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Effect of lung transplantation on heart rate response to exercise

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ABSTRACT

Objectives: To evaluate if patients have a change in percent of predicted heart rate reserve used at peak exercise (%HRR) after lung transplantation, even at matching workloads.
Background: Lung disease of obstructive, restrictive, and mixed types may be associated with an autonomic imbalance. Lung transplantation may improve the effects of pulmonary disease on cardiac function. However, the effect of lung transplantation on heart rate responses during exercise has not been investigated in detail.
Methods: Retrospective review of patients who underwent lung transplantation. Pre and post transplant cardiopulmonary exercise tests were reviewed.
Results: The %HRR significantly improved by a median of 37% ($p < 0.001$) following lung transplantation. When matching workloads were analyzed, the %HRR also decreased from a median of 36% to 24% ($p < 0.001$).
Conclusions: Corresponding to an increase in peak exercise capacity, percentage of heart rate reserve used improves significantly after lung transplantation, even at matching workloads, indicating a likely improvement in autonomic modulation.

Introduction

A chronic increase in resting heart rate (HR) has been associated with poor prognosis in various cardiovascular diseases and is associated with altered autonomic function and risk of sudden death.[1,2] Abnormalities in autonomic control and elevated resting heart rates are known to be present in patients with chronic obstructive pulmonary disease (COPD)[3–6] and respiratory failure.[6–8] An example of this is seen with reduced parasympathetic activity (determined from decreased heart rate variability parameters) that has been thought to be a potential cause of an elevated resting HR in lung transplant recipients.[2,9] An attenuated HR response to exercise, also known as chronotropic incompetence (CI), has the highest prevalence among individuals with the most impaired exercise capacity[10] but CI is also seen in healthy obese subjects, healthy smokers,[4,11] and patients with COPD.[3–5] Seshadri and colleagues have found that a reduced forced expiratory volume in one second is associated with a lower chronotropic response.[5] Additionally, they concluded that lung disease of obstructive, restrictive, and mixed types may be associated with an autonomic imbalance.

In a population-based study of normal patients and those with mild COPD, Barr et al showed that the degree of airflow obstruction is significantly associated with reduced left ventricular end diastolic volume, stroke volume and cardiac output.[12] This alludes to the fact that even in those with no or mild symptoms of lung disease, cardiac function is impaired. In our previous work, we have found that lung volume reduction surgery significantly improves the heart rate response to exercise in patients with COPD.[13]

Lung transplantation (LTx) results in a significant improvement in lung function and may improve survival for patients with advanced respiratory disease.[14] Additionally, LTx may ameliorate the effects of the pulmonary disease on cardiac function.[15] However, the effect of LTx on heart rate responses during exercise has not been investigated in detail.

The existing literature on heart rate responses after cardiac transplantation demonstrates no clear improvement due to the denervation of the heart.[16–18] However, the heart remains innervated in LTx recipients so we hypothesized that the heart rate response to

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exercise would improve after LTx. To address this uncertainty, the current study was designed using cardiopulmonary exercise testing (CPET) parameters to investigate the effect of LTx on CI.

Methods

A retrospective chart review was performed of all 498 patients at the New York Presbyterian-Columbia University Lung Transplant Program who underwent LTx between January 2001 and June 2012. Inclusion criteria included complete CPET and pulmonary function tests (PFT) before transplant and repeat testing at least 3 months after transplant. At our center, CPET is normally performed annually pre and post lung transplantation to evaluate functional status and direct pulmonary rehabilitation prescription. Since heart rate response cannot be accurately determined in patients who are not in sinus rhythm, have a left ventricular ejection fraction <45% or are on beta blockade pre- or post-transplant, these patients were excluded. Additionally, patients who were tested on supplemental oxygen post transplantation were excluded since this would be an indicator of recurrent pulmonary disease. The Institutional Review Board of Columbia University Medical Center approved this study.

Exercise and pulmonary function testing

CPET was performed on an electronically braked cycle ergometer (Ergometrics 800, SensorMedics Inc., Yorba Linda, CA) with a Viasys Sensormedics Encore metabolic cart (Viasys Corporation, Loma Linda, CA); prior to 2005 a Vmax 229 series workstation (SensorMedics Inc., Yorba Linda, CA) was used. The equipment was calibrated prior to every test. Heart rate was measured by continuous 12-lead telemetry via CardioSoft electrocardiogram software (GE/CardioSoft, Houston, TX); prior to 2005 a model Max-1 electrocardiogram was used (Marquette Medical Systems; Milwaukee, WI). Oxygen saturation was recorded with a N595 pulse oximeter, placed on the finger (Nellcor, Boulder, CO); prior to 2005 a Sensormedics Sat-Trak (SensorMedics Inc., Yorba Linda, CA) was used. Patients were tested on 30% fractional inspired oxygen via mouthpiece or room air before LTx depending on their usual requirements. All included patients were tested on room air after LTx; all calibrations were two point calibrations with hyperoxic and hypoxic points and included hypercarbic and absent carbon dioxide levels of calibration. The metabolic system was validated for use with hyperoxic testing and was stable for measurement of $FeCO_2$ at hyperoxic situations. The exercise protocol was ramping and followed the protocol used in the NETT[19] and American Thoracic Society guidelines.[20,21] The CPET variables were collected breath by breath and included the rate of carbon dioxide production (VCO_2), maximal workload (peak watts), oxygen consumption by weight (VO_2 in mL/kg/min), percent of predicted maximal oxygen consumption (VO_2, %), oxygen saturation (SpO_2), minute ventilation (VE), tidal volume (Vt), respiratory rate (RR), peak end-tidal CO_2 pressure ($PetCO_2$), HR at baseline (HR_{rest}), heart rate at peak exercise (HR_{max}), systolic blood pressure at baseline and at peak exercise (SBP_{rest} and SBP_{max}) and diastolic blood pressure at baseline and at peak exercise (DBP_{rest} and DBP_{max}). All PFTs were performed according to the NETT protocol.[19] This included the forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1), total lung capacity (TLC), and residual volume (RV). Percent of predicted PFTs were calculated for males and females as described in prior publications.[22–24]

Furthermore, an iso-workload analysis was used to compare the same workloads at both exercise tests. The maximal workload achieved by the patient during either the first or second CPET was chosen for comparison. For example if the maximal workload at the first CPET was 15 W, then 15 W was the level used for both tests to compare CPET variables. Looking at iso-workload allowed us to control for the increase in functional capacity.

Age predicted maximal HR was calculated using $208 - 0.7 \times age$.[25] Heart rate response was assessed using the percent of predicted heart rate reserve used at peak exercise (%HRR): $\%HRR = (HR_{max} - HR_{rest})/((\text{age predicted HR}) - HR_{rest}) \times 100$.[2] PFT and CPET values pre-LTx were compared to the values post-LTx to determine the effects of LTx on heart rate response during rest and exercise.

Statistics

Data were analyzed with SPSS version 18[26] and are presented as median and interquartile range (IQR) (25–75%). Comparisons between pre- and post-LTx were done with Wilcoxon matched-pair signed-rank tests. Categorical variables were compared with a chi-square test and Fisher's exact test when necessary. Statistical significance was set at $p \leq 0.05$.

Results

There were 54 patients that met the inclusion criteria. General characteristics and CPET results (age: 57 years (40–62); BMI: 25.0 kg/m^2 (20.0–27.4); 44% female) are presented in Table 1. There were 25 idiopathic pulmonary fibrosis/interstitial lung disease (ILD), 15 COPD/Emphysema/Alpha-1 antitrypsin deficiency (COPD/E/A1A) and 14 Cystic Fibrosis/Bronchiectasis (CF/B) patients who were included in the analysis. 91% of patients were tested on supplemental oxygen before transplantation. Only 10 had unilateral lung transplantations, the rest were bilateral. The time between the first CPET and lung transplantation was 230 (130–437) days and time between lung transplantation and the second CPET was 383 (361–435) days.

All patients were encouraged to attend pre- and post-transplant rehabilitation and had self-report of continued maintenance exercise. All patients were on prednisone, mean dosage 10.88 ± 7.86 mg; 93% were on tacrolimus, mean blood level 9.10 ± 3.70 ng/ml; 6% were on cyclosporine, blood level 260.67 ± 15.50 ng/ml; 4% were on sirolimus, blood level 7.30 ± 0.28 ng/ml and 50% were on cellcept, mean dosage 1300 ± 677 mg.

Effect of lung transplantation on %HRR

The %HRR significantly improved by a median of 37% ($p < 0.001$) following lung transplantation (Fig. 1). The HR_{rest} decreased

Table 1
Comparison of before and after transplant.

$n = 54$	Median (IQR)		*p*-Value
	Before transplant	After transplant	
Weight (kg)	70.9 (59.2–79.3)	75.3 (64.4–83.7)	**0.001**
Peak watts	39 (20–65)	80 (60–96)	**<0.001**
Peak VO_2 (mL/kg/min)	13.52 (8.03–19.06)	16.37 (13.77–20.10)	**0.001**
Peak VO_2 %	38% (29–57%)	55% (47–69%)	**<0.001**
O_2 pulse (mL/beat)	7.46 (4.86–11.47)	8.78 (7.13–11.55)	**0.008**
Peak VCO_2 (mL/kg/min)	0.92 (0.56–1.35)	1.45 (1.18–1.80)	**<0.001**
CO_2 pulse (mL/beat)	12.90 (7.41–18.90)	20.14 (16.49–25.50)	**<0.001**
Peak VE (L/min)	30.9 (19.9–46.3)	53.0 (42.9–62.5)	**<0.001**
HR_{rest} (beats/min)	96 (81–108)	89 (83–100)	0.062
HR_{max} (beats/min)	126 (111–143)	136 (124–149)	**0.001**
%HRR	37% (25–53%)	57% (42–67%)	**<0.001**
Peak RER	0.91 (0.80–1.04)	1.22 (1.12–1.29)	**<0.001**

BMI, body-mass index; VO_2, volume of oxygen consumed; VCO_2, rate of carbon dioxide production; VE, minute ventilation; HR_{rest}, resting heart rate; HR_{max}, maximal heart rate; %HRR, percent of predicted heart rate reserve; RER, respiratory exchange ratio; IQR, interquartile range.
Bold *p*-values indicate $p \leq 0.05$.