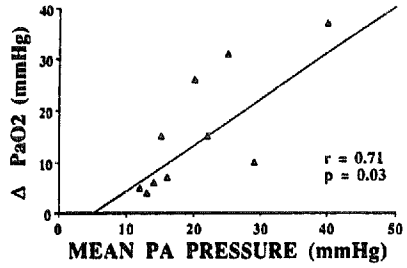

Figure 4. Relation between mean pulmonary artery (PA) pressure at 1 year after transplantation and the decline in arterial oxygen pressure (Pao_2) from baseline during 10 min of constant load cycle exercise at 70% of peak power output (n = 10).

possibly contributes to exercise intolerance in some heart transplant recipients, particularly when lung diffusion capacity is <70% of predicted. Five of 11 heart transplant recipients in the present study experienced exercise-induced hypoxemia (arterial oxygen pressure 15 to 38 mm Hg below values at rest) during strenuous submaximal exercise, and all five presented with whole lung diffusion capacity values at rest that were <70% of predicted. Chronic immunosuppression with cyclosporine had no adverse effect on pulmonary diffusion capacity.

Pulmonary function tests. Our spirometry data are consistent with data from previous studies that have reported pulmonary function in heart transplant recipients before and after heart transplantation. Hosenpud et al. (7) found increases of 16% and 13% in forced vital capacity and forced expiratory volume in 1 s, respectively, in 17 heart transplant recipients 15 ± 10 months after transplantation but did not report pulmonary diffusion values. Casan et al. (1) also reported significant improvements in forced vital capacity (12%) and forced expiratory volume in 1 s (13%) in 10 heart transplant recipients an average of 9 months after transplantation. However, our finding of a 7% improvement in whole lung diffusion capacity after transplantation is not in agreement with the posttransplantation pulmonary diffusion data of Casan et al. (1), which showed a mean reduction of 14%. Casan et al. attributed the reduction in pulmonary diffusion capacity to cyclosporine-induced lung toxicity and reported a high correlation (r = 0.87) between the reduction in diffusion capacity and the level of cyclosporine in whole blood at the time of the pulmonary function tests. In contrast, we found no relation between the change in diffusion capacity from pretransplantation to posttransplantation and whole blood cyclosporine levels (r = 0.08, p = 0.82). Posttransplantation whole lung diffusion capacity either increased (5 of 10 patients) or remained approximately the same (5 of 10 patients) when compared with pretransplantation diffusion capacity values.

One possible explanation for these divergent findings is that the cyclosporine whole blood levels maintained in our heart transplant recipients were lower (552 ng/ml). Casan et al. (1) reported mean cyclosporine whole blood levels of 923 ng/ml. However, our transplant recipients were older (50 vs. 39 years) and had also been receiving cyclosporine therapy longer (18 vs. 9 months) at the time of the study. If cyclosporine immunosuppression produces lung toxicity, we should have observed more advanced manifestations of pulmonary dysfunction in the present study. However, a relation did not exist between the change in pulmonary diffusion capacity from pretransplantation to posttransplantation and either the age of the patients (r = 0.34, p = 0.34) or the number of months receiving cyclosporine therapy (r = 0.10, p = 0.79).

Exercise-induced hypoxemia. Although our data do not support the hypothesis that cyclosporine adversely affects pulmonary diffusion capacity, we did find rest lung diffusion abnormalities and exercise-induced hypoxemia in 5 (45%) of 11 heart transplant recipients. During exercise at 70% of peak power output, all of the control subjects maintained arterial oxygen pressure within 5 mm Hg of their corresponding baseline values, and the normal diffusion group of patients had reduced arterial oxygen pressure only 5 to 10 mm Hg below values at rest. In the low diffusion group of patients, arterial oxygen pressure decreased to <90 mm Hg in all cases; between 80 and 90 mm Hg in two cases, between 70 and 80 mm Hg in one case and to <70 mm Hg in two cases.

The mechanism or mechanisms mediating exercise-induced hypoxemia in heart transplant recipients remain to be elucidated. However, four possible causes of exercise-induced hypoxemia exist: 1) hypoventilation, 2) venoarterial shunt, 3) ventilation/perfusion inequality, and 4) diffusion limitations (17). Hypoxemia in the heart transplant recipients during exercise at 70% of peak power output was not associated with hypoventilation. Of the five patients exhibiting exercise-induced hypoxemia, all showed substantial hyperventilation (arterial carbon dioxide pressure 28 to 33 mm Hg). Other investigators have also reported normal or even exaggerated ventilatory responses to exercise in heart transplant recipients (2,18). Venoarterial shunt does not play an important role in exercise-induced arterial hypoxemia in healthy persons (19). However, more data are needed to fully quantitatively describe the role of venoarterial shunt as a possible cause of exercise-induced hypoxemia in heart transplant recipients. Similarly, little information is available concerning pulmonary ventilation/perfusion in heart transplant recipients. Gledhill et al. (20) used the multiple inert gas washout technique and sulfur hexafluoride (SF_6) breathing to show that approximately 50% of the decrease in arterial oxygen tension during exercise in trained subjects is due to increased nonuniformity of ventilation/perfusion ratios that probably arise from heterogeneity within lung regions (intraregional) rather than between regions (interregional). A potential mechanism for deterioration of ventilation/perfusion ratios in heart transplant recipients during exercise may be an attenuated cardiac output response due to cardiac denervation (21). However, cardiac index values were the same in our normal diffusion and low diffusion subsets of patients at rest and at all measurement periods

during exercise at 40% and 70% of peak power output. Thus, attenuated cardiac output does not appear to be the explanation for the hypoxemia observed in the low diffusion group. We did not document the changes in ventilation/perfusion inequality during exercise, but it is possible that ventilation/perfusion inequality increases during exercise and contributes in part to the hypoxemia observed in heart transplant recipients during strenuous exercise. The final possible mediator of exercise-induced hypoxemia in heart transplant recipients is diffusion limitations across the blood-gas interface of the lung. The five heart transplant recipients experiencing exercise arterial oxygen pressure <90 mm Hg were the only subjects with pulmonary diffusion capacity values at rest <70% of predicted. We speculate that exercise-induced hypoxemia in heart transplant recipients is due in part to limitations in pulmonary diffusion capacity. The widened difference between alveolar and arterial oxygen tensions in heart transplant recipients during heavy exercise may also be due to intraregional ventilation/perfusion inequalities and a possible contribution from venoarterial shunts. However, because no direct evidence is available that clearly elucidates the mechanism to explain this exercise-induced hypoxemia, these conclusions can only be speculative.

Abnormal pulmonary diffusion. Several possible explanations for the high prevalence of abnormal pulmonary diffusion capacity in heart transplant recipients should be considered. First, moderate to severe obstructive pulmonary disease is one potential mechanism for abnormal lung diffusing capacity. However, mild airway obstruction (forced expiratory volume in 1 s ≤80% of predicted) was present in only two heart transplant recipients postoperatively (Patients 2 and 9, Table 2). Second, current and recent exsmokers can have a low pulmonary diffusion capacity compared with normal subjects without an associated airway obstruction. Although 5 of 11 heart transplant recipients were former smokers, all had stopped smoking a minimum of 12 months before the study. Moreover, impaired lung diffusion capacity (<70% of predicted) was present in two heart transplant recipients who had never smoked. Third, restrictive ventilatory defects are another mechanism that can contribute to low pulmonary diffusion capacity due to reduction in alveolar volume and surface area for diffusion (13). However, the abnormal lung diffusion capacity in five of our heart transplant recipients after transplantation was not associated with a restrictive deficit (mean total lung capacity 91% of predicted), and there was no significant relation between diffusion capacity and forced vital capacity, a relation that would be expected if the diffusion impairment was due to a reduction in lung volume.

Two other potential mechanisms for abnormal pulmonary diffusion capacity merit consideration. Chronic passive congestion in the lungs associated with congestive heart failure produces fibrosis and thickening of interalveolar septae, interstitial and alveolar edema and possible redistribution of pulmonary capillary blood volume (22). These processes can impair pulmonary diffusion by causing alveolar-capillary block (4). Most patients in the present study had moderate to severe pulmonary hypertension before heart transplantation. However, we found no significant relation between preoperative pulmonary artery pressure and posttransplantation exercise-induced hypoxemia, suggesting that the pulmonary fibrosis associated with congestive heart failure may not be directly related to hemodynamic factors. At ≈1 year after transplantation, we found significant decreases in systolic (40%), diastolic (42%) and mean pulmonary artery pressures (43%) and pulmonary vascular resistance (47%). These data indicate the reversibility of pulmonary hypertension after transplantation and demonstrate that preoperative pulmonary hypertension does not preclude a successful outcome after transplantation.

Finally, the high prevalence of posttransplantation lung diffusion abnormalities in our heart transplant recipients, despite improved pulmonary spirometry, may be related to chronic posttransplantation volume expansion. Our finding that mean pulmonary artery pressure at 1 year posttransplantation was significantly correlated ($r = 0.71$, $p = 0.03$) with exercise-induced hypoxemia suggests possible exercise-induced pulmonary edema in some ambulatory heart transplant recipients. Expanded plasma volume has been reported in heart transplant recipients (23), and these patients also demonstrate an impaired ability to regulate volume, frequently requiring diuretic agents, even in the presence of normal glomerular function and cardiac hemodynamics (24). We have previously shown that ambulatory heart transplant recipients hypersecrete vasopressin and renin, which may be one mechanism responsible for volume expansion and edema in this group of patients (8). Theoretically, diffusion distance could be lengthened sustantially and diffusion compromised if high pulmonary blood flow produced greatly elevated vascular pressures, leading to leakage of fluid across the capillary endothelium and its accumulation in the interstitial fluid space (25). Significant increases in pulmonary extravascular water volume are reported in healthy subjects during exercise (26). The effects of strenuous exercise on pulmonary vascular fluid in volume-expanded heart transplant recipients have yet to be determined. Measurement of right heart hemodynamics during exercise in heart transplant recipients with abnormal lung diffusion is critical to the resolution of this issue and is an area that we plan to investigate.

Pulmonary diffusion and exercise tolerance. Diminished peak oxygen consumption (50% to 60% of matched control) is a consistent finding in heart transplant recipients (8,21,27–29). The factors responsible for attenuated peak oxygen consumption in heart transplant recipients are not completely understood. Rudas et al. (21) recently reported that peak exercise cardiac index, secondary to attenuated chronotropic response, was reduced by 25% in heart transplant recipients compared with values in matched control subjects. However, reduced cardiac index does not entirely account for the marked difference in peak oxygen consump-

tion between heart transplant recipients and matched control subjects. Peripheral skeletal muscle or vascular abnormalities in heart transplant recipients, some of which may be attributed to long-term deconditioning and medications, also contribute to reduced peak oxygen consumption by decreasing peripheral oxygen extraction (27,30,31). Our data suggest that impaired pulmonary gas exchange possibly contributes to the diminished exercise capacity observed in some of these patients. Peak oxygen consumption during the maximal graded exercise test was diminished in the low diffusion group but not statistically different from that in the normal diffusion group (17.1 vs. 19.1 ml·kg^{-1}·min^{-1}); however, the low diffusion group was 10 years younger than the normal diffusion group (45 vs. 55 years) and could be expected to have higher peak oxygen consumption values. Powers et al. (32) reported that peak oxygen consumption is reduced ≈1% for each 1% decrement in arterial oxygen saturation. We did not sample arterial blood gases during the maximal graded exercise test, and arterial oxygen saturation was not measured. However, the exercise-induced hypoxemia (arterial oxygen pressure <70 mm Hg in two patients and <80 mm Hg in one patient) and metabolic acidosis (pH 7.28 in two patients and pH 7.30 in one patient) that we observed in some heart transplant recipients during submaximal exercise could become more severe during maximal exercise and result in reductions in arterial oxygen saturation to <85%. Reductions in arterial oxygen saturation of this magnitude cause 10% to 12% reductions in peak oxygen consumption (19).

Conclusions. Five (45%) of 11 patients demonstrated impaired pulmonary gas exchange, with or without an accompanying restrictive or obstructive ventilatory defect after heart transplantation. All five experienced exercise-induced hypoxemia (arterial oxygen pressure 15 to 38 mm Hg below values at rest) during submaximal exercise, suggesting that impaired pulmonary diffusing capacity possibly contributes to diminished peak oxygen consumption in some heart transplant recipients. The precise cause of the pulmonary diffusion impairment is unclear, and further study is required to elucidate the nature of this defect.

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