Upper airway afferents are sufficient to evoke the early components of respiratory-related cortical potentials in humans

Christine DONZEL-RAYNAUD (1,2), MD
Christian STRAUS (2,3), MD, PhD
Michela BEZZI (1, 4), MD
Stefania REDOLFI (1, 4), MD
Mathieu RAUX (1,2), MD
Marc ZELTER (2,3), MD, PhD
Jean-Philippe DERENNE(1,2), MD
Thomas SIMILOWSKI (1,2), MD, PhD

(1) Laboratoire de Physiopathologie Respiratoire, Service de Pneumologie, Groupe Hospitalier Pitié-Salpêtrière, Assistance Publique - Hôpitaux de Paris, Paris, France
(2) UPRES EA 2397, Université Pierre et Marie Curie Paris VI, Paris, France
(3) Service Central d'Explorations Fonctionnelles Respiratoires Groupe Hospitalier Pitié-Salpêtrière, Assistance Publique - Hôpitaux de Paris, Paris, France
(4) Servizio di Medicina Interna 1, Spedali Civili, and Universita di Brescia, Brescia, Italy

Funding:
- Contrat de recherche triennal "Legs Poix" de la Chancellerie de l'Université de Paris
- Association pour le Développement et l'Organisation de la Recherche en Pneumologie (ADOREP), Paris, France.
- Michela Bezzi and Stefania Redolfi are scholars of Universita di Brescia, Brescia, Italy

Running title: upper airway and respiratory-related evoked potentials

Correspondence and reprints:
Pr Thomas SIMILOWSKI
Laboratoire de Physiopathologie Respiratoire Service de Pneumologie et de Réanimation
Groupe Hospitalier Pitié-Salpêtrière
47-83, Bd de l'Hôpital
75651 Paris Cedex 13
France
tel: 33 1 42 17 67 61
fax: 33 1 42 17 67 08 (Pr Similowski)
e-mail: thomas.similowski@psl.ap-hop-paris.fr

Copyright © 2004 by the American Physiological Society.
Abstract
Repeated inspiratory occlusions in humans elicit respiratory-related cortical potentials, the respiratory counterpart of somatosensory-evoked potentials. These potentials comprise early components (stimulus detection) and late components (cognitive processing). They are considered as the summation of several afferent activities from various part of the respiratory system. This study assesses the role of the upper airway as a determinant of the early and late components of the potentials, taking advantage of the presence of a tracheotomy in patients totally or partially deafferented. Eight patients who could breathe either through the mouth or through a tracheotomy orifice (whole upper airway bypassed) were studied (four quadriplegic patients with phrenic pacing, four patients with various sources of inspiratory pump dysfunction). Respiratory-related evoked potentials were recorded in Cz-C3 and Cz-C4. They were consistently present after mouth occlusions, with a first positive P1 and a first negative N1 components of normal latencies (P1: 40.4±6.1ms in Cz-C3; 47.6±7.6ms in Cz-C4; N1: 84.4±27.1ms in Cz-C3 and 90.2±17.4ms in Cz-C4) and amplitudes. Tracheal occlusions did not evoke any cortical activity. Therefore, in patients with inspiratory pump dysfunction, the activation of upper airway afferents is sufficient to produce the early components of the respiratory-related evoked cortical potentials. Per contra, in this setting, pulmonary afferents do not suffice to evoke these components.

Keywords
respiratory-related evoked potentials
somatosensory evoked potentials
visceral afferents
respiratory sensations
dyspnea
upper airway
Introduction

Respiratory-related evoked potentials reflect the activity of cortical neurones in response to occlusions of the airway at the mouth during inspiration (4). They represent the respiratory counterpart of somatosensory evoked potentials. Typically, they begin with a first positive component (P1, 40-60 ms after the beginning of the load-related change in mouth pressure), considered to reflect the cortical arrival of the afferent message (6). It is at times referred to as "exogenous". P1 is followed by a negative component N1, and by later components positive and negative again (P2, and N2). P2 and N2 are considered to reflect the cognitive processing of the sensory information (6), as do further components occurring circa 300 ms after the stimulus (e.g. the P3 component discussed by Zhao et al. (18)). Indeed, the late components (at times referred to as "endogenous") are influenced by attention. N1 may have an intermediate status between exo-and endogenous (precognitive processing). Respiratory-related evoked potentials are considered to be the neurophysiological substrates of certain types of respiratory sensations. In support of this contention, the amplitude of their P1 peak increases with the level of inspiratory pressures developed to overcome a load (12, 13), and this increase parallels the magnitude estimation of the corresponding load (12, 13). In children having suffered near-fatal attacks of asthma (as opposed to other asthmatic children and to controls)(3), the respiratory-related evoked potentials can lack, a feature that is consistent with the blunted perception of loads featured by severe asthmatics (11). Respiratory-related evoked potentials may provide insights into the cortical processes underlying perception of respiratory sensations and thus could lead to better understanding of dyspnea, hence the physiological and clinical relevance of studying their determinants.

The respiratory afferent system is inherently and necessarily redundant, and many structures can contribute to the respiratory-related evoked potentials. These potentials are thus considered to represent the summation of several afferent activities, possibly arising from the upper airway (2) and from downstream sources such as the bronchi, the lungs, the respiratory muscles or the chest wall. In support of this contention, studies of double lung transplantation patients have shown that elimination of pulmonary afferents slows
down the late components of the cortical potentials following an inspiratory occlusion and decreases their amplitude (18). This is interpreted as an impairment of the cognitive processing of the stimulus due to an impoverishment of its sources (18). However, selective deafferentation does not significantly alter the early cortical components following an inspiratory occlusion (18). This could indicate that pulmonary afferent play no role in the origin of these components, or that this role is considerably less important than that of other structures, including the upper airway. This would be in line with the results reported by Daubenspeck et al. (2), who, studying the respiratory related evoked potentials in terms of global field power, described major alterations in both the early and late activity evoked by brief negative pressure pulses applied through a laryngeal mask. With this technique, most of the upper airway is bypassed, but laryngeal afferents, which are very dense (16), are still apt to contribute to the cortical responses to respiratory stimuli. The present study was designed to determine whether or not the upper airway are sufficient for these responses to occur: in patients in whom the upper airway could be completely bypassed owing to the presence of a tracheotomy, the cortical responses to inspiratory occlusions applied at the mouth were compared with the cortical responses to occlusions applied at the tracheotomy orifice.

Methods

After completion of the French legal procedure for human biomedical research, eight tracheotomized patients were enrolled (2 women, 6 men; 48 ± 19 years). They were informed in detail of the purpose of the study and methods used, and gave written consent. The tracheotomy had been performed because of chronic respiratory failure in four cases (chronic obstructive pulmonary disease, n=2; kyphoscoliosis, n=1; diaphragmatic dysfunction, n=1), and because of respiratory paralysis following high cervical spinal lesions in four patients in whom negative pressure breathing was provided by phrenic nerve pacing. The quadriplegic patients suffered from C1 to C3 complete spinal section, documented by magnetic resonance imaging, and leading to complete paralysis and sensory deafferentation below the lesion. The quadriplegic patients breathed permanently
through their tracheotomy. The non-quadriplegic ones also breathed permanently through their tracheotomy, using a positive pressure ventilator during the night and breathing spontaneously during the day.

The patients were studied seated in a reclining lounge chair or semi-reclined in their bed, with the back, neck, and head comfortably supported. They were instructed to relax but to keep their eyes open in order to avoid any risk of falling asleep or producing slow brain waves. They wore earplugs and headphones through which they listened to a quiet musical piece of their choice, in order to mask auditory cues. The breathing circuit was firmly held by a metallic frame at the level of their mouth, in order to minimise artefacts due to the activity of facial muscles. Three of the quadriplegic patients received baclofen orally, against spasticity. One of the non-quadriplegic patients received inhaled bronchodilators. None of the patients were under psychotropic or sedative medication at the time of the study.

The patients breathed alternatively through a mouthpiece (wearing a nose clip) or through their tracheal cannula (tracheal cuff inflated). In both cases, the airway opening was connected to a heated pneumotachometer (Hans-Rudolf 3700, KansasCity, MO, USA) combined with a ±2cmH2O linear differential pressure transducer (Validyne, Northridge, CA, USA) to measure ventilatory flow, and connected to a nonrebreathing valve (Hans-Rudolf 2600) of which the inspiratory port could be occluded by an inflatable balloon (Hans-Rudolf 9340 occlusion valve and 9330 compressor). Airway opening pressure (Pao) was measured from a side port of the valve proximal chamber.

The electroencephalographic activity (EEG) was recorded using standard surface electrodes placed at CZ, C3, C4 on the basis of the international 10-20 System. C3 and C4 were referenced to CZ to record the left and right activity, respectively. Electrode impedances were maintained below 5 k-ohms. Respiratory-related potentials were evoked by 400-500 ms mid-inspiratory occlusions (15), randomly presented every two to four breaths. Two series of 100 occlusions were presented in each of the "mouth" and "trachea" condition (order of conditions randomized among subjects) interspaced by rest periods. The signals were sampled at 1 kHz over a 0.5Hz-500 Hz bandwidth, digitized 100
milliseconds before and 2 seconds after the inspiratory onset determined from the flow trace, and stored on an Apple MacIntosh computer.

Data analysis was performed off-line. The individual presentations for a given trial were recalled from computer memory and displayed on screen. The occluded inspirations were then selected using the Pao signal. A given occluded breath was retained for averaging only in the presence of a stable EEG signal baseline and in the absence of obviously aberrant accidents. In addition, "control" trials were obtained by averaging the same number of unoccluded breaths. Four peaks were defined: P1, first positive deflection, 35-60 milliseconds after the stimulus; N1, next negative deflection; P2 and N2, subsequent positive and negative deflections. For the "mouth" and the "trachea" conditions, the averaged tracings of the two series of occlusions performed were first superimposed to assess reproducibility. Then, all the "mouth" occlusions were pooled together and, on the other hand, all the "trachea" occlusions were pooled separately, to obtain one set of measurements per patient. The latencies of the components were measured according to Davenport et al. (5). Amplitudes were measured from baseline to peak. Latencies and amplitudes were determined separately for each component at each site. Additionally, the occluded breaths retained for analysis in the eight patients were pooled together for each conditions ("mouth" and "trachea"). This grand averaging procedure was also applied separately to the 4 quadriplegic and the 4 non-quadriplegic patients.

The results are expressed as means ± standard deviations. The comparison between the mouth and tracheal pressure drops following the inspiratory occlusions was conducted using a paired t-test. A right-to-left comparison of the latencies and amplitudes of the potentials was conducted using a paired t-test. The comparison between the "mouth" and "trachea" conditions was planned with the Fischer's exact test, but finally not performed in the absence of any potentials in the "trachea" condition (see results).
Results

The number of averaged epochs was similar in both conditions ("mouth": 151 ± 35, "trachea": 166 ± 30),

The inspiratory occlusion related decreases in mouth pressure and in tracheal pressure were similar (7 ± 4 cmH2O vs 9 ± 6 cmH2O, respectively, \(p=0.31\)). This was true both in the quadriplegic patients (9 ± 4 cmH2O vs 11 ± 7 cmH2O) and in the non-quadriplegic ones (5 ± 2 cmH2O vs 6 ± 2 cmH2O).

An evoked activity was present at least in Cz-C3 or in Cz-C4 in all the patients in the "mouth" condition (Table 1, Figures 1, 2 and 3). This activity consisted in a P1 component in all cases (bilateral in 4 patients, unilateral in one of the non-quadriplegic patients and in three of the quadriplegics) with an average latency of 40.4±6.1ms in Cz-C3 and 47.6 ± 7.6 ms in Cz-C4, and with an average amplitude of 2.1±1 µV in Cz-C3 and 2.6±1.6 µV in Cz-C4. A N1 component was visible in 7 cases, with an average latency of 84.4±27.1ms in Cz-C3 and 90.2±17.4 ms in Cz-C4, and with an average amplitude of 3.1±1.4 µV in Cz-C3 and a 3.1±1.4 µV in Cz-C4. There was no significant right-to-left difference. In two quadriplegic patients, the first visible component in C4 was N1 rather than Table 2 shows that the characteristics of P1 and N1, when present, were roughly similar in the quadriplegic and non-quadriplegic patients. Overall, the full P1-N1-P2-N2 sequence was present bilaterally in only two cases, and unilaterally in one case (the patient with chronic obstructive lung disease). The P2 and N2 components lacked bilaterally in all the quadriplegic patients and in one of the non-quadriplegic patients (the one suffering from diaphragmatic dysfunction).

Conversely, in the "trachea" condition, the inspiratory occlusions never evoked any identifiable EEG components, neither early nor late (Figures 1, 2 and 3). This was the case in all the patients, quadriplegic and non-quadriplegic.

Averaging the data from the four quadriplegic patients (Figure 2) showed the presence of the P1 component in response to mouth occlusions (but the averaging procedure suppressed the N1 response), and the absence of any cortical response after tracheal occlusions. Averaging the data from the four non-quadriplegic patients showed
the same pattern with, in addition, the presence of the P2 and N2 components in the "mouth" condition (Figure 3). Again, no cortical response was visible in response to tracheal occlusions.

Discussion

This study demonstrates that in patients with inspiratory pump dysfunction, the activation of upper airway afferents by inspiratory occlusions is sufficient to produce the early components of the respiratory-related evoked potentials.

Methodological considerations

Our study population is peculiar by its nature and its duality (cervical cord lesions in the 4 quadriplegic patients, marked respiratory abnormalities in the 4 non-quadriplegic ones). This implies that the interpretation of our data must be careful. In particular, it is not possible, from this study, to state that the upper airway are the sole source of the respiratory-related evoked potentials as a whole in normal humans. However, in our patients, inspiratory occlusions applied at the mouth consistently evoked cortical potentials resembling the respiratory-related evoked potentials observed in normal subjects or in other types of patients with the same technique. The latencies and amplitudes of the P1 and N1 components of these potentials were similar to values previously reported (P1 latencies of 48±8 ms in Cz-C3 and of 46±12 ms in Cz-C4, and N1 latencies of 86±11 ms in Cz-C3 and of 87±12 ms in Cz-C4 in (15); comparable figures in asthmatic children (3)). We feel that this permits the use of our data to discuss some of the mechanisms underlying the respiratory-related evoked potentials.

The lack of evoked activity in response to tracheal occlusions could be a function of the signal-to-noise ratio, P1 being reduced rather than suppressed in the trachea condition, and particularly so in the phrenic pacing patients in whom electronic noise could not always be suppressed -Fig. 2- (however, we consistently failed to observe responses after tracheal occlusions, even in the best quality tracings). Such an explanation would not, in view of the mouth-trachea differences, drastically change the interpretation of the results.
Information derived from the quadriplegic patients

In these patients, potential sources of respiratory-related evoked potentials only include the upper airway and lung vagal afferents, because the pathways from the rib cage and respiratory muscles are interrupted. The disappearance of the potentials after fully bypassing the airway implies that that vagal afferents do not constitute a sufficient source to the early components of the respiratory-related evoked potentials. This is consistent with the lack of change in these components reported by Zhao et al. (18) in double lung transplant recipients. The persistence of P1 in response to mouth occlusions in quadriplegic patients indicates than such a response can be observed in the absence of any chest wall afferent information. Of note, P1 was present only unilaterally (right side) in 3 of these patients (Table 1). Numbers are far too small to draw conclusions at this stage, but if confirmed this observation could support the lateralization of certain of the mechanisms involved in respiratory sensations (see (14)).

Information derived from the non-quadriplegic patients.

In these patients, the compromise of the respiratory motor pump activity was not severe enough for inspiratory occlusions evoked potentials to be absent in the "mouth" study condition. The pressure drops observed after inspiratory occlusions at the trachea were of similar magnitude as those observed after inspiratory occlusions at the mouth (5 ± 2 cmH2O vs. 6 ± 2 cmH2O, respectively), and were above the threshold value needed to evoke respiratory-related potentials (13). Thus it does not seem possible to attribute the differences between the "mouth" and the "trachea" conditions in this subset of our study population to a decreased output of the respiratory muscles. This confirms that upper airway afferents are sufficient for the early components of the respiratory-related evoked potentials to form.

Nevertheless, the afferent information from the chest wall was probably not normal in these patients. This may account for the fact that the respiratory-related potentials evoked by mouth occlusions were different from what would have been expected in normal subjects. The full P1-N1-P2-N2 sequence indeed lacked in six cases out of 8 (the four quadriplegic patients, plus the the patient with a documented severe diaphragmatic
dysfunction and the patient with chronic obstructive lung disease). This could indicate that respiratory muscle and chest wall afferents are necessary for the late components of the respiratory-related evoked potentials to occur after the early one.

Role of upper airway and non-upper airway afferents

Our study shows that in patients breathing through a tracheotomy, namely with the whole upper airway fully bypassed, there is a complete abolition of the cortical activity in response to inspiratory occlusions as recorded on the scalp with our montage. The major contribution of the upper airway to respiratory-related evoked potentials has been established before by Daubenspeck et al. (2), who showed that bypassing most of the upper airway with a laryngeal mask dramatically modified the cortical potentials evoked by negative pressure pulses (17). In this study, subglottal receptors contributed less than 40% to the global field power of these potentials. However, Daubenspeck et al. (2) did not observe an eradication of the response. This can be interpreted as reflecting a contribution of downstream afferents (namely from the lungs, bronchi, respiratory muscle or chest wall) to the cortical potentials. This can also be due to the fact that a laryngeal mask, by definition, does not bypass the entire upper airway. With such a device in place the vocal cords and the larynx would still be exposed to the stimulus arising from an inspiratory occlusion or a negative pressure pulse. These structures having a very rich somatosensory innervation (the larynx is the most densely innervated region of the upper airway, see16), this could account for the persistence of the cortical activity described by Daubenspeck et al. (2). It should be noted that the pressure drops following inspiratory occlusions tended to be greater in our quadriplegic patients than in the non quadriplegic patients (Figures 2 and 3). The amplitude of the P1 component also tended to be greater in the quadriplegic patients than in the non quadriplegic ones (Figures 2 and 3, Table 2). Although caution is needed because of small numbers and a different experimental paradigm, this is consistent with the data reported by Knafelc et al. (12), suggesting a relationship between the magnitude of the somatosensory dipole (amplitude of P1) and the magnitude of the afferent activation (airway pressure).
Our study also confirm that vagally mediated afferents and chest wall afferent have little role if any in the constitution of the P1 component of the respiratory-related evoked potentials. This does not contradict the current knowledge on the topic. Regarding respiratory muscle afferents, Huang et al. (9) observed some changes in the early components of the respiratory-related evoked potentials after inspiratory muscle training. These changes were not statistically significant, perhaps because of a very conservative statistical treatment. However, Bezzi et al. (1) failed to observe any difference in the amplitudes and latencies of P1 after an experimentally induced acute diaphragm dysfunction. Regarding vagally mediated afferents, Zhao et al. (18), studying double lung transplant recipients, found that these patients did not differ from controls in terms of the P1 and N1 components. In the presence of the P1 component (namely after stimulation of upper airway afferents), the lack of later components in most of our patients suggests that chest wall afferents could contribute to the constitution of the typical P1-N1-P2-N2 sequence that is normally observed in response to an inspiratory occlusions, and perhaps also to the further components of the response (P3, that our experimental montage was not apt at detecting). The same reasoning applies to vagally mediated afferents. Indeed, Zhao et al. (18), if they did not observe modifications of P1 in the lung transplant recipients that they studied (see above), showed that these patients differed from the controls by a prolonged central processing time (defined as the difference in latency between P1 and P3) and by a reduced amplitude of P3 (18).

The differential contributions of the various afferents to the successive components of the respiratory-related evoked potentials could perhaps be explained by difference in the time variance of signals. An occlusion applied at mid-inspiration will cause a sharp change in extrathoracic airway transmural pressure likely to cause a sharp volley in mechanoreceptor action potentials lending itself to generation of evoked potentials. Conversely, the will be no sharp change in transpulmonary pressure, only a leveling off. Lung receptors will thus be weakly stimulated. Chest wall receptors are also likely to be relatively weakly stimulated, and less synchronously with mouth pressure than upper airway afferents.
**Nature of the stimulus**

Somatosensory potentials are elicited by a stimulation that is external to the subject. Conversely, inspiratory-occlusion related potentials arise from a negative pressure stimulus built up by the inspiratory activity of the subject. However, upper airway pressure changes can give rise to cortical potentials independently of any active behaviour (namely, proto-inspiratory negative pressure pulses (17), negative expiratory pressure time-locked to expiration (7), respiratory occlusions performed during tidal (hence passive) expiration (8)). From these results and from our observations, it can be postulated that the upper airway serve as a "transducer" relaying the pressure prevailing within the respiratory system to the brain. This is compatible with the observation by Grippo et al. (7) of a relationship between the amplitude of the cortical response and the level of expiratory transmural pressure applied to the airway. This is also compatible with the observations of Peiffer et al. (14), who found a positive correlation between the amplitude of mouth pressure swings during inspiratory resistive breathing and the regional cerebral blood flow in the right anterior insula, cerebellar vermis and medial pons. The regional cerebral blood flow in these brain regions was also correlated with the perceived intensity of respiratory discomfort. Isaev et al. (10) confirmed the idea of a relationship between airway pressure, cerebral activation, and respiratory sensations. They observed that the sudden application of an inspiratory resistive load to normal subjects induced significant activations in inferior parietal cortex, prefrontal cortex, midbrain, basal ganglia and multiple cerebellar sites (but no activations in the primary sensorimotor cortex). They postulated that there is a pattern of motor behavioural response to the uncomfortable sensation that inspiration is impeded, which results in breathing pattern modifications reducing the degree of discomfort, presumably because of the reduction of mean negative pressure in the airways. This hypothesis (upper airway as a relay between inspiratory pressures and the brain) fits with the link between the amplitude of the P1 peak of the respiratory-related evoked potentials and the magnitude of an inspiratory effort that has been reported by Knafelc et al. (13).

**Conclusions**
Data available from the literature and the present study suggest that 1) removal of the whole airway in patients with inspiratory pump dysfunction makes the cortical response to inspiratory occlusions undetectable, because this prevents the initial component of this response to occur or dramatically reduces it; 2) multiple afferent sources, including the upper airway, vagally mediated afferents and respiratory pump afferents, are necessary for the "normal" cortical response to inspiratory occlusion to fully develop (P1-N1-P2-N2 sequence and later components). Although they should be confirmed in normal subjects, our results should help interpreting of respiratory-related evoked potentials, and possibly contribute to a better understanding of respiratory sensations in patients with known upper airway diseases or abnormalities.
References


Table 1

Localisation and occurrence of the various components of the respiratory-related evoked potentials elicited by inspiratory occlusions at the mouth in the eight patients (inspiratory occlusions at the tracheotomy orifice never elicited respiratory-related evoked potentials).

<table>
<thead>
<tr>
<th></th>
<th>P1</th>
<th>N1</th>
<th>P2</th>
<th>N2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Quadriplegic patients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient 1</td>
<td>C4</td>
<td>C3 and C4</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>Patient 2</td>
<td>C4</td>
<td>no</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>Patient 3</td>
<td>C4</td>
<td>C3 and C4</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>Patient 4</td>
<td>C3 and C4</td>
<td>C3 and C4</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td><strong>Non quadriplegic patients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient 5</td>
<td>C3 and C4</td>
<td>C3 and C4</td>
<td>C3 and C4</td>
<td>C3 and C4</td>
</tr>
<tr>
<td>Patient 6</td>
<td>C3 and C4</td>
<td>C3 and C4</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>Patient 7</td>
<td>C3 and C4</td>
<td>C3 and C4</td>
<td>C3 and C4</td>
<td>C3 and C4</td>
</tr>
<tr>
<td>Patient 8</td>
<td>C3</td>
<td>C3</td>
<td>C3</td>
<td>C3</td>
</tr>
</tbody>
</table>

Table 2
Latencies and amplitudes of the various components of the respiratory-related evoked potentials elicited by inspiratory occlusions at the mouth in the four quadriplegic and the four non-quadriplegic patients

<table>
<thead>
<tr>
<th></th>
<th>quadriplegic patients (n=4)</th>
<th>non-quadriplegic patients (n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P1</td>
<td>N1</td>
</tr>
<tr>
<td>Cz-C3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Latency (ms)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>48</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td></td>
<td>± 30</td>
</tr>
<tr>
<td>Cz-C3</td>
<td>2.2</td>
<td>-3.8</td>
</tr>
<tr>
<td>Amplitude (µV)</td>
<td></td>
<td>± 1.9</td>
</tr>
<tr>
<td>Cz-C4</td>
<td>49</td>
<td>87</td>
</tr>
<tr>
<td>Latency (ms)</td>
<td></td>
<td>± 20</td>
</tr>
<tr>
<td>Cz-C4</td>
<td>3.5</td>
<td>-4.7</td>
</tr>
<tr>
<td>Amplitude (µV)</td>
<td></td>
<td>± 1.7</td>
</tr>
</tbody>
</table>
Legends to figures

**Fig. 1.** Individual examples of the cortical responses following airway occlusions in one non-quadruple patients (left) and one quadruple one (right). In both cases, the top panel corresponds to the application of the occlusions at the mouth and the bottom panel corresponds to the application of the occlusions at the trachea (from top to bottom, averaged Cz-C3 electroencephalogram activity, averaged Cz-C4 electroencephalogram activity, and averaged mouth pressure). The vertical lines denotes the beginning of the respiratory evoked potentials.

**Fig. 2.** Grand-averaging of the cortical responses following airway occlusions in the subset of four quadruple patients with phrenic nerve pacing. The top panel corresponds to the application of the occlusions at the mouth (from top to bottom, averaged Cz-C3 electroencephalogram activity, averaged Cz-C4 electroencephalogram activity, and averaged mouth pressure). The vertical lines denotes the beginning of the respiratory evoked potentials. The bottom panel corresponds to the application of the occlusions at the trachea (upper airway fully bypassed) (from top to bottom, averaged Cz-C3 electroencephalogram activity, averaged Cz-C4 electroencephalogram activity, and averaged tracheal pressure). No potential is discernible.

**Fig. 3.** Grand-averaging of the cortical responses following airway occlusions in the subset of four non-quadruple patients. The top panel corresponds to the application of the occlusions at the mouth (from top to bottom, averaged Cz-C3 electroencephalogram activity, averaged Cz-C4 electroencephalogram activity, and averaged mouth pressure). The vertical lines denotes the beginning of the respiratory evoked potentials. The bottom panel corresponds to the application of the occlusions at the trachea (upper airway fully bypassed) (from top to bottom, averaged Cz-C3 electroencephalogram
activity, averaged Cz-C4 electroencephalogram activity, and averaged tracheal pressure).

No potential is discernible.
Fig. 1R1

![Electroencephalogram (EEG) Tracings](image)

- **Cz-C3**
- **Cz-C4**

**Mouth Pressure**
- 4 cm H2O
- 100 ms

**Tracheal Pressure**
- 4 cm H2O
- 100 ms

**Comparison of Non-Quadriplegic and Quadriplegic Patients**
- **Non-Quadriplegic Patient**
- **Quadriplegic Patient**
Fig. 2R1

Cz-C3

Cz-C4

mouth pressure

Cz-C3

Cz-C4

tracheal pressure