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

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Donzel-Raynaud, Christine, Christian Straus, Michela Bezzi, Stefania Redolfi, Mathieu Raux, Marc Zelter, Jean-Philippe Derenne, and Thomas Similowski. Upper airway afferents are sufficient to evoke the early components of respiratory-related cortical potentials in humans. J Appl Physiol 97: 1874–1879, 2004. First published June 25, 2004; doi:10.1152/japplphysiol.01381.2003.—Repeted 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 (4 quadriplegic patients with phrenic pacing, 4 patients with various sources of inspiratory pump dysfunction). Respiratory-related evoked potentials were recorded in C3-C4 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 ± 6.1 ms in Cz-C4 and 47.6 ± 7.6 ms in Cz-C3; N1: 84.4 ± 27.1 ms in Cz-C3 and 90.2 ± 17.4 ms 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.

somatosensory evoked potentials; visceral afferents; respiratory sensations; dyspnea

Respiratory-related evoked potentials reflect the activity of cortical neurons 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 “exoogenous.” 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 ~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 asthmatic patients (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 after 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 after an inspiratory occlusion (18). This could indicate that pulmonary afferents 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

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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 the upper airways 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 yr). 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 after 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 nonquadriplegic 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 semireclined in bed, with the back, neck, and head comfortably supported. They were instructed to relax but to keep their eyes open 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 to mask auditory cues. The patients were instructed to relax but to keep their eyes open to avoid any risk of falling asleep or producing slow brain waves. They were informed in detail of the purpose of the study and methods used and gave written consent.

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, Kansas City, MO) combined with a ±2-cmH 2 O linear differential pressure transducer (Validyne, Northridge, CA) to measure ventilatory flow and connected to a nonbreathing 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 was measured from a side port of the valve proximal chamber.

The electroencephalographic activity (EEG) was recorded by using standard surface electrodes placed at Cz, C3, and 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 kΩ. Respiratory-related potentials were evoked by 400- to 500-ms midinspiratory occlusions (15), randomly presented every two to four breaths. Two series of 100 occlusions were presented in each of the mouth and trachea conditions (order of conditions randomized among subjects) interspersed by rest periods. The signals were sampled at 1 kHz over a 0.5–to 500-Hz bandwidth, digitized 100 ms before and 2 s after the inspiratory onset determined from the flow trace, and stored on an Apple Macintosh computer.

Data analysis was performed offline. The individual presentations for a given trial were recalled from computer memory and displayed onscreen. The occluded inspirations were then selected by using the airway opening pressure 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 ms 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 condition (mouth and trachea). This grand averaging procedure was also applied separately to the four quadriplegic and the four nonquadriplegic patients.

The results are expressed as means ± SD. The comparison between the mouth and tracheal pressure drops after the inspiratory occlusions was conducted by using a paired t-test. A right-to-left comparison of the latencies and amplitudes of the potentials was conducted by using a paired t-test. The comparison between the mouth and trachea conditions was planned with the Fischer’s exact test but finally was 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 vs. 9 ± 6 cmH 2 O, respectively, P = 0.31). This was true both in the quadriplegic patients (9 ± 4 vs. 11 ± 7 cmH 2 O) and in the nonquadriplegic ones (5 ± 2 vs. 6 ± 2 cmH 2 O).

An evoked activity was present at least in Cz-C3 or in Cz-C4 in all the patients in the mouth condition (Table 1, Figs. 1–3). This activity consisted of a P1 component in all cases (bilateral in 4 patients, unilateral in 1 of the nonquadriplegic patients and in 3 of the quadriplegic patients) with an average latency of 40.4 ± 6.1 ms 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. An N1 component was visible in seven cases, with an average latency of 84.4 ± 27.1 ms 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 P1. Table 2 shows that the characteristics of P1 and N1, when present, were roughly similar in the quadriplegic and nonquadriplegic 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 nonquadriplegic 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 (Figs. 1–3). This was the case in all the patients, quadriplegic and nonquadriplegic.

Averaging the data from the four quadriplegic patients (Fig. 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 nonquadriplegic patients showed the same pattern with, in addition, the presence of the P2 and N2 components in the mouth condition (Fig. 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 nonquadriplegic ones). This implies that the interpretation of our data must be done carefully. In particular, it is not possible, from this study, to state that the upper airways 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 C2-C3 and of 46 ± 12 ms in C2-C4, and N1 latencies of 86 ± 11 ms in C2-C3 and of 87 ± 12 ms in C2-C4 (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.

Fig. 1. Individual examples of the cortical responses after airway occlusions in 1 nonquadriplegic patient (A and C) and 1 quadriplegic one (B and D). A and B: application of the occlusions at the mouth. C and D: application of the occlusions at the trachea. The vertical marks denote the beginning of the respiratory evoked potentials.
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 that 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 three 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 Ref. 14).

Information derived from the nonquadriplegic patients. In these patients, the compromise of the respiratory motor pump activity was not severe enough for inspiratory occlusion 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 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 of eight cases (the four quadriplegic patients, plus 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 nonupper 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 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 <40% to the global field power of these potentials. However, Daubenspeck et al. 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; see Ref. 16) could account for the persistence of the cortical activity described by Daubenspeck et al. It should be noted that the pressure drops after inspiratory occlusions tended to be greater in our quadriplegic patients than in the nonquadriplegic patients (Figs. 2 and 3). The amplitude of the P1 component also tended to be greater in the quadriplegic patients than in the nonquadriplegic ones (Figs. 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 and Davenport (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 confirms 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 occlusion and perhaps also to the further components of the response (P3, which our experimental montage was not apt at detecting). The same reasoning applies to vagally mediated afferents. Indeed, Zhao et al., 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 midinspiration 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, there 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 weakly stimulated, and less synchronously so with mouth pressure than with 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 behavior [namely, postinspiratory negative pressure pulses (17), negative expiratory pressure time locked to expiration (7), or respiratory occlusions performed during tidal (hence passive) expiration (8)]. From these results and from our observations, it can be postulated that the upper airway serves as a “transducer” relaying the pressure prevailing within the respiratory system to the brain. This is compatible with the observation by Grippi 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

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**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 nonquadriplegic patients**

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<th>Nonquadriplegic Patients (n = 4)</th>
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<td>P1</td>
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<td>Cz-C3</td>
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<td>−3.8±1.9</td>
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Values are means ± SD; n, no. of subjects.
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 respiratory sensations. They postulated that there is a pattern of motor behavioral 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 and Davenport (13).

In conclusion, 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; and 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 interpretation of respiratory-related evoked potentials and possibly contribute to a better understanding of respiratory sensations in patients with known upper airway diseases or abnormalities.

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