Magnitude estimation of inspiratory resistive loads by double-lung transplant recipients

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The purpose of this study was to investigate the role of afferent input from the lung and lower airways in magnitude estimation of inspiratory resistive loads. To assess the role of lung vagal afferents in respiratory sensation, sensations related to inspiratory R, reflected by subjects' percentage of handgrip responses (HG%), were compared between double-lung transplant (DLT) recipients with normal lung function and healthy control (Nor) subjects. Perceptual sensitivity to the external load was measured as the slope of HG% as a function of peak mouth pressure (Pm), and the slope of HG% as a function of R, after a log-log transformation. The results showed that the DLT group had a similar HG% response, as well as the slopes of log HG%-log Pm and log HG%-log R, compared with the Nor group. Furthermore, the ventilatory responses to external loads were also similar between the two groups. These results suggest that lung vagal afferents do not play a significant role in magnitude estimation of inspiratory resistive loads in humans.

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estimation and perceptual sensitivity to the load, compared with matched normal (Nor) subjects.

METHODS

Subjects. Studies were performed with 10 DLT patients and 12 Nor subjects. All subjects were Caucasian. The DLT subjects were recruited from the University of Florida Medical Center. The time since the DLT patients received transplant surgery varied from 1.5 to 5.5 yr. None of the DLT subjects had any evidence of current respiratory or neurological disease, and no evidence of rejection was found in those patients when they participated in the study. All of the DLT subjects were still on immunosuppressive agents (Imuran, Prograf, etc.) and steroid medications (Prednisone, etc.) when they participated in this study. Forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV₁) were tested for each subject. Subjects with a FVC or FEV₁ <70% of predicted values were excluded from this study. Only one DLT subject was excluded from this study because of abnormal lung function (FVC: 60.8% of predicted value; FEV₁: 41.9% of predicted value). The Institutional Review Board of University of Florida reviewed and approved this study. All participants provided informed consent before participating in this study.

Procedures. Subjects were asked to refrain from strenuous physical activity, large meals, and caffeine for at least 4 h before the test. All subjects performed pulmonary function testing in a sitting position. Spirometry testing conformed to American Thoracic Society Standards. Standard instructions were given to each subject. All subjects performed a FVC maneuver. Each test was repeated two to four times with at least a 1-min rest between each repetition. The results were contrasted with age- and sex-predicted reference values and were expressed as a percentage of predictive values.

Background respiratory resistance was measured by using the forced oscillation method. The subject was seated in front of the apparatus and breathed “normally” through the mouthpiece, with his or her cheeks supported by both hands. Approximately 10 tidal breaths were collected continuously to analyze the resistance by computer (Jaeger Toennies, Medizintechnikmit System, version 4.5). The test was repeated at least three times for each subject with a 1-min rest between repetitions. The average of three acceptable measurements was used as the subject’s respiratory system resistance.

Inspiratory muscle strength was measured as the maximal inspiratory pressure (MIP). Subjects were in a standing position when they performed the test. After exhaling to residual volume, subjects were instructed to place their lips around the mouthpiece and inspire as forcefully as possible with their nose clamped. The test was repeated until three measurements within 10% variation were obtained. There was at least a 1-min rest between repetitions. The maximal value obtained was recorded as the subject’s MIP.

During the magnitude estimation experiment, the subject was seated in a lounge chair in a sound-isolated chamber, separated from the experimenter and the experimental apparatus. The subject was instructed to breathe through a mouthpiece connected to a non-rebreathing valve (2600 series, Hans Rudolph) with their nose clamped. The inspiratory port of the valve was connected to the resistive loading manifold. Pressure (Pm) was measured at the center of the non-rebreathing valve and recorded on a polygraph. Inspiratory airflow was measured with a differential pressure transducer (model MP45, Validyne) and a signal conditioner (model CD316, Validyne) connected to a pneumotachograph. Inspired volume was obtained by electrical integration of the airflow signal. Pm, inspiratory airflow, and tidal volume were recorded on a polygraph (Grass Instruments), stored, and analyzed on a computer (model 7, Chart, Powerlab AD Instrument). The R values were sintered bronze disks placed in series in the loading manifold and separated by stopped ports.

Initially, subjects were asked to breathe normally with eyes closed. A line was placed on the oscilloscope screen placed in front of each subject that coincided with the peak inspiratory flow rate with quiet breathing. This was set as the target flow rate. The subjects then opened their eyes and breathed while watching the oscilloscope screen. They were instructed to let their inspiratory airflow signals of each breath “hit” the target line during the entire experiment. Occasionally a light was illuminated on top of the oscilloscope during expiration, cueing subjects that the next inspiration would be loaded. Subjects estimated the test inspiration each time the light above the oscilloscope was illuminated. They squeezed the handgrip by using their dominant hand, according to the degree of difficulty of the perceived inspiratory effort (sense of effort).

Before the resistive loading sessions, each subject squeezed the handgrip as hard as possible three times and his or her handgrip response was recorded on the polygraph. All handgrip magnitude estimations were expressed as a percentage of their maximum handgrip response. A practice session was then presented while informing the subject of the size of the load ("large" or "small"). After a rest period, a series of R values (1.64, 2.48, 3.26, 6.95, 11.46, 20.48, and 42.62 cmH₂O·1·⁻¹·s⁻¹) were presented in a randomized block design during the experimental session. Each loaded breath was separated by two to six unloaded breaths. The load was applied for the entire inspiration. A total of 10 presentations of each load were presented in two trials with a 5-min rest period between trials. Subjects were monitored by video camera throughout the study.

Data analysis. The handgrip response during loaded breathing was divided by the maximal handgrip response for each subject to obtain the percentage of handgrip response (HG%). Only the handgrip responses that corresponded to the load level greater than each subject’s detection threshold, which was predetermined for each subject before the study, were used for analysis. The HG% was plotted against R magnitude and peak Pm by using a log-log transformation. The regression line was obtained by using the method of least squares, and the slopes from each subject were determined (slope of log HG%-log R and slope of log HG%-log Pm).

Pm, peak volume (Vmax), peak inspiratory airflow, inspiratory duration (TI), expiratory duration (Te), time to peak airflow (TP), breathing frequency (f), and minute ventilation (Ve) were recorded for each loaded breath. A one-tailed t-test was used to compare the slope of the DLT group with the slope of the Nor group. A two-way repeated-measures ANOVA was performed to estimate the effects of group and different level of loads on the value of HG%, Pm, peak inspiratory airflow, Vmax, Ti, Te, f, and Ve. Contrast analysis was performed to compare the effects of different loads. The P value for each contrast test was corrected by dividing 0.05 by the total number of contrasts.

The descriptive statistics of all the variables were calculated and expressed as means ± SE. Significance level was set at 0.05, unless multiple contrast analysis was used.

RESULTS

The group mean demographic characteristics and pulmonary functions of all the subjects that participated in this study are shown in Table 1. The DLT and...
the Nor groups were comparable in age, height, and weight. Background respiratory resistance and MIP between the two groups were not significantly different. Both FVC and FEV1 were significantly lower in the DLT group than in the Nor group (97.0 ± 4.9% vs. 119.5 ± 5.0% of predictive value and 83.8 ± 3.7% vs. 108.3 ± 3.7% of predictive value, respectively). However, both FVC and FEV1 were still within normal range in the DLT group. FEV1-to-FVC ratio was not significantly different between the two groups (88.1 ± 6.0% of predicted value for the DLT group vs. 93.9 ± 2.8% of predicted value for the Nor group; P = 0.371).

Two-way repeated-measures ANOVA showed no main effects of group for Pm (Fig. 1), Vmax, peak airflow (Fig. 2), Ti, Te, TP, f, and Ve. This indicated that the loaded breathing pattern during magnitude estimation was not significantly different between the DLT group and the Nor group. All of the above breathing pattern parameters displayed a significant load effect (P < 0.05), except Te (P = 0.068). Specifically, as the magnitude of R increased, Pm, Vmax, Ti, and TP increased significantly, whereas airflow, f, and Ve decreased. Load and group interaction effects were significant for airflow, Ti, and f (P < 0.05). The range of Pm during loaded breathing was not significantly different between the DLT patients and the Nor subjects (12.22 ± 1.2 vs. 15.14 ± 1.5 cmH2O; P = 0.155), as shown in Fig. 3.

The relationships between the magnitude estimate of breathing difficulty (represented by HG%) and stimulus intensity (R and Pm) are displayed in Fig. 4. As the magnitude of R increased, Pm and HG% increased. For both DLT and Nor subjects, the peak handgrip response occurred at approximately midinspiration when mouth pressure and inspiratory airflow reached peak. This suggested that, at higher loads, the subjects generated higher Pm and squeezed the handgrip harder. The main effect of load on HG% is significant (P < 0.001). Two-way repeated-measures ANOVA found no significant difference between the DLT group and the Nor group in their handgrip response (P = 0.93).

Table 1. Demographics and pulmonary functions of subjects

<table>
<thead>
<tr>
<th></th>
<th>DLT</th>
<th>Nor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>5 women, 5 men</td>
<td>7 women, 5 men</td>
</tr>
<tr>
<td>Age, yr</td>
<td>46.5 ± 4.4</td>
<td>46.6 ± 4.4</td>
</tr>
<tr>
<td>Height, cm</td>
<td>167.4 ± 2.9</td>
<td>173.8 ± 2.7</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>71.0 ± 4.4</td>
<td>81.1 ± 6.2</td>
</tr>
<tr>
<td>MIP, cmH2O</td>
<td>77.0 ± 5.1</td>
<td>86.7 ± 7.6</td>
</tr>
<tr>
<td>R, cmH2O/l·s1/4</td>
<td>4.7 ± 0.8</td>
<td>3.7 ± 0.3</td>
</tr>
<tr>
<td>FVC, %predicted</td>
<td>97.0 ± 4.9</td>
<td>119.5 ± 5.0</td>
</tr>
<tr>
<td>FEV1, %predicted</td>
<td>83.8 ± 6.1</td>
<td>108.3 ± 3.7</td>
</tr>
<tr>
<td>FEV1/FVC, %predicted</td>
<td>88.1 ± 6.0</td>
<td>93.9 ± 2.8</td>
</tr>
</tbody>
</table>

Values are means ± SE. DLT, double-lung transplant subjects; Nor, normal subjects; MIP, maximal inspiratory pressure; R, background respiratory resistance; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity. *Significant different between DLT and Nor, P < 0.05.
The exponents of the power function relationships between load and estimated magnitude of load, i.e., the slope of log HG%-log R and the slope of log HG%-log Pm, reflect the sensitivity of the subject to the load (Fig. 5). The mean slope of log HG%-log R for the DLT group and the Nor group was 0.39 ± 0.08 and 0.42 ± 0.06, respectively. The mean slope of log HG%-log Pm for the DLT group and the Nor group was 0.66 ± 0.15 and 0.57 ± 0.07, respectively. There was no significant difference between the two groups for either slope (P = 0.38 for log HG%-log R, and P = 0.29 for log HG%-log Pm).

DISCUSSION

The results of the present study showed that the DLT and the Nor groups were both able to target their breathing with a similar loaded breathing pattern. The handgrip responses were also similar between the DLT and the Nor group. No significant differences were found in the sensitivity to inspiratory R values between the two groups. These results suggest that the ability of the subjects to behaviorally control their inspiration and to estimate inspiratory R magnitude and the sensitivity of the subjects to load magnitude were not changed after lung denervation.

Many studies have examined the relationship between the perceived magnitude of loads and the intensity of the load (3, 9, 12, 23–25). In the present study, the subjects were asked to provide an estimate of the magnitude of R by using their handgrip response (HG%). Similar to previous studies, as the load increased, larger handgrip responses were given by all subjects. The sensitivity of the person to the stimulus, i.e., the mean slope, obtained in Nor subjects in the present study (0.57 ± 0.07 for log Hg%-log Pm, and 0.42 ± 0.06 for log Hg%-log R, respectively) was lower compared with previous reports, in which the exponents varied from 0.57 to 0.96 (3, 9, 12, 14, 21). The difference might be due to the difference in the subjects’ age, the load range, the scale used to estimate magnitude, and airflow targeting. The mean age of Nor subjects in this study was 46.6 ± 4.4 yr, which was older than those reported in previous studies. Tack et al. (23) studied the effect of age on magnitude estimation. They found that the exponent for both inspiratory...

Fig. 5. Group mean slope of the log-log relationship between HG% and resistive loads (A) and between HG% and peak inspiratory Pm (B) in the DLT group and the Nor group. Values are means ± SE.
and expiratory loads was reduced in older subjects, which was probably due to age-related changes in sensory perception. In the present study, the R values ranged from 1.64 to 42.62 cmH2O·1−1·s. A “range effect” is another possible explanation to account for the differences in exponent obtained from other studies. This refers to a general law in psychophysics stating that the higher the range of a given stimulus, the lower the rate of increase in the intensity of the induced sensation (19). Therefore, the lower slope found in this study might be due to a relatively large load range used in the magnitude estimation task. Moreover, some studies used numerical scales (e.g., Borg scale) (9, 12, 14), whereas others (including the present study) used cross-modality matching (e.g., handgrip response) (3, 21) to estimate load magnitude. Unlike the Borg scale, for which subjects only needed to select a number from the Borg scale to match their breathing difficulty, cross-modality matching method involves a more complicated process. First, the subject has to detect and quantify the load. Then, the subject has to translate the respiratory sensation into a handgrip response quantitatively. At the same time, the subject’s sensation arising from their handgrip squeezing has to be transferred back to the higher brain center to match the previous sensations about the external load that the subject breathes against. It is possible that handgrip and Borg scale magnitude estimates result from two different types of neural processing. Muzza and Zechman (16) compared different scales in magnitude estimation. The mean exponent and correlation coefficient obtained from numerical estimates were 1.11 ± 0.16 and 0.94 ± 0.04, respectively, whereas the exponent and correlation coefficient simultaneously obtained from handgrip matching was 0.73 ± 0.10 and 0.91 ± 0.05, respectively. Therefore, the choice of a different scaling method will affect the absolute value of the exponent. However, both scaling methods have been found to be able to reflect the effect of the resistive load level, and both correlated well with load size and Pm in our laboratory (unpublished observations). The use of handgrip scaling method provides more information about the subjects’ perceptual response (e.g., the temporal pattern of response). A final explanation about the difference in exponent among studies might be due to whether or how well airflow was targeted in those studies. In the present study, even though the subjects were instructed to reach the peak airflow target during loaded breathing, airflow still decreased as load magnitude increased (Fig. 2), especially for the three highest loads (11.46, 20.48, and 42.62 cmH2O·1−1·s). Therefore, it was possible that the actual impedance of those high loads was underestimated, which might flatten the regression line when log HG% was plotted against log R.

Few studies have investigated the role of vagal afferent inputs in inspiratory load magnitude estimation tasks. Burki et al. (3) found that anesthesia of the upper and lower airways did not significantly alter the slope between log added resistive load and log handgrip response. However, it is possible that some pulmonary stretch receptors may escape topical anesthetia because the anesthetic could not penetrate to the smooth muscle or because the drug was carried away rapidly by rich blood flow (2). Moreover, because both upper and lower airway receptors were blunted in their methods, it is not possible to make a conclusion about the specific role of lung and lower airway afferents in load magnitude estimation.

Lung transplantation, through a total interruption of afferent nerve fibers from the lung and lower airways, provides an opportunity to study the contribution of neural feedback from lung and lower airways to respiratory sensation. The present study found that the loaded breathing pattern and handgrip response during the magnitude estimation experiment were similar between the DLT group and the Nor group. It has been found in our laboratory that those DLT subjects had a similar resting breathing pattern compared with Nor subjects (26). Therefore, the influence of breathing pattern on the subjects’ respiratory perceptual response should be minimal. Both groups showed a higher handgrip response as load magnitude increased. There were no significant differences in the slope of log HG%-log Pm (0.66 ± 0.15 in DLT vs. 0.57 ± 0.07 in Nor; P = 0.59) and the slope of log HG%-log R (0.39 ± 0.08 in DLT vs. 0.42 ± 0.06 in Nor; P = 0.76). These results suggest that lung vagal afferents are not essential to magnitude estimation of suprathreshold loads. Recently, Peiffer et al. (20) compared sensations related to inspiratory resistive loaded breathing in lung transplant recipients and healthy control subjects. In contrast to our results, they found that the slope of Borg scale as a function of peak Pm was significantly lower in lung transplant recipients than controls (0.63 vs. 1.26; P < 0.01). Although they did not report the analysis in absolute Borg scale scores between the two groups, it appeared that the difference in the slope of Borg scale as a function of Pm was only due to the difference in Pm between the two groups. Indeed, their lung transplant recipients had a significantly higher peak Pm and higher individual range of Pm than normal subjects (10.4 ± 5.6 vs. 4.8 ± 0.96 cmH2O, respectively) during loaded breathing. Therefore, the lowered slope found in lung transplant patients might result from the higher range of stimulus, i.e., a range effect (19), instead of from lung denervation. In the present study, Pm range was not significantly different between the DLT group and the Nor group (12.22 ± 1.2 vs. 15.12 ± 1.5 cmH2O, respectively; P = 0.159), nor was peak Pm (Fig. 1). The difference in lung transplant subjects’ loaded responses between the present study and that of Peiffer et al. (20) might also be a result of the methodology difference. In their protocol, airflow was not targeted. Therefore, it is likely that the subject may underestimate the load magnitude if their inspiratory airflow is reduced during loaded breathing. Moreover, according to their methods, inspiratory resistive loads were presented for the duration of two consecutive inspiratory breaths. It is not known whether their magnitude estimates come from the first or the second loaded breath. Load re-
responses will be different for the first breath compared with the second breath. Furthermore, inspiratory muscle strength was not measured. Lung transplant recipients usually have weakened respiratory muscles because of the use of steroid medications and/or deconditioning after surgery (22). Most studies demonstrated a close relationship between weak muscle strength and increased respiratory drive (1, 8). However, weakened inspiratory muscles and increased drive should increase the intensity of respiratory sensations, which was opposite to their results. The DLT subjects in the present study had similar inspiratory muscle strength compared with the Nor group. Although we did not measure inspiratory drive directly, it would be reasonable to believe the drive would be similar due to similar inspiratory muscle strength in these two groups. Therefore, the impact of inspiratory muscle strength and drive on load magnitude estimation is minimal in this study.

There is a possible contribution of vagal afferents from receptors proximal to the anastomosis to the load magnitude estimation in the DLT subjects. However, the vagal innervation remaining in the transplanted patients is a small portion of the vagal innervation in the lower airway and lung. Therefore, the impact of the remaining vagal input should be minimal. An important assumption of this study is that DLTs are, and remain, entirely denervated after surgery. The results of several investigations performed in animals found reappearance of a weak Hering-Breuer inflation reflex as early as 5 mo after pulmonary autotransplantation (6, 15). However, reinnervation would be less likely in the context of human allotransplantation than with simple reimplantation of an excised lung in the canine model because no attempt is made to approximate nerves in DLT patients (13). In a study investigating the integrity of the cough reflex, which is mediated mostly by pulmonary receptors, after lung transplant, Higenbottam and co-workers (10) observed a significantly diminished cough response to ultrasonically nebulized distilled water for up to 3 yr after lung transplant. More compelling evidence for persistent lung denervation after human lung transplant has been provided by Iber et al. (11). They reported persistently absent expiratory prolongation after passive lung inflation during sleep in bilateral lung transplant recipients for a period of 49 mo after surgery. In contrast to the above findings, Butler et al. (4) reported that respiratory events (cough or apnea) and noxious sensations evoked by injections of lobeline (>30 μg/kg) occurred in a few bilateral lung transplantation subjects who were studied >1 yr after transplantation. Their results suggested that there might be functional reinnervation of the lungs after bilateral lung transplantation. However, changes in nonpulmonary receptors may have occurred over time to recover the sensitivity to lobeline in those patients. In the present study, the time since the patients received DLT surgery varied from 1.5 to 5.5 yr, with an average of 3.45 yr. Although we did not test the reinnervation in our patients, it seems unlikely that reinnervation had occurred on the basis of previous findings (10, 11). Interestingly, a previous study in our laboratory showed that the DLT subjects had a significantly elevated inspiratory R detection threshold as well as Weber fraction (26). In addition, the activation of cortical neurons by breathing against mechanical loads has been studied by using the respiratory-related evoked potential (RREP) method in the DLT subjects (27). Early-latency RREP components were not affected by lung denervation, whereas the late-latency RREP component (P3) was found to be significantly delayed and attenuated in the DLT subjects. This suggests that lung vagal afferents may play a role in respiratory load perception. However, the presence of both early- and late-latency RREP components in DLT patients, as well as the fact that these DLT patients were able to detect inspiratory R and magnitude estimate loads similarly to normal subjects, indicates that lung vagal afferents are not the sole input and they are not essential to perceptual processing of respiratory mechanical loads. Load perception is certainly a multimodal process; however, further studies are needed to investigate the interactions among different afferent mechanisms in respiratory load perception.

Conclusions. In summary, we found that the hand-grip response and loaded breathing pattern were similar in the DLT group and the Nor group. Furthermore, the slopes of log HG%-log Pm and logHG%-log R were also comparable in the two groups. These findings suggest that neural feedback from the lung and lower airways does not play a significant role in inspiratory resistive load magnitude estimation tasks. It is possible that the relative importance of other potential afferent mechanisms (upper airway, respiratory muscle, chest wall, etc.) may be altered as one site is blocked, e.g., lung denervation. Similarly, a nonexclusive role in respiratory sensation has been previously demonstrated for other potential paths, such as chest wall, phrenic nerve, or upper airway, suggesting that respiratory sensation related to loaded breathing may be due to multiple and simultaneous sensory inputs.

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REFERENCES


