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RESEARCH PAPER

Postural respiratory-related cortical activation and rostral fluid shift in awake healthy humans

Claire Launois¹  | Elisa Perger² | Valérie Attali^{1,2}  | Marie-Cécile Nierat¹ | Mathieu Raux^{1,3} | Isabelle Arnulf² | Thomas Similowski^{1,4} | Stefania Redolfi^{1,2}

¹Sorbonne Université, INSERM UMRS 1158 Neurophysiologie Respiratoire Expérimentale et Clinique, Paris, France

²AP-HP, Groupe Hospitalier Pitié-Salpêtrière Charles Foix, Service de Pathologies du Sommeil, Département R3S, Paris, France

³AP-HP, Groupe Hospitalier Pitié-Salpêtrière Charles Foix, Département d'Anesthésie Réanimation, Paris, France

⁴AP-HP, Groupe Hospitalier Pitié-Salpêtrière Charles Foix, Service de Pneumologie, Médecine Intensive et Réanimation, Département R3S, Paris, France

Correspondence

Claire Launois, Service des Maladies Respiratoires, 45, rue Cognacq-Jay, Reims Cedex, 51092 Reims, France.
Email: claunois@chu-reims.fr

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Abstract

Moving from sitting upright to lying supine causes anatomical modifications and a fluid shift to the neck, which represent inspiratory loads that predispose to upper airway collapse. The pre-inspiratory potential (PIP) corresponds to the cortical activity observed during inspiratory load. In the sitting position during wakefulness, some obstructive sleep apnoea patients exhibit PIP, probably in relationship to upper airway abnormalities. The aim of this study was to investigate whether moving to the supine position induces respiratory-related cortical activation (PIP) in awake healthy subjects. The ECG was analysed to detect PIP, and EMG activity of the genioglossus muscle and ventilation were measured in the sitting position, immediately after moving to the supine position, and during application of leg positive pressure in the supine position to promote fluid shift, which was measured by bioelectrical impedence. Twenty-four subjects were included. From sitting to lying, PIP prevalence increased from 1/24 to 11/24 ($P = 0.002$), and ventilation decreased with no change in genioglossus activity. The fluid shift from sitting to supine was higher in the subjects exhibiting PIP while supine compared with the subjects without PIP [median (25th; 75th centiles) 440 (430; 520) versus 320 (275; 385) ml, $P = 0.018$], without any other differences. From before to during leg positive pressure, PIP disappeared ($P = 0.006$). These results indicate that moving from sitting to lying induces transient respiratory-related cortical activity in awake healthy subjects with greater fluid shift, supporting possible cortical participation in the response to upper airway loading induced by moving from sitting upright to lying supine. This study offers new perspectives in the understanding of obstructive sleep apnoea pathogenesis.

KEYWORDS

control of breathing, fluid displacement, posture

1 | INTRODUCTION

Obstructive sleep apnoea (OSA) is a common disorder characterized by repetitive upper airway (UA) collapse during sleep and is associated with important adverse consequences (Javaheri et al., 2017). The pathophysiology of OSA is complex and has not yet been elucidated fully. Current understanding suggests that OSA develops in the presence of UA anatomical abnormalities accompanied by increased inspiratory load and defects in the compensatory neuromuscular response to this load during sleep (Javaheri et al., 2017).

Moving from the sitting upright to lying supine position causes anatomical modifications of the UA owing to the gravitational effect

on soft tissues. Importantly, the tongue moves backward, causing UA calibre reduction (Jan, Marshall, & Douglas, 1994; Van Holsbeke et al., 2014). In addition, gravity displaces the abdominal contents towards the thorax, reducing lung volume (Behrakis, Baydur, Jaeger, & Milic-Emili, 1983), which in turn decreases UA wall tension, thereby increasing its collapsibility (Sériès, Cormier, & Desmeules, 1990). Furthermore, lying down involves redistribution of fluid from the legs to the neck, which also decreases the UA calibre and therefore increases resistance and collapsibility (White & Bradley, 2013). These mechanisms all increase inspiratory load and predispose to UA collapse in the supine posture. Accordingly, reduction in ventilation has been shown previously in awake healthy subjects moving from the sitting

upright to lying supine position (Romei et al., 2010; Yoshizaki, Yoshida, Hayashi, & Fukuda, 1998). However, obstructive apnoea does not occur during wakefulness, which has been attributed to a wakefulness-dependent increase in UA dilator muscle (especially the genioglossus muscle) activity by way of an underlying mechanism that has not yet been elucidated (Eckert, Malhotra, Lo, White, & Jordan, 2009). Some data suggest that one of the possible mechanisms might have a cortical origin, because a modification of corticomotor conduction of the genioglossus muscle has been reported in awake OSA patients compared with control subjects (Sériès, Wang, & Similowski, 2009). We have also shown that a large proportion of patients with severe OSA, while awake in the sitting position, present respiratory-related cortical activity that is not usually present in healthy subjects (Launois et al., 2015). This cortical activity can be visualized on EEG in the form of pre-inspiratory potentials (PIPs) and resembles the response observed in healthy subjects to experimental inspiratory loading (Raux et al., 2007; Tremoureux, Raux, Jutand, & Similowski, 2010).

The aim of the present study was to investigate cortical participation in the maintenance of UA patency during wakefulness. We hypothesized that moving from the sitting upright to the lying supine posture and application of leg positive pressure, intended to induce fluid shift into the neck (White & Bradley, 2013), would induce respiratory-related cortical activity by increasing inspiratory load. We tested this hypothesis by looking for postural and leg positive pressure-evoked PIPs in awake healthy subjects.

2 | METHODS

2.1 | Ethical approval

The study conformed to the standards set by the *Declaration of Helsinki*, except for registration in a database, and received ethical clearance from the appropriate authority (Comité de Protection des Personnes Ile-de-France 6, Pitié-Salpêtrière, France) with the reference number ID RCB: 2014-A01720-47, as of 3 April 2015. The participants received detailed information about the methods used but were naive concerning the purpose of the study. They provided written participation consent.

2.2 | Participants

Eligible subjects were healthy, non-obese (body mass index $<30 \text{ kg m}^{-2}$), 18 years of age or older, with no history of cardiovascular, respiratory or neurological disease, no history of habitual snoring or daytime sleepiness and no medication. Demographic data, body mass index and neck circumference were recorded. Of the 24 subjects taking part in the present study, 11 had participated in a previous study (Launois et al., 2015) as the 'non-OSA group'.

2.3 | Protocol

In all subjects, we looked for PIPs during a 15 min period of rest, breathing through the nose with the mouth closed in the sitting position, and during another 15 min period in the supine position

New Findings

- **What is the central question of this study?**

Moving to supine induces upper airway modifications and a fluid shift to the neck, which represent inspiratory load that predisposes to upper airway collapse. Is there cortical participation in the response to the load induced by transition to a supine posture in awake healthy subjects?

- **What is the main finding and its importance?**

Moving to supine induces transient cortical activation in awake healthy subjects, with greater fluid shift, supporting possible cortical participation in the response to upper airway load induced by transition to a supine posture. Our findings open new perspectives in the understanding of the pathogenesis of obstructive sleep apnoea.

immediately after lying down. In a subgroup of 12 subjects, we looked for PIPs during an additional 15 min period in the supine position while applying positive pressure to the legs. For these 12 subjects, body composition was evaluated at baseline, and leg fluid volume modifications, genioglossus EMG activity and ventilation were recorded during three periods of 15 min.

2.4 | Pre-inspiratory potentials

Fifteen minute EEG recordings were performed with six scalp electrodes at Fz, Cz, Fp1, O1, A1 and A2 (Grael HD, PSG-EEG; Compumedics, Abbotsford, Victoria, Australia). Electrode impedance was maintained $<5 \Omega$. The signals were digitized at 2000 Hz. Nasal airflow was measured by a pneumotachograph (resistance $<0.027 \text{ cmH}_2\text{O l}^{-1} \text{ min}^{-1}$ over the complete flow range, from -180 to $+180 \text{ l min}^{-1}$; Hamilton Medical, Switzerland) connected to a tightly fitting nasal mask and to a differential pressure transducer (model CD15 sine wave carrier demodulator; Validyne, USA).

The EEG and nasal airflow were processed offline according to a previously described method (Launois et al., 2015; Raux et al., 2007). Briefly, the onset of inspiration was detected on the nasal airflow signal, and the EEG signal was split into respiratory-synchronized segments starting 2.5 s before and ending 1 s after the beginning of inspiration. EEG segments with obvious artefacts (EEG gradient $>5 \mu\text{V ms}^{-1}$; EEG amplitude $>50 \mu\text{V}$; visible baseline fluctuations) were rejected. The remaining 50–100 segments were ensemble averaged point by point, with the aim of reducing the signal-to-noise ratio, revealing the PIPs. This is the reason we selected 15 min periods for each set of conditions. To identify PIPs, the averaged EEG was visually inspected to detect negative inflections from baseline during the time window at which the potential was expected, namely 0.5–2 s before the onset of inspiration. This identification was conducted by two investigators (T.S. and M.R.) in blinded conditions. In the case of discordance between the two investigators,

a third investigator (S.R.), also in blinded conditions, was asked to decide.

2.5 | Body composition

Body composition, including fat mass, muscle mass, bone mass and water, was measured by bioelectrical impedance with a bioelectrical body composition analyser (BC-420MA; Tanita, Japan).

2.6 | Leg positive pressure

Medical anti-shock trousers (Jacob anti-shock pants; Spencer, Italia) were worn by the subjects and were deflated at the beginning of the experiments. At the end of the first 15 min period in the supine position, the trousers were rapidly inflated to apply a positive pressure of 40 mmHg on both legs from the ankles to the upper thighs (only the leg bladders were inflated) during a 15 min period.

2.7 | Fluid shift

As previously described in detail (Redolfi et al., 2009), the fluid volume of each leg was measured by bioelectrical impedance (Hydra 4200; Xitron Technologies, USA). This well-validated technique uses impedance to electric current within a body segment to measure its fluid content (Kyle et al., 2004). Two pairs of electrodes were applied to each leg: one pair to the upper thigh and the other to the ankle. The fluid volume of the two legs, referred to as leg fluid volume, was used in the analysis. The difference in leg fluid volume between the beginning and the end of each period was considered to have moved from the legs to the upper part of the body and was called fluid shift.

2.8 | Genioglossus EMG activity

The EMG activity of the anterior part of the genioglossus muscle (EMG_{gg}) was recorded unilaterally (O'Connor et al., 2007) from two gold-coated ball surface electrodes, which were connected to a pliable shank that maintained its shape when bent (Natus, 3 mm, 100 mm, 1.5 m wire). The electrodes were placed in contact with the mucosa of the mouth floor on one side of the mouth, ~20 mm posterior to the lower incisors, separated by ~5–10 mm. The electrodes were fixed by a pliable shank to the lower dental arch and secured with tape to the lower lip to remain in place throughout the experiment. The raw EMG_{gg} signal was bandpass filtered (10–100 Hz), rectified and electronically integrated on a moving time average basis with a time constant of 100 ms before being expressed as a percentage of the maximal activity observed during swallowing. Tonic activity was defined as the mean activity during expiration, phasic activity as the mean activity during inspiration and peak activity as the highest activity during inspiration (Vranish & Bailey, 2015) throughout each 15 min period.

2.9 | Ventilation

From the nasal airflow measured by a pneumotachograph as described above, the frequency of breathing (f_b), inspiratory duration (t_i),

expiratory duration (t_e), and tidal volume (V_T) were obtained by offline signal analysis (ChartTM software; AD Instruments, Castle Hill, NSW, Australia). Minute ventilation (\dot{V}_E) was calculated from the averaged V_T multiplied by f_b . Oxyhaemoglobin saturation (S_{pO_2}) and transcutaneous carbon dioxide pressure (P_{tc,CO_2}) were measured by an earlobe sensor during the whole experiment (Tosca 500 monitor; Radiometer, Denmark). Before starting the measurements, calibration of the system was carried out. For all ventilatory variables, we considered the mean throughout each 15 min period.

2.10 | Statistical analysis

All statistical analyses were performed using online university resources (biostatgv.sentiweb.fr). The normality of the data distributions was first tested with the Shapiro–Wilk test. With normality not being consistent, data are expressed as the median and interquartile range. Differences between the three sets of conditions (sitting, supine before leg positive pressure and supine during leg positive pressure) in PIP prevalence were tested with Fisher's exact test (3×2 contingency table for global significance followed by 2×2 contingency tables for two-by-two comparisons). For continuous variables (EMG_{gg} and ventilation), the differences between the three sets of conditions were tested with a Friedman non-parametric analysis followed by Wilcoxon test for two-by-two comparisons. The difference in fluid shift from sitting upright to lying supine before application of leg positive pressure and from before to after application of leg positive pressure was tested with the Wilcoxon test. Subjects were stratified according to the presence or absence of PIPs in the supine position before application of leg positive pressure. Comparisons between these two groups were conducted using the Mann–Whitney U test. For all analyses, a P value of <0.05 was considered statistically significant.

3 | RESULTS

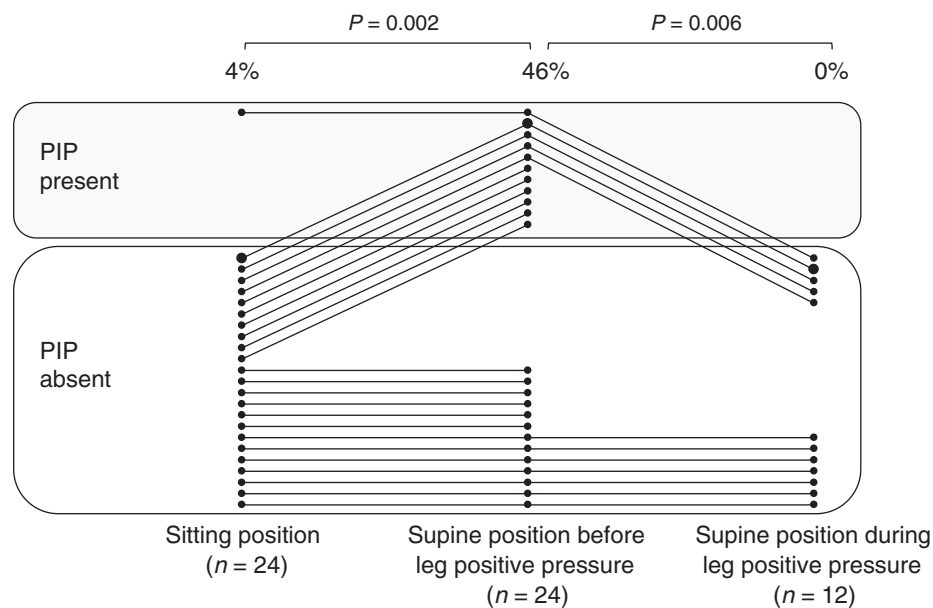
The characteristics of the participants ($n = 24$) are reported in Table 1. Respiratory-related cortical activation appeared at the vertex (Cz-EEG) as a PIP. One subject exhibited PIP while sitting (4%). Pre-inspiratory potentials appeared when moving from sitting upright to lying supine in 11 subjects (46%). This activation was transient, insofar as none of the subjects still exhibited PIPs during application of leg positive pressure (Figures 1 and 2). In the 12 subjects in whom fluid shift was measured, most of the fluid was displaced from the leg upon lying down, and a lesser amount was displaced by the application of leg positive pressure (Figure 3). Upon shifting to the supine position, minute ventilation decreased and P_{tc,CO_2} increased (Table 2). All ventilatory related variables remained stable during application of leg positive pressure. The EMG_{gg} was unchanged in the three sets of conditions (Table 2).

The comparison of the subjects exhibiting PIPs in the supine posture with those not exhibiting PIPs in these conditions did not yield significant differences in anthropometric characteristics and body composition (Table 1). However, the amount of rostrally shifted fluid

TABLE 1 Characteristics of all subjects according to the absence or presence of pre-inspiratory potentials (PIPs) in the supine position

Characteristic	All subjects (n = 24)	Subjects without PIPs while supine (n = 13)	Subjects with PIPs while supine (n = 11)	P value
Sex (females/males)	6/18	3/10	3/8	1
Age (years)	28 (26; 32)	28 (26; 31)	27 (26; 33)	1
Weight (kg)	68.3 (63.8; 73.4)	68.5 (64; 74.1)	67 (64; 69.8)	0.706
Body mass index (kg m ⁻²)	22.0 (20.1; 23.4)	22.0 (20.2; 23.2)	22.6 (20.0; 23.6)	1
Neck circumference (cm)	37 (34; 38)	37 (34; 37)	37 (35; 38)	0.780
Body composition* (%)				
Fat mass	10.5 (8.0; 13.8)	13.3 (9.7; 17.8)	8.7 (7.7; 11.7)	0.149
Muscle mass	86.6 (81.9; 87.7)	83.8 (77.9; 87.0)	86.7 (83.8; 87.7)	0.290
Bone mass	4.5 (4.3; 4.6)	4.4 (4.1; 4.5)	4.6 (4.4; 4.6)	0.214
Body water	62.2 (60.5; 63.4)	60.5 (56.8; 63.6)	62.4 (62.2; 63.4)	0.202

Data are expressed as medians (25th; 75th centiles). *Evaluated in 12 subjects, seven without and five with PIPs in the supine position. The P values are for comparison between subjects without and with PIPs in the supine position. P value of <0.05 was considered statistically significant.

**FIGURE 1** Proportion of subjects exhibiting pre-inspiratory potentials (PIPs) in the three sets of study conditions. Only one of 24 subjects exhibited PIPs in the sitting position. PIPs appeared transiently in 46% of subjects when moving from sitting upright to lying supine and disappeared completely during the additional 15 min in the supine position during application of leg positive pressure

was significantly higher in the subjects with PIPs than in the subjects without PIPs (Figure 4). Between these two groups, no differences were noted regarding posture-related changes in genioglossus activity and ventilation except for inspiratory time, which slightly increased in subjects without PIPs and stayed stable in those with PIPs (Table 3).

4 | DISCUSSION

This study shows that moving from the sitting upright to the lying supine posture can elicit a transient respiratory-related cortical activation in non-obese awake healthy subjects (46% of subjects). In subjects exhibiting such activation, the rostral shift of fluid induced by postural change is significantly higher than in subjects not exhibiting this activation.

4.1 | Respiratory-related cortical activity

Resting ventilation is under the control of brainstem automatic neural activity (Feldman, Del Negro, & Gray, 2013). Healthy humans do not exhibit EEG-detectable respiratory-related cortical activity during resting breathing in the sitting position (Dubois et al., 2016; Launois et al., 2015; Raux et al., 2007; Raux, Tremoureux, Couturier, Hug, & Similowski, 2010; Tremoureux et al., 2010; Tremoureux et al., 2014a, b), and this was confirmed in our subjects. In the present study, we show that moving from the sitting upright to lying supine position induces transient PIPs in half of the non-obese healthy subjects. The same EEG pattern has been shown in healthy subjects during experimental application of inspiratory loads (Raux et al., 2007; Tremoureux et al., 2010) and in patients with severe OSA in the sitting position during wakefulness (Launois et al., 2015). The PIP has

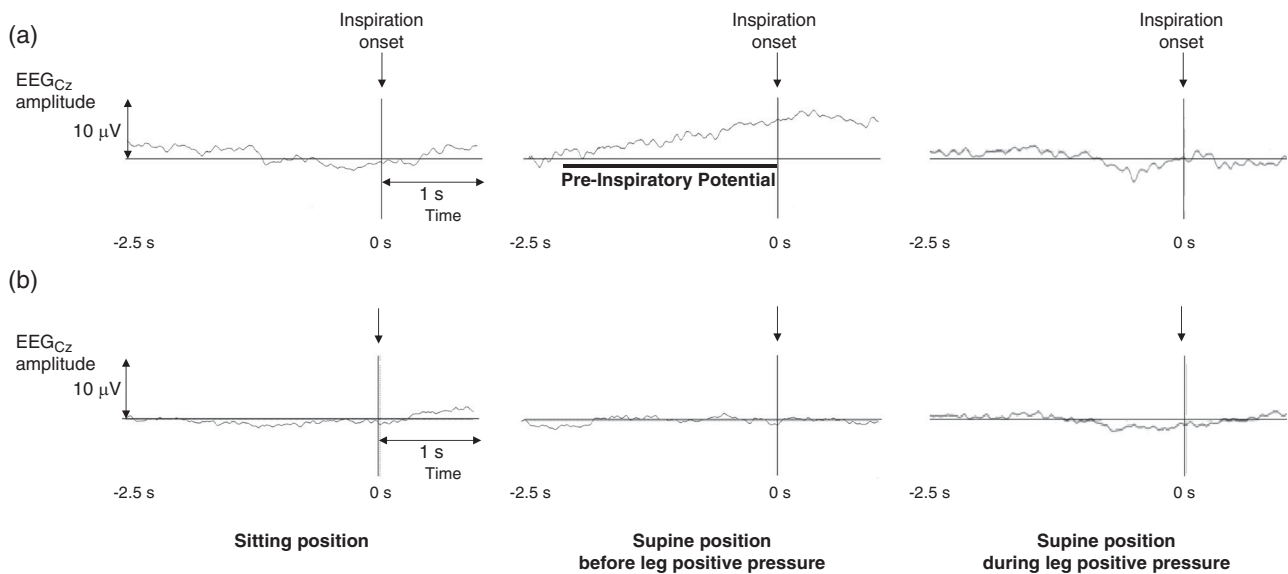


FIGURE 2 Average EEG obtained in two representative subjects. (a) Subjects with pre-inspiratory potentials (PIPs) transiently appearing in the supine position: no PIPs during sitting, but PIPs appearing during the 15 min after the transition to supine and disappearing in the following 15 min during application of leg positive pressure. (b) Subject without PIPs in any conditions

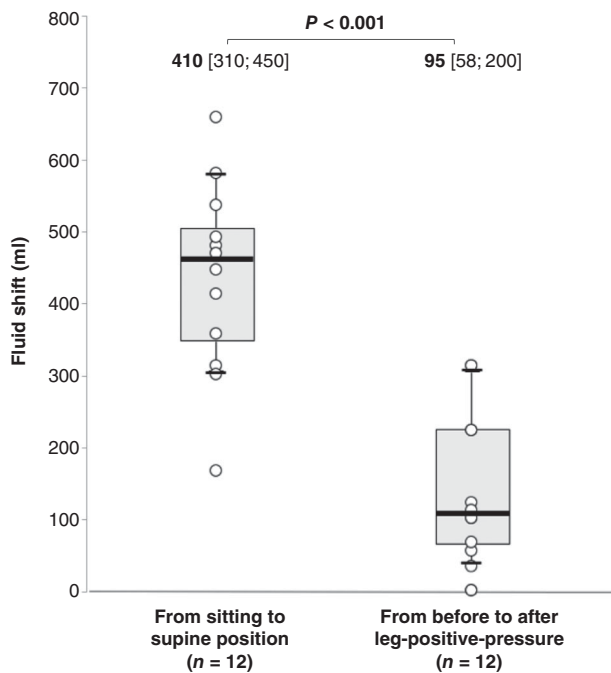


FIGURE 3 Box plots of fluid shift from the legs to the upper part of the body when moving from sitting upright to lying supine and before and after application of leg-positive-pressure

been interpreted as a respiratory-related cortical activation reflecting a cortical-subcortical cooperation acting to maintain ventilation in face of inspiratory loading (Raux et al., 2013). In accordance, PIPs appearing in the supine position in subjects with greater fluid shift might reflect cortical activation in the face of inspiratory loading induced by greater fluid accumulation in the neck. Conversely, the absence of PIPs in subjects with less fluid shift could therefore reflect lower inspiratory load, which is not sufficiently severe to induce

cortical activation. In accordance, it has been demonstrated, in healthy subjects, that although high experimental inspiratory loads (17–25 cmH₂O resistance) almost systematically induce the appearance of PIPs (Raux et al., 2007; Tremoureux et al., 2010), this is rarely the case in response to low experimental inspiratory loads (7 cmH₂O resistance; Hudson, Niérat, Raux, & Similowski, 2018).

4.2 | Inspiratory loading induced by postural change

It has been shown in previous studies in awake healthy subjects that the transition from sitting upright to lying supine is accompanied by UA modifications, such as calibre reduction (Jan et al., 1994; Martin, Mathur, Marshall, & Douglas, 1997; Van Holsbeke et al., 2014; Yildirim et al., 1991) and increased resistance (Anch, Remmers, & Bunce, 1982; Van Holsbeke et al., 2014), that cause an increase in inspiratory load. This is related to different mechanisms, such as anatomical modification of the UA owing to a gravitational effect on soft tissues (Pae et al., 1994; Yildirim et al., 1991), lung volume reduction (Sériès et al., 1990) owing to gravitational displacement of the abdominal contents up into the thorax (Behrakis et al., 1983) and redistribution of fluid from the legs to the neck (White & Bradley, 2013). According to this evidence, the respiratory-related cortical activation observed during the first 15 min after moving from sitting upright to lying supine in 46% of our subjects might reflect the cortical response to the inspiratory load imposed by moving into the supine position. Conversely, the absence of PIPs in the remaining subjects might reflect a non-significant increase in inspiratory load to induce cortical activation. In fact, it has been shown that a small experimental inspiratory load does not induce cortical activation in healthy subjects (Hudson et al., 2018). In support of this hypothesis, subjects with PIPs in the supine position had a significantly greater fluid shift from the legs induced by the transition into the supine position than

TABLE 2 Electromyographic activity of the genioglossus (EMG_{gg}) and ventilation in the three different sets of conditions ($n = 12$)

Parameter	Sitting position	Supine position before leg positive pressure	Supine position during leg positive pressure	P value 1	P value 2
EMG _{gg} (% swallow)					
Tonic	2.4 (2; 4.5)	2.9 (1.8; 4.3)	3.3 (2.6; 5.2)	1	0.155
Peak	3.8 (2.7; 6.1)	4.3 (3.3; 5.9)	5.3 (3.8; 7.0)	0.636	0.308
Phasic	2.6 (2.1; 4.3)	3.2 (2.1; 4.5)	3.7 (2.6; 5.3)	0.726	0.414
Ventilation					
f_b (breaths min^{-1})	14.2 (12.7; 16.5)	14.9 (12.1; 16.2)	14.9 (11.8; 16.4)	0.894	0.695
t_i (s)	1.7 (1.6; 1.8)	1.9 (1.6; 2.0)	1.8 (1.6; 2.2)	0.305	0.359
t_E (s)	2.6 (2.1; 3.1)	2.3 (2.1; 3.1)	2.4 (2.2; 2.8)	0.202	0.366
V_T (ml)	498 (406; 552)	446 (396; 477)	453 (425; 522)	0.064	0.388
\dot{V}_E (l min^{-1})	7.6 (5.9; 8.3)	7.0 (5.8; 7.4)	6.6 (6.2; 7.2)	0.026	0.610
P_{tcCO_2} (mmHg)	38.9 (36.4; 40.2)	40.7 (38.7; 41.5)	39.6 (38.3; 41)	0.004	0.213
S_{pO_2} (%)	96.7 (96.3; 97.3)	97.3 (96.6; 97.5)	97.7 (97.1; 98)	0.213	0.101

Data are expressed as medians (25th; 75th centiles). P value 1 is for the comparison between the sitting and supine positions before application of leg positive pressure, and P value 2 is for the comparison between the supine position before and during application of leg positive pressure. P value of <0.05 was considered statistically significant. Abbreviations: EMG_{gg} peak, highest activity during inspiration; EMG_{gg} phasic, mean activity during inspiration; EMG_{gg} tonic, mean activity during expiration; f_b , frequency of breathing; P_{tcCO_2} , transcutaneous carbon dioxide pressure; S_{pO_2} , oxyhaemoglobin saturation; t_E , expiratory duration; t_i , inspiratory duration; \dot{V}_E , minute ventilation; and V_T , tidal volume.

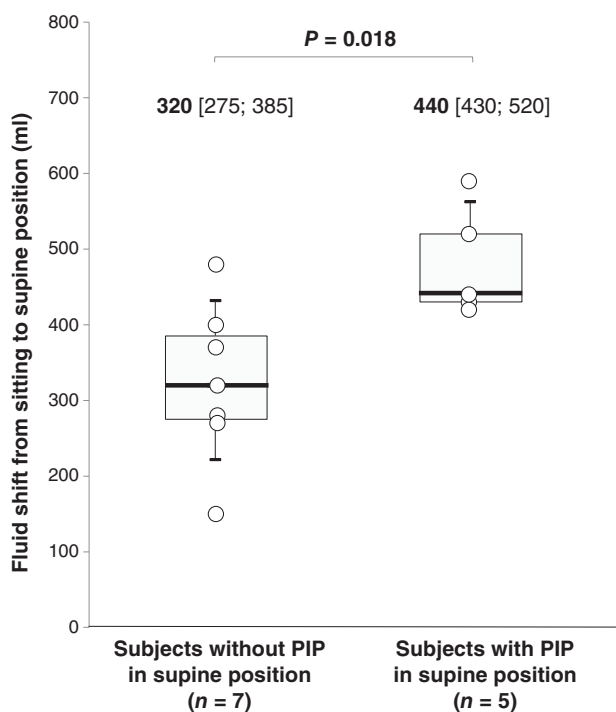


FIGURE 4 Box plots of the fluid shift from the legs to the upper part of the body when moving from sitting upright to lying supine. A significantly greater fluid shift was found in subjects with pre-inspiratory potentials (PIPs) than in subjects without PIPs in the supine position

subjects without PIPs, without differences in sex, age, body mass index, neck circumference and body composition. It has been shown in non-obese healthy subjects that 350 ml of fluid shift is associated with a decrease in the size (Shiota et al., 2007) and increase in the resistance

(Chiu et al., 2006) and collapsibility (Su et al., 2008) of the UA. In particular, fluid reaching the neck accumulates in the internal jugular vein and in the soft tissues surrounding the UA, causing a reduction in the lumen (White & Bradley, 2013). Accordingly, the significant difference we found between the two groups (with and without PIPs) in the fluid shift might induce a significantly different inspiratory load. We acknowledge, however, that in the absence of measurements of the inspiratory loads induced by the change in posture in our subjects, this remains speculative.

4.3 | Respiratory-related cortical activity induced by the supine position is transient

Respiratory-related cortical activation appeared in the first 15 min after moving from sitting upright to lying supine but disappeared after the first 15 min, when lower-body positive pressure (LBPP) was applied. This is counter to expectations, because it was hypothesized that a greater fluid shift would lead to increased pharyngeal resistance, more inspiratory load, and therefore, appearance of PIPs. It is important to point out that LBPP induced a smaller fluid shift than reported previously (250–400 ml) (White & Bradley, 2013) because it was applied after 15 min, after much of the fluid had shifted out of the legs (410 ml). Indeed, in past studies LBPP was applied immediately or shortly after lying supine. Considering that it has been shown previously that the inspiratory loading-induced respiratory-related activity persists for as long as the load is applied in healthy subjects (Tremoureux et al., 2010), the transient nature of PIPs in our subjects suggests that the increase in inspiratory load is also transient (i.e. dissipates after 15 min). Other studies have shown neck fluid accumulation to have a transient effect on UA cross-sectional area and resistance. Specifically, Shiota et al. (2007) and Chiu et al. (2006)

TABLE 3 Electromyographic activity of the genioglossus (EMG_{gg}) and ventilation after the transition from sitting upright to lying supine in subjects without and with pre-inspiratory potentials (PIPs) in the supine position

Parameter	Subjects without PIPs while supine (n = 7)	Subjects with PIPs while supine (n = 5)	P value
EMG _{gg} modification (% swallow)			
Tonic	0 (0; +0.8)	0 (-0.9; +0.7)	0.672
Peak	0.2 (-0.1; +0.4)	-0.1 (-0.7; +1.6)	0.917
Phasic	0 (-0.1; +0.9)	0 (-0.7; +1.3)	0.917
Ventilation modification			
f_b (breaths min ⁻¹)	-0.7 (-0.9; -0.1)	+1.6 (-0.1; +0.9)	0.192
t_i (s)	+0.2 (+0.2; +0.3)	0 (-0.2; +0.1)	0.039
t_E (s)	0 (-0.1; 0)	0 (-0.2; 0)	1
V_T (ml)	-4 (-53; +20)	-65 (-68; -61)	0.268
\dot{V}_E (l min ⁻¹)	-0.4 (-0.5; -0.2)	-0.7 (-1.4; 0)	0.639
P_{tc,CO_2} (mmHg)	+1.3 (+0.6; +1.7)	+3.3 (+1.6; +6.1)	0.164
S_{pO_2} (%)	-0.2 (-0.3; +0.1)	+0.8 (+0.3; +1.2)	0.051

Data are expressed as medians (25th; 75th centiles). The *P* values are for the comparison between subjects without and with PIPs. *P* value of <0.05 was considered statistically significant. Abbreviations are as in Table 2.

showed that LBPP increases neck circumference (signalling neck fluid accumulation) and led to narrowing of the pharynx and increased pharyngeal resistance, after 5 min in healthy subjects. However, after 15 min, application of LBPP still leads to increased neck circumference, but pharyngeal cross-sectional area and resistance remain similar to pre-fluid shift levels in healthy subjects, but not in OSA patients (Kasai et al., 2014; White et al., 2014). One possible explanation is that the fluid shift occurring immediately upon lying down might induce a transient intravascular fluid accumulation in the neck, with fluid moving elsewhere other than in the neck during the application of leg positive pressure when a smaller amount of fluid was displaced.

4.4 | Significance of supine respiratory-related cortical activity

In the literature, the PIP has been interpreted as a respiratory-related cortical activation acting to maintain ventilation in the face of inspiratory loading (Raux et al., 2013). In the present study, PIPs were observed upon lying supine in a subgroup of subjects in whom fluid shift was significantly higher (and probably with greater inspiratory load) compared with those without PIPs. However, we showed a decrease in ventilation with an increase in P_{tc,CO_2} upon lying supine, which was not different between subjects with and without PIPs, suggesting that postural respiratory-related cortical activation does not completely compensate for the postural load, but probably prevents an excessive reduction in ventilation.

In contrast, in the present study, the EMG_{gg} activity remained stable after moving to the supine position, unlike previous studies that showed an increase in the EMG_{gg} during a 30 s to 3 min period after moving to the supine position (Otsuka, Ono, Ishiwata, & Kuroda, 2000; Pae, Blasius, & Nanda, 2002; Sauerland & Mitchell, 1975; Vranish & Bailey, 2015). A possible explanation could be a technical limitation related to the use of surface electrodes in our study, which are

less sensitive than intramuscular electrodes used in the majority of previous studies.

4.5 | Study limitations

Our study has limitations. First, we did not measure the UA resistance, in order to avoid discomfort related to the introduction of two catheters (one at the nasopharynx and another at the hypopharynx level), which could have induced subjects to focus on respiration, promoting a respiratory-related cortical activation because of the experimental setting. Second, we used surface electrodes for recording EMG_{gg} activity, which, as already discussed, are less sensitive than intramuscular electrodes but have the advantage of being non-invasive, thereby avoiding interference of the experimental setting with quiet breathing.

4.6 | Conclusions

The results of this study indicate that a transition from sitting upright to lying supine induces transient respiratory-related cortical activity in awake healthy subjects, with a large fluid shift, supporting possible cortical participation in response to the inspiratory load imposed on the UA by moving to the supine position. This study sheds new light on UA control and provides a new perspective in the understanding of OSA pathogenesis.

COMPETING INTERESTS

None declared.

AUTHOR CONTRIBUTIONS

All work was performed in the Service des Pathologies du Sommeil, Groupe Hospitalier Pitié-Salpêtrière and in the Laboratoire de

Neurophysiologie Respiratoire Expérimentale et Clinique, INSERM UMRS 1158, Sorbonne Université, Paris, France. Conception or design of the work, and drafting the work or revising it critically for important intellectual content: C.L., T.S. and S.R. Acquisition or analysis or interpretation of data for the work: all authors. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors are qualified for authorship, and all those who qualify for authorship are listed.

ORCID

Claire Launois  <https://orcid.org/0000-0002-6429-666X>

Valérie Attali  <https://orcid.org/0000-0001-5444-9223>

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