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# Evening sock marks as an adjunct to the clinical prediction of obstructive sleep apnea

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## Abstract

**Study objectives** Fluid overload shifting from the legs to the upper airway during sleep promotes obstructive sleep apnea (OSA) and interventions targeting fluid attenuate OSA. Fluid shift has been previously measured by bioelectrical impedance, a complex and time-consuming technique not applicable in the daily clinical settings. The aim of this study is to evaluate the presence of clinically detectable fluid overload and shift and its association with OSA.

**Methods** Patients undergoing sleep study for suspected OSA were asked to report the presence of 11 signs/symptoms associated to excessive accumulation of fluid in different parts of the body at different times of the day.

**Results** Among 392 patients (male: 53%, median [interquartile range] age: 56 years [1], body mass index, BMI: 29 kg/m<sup>2</sup> [2]) included in the study, 135 (34%) had moderate-to-severe OSA (apnea hypopnea index, AHI  $\geq$  15). Daytime fluid accumulation and nocturnal fluid shift, clinically detectable by patient-reported “evening sock marks,” “heavy legs during the day,” and “morning stuffed nose,” were prevalent in the entire population (46%, 43%, and 33%, respectively). In multivariate analysis, evening sock marks was an independent correlate of having an AHI  $\geq$  15, together with male sex, older age, and self-reported snoring and apneas.

**Conclusions** Clinically detectable fluid overload and shift are prevalent in patients addressed for suspected OSA, and evening sock marks, a marker for leg swelling, is an independent correlate of moderate-to-severe OSA. This sign might contribute to OSA diagnosis and identification of patients likely to be treated by interventions targeting fluid overload and shift.

**Keywords** Obstructive sleep apnea · Diagnosis · Fluid shift · Ventilatory polygraphy · Polysomnography

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## Introduction

Obstructive sleep apnea (OSA) is a common condition, characterized by an increased risk of motor vehicle accidents due to sleepiness and of cardiovascular and cerebrovascular diseases [3]. Although OSA is adequately treated by continuous positive airway pressure (CPAP) and oral appliances, these treatments are poorly tolerated by some patients.

The pathophysiology of OSA is multifactorial. Attention has been recently focused on detecting different OSA phenotypes, which would permit individualized treatment targeting a specific factor [4, 5] as alternative to CPAP. In the last decade, the role of fluid overload and its overnight shift from the legs to the upper airway in

OSA pathogenesis has been established. During the day, gravity causes fluid to accumulate in the legs proportionally to the time spent quietly standing or sitting, and upon lying down at night, fluid redistributes to the upper part of the body [6]. Some of the fluid shifting rostrally may reach the neck and accumulate in the internal jugular veins that lie lateral to the pharynx and in the soft tissues surrounding the pharynx, thereby predisposing to OSA [7]. The amount of overnight fluid shifting was shown to correlate with OSA severity [7].

Interventions counteracting fluid overload and daytime fluid accumulation in the legs consistently attenuate nocturnal fluid shift and OSA severity: the greater the reduction in fluid shift, the greater the reduction in the apnea-hypopnea index (AHI). Different interventions targeting fluid, such as diuretics, ultrafiltration/dialysis, physical activity, compression stockings, and salt restriction, have been shown to have some efficacy in attenuating OSA, supporting the prevention of fluid shift as an alternative OSA treatment [8]. Despite this evidence, up to now, these promising ways of treating OSA have rarely been used in clinical practice because of the difficulty in identifying patients with relevant fluid overload and shift and hence who are likely to benefit from a targeting fluid treatment. Currently, accurate methodologies for measuring body fluid volumes are based on radio-isotopic dilution, which represents the gold standard despite its invasiveness [9], or on bioelectrical impedance [10], which is non-invasive. Therefore, bioelectrical impedance has been used to measure leg fluid volume in all previous studies on fluid shift in sleep apnea [2]. However, this technique requires measurements to be performed immediately before and immediately after sleep so as to calculate the amount of fluid shifting from the legs to the upper part of the body during night. This requires the patient to spend the night at the sleep clinic. Moreover, this technique needs to be performed with extreme accuracy, which is time consuming [6], and makes its routine application difficult. Consequently, techniques capable of easily detecting relevant fluid overload and shift are needed to identify OSA patients suitable for treatment with interventions targeting fluid. In this perspective, considering that excessive accumulation of fluid causes an increase in volume and that the distribution of the fluid depends on the body position, we identified 11 signs/symptoms possibly associated to fluid accumulation in the legs during and at the end of the day, and in the upper part of the body (lungs, pharynx, nose, face and arms) during and at the end of the night spent lying down. The aim of this study was to assess the frequency of these signs/symptoms associated to excess of fluid and fluid shift in a population of patients addressed for suspected sleep apnea and to test the predictive value of these signs/symptoms for moderate-to-severe OSA.

## Methods

### Patients

Patients addressed to our sleep clinic for suspected sleep apnea from May 2015 to May 2016 were prospectively considered for participation in this study. Patients with central sleep apnea, defined as  $\geq 50\%$  apneas and hypopneas central in nature, with severe neurological diseases such as multiple sclerosis, advanced Parkinson disease, and recent (less than 3 months) stroke; who did not fill in the sleep questionnaire; or had already been treated for OSA, were excluded from the study. The population was then divided into patients with moderate-to-severe OSA (apnea-hypopnea index, AHI  $\geq 15$ ) and patients with mild or no OSA (AHI  $< 15$ ). We chose this cut-off for the AHI because it is the one used to decide whether to treat OSA or not. The study conformed to the standards set by the Declaration of Helsinki and received ethical clearance from the appropriate authority. All patients signed informed consent for the collection of the results of their routine clinical interview, questionnaires, and sleep tests in a database, and for their use for research purposes.

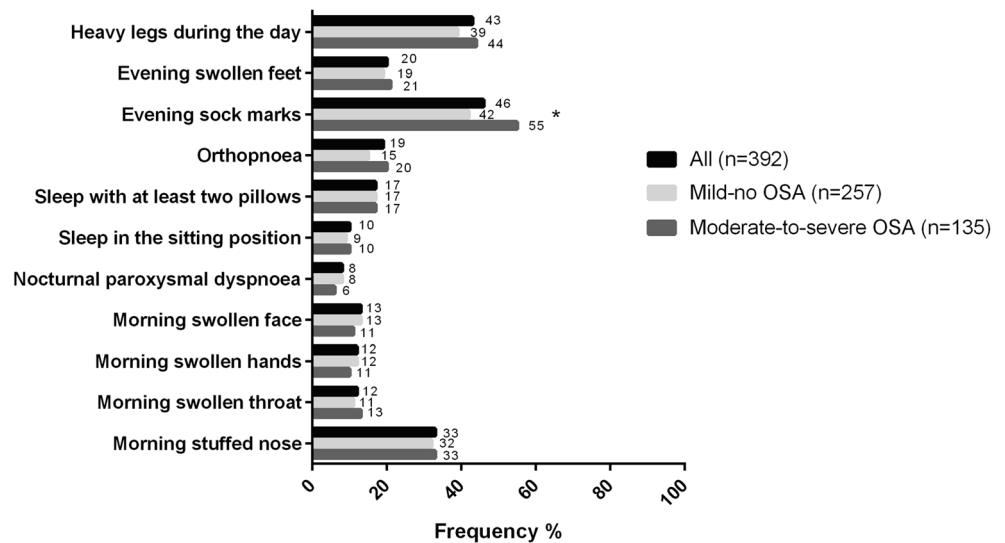
### Clinical sleep evaluation

Demographic data such as age, sex, weight, and height were collected by technicians prior to the sleep study. As routinely conducted in our sleep clinic, before undergoing the sleep study, each patient filled in a questionnaire with specific questions about sleep time habits, presence of insomnia and sleep fragmentation, presence of symptoms classically associated with OSA, such as snoring, breathing pauses reported by the bed-partner, nycturia ( $\geq 2$  miction/night), morning headache, non-restoring sleep, memory, and concentration difficulties. Life style information, such as hours per day spent sitting and hours per week spent practicing sport, comorbidities, and current treatments were also collected. Daytime sleepiness was assessed using the Epworth Sleepiness Scale (ESS) and defined as abnormal if  $> 10$ .

### Signs/symptoms of fluid overload and shift

Considering that excessive accumulation of fluid causes increase in volume and that the distribution of the fluid depends on the body position, we pragmatically identified 11 signs/symptoms possibly associated to excessive fluid accumulation in different parts of the body at different times of the day: in the lower body during and at the end of the day (heavy legs, swollen feet and sock marks), in the upper body during the night (orthopnea, sleep with at least two pillows, sleep sitting and nocturnal paroxysmal dyspnea), and in the morning (swollen face, hands, throat, and obstructed nose) (Fig. 1).

**Fig. 1** Frequency of reported signs/symptoms associated with fluid overload and shift among all the patients included in the study and among the two groups separately (mild-no OSA and moderate-to-severe OSA). \* $p < 0.01$  for comparison between mild-no and moderate-to-severe OSA



Patients were asked to report the presence (always or often) or absence (never or sometimes) of these signs/symptoms.

**Sleep studies**

Clinical evaluation was performed by a medical doctor who, according to the pre-test risk of sleep apnea and considering comorbidities, decided to prescribe a ventilatory polygraphy (PV) or a polysomnography (PSG). The sleep study was performed in our sleep clinic using a Graef HD PSG/EEG, Compumedics, Australia. The PSG recording included 3-lead (Fp1/A2, C3/A2, O1/A2) electroencephalogram, right and left electro-oculograms, electromyogram (EMG) of the levator menti muscle for sleep stage assessment, and right and left tibialis anterior EMG for periodic leg movement assessment. Both PSG and PV recordings included nasal pressure and oral thermistor for oro-nasal flow assessment, thoracic, and abdominal respiratory inductance plethysmography belts for assessment of respiratory efforts, pulse-oximetry, and 1-lead electrocardiogram. Sleep stages [11], arousals [12], periodic leg movements, and respiratory events [13] were scored by visual inspection according to the standard criteria. Based on the international criteria, we defined (1) mild or no OSA as  $AHI < 15/h$  and (2) moderate-to-severe OSA as  $AHI \geq 15/h$ .

**Statistical analysis**

Normality was tested with Shapiro-Wilk’s test. Many variables being non-normal, data were expressed in terms of median and interquartile range. Continuous variables were compared between moderate-to-severe OSA and mild or no OSA groups using Mann-Whitney’s nonparametric test. Nominal variables were compared between the two groups using Fisher’s exact test. To identify factors associated with the

presence of moderate-to-severe OSA, multivariate logistic regression was used. Variables with  $p < 0.2$  in the univariate analysis were considered as candidate factors. Missing data (4.3%) was imputed with the nearest neighbor method. The final models were determined using a forward or backward stepwise logistic regression. The Hosmer–Lemeshow chi-square test [14] was used to check the goodness-of-fit of the final model. All tests were two-tailed and  $p$  values  $< 0.05$  were considered statistically significant. Odds ratios (ORs) and their 95% confidence intervals were calculated for significant factors. The area under the receiver operating characteristic (ROC) curve [15] was used to evaluate the ability of the models to discriminate between moderate-to-severe OSA patients and mild or no OSA patients. Analyses were performed using Matlab™ (Natick, MA, USA) 9.3.0.713579 (R2017b) and its Statistics and Machine Learning Toolbox Version 11.2.

**Results**

**Population**

A total of 430 patients addressed for suspected sleep apnea were consecutively considered for study participation. Sixteen of them presented a prevalent central sleep apnea, six had severe neurological diseases, seven did not complete the questionnaire or refused to take part in the study, and seven were already in treatment for sleep apnea. Among a total of 392 patients analyzed, 216 underwent a PSG and 176 a PV. A total of 257 patients had an  $AHI < 15/h$  and 135 had an  $AHI \geq 15/h$ . Their demographic and clinical characteristics are shown in Table 1.

The moderate-to-severe OSA patients were older, mainly men with a higher BMI compared to mild or no OSA patients. There was no difference in comorbidities prevalence between

**Table 1** Demographic characteristics, comorbidities, and treatments

	All	Mild and no OSA	Moderate-to-severe OSA	<i>p</i>
	<i>n</i> = 392	<i>n</i> = 257	<i>n</i> = 135	
Age, years	56 [16]	54 [16]	58 [17]	2.3 10 <sup>-4</sup>
Male, %	53	45	70	2.6 10 <sup>-6</sup>
Body mass index, kg/m <sup>2</sup>	29 [2]	28 [2]	31 [11]	4.3 10 <sup>-4</sup>
Smokers, %	46	43	50	2.3 10 <sup>-1</sup>
Comorbidities:				
Hypertension, %	42	39	46	1.9 10 <sup>-1</sup>
Diabetes, %	21	18	26	6.2 10 <sup>-2</sup>
Dyslipidaemia, %	21	21	21	8.9 10 <sup>-1</sup>
Ischaemic cardiomyopathy, %	7	6	11	9.5 10 <sup>-2</sup>
Arrhythmia, %	22	23	19	5.1 10 <sup>-1</sup>
Cerebrovascular diseases, %	18	20	16	3.3 10 <sup>-1</sup>
Heart failure, %	4	4	6	4.0 10 <sup>-1</sup>
Depression, %	22	23	21	6.1 10 <sup>-1</sup>
Venous insufficiency %	24	24	24	9.0 10 <sup>-1</sup>
ORL surgery, %	36	32	42	5.7 10 <sup>-2</sup>
Chronic sinusitis or rhinitis, %	19	21	15	2.2 10 <sup>-1</sup>
Renal failure, %	4	4	6	4.3 10 <sup>-1</sup>
Treatments:				
ACE inhibitors, %	11	8	19	3.8 10 <sup>-3</sup>
ARBs, %	21	18	26	9.3 10 <sup>-2</sup>
β-blockers, %	14	9	23	1.1 10 <sup>-3</sup>
Calcium antagonists, %	18	15	24	3.8 10 <sup>-2</sup>
Diuretics, %	16	14	20	2.2 10 <sup>-1</sup>
Statins/fibrates, %	22	17	30	5.8 10 <sup>-3</sup>
Oral antidiabetics or insulin, %	14	11	19	2.3 10 <sup>-3</sup>
Platelets aggregation inhibitors, %	16	12	23	1.2 10 <sup>-2</sup>
Anticoagulants, %	6	5	8	3.2 10 <sup>-1</sup>
Antiarrhythmics, %	4	3	4	7.6 10 <sup>-1</sup>

Data are expressed in terms of percentage or of median [interquartile range]

OSA obstructive sleep apnea, AHI apnea-hypopnea index, ESS Epworth sleepiness scale, ORL otorhinolaryngological, ACE angiotensin converting enzyme, ARB angiotensin receptor blockers

the two groups. However, the use of angiotensin-converting-enzyme inhibitors, beta-blockers, calcium antagonists, statins/fibrates, and platelet aggregation inhibitors was higher in the moderate-to-severe group compared to the other one. Regarding sleep symptoms, snoring, reported apneas, and memory and attention difficulties were more frequent in the moderate-to-severe OSA than in the mild or no OSA group (Table 2).

### Signs/symptoms of fluid overload and shift

When all patients were considered, the most prevalent reported signs/symptoms associated with excessive accumulation of fluid were “evening sock marks,” “heavy legs during the day,” and “morning stuffed nose” (Fig. 1). When patients with moderate-to-severe OSA were compared to patients with mild

or no OSA, only the prevalence of evening sock marks was different with a high prevalence in more severe OSA ( $p = 0.01$ ). As shown in Table 3, multivariate forward or backward logistic regression analysis identified older age, male sex, greater BMI, snoring, reported apneas, and evening sock marks as correlates of having moderate-to-severe OSA (these variables have no missing values), the corresponding model having an AUC of 77.2%.

### Discussion

The findings of this study are twofold: (1) reported clinical signs of daytime fluid accumulation and of nocturnal rostral fluid shift are prevalent in patients referred for suspected sleep apnea; (2) having evening sock marks is significantly more

**Table 2** Sleep disorders symptoms and life style information

	All <i>n</i> = 392	Mild and no OSA <i>n</i> = 257	Moderate-to-severe OSA <i>n</i> = 135	<i>p</i>
AHI	11 [18]	4 [9]	29 [1]	$1.9 \cdot 10^{-2}$
ESS	9 [10]	9 [10]	8 [10]	$2.3 \cdot 10^{-1}$
Sleep disorders symptoms evaluation:				
Difficulties falling asleep, %	36	39	28	$3.5 \cdot 10^{-2}$
Nocturnal waking, %	60	58	61	$5.9 \cdot 10^{-1}$
Snoring, %	78	69	90	$3.1 \cdot 10^{-6}$
Reported apneas, %	39	29	45	$1.7 \cdot 10^{-3}$
Nycturia, %	45	44	46	$6.7 \cdot 10^{-1}$
Morning headache, %	31	33	26	$2.3 \cdot 10^{-1}$
Non-relieving sleep, %	39	35	38	$6.6 \cdot 10^{-1}$
Memory and concentration difficulties, %	42	44	31	$1.6 \cdot 10^{-2}$
Life style information:				
≥ 8 h a day spent sitting, %	25	25	26	$8.1 \cdot 10^{-1}$
< 3 times/week practicing sport, %	58	56	64	$1.6 \cdot 10^{-1}$
> 10 years sedentary, %	23	21	27	$2.1 \cdot 10^{-1}$

Data are expressed in terms of percentage or of median [interquartile range]

OSA obstructive sleep apnea, AHI apnea-hypopnea index, ESS Epworth sleepiness scale

<sup>a</sup> The fluid questionnaire is shown in Fig. 1

prevalent in moderate-to-severe OSA compared to mild or no OSA group, and it is an independent correlate of having moderate-to-severe OSA.

Almost half of the patients addressed to the sleep clinic for suspected OSA had heavy legs and evening sock marks, and one third had morning stuffed nose. These results suggest

**Table 3** Multivariate analysis: correlates of having AHI ≥ 15/h

Multivariate analysis	Odds ratio	95% IC min-max	<i>p</i>
Age	1.05	1.03–1.07	$2.5 \cdot 10^{-7}$
Sex (female)	0.26	0.15–0.43	$3.4 \cdot 10^{-6}$
Body mass index	1.01	1.05–1.13	$7.8 \cdot 10^{-6}$
Snoring	2.66	1.35–5.26	$4.7 \cdot 10^{-3}$
Reported apneas	1.7	1.03–2.81	$3.7 \cdot 10^{-2}$
Evening sock marks	1.68	1.04–2.71	$3.3 \cdot 10^{-2}$

excess fluid in the legs at the end of the day and in the upper airway at the end of the night, which is consistent with relevant fluid overload and overnight fluid shift. As expected, patients with moderate-to-severe OSA presented a higher prevalence of snoring, apnea reported by the bed partner, and memory and concentration difficulties compared to mild or no OSA. We showed for the first time that having sock marks in the evening, a sign of leg fluid accumulation predisposing to overnight fluid shift, is more prevalent in moderate-to-severe OSA compared to mild or no OSA, and that it is an independent correlate of having moderate-to-severe OSA, besides the already known OSA correlate (including older age, male gender, higher BMI, snoring, and reported apnea).

It has been previously shown that fluid overload and shift are OSA risk factors. Indeed, the prevalence of OSA is much higher in patients with fluid-overload conditions, such as heart failure, renal failure, resistant hypertension, and sedentary behaviour, than in the general population [19]. In these patients,

fluid accumulated in the legs during the day redistributes rostrally upon lying down at night, owing to gravity. Some of this fluid may accumulate in the neck, leading to a narrowing of the upper airway, increasing its resistance and collapsibility and predisposing to OSA [7, 17, 19, 20]. Consistently, strong relationships have been found between the overnight rostral fluid shift and OSA severity: the greater the fluid shift, the greater the AHI [16, 19, 21, 22]. Finally, to prove the causal relationship between fluid shift and OSA, interventions targeting fluid overload and shift were effective in attenuating OSA severity [1, 18, 23–26]. This study confirms the role of fluid shift in OSA. It does so from a clinical perspective and opens new perspectives for assessing patients addressed for suspected OSA.

It is important to underline that 39% of patients with mild or no OSA reported the presence of evening sock marks, indicating that the presence of clinically relevant fluid overload may determine OSA only in certain susceptible subjects. Indeed, OSA etiology has been attributed to different specific anatomical and physiological factors [4, 27], fluid overload and shift being one of them. The association of various factors each one with different relevance in a given patient defines a specific OSA phenotype. In this view, we can imagine that, in a patient with a very stable upper airway, the occurrence of an important fluid shift would not be enough to determine upper airway obstruction during sleep. Conversely, we can imagine a patient with unstable upper airway for one or more other OSA factors, in which fluid shift might be a key element in causing OSA. This would be the ideal OSA patient to treat with a fluid addressing therapy as an alternative to CPAP therapy [8].

The main limitation of our study is that we used a clinical-based sample of patients referred for suspected OSA without a control healthy group which limits the finding generalization. However, the fact that this sign of leg swelling is a correlate of moderate-to-severe OSA in patients with a high pre-test risk of OSA in the current clinical real-life setting supports that its added value in the OSA diagnosis merits to be evaluated in a more general setting. Another limitation of this study is the absence of a quantitative measurement of fluid overload in the evening and fluid shift between the evening and the morning, as performed by bioelectrical impedance in all previous studies on fluid shift and OSA. However, the signs observed are indicative of a fluid accumulation in different parts of the body at different times of the day and of possible overnight movement of fluids. Indeed, sock marks present in the evening indicate fluid accumulation in the legs, while a stuffy nose indicates excessive fluid accumulated in the upper airway, present in the morning. In contrast to other techniques, patient-reported signs of fluid overload and shift do not require sophisticated measurements and physicians might explore these signs during the visit to identify fluid overload and shift in early stages, before the presence of the classic

edema. Indeed, the presence of morning stuffed nose or sock marks in the evening would not be clinically obvious during a routine daytime visit unless it was specifically investigated.

In conclusion, looking for evening sock marks appears to be a useful and simple approach in clinical practice for identifying patients with higher risk of OSA among patients addressed to the sleep clinic for suspected OSA, and for detecting fluid OSA-phenotype patients suitable for initial treatment by targeting fluid therapies prior to introducing CPAP or oral appliance. This study therefore opens new perspectives in OSA diagnosis and treatment.

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standard.

**Informed consent** Informed consent was obtained from all individual participants included in the study.

**Disclosure statement** All the authors have seen and approved the manuscript.

**Abbreviations** OSA, Obstructive sleep apnea; CPAP, Continuous positive airway pressure; AHI, Apnea hypopnea index; PV, Ventilatory polygraphy; PSG, Polysomnography; EMG, Electromyogram; OR, Odds ratio; ROC, Receiver operating chanel; BMI, Body mass index; AUC, Area under the curve

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