Clinical Neurophysiology 125 (2014) 1783–1791

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Characterizing the phenotypes of obstructive sleep apnea: Clinical, sleep, and autonomic features of obstructive sleep apnea with and without hypoxia

Jose-Alberto Palma [a,b], Jorge Iriarte [a,*], Secundino Fernandez [c], Miguel Valencia [d], Manuel Alegre [a,d], Julio Artieda [a,d], Elena Urrestarazu [a]

[a] Sleep Unit, Clinical Neurophysiology Section, University Clinic of Navarra, Pamplona, Spain
[b] Dysautonomia Center, Department of Neurology, New York University Medical Center, New York, USA
[c] Department of Otoralyngology, University Clinic of Navarra, Pamplona, Spain
[d] Neurophysiology Laboratory, Neurosciences Area, CIMA, University of Navarra, Pamplona, Spain

See Editorial, pages 1717–1718

ARTICLE INFO

Article history:
Available online 15 February 2014

Keywords:
Obstructive sleep apnea
Autonomic nervous system
Cardiovascular function
Hypoxemia
Heart rate variability

HIGHLIGHTS

- We studied the differences between patients with OSA without hypoxia (OSA−h) and OSA with hypoxia (OSA+h).
- Both groups exhibited differences in terms of clinical features, sleep characteristic and cardiac sympathetic modulation during sleep.
- This study suggests that OSA is a heterogeneous disorder and that the differences among OSA subgroups must be considered in future research.

ABSTRACT

Objective: The pathophysiological basis of obstructive sleep apnea (OSA) is not completely understood and likely varies among patients. In this regard, some patients with OSA do not exhibit hypoxemia. We aimed to analyze the clinical, sleep, and autonomic features of a group of patients with severe OSA without hypoxia (OSA−h) and compare to OSA patients with hypoxia (OSA+h) and controls.
Methods: Fifty-six patients with OSA−h, 64 patients with OSA+h, and 44 control subjects were studied. Clinical and sleep features were analyzed. Besides, time- and frequency-domain heart rate variability (HRV) measures comprising the mean R–R interval, the standard deviation of the RR intervals (SDNN), the low frequency (LF) oscillations, the high frequency (HF) oscillations, and the LF/HF ratio, were calculated across sleep stages during a one-night polysomnography.
Results: OSA−h patients had a lower body mass index, a lower waist circumference, lower apnea duration, and a higher frequency of previous naso-pharyngeal surgery when compared to OSA+h patients. In terms of heart rate variability, OSA+h had increased LF oscillations (i.e., baroreflex function) during N1–N2 and rapid eye movement (REM) sleep when compared to OSA−h and controls. Both OSA+h and OSA−h groups had decreased HF oscillations (i.e., vagal inputs) during N1–N2, N3 and REM sleep when compared to controls. The LF/HF ratio was increased during N1–N2 and REM sleep, only in patients with OSA+h.

* Corresponding author. Address: Sleep Unit, Clinical Neurophysiology Section, University Clinic of Navarra, Av. Pio XII, 36, 31008 Pamplona, Spain. Tel./fax: +34 948255400.
E-mail address: jiriarte@unav.es (J. Iriarte).

http://dx.doi.org/10.1016/j.clinph.2014.01.029

Conclusions: Patients with OSA−h exhibit distinctive clinical, sleep, and autonomic features when compared to OSA with hypoxia.
Significance: OSA is a heterogeneous entity. These differences must be taken into account in future studies when analyzing therapeutic approaches for sleep apnea patients.

1. Introduction

Obstructive Sleep Apnea (OSA) is a sleep breathing disorder that affects over 5% of men and 2% of women (Parati et al., 2007). OSA, which is considered an independent risk factor for cardiovascular disease (Bradley and Floras, 2009), is characterized by repetitive episodes of partial or complete closure of the upper airway which give rise to hypoxemia, changes in intrathoracic pressure, surges in sympathetic activity, and changes in the heart rate regulation (Hakim et al., 2012). The repetitive nature of apneas and the arousal events result in significant sleep fragmentation and sleepiness, and may contribute to arrhythmia and cardiac sudden death (McNicholas et al., 2007).

The pathophysiology of OSA is not completely understood (Eckert and Malhotra, 2008). Arousal from sleep at the cessation of an apnea or hypopnea is considered a key protective mechanism for airway reopening (Remmers et al., 1978). In fact, most respiratory events are associated with cortical arousals and more severe events result in longer arousals (Nigro and Rhodius, 2005). However, the intuitive idea that the breakpoint breath and the arousals after the apneas are a direct consequence of hypoxia is not accurate, given that other mechanisms, such as the level of pleural pressure (Gleeson et al., 1990), and the activity of inspiratory muscles/diaphragm (Vincken et al., 1987; Parkes, 2006), generated by increased respiratory effort during the obstructive apneas (regardless of the degree of hypoxia), are probably the key triggers for inducing arousal.

The existence of a particular subgroup of OSA patients without hypoxia (OSA−h) with significant sleep fragmentation and sleepiness seems to corroborate this idea. Patients with OSA without hypoxia are occasionally seen on the sleep clinic. However, the physiopathologic mechanisms by which these patients have normal oxygen saturation in spite of the apneas are unknown. With the exception of a study focusing on the severity of cognitive impairment in patients with OSA with and without hypoxia (Findley et al., 1986), features of OSA−h have not been comprehensively studied yet, so it is unknown whether this group of patients exhibits any distinctive features in terms of pathophysiologic mechanisms when compared to OSA with hypoxia (OSA+h).

There is evidence that the autonomic nervous system (ANS) is dysregulated during sleep and wakefulness in OSA patients, even in those without cardiovascular disease. When heart rate variability (HRV) during sleep is studied, OSA patients exhibit increased sympathetic and decreased parasympathetic modulations (Gula et al., 2003; Jo et al., 2005). CPAP therapy seems to reverse these changes, even in the first night of treatment (Kufoy et al., 2012). Besides, there is increasing evidence that points to hypoxia (and not to the apneas) as the main etiopathogenic factor for the cardiac autonomic impairment seen in OSA (Hakim et al., 2012; Palma et al., 2013). In this regard, OSA−h patients represent a uniquely valuable group of subjects to explore this question, as they have significant respiratory events during sleep, but oxygen desaturations are virtually absent. We hypothesized that, if HRV changes are a consequence of hypoxemia (and not a consequence of the changes in intrathoracic pressure during respiratory events), cardiac autonomic tone during sleep should be less impaired in patients with OSA−h than those with OSA+h.

This study aimed to analyze, first, the clinical and sleep features of a group of patients with OSA−h and compare it with a group of OSA+h patients and control subjects. And second, it also intended to evaluate the autonomic cardiovascular function during sleep in OSA−h patients using time- and frequency-domain HRV analysis during one-night polysomnography (PSG).

Deepening our understanding in the clinical, sleep and autonomic features of OSA−h patients may offer a valuable insight into the physiopathology of sleep related breathing disorders and into the relevance of hypoxia in the cardiac autonomic dysregulation, which may provide a better understanding for the development of novel therapeutic approaches that target underlying mechanisms of individual OSA patients.

2. Methods

2.1. Subjects

Subjects with severe OSA, defined as apnea/hypopnea index (AHI) > 30 events/h of sleep, were consecutively recruited during a 1-year period, between February 2012 and February 2013. Other than OSA, participants were healthy and were not taking any medication known to affect sleep or other parameter measured in the first part of the study. Informed written consent, as approved by the Institutional Review Board (IRB) of the University of Navarra, was obtained.

The first aim of this study was to define whether there exist any differences in term of clinical and polysomnographic features between OSA−h and OSA+h patients. Patients with OSA−h were selected if they fulfilled the following inclusion criteria: (i) AHI > 30 events/h of sleep; (ii) PSG showing a minimal $SatO_2$ > 88%; (iii) more than 80% of total sleep time with a $SatO_2$ > 96%; (iv) age between 35 and 75.

Inclusion criteria for OSA+h patients (i.e., OSA with hypoxia) comprised: (i) AHI > 30 events/h of sleep; (ii) PSG showing a minimal $SatO_2$ < 88%; (iii) less than 80% of total sleep time with a $SatO_2$ > 96%; (iv) age between 35 and 75.

Inclusion criteria for control subjects comprised: (i) AHI < 5 events/h of sleep; (ii) PSG showing a minimal $SatO_2$ > 88%; (iii) more than 80% of total sleep time with a $SatO_2$ > 96%; (iv) age between 35 and 75; (v) absence of snoring.

Our second objective was to ascertain whether the cardiac autonomic impairment across sleep stages was different between OSA+h and OSA−h as measured by HRV. Given that HRV can be influenced by several factors, we excluded certain patients from the initial cohort to ensure the accuracy of HRV results. Patients were excluded from the HRV analysis if they had a history of: (i) atrial fibrillation and other cardiac arrhythmias; (ii) myocardial ischemia, cardiomyopathy or myocardial infarction; (iii) cardiac pacemaker; (iv) history of neurologic disorders (including stroke, epilepsy, demyelinating disorders, dementia, movement disorders, migraine and trigeminal-autonomic cephalalgias, as these conditions have been associated with abnormal cardiac autonomic tone); (v) history of psychiatric or functional disorders (such as irritable bowel syndrome, chronic fatigue syndrome, and fibromyalgia); (vi) diabetes mellitus or thyroid diseases; (vii) other sleep