Calcium channel blockers are independently associated with short sleep duration in hypertensive patients with obstructive sleep apnea

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Objective **Obstructive sleep apnea (OSA) and hypertension (HYP) frequently coexist and have additive harmful effects on the cardiovascular system. There is also growing evidence that short sleep duration may contribute independently to poor cardiovascular outcome. The aim of this study was to evaluate the potential influence of antihypertensive medication on sleep parameters objectively measured by standard polysomnography in hypertensive patients with OSA.**

Methods **We evaluated consecutive patients with a recent diagnosis of OSA by full polysomnography (apnea hypopnea index ≥5 events/h) and HYP. Smokers, patients with diabetes mellitus, heart failure, or using hypnotics and benzodiazepines were excluded.**

Results **We evaluated 186 hypertensive patients with OSA, 64% men. All patients were on at least one antihypertensive medication, including angiotensin-converting enzyme inhibitors (37%), beta-blockers (35%), angiotensin receptor blockers (32%), diuretics (29%) and calcium channel blockers (21%). Backward multiple regression analysis showed that age ($P \leq 0.001$) and the use of calcium channel blockers ($P = 0.037$) were the only factors inversely associated with lower total sleep time. Sleep efficiency was inversely associated only with age ($P \leq 0.001$), whereas the use of calcium channel blockers had a nonsignificant trend ($P = 0.092$). Use of calcium channel blockers was associated with significant reduction in total sleep time (−41 min, $P = 0.005$) and 8% lower sleep efficiency ($P = 0.004$). No other antihypertensive medication, including diuretics and beta-blockers, was associated with sleep impairment.**

Conclusion **Calcium channel blockers may impact negatively on sleep duration in hypertensive patients with OSA. The mechanisms and significance of this novel finding warrants further investigation.** *J Hypertens* **29:1236–1241**

Journal of Hypertension 2011, **29**:1236–1241

Keywords: antihypertensive medication, calcium channel blockers, hypertension, obstructive sleep apnea, short sleep duration

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AHI, apnea–hypopnea index; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; CPAP, continuous positive airway pressure; HYP, hypertension; InCor, Heart Institute; OSA, obstructive sleep apnea; REM sleep, rapid eye movement sleep; S1, stage 1 of sleep; S2, stage 2 of sleep; SpO_2, oxyhemoglobin saturation; SWS, slow wave sleep; TTS, total sleep time

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Received 26 October 2010 **Revised** 3 February 2011
Accepted 25 February 2011

Introduction

Obstructive sleep apnea (OSA) is characterized by repetitive events of total or partial upper airway obstruction resulting in intermittent hypoxia, fragmented sleep and multiple daytime consequences [1]. OSA is now recognized as a major health problem due to its high prevalence and the association with cardiovascular morbidity and mortality [2,3]. OSA and hypertension (HYP) frequently coexist in the same patient [4,5]. The prevalence of HYP among patients with OSA is estimated to be 50% [6], reaching 80% among patients with resistant HYP [7]. OSA and HYP have independent and additive effects on several cardiovascular markers, including artery rigidity and heart remodeling [8]. On the contrary, there is also growing evidence that short sleep duration, independent of OSA, may contribute independently to HYP [9–11] and future cardiovascular risk [12].

Despite the well recognized association between OSA and HYP, the effects of antihypertensive medications on sleep have received little attention. Calcium channel blockers (CCBs) are potent systemic vasodilators that may have several side effects, including leg edema [13–15] and inhibition of the hypoxic pulmonary vasoconstriction [16]. One recent investigation showed an association between CCB and reduction of rapid eye movement (REM) sleep time in patients with refractory hypertension [17]. On the contrary, beta-blocker may impact on sleep [18,19], mainly because it affects central adrenergic mechanisms [20]. Thus, the main aim of this study was to evaluate the association of antihypertensive

0263-6352 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins DOI:10.1097/HJH.0b013e3283462e8b

drugs with sleep parameters objectively measured by standard polysomnography in hypertensive patients with OSA.

Methods

Patients

We analyzed consecutive patients referred to the Sleep Laboratory at the Heart Institute (InCor), University of São Paulo School of Medicine, São Paulo, Brazil, between January 2005 and June 2009 for full polysomnography. Demographic, clinical and medication status were obtained at the time of the polysomnograpy. Inclusion criteria were the presence of OSA [apnea–hypopnea index (AHI) >5events/h] [21], an established diagnosis of HYP [22] and use of at least one antihypertensive medication. We excluded patients with comorbid conditions that could interfere with sleep parameters, including smokers [23], patients with diabetes [24], heart failure [25], and use of hypnotics and benzodiazepines. In addition, patients with previous diagnosis of OSA referred for continuous positive airway pressure (CPAP) titration or that were already on CPAP therapy were excluded from the study.

Sleep study

All participants underwent a standard overnight polysomnography (EMBLA – Flaga hf. Medical Devices, Reykjavik, Iceland), including electroencephalography, electro-oculography, electromyography, oximetry, measurements of airflow (oronasal thermistor, and pressure canula), and measurements of rib cage and abdominal movements during breathing, as previously described [26]. Apnea was defined as complete cessation of airflow for at least 10 s, associated with oxygen desaturation of 3%. Hypopnea was defined as a significant reduction (>50%) in respiratory signals for at least 10 s associated with oxygen desaturation of 3%. The AHI was calculated as the total number of respiratory events (apneas and hypopneas) per hour of sleep [21]. Mild, moderate and severe OSA was defined according to current criteria (AHI between 5 and 14.9, 15 and 29.9 and $\geq$30 events/h, respectively).

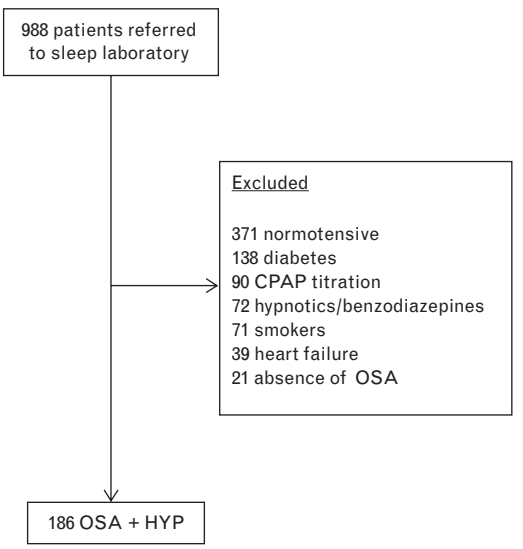
Statistical analysis

Data were analyzed with SPSS 17.0 statistical software (SPSS Inc., Chicago, Illinois, USA). Quantitative variables are expressed as mean $\pm$ SD, median [interquartile range (IQR)] or in percentages, when appropriate. The Student's *t*-test for independent samples and Mann–Whitney *U* test were used to compare quantitative variables when appropriated. The chi-squared test was used for qualitative variables. Kruskal–Wallis test was used to compare means between all three OSA groups. Univariate linear regression analysis was used to evaluate independent variables associated with total sleep time and sleep efficiency. We used as independent variables age, sex, BMI, antihypertensive drugs (including diuretics, beta-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitor and angiotensin receptor blockers), arousals, time SpO_2 less than 90%, and OSA severity as expressed by the AHI. We performed backward multiple regression analysis to determine associations with total sleep time and sleep efficiency. A P value less than 0.05 was used as significant.

Results

We evaluated 988 consecutive patients referred to the sleep laboratory and excluded 802 patients, resulting in 186 patients with OSA and HYP. Most patients were excluded because of the absence of hypertension, or the presence of comorbidities, as shown in Fig. 1. All patients were on at least one antihypertensive medication. The demographic, sleep and antihypertensive medications of the entire population, as well as divided according to the severity of OSA, are presented in Table 1. Patients with severe OSA were predominantly men and were more obese than patients with mild and moderate OSA. The variables associated with total sleep time and sleep efficiency on univariate analysis are presented in Tables 2 and 3, respectively. The variables associated with reductions in total sleep time were age, arousals, time of SpO_2 less than 90% and CCB therapy. Thirty-one out of 39 patients on CCB were on use of dihydropiridine class (amlodipine, $n = 29$; lacidipine, $n = 2$). Among the other eight patients on CCB, four were on benzothiazepine class (diltiazen) and four patients were on use of phenylalkylamine class (verapramil). Backward multiple regression showed that only age ($P \leq 0.001$) and CCB therapy ($P = 0.037$) correlated independently with total sleep time reduction ($P \leq 0.001$ and adjusted $R^2 = 18\%$) (Table 2). The variables associated with lower sleep efficiency were age, CCB therapy and time SpO_2 less

Fig. 1



Patients included in study. CPAP, continuous positive airway pressure; HYP, hypertension; OSA, obstructive sleep apnea.

Table 1 Characteristics of the population studied according to the severity of obstructive sleep apnea

	Total ($n=186$)	Mild ($n=46$)	Moderate ($n=53$)	Severe ($n=87$)	P
Age (years)	57 ± 12	53 ± 11	57 ± 11	56 ± 12	0.102
Men [n (%)]	119 (64)	23 (50)	29 (55)	67 (77)	0.003*
BMI (kg/m^2)	29.7 (26.6–34.1)	29.1 (24.8–33.3)	28.3 (26.0–31.1)	31.8 (27.9–35.8)	≤0.001*
SBP (mmHg)	131 ± 15	132 ± 12	130 ± 19	130 ± 15	0.946
DBP (mmHg)	82 ± 10	85 (80–90)	79 (70–85)	82 (80–90)	0.179
Diuretics [n (%)]	54 (29)	15 (33)	14 (26)	25 (29)	0.792
BB [n (%)]	65 (35)	14 (30)	16 (30)	35 (40)	0.286
CCB [n (%)]	39 (21)	8 (17)	9 (17)	21 (24)	0.398
ACEI [n (%)]	69 (37)	16 (35)	18 (34)	35 (40)	0.598
ARB [n (%)]	60 (32)	18 (39)	17 (32)	24 (27)	0.380
Epworth	9 ± 5	9 (5–12)	9 (6–13)	8 (5–13)	0.737
Total sleep time (min)	392 (351–428)	399 (361–443)	393 (343–424)	392 (347–425)	0.438
Efficiency (%)	89 (78–93)	90 (85–95)	89 (74–92)	86 (78–92)	0.093
Arousals (n)	163 (113–224)	114 (82–158)	132 (111–177)	226 (157–324)	≤0.001*
AHI (event/h)	27.3 (15.6–49.1)	10.1 (7.4–12.8)	20.4 (18.0–23.8)	50.0 (38.0–69.5)	≤0.001*
S1 (%)	4.8 (1.9–9.0)	4.7 (1.9–7.2)	4.9 (2.3–9.1)	4.8 (1.9–9.5)	0.839
S2 (%)	62.0 (56.6–70.2)	60.3 (55.9–65.1)	58.1 (54.3–67.9)	67.0 (58.2–74.9)	0.001*
SWS (%)	12.8 ± 8.5	15.5 ± 9.4	15.0 ± 8.4	9.9 ± 7.2	≤0.001*
REM (%)	17.4 ± 7.1	18.8 ± 7.4	18.4 ± 6.0	16.0 ± 7.2	0.058
Time SpO_2 <90% (min)	3.1 (0.5–15.2)	0.4 (0.1–2.2)	1.1 (0.2–4.0)	10.8 (3.2–34–9)	≤0.001*

Statistical analysis was performed between patients from mild, moderate and severe OSA groups. Values are mean ± SD. Variables with skewed distribution are presented as median (interquartile range) or percentage. ACEI, angiotensin-converting enzyme inhibitor; AHI, apnea–hypopnea index; ARB, angiotensin receptor blocker; BB, beta-blocker; CCB, calcium channel blocker; REM, rapid eye movement sleep; S1, stage 1 of sleep; S2, stage 2 of sleep; SWS, slow wave sleep. *$P<0.05$.

than 90% (Table 3). Backward multiple regression analysis showed that lower sleep efficiency was independently associated with age ($P\leq0.001$ and adjusted $R^2=19\%$), whereas CCB therapy showed an association that did not reach statistical significance ($P=0.092$) (Table 3). Therefore, the only drug associated with short sleep duration and low sleep efficiency was CCB. The demographic and sleep characteristics of patients with and without use of CCB therapy are present in Table 4. Despite similar levels of AHI and BMI, patients on CCB therapy slept on average 41 min less, had significantly lower sleep efficiency and spent more time on light sleep (stage 1) than patients without CCB therapy. In addition, patients on CCB therapy spent three times more with SpO_2 less than 90%, than patients without CCB therapy did.

Discussion

Our study conveys several new findings, regarding the association of antihypertensive drugs with sleep, in patients with OSA and HYP. Beyond the role of age, a traditional factor associated with short sleep duration, our study showed that CCB therapy was negatively and independently associated with short sleep duration and lower sleep efficiency. The association of CCB with short sleep duration remained significant after correction for possible confounders. In contrast, no other antihypertensive drug was associated with differences in sleep parameters.

The most important finding of this study was that CCB therapy was associated with an average of 41 min lower total sleep time, which corresponded of a reduction in 10% of sleep duration. It is unlikely that this difference can be explained by the small (~6 years) but significant difference in age between patients with and without CCB therapy (Table 4). This view was supported by the results obtained on backward multiple regression, which showed that CCB therapy was independently associated with

Table 2 Univariate analysis and backward multiple regression correlation coefficients between total sleep time with anthropometric variables, antihypertensive medications and polysomnographic variable

	Univariate analysis			Backward multiple regression		
Variables	Coefficient (β)	SE	P	Coefficient (β)	SE	P
Age	−0.396	0.434	≤0.001*	−2.24	0.44	≤0.001*
Sex	−0.029	11.755	0.695	–	–	–
BMI	0.060	0.973	0.417	–	–	–
Diuretics	−0.97	12.337	0.186	–	–	–
BB	0.016	11.842	0.829	–	–	–
CCB	−0.234	13.437	0.001*	−27.44	13.03	0.037*
ACEI	−0.125	11.592	0.090	–	–	–
ARB	−0.108	11.966	0.144	–	–	–
AHI	−0.073	0.221	0.321	–	–	–
Arousals	0.151	0.051	0.040*	0.08	0.05	0.068
Time SpO_2 <90%	−0.170	0.228	0.022*	–	–	–
Constant	–	–	–	499.75	27.45	≤0.001*

ACEI, angiotensin-converting enzyme inhibitor; AHI, apnea–hypopnea index; ARB, angiotensin receptor blocker; BB, beta-blocker; CCB, calcium channel blocker; SE, standard error. *$P<0.05$.

Table 3 Univariate analysis and backward multiple regression correlation coefficients between sleep efficiency with anthropometric variables, antihypertensive medications and polysomnographic variables

	Univariate analysis			Backward multiple regression		
Variables	Coefficient (β)	SE	*P*	Coefficient (β)	SE	*P*
Age	−0.426	0.076	≤0.001*	−0.45	0.07	≤0.001*
Sex	−0.085	2.072	0.248	–	–	–
BMI	0.096	0.172	0.190	–	–	–
Diuretics	−0.095	2.182	0.195	–	–	–
BB	−0.007	2.095	0.924	–	–	–
CCB	−0.200	2.395	0.006*	−3.84	2.26	0.092
ACEI	0.071	2.061	0.333	–	–	–
ARB	−0.050	2.126	0.502	–	–	–
AHI	−0.130	0.039	0.077	–	–	–
Arousals	0.121	0.009	0.100	–	–	–
Time $SpO_2 < 90\%$	−0.152	0.040	0.041*	–	–	–
Constant	–	–	–	110.37	4.40	≤0.001*

ACEI, angiotensin-converting enzyme inhibitor; AHI; apnea–hypopnea index; ARB, angiotensin receptor blockers; BB, beta-blocker; CCB, calcium channel blocker; SE, standard error. *$P < 0.05$.

lower total sleep time (Table 2). The patients studied are at increased cardiovascular risk due to the association of OSA and HYP [4,5]. There is growing evidence that short sleep duration may be another important factor associated with poor cardiovascular outcome. Epidemiological studies have shown an association between short sleep duration and development of HYP [9–11]. A recent study showed that among patients with insomnia, those sleeping less than 5 h and those sleeping between 5 and 6 h had, respectively, a 500 and 350% risk of HYP, as compared to the patients who slept for more than 6 h and had no sleep complaints [27]. More importantly, there is also recent evidence that short sleep duration among patients with HYP is independently associated with future cardiovascular events [12], including stroke [12,28], myocardial infarction and sudden cardiac death [12]. Therefore, it is possible that short sleep duration may represent an additional cardiovascular burden among patients with OSA and HYP.

A few studies have evaluated the impact of antihypertensive drugs on sleep parameters. Clonidine may suppress REM sleep time [29]. Beta-blockers are the most explored antihypertensive drug [19,20] and seems to be associated to higher total wakefulness after sleep onset, increased number of awakenings during the night, increased sleep latency and decreased sleep efficiency [18]. Mayer *et al.* [30] showed that both metoprolol and cilazapril promoted reductions in AHI, but with no changes in total sleep time (TST) and the proportion of REM sleep. Kraiczi *et al.* [31] tested the effects of five different antihypertensive drugs, including atenolol, amlodipine, enalapril, hydrochlorothiazide and losartan, on blood pressure in HYP patients with OSA. The authors found no significant changes in AHI measured by overnight respiratory monitoring and subjective sleep symptoms. However, the authors did not objectively measure sleep by polysomnography. In our study the only drug associated with short sleep duration was CCB. Our study to some extent parallels the findings of Ruttanaumpawan *et al.* [17] that also found that CCB was the only antihypertensive drug associated with sleep impairment among patients with OSA and HYP. The authors found that patients under treatment of CCB therapy presented significantly lower REM sleep time, compared with those who were not on CCB therapy. We did not find differences in REM sleep time, but we found that patients on CCB therapy had more light sleep (longer S1 stage of sleep) and 8% lower sleep efficiency as compared with patients with OSA and HYP, but without CCB therapy. The association of CCB and sleep efficiency in our study showed only a trend that did not reach statistical significance ($P = 0.092$) on multivariate analysis (Table 3). In conclusion, although there are some variations between studies that may be related to the population studied, data coming from different laboratories are consistently showing that no other antihypertensive than CCB is associated with sleep alterations.

Table 4 Characteristics of patients using and not using a calcium channel blocker

Variables	Calcium channel blocker		
	No ($n = 147$)	Yes ($n = 39$)	*P*
Age (years)	56 ± 12	62 ± 11	0.003*
Men [*n* (%)]	94 (64)	27 (69)	0.670
BMI (kg/m^2)	29.5 (26.6–33.3)	30.3 (26.7 –35.4)	0.442
Antihypertensive (*n*)	2 (1–2)	3 (2–3)	0.001*
Total sleep time (min)	399 (361–434)	358 (279–425)	0.005*
Efficiency (%)	90 (82–94)	82 (68–90)	0.004*
Arousals (*n*)	157 (112–237)	171 (125–268)	0.330
AHI (event/h)	25.2 (14.8–45.8)	35.3 (18.3–58.8)	0.100
S1 (%)	4.5 (1.9–7.6)	6.1 (3.4–14.9)	0.031*
S2 (%)	62.7 (56.9–70.2)	58.8 (55.3–71.5)	0.323
SWS (%)	12.9 ± 8.6	12.3 ± 8.5	0.682
REM (%)	17.5 ± 6.8	16.9 ± 8.2	0.704
Time SpO_2 <90% (min)	2.3 (0.4–12.1)	9.2 (2.4–36.3)	0.007*

Values are mean (±SD). Variables with skewed distribution are presented as median (interquartile range). AHI, apnea–hypopnea index; REM, rapid eye movement sleep; S1, stage 1 of sleep; S2, stage 2 of sleep; SWS, slow wave sleep. *$P < 0.05$.

In the present study patients receiving CCB therapy had a longer duration of time with SpO_2 below 90%, than

patients without CCB therapy (Table 4). There are several potential mechanisms that may help to explain this finding. CCB causes inhibition in hypoxic pulmonary vasoconstriction [32] and may, for instance, contribute to hypoxia in patients with acute respiratory failure treated with nifedipine [16]. In addition, CCB may cause leg edema, by increasing the number of open capillaries and enhancing capillary filtration into the interstitial space [13]. It is therefore possible to speculate that a second mechanism related to rostral fluid shift to the lungs, when one is lying down, during sleep could contribute to hypoxia. Another speculation is that rostral fluid shift to the neck could contribute to worsening of OSA [33,34]. Interestingly enough, patients on use of CCB therapy had a nonsignificant trend to a higher AHI than patients without CCB therapy had (Table 4).

Our study has several potential limitations. Because of the cross-sectional nature of the present study, we cannot conclude on a cause–effect relationship and our results should be interpreted with caution. The majority of our patients were on amlodipine (74%) and we had no power to determine if the effects observed on sleep parameters are modulated by the class of CCB. One important hypothesis raised by Friedman *et al.* [35] is that reductions in total sleep time and REM sleep time in patients with OSA may be associated with the severity of hypertension. In our study, patients on CCB therapy used significantly more antihypertensive drugs than patients without CCB therapy used ($P = 0.001$). However, because of the strong co-linearity between use of CCB and the number of antihypertensive drugs, we were not able to separate the independent effect of the association of drugs on sleep parameters. In addition, the present study does not provide a strong rationale to explain why the use of CCB would be associated with short sleep duration. Therefore, it is possible that the use of CCB is simply a marker of HYP severity. It has been speculated that resistant HYP may be associated with an increase in stimulation in sympathetic vasoconstriction outflow and impaired baroreflex function [17] that could contribute to short sleep duration. Conversely, short sleep duration could contribute to sympathetic over stimulation [36,37] and the risk of development of HYP [9–11].

In conclusion, our data showed that the use of CCB therapy was independently correlated with short sleep duration, in HYP patients with OSA, objectively measured by full polysomnography. No other antihypertensive drugs seem to have an association with sleep parameters. The reasons for this novel finding cannot be clarified in this study and further investigations are warranted.

Acknowledgement

This study was supported by FAPESP.

There are no conflicts of interest.

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