Respiratory-related evoked potential elicited in tracheostomised lung transplant patients

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ABSTRACT: The present study investigated the role of removal of upper airway and lung vagal afferents in the respiratory-related evoked potential (RREP) response to inspiratory occlusions in two patients with a tracheostomy, who had undergone double lung transplantation (DLT).

The patients were 1.5 and 3 months post-DLT and surgical placement of the tracheostomy. RREP recordings in response to inspiratory occlusions were obtained under four conditions: mouth breathing ignore trial; mouth breathing attend trial; tracheostomy breathing attend trial; and tracheostomy breathing ignore trial.

The RREP peak components, N_r, P₁ and N₁, were present in both mouth and tracheostomy ignore breathing trials. The P₃₀₀ was present in both mouth and tracheostomy attend trials. RREP peak latencies were similar between conditions. The peak amplitudes were greater with mouth breathing due to greater occlusion-related inspiratory pressure.

These results demonstrate that the respiratory-related evoked potential can be elicited with inspiratory occlusion in the absence of mouth, upper airway and lung vagal afferent input. This suggests that inspiratory occlusion can elicit cortical activity with activation of inspiratory pump mechanoreceptors.

KEYWORDS: Cerebral cortex, inspiratory occlusion, respiratory muscles

When ventilation is obstructed, stimulated, challenged or attended to, these changes induce cognitive awareness of breathing. Cognitive awareness of the mechanical status of ventilation is essential for patient respiratory self-management and requires that respiratory-related afferent information be made available to regions of the cerebral cortex that permit conscious awareness of, and attention to, breathing. The respiratory-related evoked potential (RREP) is a unique measure of cerebral cortical activity elicited by breathing against a mechanical load. It provides quantification of both the initial arrival and processing of afferent information at the primary sensory cortex and its subsequent cognitive processing by other associative cortical areas. These neural processes result in patients orienting attention towards ventilation, fear, anxiety, sleep state and behaviour. Induced awareness of ventilation is of profound protective importance, alerting the patient to disrupted ventilation. Failure of cognitive awareness of respiratory mechanical changes is one cause of life-threatening asthmatic attacks [1–3]. It is likely that the RREP is mediated by

multiple respiratory mechanoreceptor populations; however, the afferents mediating the RREP remain unknown.

The RREP has been elicited *via* inspiratory occlusion, inspiratory loads and negative pressures applied during an inspiration [4–8]. The RREP has been recorded from scalp electrodes in humans and subdural electrodes in lambs [4, 9]. The short-latency P₁ peak of the RREP is generated in the somatosensory cortex [9, 10]. The P₁ peak of the RREP can be elicited *via* inspiratory occlusion in humans with lung vagal denervation [8]. However, it is not known whether inspiratory occlusion, in humans who have undergone double lung transplantation (DLT; and lung denervation) and are respiring *via* a tracheostomy (upper airway bypass), elicits the RREP. The long-latency peak of the RREP associated with attention, P₃₀₀, has also been reported in normal subjects and patients who have undergone DLT [11–14]. The respiratory P₃₀₀ amplitude is greatest when the subject attends to the occlusion [15]. However, it is not known whether the P₃₀₀ is present in patients who have had their upper airway bypassed.

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Candidates for DLT occasionally require the placement of a tracheostomy prior to lung transplantation. Following DLT, the tracheostomy is closed and the patient respire normally through their mouth and upper airways. The transplanted lung mechanics are normal and respiratory muscle function is also normal [11, 16]. Two adult DLT patients who were 1.5 and 3 months post-DLT and had a capped tracheostomy in place were studied. The patients normally respired *via* their mouth. When respiring through the cuffed tracheostomy tube, the upper airways were not exposed to respiratory mechanical changes and the lungs were deafferented by the DLT. It was hypothesised that the P1 and P300 peaks of the RREP could be recorded in patients with mouth breathing and upper airways intact (lung deafferented) and also with tracheostomy breathing with upper airways bypassed (lung deafferented).

METHODS

Subjects

The Institutional Review Board of the University of Florida (Gainesville, FL, USA) reviewed and approved the present study. The tracheostomised DLT patients were recruited from the University of Florida Health Science Center. Patient No. 1 was a female aged 31 yrs. The time elapsed since DLT surgery was 3 months. The patient was on a medical regimen of Imuran, prednisone, Torpal, Previset, cyclosporin and Septra. The patient showed no evidence of rejection or neurological disease. Patient No. 2 was a male aged 45 yrs and was 1.5 months post-DLT. This was the patient's second DLT. The patient was on a medical regimen of Imuran, Prograf, prednisone, Septra, Lopressor, insulin and Humalen. The patient showed no evidence of rejection or neurological disease. The patients provided informed consent prior to participating in the present study.

Nine healthy nonsmoking control subjects were tested (three males and six females). The subjects were in good general health based on their self-reported medical history of no chronic or acute neurological or respiratory disease. The subjects refrained from consuming alcohol and caffeinated beverages for ≥ 24 h before the study. Each subject was brought to the laboratory and informed of the nature of the study. The general nature of the experiment was described and their consent obtained.

Procedures

The methods used in the present study have been described previously [8]. The subjects were seated with their back, neck and head supported. Electroencephalographic (EEG) activity was recorded at scalp positions F3, F4, C3', C4' and Pz referenced to the joined ear lobes. Electrodes were placed over the lateral edge of the eye for recording a vertical electro-oculogram. The impedance levels were maintained below 5 k Ω . EEG activity was recorded (Model 12, Neurodata Acquisition System; Grass Instruments, Quincy, MA, USA), band-pass filtered (0.3–1 kHz), amplified and led into a computer system (Model 1401; Cambridge Electronic Design, Cambridge, UK).

The patients respired through a non-rebreathing valve with the inspiratory port connected to an occlusion valve. Each inspiratory interruption occlusion was separated by two to six unoccluded breaths. There were four RREP experimental

conditions: 1) mouth breathing ignore trial; 2) mouth breathing attend trial; 3) tracheostomy breathing attend trial; and 4) tracheostomy breathing ignore trial. The control subjects respired through the same apparatus and were presented with the same protocol except that only the mouth ignore and mouth attend occlusion trials were presented.

Data analysis

The EEG activity was averaged for each RREP trial as described previously [8]. The presence, latency and amplitude of RREP components Nf, P1, N1 and P300 were determined from the averaged EEG traces. The nomenclature for the peaks is based on previous RREP reports [11, 15].

RESULTS

The Nf peak was observed in the frontal region and the P1 and N1 peaks in the somatosensory region in the mouth breathing ignore trial (fig. 1a, 2a) and the tracheostomy breathing ignore trial (fig. 1b, 2b). The RREP for ignore breathing was similar to that of control subjects (fig. 3).

The latencies between mouth and tracheostomy breathing were similar for all three peaks (table 1). The tracheostomy breathing peak amplitudes were smaller than for mouth breathing (table 1). The Nf, P1 and N1 peak amplitudes and latencies of the two patients were similar to those of the control subjects (table 1).

The P300 peak was observed in the Pz electrode recording of the mouth and tracheostomy attend trials (figures 4 and 5). The RREP for attend breathing was similar to that of control subjects (fig. 3).

The attend P300 latencies were similar with mouth and tracheostomy breathing (table 2). The mouth-breathing P300 amplitude was greater than that with tracheostomy breathing (table 2). The P300 peak amplitudes and latencies for the two patients were similar to those of the control subjects (table 2).

Maximum mouth pressure was more negative during mouth breathing than during tracheostomy breathing (figures 4 and 5). The time to maximum mouth pressure change for tracheostomy breathing was approximately half the latency of mouth breathing (table 2). The maximum changes in mouth pressure for the two patients were similar to those of the control subjects (table 2). The time to maximum mouth pressure was longer for the control subjects, with mouth pressure maximum change occurring at the end of the occlusion (table 2).

DISCUSSION

The results from the present study demonstrate that the RREPs elicited by inspiratory occlusion are recorded breathing through either the mouth or the tracheostomy alone. The present patients were unique. Normally, DLT transplant patients have their tracheostomy closed within 2 weeks after surgery. The institutional review board approved protocol required a minimum of 30 days' recovery from DLT surgery before patients were enrolled in the RREP protocol. Thus it was difficult to match both patient and study criteria. At the time of testing, the patients were not hospitalised and were able to breathe normally. Both patients were participating in vigorous endurance and strength training rehabilitation. The study

TABLE 1 Early respiratory-related evoked potential peaks during ignore breathing trials

	Subject No.	Tracheostomy	Mouth
Nf			
Latency ms	1	53.0	49.0
	2	25.7	45.9
	Controls		40.6±1.9
F3 amplitude µV	1	-2.24	-8.82
	2	-2.94	-5.51
	Controls		-3.63±0.66
F4 amplitude µV	1	-1.25	-7.44
	2	-1.76	-6.33
	Controls		-4.00±0.95
P1			
Latency ms	1	65.0	65.0
	2	73.1	65.5
	Controls		51.5±5.2
C3' amplitude µV	1	0.40	2.23
	2	1.41	2.95
	Controls		1.74±0.74
C4' amplitude µV	1	0.56	3.22
	2	1.49	1.96
	Controls		1.91±0.63
N1			
Latency ms	1	117.0	102.0
	2	101.5	90.6
	Controls		98.5±5.7
C3' amplitude µV	1	-6.36	-9.94
	2	-0.80	-3.81
	Controls		-4.90±1.32
C4' amplitude µV	1	-3.46	-8.26
	2	-1.34	-2.31
	Controls		-3.99±0.86

Control data are presented as mean±SEM (n=9). Subjects 1 and 2 had undergone double lung transplantation and tracheostomy.

protocol did not influence the medical decision as to retention or removal of the tracheostomy. The RREP was present under both ventilatory conditions, demonstrating that at least one population of inspiratory-occlusion-activated mechanoreceptors remained intact after DLT surgery and while patients respired through their tracheostomy.

The Nf, P1, N1 and P300 RREP components were identified in the DLT tracheostomy patients in the present study and were similar to those of the control subjects. The P1 RREP component is believed to reflect the arrival of sensory information in the primary sensory area [4, 10]. Therefore, the fact that these peaks are present with subjects respiring through their tracheostomy demonstrates that inspiratory-occlusion-related respiratory mechanoreceptors activate the somatosensory cortex.

The P300 peak was identified in both mouth and tracheostomy trials, with similar patterns to those previously found in DLT patients [11] and control subjects. These results, during both ignored and attended trials, are consistent with previous findings regarding the effect of attention on the P300 peak of

the RREP [15]. The presence of the Nf, P1, N1 and P300 peaks of the RREP during tracheostomy breathing demonstrates that the RREP is present when lung and upper airway afferents are not stimulated by the inspiratory occlusion.

Inspiratory pump mechanoreceptors are the most likely afferents to provide sensory information activated by inspiratory occlusion. Studies in animals have demonstrated somatosensory cortical-evoked potentials elicited by stimulating the phrenic nerve and intercostal muscle afferents [17, 18]. Therefore, the respiratory muscles possess the afferent substrate and central pathways to provide one source of the RREP, and these mechanoreceptors remain intact in the present patients breathing through their tracheostomy. This supports the hypothesis that occlusion-related loading of the inspiratory muscles activates muscle mechanoreceptors that can elicit the RREP.

The conclusion of the present study that the RREP is elicited by multiple respiratory mechanoreceptor modalities is consistent with the study of DONZEL-RAYNAUD *et al.* [19]. DONZEL-RAYNAUD *et al.* [19] recorded the RREP under ignore conditions using a vertex reference (Cz) in eight patients, four with high cervical spinal lesions receiving phrenic nerve pacing and four with chronic respiratory failure requiring tracheostomy. They found that loss of inspiratory muscle function (quadriplegic) or decreased inspiratory muscle function, to the point of requiring a tracheostomy and night-time external ventilatory support, resulted in the absence of the RREP with bypass of the mouth. Inclusion of the mouth resulted in a normal RREP in only two of the eight patients. The patients in the present study were markedly different. The subjects in the present study showed normal pulmonary mechanics, respiratory muscle innervation and inspiratory-force-generating capacity compared with control subjects. They did not require external ventilatory support, could exercise without external ventilatory support and did not normally respire *via* their tracheostomy. Unlike the quadriplegic patients, the only respiratory denervation in the present patients involved lung vagal afferents. In addition, the present study used a noncephalic reference and two attentional states that permitted recording of the P300 peak. The vertex reference does not permit observation of the frontal Nf [20] nor the P300 peaks; thus these peaks, present during tracheostomy breathing in the present study, could not be observed in the study of DONZEL-RAYNAUD *et al.* [19]. The RREP P1 peak during tracheostomy breathing in the present study was recorded under significantly different conditions; the inspiratory muscles were normal and exclusion of mouth mechanoreceptors resulted in a reduced and observable RREP. It has also been reported that increased background inspiratory load reduces the amplitude and even abolishes the resistive-load-elicited RREP in normal subjects [21]. The nonquadriplegic patients have a very high background load, and this may explain why the RREP was not observed in the reduced afferent (tracheostomy) condition. Thus there are major differences in the baseline condition of both groups of patients and RREP recording that may explain the inability of DONZEL-RAYNAUD *et al.* [19] to observe the RREP with tracheostomy breathing. The results of these two studies are consistent with the present study's conclusion that multiple afferent inputs into the cerebral cortex elicit the RREP. The present study demonstrates that the RREP can be elicited by

FIGURE 1. a, b) Respiratory-related evoked potentials and c, d) mouth pressures (P_m) elicited during ignore breathing trials for double lung transplantation subject No. 1. a, c) mouth breathing and b, d) tracheostomy breathing (trace 1: A1A2-F3; trace 2: A1A2-Pz). In the mouth breathing ignore trial, positive voltage is reduced. The Nf peak is indicated. The P1 and N1 peaks were observed in the Pz trace similar to the C3' and C4' recordings. EEG: electroencephalography.

inspiratory-obstruction-mediated activation in inspiratory pump afferents but with reduced amplitude. The results of DONZEL-RAYNAUD *et al.* [19] support this by not observing the RREP during tracheostomy breathing in patients with paralysed inspiratory muscles or background inspiratory loads of sufficient magnitude to require external ventilatory support. Thus these two studies support contributions of the inspiratory muscle and upper airway mechanoreceptors in eliciting the RREP. This is also consistent with the report that airway anaesthesia does not alter the RREP [22]. Hence, multiple sources of afferent activity that can elicit the RREP are broadly

distributed throughout the respiratory system [4, 6, 7, 23, 24]. The present study is consistent with these results and demonstrates that inspiratory occlusion can activate one of those input sources, mechanoreceptors in the respiratory pump, and elicit the RREP.

The results of the present study suggest that both upper airway afferents and respiratory muscle afferents may be involved in cognitive processing of respiratory information related to inspiration against mechanical loads. Thus, the central nervous system has multiple afferent populations that provide

FIGURE 2. a, b) Respiratory-related evoked potentials and c, d) averaged mouth pressures (P_m) elicited during ignore breathing trials in double lung transplantation subject No. 2. a, c) mouth breathing and b, d) tracheostomy breathing (trace 1: A1A2-F3; trace 2: A1A2-Pz). In the mouth breathing ignore trial, positive voltage is reduced. The Nf peak is indicated. The P1 and N1 peaks were observed in the Pz trace similar to the C3' and C4' recordings. EEG: electroencephalography.

FIGURE 3. a) Respiratory-related evoked potentials (trace 1: A1A2-F3 average ignore; trace 2: A1A2-Pz ignore; trace 3: A1A2-Pz attend), and b) averaged mouth pressures (P_m ; ----: attend breathing; —: ignore breathing) elicited during ignore and attend mouth breathing trials in a control subject. Trace 1 demonstrates the N_f peak in the frontal region represented by the F3 recording site and trace 2 the P1 and N1 peaks observed in the Pz trace, which was similar to the C3' and C4' recordings. Trace 3 shows the P300 peak at the Pz recording site. EEG: electroencephalography.

FIGURE 4. a) Respiratory-related evoked potentials (trace 1: mouth breathing; trace 2: tracheostomy breathing (both A1A2-Pz)), and b) averaged mouth pressures (P_m ; ----: mouth breathing; —: tracheostomy breathing) elicited during attend breathing trials for double lung transplantation subject No. 1. The averaged electroencephalographic (EEG) activity is from the same subject as in figure 1. In the mouth breathing attend trial, positive voltage is reduced. The P300 peak is indicated.

mechanical information on respiratory loaded breathing to the cerebral cortex. The input from multiple mechanosensory modalities is essential for patients to self-monitor their ventilatory status, localise the origin of their pulmonary dysfunction and motivate behaviour for treatment.

FIGURE 5. Respiratory-related evoked potentials elicited during attend breathing trials in double lung transplantation subject No. 2 (trace 1: mouth breathing; trace 2: tracheostomy breathing (both A1A2-Pz)). The averaged electroencephalographic (EEG) activity is from the same subject as in figure 2. Positive voltage is reduced. The P300 peak is indicated.

TABLE 2 P300 respiratory-related evoked potential peak					
	Subject No.	Tracheostomy		Month	
		Ignore	Attend	Ignore	Attend
P300 latency ms	1	328	362	319	326
	2	318	337	308	298
	Controls				305±37
P300 Pz amplitude µV	1	1.72	9.06	1.18	10.30
	2	0.88	4.29	2.67	3.52
	Controls				15.57±4.54
Pm,max cmH2O	1	-7.6	-7.3	-13.4	-15.3
	2	-2.8	-4.6	-6.7	-7.4
	Controls			-16.4±1.6	-11.0±1.2
Time to Pm,max ms	1	174	170	377	430
	2	215	1177	124	120
	Controls			620±14	592±19

Control data are presented as mean±SEM (n=9). $P_{m,max}$: maximal mouth pressure. Subjects 1 and 2 had undergone double lung transplantation and tracheostomy. There was no P300 for eight of the nine control subjects in the mouth ignore condition.

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