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Mandibular advancement reveals long-term suppression of breathing discomfort in patients with obstructive sleep apnea syndrome

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ABSTRACT

Obstructive sleep apnoea syndrome (OSAS) patients do not report breathing discomfort in spite of abnormal upper airway mechanics. We studied respiratory sensations in OSAS patients without and with mandibular advancement device (MAD).

Fifty-seven moderate to severe non obese OSAS patients were asked about breathing discomfort using visual analogue scales (VAS) in the sitting position (VAS-1), after lying down (VAS-2), then with MAD (VAS-3). Awake critical closing pressure (awake Pcrit) was measured in 15 patients without then with MAD.

None of the patients reported breathing discomfort when sitting but 19 patients (33%) did when lying (VAS-2: -20% or less). A feeling of "easier breathing" with MAD was observed and was more marked in patients reporting breathing discomfort when supine (VAS-3: +66.0% [49.0; 89.0]) than in those not doing so (VAS-3: +28.5% [1.0; 56.5], p = 0.007). MAD-induced change in awake Pcrit was correlated to VAS-3.

In conclusion, MAD revealed “latent dyspnea” related to the severity of upper airways mechanics abnormalities in OSAS patients.

1. Introduction

The obstructive sleep apnoea syndrome (OSAS) is characterized by recurrent episodes of upper airway obstruction that interrupt ventilation during sleep (Jordan et al., 2014). OSAS is associated with increased upper airway resistance and collapsibility during sleep (Gold et al., 2002) but also while awake (Lin et al., 2004; Verin et al., 2002) that constitute mechanical constraints to inspiration (inspiratory loading). Compensatory mechanisms such as increased baseline activity of upper airway dilators (Mezzanotte et al., 1992) and increased resting diaphragmatic activity (Steier et al., 2010), prevent upper airway collapse during wakefulness. Peripheral neurogenic changes leading to increased multiunit electromyographic signal may partly explain the increased baseline activity of the genioglossus while awake (Saboisky et al., 2007) however some of these compensatory mechanisms are cortical in nature (Series et al., 2009), including a respiratory-related premotor and motor cortical activity (Launois et al., 2015). Increased inspiratory load due to abnormal upper airways mechanics, increased neural ventilatory drive, and respiratory-related cortical activation are generally associated with breathing discomfort or dyspnea. This has been verified experimentally (Morawiec et al., 2015; Raux et al., 2007) and in various clinical contexts, like chronic obstructive pulmonary disease (COPD) (Jolley et al., 2015), idiopathic pulmonary fibrosis (Bonini and Fiorenzano, 2017), cystic fibrosis (Reilly et al., 2011),

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laryngeal obstruction (Walsted et al., 2018), or amyotrophic lateral sclerosis (Georges et al., 2016). Yet OSAS patients typically do not complain spontaneously from breathing discomfort at rest. This constitute a clinical abnormality even though it is plausible that OSAS-related inspiratory loading is smaller in magnitude than the loading associated with other respiratory disorders.

Repeated and sustained exposure to aversive respiratory stimuli can result in habituation, a process that blunts or suppress the corresponding respiratory sensations. This has been demonstrated experimentally (Subhan et al., 2003; von Leupoldt et al., 2011; Wan et al., 2009) and suspected clinically (Kikuchi et al., 1994; Reilly et al., 2016). Habituation could proceed, at least in part, from downregulation of the insular cortex (Stoeckel et al., 2015; von Leupoldt et al., 2009). It could also proceed from altered somatosensory processing of respiratory stimuli (Davenport et al., 2000; Fauroux et al., 2007), a phenomenon that can be present in OSAS patients (Donzel-Raynaud et al., 2009; Grippo et al., 2011). Habituation could therefore explain why OSAS patients do not complain from dyspnea. Of note, this is clinically relevant because dyspnea is a strong incentive to seek medical attention: its absence in OSAS patient could contribute to delay diagnosis and treatment.

Mandibular advancement devices (MAD) enlarge and stabilize the upper airway and induce reduction of upper airway resistance in awake OSAS patients (Gakwaya et al., 2014). They constitute a valid alternative to continuous positive airway pressure (CPAP), the reference treatment of OSAS (Bratton et al., 2015). From anecdotal clinical observations, we hypothesized that habituation to dyspnea would result in a sensation of "easier breathing" with MAD in OSAS patients not complaining from dyspnea during resting breathing. We therefore undertook the present study to: 1) verify this hypothesis by systematically studying respiratory sensations in OSAS patients in the sitting position, the supine position, and with MAD; 2) test the secondary hypothesis that the sensation of easier breathing induced by MAD relates with the severity of upper airway mechanical abnormalities.

2. Materials and methods

The study was conducted in accordance with the Declaration of Helsinki. The protocol was approved on October 22, 2014 by the ethics committee of the French national sleep medicine society (*Société Française de Recherche et Médecine du Sommeil)*. The patients received detailed information and provided their written consent to participate. OSAS patients participated in the two substudies. Non-OSAS patients (see below) participated only in study 1, to serve as controls.

2.1. Study 1: systematic description of the effects of MAD on breathing sensations

2.1.1. OSAS patients population

OSAS patients were selected among patients referred to the sleep medicine department of our institution and in whom the diagnosis was confirmed by a full-night polysomnography according to standard procedures; respiratory events were measured during a full-night polysomnography according to the international guidelines (Berry et al., 2012). On a period of 6 months, we consecutively studied all patients with a diagnosis of OSAS selected for MAD on the basis of standard criteria (namely: AHI ≥ 15/h, severe daytime sleepiness, intolerance to or refusal of continuous positive airway pressure (CPAP) therapy, at least eight healthy teeth per jaw, absence of periodontal disease or temporomandibular joint disease) (Marklund et al., 2012) (n = 57; Table 1). All patients were naïve of MAD treatment. Exclusion criteria were any underlying neurological, respiratory or cardiac disease possibly associated with dyspnoea or with altered central neural processes.

2.1.2. Non-OSAS patients population

Twelve patients referred to our department to investigate suspected hypersomnia (n = 7), non REM parasomnia (n = 2), restless legs syndrome (n = 1) or REM sleep behavior disorder (n = 1) were studied A full-night polysomnography confirmed that they were free of OSAS (Table 1).

2.1.3. Mandibular advancement devices

In the OSAS patients, two MAD were used, both consisting of custom-made bi-block titratable device (Narval™, ResMed, Saint-Priest, France; Somnodent™, SomnoMed Ltd., Sydney, Australia). The MAD was fitted and titrated at one or more visits (median number of titration visits was 2 [1–2]) by the dental sleep specialist. During each titration visit, patients were firstly asked about OSA symptoms. Then the MAD was titrated in the supine position, mm by mm, starting at 50% of the patient's maximum mandibular protrusion, by replacing the connecting rod by the immediately smaller one for the Narval™ and by advancing the screw by 1 mm for the Somnodent™. Between titration visits patients were encouraged to use their MAD several hours during several days at home. Mandibular advancement was of 67% [60; 71] at the first level of titration and 80% [75; 89] at the last level of titration ($p < 0.00001$) without any difference between Somnodent™ and Narval™ sub-groups (respectively 86% [68; 88] and 83% [76; 90] ($p = 0.656$)).

In the non-OSAS patients mandibular advancement was performed one mm at a time with the BluePro® titratable thermoplastic device (BlueSom, Orvault, France) (Gagnadoux et al., 2017), to 100% of the subject's maximum active protrusion (median: 6.5 mm [6.0–7.0]).

At each level of mandibular advancement, OSAS and non-OSAS patients were asked about MAD comfort.

The three devices used in this study cover only the maxillary and the mandible and nothing constraints tongue mobility. The respective volumes of the devices were assessed using a micro-computed tomography (micro-CT) (μCT100 Scanco Medical Brüttisellen Switzerland). They were of 7.3, 12.1 and 13.8 ml respectively for the Narval™, the Somnodent™ and the BluePro® MAD (see supplemental material).

2.1.4. Psychophysiological evaluation of breathing discomfort (see Fig. 1)

This evaluation was done at the last titration visit. Patients were firstly asked about OSA symptoms and MAD comfort. Then, the participants were asked to positively or negatively answer an open question about the presence of breathing discomfort at rest. Irrespective of the answer, they were then asked to rate their breathing discomfort on a non-graduated 100-mm visual analogue scale anchored by "no breathing discomfort" at the left end, and "intolerable breathing discomfort" at the right end ("baseline" scale ; results expressed in % full scale; VAS-1 dataset). The patients were told that in case of a negative answer to the open question, they could choose "no breathing discomfort" on the scale but that they could also choose otherwise, the two assessments being independent. VAS-1 was first applied with the patients seated in a comfortable chair, and then reapplied after they had assumed a fully supine position (VAS-1seated dataset and VAS-1supine dataset, respectively). A second non graduated 100-mm visual analogue scale was used to evaluate the changes in breathing comfort (in either direction) between the sitting and the supine positions ("transitional" scale; from "extreme deterioration" on the left end to "extreme improvement" on the right, with a middle marker to indicate "no change"; the results are expressed in percentage of the full scale, the latter being defined as the distance between the central landmark and either of the extremes, with a "+" sign for improvement and a "-" sign for deterioration; VAS-2dataset). With the patients remaining supine the MAD was fitted and mandibular advancement was titrated. The transitional scale was then used again to evaluate the changes in breathing comfort at the end of titration (VAS-3 data set).

Table 1
Characteristics of OSAS patients and MAD titration.

	OSAS N = 57	Non OSAS N = 12	p
Age (years)	57 [48 ; 64]	52 [39-59]	0.12
Gender (M/F)	40/17	7/5	0.42
BMI (kg/m^2)	28 [25 ; 30]	27 [24-30]	0.54
BMI ≥30 kg/m2 (% of patients)	32	25	0.35
Baseline AHI (/h)	25 [20 ; 40]	4 [2-8]	< 0.0001
AHI > 30/h (% of patients)	40	0	< 0.0001
Desaturation index ≥3% (/h)	20 [12 ; 30]	1 [0-3]	< 0.0001
% SpO_2 < 90% (%)	2 [0;4]	0 [0-0]	0.006
Epworth (/24)	11 [8 ; 13]	15 [9 ; 18]	0.08
Maximal mouth opening (mm)	43 [40 ; 50]	ND	
MA from end to end in maximum protrusion (mm)	5.0 [4.0 ; 7.0]	5.0 [5.0 ; 5.0]	0.55
Dental overjet (mm)	3.0 [2.0 ; 4.0]	2.0 [1.0 ; 3.0]	0.15
Maximum jaw protrusion (mm)	8.0 [7.0 ; 9.0]	7.0 [6.0 ; 7.0]	0.053
Dental overbite (mm)	3.0 [2.0 ; 4.0]	ND	
Midline deviation in maximum protrusion (nb)	7	0	0.34
Type of MAD Somnodent/Narval/ BluePro®	11/46/0	0/0/12	
MA (mm)	7.0 [6.0 ; 7.0]	6.5 [6.0 ; 7.0]	0.81
MA (% of maximal MA)	80 [75 ; 89]	100 [97 ; 100]	0.005
AHI with MAD at the 3-month follow-up(/h)	9.0 [5.0 ; 14.0]	ND	

Values are median and interquartile range, or when specified, % or number (nb). BMI, body mass index; AHI, apnoea-hypopnoea index; SpO2, transcutaneous oxygen saturation by pulse oximetry; MA, Mandibular Advancement ; ND, Not Done.

2.2. Study 2: relationship between MAD-induced changes in respiratory sensations and awake critical closing pressure (awake Pcrit)

This study was conducted in a subset of 15 of the 57 OSAS patients. The airway pressure/flow relationship was established to determine the awake critical closing pressure (awake Pcrit), defined as the negative pressure that induces closure of the upper airways (absence of air flow). Awake Pcrit was determined while awake according to the method validated by Su et al. (Su et al., 2008) and measured as described previously (Jacq et al., 2017; Patil et al., 2004; Schwartz et al., 1985; Su et al., 2009). The patients were installed in the supine position with the head resting in a neutral position on a flat pillow. The position of the head was maintained with a foam collar and patients were instructed to relax them and to breathe naturally exclusively through the nose. A nasal mask was applied and connected to a circuit allowing the generation of an increasingly negative pressure. Six negative pressure (-0.3, -0.9, -2.5, -6, -10, -13 cmH2O) were abruptly applied consecutively. Each negative pressure was applied at the end of a natural expiration for five to ten cycles, followed by a 60-second period of rest at the atmospheric pressure. An habituation measure was followed by two similar series of negative pressure for the awake Pcrit assessment. Airflow and pressure in the mask were measured by a pneumotachograph (Hans Rudolph Model 4700; Hans Rudolph, Inc., Kansas City, MO). At each level of negative pressure, the second and the third breath after applying the negative pressure were examined. Awake Pcrit was then estimated, as the nasal pressure at zero flow, by linear regression, plotting pressure against flow values, measured from cycles with apparent inspiratory flow limitation, at each imposed pressure phase (Patil et al., 2004).

2.3. Statistical analysis

Data are expressed as medians and interquartile ranges. Continuous variables were compared with Mann-Whitney's test and proportions were compared by Fisher's exact test. Regarding study 1, multivariate logistic regression was used to identify the factors associated with a variation of VAS-3 ≥ 20%. First, each potential factor was evaluated in a univariate comparison between patients meeting this criterion and patients not meeting it. Except when redundant with other factors, factors yielding p-values ≤ 0.20 were considered for a stepwise logistic regression, either forward or backward. All tests were two-tailed, and p-values < 0.05 were considered statistically significant. The Hosmer-Lemeshow chi-square test was used to assess the goodness-of-fit of the final model. Odds ratios (ORs) and their 95% confidence interval were computed for the significant factors. The area under the receiver operating characteristic curve (AUC) was used to evaluate the discriminative power of the models. The logistic regressions were performed using MatlabTM (Natick, MA, USA) version 9.1.0.441655 (R2016b) and its Statistics Toolbox version 10.0.

Regarding study 2, associations between VAS and awake Pcrit were evaluated using Spearman's correlation coefficient ().

3. Results

3.1. Study 1: systematic description of the effects of MAD on breathing sensations

None of the OSAS patients reported resting respiratory discomfort when sitting, either spontaneously or when prompted by an open "yes-no" question. The corresponding median VAS-1 rating was 3% of full scale [0.0; 10.0]). Supine VAS-1 scores were significantly higher than sitting scores (10.0% full scale [2.0; 23.0], p = 0.00007). The median VAS-2 was of 0.0 % [-27.0; 0.0] but 19 patients (33%) reported deteriorated breathing comfort defined by a -20% or more negative values on VAS-2 (Fig. 2). Mandibular advancement was generally associated with a subjective impression of "easier breathing", with VAS-3 scores showing a 30% improvement [0; 50] at the first level and 42% [6 ; 76] at the last level of titration (first versus last level, p = 0.007). This figure for the last level of titration was 66.0% [49.0; 89.0] in the 19 patients who reported a deterioration of breathing comfort when lying supine and 28.5% [1.0; 56.5] in the 38 others (p = 0.007) (Fig. 3). Note that there was no significant difference on VAS-3 score between patients using the Somnodent™ and patient using the Narval™ (respectively 50% [33; 57] and 34% [5; 75]; p = 0.785).

None of the non-OSAS patients reported respiratory discomfort at rest in either the sitting or supine positions and they consistently rated 0 on the VAS-1 scale, both sitting and supine. Their median VAS-3 score after mandibular advancement was 0% [-21.0; 9.0], with a majority of patients tending to consider their breathing to be less comfortable with mandibular advancement than without (in complete contrast with OSAS patients, who never reported worsening).

Univariate analysis identified several variables that differed

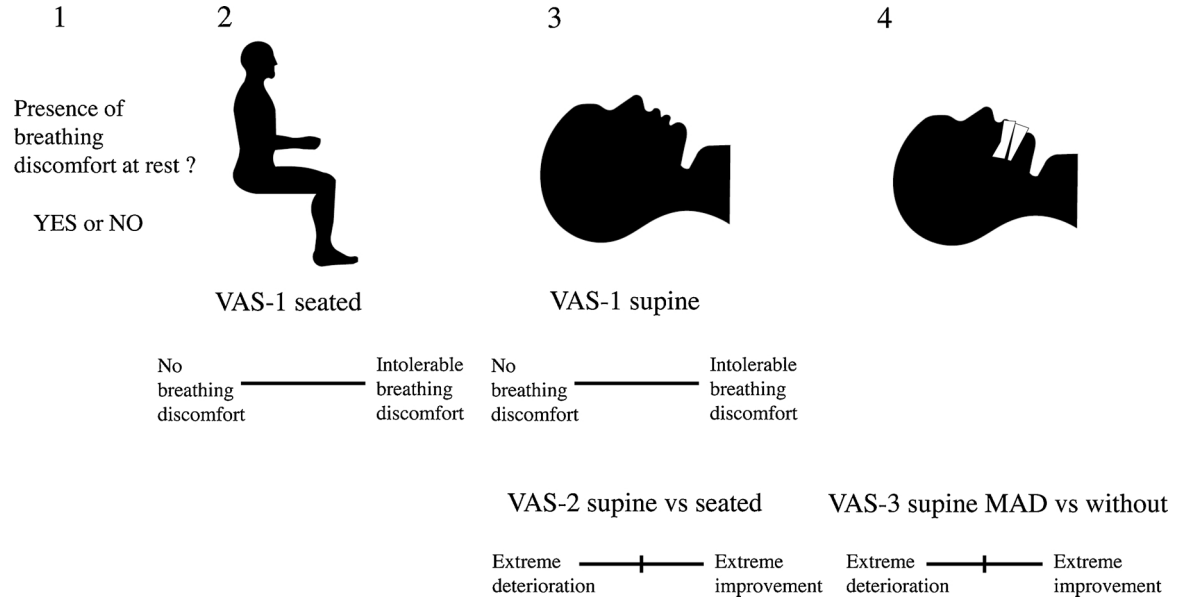

Fig. 1. Psychophysiological evaluation of breathing discomfort with visual analogic scales (VAS).
VAS-1 was on a non-graduated 100-mm visual analogue scale anchored by "no breathing discomfort" at the left end, and "intolerable breathing discomfort" at the right end. VAS-2 was a non-graduated 100-mm visual transitional analogue scale aiming at evaluating the changes in breathing comfort between the sitting and the supine positions: “extreme deterioration” on the left end (with a “- “sign), to “extreme improvement” on the right (with a “ + ” sign), with a middle marker to indicate "no change". VAS-3 was a similar non graduated 100-mm visual transitional analogue scale to evaluate the changes in breathing comfort between the supine position witout and then with the mandibular advancement device.

significantly between the patients who reported an improvement of 20% of full scale or more on VAS-3 (n = 37) and the patients who did not (n = 20) (Table 2). Backward and forward logistic regression led to same final logistic model with an AUC of 84.1%. Two factors were retained as independent predictors of MAD-related improvement in breathing comfort: maximal mouth opening (in mm) (odds ratio [OR] 1.24, 95% confidence interval [CI] 1.07–1.44; p = 0.0039; the wider the maximal mouth opening, the higher the probability of MAD-related

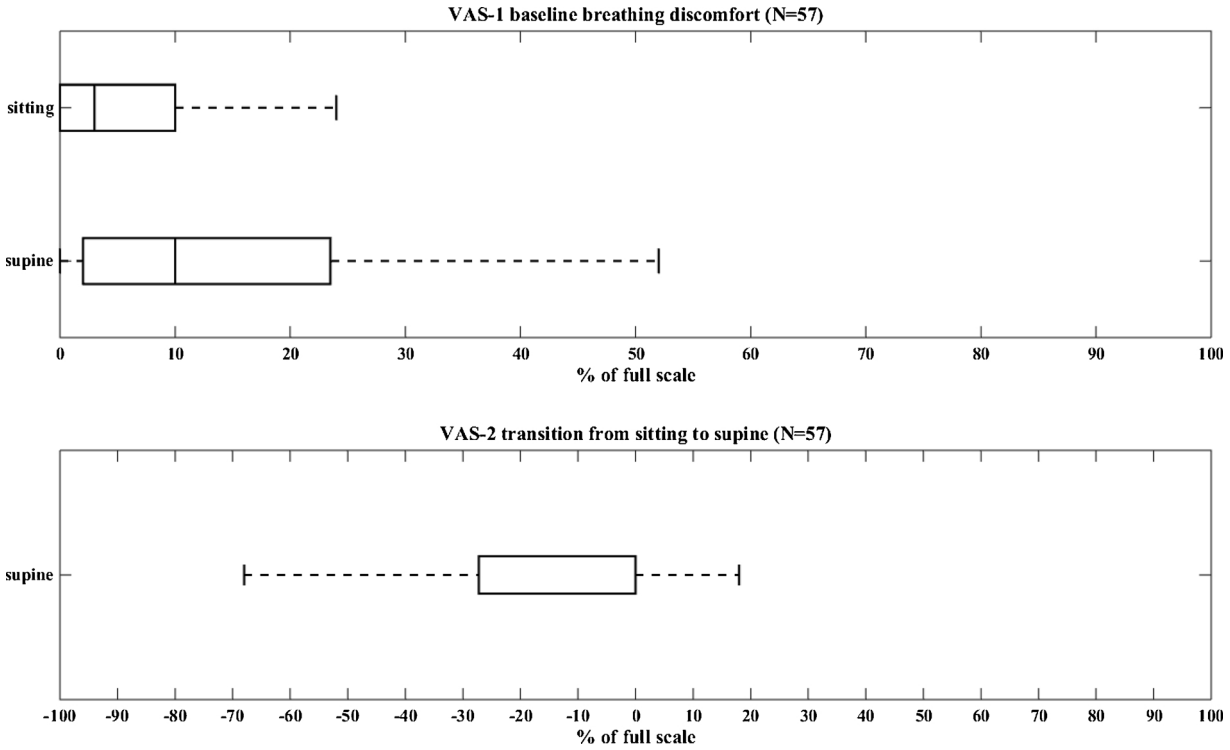

Fig. 2. Breathing discomfort at baseline evaluated in the sitting and supine positions.
VAS-1 was on a non-graduated 100-mm visual analogue scale anchored by "no breathing discomfort" at the left end, and "intolerable breathing discomfort" at the right end. VAS-2 was a non-graduated 100-mm visual transitional analogue scale aiming at evaluating the changes in breathing comfort between the sitting and the supine positions: “extreme deterioration” on the left end (with a “- “sign), to “extreme improvement” on the right (with a “ + ” sign), with a middle marker to indicate "no change".

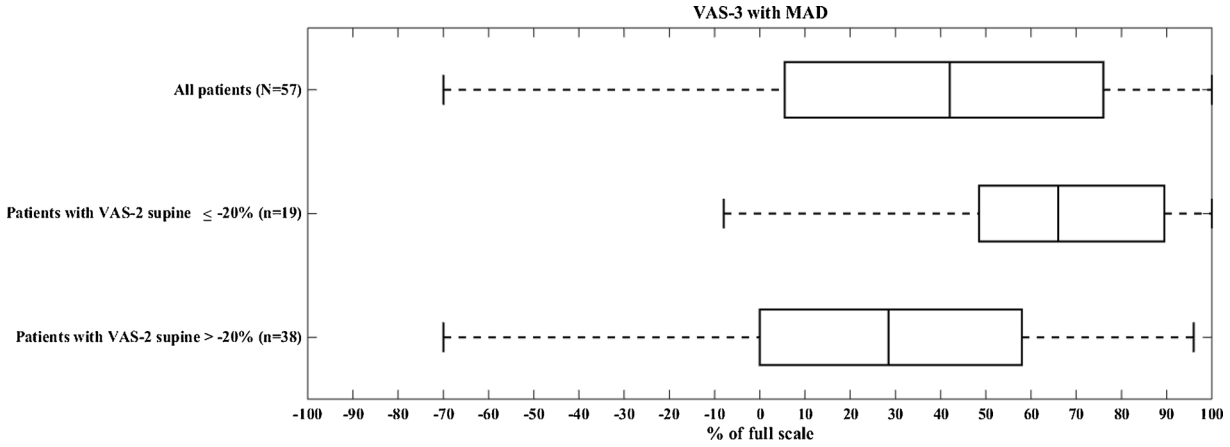

Fig. 3. Improvement of breathing comfort with the mandibular advancement device.
Improvement of breathing comfort with the mandibular advancement device in the supine position, evaluated by the transitional visual analogue scale (VAS-3) respectively, in all patients, in patients with deteriorated breathing comfort in the supine position (VAS-2 supine ≤ -20%, and in patients without deterioration of breathing comfort in the supine position (VAS-2 supine > -20%). VAS-2 was a non-graduated 100-mm visual transitional analogue scale aiming at evaluating the changes in breathing comfort between the sitting and the supine positions: “extreme deterioration” on the left end (with a “- “sign), to “extreme improvement” on the right (with a “ + ” sign), with a middle marker to indicate "no change". VAS-3 was a similar non graduated 100-mm visual transitional analogue scale to evaluate the changes in breathing comfort between the supine position without and then with the mandibular advancement device.

Table 2
Univariate predictors of changes in respiratory comfort with MAD (variation of VAS-3 ≥ 20%).

	Improvement (n = 37)	No change (n = 20)	p
BMI (kg/m^2)	28.0	25.5	1.05e-01
Maximal mouth opening (mm)	46.0	41.0	1.71e-03
Midline deviation in maximum protrusion (mm)	5.4	25.0	8.37e-02
Supine VAS-1 (mm)	14.0	5.0	6.25e-02
Supine VAS-2 (%)	−12.0	0.0	1.37e-01
Desaturation index ≥3% on MAD (/h)	9.4	4.2	1.60e-01
MAD discontinuation (% patients)	5.4	20.0	1.70e-01

BMI, body mass index; VAS, Visual Analogic Scale; MAD, Mandibular Advancement Device.

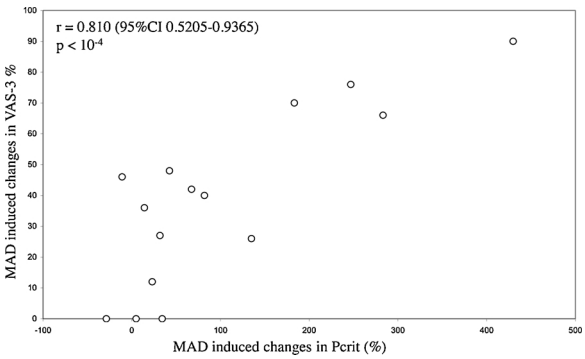

Fig. 4. Spearman’s correlation between the change in critical upper airway closing pressure (awake Pcrit, as percent of baseline) induced by the mandibular advancement device and the corresponding variation of respiratory sensations in the supine position (VAS-3).

improvement) and supine VAS-1 (OR 1.06, 95% CI 1.01–1.12; p = 0.025; the higher supine VAS-1, the higher the probability of improvement).

3.2. Study 2: relationship between MAD-induced changes in respiratory sensations and awake critical closing pressure (awake Pcrit)

In the 15 patients where awake Pcrit was measured, baseline awake Pcrit was of -15.8 [-18.0; -5.0] cm H_20 and awake Pcrit with MAD was of -16.6 [-23.8; -9.3] cm H_20 (difference -5.4 [-8.2 ; -2.6] in favour of a better stability of the upper airways, but not significant; p = 0.065). A significant correlation was however observed between the reduction in awake Pcrit induced by MAD (improved upper airway stability) and the corresponding improvement in breathing comfort evaluated with VAS-3 (Spearman’s r = 0.81, 95%CI 0.52−0.94, p < 10^{-4}) (Fig. 4).

4. Discussion

This study confirms the empirical notion that OSAS patients do not perceive significant breathing discomfort at rest in the sitting position, spontaneously of after being prompted (but breathing discomfort can appear in the supine posture). Yet OSAS patients not complaining from dyspnea described a feeling of breathing more easily in response to MAD, the intensity of which correlated with the degree of improvement of upper airway stability as assessed by the measurement of awake Pcrit. We submit that this supports the existence of habituation as an explanation to the lack of breathing discomfort at rest in OSAS patients.

4.1. MAD-associated breathing improvement and upper airway mechanical properties

Going from the sitting to the supine position deteriorates upper airway mechanical properties and patency (Ingman et al., 2004; Penzel et al., 2001). Conversely, MAD improves upper airway mechanical properties during sleep (Kato et al., 2000) and during wakefulness (Bosshard et al., 2011; Gakwaya et al., 2014). Our observations are fully in line with these data: in our OSAS patients, breathing comfort deteriorated when lying down and improved on MAD. This suggests a direct relationship between upper airway anatomy and mechanics and respiratory sensations. This is supported by the results of the multivariate analysis showing that maximal mouth opening, an anatomic factor, was an independent predictor of the MAD-related improvement in breathing comfort. This was confirmed by the correlation between the magnitude of the MAD-related decrease in awake Pcrit and the MAD-related improvement in breathing discomfort (Fig. 4). This is also independently supported by the absence of deterioration of breathing comfort when lying down and the absence of improvement on MAD in controls.

4.2. Blunted respiratory sensations in OSAS patients

Respiratory sensations arise from one or several stimuli, the transmission of these stimuli to the brain, and cognitive and affective processing of the corresponding sensory information. In OSAS patients, several types of neural lesions could interfere with this process and explained both blunted perception of inspiratory resistive loading (Tun et al., 2000) and our present results. These lesions include peripheral pharyngeal neuropathy (Sunnergren et al., 2011; Tsai et al., 2013) that could blunt the perception of respiratory abnormalities in the same way as it blunts the perception of mucosal airflow (Dematteis et al., 2005) or the perception of cold (Sunnergren et al., 2011). Central nervous system lesions could also interfere with the central processing of respiratory stimuli. Likewise diffuse gray matter loss has been described (Harper et al., 2012; Macey et al., 2002; Rosenzweig et al., 2015). In addition, abnormal brain responses to inspiratory loading have been described (Macey et al., 2006) and a recent study relying on magnetic resonance spectroscopy data has shown altered anterior insular levels of GABA and glutamate that may modify the brain processing of aversive respiratory stimuli (Macey et al., 2016). However, we believe that the immediate changes in respiratory sensations reported by our patients in response to MAD indicate that peripheral or central neural lesions cannot constitute the sole explanation of their suppressed respiratory sensations. This fast dynamics, consistent with the immediate MAD-induced improvement of upper airway mechanics advancement (Gakwaya et al., 2014; Sam et al., 2006; Verin et al., 2006), is compatible with a respiratory ungating mechanism or, in other words, with an habituation process. In normal subjects, subjective habituation of respiratory perception has been paralleled by objective habituation of the neural processing of respiratory stimuli (von Leupoldt et al., 2011). In this study, the magnitude of respiratory-related evoked potentials elicited by inspiratory occlusions was reduced between early and late experimental periods in healthy subjects (von Leupoldt et al., 2011). In this regard, it is interesting to note that several studies have evidenced abnormal respiratory-related evoked potentials in OSAS patients (Donzel-Raynaud et al., 2009; Grippo et al., 2011). These abnormalities could possibly be the results of habituation.

Another phenomenon that could contribute to explain our observations would be the activation of respiratory relief neural circuits by MAD. Such circuits have been described in inspiratory loading experiments conducted in normal subjects (Peiffer et al., 2008). In these experiments, dyspnea relief was associated not only with the deactivation of load-activated networks, but also with the activation of a specific network (Peiffer et al., 2008).

The magnitude of VAS-3 related breathing comfort improvement on MAD (the 42% observed improvement corresponds to 21 mm) was higher than the VAS-related dyspnoea improvement previously described in acute heart failure (Pang et al., 2017). In this study a 10.5 mm change in VAS in the upright position, and 14.5 mm in the supine position were considered as minimal clinically important differences within six hours after initiation of treatment. This indicates that breathing discomfort related to abnormal upper airway mechanics in our patients, although masked was clinically relevant. Of note similar amplitudes were observed in the supine position on VAS-1 (50% of patients reported a breathing discomfort higher than 10 mm) and VAS-2 (33% of patients reported a 20% i.e. 10 mm improvement in breathing discomfort).

4.3. Study limitations

We acknowledge that several elements can limit the generalisability of our results: the study population is of limited size and had to be determined empirically in the absence of previous data on respiratory sensations in OSAS; in addition, we focused on OSAS patients free of any associated respiratory or cardiac disorder, frequent conditions which are liable to interfere with respiratory sensations. Even questionable as they were trying a new treatment for the first time, patients had probably none expectation about breathing improvement while not complaining from any breathing difficulties. Moreover at each visit they were asked firstly about their symptoms and MAD comfort and their attention was not focussed only on breathing comfort at any time. Eighteen patients (32%) were obese that would be factor of deteriorated breathing comfort while lying, however the majority (13 patients) had a BMI $< 35\,kg/m^2$ which represents mild obesity. We also acknowledge that our control group was not matched to the index group, that we did not randomly compare several levels of mandibular advancement, and that we did not use a placebo control procedure with which to compare the effects of MAD. However there was no significant difference between patients and controls in terms of BMI and age. We believe that the complete divergence between the behaviour of our OSAS and control patients (even without MAD), as well as the significant relationship between MAD-induced breathing comfort improvement and awake Pcrit, are strong arguments against a placebo effect of MAD. In addition, in OSAS patients there was a significant improvement in breathing comfort from the first to the last level of titration, which is in favour of a "dose-effect" in MAD-induced breathing comfort. Of note, a similar dose-effect was previously shown for MAD-induced pharyngeal stability (Kato et al., 2000), which is in line with the correlation observed in our study between awake Pcrit and magnitude of mandibular advancement. We are therefore convinced that our observations are correct.

Though we used two different custom-made devices in the OSAS group, and the Somnodent™ was slightly larger than the Narval™. However, we are confident that our results were not volume dependent since there was no difference between both devices in terms of mandibular advancement and related breathing comfort. Note that both devices have previously demonstrated similar efficacy and tolerability in the treatment of OSAS (Milano et al., 2013; Vecchierini et al., 2016; Verburg et al., 2018). In controls, we used a titratable thermoplastic device for regulatory reasons (in France custom-made devices are not considered in non OSAS patients). The BluePro® is as retentive (Braem, 2015) has a similar volume and is well-tolerated in terms of mouth comfort as the Somnodent™ (Gagnadoux et al., 2017). The three devices used in this study cover only the maxillary and the mandible (nothing constraints tongue mobility) which limits intra oral volume and volume-related breathing sensations.

Perhaps more importantly from a physiological point of view, we did not quantify the respiratory neural drive to breathe in our patients. Future studies will be necessary to characterize this aspect of the phenomenon that we describe. In particular, it will be interesting to characterize putative relationships between the unmasking of respiratory discomfort by MAD and OSAS-related activation of cortical respiratory networks (Launois et al., 2015). It would also be interesting to conduct functional imaging studies aimed at determining whether MAD deactivates abnormally activated networks (as in studies of MAD to relieve experimental inspiratory loading, (Hashimoto et al., 2006)) or activate the relief network (Peiffer et al., 2008).

4.4. Possible implications

An emerging body of evidence suggests that dyspnea can interfere with various types of cognitive tasks (Allard et al., 2017; Nierat et al., 2016; Vinckier et al., 2018). The underlying mechanisms are not yet clear, but both attentional effects and competition for cortical resources have been hypothesized to play a role. In OSAS patients, suppressed respiratory sensations are by nature unlikely to interfere with cognition through an attentional effect. However, our present data are compatible with the silent respiratory-related cortical activation shown before (Sharman et al., 2014): it would be interesting to test the hypothesis that a respiratory-related cortical activation could play a role in OSAS-related alterations of cognitive performances. A similar mechanism has been evidenced in a dyspnea-free patient suffering from congenital

central alveolar hypoventilation and relying on cortical activation to maintain breathing during wakefulness (Sharman et al., 2014). From a clinical point of view, the absence of breathing discomfort deprives OSAS patients from a strong incentive to seek medical attention. It would be interesting to test the screening value of actively looking for breathing discomfort induced by the supine position (and possibly for breathing improvement by active mandibular advancement) in patients suspect of having OSAS on clinical grounds. OSA phenotypic traits may help to personalize the OSA treatment (Messineo et al., 2017), however assessing phenotype is not easily feasible in routine practice, as it requires Pcrit measurement during sleep (Wellman et al., 1985). In our study, the VAS-3 scale was correlated to awake Pcrit, and could be proposed as a simple tool to assess the phenotype of OSA in routine practice.

Author contributions statement

VA, TS and JMC contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript. OJ, SS, IA, PG, IR, JBK and CMP contributed substantially to the data analysis and interpretation, and the writing of the manuscript.

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Conflict of interest

V. ATTALI reports personal fees from Resmed, personal fees from Nyxoah, outside the submitted work; I. Arnulf reports personal fees from UCB Pharma, personal fees from Novartis, outside the submitted work; C. Morélot-Panzini reports personal fees from Astra-Zeneca, personal fees from Chiesi, personal fees from Boehringer Ingelheim, personal fees from Novartis, personal fees from Philips, personal fees from ADEP, personal fees from SOS oxygene, outside the submitted work; T. Similowski reports personal fees from AstraZeneca, personal fees from Boerhinger Ingelheim France, personal fees from GSK, personal fees and non-financial support from NOVARTIS, personal fees from Lungpacer Inc., personal fees from TEVA, personal fees from Chiesi, personal fees from Pierre Fabre, personal fees from Invacare, outside the submitted work; In addition, Dr. SIMILOWSKI has a patent about a "brain-ventilator interface to improve the detection of dyspnea" licensed to Air Liquide Medical Systems and MyBrainTechnology. JM. Collet, P. Goudot, I. Rivals, O. Jacq, JB Kerbrat and S. Souchet have nothing to disclose.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.resp.2019.03.005.

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