



Original Article

The effect of sildenafil on sleep respiratory parameters and heart rate variability in obstructive sleep apnea

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ABSTRACT

Objective: To evaluate the magnitude of effects of sildenafil on respiratory parameters and heart rate variability (HRV) in slow wave sleep (SWS) and REM sleep of patients with severe obstructive sleep apnea (OSA).

Methods: Thirteen male patients with untreated severe OSA (aged 43 ± 10 years, body mass index of 26.7 ± 1.9 kg/m²) were studied on two nights, one with sildenafil 50 mg and one with a placebo, in a double-blind, randomized fashion. All-night polysomnography and HRV were simultaneously recorded. Short-term HRV measures were performed in apnea-free intervals. Respiratory parameters were separately assessed in non-REM and REM sleep and compared to total sleep time (TST). Short-term HRV analysis was conducted in samples with regular respiration obtained in SWS and REM sleep.

Results: Comparing to placebo, during sildenafil night there was an increase in apnea-hypopnea index (AHI) in TST and also in non-REM and REM sleep. Increase in central AHI occurred in non-REM sleep; increase in obstructive AHI and decrease in oxyhemoglobin saturation occurred in both non-REM and REM sleep. Additionally, an increase in arousal index and in low/high frequency component of HRV ratio (LF/HF) was significant only in REM sleep. Correlation between sleep architecture and respiratory parameters were more frequent in non-REM sleep for placebo and in REM sleep for sildenafil.

Conclusion: In severe OSA, the use of sildenafil 50 mg at bedtime plays a detrimental role on respiratory parameters in both non-REM and REM sleep, fragmentation in REM sleep, and a prolonged increase in LH/HF component of HRV after resumption of ventilation.

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1. Introduction

A concern regarding the increasing percentage of men using selective phosphodiesterase-5 (PDE-5) inhibitor drugs to treat erectile dysfunction [1] is justified by the magnifying effect of sildenafil on the respiratory events in severe OSA, as previously demonstrated by our group [2]. In this previous study we speculated that nasal congestion, frequently reported by sildenafil users [3], may underlie the increase in number and duration of obstructive respiratory events. In addition, ventilation–perfusion mismatch may be attributed to the nitric oxide (NO)-dependent pulmonary vasodilatory effect of sildenafil, occurring in the absence of ventilation, with

consequent enhancement in oxyhemoglobin desaturation. Besides a deleterious impact of NO-increased bioavailability on hemodynamic parameters in severe OSA, the decrease in percentage of SWS after sildenafil, in comparison to placebo, might evidence OSA severity, as has been proposed by other authors [4–6].

Clinically, OSA is very much a REM-sleep related disease [7], however, the degree of sleep synchronization also influences the magnitude of hypoxemia, intensity of upper airway occlusion, and arousability [8,9]. The low synchronization of REM sleep contrasts with the highly synchronized slow wave sleep (SWS, defined as the sum of non-REM sleep stages 3 and 4) also in terms of impact on heart frequency. Taking into account the influence of sleep stage and respiration on HRV, this study was conducted with the aim to evaluate to which extent the NO-mediated effects of sildenafil act upon respiratory and HRV parameters in SWS and REM sleep. The primary endpoint was to separately assess central and obstructive respiratory events and the distribution of arousals in both non-REM and REM sleep. As a second outcome, HRV parameters were analyzed in apnea-free samples during SWS and REM sleep.

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2. Methods

The present study is an extension of an earlier project and was conducted based on experimental data obtained from 13 patients prospectively enrolled in our previous double-blind, randomized, controlled study on the effect of sildenafil in sleep parameters in severe OSA [2].

Details of the study design, sampling plan, and methodology have been reported elsewhere [2]. In brief, 13 of 49 middle-aged men with OSA consecutively recruited for this study were selected (age 53.1 ± 9.8 years, BMI 26.7 ± 1.9 kg/m² – mean \pm SD). Regarding criteria for selection, subjects with any medical problems affecting the upper airway (other than OSA), with cardiovascular or cerebrovascular diseases, or in use of nitroderivate drugs or of continuous positive airway pressure (CPAP) devices during the previous 6 months were also eliminated from the study. Current or previous smokers (≥ 10 pack-years during the last 5 years), alcoholics, drug abusers, and those with potential autonomic dysfunction due to diseases (such as diabetes) or to the use of medications (such as beta-blockers) were also discharged. In order to detect pulmonary hypertension (defined as pulmonary arterial pressure ≥ 20 mm Hg), cardiac and other respiratory diseases, echocardiogram, electrocardiogram, and respiratory function tests were obtained.

The protocol was approved by the local Ethics Review Committee, and Written Informed Consent was signed by all participants.

2.1. Study design

All participants, after signing Written Informed Consent were evaluated as previously described [2]. After a baseline polysomnography recording (used as an adaptation night), subjects were studied on two nights under two different conditions: a single dose of sildenafil 50 mg or placebo (formulated with a similar appearance of the drug) taken orally immediately before sleep recording. For randomization purposes, each pill was put in separated coded envelopes for aleatory selection by the patient. The code of the randomization was revealed after all data analysis. One-week washout period separated the administration of each pill.

Sleep studies were carried out in our Sleep Unit, usually from midnight to 8 am. Patients were prospectively evaluated for heart rate variability obtained by nocturnal Holter recording, carried out simultaneously to polysomnography.

2.2. Polysomnography

Bedtime was based on each patient's habits. A minimum of 7 h of recording time was obtained. The following variables were collected: an electroencephalogram (at positions C3–A2, C4–A1, and O1–A2 of the International 10–20 System), a bilateral electrooculogram, a submental electromyogram, and an electrocardiogram (modified V₂ lead). Respiration was monitored as follows: airflow was measured with a nasal cannula/pressure transducer system (Pro-Tech Services Inc.; Mukilteo, WA, USA) and a mouth thermocouple; chest and abdominal efforts were measured with uncalibrated, inductive, respiratory plethysmographic belts; arterial oxygen saturation (SaO₂) was measured with pulse oximetry (Ohmeda Hatfield, Herts, England), and body position movements were measured with a mercury gauge and determined by a sensor. Data were collected using a 16-channel computerized sleep system (Harmonie 5.2; Stellate Systems Inc., Montreal, Quebec) which offers the possibility of obtaining a recording with a sampling rate of 512 Hz.

The polysomnographic register was analyzed in periods of 30 s and during total sleep time (TST), non-REM and REM stages, according to the method of Rechtschaffen and Kales [10]. Non-

REM sleep stages 3 and 4 were considered together as SWS. Total sleep time was defined as the time elapsed between the first and last recorded epoch of sleep, excluding the wakefulness. Sleep study was repeated in the absence of SWS or REM sleep or if there was a TST decrease of more than 20% of the habitual number of sleep hours.

An arousal was defined as an abrupt shift in EEG frequency which included the theta–alpha pattern and/or a frequency higher than 16 Hz (but not spindles) lasting more than 3 s [9].

Apnea was defined as a period of breathing cessation and hypopnea, as 50% reduction in breathing or less than 50% of reduction in breathing associated with a 4% desaturation of oxihemoglobin or arousal. Minimum event duration was considered 10 s. The apnea–hypopnea index was defined as the total number of apneas and hypopneas/hour of TST. An obstructive AHI was defined as the number of obstructive apneas plus hypopneas/hours of TST, mixed AHI as mixed apneas plus hypopneas/hours of TST, and central AHI as central apneas plus hypopneas/hours of TST [11]. Percentage TST elapsed in apnea/hypopnea events was calculated to estimate the duration of respiratory events during sleep. Desaturation index (DI) corresponded to the number of arterial oxygen desaturations/hour of TST with drop higher than 4%. The percentage of TST with <90% oxyhemoglobin saturation was also measured. The mean oxygen saturation (SaO₂) was calculated by averaging the high and low values for each 30-s period.

Respiratory analysis was performed by two observers (CN and SR), separately, in a blind fashion. For the selection of central or obstructive sleep apnea–hypopneas and for arousals (interscorer agreement of 83% and 71%, respectively), interscorer differences were reconciled.

Respiratory parameters were analyzed in non-REM sleep as a whole rather than in SWS because, particularly after sildenafil, many of the apnea–hypopnea and desaturation events exceeded SWS stage limits.

2.3. Heart rate variability

Considering that apnea is defined as a respiratory arrest lasting ≥ 10 s, including the awakening response after apnea, the most common minimum cycle length of one apneic episode during non-REM lasts approximately 25 s (0.04 Hz) [12]. During REM sleep, besides the physiological irregularity of the respiratory frequency, ranging between 12 and 22 breath/min [13,14], prolonged apnea events lasting approximately 2 min (0.008 Hz) often occur [12].

In order to overcome a potential influence of respiration on the stationarity of heart frequency, we opted for short-term HRV measures to assess the apnea-free intervals during SWS and REM sleep. Therefore, 1-min samples were consecutively selected if surrounded (before and after) by 1 min of a regular respiration pattern. R–R intervals in sleep epochs with electrocardiographic or electroencephalographic artifacts, arousals or sleep stage shift were discharged.

Digital processing and filtering of periodic ventilatory oscillations of the samples were performed by means of a MATLAB[®] Software. The spectra of the selected samples were respiration-adjusted using the Welch method [15]. The parameters of spectral analysis of HRV were calculated with an equidistant tachogram with linear interpolation, smoothing with a boxcar filter with a width of 2 samples, with 128 sample Hanning windowing [16]. Finally, the fast Fourier transformation was performed with the calculation of power in the following frequency bands: low frequency band (LF – 0.04–0.15 Hz), high frequency band (HF – 0.15–0.40 Hz), and LF/HF ratio. Normalized (_{nu}) values of spectral analysis were used to quantify changes in components of HRV, such as $LF_{nu} = LF/LF + HF$ and $HF_{nu} = HF/LF + HF$ [17]. The power density in the very low frequency (VLF, 0.0033–0.04 Hz) was not

considered because short-term HRV analysis fails in detecting this larger component. Since the total power (TP) includes the sum of further components than low and high frequency power, its value was also not included in this analysis [18].

2.4. Statistics

Normality of the distribution was tested using Shapiro–Wilk test, and data were reported as mean \pm standard error (SE) and 95% confidence intervals (CIs), except for age and body mass index, which were expressed as mean value \pm standard deviation (SD) as previously [2]. Paired *t*-test or Wilcoxon matched pairs test was used for comparison between placebo and sildenafil regarding parametric and non-parametric data, respectively. Spearman rank test was used for correlation between sleep architecture and respiratory parameters obtained for each placebo (P) and sildenafil (S). Kappa statistic was calculated for the measurement of interobserver agreement. Statistical evaluations were made by means of Statistica version 6.0 for Windows package program (Statsoft Inc., Tulsa, OK, 2004). Significance was established at $p < 0.05$.

3. Results

The 13 studied patients were evaluated during sleep after placebo or sildenafil 50 mg by means of polysomnography and HRV simultaneously recorded. Some of the results of the present study have been reported previously [2].

Comparison of apnea–hypopnea index per hour of TST, non-REM sleep time and REM sleep between placebo and sildenafil are illustrated in Fig. 1. The increase in AHI (central plus obstructive events) in TST after sildenafil, in comparison to placebo [mean \pm SE (CIs), 48.1 \pm 20.6 (35.6–60.5) vs. 31.6 \pm 13.2 (23.6–39.5), $p = 0.04$], was also observed regarding central events at TST [21.1 \pm 9.4 (15.4–26.8) vs. 11.7 \pm 5.3 (8.5–14.9), $p = 0.01$, respectively], but not regarding obstructive events [27 \pm 11.8 (19.8–34.1) vs. 19.9 \pm 9.7 (14.0–25.7), $p = 0.16$, respectively].

Additionally, it can be observed in Fig. 1 that when non-REM and REM sleep were analyzed separately, significant enhancement in central AHI was observed only in non-REM sleep [mean \pm SE (CIs), 10.6 \pm 7.4 (6.1–15) vs. 3.7 \pm 2.2 (2.3–5.0), $p = 0.002$]. In this

regard, it is pertinent to consider the great variability of the data regarding central apnea count per hour of REM sleep [mean \pm SE (CIs), 64.1 \pm 32.9 (44.3–84.0) vs. 49.3 \pm 33.1 (29.2–69.3), $p = 0.09$, respectively]. Interestingly, increase in obstructive AHI became significant after sildenafil, compared to placebo, both in non-REM and REM sleep as follows: obstructive AHI in non-REM sleep: mean \pm SE (CIs) of [20.4 \pm 10.4 (14.2–26.7) vs. 12.9 \pm 4.7 (10.1–15.8), $p = 0.04$, respectively]; and in REM sleep: [29.6 \pm 7.5 (25.1–34.1) vs. 21.6 \pm 6.4 (17.7–25.4), $p = 0.002$, respectively].

In Fig. 2 it can be verified that even though average percentage of oxyhemoglobin saturation in TST did not differ significantly between sildenafil and placebo treatments [mean \pm SE (CIs), 75.5 \pm 9.5 (79.0–84.0) vs. 81.5 \pm 4.2 (81.2–94), $p = 0.10$, respectively], significant decrease was observed in both non-REM and REM sleep with sildenafil compared to placebo as follows: percentage of oxyhemoglobin saturation in non-REM sleep [70.9 \pm 11.2 (64.1–77.7) vs. 89.8 \pm 3.9 (87.5–92.2), $p = 0.0001$, respectively] and in REM [59.9 \pm 10.3 (53.7–66.1) vs. 87.2 \pm 5.6 (83.8–90.6), $p < 0.001$, respectively].

Table 1 details the polysomnography findings during TST, non-REM and REM sleep. Notably, no significant difference was verified between placebo and sildenafil with respect to arousal index in SWS ($p = 0.02$) despite the decrease in the percentage of this sleep stage ($p = 0.02$).

In Table 2 normalized values of LF and HF components of HRV are outlined. Looking at the mean amount of 1-min samples that fulfilled the selection criteria, fewer sildenafil REM-sleep samples were selected for HRV analysis in comparison to the other conditions.

Finally, in Table 3 significant correlations between sleep architecture and respiratory parameters are detailed. Particular attention should be paid to the distribution of the correlations: with sildenafil (S) correlations between sleep architecture and respiratory parameters occurring more frequently in REM sleep and with placebo (P) in non-REM sleep.

4. Discussion

The most important finding in this study is that in OSA patients, sildenafil increased apnea–hypopnea index not only as a whole,

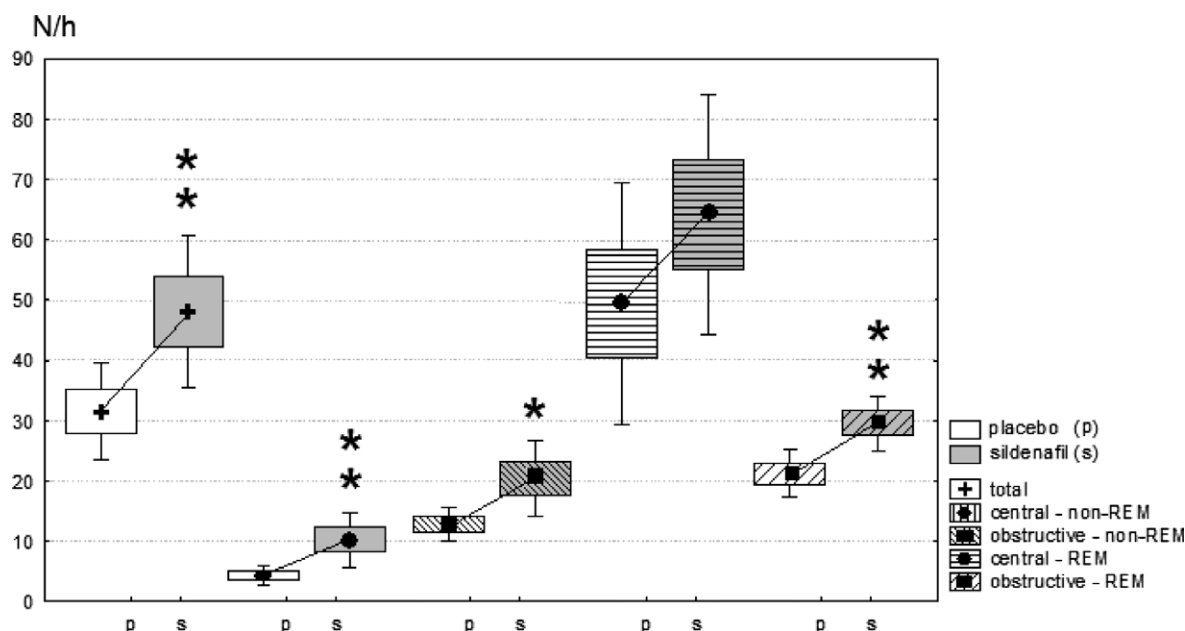


Fig. 1. Index of apnea–hypopnea in total sleep time and index of central and obstructive respiratory events during non-REM and REM sleep. Mean \pm standard error – vertical bars denotes 0.95 confidence interval. * $p < 0.05$, ** $p < 0.01$. AHI apnea–hypopnea indexes N/h = number of events per hour of total sleep time, non-REM or REM sleep.

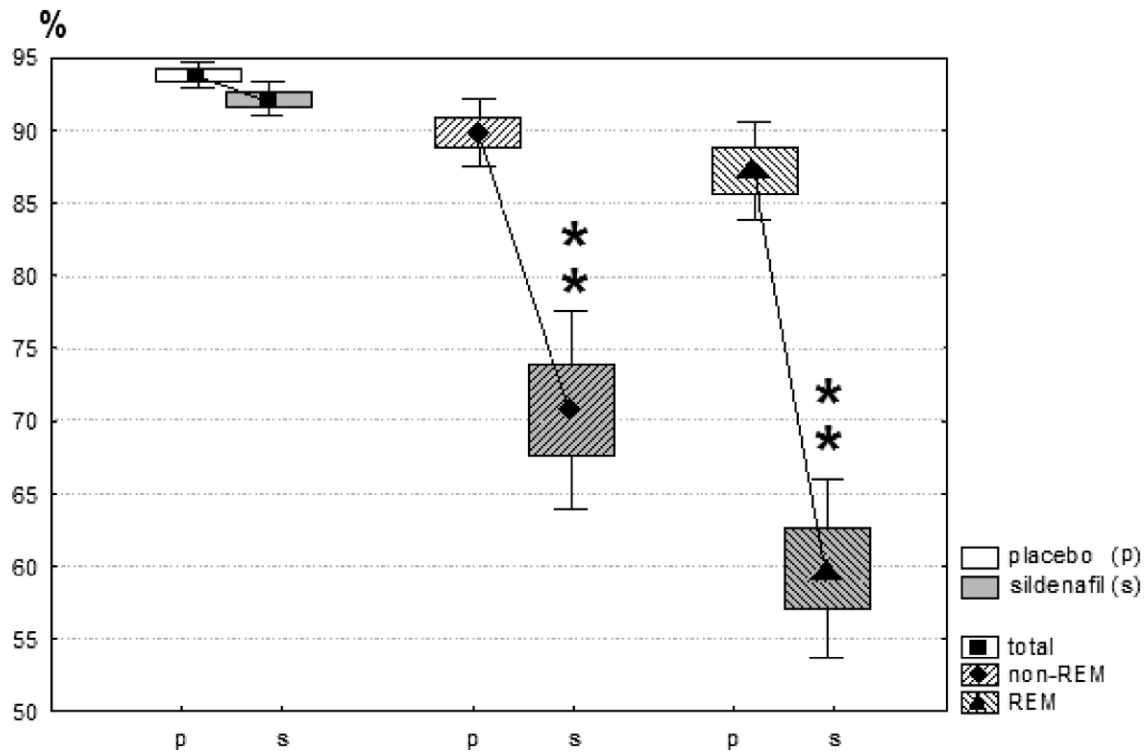


Fig. 2. Saturation of oxyhemoglobin during total sleep time, non-REM and REM sleep. Mean \pm standard error – vertical bars denotes 0.95 confidence interval. * $p < 0.05$, ** $p < 0.01$. SaO₂ – saturation of oxyhemoglobin.

but also specifically in non-REM (central and obstructive events) and in REM sleep (obstructive events) compared to placebo. In

Table 1
Sleep characteristics.

Polysomnography		Placebo	Sildenafil
Total sleep time	TST (min)	442.4 \pm 62.5 (404.6–480.2)	426.8 \pm 57.7 (391.9–461.7)
	Sleep efficiency (%)	92.1 \pm 5.9 (88.5–95.6)	91.9 \pm 5.5 (88.6–95.2)
S1 (%)		7.7 \pm 3.9 (5.4–10.1)	5.4 \pm 3.9 (3.1–7.8)
	S2 (%)	54.9 \pm 7.6 (50.3–59.5)	60.9 \pm 5.1* (57.8–64.0)
SWS (%)		17.1 \pm 5.1 (14.1–20.2)	12.5 \pm 3.1* (10.6–14.4)
	REM (%)	20.3 \pm 5.6 (16.9–23.6)	21.3 \pm 3.9 (19–23.7)
Desaturation index (N/h)		18.8 \pm 9.8 (12.9–24.7)	30.3 \pm 14.6 (21.5–39.1)
	Duration of respiratory events (% TST)	8.6 \pm 3.4 (6.5–10.6)	13.7 \pm 6.4** (9.8–17.5)
Arousal index (N/h TST)		15.2 \pm 3.8 (12.9–17.5)	15.8 \pm 3.3 (13.8–17.8)
	Desaturations (N/h)	56.0 \pm 34.9 (34.9–77.1)	98.7 \pm 56.0 (64.9–132.6)
Non-REM sleep	Duration of respiratory events (% of non-REM)	44.4 \pm 5.5 (41.1–47.7)	49.1 \pm 11.3 (42.3–56)
	Arousals in SWS (N/h)	85.8 \pm 86.8 (33.3–138.2)	20 \pm 17.3 [‡] (9.5–30.4)
REM sleep	Desaturations (N/h)	85.7 \pm 54.5 (52.8–118.7)	114.4 \pm 45.9 (86.7–142.1)
	Duration of respiratory events (% of REM sleep)	56.3 \pm 5.6 (52.9–59.7)	51.0 \pm 11.4 (44.1–57.9)
Arousals in REM sleep (N/h)		20.2 \pm 13.1 (12.3–28.1)	31.3 \pm 23.9 [‡] (16.8–45.7)

Mean \pm standard error (95% CI).

^t Student for dependent samples for data with parametric distribution.

Wilcoxon matched pairs test for data with non-parametric distribution ([‡]).

* $p < 0.05$.

** $p < 0.01$.

addition to the previously described effect of sildenafil in decreasing SWS percentage and increasing desaturation index [2], the present results clarify that the lack in concomitant arousal enhancement may be attributed to the decreased arousability observed in SWS. This study, however, goes further by analyzing heart rate variability in samples of SWS and REM sleep with regular respiration. The finding of a clear-cut correlation between respiratory impaired indexes and arousals during REM sleep is consistent with the enhanced LF/HF component of HRV during REM sleep and suggests a hemodynamic impact of REM fragmentation in response to apnea–hypopnea events after sildenafil in comparison to placebo. Therefore, in view of the persistence of increased LH/HF ratio into normal respiration, we can speculate that

Table 2

Short-term heart rate variability (HRV) analysis of samples during SWS and REM sleep.

HRV parameters		Placebo	Sildenafil
SWS	LFSWS (nu)	0.705 \pm 0.155 (0.611–0.799)	0.682 \pm 0.146 (0.593–0.771)
	HFSWS (nu)	0.999 \pm 0.001 (0.999–1.001)	0.997 \pm 0.001 (0.995–1.000)
	LF/HF SWS	0.705 \pm 0.156 (0.611–0.799)	0.683 \pm 0.147 (0.594–0.771)
REM	Samples (N)	4.2 \pm 1.0 (3.7–4.5)	4.0 \pm 0.9 (3.7–4.5)
	LFREM (nu)	0.705 \pm 0.123 (0.631–0.78)	0.841 \pm 0.07 (0.797–0.883)
	HFREM (nu)	0.965 \pm 0.123 (0.891–1.004)	0.792 \pm 0.021 (0.879–0.899)
LF/HF REM		0.733 \pm 0.097 (0.674–0.792)	0.941 \pm 0.074* (0.898–0.884)
	Samples (N)	4.1 \pm 1.0 (2.8–3.9)	2.6 \pm 1.2* (2.7–3.7)

Mean \pm standard error (95% CI).

^t Student for dependent samples for data with parametric distribution.

Wilcoxon matched pairs test for data with non-parametric distribution ([‡]).

N = number of 1-min stationary samples of regular respiration selected during SWS and REM sleep.

* $p < 0.05$.

Table 3Significant correlations between sleep architecture and respiratory variables (Sr), $p < 0.05$.

	TST (min)	Efficiency (%)	S2 (% TST)	REM sleep (% TST)	Arousal SWS	Arousal REM
Non-REM sleep	Mean SaO ₂ (mm Hg)			0.70 (S)	0.66 (S)	-0.64 (S)
	Central events (N/h)		-0.59 (P)	-0.61 (S)		0.63 (S)
	Obstructive events (N/h)					0.55 (S)
	Desaturations (N/h)	0.62 (P)		-0.64 (P)		
	Respiratory events (%)					
REM sleep	Mean SaO ₂ (mm Hg)			0.65 (S)	0.64 (S)	-0.60 (S)
	Central events (N/h)			-0.87 (P)		
	Obstructive events (N/h)	-0.64 (P)		0.71 (P)	-0.63 (P)	0.57 (P)
	Desaturations (N/h)				-0.69 (P)	
	Respiratory events duration (%)				0.58 (S)	0.64 (S)

(P) = placebo, (S) = sildenafil.

TST – total sleep time, SWS – slow wave sleep; sleep efficiency (%).

Arousals evaluated as N/h in SWS and as N/h in REM sleep.

Spearman rank order correlations at $p < 0.05$.

Only sleep variables with significant correlation with respiratory data were mentioned.

Duration of respiratory events were considered as the percentage of time of SWS or REM sleep spent in apnea or hypopnea, and desaturations, as the number of desaturation events per hour of SWS or REM sleep.

in OSA patients with a highly compromised upper airway, sildenafil may have a deleterious potential cardiovascular impact.

Intermittent hypoxia has been suggested to start a cascade of pathophysiological changes ending in endothelial dysfunction [19]. Apart from the consumption of endogenous NO by reactive oxygen species [20], the intermittent failure to transport nasal NO to the lungs, with each breath, also contributes to the decrease in NO synthesis, once oxygen is a key NO substrate [21].

Such a diminished bioavailability of NO acts as an adaptation mechanism to the hypoxia condition, and reversion of NO deficiency has been reported with the use of CPAP therapy [22]. In the present study, as it has been pointed out, pulmonary NO-mediated vasodilation induced by sildenafil takes place in the absence of simultaneous resumption of ventilation. Therefore ventilation/perfusion mismatch may underlie the ventilatory impairment reported in severe OSA patients after sildenafil [2].

In addition, nasal congestion, as a frequent adverse effect of sildenafil, may contribute to upper airway narrowing since OSA condition itself is associated with a reduced-caliber upper airway, which, despite an increase in compensatory pharyngeal dilator muscle output, is vulnerable to further narrowing or collapse [3].

In our previous study we demonstrated that after sildenafil 50 mg at bed time, severe OSA patients presented worsened respiratory parameters during sleep without increase in arousal index as should be expected. Concerning this aspect, even in healthy individuals, chemoreceptor response is blunted during sleep compared with wakefulness, leading to modest changes in blood gas tensions. In OSA, however, prominent dampening of upper airway reflexes during sleep contribute to substantial deterioration of blood gas tensions [23]. To this extent, increase in apnea-hypopnea count and duration as well as in oxyhemoglobin desaturation and the arousal response are features that significantly impact the degree of OSA severity. In the present study we observed that, after sildenafil, there was an increase in both central and obstructive apnea events and decrease in oxyhemoglobin saturations, despite the non-significant modification in the arousal count in SWS. On the other hand, during REM sleep, significant arousal index increase occurred, after sildenafil, compared to placebo. But the increase in central apnea count did not reach significance. This finding may translate a ceiling effect on the amount of central events in REM, which might be owed to the increased arousability reported in this sleep stage and which can be triggered by deterioration in blood gases tension [23].

Another aspect of the multifaceted NO functions pertinent to sleep apnea is the growing body of in vitro evidence that NO contributes to somnolence through adenosine release in basal fore-

brain [24]. Since NO output by the brain falls during sleep, particularly during sleep apnea [25], the effect of sildenafil in increasing bioavailability of NO, and thus hypoarousability of the patients, can be speculated. For a review on the potential somnogenic effect of NO see Ref. [26].

It is also interesting to state that systemic administration of a single dose of sildenafil is able to enhance expression of PDE-5 in the central nervous system, with concomitant increase of both cGMP and of cGMP-dependent protein kinase type 1 (PKG1), which has been implicated in the regulation of the timing and quality of sleep and wakefulness [27].

Apart from its effect on reentrainment after phase advances of the light–dark cycle [28], sildenafil may interfere in further sleep aspects involving the PKG1 transduction pathway, such as REM sleep duration and non-REM consolidation [27].

It has been shown that OSA patients have a higher arousal threshold when compared with controls, requiring both a greater effort and larger negative intrathoracic pressure to produce an awakening [23].

According to our data, OSA patients were more arousable in REM sleep than in the deeper stages of non-REM, particularly after sildenafil. Eased fragmentation of REM sleep, compared to non-REM sleep, is regarded to REM propensity to increase upper airway resistance [29] but also arousability due to the dynamic sympathovagal balance characteristic of this sleep stage [30].

Nevertheless, the relationship between arousal and upper airway opening appears to be incidental rather than a cause and effect relationship [31]. Even though arousals are not necessary for resumption of ventilation, repeated arousal events would be expected as a response to stimulation of arterial chemoreceptors and upper airway mechanoreceptors by altered blood gases. Together with hypercapnia, respiratory effort has been considered as the main stimulus to arousal [32,33].

The degree of pharyngeal deformation, as an attempt to overcome upper airway occlusion [23,34–37], may induce additional increase in respiratory drive required for arousal-free airway opening. Therefore, a brief period of hyperventilation has been reported after restoration of airway patency [38]. The cyclic appearance of central apneas and hyperpneas and desaturation of oxyhemoglobin after sildenafil is in line with these finding and suggests that, as a consequence of the progressive inspiratory loading against an obstructed upper airway, a greater ventilatory overshoot, as the upper airways open, may induce hypocapnia and subsequent suppression of ventilation. There is an increasing body of literature on post-apnea respiratory instability as the underlying mechanism of alternation between ventilatory

stimulation and suppression in OSA [31,39,40]. Nevertheless, our data are not sufficient to reach a conclusion on the contribution of a blunted control of breathing during non-REM sleep due to removal of the “wakefulness” drive [41].

In the present study, many of the apnea–hypopnea and desaturation events exceeded SWS stage limits, reflecting both enlargement of these events and shortening of SWS. These mechanisms may account for the disproportion between the non-significant increase in arousals and the prominent increase in apnea events during SWS after sildenafil. They also explain the increased duration of apnea events in this sleep stage [6,40–42]. In contrast, increased fragmentation was observed in REM sleep, in which percentage was unaltered after sildenafil. This study provides evidence the dynamic nature of the sympatho-vagal modulation of REM sleep in increasing arousability in this sleep stage [29,43].

During apneas, and the subsequent hyperventilation periods, a succession of bradycardia and tachycardia phases is seen in subjects with an intact autonomic nervous system. Disruption of neural circulatory control in obstructive sleep apnea is demonstrated by heightened peripheral chemoreflex sensitivity and sympathetic overactivity during both sleep and wakefulness [44].

Based on our findings, the persistence of elevated ratio of LF/HF components of HRV for at least one min after the airway opening in REM sleep, after sildenafil, may reflect a prolonged sympatho-excitation in such a condition and give support to previous literature on morbidities related to persistent sympathetic activation in sleep apnea [44,45].

Repeated episodes of inspiratory obstruction, prolonged hypoxemia, combined or not to hypercapnia, contribute to chemoreceptor resetting and subsequent increases in sympathetic tone [38] and catecholamine levels [46]. Sympathetic activation in humans in response to hypoxia may persist for 20 min or even more after cessation of the stimulus and have deleterious consequences on systemic blood pressure and autonomic nervous functions [47–49].

Because OSA can be associated with prolonged sympathetic responses, it can be supposed that, while the NO-dependent vasodilatory effect of sildenafil may be negative for OSA patients during sleep, it can be positive during wakefulness in encompassing increased peripheral resistance, systemic hypertension and other consequences of the chronically increased sympathetic efferent nerve activity [50].

Some methodological considerations should be acknowledged in this study, particularly with respect to arousal detection in SWS. A major difficulty was to determine if synchronized EEG sleep patterns after apnea–hypopnea events should be included in the selection. Considering the still ongoing controversy regarding whether they reflect an arousal response, we decided to use the conventional criteria [10], assuming that there is no formal global consensus on its use [8].

In contrast, because of the prominent fragmentation of REM sleep, particularly after sildenafil, we were able to select only a few samples for HRV analysis, significantly less than the amount obtained in SWS and in REM sleep under placebo effect.

Regarding the limitations of this study, the first aspect that should be mentioned is that the effect NO was inferred from the effects of sildenafil on respiration and heart frequency. Feasibility of performing a curve of plasmatic levels of NO during sleep should be taken into account. In addition, capnography data would be particularly useful in shedding light on the role of chemo- and baroreflex on the ventilatory and hemodynamic alterations induced by sildenafil in severe OSA patients. Finally, considering the small sample of patients studied, it can be questioned whether these data are applicable to all OSA patients. The data of the 13 studied patients are consistent in regard to the low ratio of arousals and apnea–hypopnea events as well as to desaturation measures during sleep. Additionally, since all eligible recorded apnea–hypopnea

events have been similarly analyzed, the large amount of data may be representative of the characteristics of these respiratory events.

Taken together, the effects obtained with sildenafil in the present study are in line with the concept of blunted control of breathing during SWS sleep and apnea-induced REM sleep fragmentation due to the increased sympatho-vagal balance and arousability of this sleep stage. Speculations on the underlying mechanism of the reported findings have focused on the non-physiological increase in NO effects in a context in which they are expected to be suppressed, as has been reported in OSA (for review, see Ref. [25]).

A final remark should be made on the potential cardiovascular impact of NO-induced derangement of apnea regulatory mechanisms. These findings have particular relevance for the prescription of sildenafil for severe OSA patients at bedtime.

5. Conclusion

In conclusion, the present study not only confirms our findings that the use of sildenafil at bedtime plays a detrimental role in apnea events of severe OSA patients, but also demonstrates the extent of such effects on the cardiovascular system. Exacerbation of apnea in both non-REM and REM sleep, fragmentation in REM sleep, and a prolonged increase in LH/HF component of HRV after resumption of ventilation were observed in severe OSA patients after a single dose of sildenafil 50 mg at bedtime.

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Practice points

- Persistence of increased LH/HF ratio into normal respiration suggests that in OSA patients with a highly compromised upper airway, sildenafil may have a deleterious potential cardiovascular impact.
- Uncoupling between the worsened sleep respiratory parameters and arousal index was observed in SWS, whereas sleep fragmentation and increased LF/HF component of HRV occurred during REM sleep after sildenafil 50 mg at bedtime.

Research agenda

- To assess synchronized EEG patterns which occur after apnea–hypopnea events, particularly in SWS, and evaluate their relation to apnea–hypopnea events.
- To analyze capnography data as an attempt to elucidate the role of chemo- and baroreflex on the ventilatory and hemodynamic alterations induced by sildenafil in severe OSA patients.
- To recruit a larger number of subjects, with different degrees of OSA, in order to evaluate to which extent the increased NO bio-availability induced by sildenafil impact their respiratory and hemodynamic functions during sleep.
- To confirm if daytime use of sildenafil can counteract the chronically increased sympathetic efferent nerve activity reported in OSA.

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