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## RESEARCH PAPER

# Postural preinspiratory cortical activity, genioglossus activity and fluid shift in awake obstructive sleep apnoea patients

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## Abstract

The anatomy and mechanical properties of the upper airway (UA) depend on posture. Lying in a supine position causes cephalad fluid shift to the neck, thus narrowing the UA and predisposing the individual to obstructive sleep apnoea (OSA). Increased UA dilator muscle activity during wakefulness prevents the UA collapse but the underlying mechanism has not yet been elucidated. In the sitting position during wakefulness, some OSA patients exhibit preinspiratory cortical activity (preinspiratory potential, PIP) probably related to UA abnormalities. The aim of this study was to investigate changes in the preinspiratory cortical activity and UA dilator muscle in OSA patients during postural challenge. An electroencephalogram was used to detect PIP, and the genioglossus electromyographic activity and ventilation were analysed in 17 awake, male OSA patients while they were sitting, just after lying down, and then in response to leg positive pressure to enhance cephalad fluid shift. The prevalence of PIP decreased from 53% (sitting) to 12% (supine) ( $P = 0.002$ ) in association with increased genioglossus activity (tonic from median (25th, 75th centiles) 2.3 (1.8, 2.8)% to 3.6 (1.7, 5.0)% of voluntary deglutition,  $P = 0.019$ ; phasic from 2.3 (1.9, 2.8)% to 3.7 (2.0, 6.1)%,  $P = 0.024$ ), and with increased transcutaneous carbon dioxide pressure (from 43.0 (42.4, 44.2) to 44.6 (43.5, 45.2) mmHg). No change was observed during leg-positive-pressure application. Moving from the sitting position to the supine position reduces respiratory-related premotor cortical activity in awake OSA patients. The concomitant increase in genioglossus activity, therefore, is not driven by cortical respiratory activity.

## KEYWORDS

obstructive sleep apnoea, posture, preinspiratory potential

## 1 | INTRODUCTION

Obstructive sleep apnoea (OSA) is a common disorder associated with high morbidity and mortality (Javaheri et al., 2017). It is characterised by repeat episodes of upper airway collapse during sleep. The pathophysiology of OSA is complex and has not yet been fully elucidated. It involves anatomical factors responsible for narrowing the upper airways, constituting an inspiratory load (Javaheri et al., 2017). When the patient is awake, the activity of upper airway dilator muscles is sufficient to compensate for this load. During sleep, a reduction in this activity disturbs this balance, leading to episodes of apnoea (Javaheri et al., 2017).

Changing from the upright sitting position to the lying supine position increases the mechanical load on the upper airways, as, in response to gravity, the soft tissues surrounding the pharynx, especially the tongue and soft palate, tilt posteriorly (Yildirim et al., 1991), reducing the anteroposterior diameter of the upper airways. Gravity also displaces the abdominal contents towards the thorax, resulting in decreased lung volume and consequently decreased tension exerted by the tracheopulmonary system on the pharyngeal walls, thereby increasing their collapsibility (Shore & Millman, 1984). In addition, the supine position shifts fluid from the legs to the neck, which also decreases the calibre and increases the resistance and collapsibility of the upper airway (White & Bradley, 2013). All

of these mechanisms predispose individuals to the development of obstructive apnoeas during sleep, while collapse of the upper airway is never observed during wakefulness, suggesting the role of a waking-dependent mechanism. Increased activity of upper airway dilator muscles, especially the genioglossus muscle, has been demonstrated in awake OSA patients in a 45 degrees semi-recumbent position compared to control subjects (Mezzanotte, Tangel, & White, 1992). The mechanisms responsible for this increased genioglossus activity have not yet been elucidated. They could involve an increased cortical drive to breathe. Indeed, the response of the genioglossus to transcranial magnetic stimulation is enhanced in awake OSA patients as compared to controls (Sériès, Wang, & Similowski, 2009). Also, patients with severe OSA exhibit electroencephalographic evidence of respiratory-related cortical activity when studied while awake and while in a sitting position, in the form of preinspiratory potentials (PIPs) analogous to those described in response to mechanical inspiratory loading (Launois et al., 2015). This phenomenon is generally not observed in healthy individuals. In addition, we have previously shown that moving to the supine posture, a circumstance that is highly likely to increase upper airway resistance, induces PIP in a proportion of healthy subjects (Launois et al., 2019).

We hypothesised that moving from the upright sitting position to the lying supine position might accentuate preinspiratory cortical activity in OSA patients. We tested this hypothesis using the experimental approach from our previous study with healthy subjects (Launois et al., 2019) by looking for the presence of PIP in awake OSA patients in the sitting position, the supine position and during application of positive pressure to the legs, which was designed to induce fluid shift towards the neck. We also recorded genioglossus muscle activity and ventilation under these three conditions.

## 2 | METHODS

### 2.1 | Ethical approval

This study was in agreement with the standards set by the *Declaration of Helsinki*, except for registration in a database, and was externally approved (Comité de Protection des Personnes Ile de France 6, Pitié-Salpêtrière, France; ID RCB: 2014 A01720 47); the participants provided written informed consent after having received detailed information.

### 2.2 | Participants

We studied 17 male patients with a body mass index (BMI)  $<35 \text{ kg m}^{-2}$ , with untreated OSA with more than 15 apnoeas and hypopneas per hour of sleep (apnoea-hypopnea index (AHI)  $>15 \text{ h}^{-1}$ ). These patients had no history of respiratory, cardiac or neurological disease, and were not taking any psychotropic drugs. Demographic data, BMI, neck circumference and Epworth sleepiness score were recorded. For 6 of the 17 patients data were collected during our previous study on PIP in OSA patients in the sitting position (Launois et al., 2015). This subgroup

### New Finding

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

Transition to supine posture induces an inspiratory load associated with cortical activation in awake healthy subjects. Some obstructive sleep apnoea patients exhibit this cortical activity in the sitting position contributing to the arousal-dependent compensation of their upper airway abnormalities. Does a transition to the supine posture in awake obstructive sleep apnoea patients increase this cortical activity?

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

The transition to supine posture induces a reduction in the cortical activity despite evidence of an increase in genioglossus activity, suggesting that genioglossus activation is not driven by cortical activity.

of patients was preliminarily studied in the supine position as well. The demographic data, clinical characteristics and polysomnographic data for the patients are presented in Table 1.

### 2.3 | Polysomnography

Standard polysomnography was performed in all patients (Grael HD, PSG-EEG, Compumedics, Melbourne, Victoria, Australia). Polysomnographic recordings were analysed according to the criteria defined by the American Academy of Sleep Medicine (version 2.2 2015; <https://aasm.org/clinical-resources/scoring-manual/>). Apnoea was defined as the interruption of airflow for at least 10 s and hypopnea was defined as a 30% reduction in airflow for at least 10 s associated with at least 3% oxyhaemoglobin desaturation or arousal. The AHI was calculated as the number of apnoeas and hypopneas per hour of sleep.

### 2.4 | Protocol

The present study on OSA patients and the previous study published on healthy subjects (Launois et al., 2019) are part of a general project aimed at studying control of the upper airway with postural changes. The protocol was the same as that previously used with healthy subjects (Launois et al., 2019). The presence of PIP (see below) was investigated in all patients over a 15 min period of restful breathing in the sitting position and over another 15 min period immediately after lying down in the supine position.

In a subgroup of 11 subjects, the presence of PIP was investigated over an additional 15 min period in the supine position during application of positive pressure to the legs. Modifications in fluid volume of the legs, genioglossus electromyographic activity and ventilation were recorded over the three periods in these 11 patients. The other six patients were those who participated in our previous study where these last measurements were not performed (Launois

**TABLE 1** Demographic, clinical and sleep characteristics of all patients according to the absence or presence of pre-inspiratory potential (PIP) in the sitting position

Characteristic	All patients (n = 17)	Patients without PIP while sitting (n = 8)	Patients with PIP while sitting (n = 9)	P
Age (years)	57 (49, 64)	52 (37, 63)	64 (54, 66)	0.177
Weight (kg)	85.0 (81.1, 95.1)	91.3 (79.1, 97.3)	84.0 (83.0, 90.0)	0.815
Body mass index (kg m <sup>-2</sup> )	28.7 (27.4, 32.7)	30.1 (27.4, 33.0)	28.7 (27.5, 29.4)	0.700
Neck circumference (cm)	41.5 (39.0, 42.5)	41.5 (39.0, 42.0)	42.0 (39.6, 44.0)	0.381
Epworth sleepiness score	11 (6, 12)	10 (7, 11)	11 (4, 14)	0.874
AHI (h <sup>-1</sup> )	43.3 (33.4, 58.0)	47.3 (37.8, 60.0)	40.4 (28.0, 51.9)	0.370
Supine AHI (h <sup>-1</sup> )	54.5 (42.0, 67.6)	52.7 (33.8, 71.5)	54.9 (45.8, 67.1)	0.606
Mean S <sub>po<sub>2</sub></sub> (%)	92.0 (91.0, 93.9)	92.0 (90.6, 93.3)	93.0 (91.9, 93.9)	0.439
TST (min)	436 (388, 518)	493 (406, 519)	429 (392, 442)	0.743
Sleep efficacy (%)	87.8 (72.8, 93.2)	91.2 (82, 94.4)	78.6 (72.8, 93.2)	0.334
N1–N2 sleep (% TST)	63.9 (58.5, 67.2)	64.5 (61.1, 67.2)	66.5 (56.1, 72.4)	0.888
N3 sleep (% TST)	15.2 (8.8, 17.4)	15.1 (10.5, 17.4)	15.6 (5.3, 17.4)	1.000
REM sleep (% TST)	20.4 (17.3, 26.2)	18.9 (17.6, 23)	20.8 (16.2, 26.3)	0.963
Arousal index (h <sup>-1</sup> )	29.7 (20.2, 35.9)	29.1 (25.9, 35.6)	32.9 (20.2, 35.9)	0.815

Data are expressed as median (25th, 75th centiles); P for comparison between patients without and with PIP while sitting. AHI, apnoea-hypopnea index; S<sub>po<sub>2</sub></sub>, pulse oxygen saturation; TST, total sleep time.

et al., 2015). To ensure that participants were awake throughout the study, the sleep/wake state was assessed on the polysomnographic recording.

## 2.5 | Pre-inspiratory potentials

An electroencephalogram (EEG) was recorded using six scalp electrodes positioned at Fz, Cz, Fp1, O1, A1 and A2 (Grael HD, PSG-EEG, Compumedics; electrode impedance consistently kept below 5 Ω) in order to assess the presence of PIP, which partly originates in the supplementary motor area. The ventilatory flow was measured through a nasal mask connected to a pneumotachograph (resistance <0.027 cmH<sub>2</sub>O l<sup>-1</sup> min<sup>-1</sup> over the complete flow range, from -180 to 180 l min<sup>-1</sup>; Hamilton Medical, Bonaduz, Switzerland), attached to a differential pressure transducer (CD15, Validyne, Northridge, CA, USA). Signals were digitised at 2000 Hz and processed offline in the manner described in a previous study (Launois et al., 2015). In brief, EEG recordings were segmented in epochs starting 2.5 s before the beginning of inspiration as detected from the flow signal, and ending 1 s after. These epochs were then averaged point by point after rejection of those exhibiting obvious artefacts (EEG amplitude >50 μV; visible baseline fluctuations), to reveal the PIP. The duration of the recordings was 15 min in each of the study conditions. To identify pre-inspiratory potentials, the averaged EEG segments were then analysed visually to detect a negative inflection of the baseline during the expected time window of the PIP, i.e. 0.5–2 s before the start of inspiration. PIPs were identified by two investigators (T.S. and M.R.) under blinded conditions. Any discordant assessments between the two investigators were resolved by a third blinded investigator (S.R.).

## 2.6 | Positive pressure to the legs

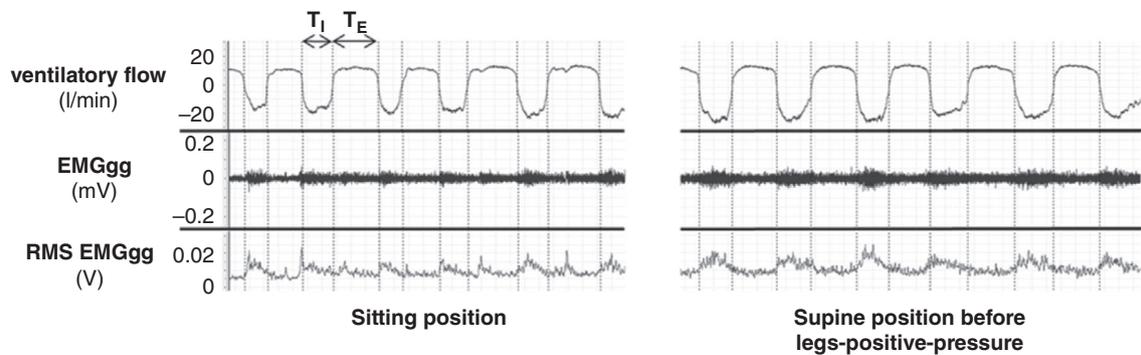
A positive pressure of 40 mmHg was applied to both legs (from the ankles to the top of the thighs) by use of rapidly inflated anti-shock trousers (Jacob, Spencer, Sala Baganza, Italy). The pressure was maintained for 15 min.

## 2.7 | Fluid shift in the legs

Leg fluid volume was estimated using bioelectric impedance (Hydra 4200, Xitron Technologies, San Diego, CA, USA) (Kyle et al., 2004; Redolfi et al., 2009). Pairs of electrodes were applied at the extremities of each lower limb, and the volume of fluid of both legs was summed for subsequent analysis. This procedure was performed in the sitting position, after moving to the supine position, and after application of positive pressure. The differences in fluid volumes of the legs between the start and the end of each period were considered to be the volume that had shifted from the legs to the upper part of the body and were called 'fluid shift'.

## 2.8 | Genioglossus electromyographic activity

Unilateral recordings of the electromyographic activity of the anterior part of the genioglossus muscle (EMG<sub>gg</sub>) were obtained (O'Connor et al., 2007) from two gold ball-tip electrodes positioned 5–10 mm apart on the floor of the mouth, approximately 20 mm posteriorly to the right or left lower incisor. The electrodes were connected to a pliable shank that maintained its shape when flexed (Natus, 3 mm, 100 mm, 1.5 m lead), which was attached to the lower dental arch with adhesive tape glued on the lower lip. This ensured that the electrodes remained in place throughout the experiment. The raw EMG<sub>gg</sub> signal was filtered (10–1000 Hz band pass), rectified (root mean square;



**FIGURE 1** Example of changes in the postural genioglossus electromyographic activity. The EMG activity of the genioglossus (EMGgg) and the ventilatory flow were recorded synchronously. The root mean square of the EMG signal was calculated (RMS EMGgg). The beginning of the inspiration and expiration was marked automatically. The beginning of the inspiration was defined as the crossing of the zero by the falling ventilatory flow signal and the beginning of the expiration as the crossing of the zero by the rising signal of the flow.  $T_E$ , expiratory duration;  $T_I$ , inspiratory duration

RMS) and electronically integrated (moving time average; 100 ms time constant). The EMGgg activity was then expressed as a percentage of the maximum activity observed during voluntary deglutition. The tonic activity was defined as the RMS activity on expiration. The phasic activity was defined as the RMS activity during inspiration. The peak activity was defined as the maximum RMS activity observed during inspiration (Vranish & Bailey, 2015) over each 15 min period (Figure 1).

## 2.9 | Ventilation

The nasal airflow signal was analysed using Chart™ software (ADInstruments, Castle Hill, Australia) to determine breathing frequency ( $F_b$ ), inspiratory time ( $T_I$ ), expiratory time ( $T_E$ ), and tidal volume ( $V_T$ ). Minute ventilation ( $V'$ ) was calculated by multiplying the mean  $V_T$  by the mean  $F_b$ . Transcutaneous carbon dioxide pressure ( $P_{tcCO_2}$ ) was measured with an earlobe transducer (Tosca 500, Radiometer, Copenhagen, Denmark) that was calibrated prior to recording the measurements.

## 2.10 | Statistical analysis

All statistical analyses were performed using on-line university resources (biostatgv.sentiweb.fr). The normal distribution of the data was first tested by a Shapiro–Wilk test. Since some data did not present a normal distribution, all results are expressed as median and interquartile range. Differences concerning the PIP between the three conditions (sitting position, supine position before application of positive pressure to the legs and supine position during application of positive pressure to the legs) were tested with Fisher's exact test ( $3 \times 2$  contingency table for overall significance followed by  $2 \times 2$  contingency tables for two-by-two comparisons). For continuous variables (EMGgg and ventilation), the difference between the three conditions was tested by Friedman's non-parametric test followed by Wilcoxon's test for paired comparisons. Subjects were stratified according to the presence or absence of PIP in the sitting position. These two groups were compared by a Mann–Whitney test. A  $P$

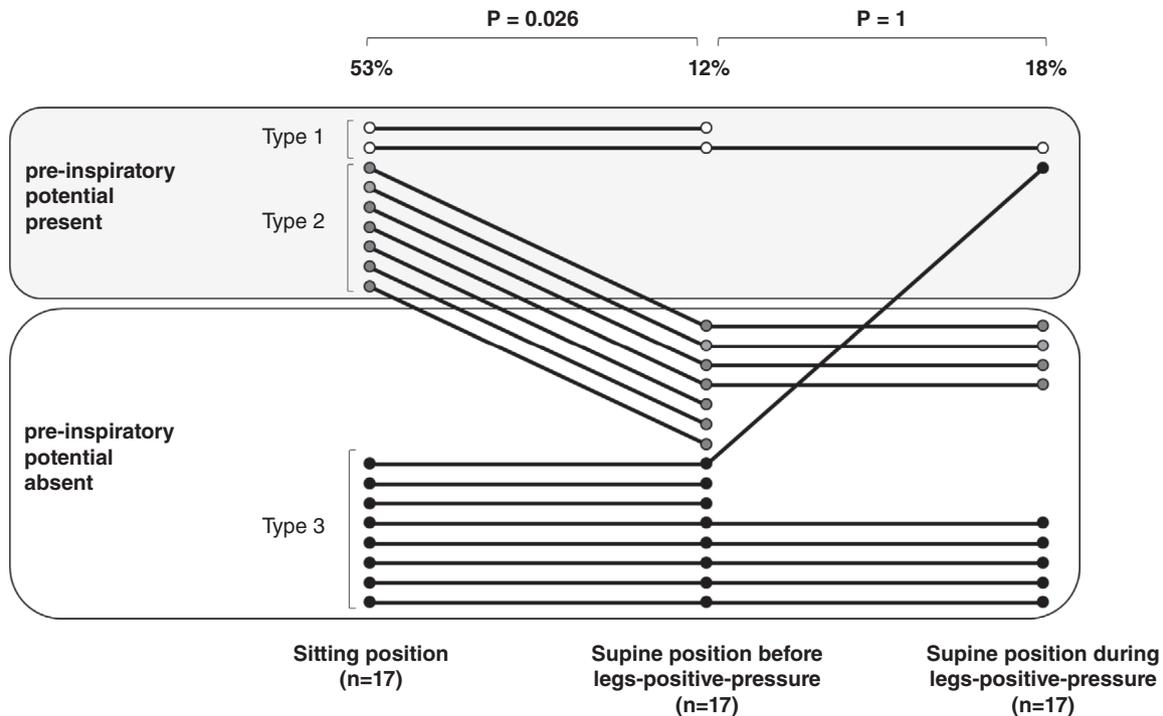
value  $<0.05$  was considered to be statistically significant for all analyses.

## 3 | RESULTS

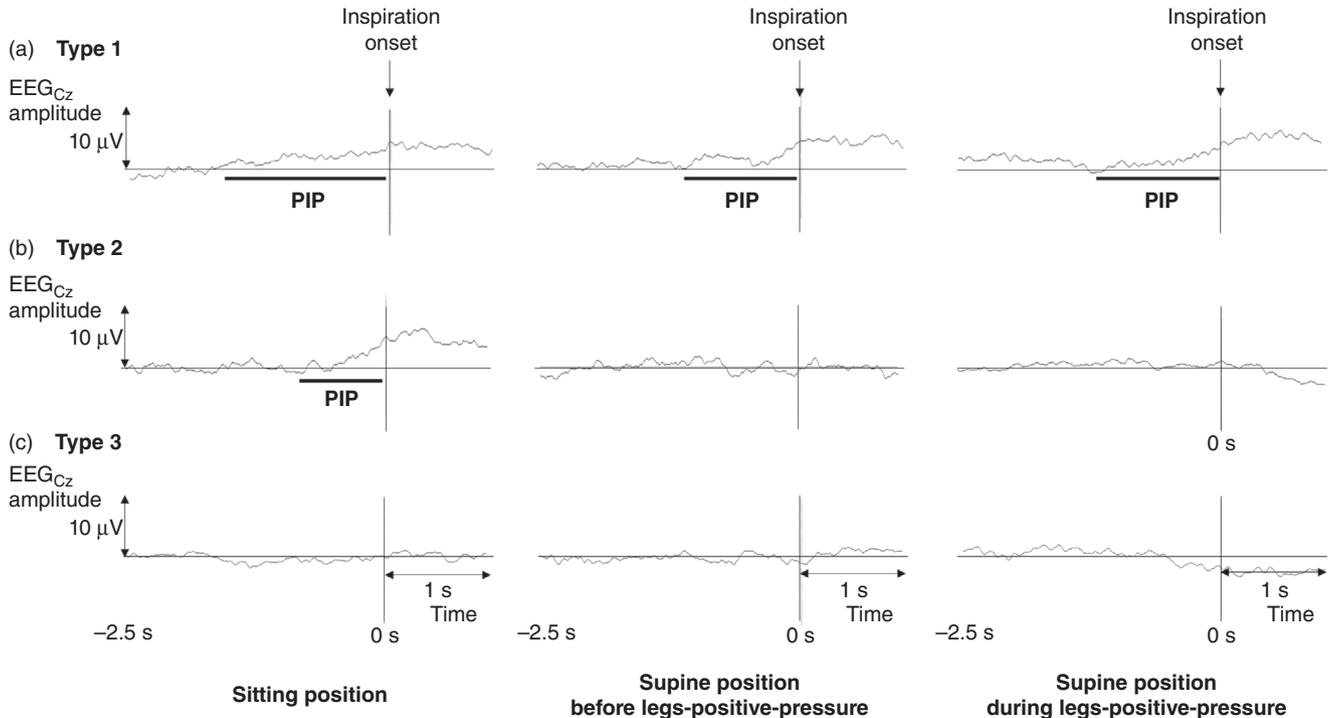
A PIP was present in 53% of patients (9 patients out of 17) in the sitting position, in 12% of patients (2 patients out of 17) during the first 15 min after lying down and in 18% of patients (2 patients out of 11) during an additional 15 min in the supine position during application of positive pressure to the legs (Figure 2). The following three patient profiles could be identified according to the presence or absence of PIP according to posture: (i) Type 1, when PIP was present in the sitting position and persisted in the supine position (2 out of 17 patients); (ii) Type 2, when PIP was present in the sitting position but no longer present in the supine position (7 out of 17 patients), and (iii) Type 3, when PIP was absent in both the sitting position and the supine position (8 out of 17 patients) (Figures 2 and 3). No subject had absent PIP when sitting and the emergence of PIP shortly after lying supine. In the overall group, after lying down for 15 min, the mean fluid shift was 180 (140, 300) ml and there was an additional fluid shift of 150 (120, 280) ml after application of positive pressure to the legs. The EMGgg activity (Figure 4) and  $P_{tcCO_2}$  (Table 2) increased significantly when moving from the sitting position to the supine position and remained stable during application of positive pressure to the legs. No significant differences in terms of demographic or clinical characteristics, polysomnographic measures, EMGgg activity and ventilation in the sitting position, and modifications of EMGgg activity and ventilation when changing to the supine position were observed between patients with or without PIP in the sitting position (Tables 1, 3 and 4).

## 4 | DISCUSSION

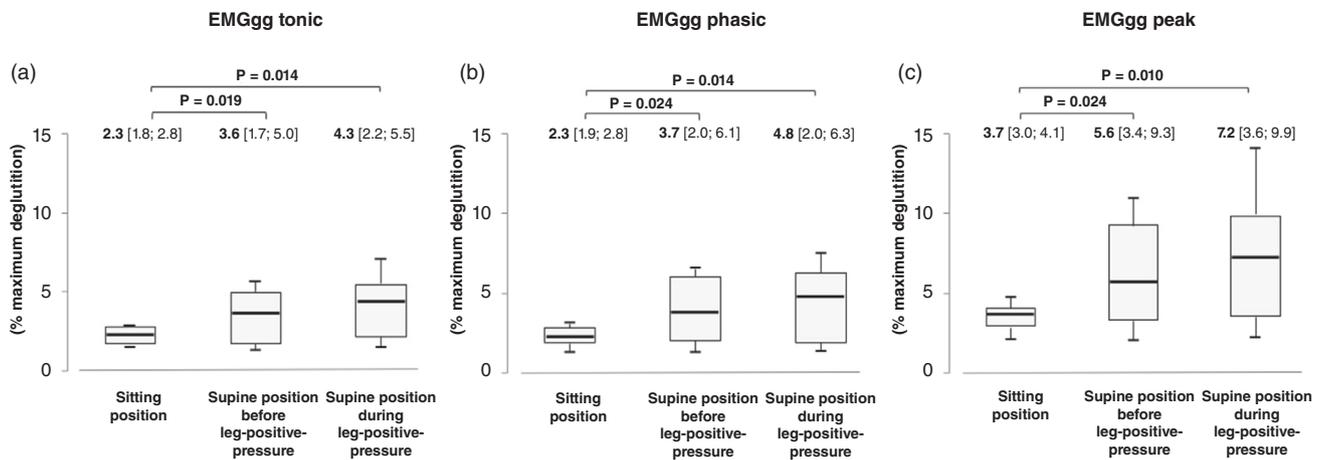
Contrary to what was expected, the preinspiratory cortical activity was observed less frequently in the supine position than in the sitting position in patients with moderate-to-severe OSA, whereas the



**FIGURE 2** The prevalence of pre-inspiratory potentials (PIP) under the following three study conditions: sitting position, supine position before application of positive pressure to the legs and supine position during application of positive pressure to the legs. Each point represents one patient. Type 1 is when PIP is present in the sitting position and it persists in the supine position (2 out of 17 patients). Type 2 is when PIP is present in the sitting position and it is no longer observed in the supine position (7 out of 17 patients). Type 3 is when PIP is absent in both the sitting position and the supine position (8 out of 17 patients)



**FIGURE 3** Examples of averaged electroencephalographic recordings centred on the start of inspiration looking for pre-inspiratory potentials (PIP) in three different patients (a–c) under the following three study conditions: the sitting position, the supine position before application of positive pressure to the legs and the supine position during application of positive pressure to the legs. (a) Patient presenting a PIP under the three conditions (Type 1). (b) Patient presenting a PIP only in the sitting position (Type 2). (c) Patient not presenting a PIP under any of the three conditions (Type 3)



**FIGURE 4** Box-and-whisker plots showing the genioglossus electromyographic activity expressed as a percentage of the maximum genioglossus activity during voluntary deglutition under the following three study conditions: the sitting position, the supine position before application of positive pressure to the legs and the supine position after application of positive pressure to the legs. (a) Tonic genioglossus activity. (b) Phasic genioglossus activity. (c) Peak genioglossus activity during inspiration

**TABLE 2** Ventilation during the three study conditions

	Sitting position	Supine position before positive pressure to the legs	Supine position during positive pressure to the legs	$P_1$	$P_2$
Ventilation					
$F_b$ ( $\text{min}^{-1}$ ) ( $n = 11$ )	14.2 (12.4, 15.5)	13.2 (12.4, 16.5)	13.2 (12.5, 15.9)	0.320	0.831
$T_I$ (s) ( $n = 11$ )	1.5 (1.5, 1.8)	1.6 (1.5, 1.7)	1.6 (1.5, 1.9)	1.000	0.598
$T_E$ (s) ( $n = 11$ )	2.7 (2.5, 3.5)	2.6 (2.4, 3.5)	2.6 (2.5, 3.1)	0.284	0.634
$V_T$ (ml) ( $n = 10$ )	536 (465, 560)	557 (484, 596)	551 (524, 600)	0.492	0.557
$V'$ ( $\text{l min}^{-1}$ ) ( $n = 10$ )	7.6 (7.0, 7.9)	7.7 (7.3, 7.9)	7.8 (7.2, 8.4)	0.492	0.769
$P_{\text{tcCO}_2}$ (mmHg) ( $n = 11$ )	43.0 (42.4, 44.2)	44.6 (43.5, 45.2)	44.5 (43, 46.8)	<b>0.004</b>	0.646
$S_{\text{pO}_2}$ (%) ( $n = 11$ )	95.8 (95.5, 96.6)	96.1 (95.6, 96.8)	96.8 (95.3, 97.3)	0.343	0.414

Data are expressed as median (25th, 75th centiles);  $P_1$ , comparison between sitting and supine positions before application of positive pressure to the legs;  $P_2$ , comparison between the supine position before and during application of positive pressure to the legs.  $F_b$ , breathing frequency;  $P_{\text{tcCO}_2}$ , transcutaneous carbon dioxide pressure;  $S_{\text{pO}_2}$ , pulse oxygen saturation;  $T_E$ , duration of expiration;  $T_I$ , duration of inspiration;  $V'$ , minute ventilation;  $V_T$ , tidal volume.

genioglossus activity increased when changing to the supine position in combination with increased  $P_{\text{tcCO}_2}$ .

#### 4.1 | Preinspiratory cortical activity in the sitting and supine positions

In the literature, PIPs are interpreted as reflecting a cortical contribution to the neural ventilatory drive, particularly when an inspiratory mechanical load has to be overcome (Raux et al., 2007). In the present study, a PIP was observed in the sitting position in 53% of patients with moderate-to-severe OSA, confirming our previous findings (Launois et al., 2015) that showed that 29% of patients with mild-to-moderate OSA and 58% of patients with severe OSA presented a PIP. There appears to be a correlation between the prevalence of PIP and the severity of OSA, which is probably related to the greater inspiratory load in patients with more severe OSA. The absence of PIPs in some sitting OSA patients could therefore reflect an

inspiratory load of insufficient magnitude to induce cortical activation. Indeed, in normal individuals, small inspiratory loads are known to induce PIPs less often than large inspiratory loads (Hudson, Niérat, Raux, & Similowski, 2018, Raux et al., 2007; Tremoureux, Raux, Jutand, & Similowski, 2010). Although it is generally considered that all OSA patients present anatomical abnormalities of the upper airways, it is also accepted that the extent of these abnormalities varies from one patient to another, which contributes, among other factors, to various OSA phenotypes (Horner, Grace, & Wellman, 2017). The results of the present study indicate that the preinspiratory activation of cortical resources in OSA patients also probably varies from one patient to another. Demonstration of preinspiratory cortical activity in OSA (as reflected by PIP or other types of EEG analysis) and the influence of posture on this cortical activity could therefore contribute to the definition of various patient phenotypes. By taking all of these elements into account, the cortical activation demonstrated in this study and in the previous study (Launois et al., 2015) in awake OSA

**TABLE 3** Genioglossus electromyographic activity (EMG<sub>gg</sub>) and ventilation in the sitting position in all patients and according to the absence or presence of pre-inspiratory potential (PIP) in the sitting position

	All patients (n = 11)	Patients without PIP while sitting (n = 6)	Patients with PIP while sitting (n = 5)	P
EMG <sub>gg</sub> while sitting*				
Tonic (% deglutition)	2.3 (1.8, 2.8)	1.9 (1.6, 2.3)	2.8 (2.5, 2.8)	0.240
Peak (% deglutition)	3.7 (3.0, 4.1)	3.6 (2.5, 3.7)	4.0 (3.6, 4.3)	0.352
Phasic (% deglutition)	2.3 (1.9, 2.8)	2.2 (1.5, 2.2)	2.8 (2.4, 3.0)	0.330
Ventilation while sitting				
F <sub>b</sub> (min <sup>-1</sup> )	14.2 (12.4, 15.5)	14.7 (13.5, 15.6)	12.4 (10.9, 14.7)	0.423
T <sub>I</sub> (s)	1.5 (1.5, 1.8)	1.6 (1.5, 1.6)	1.5 (1.5, 2)	0.925
T <sub>E</sub> (s)	2.7 (2.5, 3.5)	2.7 (2.5, 2.7)	3.4 (2.6, 3.5)	0.357
V <sub>T</sub> (ml)*	536 (465, 560)	428 (409, 488)	502 (433, 577)	0.609
V' (l min <sup>-1</sup> )*	7.6 (7.0, 7.9)	7.7 (7.6, 7.9)	6.4 (5.6, 7.8)	0.352
P <sub>tcCO<sub>2</sub></sub> (mmHg)	43 (42.4, 44.2)	43.1 (42.9, 46.8)	42.9 (41.9, 43.8)	0.537
S <sub>pO<sub>2</sub></sub> (%)	95.8 (95.5, 96.6)	96.1 (95.6, 96.6)	95.6 (94.1, 95.9)	0.423

Data are expressed as median (25th, 75th centiles); P, comparison between patients without and with PIP in the sitting position. \*Evaluated in 10 patients, 6 without and 4 with PIP in the sitting position. F<sub>b</sub>, breathing frequency; P<sub>tcCO<sub>2</sub></sub>, transcutaneous carbon dioxide pressure; S<sub>pO<sub>2</sub></sub>, pulse oxygen saturation; T<sub>E</sub>, duration of expiration; T<sub>I</sub>, duration of inspiration; V', minute ventilation; V<sub>T</sub>, tidal volume.

**TABLE 4** Changes in genioglossus electromyographic activity (EMG<sub>gg</sub>) and ventilation after changing from the sitting upright position to the lying supine position in patients without and with pre-inspiratory potentials (PIP) while sitting

	Patients without PIP while sitting (n = 6)	Patients with PIP while sitting (n = 5)	P
EMG <sub>gg</sub> changes*			
Tonic (% deglutition)	+0.9 (+0.4, +1.6)	+1.3 (0, +2.7)	0.792
Peak (% deglutition)	+1 (+0.7, +4.1)	+2 (0, +5.5)	0.855
Phasic (% deglutition)	+0.6 (+0.5, +2.3)	+1.4 (0, +3.4)	0.928
Ventilation modification			
F <sub>b</sub> (min <sup>-1</sup> )	+0.1 (-0.3, +1.2)	+1.1 (-0.4, +1.2)	1.000
T <sub>I</sub> (s)	+0.1 (0.0, +0.2)	-0.1 (-0.3, +0.2)	0.514
T <sub>E</sub> (s)	-0.2 (-0.3, 0)	0 (-0.2, 0.1)	0.712
V <sub>T</sub> (ml)*	-2 (-30, +39)	+40 (-24, +105)	0.762
V' (l min <sup>-1</sup> )*	+0.4 (+0.3, +0.7)	+1.0 (+0.1, +1.8)	0.762
P <sub>tcCO<sub>2</sub></sub> (mmHg)	+1.8 (+1.3, +1.9)	+1.6 (+0.7, +1.7)	0.714
S <sub>pO<sub>2</sub></sub> (%)	0 (-0.1, +0.2)	+0.4 (+0.1, +0.4)	0.762

Data are expressed as median (25th, 75th centiles); P, comparison between patients without and with PIP in sitting position. \*Evaluated in 10 patients, 6 without and 4 with PIP in the sitting position. EMG<sub>gg</sub> peak, maximum activity during inspiration; EMG<sub>gg</sub> phasic, mean activity during inspiration; EMG<sub>gg</sub> tonic, mean activity during expiration; F<sub>b</sub>, breathing frequency; P<sub>tcCO<sub>2</sub></sub>, transcutaneous carbon dioxide pressure; S<sub>pO<sub>2</sub></sub>, pulse oxygen saturation; T<sub>E</sub>, duration of expiration; T<sub>I</sub>, duration of inspiration; V', minute ventilation; V<sub>T</sub>, tidal volume.

patients in the sitting position may reflect amplification of ventilatory control in response to the anatomical abnormalities of the upper airway.

However, in contrast to what has been shown in healthy subjects (Launois et al., 2019) and with the hypothesis initially formulated, this cortical activation is no longer observed in most OSA patients in the supine position, which is nevertheless known to increase the load on the upper airway. Changing to the supine position in healthy subjects, and even more so in OSA patients, is associated with a reduction in the diameter of the upper airway (Yildirim et al., 1991) due to the effect of gravity on the soft tissues surrounding the upper airways, the

reduction in lung volume (Shore & Millman, 1984) and the fluid shift from the legs to the neck (White & Bradley, 2013). In the present study, displacement of 150 ml of fluid to the upper body was also observed when changing to the supine position, a phenomenon known to induce a significant increase in pharyngeal resistance in OSA patients (White et al., 2014). Finally, in line with data reported in the literature (Yoshizaki, Yoshida, Hayashi, & Fukuda, 1998), we observed an increase in P<sub>tcCO<sub>2</sub></sub> when changing to the supine position, which is also in favour of increased inspiratory load. The combination of increased inspiratory load and loss of preinspiratory cortical activity when changing to the supine position constitutes an apparent contradiction.

However, in the patients here, changing to the supine position was accompanied by a significant increase in tonic, phasic, and peak genioglossus EMG activity, which persisted for at least 30 min. This observation is compatible with increased inspiratory load and is consistent with published data (Douglas, Jan, Yildirim, Warren, & Drummond, 1993). The combination of increased genioglossus activity and a significant reduction in the prevalence of PIP in the supine position make it unlikely that the genioglossus muscle activation observed in the supine position in OSA patients has a cortical origin. Other factors are likely to modulate genioglossus activity in awake subjects, mainly variations of  $P_{aCO_2}$  (Onal, Lopata, & O'Connor, 1981a) and  $P_{aO_2}$  (Onal, Lopata, & O'Connor, 1981b) detected by central and peripheral chemoreceptors and the reflex response to pharyngeal negative pressure detected by upper airway mechanoreceptors (Horner, Innes, Murphy, & Guz, 1991). The increase in  $P_{tcCO_2}$  observed when changing to the supine position (Yoshizaki et al., 1998) or the reflex response to increased negative pressure in the pharynx (increased inspiratory effort in response to the increased load) could equally be responsible for the activation of the genioglossus observed in this study.

#### 4.2 | Significance of loss of cortical activity in the supine position

Regardless of the determinants, activation of the genioglossus when changing to the supine position could play a role in the concomitant loss of preinspiratory cortical activation in OSA patients. In accordance with this, we have previously shown in healthy subjects that moving to the supine position was not accompanied by genioglossus activation but by a transient PIP found in a proportion of subjects (Launois et al., 2019). Three hypotheses can be formulated. According to the first hypothesis, the increased genioglossus activity induced by the supine position would partially compensate for the increased load, which would therefore result in a decrease in the upper airway load. This compensation is only partial since an increase in  $P_{tcCO_2}$  was also observed, but it would be sufficient to induce a loss of cortical activity as a result of a reduction in the load (Hudson et al., 2018). In accordance with this, we can speculate that in healthy subjects the load increase that occurs when moving to the supine position is not high enough to activate genioglossus, thus allowing for preinspiratory cortical activation. According to the second hypothesis, activation of the genioglossus that occurs in the supine position might increase the respiratory afferents to the cortex, which could 'wrongly' interpret these afferents as compensation of the load, thereby leading to 'inappropriate' reduction in the drive resulting in the loss of the PIP. Conversely, the absence of genioglossus activation in healthy subjects would not result in an increase in afferents, thus inducing a cortical drive to compensate the load. We acknowledge that this reasoning is purely speculative, but it has the advantage of reconciling the various observations and is compatible with what is currently considered, in another field, to be a key mechanism of the pathophysiology of dyspnoea, i.e. the need to achieve equilibrium between the neural respiratory drive and the respiratory afferent input to the brain (Parshall et al., 2012). According to the third hypothesis,

the  $CO_2$  increase that occurs in OSA patients when moving to the supine position might induce an extra drive, obviating the need for preinspiratory cortical activation. Conversely, the lower increase in  $CO_2$  that occurs in healthy subjects would necessitate preinspiratory cortical activation in response to the load.

#### 4.3 | Limitations of the study

This study comprised a small number of patients and these results must therefore be confirmed in a larger patient sample, which would also allow for comparison of patients with various cortical activation profiles according to posture (Type 1, 2 and 3). It would also be interesting to confirm these data in a protocol randomising the order of the three conditions (sitting, lying down without leg-positive-pressure and lying down with leg-positive-pressure). We did not measure the pharyngeal resistance, which we acknowledge as a limitation to the study. We felt that it was important to avoid causing breathing discomfort through pharyngeal catheters, to limit the risk of having patients focusing on their breathing, which could have induced respiratory-related cortical activity, independent of mechanical loading. We also acknowledge that since, this study was only conducted in men, its results cannot be generalised to the whole OSA population.

#### 4.4 | Conclusions

The present study shows that changing from the upright sitting position to the lying supine position is associated with increased inspiratory load, a reduction in preinspiratory cortical activity and an increase in genioglossus activity in OSA patients, suggesting that the activation of the genioglossus muscle observed in the supine position in OSA patients does not have a cortical origin and it might sufficiently compensate for the increased load so as to induce loss of preinspiratory cortical activity.

#### COMPETING INTERESTS

None.

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#### AUTHOR CONTRIBUTIONS

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work or revising it critically for important intellectual content: C.L., T.S. and S.R. 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.

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