Respiratory-related evoked potentials elicited by inspiratory occlusions in double-lung transplant recipients

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Zhao, Weiying, A. Daniel Martin, and Paul W. Davenport. Respiratory-related evoked potentials elicited by inspiratory occlusions in double lung transplant recipients. J Appl Physiol 93: 894–902, 2002. First published May 3, 2002; 10.1152/japplphysiol.01218.2001.—This study investigated the role of lung vagal afferents in the respiratory-related evoked potential (RREP) response to inspiratory occlusions by using double-lung transplant recipients as a lung denervation model. Evoked potential recordings in response to inspiratory occlusions were obtained from 10 double-lung transplant (DLT) recipients with normal lung function and 12 healthy control (Nor) subjects under the attend, ignore, and unoccluded conditions. Results demonstrated that early-latency RREP components (P1, P1a, Nf, and N1) were not significantly different between the DLT and the Nor groups. The late-latency RREP component (P3) was identifiable in all DLT subjects during the attend trial. However, P3 latency was significantly longer in the DLT group compared with the Nor group. The zero-to-peak amplitude of P3 was also significantly smaller in the DLT group than that in the Nor group during the attend trial. These results suggest that lung vagal afferents were not essential to elicit RREP responses, but may contribute to the cognitive processing of respiratory stimuli.

Respiratory-related evoked potentials; respiratory sensation; cognitive process

Respiratory sensations are appreciated at a conscious level during application of external mechanical loads. Therefore, there must be pathways for the afferent information from those respiratory system receptors to the cerebral cortex and central processing. The activation of cortical neurons by breathing against mechanical loads has been studied by using the respiratory-related evoked potential (RREP) method (10, 12, 28, 32). There are two main categories of RREP components: early-latency component (appeared <100 ms after stimulus) and late-latency components (appeared >100 ms after stimulus). The early-latency components (e.g., P1, P1a, and Nf) reflect the arrival of impulses in the primary sensory and prefrontal cortices and are determined mainly by the physical characteristics of the stimuli (21, 33). It has been found that early-latency components were not affected by attention (32, 34). Late-latency components (e.g., P3) are associated with cognitive processing of the sensory information and are largely affected by cognitive factors, such as attention (15, 34), subjective probability (9, 31), etc. There may be some overlap between early-latency and late-latency RREP components that are elicited ~100 ms after the stimuli, such as the N1 peak. The effect of attention on N1 is still controversial (15, 34).

Inspiratory occlusion puts an infinite mechanical load on the respiratory system. As the inspiratory muscles contract against the closed airway, there is a large negative pressure change in mouth, resulting in decompression of the gas within the lung and tracheobronchial tree. It has been found by several studies that vagal afferent played a role in response to inspiratory airway occlusion (6, 19, 35). Afferent projections from the vagus nerve to cerebral cortex have been found in both cats and monkeys (26). It is therefore reasonable to believe that vagal afferents might be responsible for a portion of cortical activation in response to inspiratory occlusions. Double-lung transplant (DLT) recipients provide a good model to investigate the role of the lung vagal afferent system in the RREP response, because all the afferent traffic from lung and lower airways are interrupted. In this study, both early- and late-latency RREP components elicited by inspiratory occlusion were compared in DLT recipients with matched normal (Nor) subjects to investigate the role of lung vagal afferents in the RREP responses. Furthermore, RREP responses were recorded in three separate trials (the attend trial, the ignore trial, and the unoccluded trial) to investigate the effect of attention on RREP responses. We hypothesized that the absence of lung vagal afferent input will attenuate both early- and late-latency RREP components in DLT recipients. We further hypothesized that, similar to Nor subjects, attention will affect the P3 response, but will not affect early-latency RREP components in DLT recipients.

METHODS

Subjects. Studies were performed in 10 DLT patients (mean age 46.5 ± 4.4 yr) and 12 Nor subjects (mean age
RREP in Double-Lung Transplant Recipients

46.6 ± 4.4 yr). 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, with an average of 3.45 yr. None of the DLT subjects had any evidence of current respiratory or neurological disease or any evidence of rejection when they participated in the study. All DLT subjects were still on immunosuppressive (Imuran, Prograf) and steroid medications (prednisone). Forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV₁) were tested for each subject. Subjects with a FVC or FEV₁ of <70% of predicted values were excluded from this study. Only one DLT subject (an 11th subject) was excluded from this study because of abnormal lung function. The Institutional Review Board of the University of Florida reviewed and approved this study. All participants were provided with 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 tests, including forced expiratory volume (FEV₁), forced inspiratory volume (FIV₁), and forced expiratory flow (FEF₁-2) at the height of the inspiration. Spirometry data were collected by a computerized spirometer. All subjects performed a FVC maneuver. The test was repeated two to four times with at least a 1-min rest between each repetition. All values were also contrasted with age- and gender-predicted values by dividing the actual measurements by the corresponding reference value on the basis on age, gender, height, and weight information of the subject.

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 respiratory 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 each repetition. The average of three measures 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 was recorded as the subject’s MIP.

During the RREP experiment, the subjects were seated in a sound insulated room, with the back, neck and head comfortably supported. The experimenter was in the adjacent room and monitored the subject with a video camera. An electrode cap with integral electrodes (Electro-Cap International) was used to record scalp electroencephalogram (EEG) activity. The electrodes were placed at the scalp positions on the basis of International 10-20 System: Cz, C3, C4, Cz, C3’, C4’, Cz’, Fz, F3, F4, C3, Pz, P3, P4. The cap was placed on the subject’s head, positioned and secured with a strap. Scalp and electrode contact was made by the application of electroconducting paste administered through the center opening in the electrode. Two tin electrodes were placed on both earlobes, which were used as the reference. Two electrodes were placed over the lateral edge of the eye for recording vertical electrooculogram. The impedance levels for each electrode was checked and maintained below 5 kΩ. The electrode cap was connected to an EEG system (model 12, Neurodata Acquisition System, Grass Instruments, Quincy, MA). EEG activity was monitored with an oscilloscope monitor. The EEG signals were band-pass filtered (0.3 Hz to 1 kHz), amplified, and led into an on-line signal-averaging computer system (Cambridge Electronic Design).

The subjects were instructed to relax all postural and facial muscles and breathe as normally as possible through a non-rebreathing valve with the inspiratory port connected to a pneumotachograph and an occlusion valve. The inspiratory load was presented by silently inflating the occlusion valve at approximately the midinspiration point of the breath. Each occlusion was separated by two to six unoccluded breaths. A transistor-transistor logic pulse generated by the inspiratory occlusion valve controller triggered the collection of 50 ms of pretrigger and 950 ms of posttrigger EEG and mouth pressure data. The duration of the occlusion was ~350 ms.

There were three RREP experimental trials presented in a random order: the ignore trial, attend trial, and unoccluded trial. All three trials were separated by a 5-min rest period off the breathing apparatus. During the ignore trial, the subject watched a videotape. One hundred occluded breaths were presented. The unoccluded trial was designed to provide the same sounds and vibrations without occlusion. One hundred activations of the occlusion valve were presented similar to the ignore trial with the breathing circuit connected to room air by opening a separate stoppered port, so the airflow was not interrupted. During the attend trial, the subject was asked to attend to their breathing and count the number of occluded breaths. Similar to the other two trials, a total of 100 occluded breaths was presented during the attend trial. The order of the three trials was randomized for each subject.

Data analysis. The EEG activity in each subject was averaged for each RREP trial. An individual EEG sample was selected in the signal average if the onset of the occlusion-related changes in mouth pressure was present and aligned with the majority of the samples. A second criterion for inclusion was the absence of artifact (e.g., movement or electrooculogram). A minimum of 64 occlusion presentations were included in the signal averaging for each trial. The baseline trace of individual presentations was baseline corrected if necessary. The presence, latency and amplitude of RREP components (P₁, P₁a, N₁, N₁, and P₃) were determined for each scalp location from the averaged EEG traces. Peak latencies were measured as the time from the onset of the occlusion valve closure, indicated by the change in mouth pressure, to the EEG peak. The zero-to-peak amplitude was recorded at the peak of each component. The nomenclature for the peaks is based on previous reports (10, 12, 28). The RREP components were identified in the following manner: P₁ and N₁ were defined as positive and negative peaks occurring between 25 and 40 ms and between 40 and 60 ms after the onset of the change in mouth pressure, respectively. The P₁a was defined as a positive peak occurring between 50 and 60 ms after the onset of the change in mouth pressure. N₁ was defined as the negative peak, which occurred between 90 and 130 ms. P₃ was identified as a positive peak in the range of 250–450 ms.

Latencies of the RREP components were compared by using two-way repeated-measures ANOVA to determine the effects of group and trial. Peak amplitudes of the RREP components were compared by using three-way repeated-measures ANOVA to determine the effects of group, trial, and scalp location. Contrast analysis was performed to compare the amplitude of various RREP components among different scalp locations (frontal region: F₃, F₂, F₄; central region: C₃, C₂, C₄; centroparietal region: C₃’, C₂’, C₄’; and parietal region: P₃, P₂, P₄). The P value for the contrast tests

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were 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 \( P < 0.05 \), unless multiple contrast analyses were used.

**RESULTS**

The group mean demographic characteristics and pulmonary functions of all the subjects that participated in this study are shown in Table 1. Two-tailed \( t \)-test showed no significant difference in age, height, and weight between the two groups. MIP and background respiratory resistance between the DLT group and the Nor group were also not significantly different. Both FVC and FEV\(_1\) were significantly lower in the DLT group than the Nor group (97.0 ± 4.9 vs. 119.5 ± 5.0\% of predictive value and 83.8 ± 6.1 vs. 108.3 ± 3.7\% of predictive value, respectively). However, both FVC and FEV\(_1\) were well within the normal range for 3.7\% of predictive value, respectively). However, both groups and trial effects were significant for FEV\(_1\). Specifically, P\(_3\) occurred significantly later in the DLT group than in the Nor group (\( P = 0.012 \)), and significantly earlier during the attend trial than during the ignore trial (\( P = 0.004 \)). Figure 2 shows the P\(_3\) peak recorded during the attend trial in a DLT subject and a Nor subject. Central processing time (CPT) was calculated by subtracting P\(_{1a}\) latency from P\(_3\) latency. For DLT subjects, mean CPT was 282.0 ± 9.8 ms during the attend trial and 323.0 ± 23.4 ms during the ignore trial. For Nor subjects, mean CPT was 226.0 ± 11.9 ms during the attend trial, and 246.0 ± 17.0 ms during the ignore trial. The main effect of group was significant (\( P = 0.007 \)), as was the main effect of trial (\( P = 0.014 \)) (Fig. 3).

The mean zero-to-peak amplitudes of each RREP component (P\(_1\), N\(_5\), P\(_{1a}\), N\(_1\), P\(_3\)) were measured in all 12 scalp positions. When P\(_1\) was absent, amplitudes were treated as missing data in further analysis. When the P\(_3\) was absent, separate analyses were performed with amplitudes treated as missing data in one and zero amplitude in the other. Three-way repeated-measures ANOVA showed a significant main effect of scalp location for all the above RREP components. Further contrast analysis was conducted to compare the amplitude of each RREP component among frontal region, central region, centroparietal region, and parietal region. P\(_1\) was found maximally in central and centroparietal regions. N\(_5\) was found maximally in frontal regions. N\(_1\) was found maximally in central regions. P\(_{1a}\) and P\(_3\) were found maximally in centroparietal and parietal regions. Three-way repeated-measures ANOVA found no significant group main effects on amplitudes for P\(_1\), N\(_5\), P\(_{1a}\), and N\(_1\). When P\(_3\) was unidentifiable and treated as zero amplitude in analysis, there was a significant group effect (\( P = 0.0235 \)). A significant interaction effect between group and scalp location was found for P\(_1\) and N\(_1\). A significant interaction effect between trial and scalp location was found for N\(_5\) and N\(_1\). A significant group, trial, and scalp location interaction effect was found only for N\(_5\). To increase statistical power, an additional two-way repeated-measures ANOVA was conducted only for the attend trial, during which P\(_3\) were identifiable in all subjects. Results showed that the main effects for both group and scalp locations were significant. The DLT group had significantly lower P\(_3\) amplitude than the Nor group.

The grand average signals for mouth occlusion pressure are shown in Fig. 4. At the onset of occlusion, mouth pressure changes were similar in the DLT group and the Nor group during both attend and ignore trials. The mouth pressures corresponding to each

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**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, cmH(_2)O</td>
<td>77.0 ± 5.1</td>
<td>86.7 ± 7.6</td>
</tr>
<tr>
<td>R, cmH(_2)O·l(^{-1})·s</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>FEV(_1), %predicted</td>
<td>83.8 ± 6.1</td>
<td>108.3 ± 3.7*</td>
</tr>
<tr>
<td>FEV(_1)/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; FEV\(_1\), forced expiratory volume in 1 s; FVC, forced vital capacity. *Significant difference between the DLT and the Nor groups, \( P < 0.05 \).
**Table 2. Latencies of RREP components during the attend trial and the ignore trial in both DLT group and Nor group**

<table>
<thead>
<tr>
<th>Latency, ms</th>
<th>DLT</th>
<th>Nor</th>
<th>DLT</th>
<th>Nor</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>25.6 ± 1.9</td>
<td>28.1 ± 2.4</td>
<td>25.3 ± 1.1</td>
<td>26.0 ± 1.9</td>
</tr>
<tr>
<td>P1a</td>
<td>58.0 ± 2.7</td>
<td>58.7 ± 1.7</td>
<td>65.5 ± 3.7</td>
<td>66.0 ± 4.2</td>
</tr>
<tr>
<td>Nf</td>
<td>50.8 ± 3.9</td>
<td>48.2 ± 2.0</td>
<td>46.3 ± 1.4</td>
<td>48.7 ± 3.1</td>
</tr>
<tr>
<td>N1</td>
<td>107.0 ± 3.3</td>
<td>106.0 ± 3.2</td>
<td>99.0 ± 2.4</td>
<td>102.0 ± 6.9</td>
</tr>
<tr>
<td>P3</td>
<td>340.0 ± 9.9*</td>
<td>380.0 ± 2.4</td>
<td>292.0 ± 9.9*</td>
<td>314.0 ± 1.4†</td>
</tr>
</tbody>
</table>

Values are means ± SE. RREP, respiratory-related evoked potential; P1, P1a, Nf, and N1, early-latency RREP components; P3, late-latency RREP component. *Significant trial effect, P < 0.05. †Significant difference between DLT and Nor groups, P < 0.05.

**DISCUSSION**

Respiratory mechanical changes associated with extrinsic loads can be sensed by pulmonary mechanoreceptors, which are innervated by the vagus nerve. Animal studies have demonstrated that vagus nerve stimulation can elicit neural activity in the cortex (1, 2, 22, 26). However, no study has been conducted before to investigate the role of lung vagal afferents in the RREP component were not significantly different between the DLT and Nor groups. The main effect of trial on mouth occlusion pressure is not significant for all the pressure values, except that the mouth pressure corresponding to P3 was significantly lower in the attend trial, compared with the ignore trial (P = 0.003). No interaction effects between group and trial were found for all the pressure points.
RREP response in humans. DLT recipients lose all the afferent traffic from receptors distal to the surgical anastomosis after surgery. Therefore, they provide a human model to study the role of lung and lower airway receptors in perceptual and RREP responses.

The results of the present study show that a consistent pattern of RREP components (P1, Nf, P1a, N1, P3) were identified during the attend and ignore trials in most subjects for both the DLT group and the Nor group. The peak latencies and zero to peak amplitudes of early-latency components (P1, P1a, and Nf) and N1 were similar in the DLT group and the Nor group. However, the peak latency of P3 was significantly longer in the DLT group. The peak amplitude of P3 during the attend trial was also significantly lower in the DLT group. These results suggest that lung denervation did not significantly affect the early-latency RREP components and N1 but attenuated the P3 response.

Early-latency RREP components and N1. Early-latency RREP components (P1, Nf, P1a) and N1 have been identified in response to inspiratory occlusion in previous studies (10–12, 32). In the present study, all these components were still recognized in both DLT and Nor subjects, except P1 in a few subjects. The absence of P1 is probably due to its relatively small signal-to-noise ratio. All these components showed a significant main effect of scalp location. Similar to previous reports (10–12, 32), P1 was found maximally in the sensorimotor central and centroparietal regions. Nf was found maximally in the frontal regions. N1 was found maximally in the midline somatosensory central region. P1a was found maximally in the somatosensory centroparietal and parietal regions. The scalp distribution was similar in DLT patients and Nor subjects. These results demonstrated that occlusion related afferent information activated the frontal and sensorimotor cortical regions in the absence of vagal afferent information.
Early-latency components, also known as exogenous components, are believed to reflect the arrival of impulses in the primary sensory area and are determined mainly by the physical characteristics of the stimuli (21, 33). Studies have shown that the log of P1 amplitude linearly correlated with the log of the magnitude estimation of resistive loads (21, 33), supporting the hypothesis that this early component is sensory in nature. Bloch-Salisbury et al. (5) assessed the effects of stimulus magnitude on RREP components by using resistive loads. Their results showed that N1 amplitude decreased as the load size decreased, similar to the early-latency components. Early-latency RREP components P1, P1a, and Nf have been found to be unaffected by attention (34). However, the effect of attention on N1 is still controversial. Both significant and nonsignificant effects of attention have been reported (15, 34). Therefore, it seems that N1 may have both exogenous and endogenous features. Consistent with previous studies, there were no significant differences in either latency or amplitude of all the four RREP components (P1, Nf, P1a, and N1) between the attend trial and the ignore trial for both groups. It is thus suggested that the early-latency RREP components (P1, Nf, and P1a) and N1 are unaffected by attention. They are probably precognitive indicators of occlusion information processing.

The early-latency RREP components (P1, Nf, P1a) and N2 were consistently identified in DLT recipients in this study. The peak latencies and zero-to-peak amplitudes of these RREP components were similar in the DLT group and the Nor group. The occlusion mouth pressure, which reflected the stimulus intensity, was also found not significantly different between the DLT and the Nor groups. P1a is generally believed to reflect the arrival of impulses in the primary sensory area and to be determined mainly by the physical characteristics of the stimuli. Inspiratory occlusion puts an infinite load on the entire respiratory system. The neural feedback from the remaining afferent systems (e.g., upper airway, respiratory muscles) is intact and able to reach the cortex. Loss of lung vagal input during inspiratory occlusion did not affect these precognitive peaks. The presence of these exogenous RREP components in DLT patients suggests that lung vagal afferents are not essential to these RREP responses. The similarity in latency and amplitudes further suggests that lung vagal afferents may not play a significant role in the early-latency RREP responses.

An important assumption of this study is that DLT 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 (14, 24). In the context of human allotransplantation, reinervation would be less likely to occur because no attempt is made to approximate nerves in DLT patients (20). In a study investigating the integrity of the cough reflex, which is mediated mostly by pulmonary receptors, after lung transplant, Higenbottam and co-workers (16) 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. (18). They recently 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. (7) recently reported early 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 because 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 reinnervation in our patients, it seems unlikely that reinnervation had occurred on the basis of previous findings (16, 18).

Late-latency P₃ component. In the present study, a significant main effect of scalp location was found for P₃ in all subjects. The finding that P₃ was maximal at centroparietal and parietal sites is consistent with previous reports (4, 15, 32, 34). Late-latency RREP components (e.g., P₃), also known as endogenous components, are associated with cognitive processing of the sensory information and are highly sensitive to cognitive factors (9, 15, 31, 34). Increased amplitude and decreased latency of P₃ in the attend compared with the ignore condition has been observed in response to other sensory stimuli (3, 17, 25, 27). Recently, similar effects of attention on the RREP P₃ have been reported (15, 34). Consistent with previous studies, we found that P₃ was identified in all subjects during the attend trial. However, during the ignore trial, three DLT patients and one Nor subject did not have an identifiable P₃. P₃ latency was significantly shorter during the attend trial compared with the ignore trial. The main effect of attention on P₃ amplitude was significant, whether we used missing data or zero amplitude to replace those unidentifiable P₃ during the ignore trial. Specifically, P₃ amplitude was significantly larger during attend condition in all subjects. These results suggested that the P₃ is a cortical potential related to the cognitive processing of inspiratory occlusion information.

In the present study, we found that P₃ was identifiable in all DLT patients during the attend trial and in most DLT patients during the ignore trial. However, the percentage of subjects with the identifiable P₃ during the ignore trial was lower in DLT patients (70%) compared with the Nor group (91%). To increase the statistical power, two-way repeated-measures ANOVA was conducted only for the attend trial, during which P₃ was identifiable in all Nor subjects and DLT subjects. A significant group effect was found, with the DLT group having significantly smaller P₃ amplitudes. Moreover, DLT patients also had significantly delayed P₃ latencies than the Nor group. These results suggest that DLT recipients had impaired cognitive attentional processing of the inspiratory occlusion stimulus, which might be due to the loss of lung vagal afferent inputs.

P₃ is generally believed to be associated with complex cognitive functioning, such as selective attention, memory, and stimulus evaluation, rather than earlier sensory processing of stimuli. Previous studies have demonstrated that stimulus degradation could delay P₃ in response to visual stimuli, which might be due to a prolonged stimulus evaluation process when less information about the stimulus was available (29, 30). The effect of deafferentation on P₃ was studied by Cohen et al. (8). With use of a transcutaneous electrical stimulation oddball task, they compared P₃ in three groups: healthy control, paraplegic, and tetraplegic subjects. Their results indicated P₃ amplitude was significantly reduced in the two spinal cord-injury groups compared with the control group. It has been suggested that there are two cortical systems involved in respiratory central neural processing (13). In the first one, neural information arising from mechanoreceptors in the respiratory muscles enters the spinal cord, ascends in the dorsal column, relays in the brain stem, projects to the thalamus, and is projected through a thalamocortical pathway to the sensorimotor cortex (13). The second pathway involves ascending afferent information from the vagus nerve and its branches and possibly from phrenic afferents. They relay afferent information from the brain stem to the amygdala before projecting to the mesocortex (13). This circuit may deal with some of the affective aspects of respiration. Lung denervation in DLT patients resulted in loss of afferent information from lung mechanoreceptors. Early neural processing of the sensory stimuli (activation of the somatosensory and frontal cortices) may not be affected significantly because of intact function of other afferent systems. However, the less occlusion-related information available, the more uncertainty will arise about the stimulus; therefore, a longer cognitive evaluation process about the stimulus may occur. P₃ is a converged cognitive response, which is sensitive to the duration of the stimulus evaluation process. Loss of vagal afferent input thus might affect P₃, as shown by the decreased amplitude and longer latency in DLT patients. Indeed, CPT, which was obtained by subtracting the latency of early component P₁ₐ from P₃, was also significantly longer in the DLT group than in the Nor group (Fig. 3). This increase in CPT suggests that lung afferent activity related to inspiratory occlusion may contribute to the central neural processing of an inspiratory mechanical load.

On the basis of preliminary findings (23), it seemed unlikely that the DLT patients’ cognitive functions were affected by the experience of lung transplant surgery. However, it should be noted that all the DLT subjects were on immunosuppressive and steroid medications when they participated in this study. The delayed latencies and reduced amplitudes of P₃ in the DLT group may be confounded by their medications. Further studies are necessary to investigate the effect of the drugs on the RREP response. Despite the difference in medications for the DLT and Nor groups, the
exogenous and endogenous peaks of the RREP are not abolished by the pulmonary vagotomy. This means that inspiratory occlusion activates nonpulmonary vagal afferents, which elicit the RREP response.

CONCLUSIONS

In summary, the presence of both early- and late-latency RREP components in DLT patients suggests that lung vagal afferents are not essential to the RREP response to inspiratory occlusions. The similarity in latency and amplitudes suggests that lung vagal afferents may not play a significant role in the early-latency RREP responses. However, DLT recipients had a significantly delayed and attenuated P3 response, as well as increased CPT, suggesting that lung denervation impaired cognitive processing about respiratory stimulus information. These results indicate that the central nervous system uses multiple afferent systems for the cognitive processing of inspiratory occlusion information. The loss of one afferent system requires an increased central processing time and may delay the response in these DLT patients to an inspiratory load.

Furthermore, consistent with previous findings, early-latency RREP components and N1 were not affected by attention, whereas the late-latency component, P3, was observed to have a significantly shorter latency and larger amplitude during the attend trial compared with the ignore trial. These results suggest that there is multistage information processing in the central nervous system of inspiratory load-related mechanical stimuli. The early, short-latency processing is a function of the stimulus intensity. This information may be related to stimulus (load) detection. Subsequent cognitive processing involves attention to the stimulus and evaluation of the stimulus, and it may also involve stimulus discrimination.

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