Short communication

Excessive daytime sleepiness does not correlate with sympathetic nervous system activation and arterial stiffening in patients with mild-to-moderate obstructive sleep apnoea: A proof-of-principle study☆

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ARTICLE INFO

ABSTRACT

Background: Increased arterial stiffness and sympathetic nervous system activity, independent markers of cardiovascular risk, are common in patients with severe obstructive sleep apnoea, who have excessive daytime sleepiness. Among patients with mild-to-moderate obstructive sleep apnoea, however, it remains unknown whether arterial stiffness and/or increased sympathetic nervous system activity correlate with excessive daytime sleepiness.
Methods: We measured heart rate variability, as an index of autonomic nervous system activity, and arterial stiffness index, as a marker of vascular damage and cardiovascular risk, in 56 men aged 18 to 75 years, with mild-to-moderate obstructive sleep apnoea, and matched into two groups, "sleepy" (Epworth Sleepiness Scale ≥ 10) and "non-sleepy" (Epworth Sleepiness Scale < 10).
Results: We found no association of excessive daytime sleepiness with sympathetic nervous system activation (very low frequency power $18,947 \pm 11,207$ ms^2 *vs* $15,893 \pm 8,272$ ms^2, $p = 0.28$; low frequency (LH) power $17,753 \pm 8,441$ ms^2 *vs* $15,414 \pm 5,666$ ms^2, $p = 0.26$; high frequency (HF) power $7,527 \pm 1,979$ ms^2 *vs* $8,257 \pm 3,416$ ms^2, $p = 0.36$; LF/HF ratio 3.04 ± 1.37 *vs* 2.55 ± 1.01, $p = 0.15$) and mean arterial stiffness index (6.97 ± 0.83 *vs* 7.26 ± 0.66, $p = 0.18$) in mild-to-moderate obstructive sleep apnoea patients.
Conclusions: Symptoms of excessive daytime sleepiness are not associated with sympathetic nervous system activation and arterial stiffness in male subjects with mild-to-moderate obstructive sleep apnoea.

1. Introduction

Obstructive sleep apnoea (OSA) represents an independent risk factor for cardiovascular (CV) diseases; it causes recurrent episodes of upper airway collapse during sleep, resulting in apnoeas and hypopnoeas, repetitive blood oxygen desaturations, and arousal from sleep [1]. The ensuing sleep fragmentation, excessive daytime sleepiness (EDS), and alterations of autonomic activity at night, which can persist during the day [2], lead to impaired quality of life and reduce the overall chances of CV-events free survival. The autonomic nervous system (ANS) is affected by sleep-disordered breathing with a shift of the sympatho-vagal balance towards a sympathetic predominance

and a reduced vagal tone [3]. Arterial stiffness, which estimates the reduced capacity of arteries to expand and contract in response to pressure changes, is known to increase mainly in relation to ageing and atherosclerosis, and represents an independent CV risk factor [4]. It was found to be increased in hypertensive patients with concomitant severe OSA, when measured by pulse wave velocity [5] and significant improvements in all indices of arterial stiffness after continuous positive airway pressure (CPAP) treatment have been shown [6]. Recently, the photo-plethysmography-derived digital volume pulse (DVP) has been developed to quantify arterial stiffness easily and non-invasively, allowing calculation of the stiffness index (SI$_{DVP}$) that reflects systemic arterial stiffness [7].

Increased sympathetic tone and arterial stiffening are both common in patients with severe OSA [8–9], but whether this applies to mild-to-moderate OSA patients and whether EDS correlates with an increase in sympathetic drive and arterial stiffness remains uncertain. Thus, our aims were to determine: i) if patients with mild-to-moderate OSA have detectable signs of increased sympathetic nervous system (SNS)

activity and arterial stiffness; and ii) if EDS correlates with markers of CV risk.

2. Methods

After prospectively screening 458 patients newly referred to our Sleep Centre, we collected data from 56 normotensive males aged between 18 and 75 years, with no known CV risk factors, no comorbidities associated with autonomic failure, such as diabetes mellitus and Shy-Drager syndrome, or any other chronic sleep disorders, who had an apnoea-hypopnoea index (AHI) ≥5 and <30 events per hour during nocturnal polysomnography recording (NPSG) (Embla®N7000, USA). All patients were assessed with the Epworth Sleepiness Scale (ESS) [10]. Patients on medication affecting heart rate variability (HRV) and those previously treated with CPAP or with mandibular advance devices were excluded. Respiratory pattern was analysed in accordance with American Academy of Sleep Medicine (AASM) criteria [11]. The SI_{DVP} was measured by photoplethysmography of the right index finger, generated from the pulse-oximeter trace of the recorded NPSGs, during 2 min in the wake stage, prior to sleep onset, and in the morning, after completion of the study, while the patient lay relaxed without external stimuli. Heart rate parameters were derived from the NPSG electrocardiogram recording during the same two periods used for the measure of arterial stiffness, and during the whole night of the study, and analysed by the Embla® RemLogic™ PSG Software. Frequency-domain indices were calculated, as equivalent to time-domain values [12].

2.1. Power and sample size calculation

We estimated the difference in means between very low frequency power (VLF) in patients with and without EDS as 944 ± 839 *vs* 447 ± 461 ms², using data from a previous study on HRV in patients with OSA [13], and measured a common standard deviation (SD) considered as mean of the two SD. We calculated (using nQuery™, Vers.7.0) that a two group unequal number *t*-test with a 0.05 two-sided significance level will have 80% power to detect the aforementioned difference between a Group 1 and a Group 2 mean (ms²), assuming that the common SD was 650 ms², when the sample sizes in the two groups are 30 and 25, respectively.

2.2. Statistical analysis

"Non-sleepy" (ESS < 10) and "sleepy" (ESS ≥ 10) patients were compared using the independent samples *t*-test and non-normally distributed data by non-parametric Mann-Whitney test. After co-linearity issues were preliminarily excluded by formal testing, linear regression analysis (backward, Wald) was used to identify predictors of HRV and SI_{DVP}. As in this type of observational study an unbalanced distribution of potentially confounding co-variates between normal and elevated ESS groups is likely, propensity score matching was also undertaken using the identified predictors [14]. A $p < 0.05$ was considered to be statistically significant. Statistical analysis was performed using the SPSS statistical analysis programme (SPSS 23.0 for Mac, SPSS-IBM, Bologna, Italy).

3. Results

Of the 56 recruited patients, 31 had an ESS > 10 and 25 an ESS ≤ 10. The two groups did not differ significantly for baseline data (Table 1) neither for the stiffness index and HRV indices. Regression analysis

Table 1
Baseline and polysomnography data of the two subgroups.

	ESS > 10 (n = 31)	ESS ≤ 10 (n = 25)	*p* Value
Age (years)	44.1 (10.6)	45.8 (9.5)	0.53
Body Mass Index (kg/m²)	29.3 (6.1)	29.3 (4.8)	1
Epworth Sleepiness Scale (ESS)	15.6 (3.0)	6.6 (2.7)	<0.001
Apnoea/Hypopnoea Index; (events/h)	15.1 (6.7)	14.5 (7.4)	0.73
Oxygen Desaturation Index (events/h)	14.7 (6.3)	14.6 (7.0)	0.94
Mean blood oxygen saturation (%)[a]	94.9 (6.2)	94.7 (4.8)	0.97
Total sleep time (min)	368 (54)	362 (67)	0.74
Wake after sleep onset (min)[a]	57 (180)	65 (154)	0.65
Sleep efficiency (%)[a]	83.6 (41.8)	80.5 (38.5)	0.38
Wake of sleep period (%)[a]	13.1 (40.0)	14.6 (35.5)	0.56
N1 of sleep period (%)[a]	7.0 (20.3)	6.9 (20.5)	0.84
N2 of sleep period (%)	37.1 (7.7)	35.7 (7.8)	0.50
N3 of sleep period (%)	21.5 (7.7)	22.4 (7.1)	0.63
Rapid eye movement sleep of sleep period (%)	17.7 (5.4)	16.3 (5.5)	0.37
Periodic Limb Movements Index[a] (events/h)	0.2 (7.0)	0.0 (7.0)	0.32
Limb Movements Index[a] (events/h)	4.7 (22.8)	3.7 (26.4)	0.39
Heart rate (beats/min)	64.7 (7.8)	62.9 (9.0)	0.45

Data are expressed as mean ± SD.
[a] Non-normally distributed data compared by non-parametric Mann-Whitney test.

allowed identification of age, AHI, and ODI as independent predictors of arterial stiffness: a model with these variables predicted about 12% of SI_{DVP} variance ($F = 3.49$; $p = 0.022$, adjusted $R^2 = 0.120$). As regards to HRV, a regression model with the same variables predicted about 11% of HRV variance ($F = 7.509$; $p = 0.008$, adjusted $R^2 = 0.106$). Thus, these variables were used for the propensity score matching. After this, 25 cases and 25 controls could be matched and were further compared in terms of HRV (VLF power $18,947 \pm 11,207$ ms² *vs* $15,893 \pm 8,272$ ms², $p = 0.28$; low frequency (LH) power $17,753 \pm 8,441$ ms² *vs* $15,414 \pm 5,666$ ms², $p = 0.26$; high frequency (HF) power $7,527 \pm 1,979$ ms² *vs* $8,257 \pm 3,416$ ms², $p = 0.36$; LF/HF ratio 3.04 ± 1.37 *vs* 2.55 ± 1.01, $p = 0.15$) and mean SI_{DVP} (6.97 ± 0.83 *vs* 7.26 ± 0.66, $p = 0.18$). This comparison revealed no significant differences between the groups with and without EDS for these endpoints (Fig. 1).

4. Discussion

The results of this proof-of-principle study showed that validated indices of SNS activation and arterial stiffening did not differ between the groups according to the presence or absence of EDS in patients with mild-to-moderate OSA. These results complement those of a recent prospective study, which showed that although "sleepy" patients are more likely to have more severe OSA, tend to be more hypertensive, and to have uncontrolled blood pressure (BP), they do not have any features of increased arterial stiffness and CV risk compared to "non-sleepy" patients [15].

This is of interest in that current guidelines recommend CPAP therapy for patients with mild-to-moderate OSA if they exhibit symptoms like EDS [16,17]. It has already been established that not all patients with OSA benefit from CPAP on BP control. Furthermore, it has been demonstrated that patients with OSA who suffer from EDS have a higher rate of hypertension and a higher CV risk compared with those without EDS [18], and that CPAP therapy is less effective in improving BP and preventing the occurrence of hypertension in OSA patients without EDS [19]. Robinson and colleagues reported that in hypertensive "non-sleepy" OSA patients there was no significant BP reduction following CPAP treatment, suggesting that there is no clear benefit for them compared to "sleepy" OSA patients [20]. These reports suggest that subjective EDS is associated with hypertension and CV risk in OSA, and that patients with severe disease are more likely to be symptomatic and respond better to CPAP treatment than patients without EDS.

These findings could have important implications: currently, sleep studies, including full NPSG, are unfeasible in the large cohorts of patients who might be considered to require them. This means that a strategy for prior (pre-test) patients' stratification for likelihood of OSA and associated CV risk is necessary to select which patients to test. Questionnaires, such as the ESS, are already used for this purpose. Therefore, it is an important finding that our study failed to identify any significant relationship between EDS and two surrogate markers for CV risk, SNS activity and arterial stiffness. Based on these findings, a reliable identification of the patients with higher CV risk among those with mild-to-moderate OSA cannot be determined by the use of the ESS.

4.1. Limitations

This was a proof-of-principle study with several limitations and strengths, including the careful selection of patients, the undertaking of a polysomnography, the statistical power calculation, and the stratification for overall risk by means of state-of-the art criteria. However, the cross-sectional design and the small sample size were exploited in order to minimize confounders. Moreover, as we selected normotensive patients, there was a lack of BP measurements in the supine and upright posture. Likewise, the duration of OSA, which could potentially influence both SNS activation and arterial stiffening, was not measured. Lastly, our study was underpowered to address the hypothesis that REM-related-OSA is associated with BP changes, arterial stiffness and HRV.