A Double-blind, Placebo-Controlled, Crossover Study of Sildenafil in Obstructive Sleep Apnea

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Background: Sildenafil prolongs the action of cyclic guanosine monophosphate and nitric oxide by inhibiting cyclic guanosine monophosphate–specific phosphodiesterase 5. It is largely used for erectile dysfunction, a highly prevalent condition in obstructive sleep apnea. Because nitric oxide promotes upper airway congestion, muscle relaxation, and pulmonary vasodilation, the aim of this study was to establish the impact of a single 50-mg dose of sildenafil on the sleep of patients with severe obstructive sleep apnea.

Methods: Fourteen middle-aged men with severe obstructive sleep apnea were consecutively selected for this double-blind, placebo-controlled, crossover study. Exclusion criteria were obesity, cardiovascular and/or respiratory disease, and conditions that interfere with sleep. All-night polysomnography was preceded by a single 50-mg dose of sildenafil or matching placebo randomly administered at bedtime, after a washout period of 1 week.

Results: In comparison to placebo, a single 50-mg dose of sildenafil significantly increased the percentage of total sleep time with an arterial oxygen saturation of less than 90% (mean±SD, 14.2%±9.1% vs 8.5%±3.2%, \(P<.01\)), without a difference in the nadir of oxygen desaturation. The mean arterial oxygen saturation also decreased (92.1%±1.91% vs 93.8%±1.3%, \(P=.02\)), and the desaturation index increased (30.3±18.1 events per hour vs 18.5±14.6 events per hour, \(P<.001\)). There was an increase in apnea-hypopnea index (42.4±25.5 events per hour vs 34.6±24.1 events per hour, \(P=.01\)), involving mostly obstructive events.

Conclusion: In patients with severe obstructive sleep apnea, a single 50-mg dose of sildenafil at bedtime worsens respiratory and desaturation events.

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Sildenafil is a potent and selective inhibitor of cyclic guanosine monophosphate–specific phosphodiesterase 5. Therefore, it prolongs the action of cyclic guanosine monophosphate, the second messenger of nitric oxide (NO), resulting in augmented smooth muscle relaxation and vasodilation. Phosphodiesterase 5 is expressed in many tissues other than the sinusoids of the corpus cavernosum of the penis. Among the structures that may play a role in the pathogenesis of obstructive sleep apnea (OSA), phosphodiesterase 5 is expressed in nasal mucosa, tracheobronchial muscles, and pulmonary vasculature. By increasing the availability of NO, sildenafil could potentially impair respiratory function by interfering with nasal patency and by promoting relaxation of the pharyngeal muscles. Because of the vasodilatory effect of NO on the pulmonary arterial bed, an increase in the right-to-left shunt volume has been described by some authors, but not by others, in healthy individuals.

A growing body of evidence suggests that OSA is a major contributing factor in the development of erectile dysfunction; however, erectile dysfunction remains undiagnosed in 80% of patients with OSA, even in cases in which there are clear signs and symptoms of the condition. Using a double-blind, placebo-controlled, crossover design, we assessed the effects of a single 50-mg oral dose of sildenafil at bedtime on the results of polysomnography in patients with severe OSA without pulmonary hypertension.

Methods

Study Participants

Forty-nine middle-aged men with severe OSA who were consecutively selected from the database of the Sleep Laboratory of the Federal University of São Paulo, São Paulo, Brazil, were recruited for participation in our study. The inclusion criteria were age between 40 and 65 years, a body mass index (weight in kilograms divided by the height in meters squared)
of less than 30, an apnea-hypopnea index (AHI) of more than 30 events per hour of total sleep time (TST), and an oxygen desaturation (≥4%) index of 10 or more, as evidenced by recent polysomnography (performed <6 months earlier). Criteria of exclusion were daytime hypoxemia, use of nitrates or drugs that could influence sleep, current alcohol or drug abuse, and previous or current smoking of more than 10 cigarettes a day. Further exclusion criteria were acute or chronic respiratory disease based on symptoms and respiratory function test results, systemic arterial hypertension, and evidence of previous or present cardiac disease based on symptoms, 12-lead electrocardiography, or Doppler echocardiography. Subjects who participated in trials with continuous positive airway pressure were also excluded from the study. The protocol was approved by the local ethics review committee, and written informed consent was signed by all participants.

STUDY DESIGN

All participants, after signing informed consent, were evaluated for the presence of vascular or metabolic disease (ie, arterial hypertension, coronary artery disease, cerebrovascular disease, hypercholesterolemia, and diabetes mellitus) and smoking habits. To exclude cardiac and pulmonary hypertension (defined as pulmonary arterial pressure ≥20 mm Hg) and other respiratory diseases, electrocardiography, Doppler echocardiography, and respiratory function tests were performed. Subjects with negative findings (14 of 49) were submitted to baseline nocturnal polysomnography, preceded by a night of adaptation to the sleep laboratory. On the following night, each participant received 2 coded envelopes—one containing the drug and the other containing the placebo—and was asked to randomly select 1 of the envelopes and take the pill that was inside at bedtime. The pill in the remaining envelope was administered the next recording night. The codes were opened at the end of the study.

POLYSOMNOGRAPHY

Bedtime was based on each patient’s habits. A minimum of 7 hours 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 electro-oculogram, a submental electromyogram, and an electrocardiogram (modified V2 lead). Respiratory monitoring was performed as follows: airflow was measured with a nasal cannula/pressure transducer system (Pro-Tech Services Inc; Mukilteo, Wash) and a mouth thermometer; 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); snoring sounds were measured with a neck microphone, and body position movements were measured with a mercury gauge. Body position was determined by a sensor. Data analyses were collected using a 16-channel computerized sleep system (Harmonie 5.2; Stellate Systems Inc, Montreal, Quebec).

An experienced researcher who was blinded to the medication condition of the participants performed sleep scoring of the 3 polysomnograms of each subject according to the parameters previously established.16 Total sleep time was defined as the time elapsed between the first and last recorded sleep period, excluding the wakefulness. Arousals lasting more than 3 seconds were scored according to the criteria of the American Academy of Sleep Medicine, apnea was defined as a period of breathing cessation and hypopnea was defined as a 50% reduction in breathing or of a reduction in breathing of less than 50% associated with a 3% desaturation of oxygen saturation or arousal. These events had to last at least 10 seconds. The AHI was calculated as the total number of apneas and hypopneas per hour of TST.18 An obstructive AHI was defined as the number of obstructive apneas plus hypopneas per hour of TST; mixed AHI, as mixed apneas plus hypopneas per hour of TST; and central AHI, as central apneas plus hypopneas per hour of TST. The percentage of TST elapsed in apnea-hypopnea events was calculated to assess the duration of respiratory events during sleep. The desaturation index corresponded to the number of arterial oxygen desaturations per TST with a decrease greater than 4%. The percentage of TST with an SaO2 of less than 90% was also measured.

STATHICAL ANALYSIS

The results are expressed as mean with 95% confidence intervals or as mean±SD. The differences among groups were analyzed by repeated measures analysis of variance. The treatment order (placebo or sildenafil) was included in the analysis as covariate. The Bonferroni test was performed to analyze post hoc pairwise comparisons. Statistical analysis was conducted using a commercially available software package (Statistica Version 6.0; StatSoft Inc, Tulsa, Okla). Significance was defined as P<.05.

RESULTS

As mentioned, after screening for cardiovascular and pulmonary disease or metabolic syndrome, only 14 of the 49 middle-aged men with severe OSA recruited for this study were selected (age, 53.1±9.8 years; body mass index, 26.7±1.9). The most important effects of a single 50-mg dose of sildenafil at bedtime were a significant increase in desaturation index, a significant increase in the percentage of TST with an SaO2 of less than 90%, a significant increase in the maximal duration of a desaturation event, and a decrease in the mean SaO2, as well as an increase in the AHI, owing to an increase in obstructive events, and in the percentage of TST elapsed in apnea or hypopnea (Table 1). There was no significant difference in the percentage of TST spent in the supine position among baseline, sildenafil, and placebo nights: (29.8%±13.8%, 28.0%±12.0%, and 28.5%±12.1%, respectively).

Sleep structure was also modified by the use of sildenafil, with an increase in stage 2 of non–rapid eye movement (non-REM) sleep in comparison to placebo and a decrease in slow-wave sleep in comparison to baseline and placebo. These changes were seen even though no significant differences were observed among conditions in TST, sleep latency, REM latency (6.7±4.0 minutes vs 9.0±5.3 minutes [P=.10] and 99.3±43.9 minutes vs 123.6±33.1 minutes [P=.20], respectively), and percentage of the other sleep stages (Table 2). The Figure shows the results of hypnography and oximetry in 4 subjects during placebo and sildenafil intake.

Compared with those of placebo, the most common adverse effects of sildenafil were headache (2 patients vs 5 patients), flushing (1 patient vs 6 patients), and nasal congestion (2 patients vs 5 patients). Four patients reported more than 1 of these adverse effects.
COMMENT

To our knowledge, this double-blind, placebo-controlled, crossover study is the first to demonstrate that sildenafil, administered as a single 50-mg oral dose, can aggravate respiratory manifestations in middle-aged patients with severe OSA without pulmonary hypertension or other significant lung disease in terms of increase in obstructive respiratory events and in desaturation.

In order to evaluate the impact of sildenafil on patients with severe OSA, we were careful to eliminate subjects with conditions that could influence the analysis. A large number of the recruited patients were therefore excluded because of respiratory, cardiovascular, or metabolic syndrome diagnoses established previously or by our study’s screening test. Our study subjects had only severe OSA, and there may be subjects in the general population who use sildenafil and are unaware of their OSA.

Since the introduction of sildenafil in 1998,1 an increasing percentage of middle-aged men have used selective phosphodiesterase 5 inhibitor drugs to treat erectile dysfunction.19,20 Erectile dysfunction is frequent in persons with OSA, which is a condition that is related to middle-age11-14 and characterized by repetitive, complete, or partial upper airway obstruction.21 Hypoxemia can result from ventilation-perfusion mismatch, with a decrease in ventilation in normally perfused alveoli. Pulmonary vascular remodeling and hypoxic vasodilation, as a consequence of perfusion of unventilated alveolar units, is a compensatory mechanism to minimize regional ventilation-perfusion inequality during the episodic obstructions of airflow during sleep.22,23 Sildenafil increases the availability of NO, which may reverse the hypoxic vasodilation of the pulmonary circulation.24 It has been reported that in anesthetized, otherwise-normal pigs sildenafil administration augmented intrapulmonary shunt flow and lowered SaO₂.6 However, in subjects who were exposed to high altitudes, the use of sildenafil caused a suppression of the hypoxia-induced increase in mean pulmonary artery pressure, which was associated with an increase in blood oxygenation.25 Similar findings were seen in patients with lung

Table 1. Respiratory Parameters During Sleep*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Placebo</th>
<th>Sildenafil</th>
<th>F(2, 24)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SaO₂&lt;90, % TST</td>
<td>7.1 (4.6-9.6)</td>
<td>7.9 (5.9-9.9)</td>
<td>15.6† (9.8-21.4)</td>
<td>19.12</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mean SaO₂, %</td>
<td>93.8 (92.9-94.6)</td>
<td>93.8 (93.0-94.7)</td>
<td>92.2‡ (91.0-93.3)</td>
<td>4.71</td>
<td>.02</td>
</tr>
<tr>
<td>Nadir SaO₂, %</td>
<td>81.5 (79.0-84.1)</td>
<td>80.5 (77.5-83.5)</td>
<td>75.5 (69.9-81.2)</td>
<td>2.71</td>
<td>.09</td>
</tr>
<tr>
<td>Max desat, s</td>
<td>45.9 (39.4-52.4)</td>
<td>48.1 (41.1-55.1)</td>
<td>72.5† (57.8-87.2)</td>
<td>14.14</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mean desat, s</td>
<td>7.8 (5.4-10.2)</td>
<td>8.0 (5.1-10.9)</td>
<td>9.9‡ (7.0-12.7)</td>
<td>7.08</td>
<td>.004</td>
</tr>
<tr>
<td>DI</td>
<td>18.8 (12.9-24.7)</td>
<td>18.5 (13.0-24.0)</td>
<td>30.3† (21.5-39.1)</td>
<td>28.55</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>AHI</td>
<td>31.6 (23.6-39.5)</td>
<td>32.3 (25.3-39.1)</td>
<td>48.0† (35.5-60.6)</td>
<td>24.82</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Obstructive AHI</td>
<td>27.0 (19.2-34.9)</td>
<td>27.9 (21.6-34.2)</td>
<td>43.5† (31.3-55.7)</td>
<td>21.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mixed AHI</td>
<td>1.9 (1.2-2.7)</td>
<td>1.6 (1.0-2.2)</td>
<td>1.6 (0.9-2.3)</td>
<td>0.51</td>
<td>.61</td>
</tr>
<tr>
<td>Central AHI</td>
<td>2.6 (1.8-3.3)</td>
<td>2.7 (2.0-3.4)</td>
<td>2.9 (2.0-3.9)</td>
<td>0.49</td>
<td>.62</td>
</tr>
<tr>
<td>% TST AH</td>
<td>6.2 (4.3-8.1)</td>
<td>6.2 (3.8-8.7)</td>
<td>14.2† (10.9-17.5)</td>
<td>62.57</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: AH, apnea-hypopnea; AHI, AH index; CI, confidence interval; DI, desaturation index; Max desat, maximal duration of a saturation event; mean desat, mean duration of a saturation event; mean SaO₂, mean oxyhemoglobin saturation during sleep; % TST AH, percentage of total sleep time (TST) elapsed in AH events; SaO₂, oxyhemoglobin desaturation; SaO₂<90, percentage of TST with oxyhemoglobin saturation of less than 90%.

*Repeated measures analysis of variance (post hoc pairwise comparisons) was performed using the Bonferroni test.
†P<.01.
‡Differs from other conditions, P<.05.

Table 2. Sleep Architecture*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Placebo</th>
<th>Sildenafil</th>
<th>F(2, 24)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST, min</td>
<td>442.4 (404.6-480.2)</td>
<td>424.8 (394.3-455.3)</td>
<td>(391.9-461.7)</td>
<td>0.75</td>
<td>.48</td>
</tr>
<tr>
<td>Sleep efficiency, % TST</td>
<td>92.1 (85.9-95.6)</td>
<td>90.1 (85.9-94.3)</td>
<td>91.9 (88.6-95.2)</td>
<td>1.11</td>
<td>.35</td>
</tr>
<tr>
<td>Stage 1</td>
<td>7.7 (5.4-10.1)</td>
<td>8.7 (6.1-11.4)</td>
<td>5.4 (3.1-7.8)</td>
<td>2.97</td>
<td>.07</td>
</tr>
<tr>
<td>Stage 2</td>
<td>54.9 (50.3-59.5)</td>
<td>52.9 (48.4-57.4)</td>
<td>60.91 (57.8-64.0)</td>
<td>10.42</td>
<td>.001</td>
</tr>
<tr>
<td>SWS</td>
<td>17.1 (14.1-20.2)</td>
<td>17.5 (14.1-20.9)</td>
<td>12.51 (10.6-14.4)</td>
<td>9.18</td>
<td>.001</td>
</tr>
<tr>
<td>REM</td>
<td>20.3 (16.9-23.6)</td>
<td>20.8 (17.7-23.9)</td>
<td>21.3 (19.0-23.7)</td>
<td>0.27</td>
<td>.76</td>
</tr>
<tr>
<td>Arousal index, events per hour TST</td>
<td>8.5 (5.6-11.4)</td>
<td>10.4 (7.2-13.7)</td>
<td>11.3 (6.8-15.8)</td>
<td>1.63</td>
<td>.22</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; REM, rapid eye movement; SWS, slow-wave sleep; TST, total sleep time.

*Repeated measures analysis of variance (post hoc pairwise comparisons) was performed using the Bonferroni test.
†Differs from other conditions, P<.01.
fibrosis and secondary pulmonary hypertension in whom there was an improvement in pulmonary gas exchange that was probably related to selective pulmonary vasodilation in ventilated areas of the lungs. However, when nonselective vasodilators were used in patients with primary or secondary pulmonary hypertension, there was worsening of oxygenation as a result of blood flow to poorly ventilated or nonventilated areas of the lung, thereby worsening preexisting ventilation-perfusion mismatch and shunt flow.

The increase in time spent asleep with an \( \text{SaO}_2 \) of less than 90% was the major finding of this study. This increase in the severity of decreases in \( \text{SaO}_2 \) was associated not only with an increase in the frequency of obstructive apnea and hypopnea events but also with an increase in the duration of these events. These findings are consistent with the expression of undiagnosed respiratory events and may be a concern regarding the use of sildenafil by subjects with severe OSA.

It is well known that upper airway caliber is reduced during sleep and that air passage is further impaired by decreased activity of upper airway muscles, particularly the muscles involved with tonic activity (independent of the phase of respiration), such as the tensor veli palatini muscle. The mechanical consequence of reduced airway caliber is increased upper airway resistance. Because pharyngeal compliance increases during non-REM sleep, negative intrathoracic pressures normally produced in the upper airway during inspiration will result in airway collapse. Even in healthy individuals, negative intrathoracic pressure during non-REM sleep limits inspiratory flow, resulting in an inspiratory plateau that persists in the presence of increasing negative pressure.

The increase in the number and duration of apnea-hypopnea events may be related to the effect of sildenafil in prolonging the effect of NO in nasal mucosa, leading to congestion. This effect is important enough to be reported by 4% to 12% of users and may further in-

![Figure](https://jamanetwork.com/sonography/after-administration-of-placebo-and-sildenafil-in-4-patients-with-severe-obstructive-sleep-apnea)
increase nasal resistance, decrease airway passage, and increase the frequency of airway collapse during sleep. In OSA, the accumulation of muscular NO may exacerbate muscle fatigue, and the inhibition of NO synthase, which lowers NO output, seems to protect against it. Sildenafil increases NO availability, consequently yielding to accumulation of reactive nitrogen and oxygen, which may increase the tendency of upper airway collapsibility. Even though sildenafil is rapidly absorbed, reaches maximal plasma concentration within 1 hour, and has a mean terminal half-life of 3 to 5 hours after oral administration, to our knowledge there are no available studies on the duration of sildenafil’s respiratory effects. The respiratory findings cannot be attributed to change in TST or in non-REM/REM distribution. The only difference among the baseline, placebo, and sildenafil conditions was the decrease in slow-wave sleep, which can be explained by the worsening of breathing during sleep. Although less likely, the decrease in slow-wave sleep may also have contributed to a change in the AHI.

It is interesting to note that the arousal index did not increase significantly, despite the increase in the AHI and SaO2 after the use of sildenafil, which can be attributed to the great variability of the data, particularly in the sildenafil group, as shown in Table 2. Since arousal can be considered as a defense mechanism in OSA, the lack of increase in arousals is consistent with the findings of longer respiratory events in this study. Our study cannot address the question of whether a possible sleep fragmentation at the beginning of the night, when the plasma peak of sildenafil occurs, is sufficient to blunt responses to obstruction at the end of the night. One of the study’s limitations is the lack of temporal analysis of the respiratory function during sleep. Another limitation is the limited sample size. Therefore, it is premature to extrapolate our findings to all individuals with sleep-related breathing disorder before properly designed randomized, controlled trials on the effects of sildenafil and other phosphodiesterase 5 inhibitors on pulmonary gas exchange and hemodynamics are performed in patients with different severity of sleep-related breathing disorder. Nevertheless, sildenafil should be used with caution for treating erectile dysfunction in individuals with a sleep-related breathing disorder. Finally, although we were not able to clarify the mechanisms responsible for the intriguing results of the present study, we found that the use of sildenafil interfered with the compensatory mechanisms in patients with OSA, increasing the frequency and duration of respiratory and desaturation events.

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REFERENCES

Finally, Clifton’s conclusion that the high-protein, low-GI (diet 4) produced the best cardiovascular risk reduction cannot be justified for the total group or the smaller subgroup of subjects with high fasting triglyceride levels (n=38). In the latter group, diet 4 was associated with optimal mean ± SE body fat loss (−2.0±0.8 kg, −4.9±0.8 kg, −4.4±0.9 kg, and −5.6±1.0 kg for diets 1, 2, 3, and 4, respectively; P = .03) but changes in the HDL-C ratio were not significant between groups (−0.66±0.31, −0.36±0.26, −0.33±0.29, and −1.01±0.33 for diets 1, 2, 3, and 4, respectively; P = .38).

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Correction

Errors in Abstract and Text. In the Original Investigation by Roizenblatt et al titled “A Double-blind, Placebo-Controlled, Crossover Study of Sildenafil in Obstructive Sleep Apnea,” published in the September 18 issue of the Archives (2006;166:1763-1767), errors appeared in both the abstract and the text. In the “Methods” section of the abstract, the first word should have been “Thirteen” because 13, rather than 14, participants were included in the study; therefore, the “Results” section of the abstract should have read, “In comparison to placebo, a single 50-mg dose of sildenafil significantly increased the percentage of total sleep time with an arterial oxygen saturation of less than 90% (mean±SD, 15.6%±9.6% vs 7.9%±3.3%, P < .01), without a difference in the nadir of oxygen desaturation. The mean arterial oxygen saturation also decreased (92.1%±1.9% vs 93.8%±1.3%, P=.03), and the desaturation index increased (30.3±14.5 events per hour vs 18.5±9.1 events per hour, P<.001). There was an increase in apnea-hypopnea index (48.1±20.8 events per hour vs 32.3±11.3 events per hour, P<.001), involving mostly obstructive events.” Also, the first sentence of the “Results” section of the text on page 1764 should have read, “As mentioned, after screening for cardiovascular and pulmonary disease or metabolic syndrome, only 13 of the 49 middle-aged men with severe OSA recruited for this study were selected (age, 53.1±9.8 years; body mass index, 26.7±1.9).”