Dyspnea-pain counterirritation induced by inspiratory threshold loading: a laser-evoked potentials study

Guillaume Bouvier,1,6 Louis Laviolette,1,6 Felix Kindler,1 Lionel Naccache,2 André Mouraux,3 Thomas Similowski,1,4* and Capucine Morélot-Panzini1,4*

1Université Paris 6, Laboratoire de Physiopathologie Respiratoire, Paris; 2Assistance Publique-Hôpitaux de Paris, Groupe Hospitalier Pitié-Salpêtrière, Départements de Neurologie et de Neurophysiologie, Paris, France; 3Université Catholique de Louvain, Institut de Neuroscience, Louvain, Belgium; and 4Assistance Publique-Hôpitaux de Paris, Groupe Hospitalier Pitié-Salpêtrière, Service de Pneumologie et Réanimation Médicale, Paris, France

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Dyspnea is a distressing and debilitating symptom that is frequent in a wide variety of clinical conditions (10, 17, 22). Dyspnea shares many characteristics with pain (2, 7), but its intimate neurophysiological mechanisms are less precisely known. The pain-dyspnea analogy is therefore useful to gain insights into the physiological determinants of dyspnea. For instance, experimentally inducing a sensation of excessive respiratory work or effort—one of the major forms of dyspnea—results in a marked inhibition of the nociceptive flexion reflex (RIII) in healthy humans (26). This phenomenon is akin to counterirritation, defined as the attenuation of a preexisting pain by a novel heterotopic noxious stimulus. Counterirritation is thought to result, at least in part, from a descending modulation of spinal nociceptive transmission by diffuse noxious inhibitory controls (DNICs), of which the source and pathways have been well described (15, 30). The occurrence of a dyspnea-pain counterirritation (DPCI) (26) in response to a stimulus inducing a sensation of excessive respiratory work/effort reinforces the analogy between certain forms of dyspnea and pain. Of clinical relevance, studying the neurophysiological correlates of dyspnea-pain counterirritation could provide a mean to quantify dyspnea, e.g., through the potency of dyspnea to inhibit nociception, and to objectify and quantify the effects of relieving interventions. However, using the nociceptive flexion reflex (35) to study dyspnea-pain counterirritation is not realistic in clinical practice, because the technique is cumbersome and because the electrical stimulus required to elicit the nociceptive response is usually perceived as very painful.

Infrared laser stimuli applied onto the skin can be used to briefly and selectively activate heat-sensitive nociceptive free nerve endings and, thereby, elicit nociceptive event-related brain potentials (29, 37). Although the stimulus activates nociceptive afferents, it is non-noxious (i.e., it does not inflict a lesion) and is often perceived as only mildly painful. Laser-evoked potentials (LEPs) have been shown to be modulated by counterirritation (1, 21, 28, 32, 40). Therefore, we hypothesized that the dyspnea-pain counterirritation phenomenon can be evaluated by measuring the effect of dyspnea on the magnitude of LEPs. To test this hypothesis, LEPs were recorded in healthy subjects before, during, and after 10 min of experimentally induced dyspnea (inspiratory threshold loading [ITL]). Results: pain caused by the nociceptive laser stimulus was mild. ITL consistently induced dyspnea, mostly of the “excessive effort” type. Amplitude of the N2-P2 wave of LEPs decreased by 37.6% during ITL and was significantly correlated with the intensity of dyspnea (r = 0.66, CI 95% (0.08–0.92, P = 0.0319)). In contrast, ITL had no effect on the magnitude of non-nociceptive SEPs. Discussion: experimentally induced dyspnea of the work/effort type reduces the magnitude of LEPs. This reduction correlates with the intensity of dyspnea. The recording of LEPs could constitute a clinically applicable approach to assess the dyspnea-pain counterirritation phenomenon in patients.

Address for reprint requests and other correspondence: C. Morélot-Panzini, Laboratoire de Physiopathologie Respiratoire, Service de Pneumologie et Réanimation, Groupe Hospitalier Pitié-Salpêtrière, 47-83 boulevard de l’hôpital, 75651, Paris Cedex 13, France (e-mail: capucine.morelot@psl.aphp.fr).

* G. Bouvier and L. Laviolette contributed equally to this work; T. Similowski and C. Morélot-Panzini contributed equally to this work.

METHODS

Subjects

After ethical approval (Comité de Protection des Personnes Ile-de-France VI, Groupe hospitalier Pitié-Salpêtrière, Paris, France), 10 naive healthy caucasian male volunteers (age 19–30 yr; body mass index 19.4–26.6 kg/m²) were recruited to participate in the study. They were free from any past medical history and chronic or recurrent pain symptoms and did not suffer from any acute condition at the time of the study. Women were deliberately excluded to avoid any risk of
interference with menstrual pain. All volunteers received detailed information and gave written consent.

**Experimental Design**

The subjects were instructed to avoid sleep deprivation and refrain from taking analgesic medication, anti-inflammatory medication, and alcohol or psychotropic substances at least 48 h prior to the experiment. On the day of the study, they were instructed to have a light meal and to empty their bladder immediately before the experimental session to avoid any risk of interferences from visceral sources of sensory input (3, 4). During the experiments, the subjects sat comfortably in a semireclined examination chair, with their back and head fully supported.

The experimental design is illustrated in Fig. 1. Nociceptive LEPs were recorded during three distinct 10-min periods: before, during, and after inducing experimental dyspnea. After a 20-min rest period, non-nociceptive SEPs were recorded using the same procedure.

**Respiratory Measurements**

The subjects breathed through a facemask connected in series with a heated pneumotachograph (3700 series, linearity range 0–160 l/min; Hans Rudolph, Kansas City, MO) and a two-way valve (Hans Rudolph 2600 medium). The experimental apparatus had a resistance <1 cmH2O·l−1·s−1 and its dead space was ~100 ml. Special care was taken to fit the mask as comfortably as possible. Ventilatory airflow (V′) was measured by connecting the pneumotachograph to a linear differential pressure transducer (±5 cmH2O, DP45–18, Validyne, Northridge, CA). Tidal volume (Vt) was obtained by electrical integration of flow. Inspiratory time (Ti), expiratory time (Te), total time (Tt), breathing frequency (f), mean inspiratory flow (Vi/Ti), and duty cycle (Vi/Tt) were obtained using a custom MATLAB routine (VarVent, MATLAB R14, MathWorks, Boston, MA). Inspiratory airway opening pressure was measured by a differential pressure transducer (±100 cmH2O, DP15–34, Validyne) connected to a lateral port of the facial mask; peak negative values for each respiratory cycle were detected by the subject with a reaction time pulse was adjusted such as to elicit a clear pinprick sensation, which target site was 4 mm. Prior to the recording, the energy of the laser signal was amplified and digitized at 2 kHz using a V-Amp amplifier (Brain Products, Gilching, Germany). Electrode impedances were kept below 5 kΩ.

**EEG Recordings**

The EEG was recorded with an average reference at Fz, Cz, Pz, C3, C4, T3, T4, A1, and A2 (International 10–20 system), using active surface electrodes. The electrooculogram (Fp1, Fp2) was concomitantly recorded using electrodes located above both eyes. The EEG signal was amplified and digitized at 2 kHz using a V-Amp amplifier (Brain Products, Gilching, Germany). Electrode impedances were kept below 5 kΩ.

**Nociceptive LEPs**

Nociceptive stimuli were applied perpendicular to the dorsum of the right hand using a CO2 laser stimulator (Neurolas CO2 Laser System, Electronic Engineering, Firenze, Italy). Beam diameter at target site was 4 mm. Prior to the recording, the energy of the laser pulse was adjusted such as to elicit a clear pinprick sensation, which was detected by the subject with a reaction time <600 ms. Subjects were asked to rate the intensity of the elicited sensation using a visual-analog scale ranging from 0 (not painful) to 10 (intolerably painful) during this setting phase only. The subjects were not asked to rate the sensation elicited by the laser stimulation during inspiratory

![Graph A: LEPs run](image1)

![Graph B: SEPs run](image2)

**Fig. 2.** Time course of dyspnea intensity as measured with the visual analog scale (VAS) scale across the 3 experimental conditions during the LEPs run (A) and the SEPs run (B). *P < 0.0001 vs. baseline. Each bar represents the mean value, with indication of one SD.
Table 1. Descriptors chosen by the subjects to characterize their dyspnea during inspiratory threshold loading

<table>
<thead>
<tr>
<th>Descriptor of the Respiratory Sensation</th>
<th>Number of Subjects using this Descriptor</th>
<th>Number of Subjects Considering this Descriptor as the Main One</th>
</tr>
</thead>
<tbody>
<tr>
<td>My breathing requires more work*</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>My breathing requires effort*</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>My breathing requires more concentration</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>I cannot take a deep breath</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>I cannot get enough air</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>I feel a hunger for more air</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>My breath does not go in all the way</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>I feel that I am suffocating</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>My chest feels tight</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>I feel that I am smothering</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>My chest is constricted</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>I feel that my breathing is rapid</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>My breathing is shallow</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

*These descriptors belong to the “work” cluster defined by Simon et al. (34).

Table 2. Characteristics of the LEPs in relation with experimental condition

<table>
<thead>
<tr>
<th>LEP</th>
<th>N1</th>
<th>N2</th>
<th>P2</th>
<th>N2-P2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Latency, ms</td>
<td>Amplitude, μV</td>
<td>Latency, ms</td>
<td>Amplitude, μV</td>
</tr>
<tr>
<td>Base</td>
<td>171.6 (23.6)</td>
<td>2.4 (5.3)</td>
<td>220.5 (34.6)</td>
<td>16.0 (5.7)</td>
</tr>
<tr>
<td>IN</td>
<td>172.5 (14.9)</td>
<td>3.0 (2.8)</td>
<td>236.3 (29.5)</td>
<td>8.1 (3.6)</td>
</tr>
<tr>
<td>Recovery</td>
<td>182.2 (13.9)</td>
<td>1.6 (3.5)</td>
<td>231.3 (26.2)</td>
<td>9.5 (4.5)</td>
</tr>
<tr>
<td>ANOVA</td>
<td>F = 1.40</td>
<td>F = 0.82</td>
<td>F = 2.52</td>
<td>F = 19.58</td>
</tr>
<tr>
<td>P</td>
<td>0.2715</td>
<td>P = 0.4572</td>
<td>P = 0.1082</td>
<td>P &lt; 0.0001</td>
</tr>
</tbody>
</table>

Post hoc contrasts

Baseline vs. ITL

Baseline vs. recovery

ITL vs. recovery

Baseline vs. recovery

Values are mean (SD). ITL, inspiratory threshold loading; LEP, laser-evoked potential. P values for post hoc contrasts are provided only when ANOVA is significant.
N20, P25, and N140 amplitudes were measured from baseline to peak. Peak latencies were measured relative to the onset of laser.

**Statistical Analysis**

Results are reported as mean and standard deviation. Normality was assessed using the Shapiro-Wilk test. The SEP P25 amplitude was not normally distributed, but became so after logarithmic transformation. The effect of ITL on each of the different measures was assessed using repeated-measures ANOVA with a subject factor and with the following three conditions: before, during, and after ITL. Post hoc comparisons were conducted using orthogonal contrasts. Correlations coefficients between numerical measures were computed using Pearson’s R. The corresponding effect-size was estimated as Cohen’s d coefficient (6). Comparisons were considered statistically significant when the probability $P$ of a type I error was below 5%. Statistical analyses were performed using Statistix 9 (Analytical Software, Tallahassee, FL), Prism 4.0 (Graphpad Software), and JMP 7 (SAS, Carey, NC).

**RESULTS**

**Ventilatory Pattern**

In response to ITL, $V^e$, $V_T$, $T_i/T_T$, and $V_T/T_i$ significantly increased (all $P < 0.0001$ vs. baseline), whereas $f$ decreased significantly ($P < 0.0001$ vs. baseline). Inspiratory pressure became more negative during ITL ($Δ 29.1 ± 3.2$ cmH$_2$O, $P < 0.0001$ vs. baseline). Mean PetCO$_2$ decreased from baseline to ITL ($44.7 ± 4.1$ and $38.8 ± 5.1$ mmHg for baseline and ITL, respectively, $P < 0.0001$ vs. baseline). The ventilatory pattern returned to baseline values during the recovery period, with minute-by-minute PetCO$_2$ showing a steady increase over time, from $36.9 ± 4.6$ mmHg during the first minute of recovery to to $42.7 ± 5.6$ mmHg during the last of the 10th min; $P < 0.0001$). These changes were similar during the LEP run (above values) and the SEP run.

![Fig. 3. LEPs tracings across the 3 experimental conditions in 2 typical subjects without (A) and then with (B) sound isolation. EEG traces are shown at the Cz-A derivation. Polarity is negative up. Vertical line illustrates the time of laser stimulation. See METHODS for details. AEP, auditory-evoked potential.](image-url)
tion threshold was 2.5

Laser-Evoked Potentials

classified their respiratory sensation mainly in terms of the
LEP run and the SEP run (Fig. 2). However, this methodological decision allowed us to
detect a quantitative relationship between the intensity of the
induced dyspnea and the size of the N2-P2 amplitude reduction
(Fig. 5), which is of importance in interpreting the findings (see below).

Effect of Dyspnea of the Work/Effort Type on LEPs

We interpret the reduction of the N2-P2 amplitude induced
by ITL as consistent with the general hypothesis that certain
forms of dyspnea inhibit nociception through a dyspnea-pain
counterirritation phenomenon. Here, the observed effect was
significantly vary with ITL (P = 0.65 and P = 0.83 for
N20-P25 amplitude and N20 latency, respectively). The
latency of the P25 component significantly decreased during ITL
(P = 0.0053 vs. baseline). The amplitudes and latencies of
N140 did not change significantly during the three experimental
conditions.

DISCUSSION

This study shows that experimental dyspnea of the work/
effort type reduces the magnitude of nociceptive laser-evoked
membrane potentials, with a significant relationship between the
reduction of LEP amplitude and the intensity of respiratory
discomfort.

Methodological Considerations

Population size. Despite the small size of the study population
that calls for caution regarding negative comparisons, we
did observe statistically significant results with a large effect-
size, allowing a reasonable physiological discussion.

Fixed Magnitude of ITL

All subjects were exposed to the same inspiratory load (30
cmH2O) that thus represented a variable proportion of their
maximal inspiratory pressure. This is in contrast with the
choice made in a previous study (26) and probably explains the
marked dispersion of the dyspnea ratings between subjects
(Fig. 2). However, this methodological decision allowed us to
detect a quantitative relationship between the intensity of the
induced dyspnea and the size of the N2-P2 amplitude reduction
(Fig. 5), which is of importance in interpreting the findings (see below).

Experimentally Induced Dyspnea

Figure 2 shows dyspnea ratings during the LEP run (Fig. 2A)
and the SEP run (Fig. 2B). ITL induced dyspnea in all the
subjects (VAS = 5.11 ± 1.66 cm, P < 0.0001 vs. baseline).
Baseline and recovery dyspnea ratings were not significantly
different (VAS = 1.27 ± 1.1 and 1.05 ± 0.9 cm, respectively,
P = 0.15). There was no significant difference between the
LEP run and the SEP run (P = 0.95). During ITL, the subjects
characterized their respiratory sensation mainly in terms of the
respiratory effort locus of Simon’s descriptors (Table 1).

Laser-Evoked Potentials

The mean VAS pain rating corresponding to the laser perception
threshold was 2.5 ± 1.5 cm. Table 2 summarizes the LEP N1,
N2, and P2 amplitudes and latencies for all the experimental
conditions. A reduction of the magnitude of the laser-evoked
response was consistently present in all the subjects during ITL
(Figs. 3 and 4). There was a statistically significant reduction in
N2-P2 amplitude (−37.6 ± 13.8%, P = 0.0001, effect-size = 0.86; Fig. 4). Of note, some LEPs were consistently preceded
by a negative peak that was probably elicited by the noise
related to triggering the laser using the foot pedal (Fig. 3, left).
This contamination disappeared entirely when the subjects were
studied with soundproofing headphones and did not affect
the N2-P2 amplitude (Fig. 3, right).

There was a statistically significant correlation across sub-
jects between the intensity of the ITL-induced dyspnea and the
reduction, from baseline to ITL, in N2-P2 amplitude [expressed
as a %; r = 0.66, 95% CI (0.08–0.92); P = 0.0319
(Fig. 5)].

The amplitude of N1 was not significantly modulated by ITL
(Δ −18% ± 33 ; P = 0.15 vs. baseline). There were no
significant variations in the latencies of N1, N2, and P2 during
ITL compared with baseline (P = 0.99 ; P = 0.12, and
P = 0.33, respectively). During the recovery phase, N2-P2 tended
to baseline in 5 out of 10 subjects.

Somesthetic-Evoked Potentials

The average intensity of electrical stimulation used to obtain
SEPs was 3.16 ± 0.69 mA. Absolute values for amplitude and
latency are shown in Table 3. The amplitude of N20-P25
components and the latency of the N20 component did not

Fig. 5. Correlation between the magnitude of the fall in N2-P2 amplitude
during ITL in % of baseline values and the intensity of dyspnea reported by
the subjects during ITL (average of the minute by minute dyspnea evaluations, see
METHODS).
specific to nociception because we did not observe significant SEPs changes that would have suggested ITL-related alterations in the function of the posterior column-medial lemniscus pathway. In inhibiting LEPs (37.6 ± 13.8% reduction in the N2-P2 amplitude), ITL-induced dyspnea of the work/effort type behaved like other heterotopic noxious conditioning stimuli that have been studied in a similar manner. A 24–35% inhibition at the segmental level has been described in response to a cold pressor stimulus inducing a pain rated circa 5.5 on a VAS (1). Capsaicin application eliciting similar pain intensities has been shown to reduce the N2-P2 amplitude by 25% (38). The same proved true for thermal noxious stimuli (30% inhibition) (21). Muscular and cutaneous pains can induce N2-P2 inhibition above 40% in magnitude (32). In these studies, the VAS ratings of the conditioning pains were similar to the VAS ratings of the experimentally induced dyspnea in the present study.

However, and pertinent to all the above studies, caution is needed before interpreting the reduction of the LEPs N2-P2 amplitude in response to a conditioning stimulus as the result of a descending modulation of nociceptive transmission. First, LEPs may not always parallel pain perception (20, 27): excitation of central pathways that is not phase locked may also play a role in pain perception independently of LEPs. Second, LEPs are sensitive to habituation, namely they tend to decrease with repetitive stimulation (41). In addition, N2-P2 inhibition can result from a modulation of attention (25), if the conditioning stimulus (in our case ITL) distracts the subject away from the cutaneous noxious primary stimulus. This is why the target of stimulation was moved by a few millimeters between each stimulus and why our subjects were warned before each stimulation and asked to focus on the skin sensation (with the aim of minimizing between-stimulation attentional variations).

Of note, the N140 component of the SEPs that is possibly sensitive to the focus of spatial attention (11, 13) did not significantly vary across the experimental conditions (Table 2). Although the attentional conditions at the time of the stimulus were quite different for the SEPs and the LEPs, this is a small indication that the putative impact of attention on the LEPs amplitude in our subject was probably less than that of inspiratory loading. But perhaps the most important argument for ITL-induced dyspnea being an important direct source of N2-P2 inhibition in our subjects is the significant and strong correlation that we observed across subjects between the perceived intensity of the experimentally induced dyspnea and the magnitude of the N2-P2 inhibition. Although attention modulation and habituation might have played a role, close to 40% of the variance of the N2-P2 amplitude was explained by dyspnea intensity alone. The correlation between dyspnea and N2-P2 inhibition is in line with classical counterirritation experiments that point to a dose-effect relationship (23). A correlation was also observed between the inhibition of the RIII spinal nociceptive reflex and the intensity of dyspnea in a previous study (26). This correlation was apparent during the very course of the ITL experiments: dyspnea increased over 5 min despite constant stimulation (wind-up-like dynamics), and RII inhibition deepened in a parallel manner. Although the two studies cannot be directly compared, the RIII inhibition induced by ITL was of greater magnitude (~50%) than the LEP inhibition in our subjects (~35%). Yet the ITL-induced dyspnea was more severe in the RII experiments (average VAS ratings ~8) than in the present experiments (maximal VAS ratings ~5).

Finally, other experiment-related noxious sensations could also have interfered with the LEPs measured in our subjects, but very careful measures were taken so as to make the subjects comfortable before and during the study (see METHODS). Vigilance changes could also have had an effect (36), but ITL and the corresponding sensations can be expected to have increased rather than decreased vigilance. Yet an enhanced vigilance is expected to increase N2-P2 amplitude. ITL-induced hypercapnia could have elevated the pain threshold (16) and therefore interfered with the generation of the LEPs. This was not observed in our subjects who unexpectedly tended to hyperventilate during ITL (42), with the exception of two of them. Hypocapnia can be responsible for slower EEG responses (19, 24), but we did not observe lengthened LEPs latencies.

All considered, it seems reasonable to postulate that the N2-P2 inhibition in our subjects really did follow inspiratory threshold loading and the associated increased work/effort dyspnic sensation, at least in part.

Of note, the removal of the inspiratory load was not followed by a clear LEPs recovery (Fig. 4), although visible recovery was present in 5 of 10 subjects (see RESULTS). This was already observed with the nociceptive spinal reflex after the cessation of inspiratory threshold loading (26). Similar observations exist in counterirritation studies, including LEPs ones that show that recovery can be slow and partial and is quite variable depending on experimental paradigms [e.g., 20% recovery after 20 min to complete recovery within the first 6 min following the removal of the conditioning stimulus (1, 21, 38)].
Physiological Significance

The nociceptive RIII flexion reflex, described in terms of the EMG response of a muscle group to a painful electrical stimulation, is usually considered a defensive phenomenon (33). It is a polysynaptic and multisegmental spinal reflex that causes a complex flexion synergy of the stimulated limb (33). RIII inhibition by a conditioning noxious stimulus is not observed in quadriplegic patients (31) and thus involves a supraspinal component [diffuse noxious inhibitory controls (DNICS)]. Schematically, DNICS are thought to involve a spino-bulbo-spinal loop including the subnucleus reticularis dorsalis (SRD) in the caudal medulla (5). Descending projections in the dorsolateral funiculus terminate in the dorsal horn at all levels of the spinal cord and mediate the inhibition of nociception (15, 30). DNICS are triggered by noxious stimuli only (18), suggesting a pivotal role for ascending C- and aδ-fiber input. Of note, the occurrence of a DPCI (26) in response to a stimulus inducing a sensation of excessive respiratory work/effort not only reinforces the analogy between certain forms of dyspnea and pain, but it also points to a pivotal role of C- and/or aδ-fibers in the pathogenesis of this particular sensation. Studies in patients with thalamic lesions argue against a major role of attention among the determinants of RII inhibition by a heterotopic stimulus (9). Mental calculus was used by Morêt-Panzini et al. (26) as a control to test the effects of attention on the RII reflex. No interference was observed. This provides an additional argument to think that counterirritation described in terms of the RII reflex does not involve prominent cortical processing, which is coherent with the brain stem nature of the phenomenon.

In contrast, LEPs implicate several cortical and subcortical structures including the thalamus, the anterior insula, the prefrontal cortex, the anterior cingulate cortex, and the secondary somesthetic cortex (12, 39). They are influenced not only by the intensity of the laser stimulation (12, 39) but also by the perceived intensity of the corresponding sensation (14). They are modified by attentional tasks (28), and although their precise meaning and cortical origins are still incompletely understood (39) they may be closely related to attentional reorientation (27). Cortical processing is thus of major importance for LEPs. The present study therefore suggests that experimental dyspnea of the work/effort type is liable to interfere with nociception not only at the brain stem level, but also by perturbing the cortical processing of laser-induced cutaneous pain. Of note, several of the cortical areas associated with LEPs are also implicated in the sensation of dyspnea (8).

Conclusions and Perspectives

Experimentally induced dyspnea of the work/effort type inhibits the RIII nociceptive reflex (26) and LEPs (this study). The concept of dyspnea-pain counterirritation is therefore extended, which provides yet another dyspnea-pain neurophysiological analogy.

Practically speaking, the demonstration that experimentally induced dyspnea of the work/effort type can be studied through the LEPs inhibition that it provokes makes LEPs a promising tool as a quantifiable neurophysiological surrogate of this sensation that would not be difficult to use in the clinical field.


