Altered Sympathetic and Parasympathetic Activity in Lung Transplantation Patients at Rest and Following Autonomic Perturbation*

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Study objectives: To investigate the nature and extent of the alteration in autonomic function following heterotopic lung transplantation.

Design: Measures of cardiac parasympathetic nervous system activity (PNSA) and systemic sympathetic nervous system activity (SNSA) were compared in lung transplant patients and age-matched healthy subjects, both at rest and following autonomic perturbation.

Setting: Lung transplantation service of a university teaching hospital.

Patients and participants: Twenty-two lung transplant patients (mean [± SEM] age, 50.5 ± 2.4 years) and 13 healthy subjects (mean age, 48.2 ± 3.7 years).

Measurements and results: Lung transplant patients had decreased baseline time and frequency domain measures of heart rate variability compared to healthy subjects (root mean square of successive differences in R-R intervals, 11.2 ± 1.1 vs 30.3 ± 4.5 ms, respectively [p < 0.005]; LnHP, 2.4 ± 0.2 vs 4.8 ± 0.4 ms², respectively [p < 0.005]). In addition, lung transplant patients demonstrated an attenuated reduction in LnHP/LnTP following head-up tilt in comparison to healthy subjects (p < 0.05). The baseline recumbent plasma norepinephrine level was increased in lung transplant patients compared to healthy subjects (3.25 ± 0.43 vs 2.00 ± 0.27 nmol/L, respectively; p < 0.05), and levels increased in both groups with upright head-up tilt. There were no differences between the two groups in heart rate or mean systolic BP responses to both the Valsalva maneuver and cold pressor testing.

Conclusions: Lung transplant patients have both reduced PNSA and increased SNSA at rest. Furthermore, these patients appear to have a preserved capacity to respond to autonomic perturbation by increasing SNSA. The mechanisms underlying these observations and their prognostic implications remain to be determined.

Key words: autonomic; catecholamines; heart rate variability; lung transplantation

Abbreviations: ANOVA = analysis of variance; HP = high-frequency power; HR = heart rate; HRV = heart rate variability; Ln = natural log; LP = low-frequency power; NE = norepinephrine; PNSA = parasympathetic nervous system activity; rMSSD = root mean square of successive differences in R-R intervals; SNSA = sympathetic nervous system activity; TP = total power
vagal pulmonary afferent transection and/or the inadvertent disruption of cardiac efferent nerves during the surgical procedure. Furthermore, we speculated that this reduction in vagal afferent activity (which normally tonically inhibits sympathetic nervous system activity [SNSA]) centrally would, therefore, result in overactivity of the sympathetic nervous system. Studies investigating the autonomic effects of lung transplantation have been few and have involved very small sample sizes. None have systematically assessed both SNSA and PNSA at rest and following autonomic perturbation.

Therefore, the aim of the present study was to determine whether there were differences in autonomic function, at rest and following autonomic perturbation, in lung transplant patients in comparison to age-matched healthy subjects.

**Materials and Methods**

**Study Population**

The study population comprised lung transplantation patients who were clinically stable and remote (ie, > 4 months) from undergoing transplantation. Patients with known diabetes mellitus, chronic heart failure, or hypercholesterolemia and long-term smokers were excluded, as these conditions may interfere with autonomic function. Lung transplant patients also had to be in normal sinus rhythm, as is required for HR variability (HRV) analysis.

Healthy subjects were required to be free of the above diseases as well as not taking any current medications that could influence autonomic function.

Lung transplantation patients were recruited through the Department of Respiratory Medicine at the Alfred Hospital, Prahran, VIC, Australia. Healthy subjects were recruited by advertisements distributed throughout the hospital.

We studied 9 single-lung and 13 double-lung transplant patients, 9 months to 7.5 years postoperatively. Their ages ranged from 23 to 64 years (mean ± SEM, 48.2 ± 3.7 years). Thirteen patients were women, and 9 patients were men (Table 1). All patients were known to have normal cardiac function before undergoing transplantation.

Immunosuppression was maintained with cyclosporine (21 patients), tacrolimus (1 patient), azathioprine (14 patients), sirolimus (1 patient), mycophenolate (2 patients), or the study drug ramipril (Novartis; Basel, Switzerland) [1 patient], and most patients were also receiving prednisolone (21 patients). In addition, some patients were also receiving the following concomitant antihypertensive medications: calcium channel blockers (four patients); angiotensin-converting inhibitors (eight patients); angiotensin receptor II antagonists (six patients); or α1 receptor antagonists (three patients). Medications were not withheld at any stage.

Seven women and 6 men participated as healthy subjects (mean age, 48.2 ± 3.7 years; age range, 31 to 72 years).

**Study Design**

All experimental procedures were approved by the Alfred Ethics Committee, Alfred Hospital (project No. 14/00). All patients and healthy subjects gave written informed consent prior to commencing the study.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Healthy Subjects (n = 13)</th>
<th>Transplant Patients (n = 22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male 9</td>
<td>Female 7</td>
</tr>
<tr>
<td>Age, yr</td>
<td>48.2 ± 3.7</td>
<td>50.5 ± 2.4</td>
</tr>
<tr>
<td>Serum Na⁺, mmol/L</td>
<td>140.0 ± 0.47</td>
<td>139.76 ± 0.47</td>
</tr>
<tr>
<td>Serum K⁺, mmol/L</td>
<td>4.17 ± 0.06</td>
<td>4.52 ± 0.09†</td>
</tr>
<tr>
<td>Plasma urea, mmol/L</td>
<td>4.9 ± 0.52</td>
<td>13.4 ± 0.52†</td>
</tr>
<tr>
<td>Plasma glucose, mmol/L</td>
<td>4.47 ± 0.22</td>
<td>5.50 ± 0.35</td>
</tr>
<tr>
<td>Hemoglobin, g/L</td>
<td>143.46 ± 3.49</td>
<td>119.85 ± 3.77†</td>
</tr>
<tr>
<td>Resting HR, beats/min</td>
<td>60.7 ± 2.7</td>
<td>74.2 ± 2.3†</td>
</tr>
<tr>
<td>Resting SBP, mm Hg</td>
<td>113 ± 3.3</td>
<td>143 ± 4.0†</td>
</tr>
<tr>
<td>Resting DBP, mm Hg</td>
<td>70.1 ± 2.3</td>
<td>80.9 ± 2.3†</td>
</tr>
</tbody>
</table>

*pValues given as mean ± SEM unless otherwise indicated. SBP = systolic BP; DBP = diastolic BP.

The initial (screening) visit involved the collection of demographic data, a brief medical history, and a physical examination (including concomitant drug therapies), a blood test for hematologic variables (ie, full blood examination) and biochemical variables (ie, plasma urea, sodium, potassium, creatinine, and glucose levels), as well as an ECG. Lung transplantation patients were not required to undergo these tests if they had been performed <3 weeks prior to this visit.

On the day of the autonomic study, three consecutive baseline BP and HR measurements were made (Dinamap semi-automated BP monitor, model 1846 SX; Critikon; Tampa, FL) with the patient seated in a supine position. An IV cannula was then inserted into the upper part of the forearm for subsequent plasma norepinephrine (NE) blood sampling. After 20 min of supine rest, HRV variables were measured via ECG leads placed on the subject and connected to a data acquisition system (AMLAB; Associative Measurement Pty Ltd; Sydney, NSW, Australia) for continuous recording of the R-R interval over a 20-min period.

Following this, three consecutive readings of HR and BP were made, and a 10-mL sample of blood was taken for measurement of catecholamine levels, which was placed in prechilled lithium heparin tubes in duplicate, and was stored immediately on ice. The sample was centrifuged at 2,500 revolutions per minute for 10 min then was stored at –70°C for subsequent analysis.

The table then was tilted upright 80° for a further 20 min of HRV recording. BP and HR measurements were repeated, and a blood sample was taken for the measurement of catecholamine levels, as before.

Following this, the subject was seated upright in a supine position for the performance of the Valsalva maneuver. To record continuous beat-to-beat BP measurements a noninvasive BP monitoring cuff (Finapres 2300; Ohmeda; Madison, WI) was placed on the index finger. The monitoring cuff was connected to an electronic chart recorder (MacLab; AD Instruments; Sydney, NSW, Australia). Baseline HR and BP were recorded for approximately 30 s. The subject was asked to breathe into the mouthpiece of a mercury sphygmomanometer against a pressure of 40 mm Hg for a period of 15 s. The chart recorder was run continuously throughout this period and for a further 30 s after cessation of the procedure. After 5 min of rest, the procedure was repeated.
The cold pressor test was performed with the subject lying flat on the bed and the BP cuff placed on the left arm. Three consecutive baseline measurements of HR and BP were made. The subject then was asked to place the left arm into a bucket of ice-cold water for a period of 2 min. During this time HR and BP were measured continuously. The subject rested for 10 min, after which time the IV cannula was removed.

**Study Parameters**

**HRV Measures:** HRV has become a well-established method for studying cardiac autonomic modulation in humans.\(^9,10\) Measures were made in the time and frequency domains. The root mean square of successive differences in R-R intervals (rMSSD) was chosen as the measure of PNSA in the time domain as it appears to be a more robust measure of PNSA than either the square of the successive differences of adjacent R-R intervals or the percentage of successive R-R intervals of >50 ms.\(^9\) The high-frequency power (HP) component of the HRV power spectrum (0.15 to 0.40 Hz) is generally accepted as a pure measure of cardiac PNSA, as it evaluates almost exclusively respiratory sinus arrhythmia.\(^11\) The low-frequency power (LP) component of the HRV power spectrum (<0.15 Hz) has been found to reflect both SNSA and PNSA.\(^12\) The ratio of HP to the total power (TP) spectrum also is used as an indicator of PNSA to correct for baseline differences in HR between groups. The LP/HP ratio may be considered to be an index of sympathovagal balance.\(^13\) Frequency domain parameters were non-normally distributed and were therefore natural log (Ln)-transformed.

Respiratory frequency was determined from the peak of the HP spectrum. In addition to measurements made at rest, these parameters also were assessed during an 80° head-up tilt, which resulted in a baroreflex-mediated increase in SNSA and a decrease in PNSA in healthy subjects. Computer software (HRV Track, version 0.1.00; Cardiac Dynamics; Melbourne, VIC, Australia) was used to collect and analyze all HRV data.

**Plasma Catecholamines:** Plasma NE levels were measured in the laboratory of the Department of Clinical Pharmacology, Austin Hospital, Heidelberg, Australia. Plasma was extracted by washing with acid alumina in a chromatography column (μ-Bondapack CN; Waters; Milford, MA). The samples then were collected and processed for electrochemical detection with high-performance liquid chromatography.\(^14\)

**Valsalva Maneuver:** Phase II of the Valsalva maneuver occurs on commencing the maneuver and is characterized by a decrease in BP caused by an increase in intrathoracic pressure and a decrease in venous return and cardiac output. This results in sympathetically mediated reflex tachycardia. Phase IV occurs on the release of the strain and is characterized by a BP overshoot followed by baroreflex-mediated bradycardia (primarily parasympathetic).\(^15\)

We took the maximum increase in HR and maximum decrease in BP during the Valsalva as the phase II measurement, and the maximum decrease in HR and maximum increase in BP as the phase IV measurement. The average of the variables obtained during the two maneuvers was calculated.

**Cold Pressor Test:** Cold water immersion causes a non-baroreflex-mediated increase in SNSA that is caused by the activation of peripheral receptors on the skin. This is a measure of sympathetic efferent reserve.\(^16\)

The maximum BP and HR values obtained during pre-cold pressor testing and during cold pressor testing were recorded. The absolute increase in HR, as a result of cold water immersion, also was determined.

**Statistical Analysis**

All statistical analyses were performed using a statistical software package (SPSS, version 0.1.0.0; SPSS; Chicago, IL). The baseline characteristics were compared using the Student unpaired t test.

Two-way analysis of variance (ANOVA) was used to compare healthy subjects vs lung transplant patients in general, as well as the following variables: recumbency vs head tilt; rest vs phase II vs phase IV; or pre-cold pressor testing vs cold pressor testing. Pairwise comparisons were made of significant values following ANOVA. A two-tailed p value of <0.05 was accepted as being statistically significant. Data are expressed as the mean ± SEM.

**Results**

**Baseline Characteristics**

As determined by protocol, there were no significant differences between healthy subjects and transplantation patients with regards to age or sex (Table 1). However, as expected, the transplant patients had an elevation in resting HR compared to healthy subjects, confirming previous clinical observations. Furthermore, elevated resting BP and plasma urea levels were noted in the transplant patients compared to those in healthy subjects. Hemoglobin levels were significantly reduced in the transplant patients compared to healthy subjects. Respiratory frequency was higher in transplant patients than in healthy subjects, as determined from the peak of the HP (0.257 ± 0.003 vs 0.2375 ± 0.0005 ms, respectively; p < 0.05).

**HRV Analysis**

**Time Domain:** Lung transplant patients had decreased rMSSD values on recumbency (baseline) compared to healthy subjects (11.24 ± 0.17 vs 30.32 ± 14.48 ms, respectively; p < 0.005). Healthy subjects had a decrease in rMSSD after 20 min of head-up tilt (12.58 ± 2.91 ms decrease compared to recumbency; p < 0.001), while a small reduction was observed in the transplant patients (3.74 ± 1.97 ms decrease compared to recumbency; difference was not significant) [Fig 1, top, and Table 2]. This represented a 33% reduction in rMSSD in transplant patients and a 41% reduction in healthy subjects in response to the head-up tilt (difference was not significant).

**Frequency Domain:** HP: LnHP was markedly reduced in lung transplantation patients compared to healthy subjects on recumbency (2.42 ± 0.21 vs 4.82 ± 0.37 ms², respectively; p < 0.001) and following 20 min of head-up tilt (1.50 ± 0.23 vs 3.42 ± 0.33 ms², respectively; p < 0.001; Table 2). This represented a 38% reduction in HP in transplant patients and a 29% reduction in healthy sub-.
LN HP/LnTP Ratio: On recumbency, the LnHP/LnTP ratio values were decreased in lung transplant patients compared to healthy subjects (2.74 ± 0.18% vs 3.39 ± 0.29%, respectively; p < 0.05) [Fig 1, bottom, and Table 2]. In addition, lung transplantation patients had a reduced ability to decrease the LnHP/LnTP ratio after 20 min of head-up tilt (0.2 ± 0.18 reduction compared to recumbency; difference was not significant) compared to healthy subjects (1.37 ± 0.29 reduction compared to recumbency; p < 0.01) [Fig 1, bottom, and Table 2]. This represented a 7% reduction in the LnHP/LnTP ratio in transplant patients and a 40% reduction in healthy subjects in response to head-up tilt (p < 0.01 [two-way ANOVA]).

LN LP/Ln HP Ratio: Transplant patients had an elevated LnLP/LnHP ratio on recumbency compared to healthy subjects (0.77 ± 0.27 vs 1.56 ± 0.25 ms², respectively; p < 0.05). Furthermore, healthy subjects had an increased LnLP/LnHP ratio following head-up tilt (1.52 ± 0.35 ms² increase compared to recumbency; p < 0.001). In contrast, transplant patients had a reduced ability to increase the LnLP/LnHP ratio after head-up tilt (0.30 ± 0.23 ms² increase; difference was not significant) [Fig 2 and Table 2]. The absolute difference in the response to head-up tilt between the two groups was significant (p < 0.005). This represented a 19% increase in the LnLP/LnHP ratio in transplant patients and a 297% increase in healthy subjects in response to head-up tilt (p < 0.005 [two-way ANOVA]).

Plasma Catecholamines

Lung transplantation patients had an elevation in plasma NE levels compared to healthy subjects on recumbency (3.24 ± 0.40 vs 2.00 ± 0.27 nmol/L, respectively; p < 0.05) and after head-up tilt (5.12 ± 0.43 vs 3.59 ± 0.45 nmol/L, respectively; p < 0.05). However, both groups of subjects increased plasma NE levels to a similar extent in response to head-up tilt (increase in transplant patients, 2.03 ± 0.30 nmol/L; increase in healthy subjects, 1.59 ± 0.42 nmol/L; difference was not significant) [Fig 3 and Table 2]. This represented a 58% increase in plasma NE levels in transplant patients and an 80% increase in healthy subjects in response to head-up tilt (difference was not significant).

Table 2—Comparison of Autonomic Parameters Between Lung Transplant Patients and Subjects*

<table>
<thead>
<tr>
<th>Autonomic Parameter</th>
<th>Transplant Patients (n = 21)</th>
<th>Healthy Subjects (n = 13)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RMSSD, ms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recumbency</td>
<td>11.24 ± 1.07</td>
<td>30.32 ± 4.48</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>80° head-up tilt</td>
<td>7.50 ± 3.04</td>
<td>17.74 ± 7.38</td>
<td>&lt; 0.002</td>
</tr>
<tr>
<td>LnHP, ms²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recumbency</td>
<td>2.42 ± 0.21</td>
<td>4.82 ± 3.37</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>80° head-up tilt</td>
<td>1.50 ± 0.23</td>
<td>3.42 ± 0.33</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>LnHP/LnTP ratio</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recumbency</td>
<td>2.74 ± 0.18</td>
<td>3.39 ± 0.2</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>80° head-up tilt</td>
<td>2.54 ± 0.36</td>
<td>2.02 ± 0.31</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma NE, nmol/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recumbency</td>
<td>3.24 ± 0.40</td>
<td>2.00 ± 0.27</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>80° head-up tilt</td>
<td>5.12 ± 0.43</td>
<td>3.59 ± 0.45</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Valsalva maneuver</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in HR, beats/min</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase II</td>
<td>13.49 ± 1.55</td>
<td>18.02 ± 2.52</td>
<td>NS</td>
</tr>
<tr>
<td>Phase IV</td>
<td>4.23 ± 1.13</td>
<td>6.10 ± 1.73</td>
<td>NS</td>
</tr>
<tr>
<td>Cold pressor test</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increase in HR, beats/min</td>
<td>10.9 ± 1.06</td>
<td>9.55 ± 2.97</td>
<td>NS</td>
</tr>
<tr>
<td>Increases in SBP, mm Hg</td>
<td>27.35 ± 3.03</td>
<td>38.42 ± 6.42</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Values given as mean ± SEM, unless otherwise indicated. NS = not significant. See Table 1 for abbreviations not used in the text. 
†p < 0.05 for difference between baseline and head-up tilt.
Valsalva Maneuver

Lung transplantation patients had significantly higher resting HRs compared to healthy subjects (77.25 ± 2.58 vs 66.71 ± 2.36 beats/min, respectively; p < 0.02) immediately prior to this test. However, there were no significant differences found either in the tachycardic responses during phase II (+ 18.02 ± 2.52 vs + 13.49 ± 1.55 beats/min [vs baseline], respectively; difference was not significant) or in the bradycardic responses during phase IV (−6.10 ± 1.73 vs −4.23 ± 1.13 beats/min [vs baseline], respectively; difference was not significant) between healthy subjects and transplant patients (Table 2).

Cold Pressor Test

Lung transplantation patients were found to have significantly elevated resting HRs compared to healthy subjects (75.00 ± 2.21 vs 62.64 ± 3.07 beats/min, respectively; P < 0.002) immediately prior to this test.

However, there were no significant differences found in the absolute maximal increase in HR from baseline between the healthy subjects and transplant patients (9.55 ± 2.97 vs 10.9 ± 1.06 beats/min, respectively; difference was not significant) following 2 min of cold water immersion (Table 2). Similar results were found for mean systolic BP responses to the cold pressor test (Fig 4) with significant differences in resting BP (116.27 ± 2.06 vs 146.00 ± 4.22 mm Hg, respectively; p < 0.001) but no significant difference in the absolute increase in BP from baseline readings between transplant patients and healthy subjects (38.45 ± 6.42 vs 27.35 ± 3.03 mm Hg, respectively; difference was not significant).

There was no relationship observed between the time following lung transplantation and any of these autonomic responses.

Discussion

This study is the first to examine systematically both the parasympathetic and sympathetic parameters of autonomic function following lung transplantation, measured both at rest and following autonomic perturbation.

On recumbency, reduced parasympathetic activity was found in lung transplant patients together with altered sympathovagal balance favoring increased sympathetic predominance. Sympathetic activation was confirmed in these patients by an increase in plasma NE levels.

Following head-up tilt, lung transplantation pa-
patients appeared to have an attenuated withdrawal of parasympathetic activity compared to healthy subjects, chiefly based on the markedly attenuated reduction in LnHP/LnTP ratio compared to that observed in healthy subjects. In contrast, lung transplant patients were able to increase sympathetic activity further in response to head-up tilt, as determined by a significant increase in plasma NE levels.

There were no differences in responses to either the Valsalva maneuver or the cold pressor test between healthy subjects and lung transplant patients.

The present study has confirmed an elevation in resting HR in lung transplantation patients at least 4 months remote from the time of transplantation. This contrasts with the HR responses observed during the immediate postoperative period, which may include periods of bradycardia, contributed to by factors such as hypothermia, edema at the left atrial anastamotic site, and vasovagal instability.

The increase in HR observed among lung transplant patients in the present study is due at least in part to a decrease in PNSA, as determined from decreases in HRV parameters. In addition to the above, we have demonstrated that lung transplant patients may have a reduced ability to withdraw vagal tone in response to autonomic perturbation.

Previous studies of cardiac parasympathetic function in lung transplant patients have produced conflicting results. These studies focused primarily on possible cardiac nerve injury during the surgical procedure in lung transplant patients and involved small sample sizes. During lung transplantation, vagal pulmonary afferent nerves are transected in order to remove the native diseased lungs. Lung transplantation may therefore be a human model of vagal pulmonary afferent denervation. However, cardiac efferent nerves, which pass along the trachea anterior to the main dissection point, also may be inadvertently severed during surgical procedures. Corris et al. found that lung transplant patients had similar HRV responses to both phases of the Valsalva maneuver, which was thought to exclude possible surgical vagal cardiac denervation.

Another contributing factor to the decrease in HRV in lung transplant patients may be differences between the two groups in breathing pattern. HRV appears to be dependent on both respiratory rate and tidal volume. Respiratory rate differed between the two groups in this study, and tidal volume was not measured. Thus, differences in breathing pattern also may be contributing to altered HRV measures in these patients.

Lung transplant patients demonstrated an increase in sympathovagal balance toward increased sympathetic predominance (ie, increased LP/HP ratio) during recumbency compared to healthy subjects. In addition, while healthy subjects showed a significant increase in the LnLP/LnHP ratio with head-up tilt as expected, this was not observed in the transplant patients. It is not clear, however, whether the absence of a significant increase in the LnLP/LnHP ratio in lung transplant patients in response to head-up tilt occurs on the basis of impaired parasympathetic or sympathetic responses (or both). However, the measurement of plasma catecholamine levels in transplant patients following head-up tilt suggests a relative preservation of generalized sympathetic responses to autonomic perturbation. Specifically, despite an elevation in SNSA at baseline, lung transplant patients were able to further increase plasma NE levels in response to head-up tilt in a manner similar to healthy subjects. Thus, the lack of alteration of the LnLP/LnHP ratio in response to head-up tilt in lung transplant patients (in contrast to that seen in healthy subjects) is unlikely due to the inability to further increase sympathetic activity but, rather, is more likely due to an inability to further withdraw parasympathetic activity, as demonstrated by the LnHP/LnTP ratio response to head-up tilt.

Lung transplant patients appeared to exert similar absolute increases in HR from baseline levels in response to 2 min of cold water immersion as did healthy subjects. These findings suggest that although lung transplant patients have elevated levels of resting sympathetic activity, they have a relatively preserved capacity for sympathoexcitation and an intact sympathetic efferent nervous system.

Lung transplant patients and healthy subjects displayed similar HR responses during phase II (primarily a sympathetically mediated tachycardic response) and phase IV (primarily a parasympathetically mediated bradycardic response) of the Valsalva maneuver. These results again support the probable preservation of sympathetic efferent nerves as well as efferent cardiac parasympathetic nervous activity.

Generalized sympathetic activation also is associated with a poor prognosis in many cardiovascular disease states, most notably chronic heart failure. Possible causes for the increase in SNSA seen in lung transplant patients may include the following: loss of vagal pulmonary afferent control of sympathetic nervous activity; concomitant drug therapies; or differences in exercise capacity. These possibilities will be considered in turn.

1. Loss of vagal pulmonary afferent control of SNSA. Normally, cardiopulmonary receptors respond to stretch (ie, increase in intravascular volume or pressure) by relaying afferent neural signals via branches of the vagus and glossopharyngeal nerves to the CNS, inhibiting sympa-
thetic and augmenting parasympathetic activity. Therefore, the loss of vagal pulmonary afferents, as with lung transplantation, may result in reduced activity of vagal afferents projecting to the CNS that would normally tonically inhibit SNSA. Thus, lung transplantation may result in the increased stimulation of sympathetic efferent activity due to the loss of the tonic inhibition of vagal afferents projecting to the CNS.

2. Drug therapies. Increased SNSA in lung transplant patients also may be contributed by concomitant drug therapies. Kaye et al.22 investigated the possibility of sympathoexcitation being the underlying mechanism for cyclosporine-induced hypertension in renal transplantation. Interestingly, it was found that cyclosporine therapy caused renal vasoconstriction via a non-neural mechanism. Cyclosporine also causes increases in plasma renin levels, which may potentially contribute to an elevation in resting HR via activation of SNS. Thus, the net effect of cyclosporine on HR may be a balance between renin-mediated sympathoexcitation and baroreflex-mediated HR reduction in response to BP elevation. Most lung transplant patients also were receiving some form of antihypertensive medication. Some of these medications may contribute to an elevation in resting HR (e.g., dihydropyridine calcium channel blockers and prazosin), while others contribute to a reduction in resting HR (e.g., diltiazem).

3. Differences in exercise capacity. Decreases in fitness also may be a factor contributing to the elevation in sympathetic activity observed in lung transplant patients. Although lung transplantation improves exercise capacity, reduced exercise capacity in lung transplant patients compared to healthy subjects has been well-documented.22,23,24

**Clinical Significance**

The autonomic changes observed in the present study may be of clinical significance. Denervation following lung transplantation, which may contribute to these autonomic changes, has been associated with bronchial hyperresponsiveness to methacholine, although no direct association with this phenomenon and bronchiolitis obliterans has been established. In any event, the autonomic changes observed most likely represent an epiphenomenon in this regard.

While the cardiac effects of lung transplantation have not been highlighted as an important long-term complication following lung transplantation, sudden death and arrhythmia may superimpose on other, commonly cited, complications. Both sympathetic activation and parasympathetic nervous system withdrawal (as described in lung transplant patients in the present study) have been independently associated with poor prognosis.20,25 Mechanistically, these autonomic alterations are associated with a reduction in ventricular fibrillation threshold.26 Therefore, it is of interest to speculate whether the autonomic changes in lung transplant patients, as described, may potentially increase the risk of sudden cardiac death and be a factor contributing to the relatively poor long-term prognosis of these patients.

**Study Limitations**

The interpretation of the results of the current study is limited by the relatively small sample size and the array of medications taken by the lung transplant patients. Specifically, the small sample size precludes a meaningful interpretation of the effects of medication status on autonomic function. With larger sample sizes, the comparison between responses of single-lung transplant patients and double-lung transplant patients may have been possible. Incremental responses in autonomic measures according to the number of lungs removed would have provided additional evidence to support the hypothesis that lung transplant patients have reduced vagal activity due primarily to a loss of vagal pulmonary afferents. HRV, although a well-accepted measure of cardiac parasympathetic activity in healthy subjects and patients in various disease states, may be influenced by nonautonomic factors that may differ between the two study groups. Plasma catecholamines measure generalized sympathetic activity (the aim of the present analysis) rather than cardiac sympathetic activity. Last, the Valsalva maneuver and cold pressor test techniques are relatively crude measures of PNSA and SNSA.

Despite the above limitations, we have found strong evidence that autonomic dysfunction exists in these patients and that a clear distinction exists between parasympathetic and sympathetic responses to autonomic perturbation. However, given the many potential confounders inherent in studying a severely diseased population when compared to healthy subjects, the present study merely describes the nature and extent of the autonomic dysfunction present in lung transplant patients. The design of the study is such that it is unable to provide substantive evidence for mechanisms that may contribute to the autonomic dysfunction described. Further studies may be useful in addressing some of the methodological limitations of the present study and teasing out the impact of various factors that may confound the assessment of autonomic parameters. For exam-
ple, to match for drugs associated with transplantation that may affect autonomic function, these parameters should be compared between lung transplant patients and those patients who have received transplants of solid organs other than the lung, in which the cardiopulmonary autonomic pathways are undisturbed (eg, liver).

CONCLUSION

The present study has demonstrated that there is an increase in resting HR observed clinically in lung transplantation patients. This increase in HR is associated with both reduced PNSA and increased SNSA on recumbency. Transplant patients appear to have preserved the capacity to increase SNSA in the setting of autonomic perturbation, and the ability to further withdraw vagal tone may be impaired. The mechanisms underlying these autonomic disturbances are probably multifactorial in this patient population and cannot be determined from the present study. The clinical and prognostic significance of these observations is also uncertain and remains to be determined by further studies.

REFERENCES

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