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Cerebral Cortex Activation during Experimentally Induced Ventilator Fighting in Normal Humans Receiving Noninvasive Mechanical Ventilation

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Background: **Mechanical ventilation is delivered to sedated patients during anesthesia, but also to nonsedated patients (ventilator weaning, noninvasive ventilation). In these circumstances, patient–ventilator asynchrony may occur, provoking discomfort and unduly increasing work of breathing. In certain cases, it is associated with an increased inspiratory load. Inspiratory loading in awake humans activates the premotor cortical regions, as illustrated by the occurrence of electroencephalographic premotor potentials. In normal humans during noninvasive ventilation, the authors used an experimental model of patient–ventilator asynchrony to determine whether premotor cortical activation occurs in this setting.**

Methods: **Noninvasive pressure support ventilation was administered to seven healthy volunteers aged 22–27 yr with continuous electroencephalographic recordings in Cz. The ventilator settings were first adjusted to make the subjects feel comfortable ("comfort"), and then modified to induce respiratory "discomfort" (evaluated on a 10-cm visual analog scale). This was achieved by setting the ventilator to a higher trigger level, reducing the slope of the pressure support rise, and reducing the level of pressure support. The settings were finally brought back to their initial values. To identify a respiratory-related premotor activity, a minimum of 80 preinspiratory electroencephalographic epochs were averaged.**

Results: **Altering ventilator settings induced respiratory discomfort (average visual scale 4 [1.5–6.0] *vs.* 0 [0–1.0] cm during "comfort"; $P < 0.0001$). This was associated with premotor potentials in all cases, which disappeared upon return to "comfort."**

Conclusions: **This study indicates that "ventilator fighting" in healthy humans is associated with an activation of higher cerebral areas. Premotor potentials could thus be markers of patient–ventilator asynchrony at the brain level. Both corroboration in patients and the elucidation of the causative or reactive nature of the association are needed before determining clinical implications.**

MECHANICAL ventilation is among the most common life-sustaining therapy in the intensive care unit, where approximately 50% of the patients receive ventilatory support.[1] A great many of these patients are described as "fighting their ventilator" at some point in their management. This jargonistic expression is used to indicate that a mechanically ventilated patient seems to by trying to get more support from the ventilator that he or she is connected to. This is one form of the situation referred to as "patient–ventilator asynchrony," a term that has been coined to describe the fact that a mechanically ventilated patient keeps a spontaneous respiratory activity, and that this activity is not in phase with that of the machine. This encompasses several types of abnormalities, such as the "insensitive trigger asynchrony" or the "cycling transition asynchrony."[2] Patient–ventilator asynchrony results in an increased work of breathing and is a major source of discomfort for the patient, in whom it generates dyspnea and anxiety sometimes to the point of fear.[3,4] The diagnosis of patient–ventilator asynchrony relies on clinical examination (*e.g.*, tachypnea, activation of inspiratory neck muscles, ineffective triggering efforts) and on the observation of pressure and flow tracings displayed by the ventilator.[2] Patient–ventilator asynchrony is not an issue during anesthesia. However, it is relevant during awakening from sedation, during the postoperative recovery period, during ventilator weaning, and in patients who are mechanically ventilated without sedation. This is typically the case during noninvasive ventilation, an increasingly frequent ventilatory strategy,[5] during which the patients are fully awake.

Whatever its causative mechanisms, patient–ventilator asynchrony increases the mechanical ventilatory load that the patient's respiratory neuromuscular system is faced with. This modifies the pattern of breathing, as a result of compensatory mechanisms that are considered to be in part suprapontine in origin.[6] Inspiratory loading is thus also associated with modified cortical activities.[7–9] These changes include electroencephalographic signs that the premotor cortical areas are activated.[9] Indeed, breathing against a mechanical load (*e.g.*, an inspiratory resistance) gives rise to a premotor potential, defined as an electroencephalographic negativity preceding a motor action (fig. 1). These potentials, best known as Bereitschaft potentials or readiness potentials, are evidenced by averaging a variable

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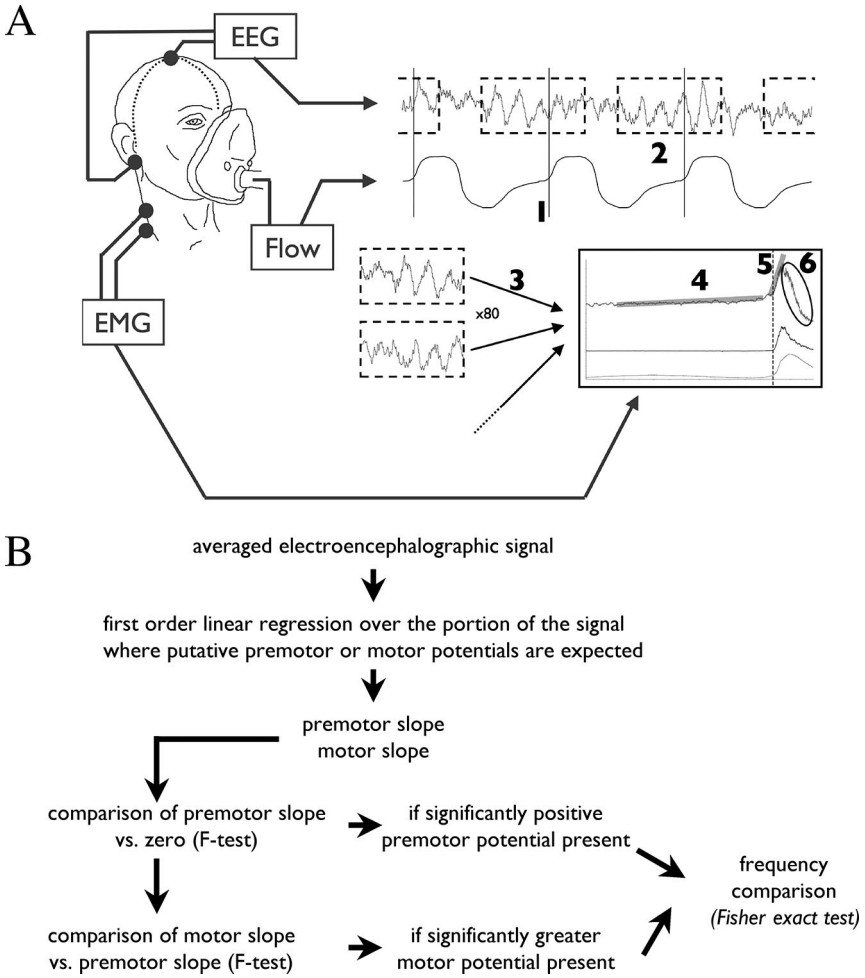

Fig. 1. (*A*) Summary of signal processing. The sequential steps are as follows: (1) identification of the onset of "mechanical" inspiration from the flow signal; (2) definition of electroencephalographic (EEG) epochs starting 2.5 s before inspiration and ending 0.5 s after; (3) averaging of 80 epochs meeting quality criteria (see Materials and Methods); the *solid-line box* at the bottom-right of the panel shows the result of this averaging (Cz electroencephalogram, *top*; scalene muscle electromyogram (EMG), *middle*; flow, *bottom*); (4) application of a first-order least-square regression over the region of the averaged signal where a premotor potential is expected; a premotor potential is considered present if the slope of this regression is positive and significantly differs from 0 according to the F test for equality of variances; the latency of the premotor potentials is measured from the first departure of the electroencephalographic signal from baseline to the onset of inspiration identified on the scalene electromyographic signal ("neural" inspiration); (5) application of a first-order least-square regression over the region of the averaged signal where a motor potential is expected; a motor potential is considered present if the slope of this regression significantly differs from the slope of the "premotor regression"; (6) visual analysis of the return to baseline after the motor potential to identify the presence of an electroencephalographic positivity, or postmotor potential. (*B*) Summary of statistical processing. Steps 1, 2, and 3 described in *A* lead to an averaged electroencephalographic signal. The presence of premotor and motor potentials is then assessed according to the steps 4 and 5 described in *A*. Finally, the occurrences of premotor and motor potentials in the different ventilatory conditions ("comfort" and "discomfort") are compared using the Fisher exact test.

number of electroencephalographic epochs preceding the studied movement. They are typically slow, with latencies of approximately 1.5 s. They take their source in the supplementary motor area.[10] They depict the slowly increasing cortical excitability related to the preparation of self-initiated movements.[11] Occurring before the awareness of the intention to move, they are considered to reflect subconscious readiness for the forthcoming movement.[11] In addition to their presence during inspiratory loading,[9] respiratory-related premotor potentials have been described in relation with self-paced, voluntary sniff maneuvers.[12]

In view of the effects of inspiratory loading on cortical activity, the increased inspiratory load that can be associated with patient–ventilator asynchrony should elicit a premotor cortical response. This could, however, be cancelled out by inhibitory effects of positive-pressure ventilation on the cortical control of breathing.[13] The aim of this study was thus to test the hypothesis of a premotor cortical activation during ventilator asynchrony in normal humans, with inspiratory-related premotor potentials as the primary endpoint. This is intended as a first step toward a putative clinical use of premotor potentials in mechanically ventilated patients.

Materials and Methods

Subjects

Seven healthy subjects (aged 22–27 yr; 1 man; body mass index 20.9 ± 3.1 kg/m^2) participated in the study after

appropriate legal and ethical clearance (Comité Consultatif de Protection des Personnes SE prêtant à des Recherches Biomédicales Pitié-Salpêtrière, Paris, France). They received detailed information about the methods used, but not on the actual purpose of the study. They gave written consent. None of the subjects had a history of respiratory or neurologic disease. They were free of psychotropic treatment. They had been asked to refrain from alcohol consumption during the 24 h preceding the experiment and to avoid sleep deprivation.

Experimental Conditions

The experiments took place in a warm and dark ambience. All the subjects were studied sitting in a comfortable easy chair that provided full support to the back, arms, neck, and head. During the entire experiment, they uninterruptedly watched a movie on a medium-sized computer screen placed at the center of their visual field. This was intended to distract their attention from the experimental setup in general and from their respiration in particular. The subjects were instructed to minimize sudden and large eye movements. They wore headphones to ensure sound insulation from experimental auditory cues. The experimenters and the equipment were hidden from their view.

Respiratory Measurements

The subjects breathed through a facemask (Ultra Mirage®; ResMed Corp., Poway, CA), connected to a Servo I ventilator (Maquet Critical Care, St-Denis, France) and attached in series to a heated pneumotachograph linear from 0 to 160 l/min (3700A series; Hans Rudolf, Kansas City, MO; dead space 14.2 ml, flow resistance 0.02–0.04 cm $H_2O \cdot l \cdot min^{-1}$). The pneumotachograph was connected to a ± 2 cm H_2O linear differential pressure transducer (DP-45-18; Validyne, Northridge, CA) to measure the ventilatory flow. Tidal volume and minute ventilation were calculated from the integrated airflow.

Airway opening pressure was measured from a side port of the facemask, using a ± 140 cm H_2O differential pressure transducer (DP 15–32; Validyne). The end-tidal partial carbon dioxide pressure was measured from another side port of the mask, using an infrared carbon dioxide gas analyzer (IR1505; Servomex, Plaine Saint-Denis, France).

The degree of respiratory discomfort during the experiment was self-evaluated by the subjects on a visual analog scale consisting in a 10-cm line over which they could displace a cursor between the indications "no respiratory discomfort" on the left side and "intolerable respiratory discomfort" on the right side. A French version of the dyspnea descriptors described by Simon *et al.*[14] was proposed to the subjects *post hoc*, for them to choose the item or items best describing their respiratory sensations.

Electrophysiologic Measurements

Electroencephalographic Activity. Electroencephalographic activities were recorded with a subcutaneous needle electrode inserted into the scalp at Cz (international electroencephalographic 10–20 system). Linked earlobe surface electrodes served as reference. The signals were fed to a Neuropack electroencephalograph (Nihon Kohden, Tokyo, Japan), amplified and filtered (0.1–500 Hz). They were digitized at 2 kHz (Chart version 5.2; AD Instruments, Castle Hill, Australia) and stored on an Apple Macintosh G4 computer (Apple, Cupertino, CA) for off-line analysis.

Electromyograms. Surface recordings of the activity of one scalene muscle were obtained with a pair of silver cup electrodes placed over the anatomical landmark of the middle body of this muscle, 2 cm above the clavicle.[15,16] The electromyographic signals were fed to a Neuropack electromyograph, amplified and filtered (20–1,000 Hz). They were digitized at 2 kHz (Chart version 5.2) and stored on an Apple Macintosh G4 computer for off-line analysis. The root mean square of the scalene muscle electromyogram, a reflection of the electrical energy spent by the contraction of the muscle, was numerically calculated using fixed windows (duration = 1 ms). For each subject, an ensemble averaging of successive breaths was performed after splitting the continuous root mean square of the scalene electromyogram and the flow signal in as many epochs starting 1 s before the onset of the mechanical inspiration determined from the flow signal and ceasing 1 s after its end (Chart version 5.2). The mean myoelectrical inspiratory activity (*i.e.*, mean root mean square value during inspiration) was calculated.[16] The time-to-trigger delay was measured from root mean square of scalene muscle electromyogram averaged traces.[16] It was defined as the period separating the onset of electromyographic activity from the onset of airway pressurization.

Electrooculogram. Electrooculograms were recorded using two silver cup electrodes taped to the skin at the external canthus of each eye.

Protocol

The subjects were first connected to the ventilator set in inspiratory pressure-support mode with the lowest available flow trigger and the highest available inspiratory slope. An initial level of 4 cm H_2O was administered, and adjusted until the subjects considered that they were completely comfortable. Ten minutes was allowed to achieve steady state, at the end of which the subjects marked their respiratory sensation on the visual analog scale. Based on previous experiments, we have determined that averaging approximately 80 epochs is necessary to see a clear signal, and that this requires the recording of approximately 120 epochs to account for rejection criteria (see Electroencephalographic Data Processing). Therefore, we calculated the minimal time necessary to

gather 120 breaths from the respiratory frequency at the end of the steady state period, and the first recording ("comfort 1" condition) was started. Respiratory discomfort was then induced by altering the ventilator settings. Pilot experiments had shown that changing a single parameter was not sufficient to unambiguously modify respiratory sensations in this model of healthy subjects. We therefore used a combination of changes, as follows. The trigger was switched from the flow mode to the pressure mode and randomly set between -4 and -20 cm H_2O. The inspiratory slope was lowered to the minimal possible value (0.25 s). The level of pressure support was decreased. After 10 min with these settings, the subjects repeated the visual analog scale evaluation of their respiratory sensation. A new recording then started ("discomfort" condition). The subjects were disconnected from the ventilator and allowed to rest for 15 min, after which they were reconnected to the ventilator with the same settings as during "comfort 1" ("comfort 2" condition). The inspiratory oxygen fraction (0.21) and positive end-expiratory pressure (0 cm H_2O) were kept constant throughout the experiment. In four subjects, the electroencephalogram was also recorded during spontaneous room air breathing off the ventilator ("unsupported breathing" condition).

Electroencephalographic Data Processing

The electroencephalographic data processing is summarized by figure 1. It included three main steps, as follows. First, an ensemble averaging was performed to improve the signal-to-noise ratio and reveal the potentials, in a manner that is classic in the field of evoked-potentials. For this purpose, the continuously recorded electroencephalographic signal was split into 3-s epochs extending from 2.5 s before to 0.5 s after the onset of mechanical inspiration defined as the zero crossing by the rising flow signal. Any epoch exhibiting obvious artifacts, electroencephalographic spurious activity exceeding 20% of the baseline signal, or intense electrooculographic activity was discarded. At the end of this selection, a minimum of 80 epochs was averaged point by point. Second, premotor potentials were looked for, their presence or absence being the primary endpoint of the analysis. On the averaged tracings, premotor potentials were identified as slow negative baseline shifts starting between 2 and 0.5 s before inspiration.[11]

To ascertain the presence or absence of such events, first-order least-square regression equations were fitted to the preinspiratory data range.[9] A premotor potential was considered to be present if, and only if, the slope of the corresponding equation was positive and significantly different from zero (F test for equality of variances). The latency of the premotor potentials was measured from the onset of neural inspiration, defined as the beginning of electromyographic scalene muscle activity. The amplitude of the premotor potentials was measured from baseline, at the start of neural inspiration. Third, motor potentials were looked for. They correspond to a negativity increase synchronous with the onset of inspiration.[9,11] To identify them, first-order least-square regression equations were fitted to the corresponding data ranges. A motor potential was considered present if, and only if, the slope of the corresponding equation was significantly steeper than the slope of the premotor potential (F test for equality of variances). In usual premotor potentials paradigms, the electroencephalographic signal returns to baseline after the motor potential is over.[11] Of note, at times we observed large postmotor positivities after the onset of inspiration (fig. 1). We term them "postmotor potentials" and interpret them as corresponding to the brain processing of the change in intrathoracic pressure induced by positive-pressure ventilation (see Discussion). Postmotor potentials were identified visually only, without resorting to mathematical modeling.

Statistical Analysis

All of the statistical analyses were performed using Prism 4c® software (GraphPad Software Inc., San Diego, CA). Regarding electroencephalographic data, the statistical process consisted of two steps (fig. 1). First, first-order linear regressions were fitted to the premotor and motor data range. The F test for equality of variances was used to test whether the premotor slope differed from zero and whether the motor slope differed from the motor one (see Electroencephalographic Data Processing, second paragraph). According to the corresponding results, premotor and motor potentials were dichotomously classified as present or absent. Second, the Fisher exact test was applied to two 3×2 contingency tables to determine whether the premotor and motor potentials were significantly more frequent in the discomfort condition than in the comfort ones. Regarding the other data, the statistical process was as follows. Continuous variables were tested for normality using the Kolmogorov-Smirnov test. The results are expressed as mean $\pm$ SD for gaussian variables that were compared using an analysis of variance for repeated measures, followed by a Tukey *post hoc* test. Nonnormally distributed variables are expressed as median and range and were compared using the Friedman analysis of variance, followed by a *post hoc* Dunn multiple comparison test.

A P value below 0.05 was considered indicative of statistical significance, namely of a less than 5% probability of erroneously rejecting the null hypothesis (type I error). This threshold was brought down to 0.025 for the identification of premotor and motor potentials using linear regressions, to account for the repeated comparison (Bonferroni correction). In the Results section, the P values are provided with indication of the degrees of freedom (under the form $F_{df\ \text{between},\ df\ \text{within}}$ for the parametric analysis of variance, and Q_{df} for Friedman test).

Table 1. Linear Regression Analysis Applied over the Premotor Region of Interest of the Averaged Electroencephalographic Signal

	Comfort 1	Discomfort	Comfort 2
1	No significantly positive slope detected	0.6605 $F_{1, 4,268} = 990.2$ $P < 0.0001$	No significantly positive slope detected
2	No significantly positive slope detected	0.1171 $F_{1, 4,108} = 12.38$ $P = 0.0004$	No significantly positive slope detected
3	No significantly positive slope detected	2.364 $F_{1, 4,668} = 4,433$ $P < 0.0001$	No significantly positive slope detected
4	No significantly positive slope detected	2.149 $F_{1, 4,438} = 2,779$ $P < 0.0001$	No significantly positive slope detected
5	No significantly positive slope detected	4.734 $F_{1, 2,198} = 1,718$ $P < 0.0001$	No significantly positive slope detected
6	1.377 $F_{1, 3,148} = 1,960$ $P < 0.0001$	2.738 $F_{1, 4,408} = 12,700$ $P < 0.0001$	4.522 $F_{1, 2,488} = 8,210$ $P < 0.0001$
7	0.1795 $F_{1, 3,248} = 12$ $P < 0.0001$	3.03 $F_{1, 3,538} = 4,542$ $P < 0.0001$	No significantly positive slope detected

F test for equality of variances comparing the premotor slope to zero (fig. 1A, step 4).

Results

Electroencephalographic Activity

Depending on the subjects, 94–368 epochs were recorded (201 ± 66). The rejection rate was 43 ± 19%; hence 108 ± 40 epochs retained for analysis on average (from 80 to 237).

In the "discomfort" condition, inspiration was always preceded by typical premotor potentials (table 1 and figs. 2 and 3). Their average latency was 1,977 ± 423 ms, and their average amplitude was 5.5 ± 2.5 μV. This was in contrast with the "comfort 1" condition, where no premotor potentials could be recorded in five subjects (table 1). The premotor potentials seen in the two remaining subjects (Nos. 6 and 7) disappeared in one case (No. 7) during the "comfort 2" condition. One of the subjects who did not exhibit premotor potentials in "comfort 1" exhibited one in "comfort 2" (No. 4). Premotor potentials were consistently lacking in the "unsupported breathing" condition, subjects 6 and 7 included. As a result, premotor potentials were significantly more frequent during "discomfort" than during any of the "comfort" conditions ($P = 0.011$, Fisher exact test).

The premotor potentials observed in the "discomfort" condition were always followed by motor potentials. This was not the case after premotor potentials during "comfort 1" or "comfort 2" (subjects 4, 6, and 7). As a result, motor potentials were significantly more frequent during "discomfort" than during any of the "comfort" conditions ($P < 0.001$, Fisher exact test). Motors potentials consistently lacked in the "unsupported breathing" condition, subjects 6 and 7 included.

Postmotor potentials were present in all the subjects but one (No. 5) during "comfort 1" and "comfort 2," whereas they consistently lacked in the "unsupported breathing condition" ($P = 0.015$, Fisher exact test). Postmotor potentials were difficult to identify during "discomfort" probably because they were partially obscured by the very presence of the motor potentials.

Respiratory Discomfort

The visual analog scale evaluation of the intensity of respiratory discomfort was significantly increased during "discomfort" as compared with both of the "comfort" conditions (4.0 [range, 1.5–6.0] cm *vs.* 0 [0–1.0] cm during "comfort 1" and 0 [0–1.0] cm during "comfort 2"; $Q_2 = 12.33$, $P < 0.0001$). There was no difference between "comfort 1" and "comfort 2." All of the subjects described their respiratory discomfort with items belonging to the "work" cluster defined by Simon *et al.*[14] ("my breathing requires effort" or "my breathing requires more work"), with occasional descriptors belonging to the "suffocating" cluster.

Respiratory Pattern

Mean inspiratory flow increased during "discomfort" compared with the two "comfort" periods (54.8 [range, 32.6–91.4] *vs.* 26.9 [18.6–30.4] and 29.6 [18.7–32.9] l/min, respectively; $Q_2 = 12.29$, $P = 0.0003$). End-tidal carbon dioxide was stable across the different conditions ($Q_2 = 2.33$, $P = 0.3046$; fig. 4).

The root mean square of the scalene muscle electromyogram was significantly higher during "discomfort" than during both "comfort" conditions (50.4 [range,

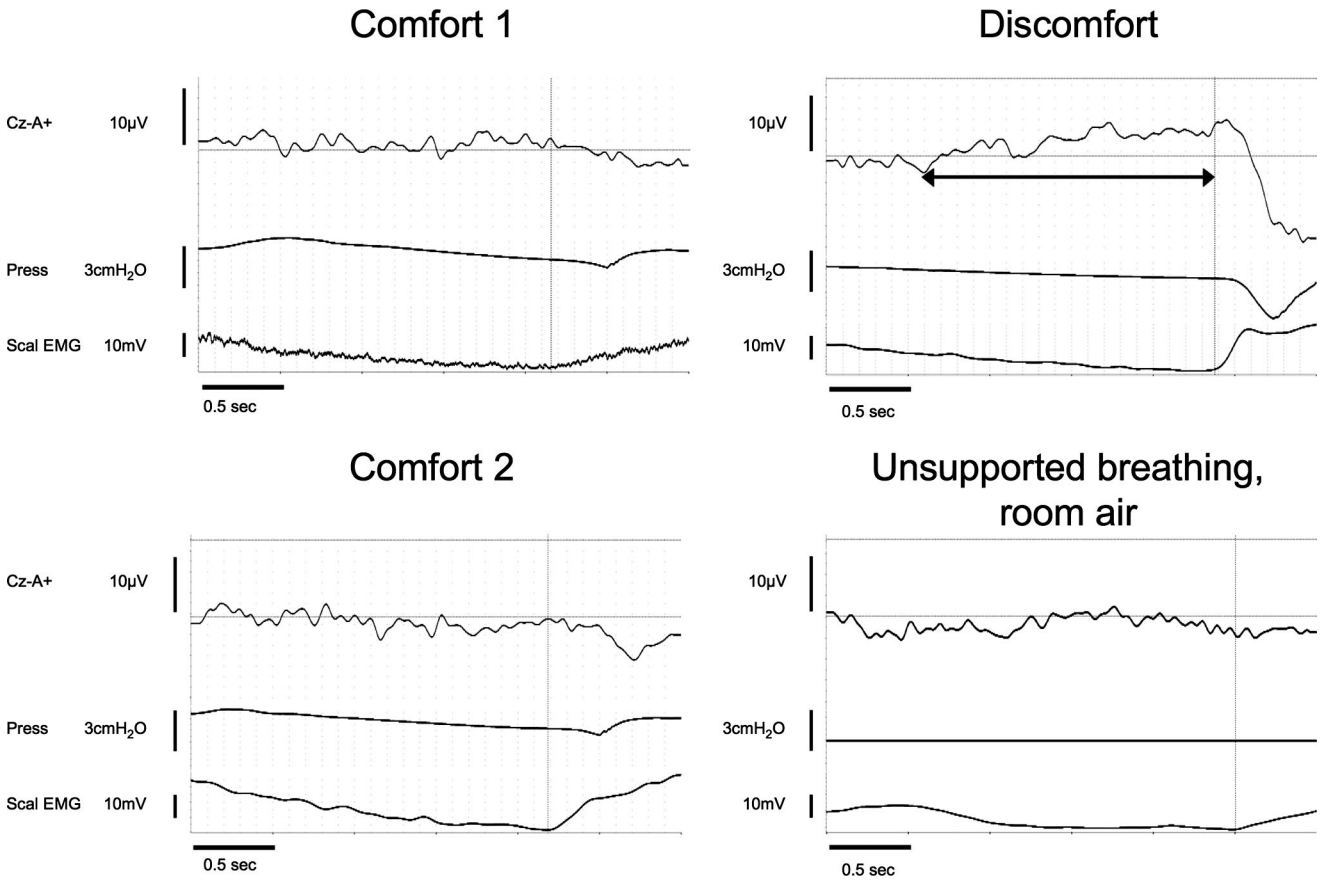

Fig. 2. Representative examples of the preinspiratory electroencephalographic activity recorded in one subject (No. 7) during inspiratory pressure-support ventilation in baseline conditions ("comfort 1" and "comfort 2"), during inspiratory pressure support with settings altered to induce discomfort ("discomfort"), and during unsupported breathing. The *double-sided arrow* depicts premotor potential latency. Cz-A+ = vertex electroencephalogram derivation; Press = airway opening pressure; Scal EMG = root mean square scalene muscle electromyogram.

13.9–121.5] *vs.* 4.4 [0.7–88.9] and 3.4 [0–89.3] mV, respectively; $Q_2 = 11.14$, $P = 0.0012$; fig. 5). The time to trigger was significantly longer during "discomfort" than during both "comfort" conditions (609 ± 308 *vs.* 305 ± 129 and 304 ± 173 ms, respectively; $F_{2,\ 15} = 6.799$, $P = 0.0137$).

Discussion

This study demonstrates that inducing ventilator fighting in normal subjects (a situation mimicking one form of patient–ventilator asynchrony) elicits premotor potentials and thus is associated with an activation of the premotor cerebral cortex. The positive pressure–related cortical inhibition[13] therefore does not offset the cortical effects of mechanical inspiratory loading.[9]

Ventilator Fighting–related Electroencephalographic Features

Breathing is typically under a dual neural control. Brainstem phasic neurons produce the ventilatory rhythm and adapt ventilation to the metabolic needs of the body, but suprapontine structures can disrupt this automatism.[17–19] They are responsible for emotional and volitional respiratory modulations, the use of the respiratory system for nonrespiratory actions such as speech. The suprapontine control of ventilation is held responsible for certain particularities of human ventilatory control. These include the fact that hypocapnia in humans does not provoke apnea despite its inhibitory effect on the automatic ventilatory command.[20] These also include the lack of hypoventilation in the presence of mechanical inspiratory loading.[6] Both features (hypocapnia-induced apnea and load-induced hypoventilation) are observed in animals but also in sleeping or anesthetized humans. Of note, spontaneous breathing in the absence of inspiratory loading is not associated with demonstrable suprapontine activities, and the carbon dioxide stimulation of breathing does not activate the cerebral cortex.[21] This indicates that the mechanisms of the physiologic response to chemical respiratory loads are completely different from the mechanisms of the response to mechanical loads. This is also in line with the very different nature of the respiratory sensations elicited by both types of stimuli ("air hunger" for carbon dioxide, "excessive inspiratory effort" for mechanical loads[22]).

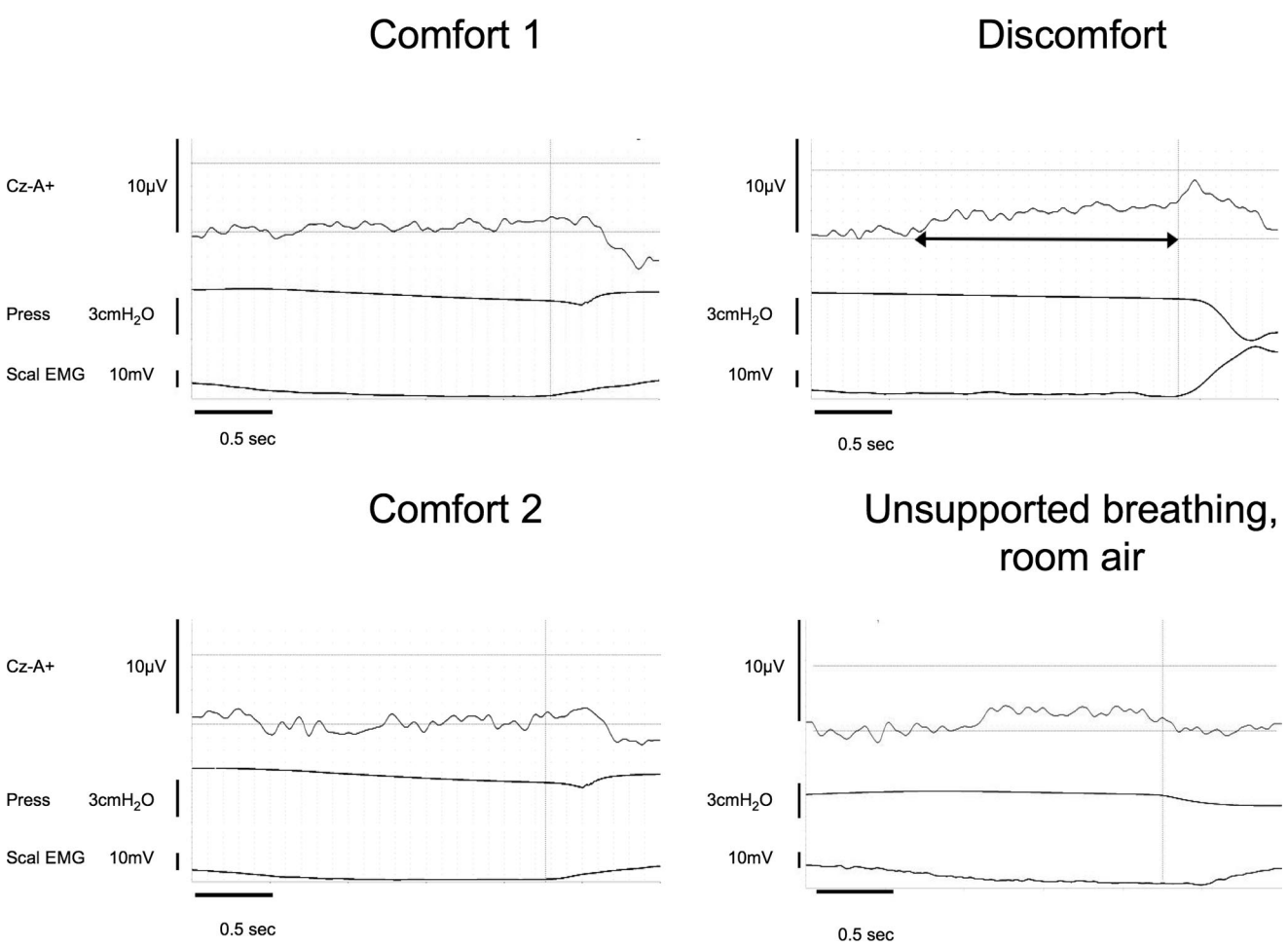

Fig. 3. Ensemble averaging (data from all the subjects) of the inspiratory premotor activities recorded, under the "comfort 1," "discomfort," and "comfort 2" and "unsupported breathing" conditions. The *double-sided arrow* depicts the premotor potential latency. Cz-A+ = vertex electroencephalogram derivation; Press = airway opening pressure; Scal EMG = root mean square scalene muscle electromyogram.

In our experiment, the electroencephalographic patterns under the "comfort" and the "unsupported" conditions were similar and did not exhibit any preinspiratory electroencephalographic activity. However, they slightly differed in that all of the electroencephalographic patterns during "comfort" supported breathing exhibited a postmotor potential, but did not during unsupported breathing. This discrepancy suggests that postmotor potentials correspond to reafferent potentials,[11] an electrophysiologic phenomenon that is in line with relative cerebral blood flow increases in the inferolateral primary sensory cortex during passive pressure-support noninvasive ventilation reported by Fink *et al.*[7] These observations indicate that connecting healthy subjects to a mechanical ventilator through a facemask and administering triggered inspiratory pressure support to them was not sufficient to elicit a response in the premotor or in the motor cortex. This was the case even though the experimental setup unavoidably attracted the attention of the subjects to their respiration. This is an important point because it argues against a contribution of attention to the occurrence of the premotor potentials. Indeed, the premotor cortical areas can be activated by the mere mental evocation of a task.[23] We did our best to minimize such a bias, by having the subjects watch a movie during the experiments. Nevertheless, we cannot completely rule out the presence of a cortical activity below the detection threshold of our technique in the "comfort" condition.

In contrast to the observations made in the "comfort" condition, experimentally inducing ventilator fighting (namely, making the subjects develop increased efforts in an attempt to get more support from the machine) consistently gave rise to premotor potentials. The link between the observed potentials and inspiration is ascertained by the very fact that it is inspiration itself that is used to trigger the electroencephalographic averaging process.[11] The occurrence of the potentials before inspiration rules out a somatosensory component. The use of needle electroencephalographic electrodes ensures a small recording volume and makes contamination by a far field potential unlikely. Of note, we used the scalene muscle electromyogram to define the onset of inspiration, because this muscle is activated phasically during

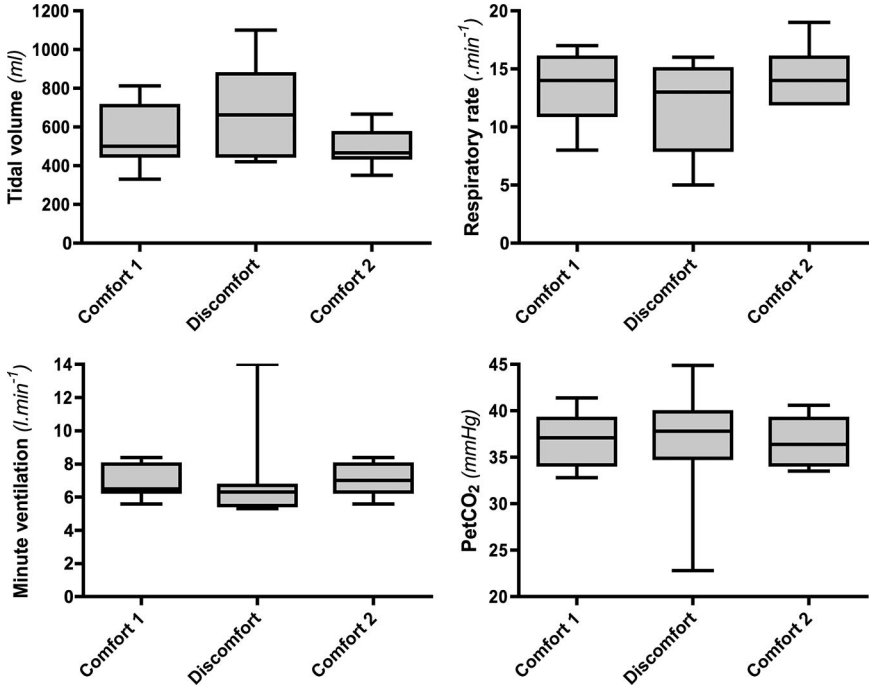

Fig. 4. Box plot representation of the tidal volume, respiratory rate, minute ventilation, and end-tidal carbon dioxide (P_{ETCO_2}) under the "comfort 1," "discomfort," and "comfort 2" conditions. The *boxes* extend from the 25th to the 75th percentile of the distribution with indication of the median, whereas the *ends of the lines* show the highest and lowest values. No statistically significant differences were detected.

inspiration in many normal individuals[24] and recruited early in the presence of loads.[25] This choice was made because we have shown previously[16] that averaging the electromyographic signal recorded by surface electrodes in the neck is efficient to identify and quantify the activity of the scalene. In addition, defining inspiration mechanically from the ventilatory flow signal can be imprecise because of fluctuations in neuromechanical coupling (*e.g.*, in the presence of intrinsic positive end-expiratory pressure, a situation where flow reversal is typically much delayed relative to electromyographic activity).

The presence of premotor potentials in the "discomfort" condition suggests that cortical processes interfered with ventilatory drive, as previously described in healthy subjects spontaneously breathing against mechanical loads.[9,26] The presence of motor potentials after the premotor ones in most of the subjects during "discomfort" further supports this contention. The significance of the premotor cortical activation that we evidenced remains to be discussed. It is not possible to know with certainty whether this activation is a simple witness of the patient–ventilator asynchrony or whether it tells something about the mechanisms set in motion to compensate the inadequacy of the ventilatory support. We think that the latter is the most likely because of our previous observations[9,26] suggesting that the load-related activation of the premotor cortex facilitates the throughput of the bulbospinal respiratory circuit, and because awake humans do not hypoventilate in the presence of a mechanical load as opposed to animals or asleep or anesthetized humans. One way to prove that the activation of the premotor cortex in the presence of inspiratory loading or during ventilator fighting has a compensatory nature would be to inhibit this area in awake humans through repetitive transcranial magnetic stimulation and observe the occurrence of load induced hypoventilation. Of note, the lack of premotor potentials despite intense dyspnea during carbon dioxide stimulation[9] suggests that respiratory sensations and respiratory premotor potentials may be completely dissociated.

Relevance of the Model

We have shown previously that an inspiratory resistance or an inspiratory threshold load can elicit cortical

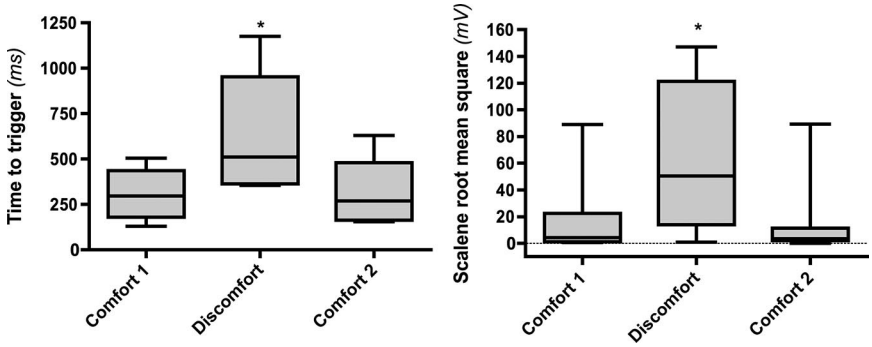

Fig. 5. Box plot representation of the time to trigger (delay between onset of scalene myoelectric activity and airway pressurization) and scalene muscle electromyogram root mean square. The *boxes* extend from the 25th to the 75th percentile of the distribution with indication of the median, whereas the *ends of the lines* show the highest and lowest values. * Significant difference *versus* the "comfort" conditions.

premotor potentials.[9] It could be argued that the changes in ventilator settings that we performed to induce respiratory discomfort in our subjects merely constituted a particular type of inspiratory loading, and therefore that finding premotor potentials in this instance is not surprising. This would overlook the fact that the situation in which our subjects were placed was much more complex than during "pure" inspiratory loading for two types of reasons.

First, positive-pressure ventilation has marked nonchemical inhibitory effects on ventilatory drive in normal humans[27–32] and interferes, also in an inhibitory manner, with the cortical control of breathing. Sharshar *et al.*,[13] studying the response of the diaphragm to transcranial magnetic ventilation in normal humans receiving noninvasive ventilation, have indeed shown a down-regulation of the corticospinal output to the diaphragm that was associated with changes at the cortical level.[13] Functional imaging studies showing increased cortical activities in the supplementary motor and premotor areas during volitional breathing and a lesser activation during mechanical ventilation go in the same direction.[33] These inhibitory effects could have interfered with the previously described excitatory effects of inspiratory loading on the premotor cortex[9] (indeed, in the "discomfort" condition, positive-pressure ventilation was maintained even though the level of assistance was diminished). Therefore, the presence of premotor potentials in response to an increased inspiratory load under mechanical ventilation was not straightforwardly foreseeable.

Second, during the index period of our experiments ("discomfort"), our subjects did not only have to face an increased inspiratory load (decreased triggering sensitivity, equivalent to a threshold loading). They were also deprived of any possibility to cope with the load by the reduction of the inspiratory slope and the decrease inspiratory pressure-support level that were simultaneously applied ("getting more air" to alleviate dyspnea during inspiratory threshold loading is possible if one develops inspiratory pressures above the threshold, which was not allowed here). Preparatory experiments showed that only such a combination was able to elicit significant respiratory discomfort in our setting, but this combination of factors has the advantage to make our model closer to what occurs during ventilator asynchrony in patients than the mere application of a load. On the negative side, we cannot evaluate the effects of the three types of changes separately. However, we do acknowledge that our model is an imperfect representation of the patient–ventilator asynchrony that is encountered in intensive care patients. In these cases, the external load imposed by the inadequate ventilator settings comes in addition to intrinsic mechanical abnormalities and a reduced neuromechanical reserve. In addition, our model does not account for all types of asynchronies,[2] *e.g.*, cycling transition abnormalities.

Significance and Perspectives

We consider this study as the first proof of a concept that will have to be further investigated in more realistic settings. Indeed, we are aware that our results cannot be extrapolated to patients directly. One reason for that is that there is an immense gap between awake healthy subjects receiving mechanical ventilation through a facemask and sedated intubated patients (but many intubated patients are not sedated, *e.g.*, during the postanesthetic recovery period or during ventilator weaning, and mechanical ventilation is increasingly often administered in intensive care units through a facemask and without sedation[5]).

The corroboration of our results in mechanically ventilated patients could be of clinical significance, as follows. Sleep is characterized by a loss in cortical connectivity that functionally separates the premotor area from the rest of the brain.[34] If mechanically ventilated patients rely on the activation of the premotor cortex to defend ventilation in the presence of an increased inspiratory loading, an inadequate support from the ventilator, a reduction of their neuromuscular performance, or any other factor or combination of factors, then a reduced wakefulness of whatever cause would be expected to be deleterious for gas exchanges. This would have a major importance in the context of general anesthesia, particularly during the recovery period and above all when ventilatory modes such as inspiratory pressure support are used. The efficacy of ventilatory assistance would then depend critically on patient–ventilator synchrony. Symmetrically, patient–ventilator asynchrony would be a putative cause of the sleep disruptions that are common in mechanically ventilated patients but incompletely explained by noise or patient care activities.[35]

In conclusion, we submit that it is worth investigating whether premotor potentials in mechanically ventilated patients could provide a central index of patient–ventilator asynchronies and whether this index is more sensitive than conventional ones. This would depend on the full automation of the electroencephalographic signal processing, which should be easy to achieve.

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