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JCSM is a peer-reviewed clinical journal addressing sleep, circadian rhythms, and the diagnosis and treatment of the broad spectrum of sleep disorders. Its mission and educational purpose is to promote the science and art of sleep medicine and sleep research. Sleep disorders medicine draws clinical and scientific applications from a wide variety of primary disciplines, including pulmonology, neurology, psychiatry, psychology, otolaryngology, and dentistry. Readers of JCSM should be able to: 1) appraise sleep research in basic science and clinical investigation; 2) interpret new information and updates on clinical diagnosis/treatment and apply those strategies to their practice; 3) analyze articles for the use of sound scientific and medical problems; and 4) recognize the inter-relatedness/dependence of sleep medicine with primary disciplines.

Articles in this issue that may be read for CME credit

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A Movement to Promote Healthy Sleep: The Case for Corporate Involvement
Laura Barger, Ph.D.; Stuart F. Quan, M.D.

Over the past 15 to 20 years, the fields of sleep medicine and chronobiology have gone through a metamorphosis made possible by exponential increases in knowledge related to sleep and circadian rhythm disorders, their diagnosis and treatment. New medical devices, pharmaceuticals and other interventions have been developed that have the potential not only to improve sleep but also the quality of life of afflicted individuals and to dramatically reduce mortality and morbidity from medical conditions associated with sleep deficiency and sleep disorders, such as cardiovascular disease and diabetes. Even the motor vehicle crash risk of drivers with obstructive sleep apnea is reduced with continuous positive airway pressure treatment.

Nevertheless, the number of Americans having problems with their sleep is not declining. In 2006, the Institute of Medicine estimated that 50-70 million Americans were afflicted by a disorder of sleep and wakefulness. Sleep disorders result not only negative personal impacts on health and wellness but also substantial adverse economic consequences for society as a whole. Furthermore, most Americans are sleeping less. Thirty percent of US workers report nightly sleep durations of ≤ 6 hours, in contrast to 50 years ago when only 3% of the population reported such short sleep duration. The reason for the vast reduction in sleep is multifactorial including: societal pressures such as working long hours; competing priorities (e.g., working multiple jobs and/or childcare); widespread use/abuse of caffeine and other stimulants; artificial lighting, internet and video game use, round-the-clock television channels, and, more generally, societal and individual attitudes towards sleep; and the perceived need to use electronic devices (e.g., smart phones, tablets) to remain “connected” 24/7.

Why do we have this paradox of increased scientific knowledge regarding the importance of sleep and people sleeping fewer hours? Although the importance of sleep may not be appreciated by some individuals, the lack of public awareness is likely not the primary explanation. This supposition is supported by results from an informal survey conducted at a recent business conference of several thousand persons attended by one of the authors. It showed the vast majority of the attendees realized adequate sleep was important for their health and well-being. Nevertheless, large numbers still reported sleeping less than 7 hours per night suggesting that knowledge is not being translated into practice.

What can be done to change behavior such that it is more in line with the current knowledge of sleep health? Certainly making easily accessible information available over the internet and other venues is helpful. However, we contend that it is time for a national movement to imbue sleep health into the public consciousness and make it part of our social fabric. Similar revolutionary movements have changed public attitudes towards smoking, and have led to more stringent laws and penalties against drunk driving. To be successful, the movement will need to engage multiple stakeholders. Entities such as professional societies (e.g., American Academy of Sleep Medicine, Sleep Research Society), and academic institutions will be needed to demonstrate leadership and energize their memberships. The real strength of the movement, however, may come from corporate America. It has been proposed that sleep health is a business issue as well as a healthcare issue. Presenteeism, accidents, poor judgment and absenteeism due to poor sleep health all have direct impacts on corporate productivity. Furthermore, when poor sleep health leads to chronic sleep disorders, corporate healthcare costs increase due the rising incidence of the comorbidities of sleep disorders.

Millions of Americans are employed by large corporations. For example, a major corporation such as Walmart employs 1.4 million people or 1% of the working population of the United States. If major corporations could be recruited to join the movement and institute sleep health friendly policies, they would be improving the health of their employees as well as their own economic “bottom line.” A simple first step for corporations would be to add sleep health to their existing wellness programs. Healthy sleep educational classes could be developed and implemented. Vulnerable individuals at high risk for sleep disorders could be identified by simple screening questionnaires and referred for further evaluation and treatment, if required. Finally, sleep-friendly corporate policies discouraging late night texts and emails could be instituted. These trailblazing corporations would be demonstrating leadership that would result in adoption of similar policies by other employers, eventually resulting in a “snowball” effect that could engage all Americans.

The science of sleep and circadian biology has demonstrated that sufficient, high quality sleep is indeed the third pillar of...
health along with nutrition and exercise. The time is ripe for a movement to translate this knowledge into action.

CITATION


REFERENCES


DISCLOSURE STATEMENT

Dr. Quan is the Editor-in-Chief of the Journal of Clinical Sleep Medicine. Dr. Barger has consulted for Alertness Solutions.
Blue-Light-Blocking Intraocular Lens Implantation Improves the Sleep Quality of Cataract Patients

Xin Wei, M.D., Ph.D.; Chunyan She, M.D.; Danian Chen, M.D., Ph.D.; Fangbing Yan, M.D.; Jihong Zeng, R.N.; Liping Zeng, R.N.; Lin Wang, M.D.

Department of Ophthalmology, Ophthalmic laboratory of Molecular Medicine Research Center, State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, Chengdu, China

Study Objectives: To evaluate whether blue-light-blocking intraocular lens implantation affects the sleep quality of cataract patients.

Design: Pre-test/post-test experiment.

Setting: N/A.

Participants: 40 patients having bilateral cataracts with level higher than N3 (LOCS II) nucleus hardness, including 26 females (65%) and 14 males (35%).

Interventions: Cataract phacoemulsification followed by blue-light-blocking intraocular lens (IOLs, SN60WF, Alcon Laboratories, USA) implantation.

Measurements and Results: Patients were contacted in site before cataract surgery and followed by telephone at least 2 months later after second-eye surgery. Pittsburgh Sleep Quality Index (PSQI) questionnaires were administered to evaluate sleep quality. Median age of patients was 74 years (IQR 70 to 78). The median PSQI globe scores were 7 before surgery and 4 after surgery (Z = -2.121, p = 0.037). More specifically, there were significant differences on subjective sleep quality (Z = -2.064, p = 0.045), sleep duration (Z = -2.037, p = 0.047) and daytime dysfunction (Z = -2.142, p = 0.034) when compared between before and after surgeries. The ratio of poor sleepers (PSQI > 5) was reduced significantly after surgery ($\chi^2 = 14.532$, p < 0.001).

Conclusions: Blue-light-blocking IOL had a significantly beneficial effect on the sleep quality of cataract patients.

Keywords: Sleep quality, cataract, blue light, IOL, PSQI

Citation: Wei X; She C; Chen D; Yan F; Zeng J; Zeng L; Wang L. Blue-light-blocking intraocular lens implantation improves the sleep quality of cataract patients. J Clin Sleep Med 2013;9(8):741-745.

With aging, the human lens becomes a strong color filter attenuating light transmission, particularly for the short wavelengths. However, light of short wavelength is important in the control of the sleep-wake cycle (circadian rhythm), which is well known as photoentrainment of circadian rhythm. Circadian rhythm is regulated by melatonin produced by the pineal gland. Photoentrainment of circadian rhythm is mainly mediated by intrinsically photosensitive retinal ganglion cells (ipRGCs) containing melanopsin that allows melatonin suppression via the retinohypothalamic tract. Even though the ipRGCs can function in the absence of rods and cones, their output is normally regulated by input from the rod and cone photoreceptors.

Brainard et al. reported the influence of various monochromatic lights on melatonin secretion and found that a peak of the action spectrum at 464 nm. Morita and Tokura also indicated that a light with more short wavelengths reduced melatonin secretion and decreased the fall of core temperature in the evening and night, causing an inhibitory effect on nocturnal sleep.

In pathological conditions such as cataract, the reduction in light transmission in the eye can be very dramatic. Short wavelength light plays an important role on the inhibition of melatonin secretion. Therefore cataract patients, whose optical systems transmit light poorly (especially short wavelengths), would be likely to experience sleepiness in the daytime because there is not enough short wavelength light to reduce melatonin secretion. Consequently, they commonly have poor sleep in the night and are susceptible to sleep disturbances. For this reason, cataract surgery may improve not only their sight but also the quality of their sleep. Initially, intraocular lenses (IOLs) implanted during cataract surgery allowed the passage of all the visible light. However, it was found erythropsia (a temporary distortion of color vision where objects appear with an abnormal reddish hue), photic retinopathy (retinal dysfunction which is induced by too much light exposure), and cystoid macular edema (fluid accumulation in the outer plexiform layer and cyst formation, a common cause of decreased vision following cataract surgery) occurred in patients with these IOLs.

Previous works suggest that long time exposure in the blue range (approximately 475 nm) may injure an aging retina and cause photoreceptor damage and possibly lead to the development of other disease processes such as age-related macular
degeneration.\textsuperscript{13-17} Therefore, in recent years, IOLs have been manufactured with a filter that blocks the passage of blue light. Although the filter can protect the posterior segment of the eye in theory, there have been few reports of its advantage, and many researchers still believed that a filter that blocks blue light may have detrimental effects.\textsuperscript{20-22} Landers and colleagues\textsuperscript{23} reported that compared to the conventional IOLs, blue-light-blocking IOLs had no detrimental effect on the sleep quality. However, Landers’ study lacked assessment of the patient’s sleep quality before surgery, and their study was conducted in a geographical region remarkable for its sunny climate. In order to confirm these initial findings in more patients and in a geographical region with less sunshine, we designed a study to evaluate whether cataract phacoemulsification (one kind of cataract extraction surgery, which uses ultrasonic power to emulsify the cataract in to aspirate it from two small incisions) combine blue-light-blocking intraocular lens implantation has an effect on sleep quality based on large sample size in Sichuan, China.

METHODS

Participants

Considering that nucleus hardness is the most important factor for light transmission, 40 bilateral cataract patients with nucleus hardness > level N3 (Lens Opacity Classification System II, LOCS II) were recruited from the outpatient clinic of the Department of Ophthalmology, West China Hospital, Chengdu, China into this study. LOCS II is a grading system for cataract according to the transparency of the lens. Focusing on the nucleus hardness, it can be divided into 4 levels (level N0: transparent nucleus, colorless; N1: soft nucleus, yellow-white color; N2: medium hardness nucleus, yellow color; N3: stiff nucleus, dark brown color). Patients were chosen who required bilateral cataract phacoemulsification followed by blue-light-blocking intraocular lens (SN60WF, Alcon Laboratories, USA) implantation due to visual acuity less than 0.2. To evaluate the nucleus hardness more accurately, 2 doctors provided independent evaluations. If one of these two doctors was not sure the nucleus hardness was > N3, a third doctor provided evaluation. Informed consent was obtained from each patient prior to the beginning of the experiment. Exclusion criteria included: IOL could not implanted during surgery, retinal or optic nerve disorders that might interfere with light perception or color perception (e.g., retinitis pigmentosa, anterior ischemic optic neuropathy, diabetes, glaucoma), color blindness, and inability to complete a questionnaire due to confusion or dementia. Postoperative refractive error and visual acuity were not exclusions.

Study Design

Study design was a pre-test/post-test experiment.

Measurements

Transmission curve measurement

The transmission curves of the blue-light-blocking intraocular lens (+20.0D SN60WF IOL, Alcon Laboratories, USA) and the typical conventional intraocular lens (+20.0D AR40e IOL, Abbott Medical Optics Inc, USA) were obtained by using an UV/Vis Spectrometer Lambda 14 (Perkin-Elmer Lambda; Shelton, CT). The sources are 2 lamps, one halogen and the other deuterium, which can cover both the UV and the visible lights. The apparatus uses 2 monochromators to select the wavelength (\(\lambda\)) accurately. Light passes through the IOLs and is measured before entering the integrating sphere. A suitable cuvette is used to place the IOLs directly in front and covering the complete entrance hole of the integrating sphere. Spectral of the human lenses were adapted from Boettner and Wolter.\textsuperscript{24}

Pittsburgh Sleep Quality Index (PSQI)

The questionnaire administered in this study was the Pittsburgh Sleep Quality Index (PSQI, Table 1). This 17-item questionnaire was designed to assess self-rated sleep quality and disturbances over a 1-month time period and to help investigators distinguish between “good” and “poor” sleepers. The PSQI included 7 component scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, daytime dysfunction, and a total global score. Each component was scored 0 to 3, with 3 indicating the worst score. The highest possible global score is 21; and a score > 5 indicates a poor sleeper. The PSQI has been in clinical use for almost 20 years and over that time has consistently shown robust validity and reliability.\textsuperscript{25-28} The surgeries of this study were carried out between January 2012 to March 2012. All eligible patients completed the questionnaire within 3 days before their cataract surgery. Investigators did not tell subjects the supposed relationship between IOL and sleep quality. This was followed by a telephone call 2 months later after they completed bilateral surgeries. During the call, the same questionnaire was administered.

Statistical Analyses

Given that the data were not normally distributed, Statistical Analysis System software (SigmaPlot 12.2, SYSTAT) was used for statistical analysis, including Wilcoxon’s signed rank test, chi-square test. Medians and interquartile ranges (IQR) were recorded. Odds ratios and 95% confidence intervals were also recorded.

RESULTS

Our study confirmed that in visible light, the shorter wavelength (380-480 nm) light’s transmittance of the blue-light-blocking lens (SN60WF) was much lower than that of the conventional intraocular lens (AR40e), but interestingly, it is very close to that of the 53-year-old human’s natural crystalline lens at short wavelengths range from 350 nm to 465 nm.

Of 40 patients who were eligible, 26 were women (65%) and 14 were men (35%). The data were not normally distributed, the median age of all patients was 74 years (IQR 70 to 78); of female patients, 73 years (IQR 67 to 79) and of male patients, 75 years (IQR 70 to 80). The median PSQI component score before surgery of all patients was 2 (IQR 0 to 3) for subjective sleep quality, 0 (IQR 0 to 1) for sleep latency, 2 (IQR 0 to 3) for sleep duration, 1 (IQR 0 to 1) for habitual sleep efficiency, 1 (IQR 0 to 2) for sleep disturbances, 0 (IQR 0 to 1) for use of sleeping medication, and 1 (IQR 0 to 1) for daytime dysfunction. The median global score of all patients was 7 (IQR 3 to 13); 30 patients (75%) had a global score > 5 and were considered to be poor sleepers (Table 2).

<table>
<thead>
<tr>
<th>TABLE 1: (\text{PsqI component score before surgery (IQR 0 to 3).} )</th>
<th>(\text{N} = \text{40} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\text{Subjective Sleep Quality} )</td>
<td>2 (IQR 0 to 3)</td>
</tr>
<tr>
<td>(\text{Sleep Latency} )</td>
<td>0 (IQR 0 to 1)</td>
</tr>
<tr>
<td>(\text{Sleep Duration} )</td>
<td>2 (IQR 0 to 3)</td>
</tr>
<tr>
<td>(\text{Habitual Sleep Efficiency} )</td>
<td>1 (IQR 0 to 1)</td>
</tr>
<tr>
<td>(\text{Sleep Disturbances} )</td>
<td>1 (IQR 0 to 2)</td>
</tr>
<tr>
<td>(\text{Use of Sleeping Medication} )</td>
<td>0 (IQR 0 to 1)</td>
</tr>
<tr>
<td>(\text{Daytime Dysfunction} )</td>
<td>1 (IQR 0 to 1)</td>
</tr>
<tr>
<td>(\text{Global Score} )</td>
<td>7 (IQR 3 to 13)</td>
</tr>
</tbody>
</table>

Journal of Clinical Sleep Medicine, Vol. 9, No. 8, 2013
Two months after patients received bilateral cataract phacoemulsification and blue-light-blocking lens implantation, the median PSQI component score of all patients was 1 (IQR 0 to 2) for subjective sleep quality, 0 (IQR 0 to 1) for sleep latency, 1 (IQR 0 to 3) for sleep duration, 1 (IQR 0 to 2) for habitual sleep efficiency, 1 (IQR 0 to 2) for sleep disturbances, 0 (IQR 0 to 1) for use of sleeping medication, and 0 (IQR 0 to 1) for daytime dysfunction. The median global score of all patients was 4 (IQR 2 to 7); only 13 patients (32.5%) had a global score > 5 and were considered poor sleepers.

Between the two timepoints, there was a significant difference in global score (Z = -2.121, p = 0.037). More specifically, there were significant differences in subjective sleep quality (Z = -2.064, p = 0.045), sleep duration (Z = -2.037, p = 0.047), and daytime dysfunction (Z = -2.142, p = 0.034) before and after surgery (Table 2).

As a result of cataract phacoemulsification with blue-light-blocking intraocular lens implantation, 56.67% of subjects went from having an abnormal PSQI (> 5) to normal ≤ 5 PSQI. The ratio of poor sleepers (PSQI > 5) reduced significantly after surgery (χ² = 14.532, p = 0.000); the odds ratios were 6.231 and 95% confidence intervals were (2.351, 12.513).

Table 1—The Pittsburgh Sleep Quality Index Questionnaire

<table>
<thead>
<tr>
<th>PITTSBURGH SLEEP QUALITY INDEX (PSQI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. During the past month, when have you usually gone to bed at night?</td>
</tr>
<tr>
<td>2. During the past month, how long (in minutes) has it usually taken you to fall asleep each night?</td>
</tr>
<tr>
<td>3. During the past month, when have you usually gotten up in the morning?</td>
</tr>
<tr>
<td>4. During the past month, how many hours of actual sleep did you get at night? (This maybe different than the number of hours you spend in bed.)</td>
</tr>
<tr>
<td>5. During the past month, how often have you had trouble sleeping because you...</td>
</tr>
<tr>
<td>(a) Cannot get to sleep within 30 minutes.</td>
</tr>
<tr>
<td>(b) Wake up in the middle of the night or early morning.</td>
</tr>
<tr>
<td>(c) Have to get up to use the bathroom.</td>
</tr>
<tr>
<td>(d) Cannot breathe comfortably.</td>
</tr>
<tr>
<td>(e) Cough or snore loudly.</td>
</tr>
<tr>
<td>(f) Feel too cold.</td>
</tr>
<tr>
<td>(g) Feel too hot.</td>
</tr>
<tr>
<td>(h) Had bad dreams.</td>
</tr>
<tr>
<td>(i) Have pain.</td>
</tr>
<tr>
<td>6. During the past month, how would you rate your sleep quality overall?</td>
</tr>
<tr>
<td>Very good</td>
</tr>
<tr>
<td>7. During the past month, how often have you taken medicine (prescribed or “over the counter”) to help you sleep?</td>
</tr>
<tr>
<td>8. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?</td>
</tr>
<tr>
<td>9. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?</td>
</tr>
<tr>
<td>No problem at all</td>
</tr>
</tbody>
</table>

Table 2—Pittsburgh Sleep Quality Index scores before and after surgery

<table>
<thead>
<tr>
<th>Cataract Phacoemulsification with IOL Implantation (SN60WF)</th>
<th>Parameter</th>
<th>Before</th>
<th>After</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSQI scores</td>
<td>Global</td>
<td>Median score</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>IQR</td>
<td>3-13</td>
<td>2-7</td>
<td></td>
</tr>
<tr>
<td>Median component scores</td>
<td>Subjective sleep quality</td>
<td>2</td>
<td>1</td>
<td>0.045</td>
</tr>
<tr>
<td></td>
<td>Sleep latency</td>
<td>0</td>
<td>0</td>
<td>0.479</td>
</tr>
<tr>
<td></td>
<td>Sleep duration</td>
<td>2</td>
<td>1</td>
<td>0.047</td>
</tr>
<tr>
<td></td>
<td>Habitual sleep efficiency</td>
<td>1</td>
<td>1</td>
<td>0.644</td>
</tr>
<tr>
<td></td>
<td>Sleep disturbances</td>
<td>1</td>
<td>1</td>
<td>0.697</td>
</tr>
<tr>
<td></td>
<td>Use of sleeping medication</td>
<td>0</td>
<td>0</td>
<td>0.921</td>
</tr>
<tr>
<td></td>
<td>Daytime dysfunction</td>
<td>1</td>
<td>0</td>
<td>0.034</td>
</tr>
<tr>
<td></td>
<td>Poor sleepers &gt; 5 global score, n (%)</td>
<td>30 (75%)</td>
<td>13 (32.5%)</td>
<td>0</td>
</tr>
</tbody>
</table>

DISCUSSION

Any medical device must be evaluated to ensure that it has no adverse effects. Our study found there is beneficial effect to cataract patients on sleep quality after cataract surgery and blue-light-blocking IOL implantation. Patients in our study who with the nucleus hardness over than level N3 (LOCS II) typically slept for a median of 5.5 hours per day, and they slept for 6.5 hours per day after cataract surgery combined blue-light-blocking IOL implantation. Very high ratio (75%) patients before surgery were considered to be poor sleepers as their PSQI
Cal fashion. The secretion of melatonin could induce sleep.32 As organs is the pineal gland which secretes melatonin in a cyclic effect.37 However in stark contrast, our results clearly indicate and insomnia or depression because of the blue light-blocking may be susceptible to sleep disturbances, daytime sleepiness, This suggests that the patients with blue-light-blocking IOLs and affective disorders not only on retina, but also on sleep quality. There are still several limitations of this observation. First, there is no control group, so we cannot compare the sleep quality between conventional IOL and blue-light-blocking IOL implantation. Second, we did not measure other circadian rhythm indicators such as the Horne-Ostberg morningness-eveningness questionnaire or core temperatures. While our patients have improved sleep quality, we have no idea if they have a normal circadian rhythm. Third, it is difficult for us to be double-blinded to the treatment, so there might be bias. Nevertheless, our data indicate that blue-light-blocking IOL has a significantly beneficial effect on the sleep quality of cataract patients. Thus blue-blocking intraocular implants could be used routinely during cataract phacoemulsification surgery.

![Figure 1 — Spectral transmittance curves of the human natural lens at age 53 years, a +20.0D blue-light-blocking IOL (SN60WF) and a +20.0D conventional IOL (AR40e)](image)

Spectral of the human lenses were adapted from Boettner and Wolter.35

scores were greater than 5 and their median PSQI scores were similar with those in a previous population-based assessment of patients of the same age.29 The circadian rhythm is controlled by suprachiasmatic nucleus in hypothalamus30,31 whose activity increases and decreases over a period of nearly 24.5 hours.32 One of its target organs is the pineal gland which secretes melatonin in a cyclical fashion. The secretion of melatonin could induce sleep.33 As mentioned above, the light-triggered melatonin suppression is most sensitive to blue light, and it has also been proved theoretically that short-wavelength light is important in maintaining a balanced circadian rhythm and a regular sleep-wake cycle.33,36 This suggests that the patients with blue-light-blocking IOLs may be susceptible to sleep disturbances, daytime sleepiness, and insomnia or depression because of the blue-light-blocking effect.33 However in stark contrast, our results clearly indicate this is not the case, blue-light-blocking IOLs actually improve the sleep quality of cataract patients. One reason for this phenomenon is that blue-light-blocking IOLs block blue lights only partially. Indeed, based on the spectral transmittance spectral curve as shown in Figure 1, though the blue light transmittance of the blue-light-blocking IOL is much lower than that of conventional IOL, but it is very close to that of a 53-year-old human natural lens, which still allows 10% to 70% of 400-500 nm light through. It seems that this amount of blue lights is sufficient to suppress the melatonin production, and thus keep the circadian rhythm. Another possibility is that patients with blue-light-blocking IOL may have more rods, cones, and ipRGCs (as this type of IOL can protect retina from light damages), thus are more sensitive to blue light. This will compensate for the lost blue lights by this type of IOL. This conclusion is consistent with Landers’ finding that the sleep quality is the same in cataract patients with conventional IOLs and blue-light blocking IOLs.35

Blue-light-blocking IOLs have beneficial effect on the retina of cataract patients. They could lower the risk of erythropsia, photic retinopathy, and cataract macular edema.9,32 Blue-light-blocking IOLs do not reduce visual acuity, contrast sensitivity, color vision,38-41 or scotopic sensitivity42-44 of cataract patients. The ophthalmologist’s only concern is whether blue-light-blocking IOLs affect the sleep quality of cataract patients. Based on our data and Landers’ results, blue-light-blocking IOL is a good choice for cataract patients because they have beneficial effects not only on retina, but also on sleep quality.

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Blue-Light-Blocking IOL Improves Sleep Quality

Author contributions: Xin Wei and Lin Wang were responsible for drafting the manuscript, study concept, data acquisition and manuscript revision; Chunyong Yan, Jihong Zeng, and Liping Zeng were responsible for data acquisition, analysis, and interpretation; Danian Chen provided comments on the manuscript. This work was supported by grants from Natural Science Foundation of China #81200887, Research Fund of Young Scholars For The Doctoral Program of Higher Education of China #20120181120014, and Science and Technology Support Program of Chengdu #12DXYB058JH-002 to Dr. Wei.

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DISCLOSURE STATEMENT

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Chronic rhinosinusitis (CRS) refers to inflammation of the nasal mucosa and the mucosa of the paranasal sinuses. Presenting symptoms of CRS can include facial pain, headache, rhinorrhea, hyposmia, and dental pain. Chronic rhinosinusitis is highly prevalent with an estimated 1 in 7 people affected in North America. The annual cost to the American health care system is estimated at $5.8 billion US. CRS significantly affects patients’ quality of life, as shown by a study by Macdonald et al. in which patients with CRS self-rated their health consistently worse than patients with allergies and back pain, and statistically equivalent to patients suffering from cancer and inflammatory bowel disease.

Obstructive sleep apnea (OSA) is another highly prevalent disorder, with an estimated 3% of women and 9% of men variably affected. Symptoms can include daytime fatigue, irritability, and personality changes. It has also been associated with cardiopulmonary changes such as systemic hypertension, pulmonary hypertension, and heart failure, as well as motor vehicle accidents. The mainstay of treatment for OSA is continuous positive airway pressure (CPAP), which delivers a stream of air to the patient’s airway continually to splint open the airway and prevent collapse.

In 2007, a study by Aydin et al. demonstrated that reusable nasal steroid spray bottles used in treatment of CRS can be positive for bacterial colonization, and that this may be associated with recalcitrant cases. More recently, in a study by Lee et al., 50% of their samples’ nasal irrigation bottles had positive microbacterial cultures. While many viruses and bacteria have the potential to cause a simple episode of acute rhinosinusitis, there are some organisms that have been known to have devastating effects when the nasal cavity is exposed to them. Naegleria fowleri is a freshwater amoeba that can lead to a rare, but nearly always fatal type of primary amoebic meningoencephalitis (PAM). In 2011, the Louisiana Department of Health and Hospitals issued a warning about proper sterilization of water used in nasal irrigations following the death of 2 people linked to PAM who developed PAM secondary to improperly sterilized tap water in their nasal rinses. These cases, therefore, highlight the importance of sinonasal infections.

While nasal irrigations and their bacterial contamination has been analyzed in the CRS literature before, to our knowledge, there are no studies that look at whether contamination and colonization of CPAP machines occurs as frequently, and whether this has significant health ramifications. Since the basis of the nasal CPAP machine involves blowing humidified air into the patient’s nose, it stands to reason that if bacteria were to colonize the CPAP machine, bacterial seeding of the nasal mucosa could occur as a result of the CPAP usage. The purpose of our study was to investigate whether bacterial colonization of the continuous positive airway pressure (CPAP) machine reservoirs occurred, and if so, if it was related to the development of chronic rhinosinusitis (CRS).

**Study Objective:** The purpose of our study was to investigate whether bacterial colonization of the continuous positive airway pressure (CPAP) machine reservoirs occurred, and if so, if it was related to the development of chronic rhinosinusitis (CRS).

**Design:** Prospective cohort study.

**Setting:** London Health Sciences Center (LHSC).

**Patients:** Regular CPAP users with obstructive sleep apnea (OSA).

**Interventions:** N/A.

**Measurements and Results:** Patient demographics were recorded and they were asked to fill out the chronic sinusitis survey (CSS) form. Patients then had their CPAP machines swabbed. An ANOVA was used to determine if the presence of microbacterial colonization was related to CSS scores. In total, 72 patients were included in the study. There was no significant difference in any of the scores between the group with positive cultures and the group without positive cultures.

**Conclusions:** Having a positive culture in the CPAP reservoir does not seem to lead to an increased symptomatology of CRS. Although the reservoirs often become colonized, there seems to be no clinical impact.

**Keywords:** CRS, sinusitis, CPAP, bacteria, contamination

**Citation:** Chin CJ; George C; Lannigan R; Rotenberg BW. Association of CPAP bacterial colonization with chronic rhinosinusitis. J Clin Sleep Med 2013;9(8):747-750.
goal of our study was to investigate whether bacterial colonization of the CPAP reservoirs occurred, and if so, if it was related to CRS.

METHODS

The Western University research ethics board approved this study. Patients were recruited from both a tertiary care Otolaryngology-Head and Neck Surgery practice as well as a Respiratory practice with a focus on Sleep Medicine. Inclusion criteria were that of any patient who was a regular CPAP user for obstructive sleep apnea purposes. Patients with a known history of CRS, known nasal allergies, used nasal sprays/rinses regularly, were smokers, or who had any prior nasal surgery, were excluded from the study. After informed consent, patient demographics were recorded and they were asked to fill out the chronic sinusitis survey (CSS) form. The CSS is a validated tool that has good test-retest reliability and is frequently used as a screen to assess patients’ quality of life as related to potential CRS. Specifically, the CSS consists of 2 parts. The first part asks the patient to rate the severity of their symptoms (divided into left and right side), while the second part asks about duration of symptoms, as well as duration of medical therapy they have received recently. Patients then had their CPAP machines swabbed in 3 locations: the mask, the tubing of the machine, and the reservoir.

Patients had their average score on the CSS form calculated for both the symptoms and duration parts of the survey. Once this was completed, the microbacterial cultures were checked, to see whether there was evidence of bacterial or fungal growth. Positive cultures (of any bacteria or fungi) were assigned a value of 1, while those swabs that failed to grow anything were assigned a value of 0. In this way, the patients were separated into 2 groups, and an ANOVA test was used to compare the groups (with p set at 0.05 a priori) to analyze whether the presence of bacteria was related to the CSS scores. Data analysis was completed using PASW Statistics 18.

RESULTS

Eighty patients were recruited into the study (8 from the Otolaryngology-Head and Neck Surgery clinic and 72 from the Respiratory clinic). Of those patients, 8 were excluded because they had incompletely completed surveys or because their microbacterial cultures were never reported, leaving 72 patients for the final study population. AHI ranged from 51.5+/-25, with a minimum of 5 and maximum of 104. Overall CPAP compliance in the study population was 85.8% ± 17.1% (~3.3 ± 0.7 h per night), with no difference between groups. Demographic details are found in Table 1. A breakdown of the various microbacterial organisms that were grown can be seen in Table 2.

While we initially planned to analyze the 3 sub-sites of the CPAP system (mask, tubing, reservoir), we found that the reservoir generated by far the widest variety of microorganisms when compared to the mask and tubing. In fact, in the mask, over 90% of the cultures were coagulase-negative staphylococci, which is not surprising given the contact the mask makes with the skin. We therefore focused our analysis exclusively on the reservoirs.

The patients were divided into 2 groups—those who had positive cultures in their reservoir and those who did not. In total, 35 patients had positive cultures (48.6%). The average scores for the various parts of the CSS can be seen in Figures 1 and 2. There was no significant difference for any of the scores between the group with positive cultures and the group without positive cultures.

<table>
<thead>
<tr>
<th>Table 1—Patient demographics</th>
</tr>
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<tbody>
<tr>
<td>Sample Size</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Males:Females</td>
</tr>
<tr>
<td>AHI (mean)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2—Microbacterial organisms found in the reservoirs, masks, and tubing systems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organism</td>
</tr>
<tr>
<td>Gram-negative rods</td>
</tr>
<tr>
<td>Coagulase-negative Staphylococcus</td>
</tr>
<tr>
<td>Bacillus Sp.</td>
</tr>
<tr>
<td>Diphtheroids Sp.</td>
</tr>
<tr>
<td>Pseudomonas</td>
</tr>
<tr>
<td>Gram-positive rods</td>
</tr>
<tr>
<td>Yeast</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
</tr>
<tr>
<td>Other</td>
</tr>
</tbody>
</table>

Figure 1—Mean scores of part 1 of the CSS divided by culture status
Next, the average scores for Part 1 (symptoms) of the CSS were calculated. In this part of the survey, patients were asked to rank how bad their symptoms were (pain, congestion, and rhinorrhea) on the left side and right side of their face. The scoring system sets 0 as “No Symptoms” and 4 as “Severe.” All symptoms had overall average scores ≤ 1.0, which indicates mild symptoms.

Then the average scores for Part 2 (duration) of the CSS were determined. This part of the survey asks patients in the past 8 weeks, how often they have had symptoms (headache, rhinorrhea, or congestion) or taken medications (antibiotics, nasal sprays, or pills [decongestants or antihistamines]). The average scores for symptoms all fell between 1 and 2 (indicating symptoms present just 1-2 weeks of the previous 8 weeks), and for medications the average was < 1.

**DISCUSSION**

In our study, we hypothesized that those patients who had positive microbacterial cultures in their CPAP reservoir would have symptomatology of CRS more frequently than those who did not, as a result of the humidified air “seeding” the nasal cavity and sinuses with the microbes present in the reservoir. However, the study results did not support this hypothesis—CRS symptoms were mild in all patients (whether CPAP culture positive or negative), and despite demonstration of some unusual flora in the CPAP reservoir, there did not appear to be an association between CPAP microbiology and CRS symptoms. Having a positive culture in the CPAP reservoir does not seem to lead to an increased symptomatology of CRS. This could be interpreted that although the reservoirs often become colonized, there seems to be no clinical impact.

Our findings were similar to the findings of a previous study, in that the patients with a positive culture in their irrigation bottle did not have an increased chance of developing symptomatic CRS. While it is generally advised that the reservoir should only be used with sterile water, a review of the literature did not demonstrate any evidence to support this recommendation at this time. Furthermore, in a 2012 Cochrane Review, Fernandez et al. found that there was no difference in infection rates of acute wounds when tap water was used as compared to sterile water. It would seem then that further investigation regarding whether water from a non-sterile source (for example, tap water) has detrimental effects is warranted.

A wide variety of microorganisms were cultured in this study. This ranged from yeast to Enterococci to *Pseudomonas* and Gram-negative rods. While certain pathogens, like the previously mentioned *Naegleria fowleri*, can have devastating clinical effects, in our study the patients with positive cultures did not seem to have any adverse clinical effects.

Likely, the reason that our patients did not develop clinically significant disease is multifactorial and can in part probably be related to our study design and its limitations. First, although the reservoir was cultured positive, this did not necessarily translate to these same microorganisms making their way through the CPAP tubing to reach the patients sinuses. Perhaps the degree of inoculation was not sufficient to cause any serious health effects. As well, just one swab was taken for each patient’s reservoir. It is possible that through sampling error, those patients who had a “negative culture” actually had other areas of the reservoir that were in fact positive. More comprehensive swabbing of the reservoirs could potentially address this issue. Another reason why the microorganisms may not have caused adverse events is that of biofilms. Perhaps the bacteria in the reservoir had created biofilms that not only ensured their survival in the reservoir, but also prevented the bacteria from being distributed throughout the CPAP system. Lastly, the compliance rate of CPAP can be variable, and although in our study there was no difference in compliance between groups, it could be that a larger population might show a difference in that regard.

In summary, in our study population, there was no association seen between floral colonization of CPAP machine and symptoms of chronic rhinosinusitis.

**REFERENCES**


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Efficacy and Safety of Adjunctive Modafinil Treatment on Residual Excessive Daytime Sleepiness among Nasal Continuous Positive Airway Pressure-Treated Japanese Patients with Obstructive Sleep Apnea Syndrome: A Double-Blind Placebo-Controlled Study

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Study Objectives: This double-blind study evaluated the efficacy and safety of modafinil for treating excessive daytime sleepiness in Japanese patients with obstructive sleep apnea syndrome (OSAS).

Methods: Patients with residual excessive sleepiness (Epworth Sleepiness Scale [ESS] ≥ 11) on optimal nasal continuous positive airway pressure (nCPAP) therapy (apnea-hypopnea index ≤ 10) were randomized to either 200 mg modafinil (n = 52) or placebo (n = 62) once daily for 4 weeks. Outcomes included baseline-week 4 changes in ESS total score, sleep latency on maintenance of wakefulness test (SL-MWT), nocturnal polysomnography, Pittsburgh Sleep Quality Index (PSQI), and safety.

Results: All 114 randomized patients completed the study. Mean change in ESS total score (-6.6 vs -2.4, p < 0.001) and SL-MWT (+2.8 vs -0.4 minutes, p = 0.009) were significantly greater with modafinil than with placebo. ESS total score decreased from > 11 to < 11 at the final assessment in 69.2% of modafinil-treated patients and 30.6% of placebo-treated patients (p < 0.001). Corresponding rates at week 1 were 57.7% and 33.9% (p = 0.014). Changes in nocturnal polysomnography, PSQI, and apnea-hypopnea index from baseline to the final assessment were similar in both groups. Adverse drug reactions occurred in 36.5% and 22.6% of patients in the modafinil and placebo groups, respectively (p = 0.146).

Conclusions: Once-daily modafinil was effective and well tolerated for managing residual daytime sleepiness in Japanese OSAS patients with residual excessive daytime sleepiness on optimal nCPAP therapy.

Clinical Trial Registration: JapicCTI-No.090777

Keywords: Randomized clinical trial, daytime sleepiness, Epworth Sleepiness Scale, modafinil, nasal continuous positive airway pressure, maintenance of wakefulness test, obstructive sleep apnea, safety


Obstructive sleep apnea syndrome (OSAS) is a chronic condition characterized by recurrent episodes of upper airway collapse that occur during sleep. OSAS frequently causes nocturnal intermittent hypoxemia, sympathetic activation and fragmented/disrupted sleep. Studies of Caucasian and Asian populations have consistently estimated that the prevalence of OSAS associated with excessive daytime sleepiness ranges from 3% to 7% in adult men and from 2% to 5% in adult women. In Japan, Nakaya-Ashida et al. reported that the prevalence of moderate to severe sleep disordered breathing (respiratory disturbance index ≥ 15) was 22.3% in male workers aged 23-59 years.

Factors predisposing to OSAS include obesity, advanced age, male sex, and craniofacial abnormalities. The diagnosis of OSAS generally requires objective measurement of obstructive respiratory events and the presence of characteristic symptoms, such as excessive daytime sleepiness and unrestored nocturnal sleep that could not be better explained by other factors. Severe OSAS is often associated with vascular morbidities, cognitive impairment, occupational and vehicular accidents attributable to excessive daytime sleepiness, and worse quality of life than unaffected individuals.

Management of OSAS requires the use of nasal continuous positive airway pressure (nCPAP) therapy, a first-line treatment, which acts as a pneumatic splint to maintain patency of
the upper airway. nCPAP therapy is widely accepted to reduce excessive sleepiness and to improve daytime functioning and self-reported health status. However, despite the reported improvements of respiratory events, clinically significant excessive sleepiness persists in some patients on optimal nCPAP. In some of these patients, the residual sleepiness may reflect the presence of other sleep disorders, including narcolepsy, behaviorally induced sleep insufficiency syndrome and periodic limb movement disorders. In other patients, this outcome may be caused by hypoxia-induced cerebral metabolic changes. In a recent study in France, 6.0% (95% confidence interval [CI] 3.9-8.0) of OSAS patients who were optimally treated with nCPAP had evidence of residual excessive sleepiness. Considering the potential adverse outcomes that may affect the health and safety of the patients, residual sleepiness requires prompt attention.

The Standards of Practice Committee of the American Academy of Sleep Medicine recommends use of the wake-promoting agent modafinil in nCPAP-treated patients without other identifiable causes for their residual sleepiness. Modafinil differs from other amphetamine-like wake-promoting agents, such as methamphetamine and methylphenidate, in its chemical structure and mechanisms of action. Modafinil mainly interacts with the dopamine transporter and affects the γ-amino butyric acid (GABA)-ergic, serotonergic, glutaminergic, noradrenergic, and histaminergic neurotransmitter systems, which may contribute to its wake-promoting activity. Double-blind placebo-controlled clinical studies on nCPAP-treated patients with residual sleepiness associated with OSAS have revealed that modafinil significantly improved objectively determined sleep latency, overall subjective severity of sleepiness, health-related quality of life, and functional status, and that it was well tolerated. To date, however, no studies have examined the effects of modafinil on residual excessive sleepiness in Japanese patients with OSAS on optimal nCPAP treatment. Furthermore, although central nervous system stimulants may theoretically disturb nocturnal sleep, previous studies have not documented the effects of modafinil on subjective or objective nocturnal sleep measures.

Therefore, in the present study, we evaluated the effects of modafinil on the efficacy and safety of modafinil in Japanese patients with OSAS and excessive daytime sleepiness despite optimal therapeutic use of nCPAP. We also examined the effects of modafinil on subjective and objective measures of nocturnal sleep in these patients.

 METHODS

Study Design

This randomized, double-blind, placebo-controlled, parallel-group study was conducted at 37 sites specialized in sleep disorders in Japan between May 2009 and December 2009. The study included a screening visit, an observation period ≥ 15 days, and a 4-week double-blind treatment period. The protocol and the informed consent form were reviewed and approved by the internal review board at each institution. All patients provided written informed consent to participate in this study.

Patients

Patients evaluated in this study were required to be receiving effective nCPAP therapy to rule out inadequate or incorrect nCPAP use as a cause of their residual sleepiness. Patients with sleep disorders other than OSAS were excluded from the study. The main inclusion criteria for eligible patients in this study were as follows: men and women aged 20-70 years; confirmed diagnosis of OSAS; and the presence of subjective excessive sleepiness (i.e., Epworth Sleepiness Scale [ESS] total score ≥ 11) despite optimal use of nCPAP; having received nCPAP therapy for ≥ 3 months and being willing and able to continue its use during the study period; the use of nCPAP for ≥ 70% of nights for ≥ 4 h/night for 14 days before the baseline visit; and an apnea-hypopnea index (AHI) ≤ 10 determined by nocturnal polysomnography (PSG) during the observation period. Definitive diagnosis of OSAS or other sleep disorders was made using PSG data obtained before randomization based on Rechtschaffen and Kales criteria and American Sleep Disorders Association arousal criteria. The data were scored according to American Association of Sleep Medicine criteria. Patients who met any of the following criteria were excluded from this study: diagnosis of other sleep disorders (e.g., narcolepsy, periodic limb movement disorders, and central sleep apnea); pregnant, potentially pregnant, or lactating women; presence of arrhythmias, angina, and clinically significant cardiac, respiratory, cardiovascular diseases, psychiatric disorders (e.g., depression), or hypertension with systolic blood pressure ≥ 160 mm Hg and diastolic blood pressure ≥ 100 mm Hg, as specified in the exclusion criteria of the U.S. OSAS study.

Patients who were concomitantly administered prohibited drugs, such as central nervous system stimulants, sedative medications, antidepressants, antiepileptic drugs, acetazolamide, warfarin, monoamine oxidase inhibitors, or antimigraine drugs, within 2 weeks before the start of the study, were also excluded. Patients fulfilling these criteria were identified by the physicians and invited to participate in the study at the physician’s request.

Randomization and Dosing

Patients were randomly assigned in a blocked randomization manner to receive 2 tablets of 100 mg modafinil (total dose, 200 mg/day) or placebo once daily in the morning, to be administered before or after meals. Randomization was performed using a computer-generated random number list prepared by an independent contract research organization. Clinicians contacted the organization via telephone to obtain the randomization sequence for each patient.

Efficacy Measures

Efficacy assessments were conducted at the start (i.e., baseline) and at Weeks 1 and 4 of the double-blind treatment period. The primary efficacy measure was ESS score at Week 4 of treatment. The secondary efficacy measure was mean sleep latency on the maintenance of wakefulness test (MWT).

The MWT was conducted in a subset of patients (modafinil, n = 22; placebo, n = 28) at baseline and at Week 4 of the double-blind period on the days immediately after nocturnal PSG. Each MWT session lasted 20 min. Because of the methodology, the MWT was only performed at study sites with the facilities required to conduct the test. Some patients at these facilities were unable...
to do the MWT because of the burden associated with the test. Other secondary variables were ESS score at each visit, and the total score of Japanese version of Pittsburgh Sleep Quality Index (PSQI),\footnote{which represents the severity of subjective sleep disturbance, and sleep parameters measured by nocturnal PSG at baseline and Week 4. PSG and MWT were conducted in an inpatient setting.}

Safety
Safety was assessed by evaluating adverse drug reactions (ADRs) as well as the results of general laboratory tests (blood and urine), physiological variables (blood pressure and pulse rate), 12-lead electrocardiograms, and physical examinations. ADRs were defined as any unfavorable or unintended symptom or disease that was considered to be associated with the study drug during the study period.

Statistical Analysis
Continuous demographic variables were compared using the 2-sample $t$-test. Categorical variables were compared using the Fisher exact test. The efficacy population ($n = 114$) was defined as patients who received $\geq 1$ dose of modafinil and underwent $\geq 1$ post-baseline evaluation for any efficacy or safety variable during the treatment period. The changes in efficacy variables (ESS and MWT) from baseline to the final assessment (Week 4) were compared between the modafinil and placebo groups using analysis of covariance with the baseline value as a covariate. To verify the efficacy of modafinil administration, the point estimate and 2-sided 95% (CI) of the difference between the modafinil and placebo groups were calculated using the least squares mean (LS mean) method. Statistical tests were performed at a significance level of 5\% using SAS System (Release 9.1.3, SAS Institute Inc., Cary, NC, USA). Changes in other secondary variables (PSQI and nocturnal PSG) from baseline were also compared between the modafinil- and placebo-treated groups. Safety data are summarized using descriptive statistics.

RESULTS
Subjects
A total of 114 patients were randomized—52 patients to modafinil and 62 patients to placebo. All 114 patients completed the study (Figure 1). There were no differences between the 2 groups in terms of demographic and baseline characteristics (Table 1). Males accounted for $> 94\%$ of the patients in both groups. Before starting treatment with the study drug, the patients in both groups had moderate levels of residual sleepiness, with mean total ESS scores $\geq 14$ despite effective nCPAP therapy; mean AHI was $\leq 10$ in both groups. The mean duration of nCPAP use per night was $6.1 \pm 1.0$ and $6.0 \pm 0.6$ h in the modafinil and placebo groups, respectively (Table 1). Concomitant diseases included hypertension (modafinil, $n = 13$ [25\%]; placebo, $n = 20$ [32\%]) and hyperlipidemia (modafinil, $n = 4$ [8\%]; placebo, $n = 14$ [23\%]).

Subjective Sleepiness
Mean ESS total scores were determined at baseline and at the final assessment in both groups. The mean changes in ESS total score from baseline to the final assessment were $-6.61$ in the modafinil group and $-2.44$ in the placebo group (LS mean). The between-group difference of $-4.17$ (95\% CI $-5.66$ to $-2.69$) was therefore significantly greater with modafinil than with placebo ($p < 0.001$). The change in mean ESS total score at 1 week after starting treatment was also significantly greater in the modafinil group than in the placebo group ($p < 0.001$; Figure 2).

The patients whose ESS total scores were $\geq 11$ at baseline and decreased to $< 11$ at the final assessment were defined as
responders with normalization of ESS. Overall, 69.2% of patients (36/52) treated with modafinil and 30.6% of patients (19/62) treated with placebo were classified as responders. The Fisher exact test showed that a significantly higher percentage of patients treated with modafinil were classified as responders compared with patients treated with placebo (p < 0.001). The corresponding response rates at week 1 were 57.7% (30/52) and 33.9% (21/62) (p = 0.014).

**Objective Sleepiness**

Fifty patients (modafinil, n = 22; placebo, n = 28) underwent the MWT. There were no differences in patient characteristics, including baseline ESS total score, between patients who did or did not undergo the MWT (p = 0.292). Mean sleep latencies determined by MWT at baseline and at the final assessment in both groups are shown in Figure 3. The LS mean change in MWT sleep latency from baseline to the final assessment was 2.8 min in the modafinil group and -0.40 min in the placebo group. The between-group difference of 3.2 min (95% CI 0.8 to 5.6) was statistically significant, showing greater effects of modafinil versus placebo (p = 0.009).

**Objective and Subjective Measures of Nocturnal Sleep**

Summary statistics for sleep parameters were determined in 101 patients who underwent nocturnal PSG at baseline and at the final assessment (modafinil, n = 45; placebo, n = 56). As shown in Table 2, there were no significant differences in the changes in any nocturnal PSG parameters between the 2 groups.

The total PSQI score decreased from 6.3 ± 2.7 at baseline to 4.8 ± 2.2 at the final assessment in the modafinil group, as compared with a change from 6.1 ± 2.3 to 5.4 ± 1.7 in the placebo group. The mean difference in total PSQI score between the 2 groups for the change from baseline to the final assessment was -0.7 points (95% CI: -1.5 to 0.0 points) and was not statistically significant.

**Safety Outcomes**

ADRs were reported by 19 patients (36.5%) in the modafinil group and 14 patients (22.6%) in the placebo group. There were no significant differences in the rate of ADRs between the 2 groups (p = 0.146; Fisher exact test). The most frequent ADRs in the modafinil group were headache (n = 6, 11.5%), insomnia (n = 2, 3.8%), and palpitation (n = 2, 3.8%). The most frequent ADRs in the placebo group were headache (n = 4, 6.5%) and upper abdominal pain (n = 2, 3.5%) (Table 3). All of these ADRs were mild or moderate in severity, and no deaths or other serious adverse events were reported. None of the patients withdrew from the study because of ADRs.

Regarding the time of onset of ADRs, the frequency of ADRs was greatest within 7 days after starting treatment in both the modafinil group (15/19 patients who experienced ADRs) and the placebo group (10/14 patients).

Laboratory test abnormalities included increased γ-glutamyl transpeptidase in one patient in each group; increased alkaline phosphatase in one patient in each group; increased alanine aminotransferase and increased thyroid stimulating hormone in one patient each in the modafinil group; the presence of urinary glucose and decreased white blood cell count in one patient each treated with placebo; and multiple liver enzyme abnormalities (increased aspartate aminotransferase, alanine aminotransferase, and γ-glutamyl transpeptidase) in one patient treated with placebo. Decreased body weight (from 77.0 kg at baseline to 73.0 kg at week 4 of the treatment period) was observed in one patient treated with modafinil. Sinus tachycardia (at Week 1 of the treatment period) and sinus bradycardia (at Week 4 of the treatment period) were observed in one patient each in the modafinil group. Ventricular extrasystole (at Week 1 of the treatment period) was observed in one patient treated with placebo. No clinically relevant abnormalities were ob-

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**Figure 2**—Mean Epworth Sleepiness Scale total score at baseline, and after 1 and 4 weeks of treatment with modafinil or placebo

**Figure 3**—Mean maintenance of wakefulness test sleep latency at baseline and after 4 weeks of treatment with modafinil or placebo

The least significant mean change from baseline ± standard error is shown in the table. *The p-values were determined by analysis of covariance.
This study was the first Asian study to investigate the efficacy of modafinil for treating residual sleepiness in patients with nCPAP-treated OSAS using both subjective and objective measures. In this study, residual sleepiness was defined as excessive daytime sleepiness in patients who were compliant with OSAS treatment but had subjective sleepiness without any other identifiable cause of sleepiness, applying enrollment criteria identical to those in studies in the United States.27,29 The degree of residual sleepiness at baseline, as represented by the ESS total score, of the patients enrolled in this study, was also comparable to that in the US studies.27,29 Interestingly, when the efficacy data for the 200 mg doses in both studies were compared, the changes in ESS score from baseline to Week 4 of treatment were -6.52 ± 5.04 (n = 52) and -3.20 ± 4.25 (n = 95) in our study and in the US study,29 respectively. The respective changes in MWT sleep latency were 2.97 ± 5.25 (n = 22) and 1.20 ± 4.33 (n = 84). These data suggest that the response to 200 mg/day modafinil is greater in Japanese patients than in US patients, which may indicate slight differences in pharmacokinetic profiles among different ethnicities, as already reported among other ethnic groups.41,42 Differences in the pharmacokinetic profiles, including the absorption and distribution of modafinil, may also be attributable to the differences in body size between Japanese and US patients, as the mean BMI of patients treated with modafinil was 27.9 ± 4.3 kg/m² in our study versus 26.2 ± 7.6 kg/m² in the US study.29 Alternatively, excess obesity is known to exacerbate daytime sleepiness,43,44 possibly resulting in more severe symptoms or less apparent improvements in symptoms in US patients than in Japanese patients. Additionally, differences in the timing or content of the morning meal may partly explain the differences in clinical outcomes between these studies. Nevertheless, the precise reasons for this difference between Japanese and US patients are unclear, and this study was conducted to evaluate safety and efficacy in Japanese OSA patients and not to elucidate the difference between US and Japanese patients. However, the trends in pos-

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**Table 2**—Comparison of nocturnal PSG indices at baseline and after 4 weeks of treatment with modafinil and placebo

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n = 56)</th>
<th>Modafinil (n = 45)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total sleep time (TST), min</td>
<td>425.2 ± 60.9</td>
<td>421.7 ± 61.4</td>
<td>0.654</td>
</tr>
<tr>
<td>Sleep efficiency (TST/TIB), %</td>
<td>85.0 ± 11.2</td>
<td>85.4 ± 11.2</td>
<td>0.577</td>
</tr>
<tr>
<td>Sleep latency, min</td>
<td>8.8 ± 12.4</td>
<td>11.4 ± 14.8</td>
<td>0.390</td>
</tr>
<tr>
<td>Stage 1, %TST</td>
<td>16.0 ± 6.7</td>
<td>13.7 ± 7.7</td>
<td>0.671</td>
</tr>
<tr>
<td>Stage 2, %TST</td>
<td>56.7 ± 8.4</td>
<td>58.0 ± 9.9</td>
<td>0.466</td>
</tr>
<tr>
<td>Stage 3, %TST</td>
<td>4.2 ± 5.5</td>
<td>5.6 ± 6.6</td>
<td>0.154</td>
</tr>
<tr>
<td>Stage 4, %TST</td>
<td>1.3 ± 3.7</td>
<td>1.3 ± 2.9</td>
<td>0.345</td>
</tr>
<tr>
<td>Stage 3-4, %TST</td>
<td>5.4 ± 7.1</td>
<td>7.0 ± 8.2</td>
<td>0.531</td>
</tr>
<tr>
<td>REM, %TST</td>
<td>21.9 ± 6.4</td>
<td>21.4 ± 5.8</td>
<td>0.505</td>
</tr>
<tr>
<td>Wake (WASO/SPT), %</td>
<td>12.28 ± 10.5</td>
<td>10.9 ± 9.0</td>
<td>0.264</td>
</tr>
<tr>
<td>AHI</td>
<td>2.6 ± 2.6</td>
<td>2.6 ± 2.8</td>
<td>0.500</td>
</tr>
</tbody>
</table>

Data are means ± SD. *Two-sample t-test to compare the change from baseline to Week 4 between the modafinil and placebo groups. TIB, time in bed; WASO, wake after sleep onset; SPT, sleep period time; AHI, apnea-hypopnea index.

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**Table 3**—Adverse events occurring in two or more patients in either treatment group

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Placebo (n = 62)</th>
<th>Modafinil (n = 52)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>4 (6.5)</td>
<td>6 (11.5)</td>
<td>0.508</td>
</tr>
<tr>
<td>Upper abdominal pain</td>
<td>2 (3.2)</td>
<td>0 (0)</td>
<td>0.499</td>
</tr>
<tr>
<td>Insomnia</td>
<td>0 (0)</td>
<td>2 (3.8)</td>
<td>0.206</td>
</tr>
<tr>
<td>Palpitation</td>
<td>0 (0)</td>
<td>2 (3.8)</td>
<td>0.206</td>
</tr>
</tbody>
</table>

Values are number of patients (%). *Fisher exact test.
Tive outcomes for patient-reported sleepiness and objectively determined sleep latency in the present study were similar to those reported in the US study.29

Of note, in this study of Japanese patients, treatment with modafinil did not significantly affect sleep parameters in terms of nocturnal PSG findings or total PSQI score. Therefore, the administration of modafinil in the morning did not seem to adversely affect the structure or quality of nocturnal sleep.

Generally, modafinil was well tolerated. The safety and tolerability findings of the current study are consistent with those of other double-blind placebo-controlled studies.27,29 Headache, insomnia, and palpitation were the most common ADRs in modafinil-treated patients. However, modafinil therapy was not associated with clinically significant changes in blood pressure or heart rate relative to placebo. Furthermore, there were no serious adverse events in either group in this study.

Some limitations of this study should be mentioned. First, most of the patients in this study were male, and there are some differences in the pharmacokinetics of modafinil between males and females.41,42,45 Second, we only included patients with OSAS on nCPAP. The efficacy of modafinil should therefore be evaluated in OSAS patients with residual sleepiness on other treatments.

In conclusion, residual daytime sleepiness was improved in Japanese patients with OSAS treated with 200 mg modafinil once daily. We found significant improvements in ESS total scores at 1 week after starting modafinil that were maintained until the end of the 4-week study. Modafinil may be an effective and well-tolerated adjunct treatment for the chronic management of residual daytime sleepiness in patients with OSAS who experience excessive daytime sleepiness despite regular nCPAP use.

ABBREVIATIONS

ADR, adverse drug reactions
AH1, apnea-hypopnea index
CI, confidence interval
ESS, Epworth Sleepiness Scale
GABA, γ-aminobutyric acid
LS, least squares
nCPAP, nasal continuous positive airway pressure
OSAS, obstructive sleep apnea syndrome
PSG, polysomnography
PSQI, Pittsburgh Sleep Quality Index
SL-MWT, sleep latency on maintenance of wakefulness test

REFERENCES


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DISCLOSURE STATEMENT

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Previous studies have shown that muscle contractions in the respiratory-related orofacial muscles (e.g., tongue) often occur after apnea and hypopnea events during sleep in patients with OSAS. Among the orofacial muscles, the jaw-closing masseter (MAS) muscle is also activated in association with apnea and hypopnea events, and jaw closures from the jaw opening posture are often observed at the termination of respiratory events without arousals, while its response rate increased significantly in association with the duration of arousals (Friedman tests: p < 0.001). A similar response pattern was found for AT muscle. Motor responsiveness of the two muscles to arousals after respiratory events did not differ from responsiveness to spontaneous arousals in two sleep stages.

Conclusion: In patients with OSAS, the contractions of MAS and AT muscles after respiratory events can be nonspecific motor phenomena, dependent on the duration of arousals rather than the occurrence of respiratory events.

Keywords: masseter muscle, leg movements, arousal response, motor responsiveness, obstructive sleep apnea

Citation: Kato T; Katase T; Yamashita S; Sugita H; Muraki H; Mikami A; Okura M; Ohi M; Masuda Y; Taniguchi M. Responsiveness of jaw motor activation to arousals during sleep in patients with obstructive sleep apnea syndrome. J Clin Sleep Med 2013;9(8):759-765.
Although it has been proposed that MAS contractions play a supporting role in reinstating the compromised upper airway,16 physiological understanding of MAS contractions in patients with OSAS is limited. MAS contractions are usually associated with the termination of apnea-hypopnea events, while MAS contractions do not always occur after respiratory events in patients with OSAS.14 Previous studies have reported that MAS contractions after respiratory events occur in association with an increase in heart rate, which is a typical sign of arousal response,2,3 suggesting that the arousals associated with respiratory events are an underlying condition for MAS contractions in association with respiratory events. In patients with OSAS, varying degrees of arousal events were found to occur in relation to respiratory events.17,21 As there is a hierarchy of arousal responses,22 motor activation is more frequently observed in response to a higher level of arousals.14,21 However, the association between MAS contractions and the level of arousals after respiratory events has not been investigated in OSAS patients. In addition, in patients with OSAS, some arousals can be associated with respiratory events, while other arousals are not related to respiratory events. It is not known whether MAS is more responsive to arousals related to or unrelated to respiratory events. It also remains to be demonstrated whether the motor responsiveness of the jaw muscles is compatible with that of other muscles in the body.

The aims of this study are to characterize the association between MAS contractions and respiratory events in patients with OSAS and to investigate the responsiveness of MAS contractions to respiratory events in comparison with that of leg muscles in terms of arousal types and sleep states.

### METHODS

#### Subjects

Fifty-four patients (F10:M44; Age: 51.9 ± 15.1 years) had been newly referred to Osaka Kaisei Hospital Sleep Medicine Center with suspected sleep apnea. They were first interviewed by sleep physicians (MO, MO, and MT) and were suspected of having OSAS based on a history of excessive daytime sleepiness, sleep disturbances, snoring, and witnessed respiratory pauses in sleep. They did not have a history of pulmonary, heart, liver or kidney disease, stroke, or other neurological disorders, and did not take sleeping pills. All patients were enrolled for a routine PSG examination. On the night of PSG recording, these patients gave written informed consent to participate in the study. They were asked to fill out a self-administered questionnaire on sleep disturbance and orofacial symptoms. After evaluating PSG data, we excluded the data of 35 patients from the final analysis for the following reasons: (1) 17 patients were aware of signs symptoms of sleep bruxism (tooth grinding during sleep and morning jaw symptoms) according to the self-administered questionnaires; (2) 4 patients did not fill out the questionnaires; (3) 4 patients with AHI index < 5 /h; (4) 9 patients had periodic leg movements in sleep (PLMS) with PLMS index > 10 /h, and (5) one patient was suspected of having an REM sleep behavior disorder. Finally, data from 19 patients (F2:M17; age: 53.1 ± 13.7 years) were used for the analysis. We also confirmed that none of these patients exhibited tooth grinding and rhythmic masticatory muscle activity (RMMA) during sleep. The study was approved by the institutional review board at the Osaka Kaisei Hospital, Osaka, Japan.

#### Polysomnographic Evaluations

PSG consisted of continuous recordings from 6 electroencephalographic (EEG) leads (F3-M2, F4-M1, C3-M2, C4-M1, O1-M2, O2-M1), 2 electrooculographic leads (ROC-M2, LOC-M2), 5 electromyographic leads (2 submental and bilateral anterior tibialis [AT] and unilateral MAS muscles), nasal cannula with a pressure transducer and thermal sensor for nasal airflow, strain gauges for thoracic and abdominal movements, pulse oximetry, and electrocardiography. Simultaneous audio-video recording was made. Subjects went to bed at their usual bedtime or before 23:30, and the recording was terminated after 6:30.

Sleep stages were scored for 30-sec epochs according to the international standard criteria.24 Apnea and hypopnea were defined following the rules of the American Academy of Sleep Medicine.24 An apnea was defined as ≥ 90% reduction in airflow for ≥ 10 sec; hypopnea as ≥ 50% reduction of airflow for ≥ 10 sec associated with arousals or with ≥ 3% reduction in oxygen saturation. Transient arousals such as microarousals ([mAR] 3-15 sec) and awakenings ([AW] > 15 sec) were scored according to the criteria.20,24,25 Arousals were scored as respiratory related when they were synchronous with the termination of the respiratory event, while those without a preceding respiratory event were scored as spontaneous arousals. To confirm that patients had no concomitant sleep related movement disorders in the jaw and leg muscles, RMMA and periodic leg movements were scored according to the criteria for sleep bruxism and PLMS.

The following sleep and respiratory variables were calculated: total sleep time (TST), total recording time (TRT), sleep efficiency (SE), sleep latency, percentage of sleep stages, and the frequency of transient events per hour of sleep (e.g., awakenings, microarousals, PLMS, RMMA, and respiratory events [apneas and hypopneas]).

### Table 1—Demographic and polysomnographic data in 19 patients

<table>
<thead>
<tr>
<th>Sex</th>
<th>F2/M17</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>53.1 ± 13.7</td>
</tr>
<tr>
<td>BMI</td>
<td>25.4 ± 4.1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sleep variables</th>
<th>Total sleep time (h)</th>
<th>Sleep efficiency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>396.2 ± 40.8</td>
<td>86.1 ± 6.9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sleep stage distribution (%)</th>
<th>Stage NREM1&amp;NREM2</th>
<th>Stage NREM3</th>
<th>Stage REM</th>
<th>Microarousals (/h)</th>
<th>Awakening (/h)</th>
<th>Apnea-hypopnea index (/h)</th>
<th>PLMS index</th>
<th>RMMA index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage NREM1&amp;NREM2</td>
<td>77.1 ± 10.3</td>
<td>5.4 ± 6.2</td>
<td>18.8 ± 6.8</td>
<td>18.2 ± 7.0</td>
<td>7.6 ± 3.8</td>
<td>31.9 ± 19.9</td>
<td>0 (0-9)</td>
<td>0</td>
</tr>
</tbody>
</table>

| BMI, body mass index; PLMS, periodic leg movements in sleep; RMMA; rhythmic masticatory muscle activity. |

#### Polysomnographic Evaluations

PSG consisted of continuous recordings from 6 electroencephalographic (EEG) leads (F3-M2, F4-M1, C3-M2, C4-M1, O1-M2, O2-M1), 2 electrooculographic leads (ROC-M2, LOC-M2), 5 electromyographic leads (2 submental and bilateral anterior tibialis [AT] and unilateral MAS muscles), nasal cannula with a pressure transducer and thermal sensor for nasal airflow, strain gauges for thoracic and abdominal movements, pulse oximetry, and electrocardiography. Simultaneous audio-video recording was made. Subjects went to bed at their usual bedtime or before 23:30, and the recording was terminated after 6:30.

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repeated measure ANOVAs with post hoc paired t-tests, the level of statistical significance was set for each muscle in either NREM or REM sleep. Due to multiple comparisons, the level of statistical significance was set at $p < 0.0125$. We used SYSTAT 11 for Windows (SYSTAT software Inc., USA) for statistical analyses.

## RESULTS

### Respiratory Events in NREM and REM Sleep

The majority of apnea-hypopnea events (204.2 $\pm$ 140.3 events) were scored in NREM sleep (84.4% $\pm$ 13.2% in NREM sleep and 15.6% $\pm$ 13.2% in REM sleep, $N = 19$). In NREM sleep, two-thirds of respiratory events (68.2% $\pm$ 15.5%) were followed by transient arousals, while half of the respiratory episodes were associated with arousals during REM sleep (52.3% $\pm$ 24.1%); transient arousals were scored more frequently after respiratory events in NREM sleep than in REM sleep (paired $t$-test: $p < 0.01$).

The following variables were analyzed for NREM sleep in 19 patients and for REM sleep in 15 patients, since either or both types of transient arousals were not scored after respiratory events. In NREM sleep, duration of respiratory events did not differ among 3 types of respiratory events (e.g., non-arousal [NA] events, events with mAR and AW; Table 2). In REM sleep, the duration of respiratory events differed among the 3 types of respiratory events (ANOVA: $p < 0.05$). The duration of respiratory events with AW was significantly elongated compared to NA events (post hoc paired $t$-test: $p < 0.05$; Table 2). The decrease in oxygen saturation was significantly different among the 3 types of respiratory events in NREM sleep (ANOVA: $p < 0.01$) and in REM sleep ($p < 0.05$). In NREM sleep, it was significantly lower for NA events than for events with mAR (Table 2, post hoc paired $t$-test: $p < 0.001$) and those with AW ($p < 0.05$). In REM sleep, the decrease in oxygen saturation was significantly larger for the event with AW than for NA events (Table 2, post hoc paired $t$-test: $p < 0.05$).

### Motor Activations in Relation to Arousals after Respiratory Events

In NREM sleep, 32.1% (7.2-88.9) of respiratory events were followed by MAS contractions. The response rate of MAS contractions to respiratory events differed significantly between NA events and those with mAR and AW (Figure 1, Friedman test: $p < 0.001$). The contractions were found to occur increasingly from 6.1% (0-100) to 40.0% (5.1-88.6) and

| Table 2—Duration and oxygen desaturation for three types of respiratory events |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                  | Total           | NA             | mAR            | AW             | $p$             |
|------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| **NREM (N = 19)**|                 |                 |                 |                 |                 |
| # of events      | 172.2 $\pm$ 132.0 | 62.6 $\pm$ 73.3 | 84.5 $\pm$ 58.1 | 25.6 $\pm$ 16.1 |                 |
| Duration (s)     | 29.4 $\pm$ 6.9  | 28.1 $\pm$ 6.3  | 30.2 $\pm$ 7.5  | 29.8 $\pm$ 8.4  | $> 0.05$        |
| Oxygen desaturation (%) | 6.2 $\pm$ 3.0 | 5.2 $\pm$ 2.5$^a$ | 7.0 $\pm$ 3.5$^b$ | 6.6 $\pm$ 4.0$^a$ | 0.004           |
| **REM (N = 15)** |                 |                 |                 |                 |                 |
| # of events      | 38.7 $\pm$ 29.5 | 20.6 $\pm$ 18.9 | 12.3 $\pm$ 12.0 | 5.9 $\pm$ 5.3   |                 |
| Duration (s)     | 35.6 $\pm$ 9.6  | 31.6 $\pm$ 7.2$^c$ | 35.9 $\pm$ 10.4 | 41.5 $\pm$ 19.6$^d$ | 0.043           |
| Oxygen desaturation (%) | 7.6 $\pm$ 4.2 | 6.1 $\pm$ 2.4$^d$ | 8.1 $\pm$ 5.3  | 11.4 $\pm$ 7.5$^d$ | 0.015           |

*Data were analyzed for respiratory events occurred in NREM sleep stages NREM1 and NREM2. For each variable, repeated measure ANOVAs between respiratory events with no arousal (NA), microarousal (mAR), and awakening (AW) were done. $p$-values of the ANOVA are shown in the right column. The results of post hoc $t$-tests are shown by $^a$(NA vs. AW, $p < 0.05$), $^b$(NA vs. mAR, $p < 0.001$), $^c$(NA vs. AW, $p < 0.05$), and $^d$(NA vs. AW, $p < 0.05$).
85.4% (18.2-100) as the duration of post-respiratory arousals became elevated from NA to AW (post hoc Wilcoxon tests: p < 0.001 [N = 19]). AT muscle was activated after 21.7% (4.2-82.0) of respiratory events during NREM sleep. A significant difference in the responsiveness of AT muscle was found between arousal levels (Friedman test: p < 0.001): AT muscle was activated more frequently when respiratory events were followed by a higher intensity of arousals in NREM sleep (NA: 4.2% [0-66.7]; mAR: 25.5% [0-85]; AW: 78.3% [14.3-100]) (Figure 1, post hoc Wilcoxon tests: p < 0.001). The number of muscles activated following a respiratory event increased significantly during NREM sleep (Figure 1, Friedman test: p < 0.001, post hoc Wilcoxon tests: p < 0.001).

In REM sleep, respiratory events (18.9% [2.4-57.1]; N = 15) were less frequently associated with MAS contractions than in NREM sleep. However, a similar significant difference between the arousal levels was found during REM sleep (Figure 1, Friedman test: p < 0.001): MAS activations became more frequent in association with arousal levels (NA: 0% [0-12.7]; MA: 20.0% [0-100]; AW: 81.8% [0-100]; post hoc Wilcoxon tests: p < 0.001 [N = 15]). AT muscle contraction was scored in 12.5% (0-75.7) of respiratory events. Similar to MAS muscle, the response rate of AT muscle was significantly associated with arousal levels (Figure 1, Friedman test: p < 0.001): the response of AT muscles increased significantly from NA (0% [0-14.5]) to mAR (8.7% [0-94.1]) and AW (85.7% [0-100]) (post hoc Wilcoxon tests: p < 0.001 [N = 15]). The two muscles were activated more frequently with arousal intensity (0.0 [0-0.3], 0.4 [0-1.4], and 1.5 [0-2.0]) (Figure 1, Friedman test: p < 0.001 [N = 15]).

Motor Responsiveness between Spontaneous and Respiratory Arousals

In 19 patients, 36.5 ± 19.3 spontaneous arousals did not follow respiratory events. Of these, the majority (87.5% ± 9.0%) occurred during NREM sleep. In NREM sleep, the response of MAS activation was significantly increased from spontaneous mAR (29.4% [4.2-92.3]) to AW (75.0% [25.0-100]) (Wilcoxon test: p < 0.001). Similarly, response rate of AT muscles were higher for AW (60.0% [9.5-100]) than for mAR (22.7% [0-87.5]) in NREM sleep (Wilcoxon

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**Figure 1**—Responsiveness of masseter and anterior tibialis muscles to three types of respiratory events during NREM and REM sleep.

During NREM and REM sleep, masseter (left column) and anterior tibialis (middle column) muscles were activated most frequently when awakenings (AW) occurred after respiratory events; they were activated least frequently when no EEG arousals (NA) occurred (Friedmann tests: p < 0.001). Right column shows the number of muscles that are activated after respiratory events increased significantly during NREM and REM sleep as the arousal levels were elevated (Friedmann tests: p < 0.001); mAR, microarousal. ***p < 0.001 for post hoc Wilcoxon tests. The data are presented by median (minimum - maximum). Please see the results of statistical analysis in the text.
The results show that jaw-closing muscles are increasingly activated in relation to the duration of arousals after respiratory events during NREM and REM sleep in patients with OSAS. The responsiveness of jaw muscles to arousals after respiratory events did not differ from that following spontaneous arousals. Moreover, the above pattern of motor response did not differ between the jaw and leg muscles. These findings suggest that, in patients with OSAS, MAS contractions after respiratory events are a nonspecific motor manifestation of the arousal response, dependent on the intensity of arousals.

Previous studies have reported that the MAS muscle was occasionally activated after respiratory events; 14.4% to 54.2% of respiratory events were followed by MAS contractions that exceeded to 20% to 40% of MVC of the MAS muscle regardless of sleep stages. In this study, 32.1% of respiratory events during NREM sleep and 18.9% during REM sleep were associated with MAS activations that exceeded to 10% MVC. Moreover, the majority of MAS activations occurred more frequently after respiratory events with arousal response than those without, as previous studies have also reported for the MAS and other craniofacial muscles. Although previous studies have shown that cardiac arousals without visually detectable EEG changes have been detected after respiratory events, these respiratory events were found to be rarely associated with MAS contractions. This is consistent with the findings of the recent studies in which respiratory efforts and electromyography of the tongue muscles were assessed in relation to respiratory events. However, when transient arousals with visually identifiable EEG changes (e.g., mAR, AW) occurred after respiratory events, the MAS was activated. This result supports a previous suggestion of an association between MAS and arousal response. In addition, the probability of the activation was elevated, as the duration of arousals increased from mAR to AW. These results suggest that, in patients with OSAS, the responsiveness of MAS contractions after respiratory events is dependent on the intensity of arousal responses, a finding consistent with results obtained in healthy subjects and patients with sleep disorders.

MAS muscles were activated more frequently after respiratory events during NREM sleep than during REM sleep in the present study and in previous studies. This suggests that the threshold for MAS activation is lower during NREM sleep than during REM sleep due to the presence of active inhibition during the latter sleep state. In addition, arousal threshold to respiratory disturbance was higher during REM sleep than NREM sleep since a respiratory event of longer duration and larger amplitude of oxygen desaturation are needed to trigger arousals in REM sleep. In this study, submental muscle activation was needed for scoring arousals during REM sleep, indicating that the motor system is released from active inhibition during arousals scored. Under such conditions, MAS muscles are activated more frequently in relation to an increase in the arousal duration. This explains why the frequency of MAS contractions after respiratory events was lower during REM sleep than during NREM sleep but the responsiveness to arousals was in a similar range for the two sleep stages.

It has been reported that respiratory effort at the end of a respiratory event is a key factor for inducing arousals and activating respiratory muscles. However, arousal-dependent MAS contractions are not explained solely by the association between the degree of respiratory efforts in relation to respiratory events, since the motor responsiveness of MAS muscle to mAR and AW did not differ between arousals with and without preceding respiratory events. Since arousals during sleep...
are not always coupled with respiratory events in patients with OSAS,\textsuperscript{18,23,28} the lack of difference in motor responsiveness between respiratory-related and spontaneous arousals, suggests that MAS contraction after a respiratory event is dependent on the arousal response rather than respiratory events per se.

Motor responses in both jaw and leg muscles after respiratory events were similarly correlated with an intensity of arousal response. This suggests that the physiological nature of muscle contractions in patients with OSAS is not specific to jaw-closing muscle. However, the two muscles are not always activated coincidently after the same respiratory event when nAR was scored. An increase in arousal duration was associated with the elevation of the probability that the two muscles would be activated. This finding is supported by the previous studies showing that, as arousal intensity increases, facilitatory influences spread over more muscles in the body.\textsuperscript{3,14}

There are several limits to interpreting the results of this study. First, respiratory events, transient arousals and motor activity were assessed using visual scoring, according to the criteria used in the clinical setting and previous studies. With visual scoring, a slight increase in muscle tone was not detected in response to arousals.\textsuperscript{3,11} In addition, subtle EEG changes that can not be detected by visual scoring can be associated with MAS contractions after respiratory events without arousals in this study. Since we could not assess respiratory efforts by measuring esophageal pressure,\textsuperscript{35} we could not demonstrate how MAS contraction is linked to respiratory efforts when it occurred after respiratory events.\textsuperscript{16} The present study did not assess all factors influencing the characteristics of apnea/hypopnea events and arousal responses (e.g., age, body position, circadian rhythm, and upper airway resistance).\textsuperscript{17,19,21,32,37} Although these factors are also associated with the severity of OSAS patients symptoms, the present study was performed using a small study sample that included mild to severe OSAS. A large inter-individual difference in arousal threshold and motor responsiveness can be associated with the severity of OSAS. We did not demonstrate whether the responsiveness of MAS contractions was modified by the severity of OSAS: we neither recorded control subjects nor assessed the effects of clinical interventions (e.g., CPAP) on the motor responsiveness.\textsuperscript{39} Obviously, all the above issues need to be assessed in the future studies.

In conclusion, MAS contraction is an orofacial manifestation of a general motor reaction to arousal occurring during sleep in patients with OSAS. Such nonspecific motor activations contribute secondarily to restoration of a compromised upper airway during respiratory events in collaboration with the activation of respiratory-related muscles in patients with OSAS.\textsuperscript{34,23,29} On the other hand, the results also show that a certain number of MAS contractions can occur in OSAS patients who have neither clinical signs of sleep bruxism nor PSG findings of RMMA. The chance of MAS contractions may be elevated in response to respiratory events and arousals when sleep structure is fragmented by transient arousals in OSAS patients. A recent study showed that an oral appliance cannot reduce some type of MAS contractions (e.g., tonic activation).\textsuperscript{39} Thus, nonspecific activations of MAS muscle would not disappear even when oral appliance therapy was successfully controlling respiratory events; they occur as an intrinsic response to arousals in OSAS patients. As well, intrinsic response to arousals can be found in the AT muscle in OSAS patients who did not exhibit PLMS. However, such nonspecific activations in jaw and leg muscles would be a confounding factor in scoring sleep bruxism and PLMS and interpreting their impacts of the commonality on clinical symptoms (e.g., orofacial pain, sleepiness) in patients with OSAS as well as various sleep disorders.\textsuperscript{24,40}

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**Impact of CPAP Use and Age on Mortality in Patients with Combined COPD and Obstructive Sleep Apnea: The Overlap Syndrome**


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**Background:** The overlap syndrome, defined by concurrent existence of chronic obstructive pulmonary disease (COPD) and obstructive sleep apnea (OSA), is associated with poor outcomes. From a large outpatient cohort we aimed to define better the risk factors for increased mortality in the overlap syndrome and hypothesized that CPAP adherence would be associated with improved survival in patients with overlap syndrome.

**Methods:** A post hoc analysis from an outpatient database of 10,272 patients from 2007-2010, identified 3,396 patients which were classified in 6 groups; patients both alive or deceased, with the known diagnosis of COPD, OSA, and the overlap of COPD plus OSA. Information regarding their gender, age, pulmonary function, obstructive sleep apnea parameters, and CPAP compliance was collected. A multivariate Cox proportional hazards model was generated for the determinants of mortality.

**Results:** 1,112 COPD patients and 2,284 OSA patients were identified by diagnostic coding and then comprehensive chart review. Of these, 227 patients were identified with the overlap syndrome. From this group, 17 patients (7.4%) died. Multivariate analysis revealed hours of CPAP use and age as independent predictors of mortality (HR 0.71 and 1.14, p < 0.001, 0.002). Greater time on CPAP was associated with reduced mortality; although age did not correlate with CPAP use (p = 0.2), mean age of those with CPAP use < 2 hours per night was significantly higher than those using CPAP > 2 hours per night.

**Conclusions:** From this observational cohort, mortality in the overlap syndrome is impacted by CPAP use. Age is also an independent factor which has a negative association with survival and CPAP usage.

**Keywords:** Mortality, OSA, COPD

**Citation:** Stanchina ML; Welicky LM; Donat W; Lee D; Corrao W; Malhotra A. Impact of CPAP use and age on mortality in patients with combined COPD and obstructive sleep apnea: the overlap syndrome. J Clin Sleep Med 2013;9(8):767-772.

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Obstructive sleep apnea (OSA) is a common disorder characterized by repeated collapse of the airway during sleep and is associated with considerable functional impairment, as well as end-organ damage and mortality. Chronic obstructive pulmonary disease (COPD) is characterized by chronic airflow obstruction, chronic bronchitis, and emphysema, and is associated with major morbidity. In addition, COPD accounts for approximately 4% of all American deaths, making it now the third most common cause of death in the US. The concurrent diagnosis of COPD and obstructive sleep apnea (the overlap syndrome) is associated with excess mortality typically from cardiovascular causes, and is above and beyond that attributable to the individual entities. Treatment with continuous positive airway pressure (CPAP) has been shown to reduce fatal and non-fatal cardiovascular events. In addition, without treatment of OSA with CPAP, poor COPD outcomes have been reported. CPAP may both improve cardiovascular outcomes and reduce exacerbations in patients with the overlap syndrome, but the mechanisms leading to these improvements remain unclear, as do the CPAP requirements. In patients with OSA alone (no COPD), the optimal level of CPAP adherence remains unclear.

However, two recent studies assessing long term CPAP use in overlap patients have suggested benefits in mortality. Machado and colleagues added the use of CPAP to long-term oxygen therapy and observed differences in long term survival of 71% versus 26%. Recently, Marin et al. have shown that hospitalization rates and mortality from COPD can be mitigated if CPAP is prescribed, compared to those with COPD alone, but the amount of use of CPAP required to achieve optimal outcomes remains unknown.

In the present study we reviewed records from a large community-based sample of patients with OSA, COPD, and overlap syndrome to assess the impact of CPAP use and other risk factors on mortality. We hypothesized greater CPAP adherence would reduce mortality in the overlap syndrome.
Study Population
A post hoc analysis on 10,272 outpatients was performed by first searching the database for diagnosis codes related to OSA/ COPD (CPT 496.0; 491.21; 492, 327.23, 327.20; 780.51; 780.53), followed by a full chart review for appropriate clinical diagnosis and categorization of all potential patients from the cohort. From this sample, 3,396 patients from 2007-2010 were identified and characterized into 6 groups: patients alive or deceased, with the known diagnosis of COPD, OSA, and the overlap of COPD plus OSA. All patients did respond to pre-visit questionnaires containing standardized clinical risk assessments for both OSA and COPD during their initial and routine clinical follow-up.

Data Series/Collection
Information regarding their gender, age, BMI, pulmonary function (FEV1 in Liters [L], FEV1% predicted, FEV1/FVC ratio), current smoking status, number of comorbid conditions (Charlson index) and baseline OSA severity/sleepiness (apnea-hypopnea index [AHI], Nadir SaO₂ (%), Epworth sleepiness score) was recorded.

Sleep Studies and Pulmonary Function
All patients identified with OSA had full in-lab polysomnograms (PSG) and CPAP titrations or split-night polysomnograms through a single American Academy of Sleep Medicine (AASM) accredited Center with 3 locations in Rhode Island. All patients with COPD had pulmonary function testing based on American Thoracic Society standards and were characterized using the GOLD guidelines.

CPAP Therapy/Compliance Data
All patients with the diagnosis of OSA were offered CPAP therapy; PAP settings prescribed were based on AASM standards after in-lab manual titration. No patients in the overlap cohort were on bilevel or auto-titrating PAP modes during the study period. All patients were treated with expiratory pressure relief (EPR or C-Flex). CPAP levels (cm H2O) and compliance data (% nights used > 4 h and median daily usage) from a 1-3 month period were recorded from the individual patient CPAP units via the hard drive of the device or a removable monitor (e.g., Smart Card) downloaded into a central databases by the patients respective durable medical equipment (DME) providers. All patients within the overlap cohort agreed to try CPAP, and no patients refused from the start of diagnosis. Patient data were recorded for a 1- to 3-month period after initiation of therapy. Patients were not included in the sample if reliable compliance data were not available. If patients were using supplemental oxygen (O₂) prior to titration, this liter flow was continued and bled into the CPAP circuit. Supplemental O₂ was recommended for patients with the overlap syndrome found to have residual hypoxemia on CPAP despite elimination of all sleep disordered breathing, based on standard AASM protocol.

Statistical Analysis
A Cox proportional hazards model was developed for the overlap patients to determine univariate and multivariate predictors of survival. The predictors of survival in this model were then analyzed controlling for the other predictors. The patient’s initial visit/treatment dates were recorded, and time-to-event data were noted. Patients remaining alive were censored at the time at which no further follow-up could be proven or at study end. Patients who died were recorded as failure at the date of their death. Continuous covariates included hours on CPAP per night, FEV1, AHI, age, BMI, and number of comorbid conditions (including concurrent CHF, atrial fibrillation, coronary artery disease, stroke, hypertension, diabetes, cancer, and pulmonary hypertension), with the comorbid conditions presented as a Charlson index. Dichotomous covariates included gender and current active smoking. Kaplan-Meier survival plots were generated for the group and were compared using a log-rank test, with Holm-Sidak test used for multiple comparisons. An additional analysis of variance was used to compare patient age across differing levels of CPAP use. Alpha was set at 0.05. The study was approved by the Rhode Island Hospital Institutional Review Board.

RESULTS
Between January 2007 and October 2010, from a cohort of 10,721 outpatients, a sample of 3,760 patients with the diagnosis of either OSA or COPD (or both diagnoses) were identified using evaluation and management CPT codes (496.0, 491.21, 327.23, 327.20, 780.51, 780.53). From this group, 227 patients were identified with the overlap syndrome. Every patient in the overlap group was offered CPAP and was initiated on PAP therapy. Data from 8 patients in this group were lost to follow-up and were “censored” at the time of last clinical visit in the survival analysis. Seventeen patients (7.4%) in the overlap group died (Figure 1). From Table 1 the FEV1 and FEV1 percent predicted (FEV1%) vs. the COPD only group were similar, as were the AHI, BMI, Epworth, and Nadir SaO₂ compared to the other groups (Table 1). The percent of patients who were current active tobacco users was more prevalent in the overlap group than the COPD group (p = 0.02). Supplemental oxygen use was relatively low in all groups (with CPAP in the overlap group in 3.2% of patients and in 3.7% of the COPD only group; p = 0.47). CPAP levels for the OSA and overlap groups were not substantially different (Table 1). The overlap alive patients (n = 210) had mean compliance with CPAP of 65.9% ± 1.8% nights used > 4 h and 5.4 ± 0.1 h/night, versus the overlap dead patients with a mean compliance of 21.2% ± 8.1% nights used > 4 h and 1.7 ± 0.2 h/night (p < 0.001 and p = 0.001; Figures 2, 3). Compliance data were not available in 10% of the cohort and were not included in the analysis.

Cox Proportional Hazards Model
The results for the univariate Cox proportional hazards model for predictors of mortality in the overlap group are presented in Table 2. Hazard ratios (HR) were 1.10 (1.05-1.17, p < 0.001) for age, 1.75 (1.32-2.32, p = 0.01) for the Carlson index (comorbid conditions), and 0.59 (0.48-0.73, p < 0.001) for CPAP. Gender, AHI, FEV1 percent predicted, BMI, and current smoking status did not have an impact on mortality in this analysis. In the multivariate Cox proportional hazards analysis (Table 3), only CPAP use ([h/night],
HR 0.71 [0.55-0.90], p = 0.004) and age (HR 1.14 [1.04-1.23], p = 0.003) significantly contributed to the model. Figure 4 reveals the Kaplan-Meier analysis comparing survival of patients with the overlap syndrome stratified by h/night CPAP usage. When the group was stratified by CPAP use (0-2 h; 2-4 h; 4-6 h, and 6-8 h/night, as determined from the first 1-3 months of use), there was increased mortality in the 0-2 h group compared to the others (log rank statistic, 0-2 h/night vs. 2-4 h/night p = 0.04; 0-2 h/night vs. 4-6 h/night p < 0.001; 0-2 h/night vs. 6-8 h/night p < 0.001; Figure 4.)

Patients in the overlap group with CPAP use 0-2 h/night group had a mean age of 68.2 years; 2-4 h/night 63.7 years; 4-6 h/night 59.4/h; 6-8 h/night 62.9 years (ANOVA: p = 0.02 for 0-2 h vs. 4-6 h). Age did not correlate with CPAP use (h/night) (r² = 0.006, p = 0.20). In addition, BMI, AHI, and FEV1% predicted did not correlate with CPAP use/adherence. The Charlson index did reveal a small but statistically significant correlation with CPAP use (r² = 0.07, p = 0.004).

**DISCUSSION**

The major finding of this observational study was the identification of age and any CPAP use at night, as determined by

![Figure 1](image1)

**Figure 1**—Flow chart of the inclusion/exclusion of patients from the outpatient cohort

![Figure 2](image2)

**Figure 2**—Box plots of mean hours per night of CPAP in overlap group deceased and alive

![Figure 3](image3)

**Figure 3**—Box plots of % nights with > 4 hours use of CPAP in the overlap group deceased and alive

<table>
<thead>
<tr>
<th>Age</th>
<th>BMI</th>
<th>Charlson</th>
<th>FEV1%predicted</th>
<th>AHI events/h</th>
<th>SaO2 nadir</th>
<th>Epworth score</th>
<th>Tobacco Use</th>
<th>CPAP cm H2O</th>
</tr>
</thead>
<tbody>
<tr>
<td>OSA</td>
<td>61.6</td>
<td>33.1</td>
<td>1.5</td>
<td>59.2</td>
<td>28.2</td>
<td>80.8</td>
<td>10.2</td>
<td>0.9</td>
</tr>
<tr>
<td>COPD</td>
<td>69.0</td>
<td>28.0</td>
<td>1.7</td>
<td>56.7</td>
<td>33.2</td>
<td>78.3</td>
<td>9.9</td>
<td>14.6*</td>
</tr>
</tbody>
</table>

* = 0.02 active tobacco use (overlap group vs. COPD and OSA group).
objective monitoring, were associated with mortality in patients with the combination of OSA and COPD (the overlap syndrome). Through objective monitoring from patient CPAP devices during the first 1-3 months of use, we determined that this association persisted after adjustment for known confounders, suggesting that overlap patients who use CPAP have a higher survival than those who do not. Any level of CPAP used was associated with some mortality benefit over no use of CPAP. Age was also a predictor of survival; although there was no correlation between hours of CPAP use and age, the mean age was greater in the patients using CPAP the least compared to those who were more adherent. Lastly, although the number of comorbid conditions seen (Charlson index) was not associated with mortality in this analysis (multivariate model), there was reduced CPAP use in those with the greatest number of comorbid conditions.

Recent studies by Marin et al. have shown that the combination of OSA and COPD leads to increased mortality and that use of CPAP reduces exacerbation rates for concurrent COPD.6 However, the optimal prescription for CPAP was unclear. Their patients were included in the group if they used CPAP ≥ 4 h/night and, if not, the device was withdrawn. Similar to the Spanish study, our analysis shows an association with high mortality when CPAP use is < 4 h/night. We have further demonstrated that any CPAP use may actually be good (i.e., better than nothing), but more use is likely better. The Cox analysis did suggest trends to further reductions in mortality with increasing time on the device; however, the changes were small. This part of the analysis was limited by low power due to low numbers of patients who died while using CPAP. However, this study adds to our growing knowledge, suggesting that longer times on CPAP are associated with better outcomes.

The issue of whether there is a true threshold for optimal CPAP use remains unanswered by this study, as some patients had significant mortality reductions with CPAP use < 4 h/night, which has previously been suggested as a minimal level needed for reductions in OSA morbidity. However, studies by Weaver et al. have suggested near linear improvements in sleepiness and cognitive function with increasing time on CPAP at night (2 versus 4 versus 6 hours).10 This linear improvement on CPAP has been confirmed even more recently by Antic et al.11 However, limited data exist for the impact of increasing CPAP usage (hours on device) on other outcomes such as cardiovascular disease morbidity or overall mortality. Interestingly, the blood pressure improvement dose response curve (recently shown by Haentjens et al.) with CPAP looks similar to the mortality curve in our analyses, with no threshold effect appreciable in either analysis.19

The compliance rates of 65% vs. 21% nights used with CPAP in the overlap alive vs. deceased patients deserve mention. The long-term rates of CPAP use in patients with OSA vary between studies; but despite the mortality advantage seen here, our rates are still low. Nonetheless these levels are similar in magnitude to those in prior reports by Kribbs et al.18 of 63% regular use. McArp developed rates of 75% long-term use and slightly bet-

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**Table 2**—Univariate Cox proportional hazards model for factors associated with mortality

<table>
<thead>
<tr>
<th>Hazard Ratio</th>
<th>95% Lower Confidence Interval</th>
<th>95% Upper Confidence Interval</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPAP (h/night)</td>
<td>0.59</td>
<td>0.48</td>
<td>0.73</td>
</tr>
<tr>
<td>Gender (m, f)</td>
<td>0.37</td>
<td>0.11</td>
<td>1.32</td>
</tr>
<tr>
<td>FEV1 (% predicted)</td>
<td>0.98</td>
<td>0.95</td>
<td>1.01</td>
</tr>
<tr>
<td>AHI (events/h)</td>
<td>0.98</td>
<td>0.96</td>
<td>1.02</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>0.95</td>
<td>0.90</td>
<td>1.09</td>
</tr>
<tr>
<td>Age (years)</td>
<td>1.10</td>
<td>1.05</td>
<td>1.17</td>
</tr>
<tr>
<td>Tobacco active use (y, n)</td>
<td>0.99</td>
<td>0.09</td>
<td>10.6</td>
</tr>
<tr>
<td>Charlson index</td>
<td>1.75</td>
<td>1.32</td>
<td>2.32</td>
</tr>
</tbody>
</table>

**Table 3**—Multivariate Cox proportional hazards model for factors associated with mortality

<table>
<thead>
<tr>
<th>Hazard Ratio</th>
<th>95% Lower Confidence Interval</th>
<th>95% Upper Confidence Interval</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPAP (h/night)</td>
<td>0.71</td>
<td>0.55</td>
<td>0.90</td>
</tr>
<tr>
<td>Age (years)</td>
<td>1.14</td>
<td>1.04</td>
<td>1.23</td>
</tr>
<tr>
<td>Charlson index</td>
<td>1.31</td>
<td>0.86</td>
<td>1.93</td>
</tr>
</tbody>
</table>

**Figure 4**—Kaplan-Meier curves for survival over the three year study period stratified by average CPAP use per night for the overlap patients

**Figure**

![Kaplan-Meier curves](image)

Mortality was reduced with more time on CPAP: 0-2 h/night vs. 2-4 h/night p = 0.04; 0-2 h/night vs. 4-6 h/night p < 0.001; 0-2 h/night vs. 6-8 h/night p < 0.001.
Our finding of age as an independent predictor of survival in the overlap group is interesting given the relatively low mean age of this population. Although age did not correlate with CPAP use, the oldest quartile was the group that used CPAP 0-2 h/night (compared to those who use CPAP 4-6 h/night). These data support the notion that older patients with overlap syndrome may have an amplification of their mortality risk due to both aging itself (which is a risk factor for worsening OSA prevalence and cardiovascular complications) and to limited use of PAP therapy. In addition, despite therapy, age may impact overall improvements with PAP therapy as reported by Ayalon and colleagues, who have noted that older patients with comorbid depression tend to have less long-term cognitive improvement than younger counterparts.

Although the Cox hazards model did not find that the Charlson index was independently associated with mortality, there was an association between numbers of comorbid conditions and CPAP use. There was a small but statistically significant correlation between the Charlson index and PAP use, suggesting that for some patients increasing numbers of comorbid conditions may negatively impact PAP use.

The lack of association between mortality and the presence of active smoking, the FEV1% predicted or the use of supplemental oxygen deserves comment. We found no difference in the number of patients using supplemental oxygen in the overlap group who died versus still living. This finding is important because in addition to the landmark studies showing reduced mortality in patients with severe COPD using supplemental oxygen, prior reports have also suggested improved sleep quality and improvements in the apnea hypopnea index in patients with OSA using supplemental oxygen at night. In addition, current smoking rates were not different between groups but were higher in those with the overlap syndrome. There was no difference in the current smoking rates of overlap patients who died versus remaining alive, but there were more active smokers in the overlap group than the COPD or OSA group alone. This observation may explain some of the amplification of symptoms noted when moderate COPD and moderate OSA are seen together in the overlap syndrome. The FEV1% predicted was not found associated with mortality in this cohort. However, the mean FEV1% predicted was lower in those who died in the overlap group than those in the COPD only group, similar to the findings of the Spanish study and that of Chaouat et al.

Despite our study’s strengths, we acknowledge a number of weaknesses. First, is the study’s post hoc, non-randomized design with CPAP use. However, the single-center large cohort without participation bias and low loss of follow-up strengthen this report. Based on the healthy user effect, some but not all data suggest that CPAP use may track with other health care outcomes. Thus, in theory, patients who were motivated and educated may use CPAP faithfully but also may use medications that reduce cardiovascular morbidity (inhaled, β-blockers, statins) and closely follow diet and exercise recommendations. Age certainly did contribute to mortality in this study, but we did not have a complete enough data set recorded from this cohort on medication or dosage changes to be able to determine clearly if patients who did not use CPAP also did not use their medications for COPD. Although increasing numbers of comorbid conditions (Charlson index) were not clearly associated with increased mortality in this cohort, the index was associated with CPAP use. Further randomized trials will be required to determine whether CPAP per se improves mortality in overlap syndrome. Second, we had only roughly three years of follow-up in our cohort. Given the poor prognosis of these patients, it is true that many more deaths would have been observed had we had longer duration of follow-up. Thus, we cannot determine whether CPAP is actually preventing death or simply delaying death somewhat. Nonetheless, we view any prolongation of life as important in these conditions where outcome is generally poor. Third, we had no patients within the overlap cohort on other PAP delivery modes and thus could not compare outcomes with CPAP and other modes such as bilevel PAP. Some would argue that patients with COPD may experience hypoventilation during sleep, particularly REM sleep, such that bilevel PAP may be required to alleviate gas exchange disturbances. For example, transient elevations in PaCO2 may promote pulmonary vasoconstriction, which could represent a burden on the right ventricle. Thus, further data will be required to determine whether bilevel PAP is superior to CPAP in terms of outcome in overlap patients. Fourth, because of the post hoc design of the study, some patients from the larger cohort may have had the overlap syndrome and may have been inadvertently left out of the analysis, which may introduce bias. We made efforts to apply clinical criteria for COPD and OSA to the available charted information to reduce risk of missing potential study patients or misclassifying them. A future randomized trial with systematic inclusion/exclusion criteria would eliminate this type of bias. Despite these limitations, we believe that our data are robust and represent an important addition to the literature. However, we clearly support further efforts in this area given that OSA has been excluded from essentially all randomized trials to date of PAP therapy in COPD.

In summary this study adds to a growing body of literature regarding the combined impact of OSA in patients with COPD. We have shown that more time on CPAP in patients with the overlap syndrome was associated with a reduced risk of death, after controlling for common risk factors. Age is also an important contributor to mortality although the mechanism of the aging effect is unclear, emphasizing the need for further research in this area.

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In obstructive sleep apnea (OSA), arousals occur at the end of most obstructive events, and help restore upper airway patency by activating pharyngeal dilator muscles. Thus, arousals generally occur at as a defense mechanism to reestablish airflow and prevent asphyxia in OSA. The role of arousals in central sleep apnea (CSA), however, is less clear. For example, it has been reported that arousals can occur several breaths after apnea termination in heart failure (HF) patients with CSA. In such cases, reinstitution of airflow prior to the occurrence of arousal suggests that such arousals may not have the same protective role as they do in OSA. In fact, arousals have been implicated in the pathogenesis of CSA by contributing to respiratory control system instability. Arousals frequently cause an abrupt increase in ventilation, which, in susceptible subjects, drives the PaCO₂ below the apnea threshold, triggering a central apnea. They may also perpetuate further events by provoking ventilatory overshoot during hyperpnea by abruptly increasing chemical ventilatory responsiveness and activating the neurogenic wakefulness drive to breathe. However, the precise timing of arousals in relation to CSA has not been quantified or compared to timing of arousals in relation to OSA in patients with HF.

Many studies of patients with OSA, both with and without HF, have shown that alleviation of OSA with continuous positive airway pressure (CPAP) dramatically lowers the frequency of arousals. This observation provides further evidence that OSA causes arousals that are reversible through treatment of OSA. However, in a large, randomized controlled trial involving 258 patients with HF and CSA, alleviation of CSA with CPAP did not reduce arousal frequency. These findings suggest that arousals in HF patients with CSA may not be acting as a defense mechanism to the same extent as they do in OSA, and indeed, in many instances may not be a consequence of central events. These observations have given rise to the concept that arousals may play a causative role or may be an incidental finding, rather than serving as a protective mechanism in CSA.

**BRIEF SUMMARY**

**Current Knowledge/Study Rationale:** Whereas in obstructive sleep apnea (OSA), arousals generally occur at apnea termination and act as a defense mechanism to reestablish airflow, in central sleep apnea (CSA), timing of arousals post-apnea termination has not been objectively assessed, and factors related to arousal timing have not been identified. We therefore tested the hypotheses that arousals would coincide closely with termination of obstructive events, in keeping with their protective role, while they would be delayed following reestablishment of airflow after central events in proportion to circulation time, suggesting a non-protective role.

**Study Impact:** Among patients with heart failure, whereas in those with OSA, arousals were closely linked to apnea termination and were unrelated to circulation time, in those with CSA arousals occurred at longer and more highly variable latencies following apnea termination that were proportional to circulation time. These findings suggest (1) unlike OSA, arousals in CSA do not serve the same protective role in facilitating airflow reestablishment following apneas, and (2) in contrast to OSA, their timing is influenced by cardiac function and circulation time.
Although suppression of CSA by CPAP may not reduce total arousal frequency, the assumption that arousals are therefore not involved in facilitating resumption of respiration at the end of central apneas remains speculative. While it has been reported anecdotally that arousals usually occur several breaths after termination of central events in HF patients, the actual timing of arousals was not quantified. We therefore compared the timing of arousals with respect to apnea and hypopnea termination between HF patients with OSA and those with CSA. We therefore tested two hypotheses: (1) that arousals would coincide more closely with termination of obstructive events (in keeping with their protective role), while they would be more delayed until after reestablishment of airflow following central events; and (2) that owing to the longer delay of transmission of blood gas tensions from the lungs to the chemoreceptors in HF patients with CSA than in those with OSA, arousals following central events, but not obstructive events, would be related to circulation time.

**METHODS**

**Subjects**

Consecutive patients with HF were recruited from Mount Sinai Hospital Heart Failure Clinic in Toronto as part of an ongoing prospective epidemiological study irrespective of signs or symptoms of sleep apnea if they met the following criteria: (1) men and women ≥ 18 years of age; (2) HF with left ventricular systolic dysfunction (left ventricular ejection fraction [LVEF] ≤ 45% by radionuclide angiography or echocardiography) secondary to ischemic or nonischemic dilated cardiomyopathy for ≥ 6 months; (3) New York Heart Association (NYHA) class I to III; (4) stable clinical status on optimal medical therapy for ≥ 1 month before entry; and (5) moderate-to-severe sleep apnea, defined as ≥ 15 apneas and hypopneas per hour of sleep (apnea-hypopnea index [AHI]). Patients were further classified as having predominantly OSA if ≥ 50% of the events were obstructive, or predominantly CSA if > 50% of the events were central. Exclusion criteria were unstable angina, myocardial infarction, cardiac surgery within the previous 3 months, and pregnancy. The protocol was approved by the local research ethics board, and all subjects provided written informed consent before entry.

**Polysomnography**

Diagnostic overnight polysomnography was performed in all subjects using standard techniques and scoring criteria for sleep stages. Wakefulness and sleep stages were identified by central (C3/A2; C4/A1), occipital (O1/A2; O2/A1), and frontal (F3/A2; F4/A1) electroencephalogram (EEG), bilateral electrooculogram (EOG), and submental electromyogram (EMGsm) recordings from surface electrodes. Arousals were defined by American Academy of Sleep Medicine 2007 criteria, and arousal index (ArI) was calculated as the total number of arousals per hour of sleep.

Thoracoabdominal movements were measured by spirometry-calibrated respiratory inductance plethysmography (Respi-trace; Ambulatory Monitoring, White Plains, NY) and airflow by nasal pressure cannulae (BiNAPS model 550; Salter Labs, Arvin, CA). Central apneas were defined as ≥ 90% reduction in tidal volume ($V_t$) ≥ 10 sec. Central hypopneas were defined as a 50% to 90% reduction in $V_t$ from baseline ≥ 10 sec either without thoracoabdominal motion, or with in-phase thoracoabdominal motion and without airflow limitation on the nasal pressure tracing. Apneas and hypopneas were classified as obstructive if out-of-phase thoracoabdominal motion or airflow limitation was present. The amplitude criterion for hypopnea termination was ≥ 50% of the baseline tidal volume. The AHI was calculated. Arterial oxygen saturation ($SaO_2$) was measured continuously with a pulse oximeter (Nellcor N200; Tyco International Healthcare, Pleasanton, CA) placed on the ear. Mean $SaO_2$ was derived as previously described.

**Data Analysis**

Ten consecutive patients with predominantly OSA and 10 with predominantly CSA from the aforementioned epidemiological study were included in the analysis. Twenty events (apneas and hypopneas) were evaluated in each patient during stage 2 NREM sleep—10 from the beginning of the night, and 10 from the end of the night. Stage 2 sleep was analyzed, as it was the dominant sleep stage in which most events occurred and in which ventilation is predominantly under metabolic control. In addition, we confined data analysis to a single sleep stage to control for the potential confounding influences of different sleep stages on arousals and respiratory events. Events from both early and late in the night were analyzed in consideration of influences of possible overnight deterioration of cardiac function. Time from the end of an event to the beginning of an arousal (apnea-to-arousal time) and time from the end of an event to the peak of hyperpnea (apnea-to-peak time) were measured. Time from the beginning of an arousal to the peak of hyperpnea (arousal-to-peak time) was calculated by subtracting apnea-to-arousal time from apnea-to-peak time. Hyperpnea time (HT) was defined as the time between the onset of inspiration of the breath terminating the apnea or hypopnea and the end of inspiration of the breath preceding the next apnea or hypopnea. Lung-to-ear circulation time (LECT), an estimate of lung-to-carotid chemoreceptor circulation time, was measured from the end of an apnea to the subsequent nadir of $SpO_2$, as previously described. This technique has been previously validated against echocardiographic Doppler as a measure of circulation time and a reflection of cardiac output.

Data are expressed as mean ± SD unless stated otherwise. Analyses were performed using SPSS 13.0 (SPSS Inc., Chicago, IL). Data from OSA and CSA patients were compared with 2-tailed unpaired t-tests for continuous variables. Nominal and ordinal variables were compared by $\chi^2$ or Fisher exact test as appropriate. Correlations among variables were performed by least-squares linear regression analysis. P-values < 0.05 were considered statistically significant.

**RESULTS**

**Characteristics of the Subjects**

Characteristics of the 10 OSA and 10 CSA patients are shown in Table 1. Patients with CSA were older and had lower body mass index (BMI) than those with OSA. There were no significant differences in LVEF or medical therapy between the 2 groups. Sleep data are shown in Table 2. Total sleep time and...
Timing of Arousals in Sleep Apnea

the proportion of stages 1, 2, and REM sleep were similar between the 2 groups, but patients with CSA had a lower proportion of slow wave sleep (p = 0.021). The frequency of arousals was also similar in the 2 groups. However, compared to the OSA group, the ratio of arousals to apneas and hypopneas was lower in the CSA group (94% vs 62%, p = 0.042). With respect to sleep apnea severity, the AHI was higher in the CSA group, but there was no significant difference in the mean or minimum \( \text{SpO}_2 \) between the 2 groups. The CSA patients had a significantly longer hyperpnea time and LECT than those with OSA.

Timing of Arousals

Representative polysomnographic tracings showing arousal timing with respect to the termination of apneas are shown in Figure 1. Note that in the patient with OSA, the arousal occurred coincident with the end of the event (Figure 1A). In contrast, in the patient with CSA, the arousal occurred much later after the end of the apnea, several breaths after resumption of respiration (Figure 1B). Grouped data in Figure 2 show that apnea-to-arousal time was highly variable and much longer in the CSA group than the OSA group (p < 0.0001), but occurred prior to peak hyperpnea so that arousal-to-peak time did not differ between the OSA and CSA groups (p = 0.416; Figure 3). Similar to the group variability, the intra-individual variability in apnea-to-arousal time was higher in the CSA patients than in the OSA patients (mean standard deviation of 4.97 ± 2.54 vs. 1.95 ± 0.68, p = 0.002).

Apnea-to-arousal time was strongly related to LECT in patients with CSA (p = 0.006, Figure 4A), but not in those with OSA (p = 0.107, Figure 4B). There was no significant relationship between arousal-to-peak time and LECT in either the CSA or OSA group (p = 0.887 and p = 0.444, respectively). Length of hyperpnea was related significantly to LECT (r = 0.771, p = 0.009) in the CSA patients, as shown in previous studies, but not in the OSA patients (p = 0.366).

DISCUSSION

The results of the present study indicate that in HF patients there are marked differences in the timing of arousals following
termination of apneas and hypopneas between those with OSA and those with CSA. Arousals were generally simultaneous with apnea termination in the OSA group, with a mean apnea-to-arousal time of 0.9 seconds. This is consistent with a defensive role in augmenting upper airway dilator muscle activity and reestablishing airway patency and airflow.\textsuperscript{1,15} In contrast, in the CSA group, apnea-to-arousal time was much longer, with a mean latency of 8.0 seconds. Moreover, the ratio of arousals to apneas and hypopneas was significantly lower in the CSA (62\%) than in the OSA group (94\%), indicating that in the former group, far fewer respiratory events were terminated by an arousal. These observations are not consistent with a similar defensive function in central than in obstructive events, since arousals were not necessary to reestablish airflow. However, the time from the onset of arousal to the peak of hyperpnea (arousal-to-peak time) was similar in the two groups, suggesting that arousals may augment hyperpnea and influence the timing of peak ventilation in both OSA and CSA.

Our data are consistent with previous studies showing that arousals occur in close proximity to termination of the great

\textbf{Figure 2—Apnea-to-arousal time}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig2}
\caption{Apnea-to-arousal time}
\end{figure}

Time from the end of an apnea or hypopnea to the beginning of an arousal (apnea-to-arousal time) was significantly longer and more variable in the 10 subjects in the CSA group compared to the 10 subjects in the OSA group (8.0 ± 4.1 vs 0.9 ± 1.1 s, p < 0.0001). Data are expressed as means and standard deviations.

\textbf{Figure 3—Arousal-to-peak time}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig3}
\caption{Arousal-to-peak time}
\end{figure}

Time from the beginning of an arousal to the peak of hyperpnea (arousal-to-peak time) did not differ between the 10 subjects with OSA and the 10 subjects with CSA (4.3 ± 1.1 vs 4.8 ± 1.6 s, p = 0.416).

\textbf{Figure 4—Apnea-to-arousal time and lung-to-ear circulation time}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig4}
\caption{Apnea-to-arousal time and lung-to-ear circulation time}
\end{figure}

A significant correlation between apnea-to-arousal time and lung-to-ear circulation time (LECT) was found in the 10 subjects with CSA (A) but not the 10 subjects with OSA (B).
majority of obstructive events, and thus play a key role in reestablishing airflow. In contrast, reports of the timing of arousals following termination of central events are inconsistent, with some indicating that they occur at the end of central events and others, several breaths later at the peak of hyperventilation. This discrepancy may be related to the inherent variability in arousal timing that we describe herein, or may be a result of the heterogeneity of the CSA population. Indeed, in non-HF patients with idiopathic CSA, most arousals were reported to occur at the resumption of ventilation following apneas. In contrast, in CSA accompanied by a Cheyne-Stokes respiratory pattern in the HF population, such as those herein, arousals have been reported to occur later during the hyperpneic phase several breaths after apnea termination. However, quantification of the actual time from the end of a central event until the onset of arousal has not been previously reported. Our data indicate that in HF patients with CSA, the timing of arousals is highly variable and most often occurs several seconds after termination of central events, but before the peak of hyperventilation.

The highly variable timing of arousals following central apneas and hypopneas, and their predominant occurrence several breaths after resumption of ventilation are not in favor of them being an important mechanism in terminating such events or in reestablishing normal airflow. In this regard, arousals in HF patients with CSA appear to have a substantially different pathophysiological significance than in those with OSA. Indeed, our previous work suggests that arousals play a provocative role in triggering and perpetuating central apneas in both HF and non-HF patients with CSA. By causing an abrupt increase in ventilation, arousals can provoke a fall in PaCO₂ below the apnea threshold that can result in central apnea. Previous studies have shown that over 90% of episodes of Cheyne-Stokes respiration in HF patients with CSA, and almost 80% of episodes of periodic breathing in non-HF patients with idiopathic CSA are precipitated by arousals that trigger an increase in £. Arousals facilitate ventilatory overshoot and ongoing respiratory cycling by increasing state-dependent chemical ventilatory responsiveness and by engaging the neurogenic wakefulness drive to breathe. Both the magnitude of hyperventilation and length of the subsequent apnea increase progressively with increasing intensity of associated arousals. Taken together, these data suggest a largely pathological effect of arousals in CSA.

If arousals were a result of CSA, then attenuating CSA should reduce arousal frequency, and vice versa. In this regard, the evidence is inconsistent. On the one hand, several small studies involving 11 to 16 HF patients with CSA showed a decrease in ArI by 52% to 57% in association with a 40% to 71% reduction in AHI with CPAP therapy. On the other hand, several studies involving 17 to 26 HF patients with CSA in which CPAP lowered the AHI by 62% to 89% showed no effect on the ArI. In the largest multicenter trial to date, in which 258 HF patients with CSA were randomized to CPAP treatment or control, CPAP lowered the AHI by 55% after 3 months but did not lower the ArI or improve sleep structure. Furthermore, there was no significant change in arousal frequency in the subgroup of 58 patients in whom CPAP reduced the AHI to < 15, nor in the 38 CPAP patients who underwent sleep studies 2 years after randomization, compared to the control group. In contrast, studies of HF patients with OSA have shown that the ArI decreases consistently and significantly in association with a reduction in the AHI in response to CPAP. CPAP has also been shown to decrease arousal frequency significantly in the non-HF OSA population. These studies therefore support the notion that arousals are less likely to be a consequence of (or defense mechanism in) HF patients with CSA than in OSA.

In OSA, arousals are triggered by inspiratory effort against the occluded airway, hypoxia, and hypercapnia. The stimuli for arousals following central apneas are not as well understood. The possibility of chemoreceptor-mediated stimuli is compatible with our finding that apnea-to-arousal time is strongly related to LECT (i.e., lung to chemoreceptor circulation time) in patients with CSA, such that the longer the LECT, the longer the apnea-to-arousal time. This suggests that the latency from blood gas changes in the lung to their perception at the chemoreceptors influences the timing of arousals that may be chemoreceptor mediated. Thus, while such stimuli might cause arousal at apnea termination and contribute to reinstatement of airflow in individuals with normal heart function and circulation time, if there is an increase in circulation time due to lower cardiac output in the setting of HF, arousals are delayed such that they occur after the onset of airflow. Accordingly, while the physiological purpose of arousals after central apneas may be to act as a defense mechanism to prevent asphyxia similar to that in obstructive events, prolonged circulation time related to HF defeats this purpose and delays arousal until after airflow has resumed. Further support for this hypothesis is provided by the discrepancy in arousal timing between CSA patients with HF and idiopathic CSA patients without HF and with normal circulation time. In the latter, arousals are coincident with apnea termination, as in OSA, while in the former, arousals are delayed until several breaths after apnea termination. This difference may well be due to lower cardiac output and longer LECT in patients with HF-related CSA than in those with idiopathic CSA and normal heart function.

If arousals following central events arise mainly due to chemostimulation, but fail to preserve a defensive role in the setting of HF due to prolonged circulation time, alleviation of CSA by CPAP should still lower the ArI. However, as described above, most studies in HF patients with CSA showed no significant reduction in the frequency of arousals in response to CPAP, despite a decrease in AHI. There are two possible reasons for this discrepancy. First, arousals may be classified as spontaneous or respiratory related. While the stimuli for arousals related to central apneas are likely chemoreceptor mediated, the stimuli for respiratory-related arousals in OSA include, in addition, inspiratory efforts against an occluded airway and generation of negative intrathoracic pressure. These additional mechanical stimuli likely underlie the shorter apnea-to-arousal time found in the OSA group, as well as the lack of relationship between apnea-to-arousal time and LECT in OSA. Moreover, the stimuli for respiratory-related arousals in CSA are thus less potent than those for OSA, and arousals are not required for apnea termination. Accordingly, respiratory-related arousals likely comprise a smaller fraction of total arousals in CSA than in OSA. Therefore, while respiratory-related arousals may be reduced by attenuation of CSA with CPAP, the larger proportion of spontaneous arousals are unaffected, ultimately yielding nonsignificant reductions in total arousal frequency.
Second, although the relationship between apnea-to-arousal time and LECT in the CSA group suggests a chemical stimulus for arousals in CSA, it is possible that these “respiratory-related” arousals are in fact, spontaneous arousals that are entrained by the Cheyne-Stokes respiratory cycle. This may be analogous to the entrainment of oscillations in heart rate and blood pressure by periodic breathing. Experimental periodic breathing and Cheyne-Stokes respiration in HF patients can amplify oscillations in blood pressure and heart rate and entrain them at the frequency of the periodic breathing, independent of hypoxia or arousals from sleep. \(^{33,35}\) It is possible, therefore, that spontaneously occurring arousals may be similarly entrained at the frequency of the Cheyne-Stokes respiratory cycle, whose duration is influenced by circulation time.\(^ {14}\) Attention of central apneas by CPAP may uncouple this relationship and unmask the spontaneous nature of the arousals, with little or no effect on the total arousal frequency.\(^ {15}\) If indeed HF patients with CSA have a high frequency of spontaneous arousals, the reason is not clear. One possibility is that higher left ventricular filling pressures and greater rostral fluid shift from the legs into the thorax in HF patients with CSA than in those with OSA cause a greater degree of pulmonary congestion.\(^ {36,37}\) Discomfort arising from such congestion might provoke arousals.

In our study, arousals following central events usually preceded the peak of post-apnea hyperpnea. Arousals abruptly augment ventilation by increasing chemical ventilatory responsiveness and activating the non-chemical wakefulness drive to breathe.\(^ {6,7}\) Both of these are neurogenic stimuli, which should not be influenced by circulation time. Indeed, arousal-to-peak time did not differ between the CSA and OSA groups and bore no relationship to LECT. It is also interesting that the arousal to peak ventilation latency was approximately 5 seconds, which is very similar to the neurogenic latency between sympathetic vasoconstrictor discharge and the peak blood pressure response.\(^ {38}\) These data also suggest that arousals may play a role in determining the timing of peak ventilation during hyperpnea in both CSA and OSA.

There are several potential limitations of this study. The detection of the start of an arousal by visual inspection has a subjective component, especially in patients who do not produce prominent alpha waves.\(^ {39}\) However, our use of occipital\(^ {10}\) and frontal\(^ {39}\) EEG electrodes should have optimized arousal detection by the standard criteria. It is also possible that the standard AASM arousal definition\(^ {18}\) we used may lack sensitivity, leading to under-appreciation of the full spectrum of arousals related to respiratory events.\(^ {40}\) In addition, our analyses were confined to stage 2 NREM sleep to control for potential confounding effects of sleep stage on arousal and respiratory events. Therefore, the influence of sleep state on arousal timing was not examined. Finally, it may not be possible to extrapolate our results to all patients with sleep apnea, as only subjects with HF were studied.

In summary, in HF patients the latency from central events to arousals is highly variable and significantly longer than those following obstructive events. Nevertheless, arousals following both central and obstructive events occur prior to peak hyperpnea. The latency between apnea termination and arousal onset is strongly related to LECT in CSA. This observation suggests involvement of chemical respiratory arousal stimuli, with a post-apneic latency to the detection of such stimuli at the chemoreceptors inversely proportional to cardiac output.\(^ {30}\) The similarity in time from arousal to peak of hyperpnea between the OSA and CSA groups probably relates to neurogenic arousal-mediated augmentation of ventilation that is not related to circulation time. These observations provide further evidence that arousals are less likely to act as a protective mechanism that facilitates resumption of airflow in HF patients with CSA than in those with OSA.

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Prevalence and Risk Factors of Sleep Disordered Breathing in Patients with Rheumatic Valvar Heart Disease

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Methods: A cross-sectional study was conducted in 260 RVHD patients. The following data were recorded: types of heart valve lesions, electrocardiographic, echocardiographic, arterial blood gas analysis findings, baseline medication, 6-minute walk test (6MWT) distance, and sleep parameters.

Results: Compared to patients with single left-sided valve lesions, patients with left- and right-sided valve lesions had a higher prevalence of SDB (46.2% vs. 31.2%, p = 0.013); the increased prevalence of SDB only involved central sleep apnea (CSA) (31.1% vs. 14.1%, p = 0.001). Patients with obstructive sleep apnea (OSA) or CSA were older and had a shorter 6MWT distance, lower left ventricle ejection fraction and PaO2, a longer lung-to-finger circulation time, and a higher prevalence of atrial fibrillation (AF) and hypertension (all p < 0.05) as compared with patients without SDB. Multinomial logistic regression analysis showed that PaO2 ≤ 85 mm Hg was the only risk factor for OSA. Male gender, AF, 6MWT distance ≤ 300 m, PaO2 ≤ 85 mmHg, and PaCO2 ≤ 40 mm Hg were risk factors for CSA.

Conclusions: Patients with RVHD had a high prevalence of SDB (predominantly CSA). RVHD patients with SDB, particularly those who had CSA, manifested more severe symptoms and greater impairment of cardiac function. Assessments of clinical manifestations of cardiac dysfunction may be important for predicting the risk factors for SDB.

Keywords: Sleep disordered breathing, rheumatic valvar heart disease, central sleep apnea, obstructive sleep apnea, chronic heart failure


Chronic heart failure (CHF) and sleep disordered breathing (SDB) are major public health problems in many countries. Studies have shown a high prevalence of SDB in CHF patients. Specifically, Sin1 observed that 38% of 450 CHF patients had obstructive sleep apnea (OSA), while 33% had central sleep apnea (CSA). Another study showed that SDB was present in 76% of patients with symptomatic CHF (40% CSA, 36% OSA).2 Several studies have demonstrated increased mortality in CHF patients with SDB in contrast to those without SDB.3-5 Other studies have also revealed that OSA is a cardiovascular risk factor and that CSA is a potential marker of the severity of CHF.3-6-8

Valvular heart disease is an important comorbidity factor for CHF. The prevalence of valvular heart disease is estimated at 2.5% in the US population and sharply increases beyond the age of 65 years because of the prevalence of degenerative etiologies.9 Although a decreased incidence of rheumatic valvular heart disease (RVHD) has been observed in the past 50 years, RVHD remains common in developing countries, where the prevalence is underestimated by clinical examination. The prevalence of RVHD is estimated at 2% to 3% when using systematic echocardiographic screening.9

Previous studies have mainly focused on the prevalence of SDB in patients with non-valvular diseases, such as coronary heart disease, myocardial infarction, dilated cardiomyopathy, and hypertrophic cardiomyopathy.2,10,11 Several studies have suggested the SDB and valvular heart disease are associated; however, instead of RHVD, most of the studies involved patients with degenerative valvular heart disease. In addition, the relationship between the types of heart valve lesions and SDB has not been elucidated. We hypothesized that in RVHD patients, the types of SDB were related to types of heart valve lesions and that some clinical characteristics might be predictive factors for SDB. Therefore, the current study was designed to investigate the epidemic characteristics of SDB in RVHD patients.
Methods

Patients

Between April 2010 and October 2011, patients with RVHD admitted to the Cardiothoracic Surgery Department of the First Affiliated Hospital of Nanjing Medical University for heart valve replacement surgery were screened for the presence of various types of SDB. Among these patients, 275 underwent full-night polysomnography (PSG). Two hundred sixty patients were enrolled, but 15 were excluded because they lacked an adequate PSG record or underwent a short PSG (< 3 h; Figure 1). None of the patients had been screened for SDB prior to the study period.

The following inclusion criteria were used: (1) age between 18 to 70 years; (2) symptomatic stable heart failure, New York Heart Association (NYHA) class ≥ II despite optimal drug therapy; (3) primary episode of rheumatic fever and current NYHA classification was assessed immediately after the patients were enrolled. Atrial fibrillation (AF) was detected by 12-lead electrocardiography. Two-dimensional Doppler echocardiography was performed to assess the left ventricular ejection fraction (LVEF). On the second morning of hospitalization, an arterial blood gas was evaluated when patients discontinued oxygen therapy for at least 1 hour.

The 6-minute walk test (6MWT) was performed within 3 days after hospital admission according to the guidelines issued by the American Thoracic Society.18 For those whose lower limb joints were damaged by rheumatic fever, 6MWT was not conducted.

Bias Control

To reduce the potential bias as much as possible, the following steps were taken: (1) patients were randomly selected and according to inclusion and exclusion criteria; (2) clinical data were collected fully to avoid any possible data loss bias; (3) the same medical instrument was used for all patients for echocardiography, electrocardiography, blood gas analysis, and polysomnography; (4) all examiners and persons who analyzed the data were blinded to this study and patients enrolled in this study.

Polysomnography

An evaluation of daytime sleepiness based on the Epworth Sleepiness Scale (ESS) was performed prior to sleep study. The sleep study was performed by unattended overnight PSG (Embla S4500 System, USA). Sleep was monitored using 5 electroencephalographic channels (EEG; F4-M1, C4-M1, O2-M1, E12-M2, and E2-M2) and a submental electromyogram. Nasal airflow was measured by continuously recording the nasal pressure, snoring, pulse oximetry, and body position, as well as chest and abdominal effort. For each participant, ≥ 80% of the total recording was considered of good quality. Analyses were performed by 2 physicians who specialized in SDB but were not directly involved in this study.

The following standard definitions were used to describe and score SDB: obstructive apnea—complete cessation of airflow with continued paradoxical chest and abdominal excursion for ≥ 10 s; mixed apnea—cessation of airflow for ≥ 10 s with complete cessation of both abdominal and chest movement in at least the first half of the apnea (first 5 s), followed by paradoxical chest and abdominal excursion in the latter half (mixed apnea was classified as part of the obstructive apnea group because both had the same pathogenesis); central apnea—complete cessation of airflow as well as complete cessation of chest and abdominal excursion ≥ 10 s; and hypopnea—reduction of airflow > 50% from the baseline ≥ 10 s and associated with 4% desaturation or an increase in EEG.

SDB was further classified as either CSA or OSA based on the predominance (> 50%) of the type of sleep apnea to ensure consistency with the criteria used in other studies.2,19,20 The apnea/hypopnea index (AHI) is used as a marker of SDB severity and graded as “mild” (5-15/h), “moderate” (15-30/h), or “severe” (> 30/h) according to AASM guidelines.21 Patients with an AHI < 5/h were considered to have no SDB.

The circulation time was measured by lung-to-finger circulation time (LFCT) instead of lung-to-ear circulation time, be-
cause the SpO₂ in our patients was assessed by a finger rather than an ear.

Statistical Analysis

Statistical analyses were performed using the SPSS statistical software (version 13.0; IBM, USA). Continuous data were expressed as mean (95% confidence interval for mean). Differences among the 3 groups (No SDB, CSA, and OSA) were compared using one-way ANOVA. Student-Newman-Keuls method was used for post hoc multiple comparisons. The χ² test was used to analyze the frequency of each parameter. Multinomial logistic regression was used to model the association between various baseline variables and the risk of CSA and/or OSA, for which the patients without SBD were used as the reference group. The candidate independent variables that were used to analyze the following risk factors for CSA and OSA: gender, age, history of symptomatic heart failure, body mass index (BMI), NYHA class, LVEF, and 6MWT, as well as the pH, PaO₂, and PaCO₂ during wakefulness. The presence of hypertension, AF, and left- and right-sided valve lesions was used to evaluate the risk factors for CSA and OSA. A p-value < 0.05 was considered to indicate statistical significance.

RESULTS

Baseline Characteristics

The average age of the 260 patients was 51.3 years (95% CI: 50.1-52.5). Of these patients, 125 (48.1%) were males and 135 (51.9%) were females. Digoxin, diuretics, nitrates, angiotensin converting enzyme inhibitors (ACEIs), and β-blockers were used by 90.4%, 89.6%, 35.4%, 61.9%, and 59.6% of the patients, respectively. Based on the NYHA classification, 12.6%, 61.9%, and 25.4% of the patients were in NYHA classes II, III, and IV, respectively. Of the patients, 49.2% (128) had left-sided valve lesions (mitral valve lesions [23.5%], or aortic valve lesions [11.2%]), or mitral valve + aortic valve lesions [14.6%]) and 50.8% (132) had left- and right-sided valve lesions (mitral valve + tricuspid valve lesions [25.0%] or mitral valve + aortic valve + tricuspid valve lesions [25.8%]). The detailed baseline characteristics of the patients are presented in Table 1.

Clinical and sleep characteristics were compared between the patients with single left-sided valve lesions and left- and right-sided valve lesions. There were no differences between the 2 groups with respect to age (p = 0.872), BMI (p = 0.525), or LVEF (p = 0.859). Patients with left- and right-sided valve lesions had a remarkably shorter 6MWT distance (p = 0.001) and LFCT (p = 0.002), and a higher percentage of symptomatic heart failure ≥ 5 years (p = 0.001), CSA (p = 0.001) and AF (p < 0.001) compared to single left-sided valve lesions patients (Table 1).

The prevalence of SDB in our population was 38.8%; 16.2% had predominant OSA and 22.7% had predominant CSA (Figure 2).

Comparisons in Patients with and without SDB

The prevalence of OSA and CSA in males was significantly higher than females (p = 0.001). Patients with OSA or CSA were older and had shorter 6MWT distances (p < 0.001) and a lower PaCO₂ (p < 0.001) than patients without SDB. Compared with patients without SDB or patients with OSA only, patients with CSA exhibited a significantly higher prevalence of AF (p < 0.001), higher NYHA class (p < 0.001), and longer LFCT (p < 0.001). Decreased LVEF (p = 0.001) and worse sleep respiratory parameters (AHI, ODI, and mean and minimal SpO₂) were likewise observed (Table 2).

Risk Factors for OSA and CSA

The risk factors for OSA are shown in Table 3. The decreasing PaO₂ level was the dominant risk factor in the entire population and females, which was defined by a PaO₂ ≤ 85 mm Hg, with adjusted odds ratios (ORs) of 3.27 (95% CI, 1.52-7.01) and 9.24 (95% CI, 2.28-37.45), respectively. PaCO₂ ≤ 40 mm Hg was a protective factor for OSA in the entire population (OR = 0.40; 95% CI, 0.19-0.85) and males (OR = 0.20; 95% CI, 0.07-0.56).

However, more risk factors were found in CSA patients than in OSA patients (both males and females). For the entire group, the risk factors for CSA were male gender, AF, 6MWT distance ≤ 300 m, PaCO₂ ≤ 40 mm Hg, and PaO₂ ≤ 85 mm Hg, in which the adjusted ORs were 4.55 (95% CI, 1.92-10.8), 3.536 (95% CI, 1.54-8.13), 12.2 (95% CI, 5.10-29.1), 3.04 (95% CI, 1.36-6.84), and 2.64 (95% CI, 1.22-5.75), respectively. Patients with a 6MWT distance ≤ 300 m had greater than a 15-fold increased risk for males and females. However, other risk factors for CSA differed between males and females. For males, AF, PaCO₂ ≤ 40 mm Hg, PaO₂ ≤ 85 mm Hg, and pH ≥ 7.45 were risk factors (OR = 5.46, 95% CI, 1.68-17.8; OR = 5.25, 95% CI, 1.53-18.1; OR = 5.13, 95% CI, 1.50-17.6; OR = 3.70, 95% CI, 1.02-13.4; respectively), whereas age (≥ 50 years) was a dependent risk factor for females (OR = 5.07, 95% CI, 1.31-19.6; Table 4). A LVEF ≤ 60% was not considered a risk factor for OSA or CSA.
DISCUSSION

In patients with CHF caused by non-valvular disease, a high prevalence of SDB has been reported; however, data on the prevalence of SDB in patients with RVHD are not available because RVHD is not the main etiology for heart failure in developed countries. Nevertheless, RVHD remains common in developing countries and is one of the top three leading common causes of heart failure in Chinese hospitals.

As compared with patients with single left-sided valve lesions, patients with left- and right-sided valve lesions had a remarkably higher prevalence of SDB (CSA only) and AF. The major reason might be a longer history of symptomatic heart failure and more severe degree of heart failure. In the early stages of rheumatic fever, the mitral and aortic valves are often involved. With progression of rheumatic heart disease, the tricuspid valve and right heart also become involved. Right heart failure leads to systemic congestion, delayed circulation, and PCO₂ fluctuation, which might cause CSA. Because peripheral edema is more severe in right heart failure patients, nocturnal rostral fluid displaced from the legs to the neck might be a significant contributor to the pathogenesis of OSA and CSA.

Furthermore, a long history of rheumatic disease causes the anatomic and functional alterations and electrophysiological modifications, which result in AF. CSA is predisposed to AF.

Table 1—Baseline clinical and sleep characteristics

<table>
<thead>
<tr>
<th>Demographic characteristics</th>
<th>Total (n = 260)</th>
<th>Left-sided valve lesions (n = 128)</th>
<th>Left- and right-sided valve lesions (n = 132)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>51.3 (50.1-52.5)</td>
<td>51.2 (49.3-53.1)</td>
<td>51.4 (49.9-53.0)</td>
<td>0.872</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td>0.036</td>
</tr>
<tr>
<td>Male</td>
<td>125</td>
<td>70</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>135</td>
<td>58</td>
<td>77</td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>23.5 (23.1-23.9)</td>
<td>23.6 (23.0-24.2)</td>
<td>23.3 (22.8-23.9)</td>
<td>0.525</td>
</tr>
<tr>
<td>Heart valve lesions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitral valve lesions, n (%)</td>
<td>61 (23.5)</td>
<td>61 (23.5)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Aortic valve lesions, n (%)</td>
<td>29 (11.2)</td>
<td>29 (11.2)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Mitral + Aortic valve lesions, n (%)</td>
<td>38 (14.6)</td>
<td>38 (14.6)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Mitral + Tricuspid valve lesions, n (%)</td>
<td>65 (25.0)</td>
<td>0</td>
<td>65 (25.0)</td>
<td></td>
</tr>
<tr>
<td>Mitral + Aortic + Tricuspid valve lesions, n (%)</td>
<td>67 (25.8)</td>
<td>0</td>
<td>67 (25.8)</td>
<td></td>
</tr>
<tr>
<td>Heart failure characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA class</td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>II, n</td>
<td>33</td>
<td>31</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>III, n</td>
<td>161</td>
<td>78</td>
<td>83</td>
<td></td>
</tr>
<tr>
<td>IV, n</td>
<td>66</td>
<td>19</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>Symptomatic heart failure</td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>&lt; 5 y, n</td>
<td>140</td>
<td>83</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>≥ 5 y, n</td>
<td>120</td>
<td>45</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>AF, n (%)</td>
<td>140</td>
<td>43 (33.6)</td>
<td>97 (73.5)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>77</td>
<td>36 (28.1)</td>
<td>41 (29.8)</td>
<td>0.604</td>
</tr>
<tr>
<td>6MWT, m</td>
<td>316 (307-325)</td>
<td>331 (319-343)</td>
<td>302 (289-315)</td>
<td>0.001</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>61.0 (60.0-62.0)</td>
<td>60.9 (59.4-62.4)</td>
<td>61.1 (59.8-62.4)</td>
<td>0.859</td>
</tr>
<tr>
<td>pH</td>
<td>7.44 (7.4-7.45)</td>
<td>7.44 (7.4-7.44)</td>
<td>7.45 (7.4-7.45)</td>
<td>0.065</td>
</tr>
<tr>
<td>PaO₂, mm Hg</td>
<td>85.9 (84.5-87.3)</td>
<td>85.9 (83.9-87.8)</td>
<td>86.0 (84.0-88.0)</td>
<td>0.937</td>
</tr>
<tr>
<td>PaCO₂, mm Hg</td>
<td>39.9 (39.2-40.5)</td>
<td>40.4 (39.6-41.2)</td>
<td>39.3 (38.3-40.4)</td>
<td>0.100</td>
</tr>
<tr>
<td>Sleep data</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SDB, n (%)</td>
<td>141 (38.8)</td>
<td>40 (31.2)</td>
<td>61 (46.2)</td>
<td>0.013</td>
</tr>
<tr>
<td>OSA, n (%)</td>
<td>42 (16.2)</td>
<td>22 (17.2)</td>
<td>20 (15.2)</td>
<td>0.656</td>
</tr>
<tr>
<td>CSA, n (%)</td>
<td>59 (22.7)</td>
<td>18 (14.1)</td>
<td>41 (31.1)</td>
<td>0.001</td>
</tr>
<tr>
<td>ESS score</td>
<td>8.84 (8.15-9.53)</td>
<td>8.39 (7.48-9.30)</td>
<td>9.27 (8.23-10.3)</td>
<td>0.209</td>
</tr>
<tr>
<td>AHI, /h</td>
<td>8.10 (6.75-9.44)</td>
<td>6.85 (5.12-8.58)</td>
<td>9.30 (7.24-11.4)</td>
<td>0.073</td>
</tr>
<tr>
<td>ODI, /h</td>
<td>6.63 (5.42-7.84)</td>
<td>5.49 (4.09-6.88)</td>
<td>7.74 (5.78-9.69)</td>
<td>0.065</td>
</tr>
<tr>
<td>Mean SpO₂ (%)</td>
<td>96.0 (95.8-96.2)</td>
<td>96.1 (95.8-96.4)</td>
<td>95.9 (95.5-96.3)</td>
<td>0.437</td>
</tr>
<tr>
<td>Minimal SpO₂ (%)</td>
<td>86.8 (86.0-87.6)</td>
<td>87.5 (86.3-88.7)</td>
<td>86.1 (85.0-87.3)</td>
<td>0.116</td>
</tr>
<tr>
<td>LFCT (s)</td>
<td>18.5 (17.5-19.5)</td>
<td>16.9 (15.6-18.2)</td>
<td>19.9 (16.9-21.5)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Data are presented as n (%) or mean (95% confidence interval for mean). BMI, body mass index; NYHA, New York Heart Association; 6MWT, six-minute walk test; LVEF, left ventricle ejection fraction; AF, atrial fibrillation; SDB, sleep disordered breathing; OSA, objective sleep apnea; CSA, central sleep apnea; AHI, apnea/hypopnea index; ODI, oxygen desaturation index; LFCT, lung-to-finger circulation time.
because of alterations in sympathetic and parasympathetic nervous system activity occurring in SDB patients, and is associated with hypoxemia, acidosis, apneas, and arousal.

A relatively lower prevalence of SDB in the study population was found. Approximately 40% of the population had OSA (16.2%) or CSA (22.7%), which was almost 50% lower than the results in previous studies.\(^1,2,10\) In addition, the mean LVEF in our study was 61.0% (62.0%, 62.2%, and 57.5% for No SDB, OSA, and CSA, respectively), which was 2-fold higher than previous studies.\(^1,2,12\) The severity and type of SDB are related to LVEF,\(^1,2,12\) which could be used as a predictor of heart systolic function. Therefore, the reduced systolic left ventricular function may lead to an increased prevalence and severity of SDB.

The patients in our study had a lower prevalence of OSA than CSA (Figure 2). Patients with OSA often have a significantly higher BMI.\(^19\) In our patients, BMI was significantly lower than previous studies,\(^1,10,26\) which may explain the lower percentage of OSA.

OSA patients had hypoxia and CO\(_2\) retention because of upper airway obstruction. However, CSA patients usually suffer from hyperventilation and hypocapnia, which occur because the background PaCO\(_2\) is closer to the apneic threshold during sleep in CSA patients than in healthy individuals. Thus, slight increases in ventilation or reductions in PaCO\(_2\) can lead to respiratory instability.\(^27\) CSA patients had a notably higher arterial blood pH and lower PaCO\(_2\) as compared with OSA patients (Table 2), which is consistent with a previous study,\(^20,27\) suggesting that the arterial blood gas differs significantly between OSA and CSA patients. Multinomial logistic regression analysis results that a PaCO\(_2\) \(\leq 40\) mm Hg was a risk factor for CSA, but a protective factor for OSA also agreed with these results (Tables 3 and 4, respectively).

The lung-to-ear circulation time, an estimate of the lung-to-carotid chemoreceptor circulation time, is always increased in patients with CSA.\(^28,29\) Circulation delay may affect not only blood flow distribution, but also the degree of increase in minute ventilation and decrease in the PaCO\(_2\), which directly caused CSA. Our finding that the patients with CSA had a significantly longer LFCT was similar to previous studies.\(^28,29\)

This study showed that the risk factors for CSA significantly differed from those for OSA, but were similar to the findings of a previous study.\(^1\) The previous study showed that risk factors for CSA were male gender, AF, age > 60 years, and hypocapnia. Two additional risk factors for CSA were demonstrated in

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**Table 2—Comparisons of clinical and polysomnography parameters in No SDB, OSA, and CSA patients**

<table>
<thead>
<tr>
<th></th>
<th>No SDB (n = 159)</th>
<th>OSA (n = 42)</th>
<th>CSA (n = 59)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>49.6 (48.0-51.2)</td>
<td>54.8 (52.1-57.6)*</td>
<td>53.4 (51.3-55.6)*</td>
<td>0.001</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td>0.002</td>
</tr>
<tr>
<td>Male</td>
<td>63</td>
<td>28</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>96</td>
<td>14</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m(^2)</td>
<td>23.0 (22.5-23.5)</td>
<td>24.7 (23.6-25.8)*</td>
<td>23.9 (23.1-24.8)</td>
<td>0.005</td>
</tr>
<tr>
<td>Heart valve lesions</td>
<td></td>
<td></td>
<td></td>
<td>0.004</td>
</tr>
<tr>
<td>Left</td>
<td>88</td>
<td>22</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Left and right</td>
<td>71</td>
<td>20</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>NYHA class</td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>II, n</td>
<td>28</td>
<td>5</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>III, n</td>
<td>99</td>
<td>90</td>
<td>32</td>
<td></td>
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<tr>
<td>IV, n</td>
<td>32</td>
<td>7</td>
<td>27</td>
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<tr>
<td>Symptomatic heart failure</td>
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<td>0.639</td>
</tr>
<tr>
<td>&lt; 5 y, n</td>
<td>86</td>
<td>25</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>(\geq 5) y, n</td>
<td>72</td>
<td>17</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>6MWT, m</td>
<td>340 (330-350)</td>
<td>307 (286-329)*</td>
<td>259 (244-274)*</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>62.0 (60.9-63.1)</td>
<td>62.2 (59.9-64.6)</td>
<td>57.5 (54.9-60.0)*</td>
<td>0.001</td>
</tr>
<tr>
<td>AF, n (%)</td>
<td>83 (52.2)</td>
<td>13 (31.0)*</td>
<td>44 (74.6)*</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>33 (20.8)</td>
<td>18 (42.9)*</td>
<td>26 (44.1)*</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>pH</td>
<td>7.44 (7.44-7.45)</td>
<td>7.43 (7.42-7.44)</td>
<td>7.45 (7.44-7.46)*</td>
<td>0.056</td>
</tr>
<tr>
<td>PaO(_2), mm Hg</td>
<td>88.7 (86.9-90.4)</td>
<td>82.6 (79.5-85.6)*</td>
<td>81.0 (78.1-83.9)*</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>PaCO(_2), mm Hg</td>
<td>39.8 (39.0-40.7)</td>
<td>42.1 (40.7-43.5)*</td>
<td>38.4 (37.2-39.6)*</td>
<td>0.002</td>
</tr>
<tr>
<td>ESS score</td>
<td>7.37 (6.54-8.20)</td>
<td>10.3 (8.15-12.2)*</td>
<td>11.8 (10.4-13.1)*</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>AHI, /h</td>
<td>1.72 (1.48-1.96)</td>
<td>13.9 (10.9-16.9)*</td>
<td>21.1 (17.8-24.5)*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean SpO(_2) (%)</td>
<td>96.4 (96.2-96.7)</td>
<td>95.8 (95.2-96.3)*</td>
<td>95.0 (94.4-95.7)*</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Minimal SpO(_2) (%)</td>
<td>88.6 (87.6-89.7)</td>
<td>84.8 (82.8-86.8)*</td>
<td>83.3 (81.8-84.8)*</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ODI, /h</td>
<td>1.91 (1.58-2.25)</td>
<td>9.25 (6.57-11.9)*</td>
<td>17.5 (13.9-21.0)*</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>LFCT (s)</td>
<td>15.5 ± 4.9</td>
<td>16.7 ± 5.14</td>
<td>25.6 ± 7.26*</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Data are presented as n (%) or mean (95% confidence interval for mean). BMI, body mass index; NYHA, New York Heart Association; 6MWT, six-minute walk test; LVEF, left ventricle ejection fraction; AF, atrial fibrillation; pH, power of hydrogen; PaO\(_2\), arterial oxygen tension; PaCO\(_2\), arterial carbon dioxide tension; ESS, Epworth sleepiness scale; AHI, apnea/hypopnea index; SpO\(_2\), pulse oxygen saturation; ODI, oxygen desaturation index; LFCT, lung-to-finger circulation time. *p < 0.05, OSA or CSA versus No SDB; **p < 0.05, CSA versus OSA.
the current study (a 6MWT distance ≤ 300 m and a PaO₂ ≤ 85 mm Hg; Table 4). Moreover, the risk factors for CSA in males differed from those in females. Specifically, AF, a PaCO₂ ≤ 40 mm Hg and a PaO₂ ≤ 85 mm Hg were risk factors for CSA in the entire population and males, but not females; however, age (≥ 50 years) was a risk factor for CSA in females only. Sforza30 showed that hypertension was significantly associated with the OSA risk in females (OR = 1.52; p = 0.04), whereas Polletti31 reported that the risk factors for CSA included old age and a higher amino-terminal fragment of pro-brain natriuretic hormone levels. These results are significantly different from those in our study. Furthermore, Sin6 demonstrated that a BMI > 35 kg/m² was the only risk factor for OSA in males and age > 60 years was the only significant risk factor for OSA in females. However, our results indicated that PaO₂ ≤ 85 mm Hg was a risk factor for OSA in the entire population and females, and neither OSA nor CSA was related to BMI. These significant differences may be associated with the different etiology of CHF.

Some potential limitations are existed in the current study. First, although an AHI threshold of 10/h has been used to define the presence of SDB in several studies,1,24 we used a cutoff AHI of 5/h according to previously described recommendations,21 which may account for differences in the reported prevalence of SDB. Second, for this single-center study, the prevalence and risk factors of our population may not be representative of all RVHD patients. Although some important risk factors for OSA and CSA were examined in the current study, the possibility of unmeasured risk factors cannot be excluded. Third, previous studies have shown that heart valvular repair or heart transplantation improves CSA in CHF patients.15,32 Thus, further study is needed to observe the effects of the cardiac valve replacement in patients with RVHD on SDB.

### ABBREVIATIONS

CHF, chronic heart failure  
SDB, sleep disordered breathing  
OSA, obstructive sleep apnea  
CSA, central sleep apnea  
RVHD, rheumatic valvular heart disease  
PSG, polysomnography  
NYHA, New York Heart Association  
ECG, electrocardiography  
LVEF, left ventricle ejection fraction

#### Table 3—Risk factors for OSA

<table>
<thead>
<tr>
<th>Whole population</th>
<th>Adjusted OR</th>
<th>p-value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaCO₂ ≤ 40 mm Hg</td>
<td>0.40</td>
<td>0.017</td>
<td>0.19-0.85</td>
</tr>
<tr>
<td>PaO₂ ≤ 85 mm Hg</td>
<td>3.27</td>
<td>0.002</td>
<td>1.52-7.01</td>
</tr>
<tr>
<td>Male</td>
<td>PaCO₂ ≤ 40 mm Hg</td>
<td>0.20</td>
<td>0.002</td>
</tr>
<tr>
<td>Female</td>
<td>PaO₂ ≤ 85 mm Hg</td>
<td>9.24</td>
<td>0.002</td>
</tr>
</tbody>
</table>

AF, atrial fibrillation; PaO₂, arterial oxygen tension; PaCO₂, arterial carbon dioxide tension.

#### Table 4—Risk factors for CSA

<table>
<thead>
<tr>
<th>Whole population</th>
<th>Adjusted OR</th>
<th>p-value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>4.55</td>
<td>0.001</td>
<td>1.92-10.8</td>
</tr>
<tr>
<td>AF</td>
<td>3.54</td>
<td>0.003</td>
<td>1.54-8.13</td>
</tr>
<tr>
<td>6MWT distance ≤ 300 m</td>
<td>12.2</td>
<td>&lt; 0.001</td>
<td>5.10-29.1</td>
</tr>
<tr>
<td>PaCO₂ ≤ 40 mm Hg</td>
<td>3.04</td>
<td>0.007</td>
<td>1.36-6.84</td>
</tr>
<tr>
<td>PaO₂ ≤ 85 mm Hg</td>
<td>2.64</td>
<td>0.014</td>
<td>1.22-5.75</td>
</tr>
<tr>
<td>Female</td>
<td>6MWT distance ≤ 300 m</td>
<td>17.2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>AF</td>
<td>5.46</td>
<td>0.005</td>
<td>1.68-17.8</td>
</tr>
<tr>
<td>PaCO₂ ≤ 40 mm Hg</td>
<td>5.25</td>
<td>0.008</td>
<td>1.53-18.1</td>
</tr>
<tr>
<td>PaO₂ ≤ 85 mm Hg</td>
<td>5.13</td>
<td>0.009</td>
<td>1.50-17.6</td>
</tr>
<tr>
<td>pH ≥ 7.45</td>
<td>3.70</td>
<td>0.047</td>
<td>1.02-13.4</td>
</tr>
</tbody>
</table>

AF, atrial fibrillation; 6MWT, 6-minute walk test; PaO₂, arterial oxygen tension; PaCO₂, arterial carbon dioxide tension.

#### REFERENCES


ACKNOWLEDGMENTS

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DISCLOSURE STATEMENT

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The central nervous system (CNS) hypersomnias manifest as excessive daytime sleepiness with or without prolonged nocturnal sleep in the absence of demonstrable nocturnal sleep pathology or insufficient sleep. They include the entities of narcolepsy with and without cataplexy, and idiopathic hypersomnia. Narcolepsy with cataplexy is a chronic disease characterized by short latencies to both sleep and REM sleep and pathologic or insufficient sleep. They include the entities of narcolepsy with and without cataplexy and idiopathic hypersomnia. Narcolepsy with cataplexy and idiopathic hypersomnia are common in clinical practice, and the presence of REM periods during the multiple sleep latency test (MSLT) is high in narcoleptics when two testing protocols are conducted within three weeks of each other. Inter-test intervals are generally much longer in clinical practice, and in that case the stability of MSLT features has not been established. We therefore evaluated the test-retest reliability of the MSLT in a clinic population of patients with narcolepsy without cataplexy and idiopathic hypersomnia.

Patient Selection

Patients with a clinical syndrome consistent with a CNS hypersomnia (i.e., reports of problematic, excessive daytime sleepiness persisting ≥ 3 months despite adequate or supra-normal habitual sleep durations, not explained by other causes of daytime sleepiness) who had undergone 2 MSLTs were identi-
Thirty-six patients met inclusion criteria (see Table 1). The cohort was 58% female with a mean age of 34 (± 13) years at the time of first MSLT (range 15-56 years). Symptoms began at the age of 22 (± 11) years. The mean Epworth Sleepiness Score was 16 (± 5). One-third of patients had a family history of a central nervous system hypersomnia or undiagnosed excessive daytime sleepiness. Two subjects were a mother-daughter pair. Cerebrospinal fluid measurements of hypocretin were available in 18 subjects (mean 290.2, SD 114.7). The time between studies ranged from 2.5 months to 16.9 years with an average length between studies of 4.2 ± 3.8 years. Based on the final MSLT, diagnoses included idiopathic hypersomnia (N = 13), narcolepsy without cataplexy (N = 7), and physiologic hypersomnia (N = 16); clinical features by diagnostic category are presented in Table 2 and were similar across groups except the presence of hallucinations, age of onset, and severity of sleepiness as measured by ESS. Based on the initial MSLT-based diagnosis, none of these 3 or other clinical features were significantly different across diagnostic categories, except female gender (85.7% of idiopathic hypersomnia patients, 33.3% of narcolepsy without cataplexy patients, and 57.1% of physiologic hypersomnia patients, p = 0.01) and age at first study (32.9 years for idiopathic hypersomnia, 38.3 years for narcolepsy without cataplexy, and 25.3 years for physiologic hypersomnia, p = 0.046). Diagnoses of comorbid mood disorders were common, primarily depression (N = 9), but also bipolar disorder (N = 2). Serious medical comorbidities occurred in 28% of subjects, and included HIV (N = 1), diabetes (N = 2), pulmonary hypertension (N = 1), anemia (N = 2), treated obstructive sleep apnea (N = 1), polycystic ovarian syndrome (N = 1), ulcerative colitis (N = 1), thyroid disease (N = 2), and epilepsy (N = 1). At the time of the first MSLT, 3 patients were taking a psychostimulant (dextroamphetamine, dextroamphetamine/amphetamine, or pemoline), and 3 were taking an antidepressant (fluoxetine, sertraline). For the second MSLT, 3 patients were taking a wake-promoting agent (dextroamphetamine/amphetamine, modafinil) and 7 antidepressants (citalopram, duloxetine, escitalopram, fluoxetine, sertraline, venlafaxine). Overall, change in stimulant or antidepressant medication between studies was not uncommon, occurring in 40% of patients.

RESULTS

Patient Characteristics

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been free of stimulant and antidepressant medications for both MSLTs, diagnosis remained the same in 45%. In exploratory analyses, a change in diagnostic category was not related to time between studies, findings on the preceding overnight polysomnography, the presence of comorbid psychiatric or medical disorders, or most symptoms of hypersomnia. The only variable that differed between those whose diagnosis changed and those whose diagnosis remained the same was the more frequent presence of hypnogogic or hypnopompic hallucinations (present in 33% of the diagnosis change group and none of the other group, p = 0.02). All 6 patients with hallucinations changed to a final diagnosis of physiologic hypersomnia, 4 from a diagnosis of narcolepsy without cataplexy and 2 from idiopathic hypersomnia.

### DISCUSSION

MSLT-based diagnoses of narcolepsy without cataplexy and idiopathic hypersomnia demonstrated poor stability in clinical practice among patients evaluated in a tertiary clinic. Diagnoses changed in half of patients over an average of four years. This occurred because of changes in both sleepiness level (i.e., the MSL) and the propensity for REM sleep (i.e., SOREMs). Over 40% of patients had a change in MSL that crossed the conventional hypersomnia threshold of 8 minutes.7 In three patients, an apparently pathological level of sleepiness emerged after the initial diagnostic MSLT was interpreted as normal. In twelve, there was presumptive resolution of previously documented objective sleepiness, despite persistence of clinically significant subjective sleepiness. Such high rates of false negative and false positive MSLT results have also been highlighted in previous studies. An 8-minute MSL threshold, for example, fails to capture 22% to 39% of patients who otherwise meet clinical criteria for a CNS hypersomnia.9,12 Consistent with this, an average MSL of 8.3 minutes has been reported for patients with idiopathic hypersomnia.13 Type I error may also be problematic, as MSL < 8 was reported in 25% of one population-based sample.14 Collectively, these studies and our data call into question the appropriateness of an 8-minute threshold in capturing the complaint of sleepiness expressed by patients with non-hypocretin deficient CNS hypersomnias, and differentiating it from asymptomatic controls.

Over thirty percent of our patients crossed the threshold of two or more SOREMs between studies. Three patients initially
diagnosed with narcolepsy met criteria for idiopathic hypersonmia on repeat testing, and one patient’s diagnosis changed from idiopathic hypersonmia to narcolepsy without cataplexy. Excellent specificity of two or more SOREMs for narcolepsy has been suggested. Extension of the MSLT to diverse medical and neurological populations, however, demonstrates that although sensitive for hypocretin-deficient narcolepsy, this test retest reliability of the MSLT in patients with primary hypersonias but spontaneous remission of symptoms.

Repeat testing was less often performed when the initial diagnostic MSLT was normal (< 20%). The choice to retest patients with MSLT-based diagnoses of idiopathic hypersonmia or narcolepsy without cataplexy might reflect physician or patient discomfort with these diagnoses, in which pathophysiology, treatment, socioeconomic, and prognostic implications remain ill-defined.

The average of 4 years between studies, with a maximum of 17 years, speaks to the chronicity of sleepiness experienced by these patients, but might have contributed to poor test-retest reliability. As all patients in the present study reported persistent subjective sleepiness, our data do not address the test retest reliability of the MSLT in patients with primary hypersonias but spontaneous remission of symptoms. Repeat testing was less often performed when the initial diagnostic MSLT was normal (< 20%). The choice to retest patients with MSLT-based diagnoses of idiopathic hypersonmia or narcolepsy without cataplexy might reflect physician or patient discomfort with these diagnoses, in which pathophysiology, treatment, socioeconomic, and prognostic implications remain ill-defined.

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The average of 4 years between studies, with a maximum of 17 years, speaks to the chronicity of sleepiness experienced by these patients, but might have contributed to poor test-retest reliability. We sought to determine the reliability of testing as it is performed in clinical practice, rather than in a controlled, prospective research setting. With such a study design, as in clinical practice, factors such as treatment effects and changes in sleep-wake cycle that may affect the MSLT could not be held constant. We were unable to detect any relationships between

### Table 2—Clinical characteristics by final diagnostic category

<table>
<thead>
<tr>
<th></th>
<th>IH (N = 13)</th>
<th>N-C (N = 7)</th>
<th>PH (N = 16)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>6 (46.2%)</td>
<td>5 (71.4%)</td>
<td>10 (62.5%)</td>
<td>0.56</td>
</tr>
<tr>
<td><strong>Weekly sleep</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>in hours</td>
<td>62.4 (14.9)</td>
<td>67.5 (13.4)</td>
<td>65.1 (12.7)</td>
<td>0.67</td>
</tr>
<tr>
<td><strong>Hallucinations</strong></td>
<td>0</td>
<td>0</td>
<td>6 (37.5%)</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Sleep paralysis</strong></td>
<td>1 (7.7%)</td>
<td>0</td>
<td>5 (31.3%)</td>
<td>0.17</td>
</tr>
<tr>
<td><strong>Age of onset</strong></td>
<td>25.2 (12.8)</td>
<td>26.1 (14.2)</td>
<td>17.3 (5.4)</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td>25.3 (3.9)</td>
<td>26.1 (4.3)</td>
<td>23.8 (3.6)</td>
<td>0.50</td>
</tr>
<tr>
<td><strong>ESS</strong></td>
<td>16.6 (3.9)</td>
<td>19.8 (2.3)</td>
<td>14.2 (5.3)</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>Family history of</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDS/hypersonmia</td>
<td>3 (23.1%)</td>
<td>1 (25%)</td>
<td>7 (43.8%)</td>
<td>0.53</td>
</tr>
<tr>
<td><strong>Mood disorder</strong></td>
<td>4 (30.8%)</td>
<td>3 (50%)</td>
<td>4 (25%)</td>
<td>0.56</td>
</tr>
<tr>
<td><strong>Medical disease</strong></td>
<td>4 (30.8%)</td>
<td>1 (16.7%)</td>
<td>5 (31.3%)</td>
<td>0.89</td>
</tr>
<tr>
<td><strong>Stimulant medication</strong></td>
<td>0</td>
<td>0</td>
<td>3 (27.3%)</td>
<td>0.10</td>
</tr>
<tr>
<td>use*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Antidepressant use</strong></td>
<td>3 (25%)</td>
<td>0</td>
<td>4 (33.3%)</td>
<td>0.62</td>
</tr>
<tr>
<td>% free of stimulant and</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>antidepressant medication</td>
<td>9 (75.0%)</td>
<td>4 (100%)</td>
<td>6 (54.6%)</td>
<td>0.23</td>
</tr>
</tbody>
</table>

Analyses are reported as mean (± SD) for continuous variables and numbers (percentages) for categorical variables. EDS, excessive daytime sleepiness; BMI, body mass index; ESS, Epworth Sleepiness Scale score; IH, idiopathic hypersonmia (with or without long sleep time); N-C, narcolepsy without cataplexy; PH, physiologic hypersonia with MSL > 8 minutes. *Sum of all nocturnal sleep periods and daytime naps as reported by the patient for a typical week. †Percentage of patients using a given class of medications at the time of the second study. ‡Physiologic hypersonia with MSL > 8 minutes.
medication changes, time between MSLTs, or other available clinical features (excluding sleep-related hallucinations) with a change in diagnosis, but our relatively small sample size does not allow us to entirely rule out this possibility. Other factors for which data were not available, such as changes in depression severity or sleep wake schedule, might have influenced

Figure 1—Bland-Altman plots for test-retest reliability of mean sleep latency and sleep onset REMs

Horizontal dashed lines are drawn at the 95% limits of agreement. MSL, mean sleep latency; MSL1, MSL on first test; MSL2, MSL on second test; SOREMs, sleep onset REM period (SOREM1 and SOREM2 for first and second test, respectively).
the results. Alternatively, differences in the performance or interpretation of MSLTs may have affected the results (e.g., the MSLTs were generally performed at different sleep laboratories and interpreted by different individuals). The MSLT, for example, is well known to be affected by physiological levels of arousal that are distinct from sleepiness. The factors influencing arousal per se can be difficult to control on a single clinical MSLT, let alone a second one performed in a unique environment and under different conditions. It is less likely that scoring variability accounts for our findings as the MSLT has high inter-rater and intra-rater reliability. Given these factors, our data suggests poor test-retest reliability of the MSLT in the non-hypocretin deficient CNS hypersomnias when used over time in clinical practice, although it is possible that test retest reliability would improve if tested within the confines of a tightly controlled research protocol.

Our results suggest that continued adherence to the 8-minute MSL threshold in defining hypersomnia syndromes in clinical practice is problematic. The distinction between narcolepsy without cataplexy and idiopathic hypersomnia based on MSLT testing alone also does not appear justified. It is possible that idiopathic hypersomnia and narcolepsy without cataplexy are manifestations of the same underlying pathology or exist along a spectrum with overlapping features. Family studies of narcolepsy (with and without cataplexy) support this assertion, as family members of narcoleptics have higher rates of narcolepsy, but also of idiopathic hypersomnia, excessive daytime sleepiness, and abnormal multiple sleep latency tests. Idiopathic hypersomnia is sometimes characterized as a rare disease, but one implication of our findings is that prevalence estimates in clinical or population cohorts are likely to underestimate. Alternative diagnostic strategies are needed to more accurately and reliably characterize the non-hypocretin deficient CNS hypersomnias. Recognizing this need, some investigators have advocated for continuous daytime polysomnography, ad libitum sleep polysomnography, or changes to the MSLT scoring criteria. Similar to the MSLT, however, these alternatives are time and labor intensive. More cost-effective measures are needed, in addition to identification of a biomarker with diagnostic and therapeutic significance. While deficiencies in histamine have been proffered as one such biomarker, these results were not replicable with more sensitive technologies. Recent work suggests that somnolence in the CNS hypersomnias may derive from a gain in function in endogenous γ-aminobutyric acid (GABA) signaling mediated by a naturally occurring constituent of cerebrospinal fluid that allosterically modulates GABA receptors. Ultimately, the identification of biomarkers will improve diagnostic accuracy in these conditions.

REFERENCES


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DISCLOSURE STATEMENT

This was not an industry supported study. Dr. Trotti has consulted for UCB Pharma, Inc. Dr. Rye has consulted for or served on advisory boards of UCB Pharma Inc., Merck, Inc., Impax Laboratories, and Jazz Pharmaceuticals. Dr. Staab has indicated no financial conflicts of interest.
The hypocretin system, also known as the orexin system, is of major importance in the regulation of sleep and sustained wakefulness. Moreover, hypocretin neurons are responsive to metabolites and hormones helping to translate signals of metabolic state into adaptive levels of activity and consciousness. Hypocretin deficiency leads to narcolepsy, a sleep-wake disorder characterized by excessive daytime sleepiness, cataplexy, and disrupted nocturnal sleep. Obesity is associated with the disorder, yet the cause of the increased body weight has been challenging to discern due to inconsistent findings on the hormonal and metabolic characteristics of this population. However, altered ingestive behavior has been consistently observed in these patients, suggesting hypocretin deficiency may dysregulate feeding behavior, and possibly energy homeostasis.

Ghrelin is a peptide hormone mainly produced by endocrine cells in the stomach and gastrointestinal tract, and is an important endogenous regulator of energy balance and growth hormone (GH) secretion. Its expression is complex and influenced by sympathetic nervous system activity. Across the wake period, plasma concentrations wax and wane episodically, providing an appetite-stimulating signal to the brain. During sleep, ghrelin levels rise sharply in the early part of the night and decrease

**BRIEF SUMMARY**

Current Knowledge/Study Rationale: Potential hormonal disturbances in response to hypocretin deficiency may provide explanation for the weight and ingestive behavior phenotype of this population. The relationship of both ghrelin and leptin with hypocretin has been shown to be of importance. Hypocretin neurons directly sense ghrelin and leptin but it is unknown if these connections are uni-or-bidirectional. Therefore, the study of hypocretin-deficient narcoleptic patients provides a unique opportunity to further explore the nature of these relationships in this population of patients in the chronic phase of this disorder.

**Study Impact:** No significant alteration in total ghrelin or leptin levels were seen in our sample of hypocretin-deficient narcoleptic subjects. Therefore, we found no evidence to support a bi-directional, integrated feedback loop for total ghrelin or leptin levels and hypocretin. To our knowledge, total ghrelin levels have not previously been reported in human narcolepsy and our findings will help others to better understand the hormonal phenotype of this population. Our findings are in support of the notion that the leptin level is not altered in this population, although we did see a significant increase in leptin pulse frequency in subjects compared to controls; the clinical significance of this finding is unknown. Our findings suggest the propensity for obesity and the altered ingestive behavior of narcolepsy are unlikely to be mediated by hypocretin-deficiency derived alterations to these hormone levels.
gradually toward morning. During sleep deprivation, however, levels gradually rise toward a plateau in the morning. Hypocretin neurons directly sense and are excited by ghrelin, and an interaction between these two systems has been shown to be involved in ingestive behavior. A study by Toshinai et al. first identified this connection. In that study, ghrelin-induced feeding was attenuated in rats pretreated with anti-hypocretin-1 IgG and anti-hypocretin-2 IgG, and suppressed in hypocretin knockout mice. Later, it was demonstrated that ghrelin plays a key role in the rewarding aspects of eating, but it requires the presence of intact hypocretin signaling to impart this effect.

Leptin is another peptide hormone involved in energy homeostasis, the dominant role of which is to signal energy deficiency to the brain. It is an adipokine produced primarily by subcutaneous white adipose tissue, and its expression is stimulated by various hormones, sympathetic outflow, energy intake, and output. Under normal conditions, blood levels display circadian variation as levels rise across the day and peak in the middle of the night. During sleep deprivation, blood leptin levels show a reduced and flattened profile. Receptors for leptin are found on hypocretin cells, and leptin can directly inhibit the expression of isolated hypocretin neurons. Indirectly, leptin can affect the activity of hypocretin cells via energy-regulating neurons in the arcuate nucleus of the hypothalamus. Conversely, because the hypocretin system greatly influences autonomic control, it is plausible that hypocretin deficiency may alter leptin expression via inhibited sympathetic activity. Indeed, obese hypocretin deficient mice have lowered sympathetic vasoconstrictor outflow, while greater heart rate variability has been observed in hypocretin deficient narcolepsy patients. Thus, leptin and hypocretin may interact to affect levels of physical activity and wakefulness in response to energy needs, and the loss of hypocretin neurons may dysregulate leptin expression and signaling.

While ghrelin levels have not been previously reported in hypocretin-deficient narcoleptic patients, abnormal leptin levels have been observed. It is unknown if the associations between hypocretin and total ghrelin or leptin are uni-or bidirectional. Because hypocretin influences sympathetic outflow and sympathetic nervous system activity affects the expression of both leptin and ghrelin, hypocretin deficiency may lead to altered levels of these hormones. This study of hypocretin-deficient narcoleptic patients provides a unique opportunity to further explore the nature of these relationships. We hypothesized that both total ghrelin and leptin levels would be abnormal in hypocretin-deficient narcolepsy patients, which might help explain the increased BMI and abnormal ingestive behavior seen in this population.

Additionally, we explored if the narcolepsy therapeutic agent, sodium oxybate, has an effect on these hormones. In a narcolepsy population, sodium oxybate improves disrupted nocturnal sleep, impaired wakefulness, and cataplexy, and promotes weight loss. Like ghrelin, sodium oxybate administration also stimulates GH release. We hypothesized that its administration would alter total ghrelin levels, the effect of which might be involved in its GH-promoting effects.

Here, we investigate whether total blood ghrelin or leptin levels are altered in hypocretin-deficient narcoleptic patients compared to controls, and whether total ghrelin or leptin levels are influenced by sodium oxybate.
trols. Each night, 3 grams of sodium oxybate were administered orally at 23:00 and 03:00. Lights were turned off after ingestion of the first dose.

**Sleep Recordings**

During the 24-h sampling periods, polysomnographic recordings were performed using an ambulant EEG-recording system (Embletta X100, Embla) and a standard EEG/EMG montage to allow sleep scoring according to AASM criteria. Using a marker-tool, the start of the sampling protocol was registered to synchronize sleep-recordings with hormone measurements. Sleep recordings were scored by an experienced technician, blinded for the subject under study.

**Assays**

Plasma total ghrelin and leptin levels were measured by radioimmunoassay (LINCO Research, St. Charles, MO, USA) with a detection limit of 93 pg/mL, and an interassay variation ranging from 14.7% to 17.8% for total ghrelin and a detection limit of 0.5 µg/L and an interassay variation ranging from 3.0% to 5.1% for leptin. Samples from each patient and matched control were handled in the same run.

**Deconvolution Analysis**

Leptin concentration time series were analyzed via a recently developed automated deconvolution method, empirically validated using hypothalamo-pituitary sampling and simulated pulsatile time series. The Matlab-based algorithm first detrends the data and normalizes concentrations to the unit interval [0, 1]. Second, the program creates multiple successive potential pulse-time sets, each containing one fewer burst via a smoothing process (a nonlinear adaptation of the heat-diffusion equation). Third, a maximum-likelihood expectation estimation method computes all secretion and elimination parameters simultaneously conditional on each of the multiple candidate pulse-time sets. The fast half-life was represented as 3.4 min constituting 19% of the decay amplitude. The slow half-life was identical between narcolepsy patients and controls (p = 0.873; Figure 1A). Mean total ghrelin levels were also not different between the 2 groups when the analyses were restricted to the dark period (p = 0.973). In fact, at no single time-point an intergroup difference could be detected (all p ≥ 0.232). Food induced suppression of total ghrelin concentration (expressed as the ratio between postprandial to preprandial total ghrelin concentration) was similar in the 2 groups (lunch: p = 0.413, dinner: p = 0.301, breakfast: p = 0.437, and mean postprandial total ghrelin levels averaged over the 3 occasions (p = 0.540) (Table 3).

**Results**

**Subjects**

Patients and controls did not differ with respect to age, BMI, waist-to-hip ratio, and body fat percentage (Table 1). Sodium oxybate was well tolerated by all participants. Apart from mild drowsiness, no other side effects were reported during the study.

**Sleep and Wakefulness Differences**

When compared to controls, during baseline conditions and after sodium oxybate administration, narcolepsy patients spent significantly less time awake across a 24 h period, and during the day (defined as the lights-on period between 07:30-23:00) they spent less time awake and more time in slow wave sleep ([SWS] p = 0.004 and p = 0.005, respectively; Table 2).

**Baseline Total Ghrelin Levels**

Mean 24-h total ghrelin levels at baseline were virtually identical between narcolepsy patients and controls (p = 0.873; Figure 1A). Mean total ghrelin levels were also not different between the 2 groups when the analyses were restricted to the dark period (p = 0.973). In fact, at no single time-point an intergroup difference could be detected (all p ≥ 0.232). Food induced suppression of total ghrelin concentration (expressed as the ratio between postprandial to preprandial total ghrelin concentration) was similar in the 2 groups (lunch: p = 0.413, dinner: p = 0.301, breakfast: p = 0.437, and mean postprandial total ghrelin levels averaged over the 3 occasions (p = 0.540) (Table 3).

**Effect of Sodium Oxybate on Total Ghrelin Levels**

Twenty-four hour mean total ghrelin levels during sodium oxybate treatment were not different between narcolepsy patients and controls (p = 0.642; Figure 1B). Similar to baseline, mean total ghrelin levels during the dark period did not differ between the 2 groups (p = 0.449), and at no single time-point a difference could be detected between groups (all p ≥ 0.05). Postprandial total ghrelin suppression, as defined above, was also similar between the 2 groups after sodium oxybate administration: lunch (p = 0.920), dinner (p = 0.261), and breakfast (p = 0.880); mean postprandial total ghrelin levels averaged over the 3 occasions (p = 0.428) (Table 3). The average change in 24-h total ghre-
lin levels between the second and first occasion amounted to -15 ± 72 pg/mL in narcolepsy patients and -63 ± 87 pg/mL in controls, but was not significantly different from zero in either group (paired t-tests: p = 0.56 and p = 0.078, respectively).

Baseline Leptin Levels

Mean 24-h total leptin levels at baseline were not significantly different between narcolepsy patients and controls (p = 0.18; Figure 2A). Mean pulse frequency was different between the 2 groups (p = 0.04), but mean 24-h basal and pulsatile secretion levels were not different (p = 0.96; p = 0.11, respectively; Table 3).

Table 2—Sleep patterns before and after sodium oxybate administration

<table>
<thead>
<tr>
<th></th>
<th>Narcolepsy</th>
<th>Controls</th>
<th>Narcolepsy vs. controls (SXB)</th>
<th>Treatment effect</th>
<th>Interaction (group x treatment)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>SXB</td>
<td>Baseline vs. controls (SXB)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wake total (%)</td>
<td>60.8 ± 2.9</td>
<td>60.8 ± 2.2</td>
<td>68.7 ± 2.0 70.1 ± 2.4</td>
<td>0.044*</td>
<td>0.58</td>
</tr>
<tr>
<td>Wake day (%)</td>
<td>79.4 ± 4.2</td>
<td>82.9 ± 3.2</td>
<td>96.6 ± 2.1 97.3 ± 1.0</td>
<td>0.004**</td>
<td>0.098</td>
</tr>
<tr>
<td>Wake night (%)</td>
<td>25.8 ± 5.7</td>
<td>19.2 ± 4.3</td>
<td>18.4 ± 4.0 21.2 ± 4.8</td>
<td>0.31</td>
<td>0.60</td>
</tr>
<tr>
<td>Stage I/II total (%)</td>
<td>29.1 ± 1.4</td>
<td>26.3 ± 1.4</td>
<td>25.0 ± 2.4 21.1 ± 2.2</td>
<td>0.16</td>
<td>0.063</td>
</tr>
<tr>
<td>Stage I/II day (%)</td>
<td>14.6 ± 3.0</td>
<td>11.1 ± 2.5</td>
<td>2.5 ± 1.6 1.6 ± 1.0</td>
<td>0.003**</td>
<td>0.005**</td>
</tr>
<tr>
<td>Stage I/II night (%)</td>
<td>55.1 ± 2.5</td>
<td>53.5 ± 3.7</td>
<td>65.6 ± 5.7 56.4 ± 5.3</td>
<td>0.11</td>
<td>0.005**</td>
</tr>
<tr>
<td>SWS total (%)</td>
<td>3.7 ± 0.7</td>
<td>7.6 ± 1.2</td>
<td>2.5 ± 0.7 6.6 ± 0.9</td>
<td>0.24</td>
<td>0.53</td>
</tr>
<tr>
<td>SWS day (%)</td>
<td>2.1 ± 0.6</td>
<td>2.7 ± 1.1</td>
<td>0.03 ± 0.03 0.05 ± 0.05</td>
<td>0.005**</td>
<td>0.49</td>
</tr>
<tr>
<td>SWS night (%)</td>
<td>6.5 ± 1.9</td>
<td>16.5 ± 3.0</td>
<td>7.1 ± 1.9 18.5 ± 2.4</td>
<td>0.84</td>
<td>0.61</td>
</tr>
<tr>
<td>REM total (%)</td>
<td>6.3 ± 1.8</td>
<td>4.7 ± 1.0</td>
<td>3.7 ± 0.8 2.1 ± 0.8</td>
<td>0.19</td>
<td>0.070</td>
</tr>
<tr>
<td>REM day (%)</td>
<td>2.9 ± 1.4</td>
<td>1.2 ± 0.5</td>
<td>0.8 ± 0.5 0.0 ± 0.0</td>
<td>0.20</td>
<td>0.032*</td>
</tr>
<tr>
<td>REM night (%)</td>
<td>12.6 ± 3.0</td>
<td>10.8 ± 2.1</td>
<td>8.8 ± 1.8 5.8 ± 2.3</td>
<td>0.31</td>
<td>0.13</td>
</tr>
<tr>
<td>No. of awakenings</td>
<td>50.5 ± 10.5</td>
<td>35.0 ± 4.8</td>
<td>35.5 ± 7.1 15.3 ± 1.7</td>
<td>0.26</td>
<td>0.005**</td>
</tr>
<tr>
<td>Sleep efficiency (%)</td>
<td>66.9 ± 7.0</td>
<td>81.5 ± 4.9</td>
<td>81.2 ± 4.0 81.9 ± 6.0</td>
<td>0.10</td>
<td>0.96</td>
</tr>
</tbody>
</table>

Percentages of sleep stages during the 24 hours of study, before and after SXB administration. Data are shown as mean ± SEM. Unpaired t tests were used to assess differences between the two groups. Mixed-effects models were applied to assess the effect of treatment and potential interaction effects between group (i.e., narcolepsy or control) and treatment. *p < 0.05 and **p < 0.01.37

Table 3—Plasma ghrelin concentrations and deconvolution of leptin levels before and after administration of sodium oxybate in both narcoleptic patients and controls

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Controls</th>
<th>p</th>
<th>Sodium Oxybate</th>
<th>Patients</th>
<th>Controls</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ghrelin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-h total integrated concentration (pg/mL)</td>
<td>936 ± 142</td>
<td>949 ± 175</td>
<td>0.873</td>
<td>920 ± 142</td>
<td>886 ± 150</td>
<td>0.642</td>
<td></td>
</tr>
<tr>
<td>Dark perioda (pg/mL)</td>
<td>1,012 ± 156</td>
<td>1,009 ± 196</td>
<td>0.973</td>
<td>983 ± 163</td>
<td>910 ± 211</td>
<td>0.449</td>
<td></td>
</tr>
<tr>
<td>Food induced suppression of ghrelin concentrationb (pg/mL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lunch</td>
<td>0.83 ± 0.10</td>
<td>0.86 ± 0.09</td>
<td>0.413</td>
<td>0.87 ± 0.08</td>
<td>0.88 ± 0.16</td>
<td>0.920</td>
<td></td>
</tr>
<tr>
<td>Dinner</td>
<td>0.93 ± 0.16</td>
<td>0.83 ± 0.17</td>
<td>0.301</td>
<td>0.89 ± 0.20</td>
<td>0.89 ± 0.10</td>
<td>0.261</td>
<td></td>
</tr>
<tr>
<td>Breakfast</td>
<td>1.05 ± 0.10</td>
<td>1.01 ± 0.09</td>
<td>0.437</td>
<td>0.98 ± 0.12</td>
<td>0.98 ± 0.06</td>
<td>0.880</td>
<td></td>
</tr>
<tr>
<td>Postprandial total ghrelic (pg/mL)</td>
<td>0.93 ± 0.08</td>
<td>0.90 ± 0.11</td>
<td>0.540</td>
<td>0.91 ± 0.08</td>
<td>0.88 ± 0.06</td>
<td>0.428</td>
<td></td>
</tr>
<tr>
<td>Leptin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total 24-h secretion (μg/Lx24h)</td>
<td>115 ± 98</td>
<td>79.0 ± 88</td>
<td>0.18</td>
<td>100 ± 113</td>
<td>64.0 ± 35</td>
<td>0.58</td>
<td></td>
</tr>
<tr>
<td>Basal 24-h secretion (μg/Lx24h)</td>
<td>64.7 ± 63</td>
<td>37.9 ± 30</td>
<td>0.96</td>
<td>56.0 ± 70</td>
<td>47.6 ± 63</td>
<td>0.94</td>
<td></td>
</tr>
<tr>
<td>Pulsatile 24-h secretion (μg/Lx24h)</td>
<td>50.3 ± 36</td>
<td>25.6 ± 11</td>
<td>0.11</td>
<td>43.8 ± 46</td>
<td>31.0 ± 27</td>
<td>0.29</td>
<td></td>
</tr>
<tr>
<td>Pulse frequency (no/24h)</td>
<td>18.5 ± 2.7</td>
<td>15.3 ± 4.6</td>
<td>0.04</td>
<td>19.8 ± 2.4</td>
<td>19.0 ± 3.0</td>
<td>0.04</td>
<td></td>
</tr>
</tbody>
</table>

*aIn both study occasions, lights were switched off (dark period) at 23:00 and then switched on at 07:30. bExpressed as the ratio between post- to preprandial ghrelin concentration. cAveraged over three occasions.

Effect of Sodium Oxybate on Leptin Levels

Mean 24-h total leptin levels during sodium oxybate treatment were not significantly different between narcolepsy patients and controls (p = 0.58; Figure 2B); neither were mean 24-h basal and pulsatile secretion rates (p = 0.94; p = 0.29, respectively). Mean pulse frequency was different between the 2 groups (p = 0.04; Table 3).

DISCUSSION

We found no differences in mean 24-h total plasma ghrelin levels or food-induced suppression of ghrelin concentrations
between narcolepsy patients and controls, nor any influence of 5 days of sodium oxybate administration in both groups. In view of the capacity of ghrelin to stimulate growth hormone secretion, it is worth noting that a report from this same research protocol showed no differences in mean hourly GH levels between patients and controls, supporting our conclusion that total ghrelin levels are not altered with hypocretin deficiency.

Despite the excitatory influence of ghrelin on hypocretin neurons and the interaction of the ghrelin-hypocretin systems to influence food reinforcement, our finding did not show the total ghrelin level to be influenced by hypocretin deficiency, suggesting a unidirectional relationship. These findings also suggest that disturbed ingestive behavior is unlikely mediated by an altered total ghrelin level in narcolepsy patients. Notably, we measured total ghrelin levels and not the biologically active, octanoylated-ghrelin fraction. While there is a high correlation between the total and octanoylated fraction ghrelin level, it remains possible that the active fraction may be altered in this population.

In contrast to earlier reports, more recent, larger, controlled studies have not demonstrated an abnormal leptin level in humans with hypocretin deficiency. Similar to the recent research on this subject, we found that the mean 24-h total leptin level, and basal and pulsatile secretion levels were not significantly different between narcolepsy patients and controls. The mean leptin pulse frequency was slightly but...
significantly higher in narcolepsy patients in both conditions, but the clinical relevance of this finding is unclear. Because sleep disruption and insulin resistance have been shown to affect leptin levels, it is plausible that previous investigations showing decreased leptin in narcolepsy may have resulted from a study sample of narcoleptic patients with relatively poor sleep or a difference in insulin sensitivity compared to the control group.

There were several limitations to the study. The small number of patients and controls raise the possibility of a type II statistical error. However, the intergroup differences were very small; therefore, a large sample size would be needed to detect a difference if present. As with many chronic diseases, compensatory mechanisms are likely involved in narcolepsy as the condition progresses from onset into the chronic stage. Studying narcoleptic patients only during the chronic stage challenges the interpretation that loss of hypocretin cells in the hypothalamus does not alter leptin and ghrelin levels since compensatory adaptation may have already taken place. However, alterations in appetite and weight regulation remain present and clinically relevant in the chronic stage of the disease, and therefore our findings remain relevant despite putative compensations. Additionally, since sleep-wake state instability is intrinsic to hypocretin deficiency, standardizing research parameters such as study environment, meal timing and composition, and predefined bedtimes may have created a setting not representative of real-life conditions for these patients. Therefore, although we did not find alterations in total ghrelin and leptin concentrations in this controlled and standardized environment, it remains possible that the release of these hormones is affected by the altered sleep, wake, and eating patterns described in this population.

As expected, in both groups nighttime administration of sodium oxybate increased SWS and reduced awakenings, and the narcoleptic patient group showed a trend towards increased wakefulness the following day. As demonstrated in other studies, acute sodium oxybate administration corresponds with a significant increase in GH release. However, we found no evidence that the GH-elevating effect is mediated through an influence on total ghrelin secretion. Various treatment effects of sodium oxybate exhibit discrete temporal dynamics with some effects occurring acutely and other effects taking place only after chronic exposure. Although the difference in total ghrelin levels between patients and controls after sodium oxybate administration was not significant, it is possible that significant differences would be seen with higher doses, prolonged periods of nightly administration, or in a larger group of subjects. Lastly, we did not see an effect of sodium oxybate on the leptin level, and to our knowledge, an interaction between this drug and hormone has not been reported elsewhere.

Therefore, mechanisms underlying increased BMI and altered ingestive behavior in narcolepsy and the effects of sodium oxybate administration on GH release and weight loss are unlikely to involve changes in total plasma ghrelin or leptin concentrations. Future investigations should further evaluate if the sleep-wake instability intrinsic to hypocretin-deficient narcolepsy promotes ingestive and activity patterns that promote positive energy balance.
32. Pardi D, Black J. Gamma-hydroxybutyrate/sodium oxybate: neurobiology, and impact on sleep and wakefulness. CNS Drugs 2006;20:993-1018.

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SUBMISSION & CORRESPONDENCE INFORMATION

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DISCLOSURE STATEMENT

This study was supported by an unrestricted grant from UCB Europe. Mr. Pardi was previously employed with Jazz Pharmaceuticals and has consulted with UCB Europe. Dr. Overeem has consulted for and received honoraria as a speaker from UCB Europe. Dr. Lammers is member of the international advisory board on narcolepsy for UCB and has received honoraria as a speaker from UCB. The other authors have indicated no financial conflicts of interest.
Narcolepsy is a chronic neurological disorder with a reported prevalence of 0.026 to 0.056% in the general adult population, although it has been suggested that up to 2.3% of subjects in the general population fulfill diagnostic criteria for narcolepsy. There is ongoing evidence that hypocretin deficiency results from an autoimmune attack on hypocretin cells, and recent genetic findings underline the importance of antigen presentation by HLA class II to T cells in its pathophysiology.

Cardinal features of narcolepsy are excessive daytime sleepiness, cataplexy, sleep paralysis, hypnagogic hallucinations, and disturbed nocturnal sleep. According to cataplexy status, two main categories of narcolepsy are differentiated. A diagnosis of narcolepsy with cataplexy requires polysomnography demonstrating a sleep latency < 8 minutes plus ≥ 2 sleep onset REM episodes in the multiple sleep latency test (MSLT), or alternatively assessment of hypocretin-1 levels in the cerebrospinal fluid ≤ 110 pg/mL.

**Studies on large, well-defined series of narcolepsy patients** have focused primarily on clinical features of narcolepsy. In contrast, there is paucity of data concerning thoroughly documented polysomnographic comorbidity in large narcolepsy patient samples.

**Study Impact:** This study is the largest monocentric polysomnographic series to date of patients with narcolepsy with a special emphasis on motor phenomena during sleep. Presence of REM sleep without atonia, a periodic leg movement in sleep index > 5/h, and sleep fragmentation can be regarded as further polysomnographic hallmarks of the disease, whereas insomnia does not speak against a diagnosis of narcolepsy.
In this light, we aimed to thoroughly describe the entity of narcolepsy concerning both clinical and polysomnographic characteristics with a special focus on sleep-related movement disorders, based on a large tertiary-referral cohort with definite narcolepsy.

METHODS

Setting

The Innsbruck sleep laboratory is a tertiary sleep disorder referral center serving a population of about 2 million. It is the only academic facility for diagnosis and treatment of sleep disorders in Western Austria and South Tyrol (Northern Italy), but serves patients from other parts of Austria as well. Patients represent the full spectrum of sleep disorders according to major categories of the second edition of the International Classification of Sleep Disorders (ICSD-2).

All patients who were entered into our clinical database since 1998 and met the diagnostic criteria for narcolepsy according to ICSD-2 criteria were included in this study. All subjects had either excessive daytime sleepiness or cataplexy as their initial presenting clinical feature. In addition to a comprehensive sleep history, all patients underwent HLA testing and polysomnographic workup. MSLT was done in all patients admitted for diagnostic evaluation or re-evaluation of narcolepsy. In a minority of patients (n = 13) who were diagnosed at external sleep centers and had an unambiguous history of cataplexy (n = 13), positive MSLT testing (n = 13), or positive cerebrospinal fluid hypocretin-1 results (n = 1), MSLT was either not repeated (n = 5) or repeated while maintaining preexisting medication (7 antidepressants, 1 sodium oxybate). Assessment of cerebrospinal fluid concentrations were performed only when needed for diagnostic purposes according to the guidelines of the European Federation of Neurological Societies for cerebrospinal fluid investigations.

Chart and Polysomnographic Review

For this study, all consecutive narcolepsy patients of the Innsbruck narcolepsy database were selected. The database included information on demographics (age, gender, body mass index), narcolepsy-specific clinical information (age at disease onset, age at diagnosis, presence and severity of daytime sleepiness, cataplexy, sleep paralysis, or hypnagogic hallucinations), information on narcolepsy workup (HLA typing, MSLT, hypocretin-1 measurements when needed for a diagnosis), as well as sleep comorbidities according to ICSD-2 categories (insomnia, sleep-related breathing disorders, parasomnias, sleep-related movement disorders). Severity of daytime sleepiness was assessed by the Epworth Sleepiness Scale score;2 severity of cataplexy, sleep paralysis, and hypnagogic hallucinations was scored on an 8-point Likert scale ranging from 1 (referring to rare and mild symptoms) to 8 (referring to very frequent and severe symptoms) as used for the genetic collaboration with the Stanford Center for Narcolepsy. Body mass index (BMI) percentiles of narcolepsy patients were compared to BMI percentiles obtained from the general population. In addition, we reviewed the polysomnographic recordings of all patients to determine the presence or absence of sleep-related motor phenomena such as REM sleep without atonia, periodic leg movements in sleep index > 5/h, high frequency leg movements (alternative terms: hypnagogic foot tremor and alternating leg muscle activation during sleep), excessive fragmentary myoclonus, and bruxism. The presence or absence of REM sleep without atonia during polysomnography was rated in line with the current ICSD-2 criteria. No quantitative scoring of EMG activity during REM sleep was performed.

In order to answer the question as to whether EMG features of REM sleep behavior disorder (RBD) in narcolepsy are apparent during the MSLT, REM sleep-related EMG activity in the mentalis muscle was quantified during the MSLT in the group of narcolepsy patients with RBD. For the MSLT, every 30-sec epoch was divided into ten 3-second mini-epochs. The percentage of mini-epochs with “any” EMG activity was divided by the total number of mini-epochs. Motor events during sleep in the MSLT were assessed with the RBD severity scale. These polysomnographic data were added to the existing database for further analyses.

The establishment of a narcolepsy database was approved by the local ethics committee of Innsbruck Medical University, and all patients gave written informed consent.

Statistics

SPSS for Macintosh, version 19.0 was used for data analysis. Normality was tested by using the Shapiro-Wilk test. All values are presented as means ± standard deviation in the case of normal distributions, or as medians (range) in the case of non-normal distributions. For assessing associations between narcolepsy subtype narcolepsy-cataplexy (NC) or narcolepsy without cataplexy (N), gender, and clinical as well as polysomnographic correlates, nonparametric statistics (χ² tests and Mann-Whitney U tests) were performed. For correlation analysis, a Spearman correlation coefficient was calculated. P-values < 0.05 were considered to indicate statistical significance.

RESULTS

Characterization of the Innsbruck Narcolepsy Cohort

As of May 2012, 100 patients (56 men, 44 women) with established narcolepsy were registered in our sleep centre’s clinical database. The median age was 39 (range 16-78) years. The median age at symptom onset was 21 (6-69) years. The median Epworth sleepiness score at time of diagnosis was 18 (10-24). The majority of cases had NC (87%); 13% of patients had N. The severity of cataplexy varied markedly (median 4.5 [range 1-8]) on an 8-point Likert scale. Additional cardinal features were sleep-related hallucinations in 56% of patients and sleep paralysis in 50% of patients. For severity of sleep-related hallucinations and sleep paralysis see Table 1. The complete narcolepsy tetrad was present in 36% of cases; 28% of patients had 3 cardinal symptoms; 29% had two cardinal symptoms; and 7% had only excessive daytime sleepiness. The median body mass index of the total group was 26.2 (18.2-43.0) kg/m². Twenty-three percent of patients (12 men, 11 women) had a BMI > 30 kg/m². More narcolepsy patients than expected were found for BMI percentiles > 50 (50 observed compared to 50 expected) and > 90 (14 observed compared to 10 expected). Sleep paralysis...
sis, sleep-related hallucinations, as well as daytime sleepiness indicated by the Epworth score tended to be more severe in NC than N patients. No other variables differed between both groups (see Table 1). Concerning gender, women had higher Epworth scores than men (19 [10-23] vs. 17 [11-24], p = 0.038). The following features did not differ between male and female narcolepsy patients: presence and severity of cataplexy (presence women vs. men: 38/44 vs. 49/56, severity: 5 [2-7] vs. 5 [3-8]), sleep paralysis (presence: 25/44 vs. 25/56, severity: 3 [1-7] vs. 4 [2-6]), hypnagogic hallucinations (presence: 28/44 vs. 28/56, severity: 5 [1-7] vs. 4 [3-7]), age at first symptoms (21.5 [12-69] vs. 20 [6-54] years), interval between first symptoms and diagnosis (8.5 [0-39] vs. 5 [0-36] years), and BMI (25.2 [18.2-43] vs. 26.4 [20.1-33.8], all ps > 0.05).

Diagnostic Workup Data

All patients underwent HLA typing for DQB1*0602 and DRB1*1501. HLADQA1*0102 was assessed in 48 cases. Ninety-three percent of patients were HLA DQB1*0602 positive; 92% were DRB1*1501 positive; and 44 (92%) were DQA1*0102 positive. All patients but one who were DQB1*0602 positive were also positive for DRB1*1501. DQB1*0602 and DRB1*1501 but not DQA1*0102 differed according to cataplexy status (NC vs. N: DQB1*0602: 85/87 vs. 8/13, p < 0.001; DRB1*1501: 84/87 vs. 8/13, p = 0.001; DQA1*0102: 39/41 vs. 5/7, p = 0.096).

Ninety-five patients (87 untreated, 8 treated [7 antidepressants, 1 sodium oxybate]) underwent a MSLT after a night of polysomnography. In the combined group of treated and untreated narcolepsy patients, the median sleep latency on the MSLT was 2.5 (0.1-11.7) min and the median number of sleep onset REM episodes (SOREMs) was 4 (0-5).

In the untreated group, the median sleep latency was 2.5 (0.1-11) min and the median number of SOREMs was 4 (0-5). 84 patients had 5 MSLT runs, 2 patients had 4 MSLT runs, and 1 patient had 3 MSLT runs. Four subjects from the untreated group did not fulfill polysomnographic criteria for a diagnosis of narcolepsy. Two subjects from the untreated group with definite cataplexy had a sleep latency > 8 min (9 and 11 min, respectively) with multiple SOREMs; 2 subjects from the untreated group with definite cataplexy had a short sleep latency < 8 min, with 0 and 1 SOREM, respectively. The two latter patients underwent lumbar puncture. Both had a non-detectable hypocretin-1 level in the cerebrospinal fluid.

In the treated group, the median sleep latency was 4.0 (1.2-11.7) min, and a median of 0.5 SOREMs (0-2) were detected. The MSLT sleep latency did not differ between NC and N patients (2.2 [0.1-11.0] vs. 2.9 [0.2-6.8], p = 0.216), whereas the number of SOREMs was higher in the NC group than the N group (4 [0-5] vs. 2 [2-5], p = 0.004). Men and women did not differ in median MSLT sleep latency (2.5 [0.3-11] min vs. 2.5 [0.1-6.8]; p = 0.373) or number of SOREMs (4 [0-5] vs. 4 [2-5]; p = 0.651).

Eight percent of cases (all with cataplexy) underwent hypocretin-1 testing in the cerebrospinal fluid. In all 8 patients, hypocretin-1 was either undetectable (n = 5) or < 45 pg/mL (n = 3).

A maintenance of wakefulness test (MWT) was performed in 10 patients: 5 of these patients participated in the H3A trial (3 × before treatment initiation, 2 in double-blind phase), 3 patients were on methylphenidate (20, 2 × 40 mg), and 2 patients were on modafinil (200 mg, 400 mg). The median sleep latency in the MWT was 5.9 (0.5-20) min in these 10 patients.

Delayed Diagnosis of Narcolepsy and Basis for Referral

The median age at symptom onset was 20 (6-69) years. The median age at diagnosis was 32 (12-74) years. The median diagnostic delay was 6.5 (median 0-39) years (see Figure 1). In the majority of NC cases, excessive daytime sleepiness occurred at a median of 3 years (0.02-30) before cataplexy (55/86, 64%) or at the same time as cataplexy (27/86, 31.4%). Cataplexy was the first symptom in only 4 patients (4.7%). There was no difference in diagnostic delay in regard to either cataplexy status (cataplexy vs. non-cataplexy: 7 [0-39] vs. 6 [2-26] years, p = 0.930) or gender (men vs. women: 5 [0-35] vs. 8.5 [0-39] years; p = 0.595).

The majority of patients were referred by medical specialists (n = 45/73, 61.6%), predominantly neurologists (n = 27); 11 (15.1%) were referred via the national narcolepsy patient group; 10 (13.7%) by their general practitioner; and 7 (9.5%) referred themselves by either word-of-mouth recommendation or information obtained in the internet or media. Gender or cataplexy status did not influence the mode of referral (all ps > 0.05).

Medication at Last Follow-Up Consultation

Of the total sample of 100 narcolepsy cases, 67% took daily medication for narcolepsy symptoms at follow-up consultation. The majority took either wake-promoting drugs alone (n = 29) or in combination with anti-cataplectic medication (n = 30). Eight subjects took anti-cataplectic medication alone. For further de-
tails see Table 2. In addition, 17% of patients took on-demand medication (16 wake-promoting medication: 13 modafinil, 3 methylphenidate; 1 clomipramine). Sixteen percent of patients took no medication at all. Cataplexy status and gender did not influence the use of wake-promoting medication (all ps > 0.05).

### Sleep Comorbidity and Additional Polysomnographic Findings

Sleep comorbidity was highly prevalent and ranged from sleep-related breathing disorders (24%), insomnia (defined as difficulty in initiating or maintaining sleep plus relevant disturbance of daytime functioning due to insomnia in addition to narcolepsy) (28%), parasomnias by history or at present (34%: 24 RBD, 10 NREM parasomnias), to sleep-related movement disorders (55%: 31 bruxism, 24 restless legs syndrome [RLS]). None of the RBD patients in this study presented at the sleep center with a main complaint of symptoms suggestive of RBD; and only one patient wished for RBD specific therapy with clonazepam 0.5 mg after revealing a diagnosis of RBD.

#### Sleep-Related Breathing Disorders

Twenty-four percent of patients were diagnosed with sleep-related breathing disorders: 14 had mild sleep apnea syndrome, as defined by an apnea-hypopnea index (AHI) between 5-15/h; 8 moderate sleep apnea syndrome with an AHI between 15-30/h; and 2 had severe sleep apnea syndrome with an AHI > 30/h. The majority had obstructive sleep apnea syndrome (21/24); 2/24 had mixed sleep apnea syndrome; and 1/24 central sleep apnea syndrome. The majority declined treatment when offered (18/24). Only the minority (6/24) accepted specific treatment for sleep-related breathing disorder when offered (5 nasal continuous positive airways pressure therapy, 1 intraoral device). All patients of the apnea treated group had moderate and severe sleep apnea syndrome. Men tended to have sleep apnea syndrome more often (19/56 vs. 5/44; p = 0.063) than women.

#### Restless Legs Syndrome

Twenty-four of the 100 narcolepsy patients had RLS. The majority of the affected patients (19/24) declined to receive specific treatment when offered. At the time of the clinical interview, only 3 patients (12.5%) were on a daily therapy with pramipexole 0.18-0.27 mg; 2 (8.3%) additionally took pramipexole 0.088-0.18 mg on demand.

#### Parasomnias and Additional Polysomnographic and MSLT Findings

Parasomnias were present in 34 patients. RBD affected 24 patients and NREM parasomnias affected 10 patients. Of note, only one of the 34 patients wished specific treatment when offered. REM sleep without atonia was present in most patients (90%). A periodic limb movement in sleep index > 5/h was present in 75%. In addition, polysomnography revealed sleep fragmentation in 68% of cases, high frequency leg movements (hypnagogic foot tremor and alternating leg muscle activation during sleep) in 35% of cases, and excessive fragmentary myoclonus in 22% of cases. Frequency of cases with NREM parasomnias or periodic leg movements differed between NC and N patients (NC vs. N: 6/87 vs. 4/13, p = 0.024 and NC vs. N: 69/87 vs. 6/13, p = 0.017, respectively). Men more often had excessive fragmentary myoclonus (20/56 vs. 2/43; p < 0.001). There was a borderline association between a PLMS index > 5/h and the presence of high frequency leg movements (p = 0.055).

MSLT recordings of 17 of the 24 narcolepsy patients with RBD were available for this review. A mean of 10.7 ± 3.2 min of REM sleep were analyzed for each MSLT run with REM sleep.
sleep. The percentage of 3-sec mini-epochs having “any” EMG activity in the chin was 55.8 ± 18.2%. The SINBAR standard cutoff of 18% was exceeded in 13 of the 17 recordings. In 15 of the 17 recordings there was evidence of REM sleep without atonia when a cutoff of 15% was used.20 All video-recordings showed visible movement activity during REM sleep. According to the Sixel-Döring classification,20 11 recordings were rated as a 2, meaning that proximal limb movements including violent behaviors were present. Six recordings were rated as a 1, meaning that small movements or jerks were present. Vocalizations (meaning a score of 1) were present in 9 recordings.

Psychiatric Comorbidity
Psychiatric comorbidity based on patients’ charts was present in 8 cases (2 major depression, 2 bipolar disorder, 2 substance abuse disorder, 1 anxiety disorder, 1 first manic episode with psychotic symptoms [acoustic hallucinations of a religious content]). Psychiatric symptoms started prior to narcolepsy onset in 6 of these 8 patients, 2 patients developed psychiatric comorbidity after onset of narcolepsy (major depression, first manic episode with psychotic symptoms). At time of the clinical interview, psychiatric comorbidity was remitted in 3 of the 8 patients (2 substance abuse disorder, 1 manic episode with psychotic symptoms), and the remaining 5 had an ongoing psychiatric disease (2 major depression, 2 bipolar depression, 1 anxiety disorder).

Educational Level (N = 92), Employment-Related Aspects, and Information on Pregnancy
Educational level varied between patients ranging from subjects with a university degree (n = 14, 15.2%) to subjects with compulsory schooling of 9 years (n = 10, 10.9%). See Table 3 for further information. NC patients had a higher educational level than N patients although this difference was only borderline significant (p = 0.08). Men and women had a comparable educational level (p = 0.226). At the time of last follow-up, 57/92 subjects had a regular job, 17/92 were retired (8 early, 9 regular retirement), 12/92 unemployed, 5/92 on maternity leave, and 1/92 were studying at university.

Forty-six of the 92 patients (50%) answered positively to the question if they had difficulties at their work place due to narcolepsy. Twenty-one of these 46 patients (45.6%) selected or switched their jobs in order to better cope with their disease.

Twenty-eight of the 44 female narcolepsy patients (63.6%) had at least one pregnancy. None of the patients reported disease-related complications during pregnancy. During delivery, 2 of the 44 patients reported on disease-related complications (sleep attacks during delivery, prolonged awakening after anesthesia). Seven patients reported disease-related complications in the time period after delivery (sleep attacks during breastfeeding: n = 6, problems due to excessive daytime sleepiness: n = 5, cataplexy when holding the baby: n = 1). Of note, only a minority of patients took wake-promoting or anticitaplectic medication when becoming pregnant (1 modafinil, 1 methylphenidate, 2 clomipramine). Abnormalities of development or malformations were not observed.

DISCUSSION
The current study is one of the largest monocentric polysomnographic studies to date of patients with definite narcolepsy9,10 and confirms the frequent comorbidity of narcolepsy with many other sleep disorders, some of which were previously investigated in a small number of studies only.9,21-24 One of the key and original findings of our study is that minor motor abnormalities during sleep which are classified in the ICSD-2 as “isolated symptoms, apparently normal variants and unresolved issues” such as high frequency leg movements (alternative terms: hypnagogic foot tremor and alternating leg muscle activation during sleep) and excessive fragmentary myoclonus are common in narcolepsy patients with frequencies of 35% and 22%, respectively.

Other major findings are the considerable diagnostic delay between first symptoms and narcolepsy diagnosis, the diversity of narcolepsy symptoms and the various degrees of symptom severity as well as the marked proportion of significant sleep comorbidity in narcolepsy. In the present study, the median diagnostic delay is marked at with 6.5 years, with a range from 0 to 39 years. This diagnostic delay is well in line with that of other recent studies in both European and overseas countries.25,26 The presence of cataplexy surprisingly did not shorten the diagnostic interval. This might be explained by the fact that narcolepsy is still underrecognized by health care professionals. Especially in the light of the impact of a lifelong disabling diagnosis with important health, social and economic consequences such as narcolepsy,27 careful education of healthcare professionals on narcolepsy is crucial to reduce the current diagnostic interval.

The clinical spectrum of narcolepsy in this cohort is broad, ranging from patients with the complete narcoleptic tetrad to patients whose only complaint is excessive daytime sleepiness. In the present study, 36/100 patients had all four cardinal symptoms of narcolepsy, 28/100 patients had three cardinal symptoms, 29/100 two cardinal symptoms, and 7 had only excessive daytime sleepiness. Symptom severity also varied. Cataplexy severity ranged from patients with daily severe cataplectic attacks which have led to serious self-injury in the past to patients

| Table 3—Educational level of the Innsbruck narcolepsy cohort |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| University degree | 14 (15.2%) | 14 (17.1%) | 0 (0%) | N.A. |
| College         | 24 (26.1%) | 18 (22.0%) | 6 (60.0%) | 0.014 |
| Vocational education | 44 (47.8%) | 42 (51.2%) | 2 (20.0%) | 0.001 |
| Compulsory schooling | 10 (10.9%) | 8 (9.8%) | 2 (20.0%) | 0.058 |

NC, narcolepsy with cataplexy; N, narcolepsy without cataplexy.
with only very few attacks with involvement of the head/neck on rare occasions without any relevant subjective complaint. Sleep paralysis and hypnagogic hallucinations, which affected half of our subjects varied also markedly in their frequency and severity. Surprisingly, 62% of patients had a regular job, perhaps pointing to minor severity or excellent coping strategies. The percentage of unemployment or early retirement is lower to that reported in a German study, which found that 59% of the patient collective were unemployed mainly due to the disease itself. Moreover, approximately one-third of subjects preferred to refrain from medication despite being offered or to take only on-demand medication when necessary, whereas two-thirds of patients needed a daily treatment of narcoleptic symptoms.

In addition, we confirmed and expanded the knowledge on sleep comorbidity in narcolepsy. Ninety percent of the patients had REM sleep without atonia and 24% had a diagnosis of RBD, indicating symptomatic RBD. In contrast to the idiopathic form of RBD, RBD in narcolepsy affected both men and women equally. In addition, our findings confirm the results of Ferri et al. who demonstrated that in NC increased phasic and tonic electromyographic activity characteristic of REM sleep without atonia during REM sleep is present irrespective of the presence of a comorbidity of RBD. Our findings of the presence of REM sleep without atonia in narcolepsy are consistent with those of other authors who found REM sleep without atonia in up to 50% of narcolepsy cases. However, their figure of 50% is still admitted lower than our figure of 90%. Part of the reason for this discrepancy may be that these other authors used a quantitative 20% EMG cutoff of tonic EMG activity in the chin for the definition of RWA. We on the other hand evaluated the presence of RWA qualitatively in line with the currently valid ICSD-2 criteria. We assume when applying a 20% cutoff—which was arbitrarily chosen for RBD at that time—our frequency of RWA might also have been lower. Moreover, the frequency of RBD in our narcolepsy cohort is intermediate to the frequencies reported in the literature so far, ranging from 12% to 36% compared to 0.5% in the general population. Of note, EMG typical features of RBD were not only present during the nocturnal video-polysomnography but also during the MSLT recording, and up to 80% of our narcolepsy RBD patients were above the recently published RBD cutoff value of 18% during the MSLT.

Of note, 75% of subjects had a periodic leg movement in sleep index > 5/h, and approximately 20% of patients fulfilled minimal diagnostic criteria for RLS. In contrast, only a minority of patients considered themselves as needing treatment for the restless legs symptoms. The frequency of RLS is in line with a recent study showing that 15% of the investigated narcolepsy patients had RLS symptoms at least twice per week compared to 3% of age-matched controls.

The demonstration of a high amount of minor motor abnormalities during sleep in narcolepsy in the present study is consistent with a recent video analysis which demonstrated that motor events detected in time-synchronous video-polysomnography are very frequent during both NREM and REM sleep in narcolepsy patients compared to controls. Of note, in narcoleptic children wakefulness-related motor disturbances are frequently observed at disease onset. Based on high rates of REM sleep without atonia and periodic leg movements in sleep in narcolepsy, one might suggest both sleep-related motor features and sleep fragmentation, (present in 68% of narcoleptics in this cohort) as additional hallmarks of narcolepsy, while insomnia, which was present in 28% of patients, does not exclude a diagnosis of narcolepsy.

Twenty-four percent of the patient cohort had predominantly obstructive sleep apnea syndrome. This frequency is increased compared to a prevalence of 4% in the general population, and is similar to the findings of other large studies in narcolepsy with prevalences ranging from 18% to 29%. The finding of multiple sleep comorbidities in narcolepsy strongly corroborates the recommendation of the ICSD-2 criteria to perform polysomnography even in definite NC. Of 100 narcolepsy patients in this series, all but 4 could be diagnosed based on clinical history and multiple sleep latency testing alone, suggesting that cerebrospinal fluid examinations for hypocretin/orexin levels are not a diagnostic necessity.

Obesity defined as a BMI > 30 kg/m² was present in 23% of narcolepsy patients. Moreover, patients with narcolepsy in this cohort had a 1.5-fold increased percentage of subjects with BMI percentiles above 90, which was somewhat lower than the rate of obesity in narcolepsy reported by a German study (which found a mean BMI percentile of 75 and a three-fold increased percentage of subjects with BMI percentiles above 90), and a Norwegian study which found that 29% of narcolepsy patients were obese. An association between obesity and the presence of cataplexy and hence a decreased or undetectable hypocretin/orexin level has been claimed by some authors. In the present cohort, there was no difference between NC and N patients in regard to BMI, although this comparison is of limited value given the small sample size of 13 patients in the N group.

Findings of the current study revealed that presence of cataplexy went along with more severe excessive daytime sleepiness, more severe and frequent sleep paralysis, and sleep-related hallucinations, as well as more sleep onset REM episodes and a higher association with DQB1*0602 and DQB1*0501, suggesting a continuum between N with milder disease features and NC with more severe features. Earlier clinical observation that men are more severely affected by narcolepsy than women was not confirmed by our study. On the contrary, women scored higher than men on the Epworth Sleepiness Scale.

One of the strengths of the present study is that all included patients had symptoms of narcolepsy as their initial clinical presentation. Thus we feel that our findings are more likely to be generalizable to the general population of narcolepsy patients, barring the possibility that a community sample of narcoleptics could be milder and thus less likely to have as many comorbid sleep disorders. A polysomnographic study of a community sample is needed to further verify our findings. In addition, multicenter studies are highly warranted, as increasing substantially the number of patients allows for multivariate approaches.

Another potential caveat of this study is that questions on symptom onset were assessed retrospectively. Therefore some wrong estimations cannot totally be excluded.

In summary, this study demonstrates that the clinical spectrum of narcolepsy is broad in regard to symptom diversity and severity. Whether this clinical spectrum is responsible for the marked diagnostic delay of this disease remains speculative. Moreover, sleep comorbidities in narcolepsy are a non-trivial...
issue, which is an additional argument in favor of the use of polysomnography for a definite diagnosis of narcolepsy. Based on our data, presence of REM sleep without atonia, periodic leg movement in sleep indices > 5/h, and sleep fragmentation can be regarded as further polysomnographic hallmarks of the disease, whereas insomnia does not speak against a diagnosis of narcolepsy. The new finding of a high percentage of narcolepsy patients with high frequency leg movements as well as excessive fragmentary myoclonus adds to the literature suggesting that narcolepsy, in general, is characterized by motor instability.

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Obstructive Sleep Apnea (OSA) in Preadolescent Girls is Associated with Delayed Breast Development Compared to Girls without OSA

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Study Objective: Adults with obstructive sleep apnea (OSA) have lower sex steroid levels than controls. We sought to determine whether OSA also interferes with reproductive hormones in adolescence by tracking the pace of pubertal development.

Methods: One hundred seventy-two children in the Tucson Children’s Assessment of Sleep Apnea study (TuCASA) underwent two home polysomnographic studies, spaced 4-5 years apart. Height and weight were measured at both visits, and Tanner staging of breasts/genitals and pubic hair were self-assessed by a pictorial questionnaire at follow-up.

Results: Eighty-seven girls and 85 boys, age 8.9 ± 1.6 years (mean ± SD) at baseline and 13.4 ± 1.6 years at follow-up, participated. Twenty-seven percent of participants were overweight or obese at baseline, and the majority remained so at follow-up. Twenty-six percent of girls and 28% of boys met criteria for OSA, defined as a respiratory disturbance index (RDI) ≥ 1/h associated with a 3% desaturation (RDI 3%), at baseline. There was an inverse relationship between baseline log RDI 3% and Tanner breast stage at follow-up (coefficient -1.3, p = 0.02) in girls after adjusting for age (p < 0.001), body mass index (p < 0.005), and ethnicity. Girls with OSA at baseline were more than 1 Tanner breast stage behind girls without OSA at follow-up. OSA did not affect genital development in boys or pubic hair development in either sex.

Conclusions: OSA in preadolescent girls predicts delayed breast development relative to girls without OSA. Sleep fragmentation and/or hypoxia seen in OSA may interfere with reproductive development in girls.

Keywords: Obstructive sleep apnea, puberty, adolescence, sex steroids, lung

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on the close temporal, and likely physiologic, connection between sleep and the reproductive axis during puberty, we hypothesized that children with OSA would have delayed puberty relative to controls.

**METHODS**

The TuCASA study protocol has been previously described in detail. Briefly, nearly 500 Caucasian or Hispanic children, ages 6-11 years, without a chronic medical condition were recruited from the Tucson Unified School District and underwent unattended home polysomnography (PSG). Approximately 5 years later, 304 of the children completed a second in-home PSG study of acceptable quality. Height and weight were measured at each home study visit, and body mass index (BMI) percentiles and standard deviation scores were calculated using the 2000 U.S. Centers for Disease Control and Prevention childhood growth charts. Children with BMI between the 85th and 95th %tile or ≥ 95th %tile for age and gender were considered to be overweight or obese, respectively. At each home visit, the presence of habitual snoring (defined as snoring loudly “frequently” or “almost always”) was determined by parental report. At the second home study (follow-up) visit, 172 of the children completed a validated pubertal self-assessment questionnaire without parental supervision that consists of simple line drawings based on photographs of the Tanner and Marshall standards for pubic hair and breast or genital development and a small amount of descriptive text. The 172 children who completed two home PSG studies and a pubertal assessment questionnaire at the follow-up study are the focus of this report.

Unattended overnight PSGs were obtained with the Compumedics PS-2 system (Abbotsford, Victoria, Australia) using the following signals: C3/A2 and C4/A1 electroencephalogram, right and left electrooculogram, a bipolar submental electroymyogram, thoracic and abdominal displacement (inductive plethysmography band), airflow (nasal/oral thermistor), nasal pressure cannula, finger pulse oximetry, electrocardiography (single bipolar lead), snoring microphone, body position (Hg gauge sensor), and ambient light.

Scoring of sleep was performed by a single registered polysomnographic technologist using Rechtschaffen and Kales criteria. Arousalas were identified using the American Academy of Sleep Medicine criteria. Apneas were scored if the amplitude (peak to trough) of the thermistor airflow signal decreased below 25% of the amplitude at baseline breathing (identified during a period of regular breathing with stable oxygen levels) > 6 sec or 2 breath cycles, as previously described. Hypopneas were scored if the amplitude any respiratory signal decreased below 70% of the amplitude of baseline and if the thermistor signal did not meet the criterion for apnea. The respiratory disturbance index (RDI) was defined as the number of apneas and hypopneas associated with a 3% desaturation per hour of total sleep time (RDI 3%). OSA was defined as an RDI ≥ 1 event per hour of total sleep time based on our previous studies, demonstrating that this degree of respiratory disturbance is clinically meaningful (e.g., associated with excessive daytime sleepiness and learning problems).

The TuCASA study was approved by the University of Arizona Institutional Review Board and the Tucson Unified School District Research Committee. Informed consent and assent was obtained from all parents and children, respectively, prior to participation.

**Data Analysis**

Student’s t-test and the χ² test were used to compare sleep study parameters at baseline and follow-up (paired t-test) and between boys and girls (unpaired t-test). The effect of OSA at baseline on pubertal stage determined at follow-up was investigated using multiple linear regression, controlling for known predictors of pubertal development (age, BMI, and ethnicity). RDI was log-transformed prior to analysis to improve normality. Statistical analyses were performed using SigmaStat 11 (Systat Software Inc, San Jose, CA).

**RESULTS**

The study population consisted of 87 girls and 85 boys who were 8.9 ± 1.6 years old (mean ± SD) at the time of their baseline PSG study and 13.4 ± 1.6 years old at follow-up (Table 1), with no difference in age between boys and girls. Sixty-eight percent of the cohort was Caucasian; 32% was Hispanic. Twenty-seven percent of children were overweight or obese at baseline with no differences between girls and boys, and the majority (83%) of these children remained obese at follow-up approximately 4 years later. Twenty-six percent of girls and 28% of boys met criteria for OSA (RDI ≥ 1 event/h with 3% desaturation) at

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**Table 1**—Subject characteristics at baseline and follow-up visits

<table>
<thead>
<tr>
<th></th>
<th>Baseline Examination</th>
<th>Follow-up Examination</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Girls (n = 87)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years, mean (SD)</td>
<td>8.9 (1.7)</td>
<td>13.4 (1.8)</td>
</tr>
<tr>
<td>BMI Z-score, mean (SD)</td>
<td>0.2 (1.2)</td>
<td>0.3 (1.1)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>68% Caucasian 32% Hispanic</td>
<td>NA</td>
</tr>
<tr>
<td>RDI 3%, events/h, median (IQR)</td>
<td>0.5 (0.3-1)</td>
<td>0.2 (0.1-0.5)</td>
</tr>
<tr>
<td>% SDB, RDI 3% ≥ 1</td>
<td>26% (23/87)</td>
<td>10% (9/87)</td>
</tr>
<tr>
<td>% Snoring</td>
<td>11.5% (10/87)</td>
<td>5.7% (5/87)</td>
</tr>
<tr>
<td>Tanner stage, median (range)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>NA</td>
<td>3 (1-5)</td>
</tr>
<tr>
<td>Pubic hair</td>
<td>NA</td>
<td>3 (1-5)</td>
</tr>
<tr>
<td><strong>Boys (n = 85)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years, mean (SD)</td>
<td>8.8 (1.5)</td>
<td>13.5 (1.5)</td>
</tr>
<tr>
<td>BMI Z-score, mean (SD)</td>
<td>0.3 (1.3)</td>
<td>0.3 (1.3)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>68% Caucasian 32% Hispanic</td>
<td>NA</td>
</tr>
<tr>
<td>RDI 3%, events/h, median (IQR)</td>
<td>0.6 (0.2-1.1)</td>
<td>0.2 (0.1-0.8)</td>
</tr>
<tr>
<td>% SDB, RDI 3% ≥ 1</td>
<td>28% (24/85)</td>
<td>20% (17/85)</td>
</tr>
<tr>
<td>% Snoring</td>
<td>18.8% (16/85)</td>
<td>7.1% (6/85)</td>
</tr>
<tr>
<td>Tanner stage, median (range)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genitals</td>
<td>NA</td>
<td>3 (1-5)</td>
</tr>
<tr>
<td>Pubic hair</td>
<td>NA</td>
<td>3 (1-5)</td>
</tr>
</tbody>
</table>

*p < 0.001, p < 0.05, p-values indicate baseline and follow-up comparisons using unpaired t-tests or χ².
baseline (RDI 3% of 1-6.6 in girls with OSA, 1-7.2 in boys with OSA). Parents reported habitual snoring in only 17% of children found to have OSA. At the follow-up study, OSA had persisted in 30% of the subjects diagnosed at baseline, and an additional 12 subjects were newly diagnosed with OSA, for a total of 26 subjects (RDI 3% of 1-5.3 in girls with OSA, 1-7.2 in boys with OSA). There was no difference in the percent of girls (26%) and boys (33%) with OSA at both baseline and follow-up. Only 2 children with OSA at baseline underwent tonsillectomy prior to follow-up, and no child was treated with CPAP.

Self-assessment of Tanner staging at the follow-up visit revealed a median stage of 3 (range 1-5) for pubic hair and breast/genital development in both boys and girls. RDI 3% at visit 1 had no effect on breast/genital stage ascertainment at follow-up after controlling for age (β coefficient 0.4, p < 0.001), BMI Z-score at visit 2 (coefficient 0.1, p = 0.07), and ethnicity (coefficient -0.2, p = 0.2). However, when limited to girls, the same linear regression model revealed an inverse relationship between baseline RDI 3% and Tanner breast stage at follow-up, suggesting that OSA delays pubertal development in girls (Table 2). On average, girls with OSA at baseline were approximately one Tanner breast stage behind girls without OSA at the follow-up evaluation after controlling for age, BMI, and ethnicity. Higher BMI Z-scores at visit 2 were associated with a prolonged period of diminished GnRH activity.1

Following a prolonged period of childhood quiescence, the central driver of the reproductive axis—the hypothalamic GnRH neuron—reactivates, thereby initiating puberty. Intriguingly, the increase in reproductive hormone secretion during puberty initially occurs only during sleep.1 The cause of this sleep-specific rise is unknown, but its conservation across a number of species suggests that it has physiologic significance.2,21 Furthermore, the sleep sensitivity of GnRH neurons is observed not only during their reactivation during puberty, but reappears in adulthood during the recovery phase of anorexia nervosa22 and hypothalamic amenorrhea,23 two disorders associated with a prolonged period of diminished GnRH activity.

Given the sensitivity of GnRH neurons to the sleep/wake state, we hypothesized that disordered sleep secondary to OSA would disrupt normal pubertal maturation. Indeed, the current study demonstrates that otherwise healthy preadolescent girls with OSA have delayed pubertal development relative to girls without OSA. Although the increase in GnRH activity with sleep occurs to the same degree in boys as in girls, the reproductive axis in boys appears to be more resistant to disorganized sleep, as OSA did not have a significant effect on pubertal maturation in boys. A similar gender difference in seen in the sensitivity of the reproductive axis to other stressors, such as exercise. Hypogonadism is common among female athletes (so-called hypothalamic amenorrhea) but is

### Table 2—Linear regression model for effect of OSA on breast development in girls and genital development in boys, controlling for age, BMI, and ethnicity

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Coefficient</th>
<th>p-value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Girls: Breast Development</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at follow-up</td>
<td>0.4</td>
<td>&lt;0.001</td>
<td>0.28, 0.52</td>
</tr>
<tr>
<td>BMI Z-score at follow-up</td>
<td>0.3</td>
<td>&lt;0.005</td>
<td>0.1, 0.5</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>-0.02</td>
<td>0.9</td>
<td>-0.4, 0.4</td>
</tr>
<tr>
<td>Log baseline RDI 3%</td>
<td>-1.3</td>
<td>0.02</td>
<td>-2.3, -0.3</td>
</tr>
<tr>
<td><strong>Boys: Genital Development</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at follow-up</td>
<td>0.4</td>
<td>&lt;0.001</td>
<td>0.24, 0.56</td>
</tr>
<tr>
<td>BMI Z-score at follow-up</td>
<td>-0.05</td>
<td>0.5</td>
<td>-0.23, 0.13</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>-0.5</td>
<td>0.03</td>
<td>-1.0, -0.04</td>
</tr>
<tr>
<td>Log baseline RDI 3%</td>
<td>1.2</td>
<td>0.06</td>
<td>-0.04, 2.4</td>
</tr>
</tbody>
</table>

*p < 0.01, p < 0.001. p-values indicate group comparisons using unpaired t-tests or χ². All values are reported as mean (SD) except for RDI 3%, which is reported as median (IQR).

### Table 3—Characteristics of girls with and without OSA at the baseline study visit

<table>
<thead>
<tr>
<th></th>
<th>RDI 3% ≥ 1 (n = 23)</th>
<th>RDI 3% &lt; 1 (n = 64)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td>8.8 (3.0)</td>
<td>9.0 (3.8)</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td>60% Caucasian</td>
<td>70% Caucasian</td>
</tr>
<tr>
<td></td>
<td>40% Hispanic</td>
<td>30% Hispanic</td>
</tr>
<tr>
<td><strong>BMI Z-score</strong></td>
<td>0.3 (1.0)</td>
<td>0.1 (1.1)</td>
</tr>
<tr>
<td><strong>RDI 3%, events/h</strong></td>
<td>1.8 (1.3-3.2)</td>
<td>0.4 (0.2-0.5)</td>
</tr>
<tr>
<td><strong>Arousal index, events/h</strong></td>
<td>3.4 (1.5)</td>
<td>3.3 (1.3)</td>
</tr>
<tr>
<td><strong>Sleep efficiency, %</strong></td>
<td>90.6 (6.3)</td>
<td>91.4 (4.9)</td>
</tr>
<tr>
<td><strong>Total sleep time, h</strong></td>
<td>7.8 (1.6)</td>
<td>8.3 (1.3)</td>
</tr>
<tr>
<td><strong>Sleep staging</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>stage 1, %</td>
<td>3.5 (2.6)</td>
<td>4.1 (3.4)</td>
</tr>
<tr>
<td>stage 2, %</td>
<td>54.3 (15.0)</td>
<td>51.7 (5.6)</td>
</tr>
<tr>
<td>stage 3/4, %</td>
<td>21.8 (8.5)</td>
<td>22.8 (6.3)</td>
</tr>
<tr>
<td>REM, %</td>
<td>20.4 (7.6)</td>
<td>21.5 (4.2)</td>
</tr>
</tbody>
</table>

*OSA and Puberty in Girls*
rare among male athletes.24 OSA had no effect on pubarche (the development of pubic hair) in boys or girls. Although pubic hair and genital development occur simultaneously during adolescence, the two are independent processes, with pubic hair development driven primarily by adrenal androgen production and genital development driven solely by maturational changes within the brain.25

An association between OSA and decreased sex steroid and/or gonadotropin levels, as would be predicted to occur in adolescents with OSA and delayed puberty, has previously been reported in adults. Most,3,6,8 but not all,26,27 studies demonstrate that men with moderate-to-severe OSA have significantly lower T levels than healthy controls and lower26 or inappropriately normal3,4,8 LH levels. Of note, however, many of these studies have been limited by small sample sizes, differences in BMI and/or age between cases and controls, both of which influence serum T, and assessment of gonadal function based on single measurements of T, which is influenced by time of day,28 or LH, which is secreted in a pulsatile manner.29 Only one study has been conducted in adult women with OSA,7 and like men with OSA, women with OSA were found to have lower sex steroid levels (estradiol and progesterone) than age- and BMI-matched controls after adjusting for menstrual cycle phase and pre- or postmenopausal status.

The cause of reproductive dysfunction among adults with OSA is unclear but has been attributed to the hypoxia and sleep fragmentation that characterize OSA. Several studies have demonstrated an inverse correlation between T level and the RDI3,5 in men; however, studies of total sleep deprivation for 48 hours29 or partial sleep deprivation and sleep fragmentation for 24 hours31 reported no adverse effect on gonadotropin or T levels in healthy men. Sleep disruption studies have not yet been conducted in preadolescents whose reproductive axis would be expected to be more vulnerable to sleep disruption than that of adults, given the tight association between LH secretion and sleep during the early stages of puberty.1 The negative correlation between T and the desaturation index in men with OSA and the finding that mean nocturnal oxygen saturation in men with and without OSA is independently associated with erectile dysfunction32 also suggests that hypoxia may play a role in the lower T levels observed in men with OSA. In a rodent model, intermittent hypoxia without concomitant sleep deprivation activates the inflammatory cascade, increases free radical production, and induces neuronal apoptosis in the hippocampus and cortex33; however, the effect of hypoxia on the hypothalamus, the seat of the central components of the reproductive axis, including kisspeptin and GnRH neurons,34 has not yet been investigated. Studies are also necessary to determine whether hypoxia and/or sleep disruption explain the defects in reproductive hormone secretion in women with OSA, as observed in men.

In contrast to the above studies in adults with moderate to severe OSA, the children in the current study had relatively mild OSA (RDI 3% 1-7.2) based on conventional scoring methods. However, it is well recognized that standard PSG measures in children, including arousals and the percent time spent in each sleep stage (as were measured in the current study) are likely to underestimate the degree of sleep disruption as they do not correlate with measures of neurobehavioral morbidity.35,36 This concept has led to the suggestion that alternative measures, such as the number of subcortical arousals identified by spectral analysis,37 sleep dynamics analyses,38 and autonomic arousal measures,39,40 be incorporated into the interpretation of pediatric PSG studies. The use of these more sensitive measures may also help explain why LH pulses, which occur most frequently during slow-wave sleep and rarely during REM sleep during puberty,41 might be diminished in children with OSA who have the greatest number of obstructive events during REM.42 Thus, although the children in the current study appear to have mild OSA according to standard scoring methods, current methods may miss arousals and/or subtle defects in sleep architecture that can explain the detrimental effect of OSA on the reproductive axis in girls during puberty.

Due to the large scale and home-centered approach of the TuCASA study, pubertal staging was determined by a self-assessment questionnaire rather than by a physician’s physical examination. It is therefore possible that the present findings are due to an underestimation of pubertal development among girls with OSA. However, a number of studies have demonstrated that adolescent girls (and boys) can accurately determine their degree of pubertal maturation to within one Tanner stage of a trained examiner’s assessment using a self-assessment questionnaire that is based on line drawings of pubertal stages.43–45 While girls with and without OSA were of similar age and ethnic background, girls with OSA were more likely to be overweight or obese. Obesity, however, would be expected to lead to an overestimation rather than underestimation of true breast development, in part due to the difficulty in distinguishing lipomastia from true breast tissue. In a study of 135 girls (mean age 9.3 years), Bonat et al. found that obese girls significantly overestimated their actual breast size (by 0.5 Tanner stages)46; other investigators, however, have found that BMI does not bias pubertal assessment in either direction in girls.47–49 Lastly, although we controlled for BMI in our regression model, the increased incidence of obesity among girls with OSA would be expected to have accelerated, rather than delayed, pubertal development, as recent studies have demonstrated that obese girls enter puberty at a slightly younger age than normal weight girls.49 Thus, our estimate of the effect of OSA on female pubertal development is likely to be conservative.

In summary, the current study demonstrates that OSA among preadolescent girls is associated with relatively delayed pubertal maturation. The pathophysiologial connection between OSA and the reproductive axis is unknown, but the critical role of the hypothalamus in pubertal development suggests that hypoxia and/or sleep fragmentation may have direct effects on the brain. A central mechanism of action is also suggested by the neuropsychological deficits found in children with OSA50 and more recently, by magnetic resonance spectroscopy studies demonstrating neuronal metabolite alterations in children with OSA.51 While in the current study Tanner breast stage at follow-up remained within the normal range in girls with a history of OSA despite a significant delay relative to girls without OSA, future studies will be necessary to address the important question of whether or not childhood OSA has any long-term effects on the reproductive axis beyond early adolescence.
REFERENCES


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SUBMISSION & CORRESPONDENCE INFORMATION

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DISCLOSURE STATEMENT

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Insomnia is characterized by difficult initiating and/or maintaining sleep or non-restorative sleep, which causes at least one area of impairment, such as depressed or irritable mood, decreased concentration, daytime sleepiness, or physical malaise. Chronic insomnia is present in 10% to 15% of the population. Insomnia is more prevalent in women and prevalence increases with age. It is estimated that up to 35% of older adults have insomnia. Consequences of insomnia among older adults include decreased quality of life, lower cognitive function, and risk for hip fractures. Non-pharmacological treatments are often preferred by patients and physicians due to concern over side effects and increased mortality in hypnotic users.

Aerobic exercise has been tested in multiple studies as a non-pharmacological intervention for sleep in older adults that has general health benefits and is readily accessible to most individuals. The benefits of exercise on insomnia symptoms are most consistent for self-reported sleep quality and sleep diary based measures. A systematic review of 6 randomized trials of exercise in older adults (with and without insomnia) demonstrated improvements of self-reported global sleep quality, decreased self-reported sleep latency, and increased sleep medication use. Only a few studies have reported objective sleep data. In a study of older adults, King and colleagues demonstrated that 12 months of moderate intensity aerobic activity led to improvements in self-rated and diary-based measures of sleep quality, as well as modest improvement in some polysomnographic measures (such as fewer awakenings in the first third of the night) in a sample of older adults with poor sleep quality. A recent study conducted in Brazil demonstrated improvements in both self-reported sleep and PSG measures in a sample of middle-aged adults with insomnia. In this study, 6 months of aerobic exercise (50 min, 3 times/week) led to objective and subjective improvements, including decreased sleep onset latency, decreased wake after sleep onset, increased sleep efficiency (SE), and increased ratings of sleep quality and feeling rested. There have been fewer investigations into the acute effects of exercise in patients with insomnia. In clinical settings, patients often have the expectation that exercising—particularly vigorous exercise—will lead to rapid improvement in their sleep that night (e.g., “I exercised until I was exhausted and I still couldn’t sleep”). Although the relationship between acute
exercise and sleep has been studied extensively in laboratory studies of healthy populations, the relationship between acute exercise and sleep has been investigated in only two prior studies in participants with sleep disturbance. King and colleagues found no correlation between polysomnographic variables and exercise when evaluating whether the assessment was conducted on a night that followed or did not follow exercise in older adults with sleep complaints. However, one study demonstrated acute improvements in polysomnographic measures among adults with insomnia. Compared with a control night without exercise, one session of moderate aerobic exercise lead to a reduction in sleep onset latency (SOL) and total wake time, and increases in total sleep time (TST) and SE during the corresponding night. There were no significant improvements in sleep during the night following high-intensity exercise or moderate-intensity resistance training.

The prior studies of acute exercise for sleep disturbance have only evaluated one or two nights of exercise and sleep. This is potentially problematic in insomnia because the disorder itself is characterized by variability in sleep pattern. Therefore, one or two nights may not adequately capture the sleep of persons with insomnia. The use of wrist actigraphy allows for the evaluation of estimated sleep patterns in the home environment for a longer period of time with minimal participant burden. The goal of the present study is to explore the acute relationship between exercise and sleep through 16 weeks of daily data (daily sleep diary, logs, and actigraphy) collected in women enrolled in an exercise intervention for insomnia. The structure of the data (daily values over 16 weeks) allows us to evaluate the directionality of the effect. We previously reported improvements in self-reported sleep quality, quality of life, daytime sleepiness, TST, and SE associated with 16 weeks of aerobic exercise in this sample. This analysis extends these findings by evaluating the day-to-day relationships between exercise and sleep.

METHODS

Data from this study were drawn from a larger study, which tested the effects of a 16-week exercise and sleep hygiene intervention versus 16 weeks of non-physical activity and sleep hygiene intervention on sleep, daytime function, and metabolism in older adults with insomnia. Data from the exercise group alone was used for these analyses. This study was approved by the Northwestern University Institutional Review Board and all participants provided written informed consent.

Additional details of the study are listed elsewhere. Participants included in this analysis were 11 healthy, community-dwelling sedentary older adults (≥ 55 years) with sleep disturbance ≥ 3 months. All participants met DSM-IV criteria for primary insomnia. In addition, this study included the following subjective and objective criteria: Pittsburgh Sleep Quality Index Score ≥ 5, SE < 80% and/or waking earlier than desired if before 06:00, and TST ≤ 6.5 h demonstrated on 7 days of wrist actigraphy. Sedentary behavior was defined as participation in mild to moderate intensity exercise < 30 min per day on < 2 days per week. Inclusion criteria also included the minimal status exam (MMSE) > 26.

Exclusionary criteria included the following: (a) significant comorbid sleep disorders documented on screening polysomnography (apnea index > 10, periodic leg movement arousal index > 15, REM behavior disorder); (b) history of cognitive or other neurological disorders; (c) history of DSM-IV criteria for any major psychiatric disorder, including mania or alcohol or substance abuse; (d) significant depressive symptoms as assessed by the Center for Epidemiological Studies Depression Scale (CES-D score > 22); (e) unstable or serious medical conditions or cardiopulmonary disease that contraindicate exercise; (f) current use or use within the past month, of psychoactive, hypnotic, stimulant, or analgesic medications; (g) shift work or other types of self-imposed irregular sleep schedules; (h) BMI > 35 kg/m²; (i) history of habitual smoking (≥ 3 cigarettes per week) or caffeine consumption (> 300 mg).

After initial eligibility was determined through telephone screening, participants were screened with overnight polysomnography, screening questionnaires (MMSE, CES-D, PSQI), and 7 days of activity monitoring using wrist actigraphy and a sleep log. If participants met inclusion criteria, they were randomized to treatment groups—exercise plus sleep hygiene or a mental (non-physical) activity and sleep hygiene. At Baseline, participants were admitted to the clinical research unit (CRU) for a 4-day baseline admission which involved exercise testing, questionnaires, polysomnography, health measures (e.g., oral glucose tolerance test), and performance testing. Seven days of baseline actigraphy was also completed prior to beginning the intervention. At the end of the 16-week intervention period, participants completed another 4-day CRU admission for a similar battery of tests and questionnaires. Participants completed 7 days of actigraphy at the end of the intervention.

Interventions

Sleep Hygiene

Participants received sleep hygiene education which consisted of a sleep hygiene appointment with a sleep specialist, in which they were provided with verbal and written sleep hygiene instructions according to materials published by the American Academy of Sleep Medicine. Patients were encouraged by research staff to continue practicing sleep hygiene instructions during study visits every 2 weeks.

Exercise Intervention

Baseline exercise testing was performed to determine exercise capacity and tailor the exercise intervention to each participant. The exercise testing protocol used the modified Bruce protocol and was designed for participants to reach their anaerobic threshold (a marker of oxygen demand exceeding the supply, indicated by increasing CO₂ levels in the airway) no sooner than 5 and not longer than 15 minutes. The anaerobic threshold was determined by measurements of oxygen consumption and end-tidal CO₂. A symptom-limited maximal ergometer test with a 10 to 40 watt/minute-step protocol was used to measure VO₂ max for each subject.

The conditioning period (week 1-6) was conducted under the supervision of an exercise physiologist. The conditioning protocol included exercise sessions 4 times per week with the following specifications: (Week 1) 10-15 min/day at 55% max heart rate (HR) as measured with a heart rate monitor (Protrainner, Polar Electro Inc., Port Washington, NY); (Week 2) 15-20
min/day at 60% max HR; (Week 3) 20-25 min/day at 65% max HR; (Week 4) 25-30 min/day at 70% max HR; (Week 5-6) attaining 75% of max HR for 30-40 min.

After completion of the conditioning period, participants were asked to exercise for either two 20-min sessions or one 30- to 40-min session at 75% of their maximum HR 4 times per week for the duration of the study. Exercise sessions were conducted in the afternoon or evening (13:00-19:00), and participants were required to miss no more than 1 exercise session per week. Participants engaged in ≥ 2 of 3 aerobic activities (walking, stationary bicycle, or treadmill) and engaged in each activity at a similar level of exertion, as measured by the BORG scale of Perceived Exertion and heart rate monitor.

Measures

Subjective sleep quality was measured by The Pittsburgh Sleep Quality Index (PSQI). This 19-item measure assessed self-reported sleep quality and disturbances over a 1-month time interval. There are 7 component scores, which are scaled from 0 to 3. The PSQI global score is the sum of the component scores (range, 0-21). A higher PSQI global score indicates greater sleep disturbance. Scores ≥5 are associated with clinical sleep disturbances over a 1-month time interval. Scores ≥ 5 are associated with clinically significant sleep disturbance. Although not specific to insomnia, this measure has been designed for use in clinical populations and validated in older adults.

Self-reported sleepiness was measured using the Epworth Sleepiness Scale (ESS). On this 8-item questionnaire, participants rated the likelihood of dozing off in daily situations, such as sitting and reading, watching TV, as a passenger in a car for an hour without a break, and laying down in the afternoon if circumstances permit, from 0 (not at all likely) to 3 (very likely). Scores range from 0-24, with higher scores indicating greater sleepiness. Adequate reliability and validity have been reported for this measure.

Participants completed daily sleep logs and turned them in to study staff for review and to assist in scoring actigraphy at 2 week intervals. Participants recorded bedtime, rise time, number of awakenings during the night, and daily subjective rating of sleep quality from 1 (excellent) to 4 (poor).

Daily rest-activity rhythms were assessed via wrist actigraphy during the duration of the study (AW-64 Actiwatch, Mini Mitter Co. Inc., Bend, OR). Actiwatches were set with 30-sec epoch length and medium sensitivity. Sleep onset was scored as the first epoch with 10 min of inactivity. Sleep onset time, sleep offset time, minutes of awake after sleep onset (WASO), TST, sleep efficiency, and fragmentation index were calculated from actigraphy recordings using Actiware-Sleep 3.4 software (Mini Mitter Co. Inc., Bend, OR). Sleep diary based measures of bedtime and rise time were manually entered and used for calculation of sleep onset latency and sleep efficiency. Periods of bedtime and rise time were manually entered and used for calculation of sleep onset latency and sleep efficiency. Periods of bedtime and rise time were manually entered and used for calculation of sleep onset latency and sleep efficiency.

RESULTS

Participant Characteristics and Sleep Variables (Table 1)

Of the 23 participants who were eligible for the study, this analysis includes the 11 participants who were randomized to the exercise group. There were no dropouts from this group, but data from one participant were censored at 12 weeks due to a stressful life event that affected sleep and mood. All participants in this analysis were female, and average age was 61 years (SD 4.4). Participants completed an average of 54.4 (SD 14.4) exercise sessions over the 16 weeks. Average duration of exercise was 32.5 (SD 3.8) min. Treadmill was the most common type, comprising 65% of sessions. Average BMI was 26.7 (4.9) kg/m². Average ESS was 9.2 (SD 5.3). Sleep-wake estimates measured via actigraphy as well as self-report.
reported sleep quality ratings are listed in Table 1. Participants demonstrated significant increases in TST (p < 0.01) and sleep efficiency (p < 0.05), and decreases in global ratings of sleep quality on the PSQI (p < 0.001). There was a trend for a reduction in WASO (p < 0.10). Timing of sleep onset, offset, time in bed, sleep latency, fragmentation index, and daily diary based ratings of sleep quality did not significantly change from baseline to 16 weeks.

Correlations Between Baseline Sleep Variables and Exercise Duration
Participants with higher self-reported sleepiness on the ESS at baseline reported shorter average duration of their exercise sessions (r = -0.67, p = 0.03). Exercise duration was not correlated with baseline actigraphy or self-reported sleep variables or VO_{2 max}.  

Daily Exercise and Sleep During the Corresponding Night
In the first set of multilevel models, we tested exercise duration as a predictor of sleep during the corresponding night. Results demonstrated that exercise was not associated with SOL, TST, WASO, SE, or subjective ratings of sleep quality. There was not significant variability in level 1 effects, therefore moderators could not be tested in level 2 of the model. Exercise also did not predict sleep variables in 2-day lag models.

Sleep and Next Day Exercise
The next set of models tested sleep as a predictor of next day exercise. SOL was negatively associated with next day exercise. SOL was negatively associated with next day exercise duration. For shorter sleepers, there was a stronger relationship between poor sleep and decreased next day exercise duration. We also found an interaction between habitual TST and the daily relationship between sleep and next day exercise. Specifically, coefficients from the HLM model indicate that for every 30-minute increase in sleep onset latency above the individual’s own average value, there was a one-minute decrease in next day exercise duration. There was positive association between TST and next day exercise (b = 1.41, standard error = 0.66, p = 0.06), but this did not reach statistical significance. Variability in level 1 effects of this model allowed us to test moderators in level 2. Baseline TST was a significant moderator of the within subject effects of daily TST and next day exercise (b = -2.66, standard error = 0.93, p = 0.02; Figure 2). Participants with shorter baseline TST had a stronger daily relationship between TST at night and next day exercise duration. SE, WASO, FI, and daily ratings of subjective sleep quality were not associated with next day exercise. Sleep variables did not predict exercise 2 days later. There was significant variability for in the 2-day lag model for SOL (p = 0.03), but none of the moderator variables tested in level 2 explained this variability.

DISCUSSION
Results of this study provide new insight into the relationship between exercise and sleep. In this study, we used the structure of the daily actigraphy, sleep, and exercise log data that were collected over 16 weeks for a unique perspective on the daily relationships between these variables in participants’ home environment over many nights. We found that exercise during the day was not associated with sleep during the corresponding night. However, sleep at night did predict next day exercise. Specifically, coefficients from the HLM model indicate that for every 30-minute increase in sleep onset latency above the individual’s own average value, there was a one-minute decrease in next day exercise duration. We also found an interaction between habitual TST and the daily relationship between TST and next day exercise. For shorter sleepers, there was a stronger relationship between poor sleep and decreased next day exercise duration.

Our finding that exercise did not correlate with sleep during the corresponding night is consistent with data reported by...
King and colleagues, who also evaluated the acute effects of exercise on sleep in a 12-month study conducted in older adults with sleep complaints. In this study, King and colleagues did not find a difference in sleep measured by home polysomnography on 2 consecutive nights if one night followed exercise and one night did not. In a laboratory study, Passos and colleagues found that only moderate-intensity aerobic exercise, not strenuous aerobic exercise or resistance training improved PSG measures of sleep in a sample of middle-aged adults with insomnia. There are far more studies of effects of acute exercise in healthy populations without insomnia. Results from a meta-analysis of 38 laboratory studies of acute exercise in healthy participants demonstrated that acute exercise improved polysomnographic measures of sleep including reducing sleep onset latency and increasing TST. This suggests that understanding the influence of factors such as age, presence of an insomnia diagnosis, and exercise type is important to understanding the acute effects of exercise on sleep. For example, among studies conducted in healthy populations, age has been associated with a larger effect size for exercise on polysomnographic measures of sleep.

In our study, individuals with shorter habitual TST were more responsive to the daily effects of each night of sleep. This finding is interesting, given that our sample were all patients with insomnia and short TST (≤ 6.5 h). Research has demonstrated that sleep loss affects exercise tolerance, motivation, and mood. Laboratory studies conducted in young, healthy samples have demonstrated that sleep deprivation increases perceived exertion and time to exhaustion in exercise testing. In addition, the combination of exercise and sleep loss may further affect mood and motivation. In a laboratory study that combined exercise with 30 hours of sleep loss compared to sleep loss alone, those assigned to sleep loss and exercise demonstrated greater decreases in vigor, as well as greater increases in depression and fatigue. Although 30 hours of sleep deprivation is different from insomnia, this does suggest that the combination of sleep loss and exercise may have additive effects. To date, there are no studies evaluating whether improving insomnia or extending sleep among healthy individuals will increase exercise. However, increasing time in bed for college basketball players improved sprint times and free throw accuracy as well as decreased fatigue and increased vigor.

There are several plausible mechanisms that could link better sleep to increased exercise, including decreased HPA activation, inflammation, improved metabolism, greater energy conservation. One study demonstrated that inflammatory response to physical exercise was greater after partial sleep deprivation. Sleep deprivation has also been related to increased pain ratings. In a daily questionnaire study, sleep at night was predictive of next day pain ratings. Thus, disrupted sleep may lead to decreased desire to exercise and increased pain, which decreases next day exercise.

In correlations between baseline variables and exercise adherence over the duration of the study, we also found that participants with higher self-rated sleepiness at baseline had shorter average duration of their exercise sessions. This suggests that the feeling of sleepiness may interfere with exercise participation. Furthermore, in the setting of insomnia, the effect of sleep loss and dysregulated affective control may magnify the effects of sleep loss on motivation to exercise.

Although there is no consensus as to how to calculate statistical power in multilevel models, it is likely that our small sample limited power to discern and contributed to many marginal findings. Furthermore, our results may not be generalizable to younger age groups, adults without insomnia, or men. It is also important to note that exercise timing, frequency, and duration were prescribed by the protocol to be conducted for at least 30 min in the afternoon, 3-4 times per week. This is an important point because acute effects of exercise may greatly differ based on time of day, and the effect size may be larger in participants who were not monitored on compliance. In addition, this study only evaluated exercise duration, and there may be other effects of exercise intensity and type of exercise. Strengths of this study are the use of daily data continuously monitored over 16 weeks, which included over 100 observations per participant. In addition, use of a monitored exercise protocol using actigraphy allowed us to control the delivery and at the same time observe these relationships over a long duration in a real-world setting.

In conclusion, results suggest despite many patients’ expectations that exercise will immediately improve sleep, we found that sleep affects exercise participation. Data demonstrate that aerobic exercise is an effective intervention that improves objective and self-rated sleep in older women with insomnia. However, the duration of exercise was unrelated to sleep during the corresponding night. Patients with insomnia should be encouraged to exercise regularly and monitor improvement in sleep over longer periods of time rather than focusing on daily improvement. Understanding the daily relationship between exercise and sleep may help inform the development of behavioral interventions for insomnia and identify those at risk for poor adherence to exercise interventions.
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Vallecular Cyst as a Cause of Obstructive Sleep Apnea in an Infant

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A 3-month-old baby was diagnosed with obstructive sleep apnea (OSA) on polysomnography (PSG) with a high apnea hypopnea index (AHI). On further investigations he was found to have a vallecular cyst that was successfully treated. We discuss the clinical presentation of vallecular cysts and the importance of polysomnography in identifying this rare condition.

Keywords: Vallecular cysts, laryngeal cysts, obstructive sleep apnea in infants, cleft lip and sleep apnea

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OSA can present in infancy and is usually caused by craniofacial abnormalities or upper airway obstruction. The pathophysiology is multifactorial and determined by anatomical and neuromuscular factors that influence upper airway size, tone, and function. Laryngeal cysts can potentiate upper airway obstruction but have rarely presented as OSA in the pediatric population.

REPORT OF CASE

A 3-month-old baby with a history of incomplete right cleft lip and alveolus was referred by the Craniofacial Surgery team for PSG for evaluation prior to surgical closure. Patient was born full term via C-section for fetal decelerations with an uneventful perinatal course. He had stridor, snoring, and gasping during sleep since birth. A PSG was performed during daytime nap. He slept for 64 minutes with an arousal/awakening index of 5.6 per hour. He was found to have 45 obstructive apneas, 2 obstructive hypopneas, and 4 mixed apneas (AHI 64.8/h, baseline oxygen saturation 94% to 96%, desaturation index 12/h; SpO₂ nadir 76%, PETCO₂ highest 44 torr). His need for supplemental oxygen was reduced to 0.25 Lpm. He had his cleft lip successfully repaired at 9 months of age, and a follow-up PSG during daytime nap was completely normal (AHI 0.2/h; baseline oxygen saturation 95% to 97%; desaturation index 1.2/h; SpO₂ nadir 91%, PETCO₂ highest 45 torr).

DISCUSSION

Laryngeal cysts are a rare cause of stridor in infants. They are more commonly seen in adults.1,2 They have been variously classified based on location, histology, size, and contents.1 The vallecula is the depression behind the root of the tongue between the median and lateral epiglottic folds on each side. Vallecular cysts belong to the category of ductal cysts described in DeSanto’s early classification system of laryngeal cysts.1 This system classified laryngeal cysts into ductal, saccular, and thyroarytenoid subtypes. Ductal cysts are caused by mucus retention in the submucosal collecting ducts. Vallecular cysts can contribute to upper airway obstruction by posterior displacement of the supraglottis.

Clinical presentations of vallecular cysts include stridor, feeding problems, failure to thrive, gastroesophageal reflux, apnea/cyanosis, chest retractions, hoarse cry, as well as respiratory distress and life threatening events.3,4 Laryngomalacia can coexist with vallecular cysts.5 Diagnosis is by direct laryngoscopy and bronchoscopy, though imaging studies, particularly magnetic resonance imaging, can provide valuable information. Management is by trans-oral endoscopic surgical removal or marsupialization.

Our patient was diagnosed with OSA on PSG. It should be noted that PSG performed during daytime nap may underestimate the severity of OSA. OSA has often been the initial presentation in adults with laryngeal cysts but rarely in children.
One report mentions PSG as part of diagnostic evaluation of an infant, but no details were provided.

The mechanism of upper airway obstruction in infants is multifactorial. The presence of an obstructing lesion in the hypopharynx has the potential of causing severe upper airway obstruction in the immature infant airway. Infants with cleft lip and or palate have a higher incidence of airway obstruction and sleep disordered breathing. In the presence of a single underlying anatomic defect as cleft lip, it is prudent to look for possible coexistent etiologies contributing to OSA which could be treatable. Our patient also had laryngomalacia and recurrent respiratory infections. This case highlights the importance of maintaining a heightened index of suspicion and performing a complete upper airway exam, including an endoscopic examination to identify structural and anatomical lesions in an infant with OSA and a high AHI. Our patient had laryngomalacia and recurrent respiratory infections. With time and after successful closure of cleft lip, his OSA completely resolved. This case is an example of coexistent anatomic and structural lesions culminating in severe OSA in infancy.

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SPECIAL  ARTICLE

Integration of benefits, both insurance-related and clinical. Patient care, continuity of treatment, and the central coordination of clinical and insurance-related benefits.

Keywords: Integrated sleep medicine, dental sleep medicine, delivery of care

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Although sleep science has significantly advanced in the last decade, the delivery of care for sleep-related breathing disorders remains fragmented. Oral appliances in particular have historically been underutilized. This article discusses some of the challenges we have faced and proposes a multidisciplinary care delivery model that integrates dental sleep medicine and sleep medicine under the same roof with educational and research components. The model promises to offer distinct advantages to improved patient care, continuity of treatment, and the central coordination of benefits, both insurance-related and clinical.

Past Challenges to Integrated Care

Reasons for the inability of dental sleep medicine to integrate fully with the delivery of sleep medicine care have been many. First, the growth of dental sleep medicine has not kept pace with the exponential growth of sleep medicine in the treatment of obstructive sleep apnea syndrome (OSA). Dentists who provide appliance therapy for sleep-related breathing disorders are seemingly few in number. Although the American Academy of Dental Sleep Medicine (AADSM) website (http://www.aadsm.org/FindADentist.aspx) lists about 3,000 US dentists as members, only about 200 dentists have obtained diplomat status with the American Board of Dental Sleep Medicine (ABDSM) (http://www.abdsm.org/Diplomates.aspx), and only about a dozen dental practices have been accredited as dental sleep centers. (http://www.aadsm.org/PDFs/AccreditationStandards.pdf). Thus, with the possible exception of using these websites, the thousands of sleep disorders centers (both accredited and non-accredited) in the United States have found no easy way to identify dental sleep medicine experts to whom patients can be referred for evaluation and treatment with oral appliances and for whom the specialized training and experience in oral appliance therapy can be assured.

Second, the lack of education in the specialized use of oral appliance therapy for sleep disordered breathing among dentists and sleep physicians has been a limiting factor. A survey of dentists found that 40% knew little or nothing about oral appliances for treatment of OSA. Moreover, 49 responding dental schools of the 58 US schools recently surveyed reported only 3 hours of total curriculum time devoted to sleep medicine. With the exception of short courses offered by the AADSM, dentists have relied on training from marketing groups often associated with specific appliances and products for sleep medicine. Knowledge of new materials, techniques, procedures, and continuing education has also been attained from dental journals, periodicals, and advertisements. Efforts are under way to formalize dental sleep medicine training in our dental schools. The University of North Carolina School of Dentistry is hosting a conference for dental educators across the United States and Canada to begin the process of developing pre-doctoral DDS and clinical residency programs.

Education to sleep physicians and technologists about oral appliances has been virtually nonexistent. Indeed, there have been recent efforts to train physicians to practice oral appliance therapy at professional meetings. Although this practice raises awareness of oral appliance therapy, it can undermine recognition of the training dental sleep experts undergo to properly evaluate the integrity of the teeth, the surrounding bone, and temporomandibular joints; to obtain accurate impressions and fit removable oral appliances (such as dentures and bite guards) to the teeth; and to minimize negative side effects of their presence.

Third, communications between sleep physicians and dentists have been suboptimal in most healthcare settings. Even in academic settings, interactions between medical and dental...
professionals have been limited by their separate and different clinics, patient record systems, administrative priorities, and business models. There has been little need to co-treat patients in the past; thus the infrastructure and administrative support to encourage good communication between medical and dental sleep providers are lacking.

Fourth, the co-treatment of patients with dental clinicians has been viewed as vaguely competitive to some physicians who provide CPAP as the primary treatment modality. This view has likely limited referral of patients for oral appliance therapy. However, a truly successful relationship between physicians and dentists will only be established by close communication and sharing the common goal of patient-centered treatment.

Fifth, referrals to dentists have been discouraged by the lack of, or limited reimbursement for, oral appliances by insurance carriers. Although the AASM recognized oral appliance therapy in 2005 as a potential first-line therapy for mild and moderate OSA and for patients with severe OSA who fail positive airway pressure therapy, many medical insurance carriers (including Medicare) are now only beginning to provide benefits for oral appliance therapy.13 Progress on this front has been slow and severely challenged by (i) claims processing centers that are not prepared administratively to negotiate contracts with, or process claims from, dentists who are treating a medical condition, (ii) dental practices that are unfamiliar with submission of medical insurance claims and the appeal process upon denial, and (iii) reduced reimbursement rates for appliances that may not meet the dentist’s costs for high quality oral appliances and the chair time required for comprehensive follow-up care.

Sixth, post-intervention care with oral appliances has left much to be desired. Many patients are reluctant to return to the referring physician for follow-up evaluation of the efficacy of the oral appliance therapy, often citing the costs of another sleep study or its inconvenience as reasons for their reluctance. In one study, only 18% of patients receiving oral appliances underwent polysomnography after the initiation of therapy.6 For those patients who do return for a follow-up sleep study and for whom there is residual sleep disordered breathing, another sleep study with yet further costs and inconvenience may be indicated after the dentist or patient adjusts the appliance.

Seventh, outcome measures have not been well documented for oral appliance therapy. While some controlled trials have shown improvement in daytime sleepiness and blood pressure on a short-term basis, the impact of oral appliances on cardiovascular disease on a long-term basis remains largely unknown.7,8 Such data on robust outcomes measures are needed to substantiate the long-term benefit of oral appliance therapy when compared to those of nightly use of positive airway pressure.

Future Demand for Integrated Care

The future of sleep medicine will invariably be influenced by healthcare system reforms to focus more on prevention, multidisciplinary care, and longitudinal disease management in a patient-centered medical home concept. It is, therefore, in the best interest of sleep medicine that a dialogue on innovative improved models of care be reviewed, discussed, and implemented to address the above-mentioned barriers to achieve comprehensive care. We feel that a strong partnership model, based at least initially in academic tertiary care centers, will be able to initiate and to build all aspects of the program including clinical, educational, and research components. Such an integrated model will be able to provide the much needed leadership and backbone that can then successfully form a blueprint for community-based programs.

Our model is based on an integration of the academic center’s sleep medicine program (American Academy of Sleep Medicine [AASM]-accredited sleep disorders center) and its dental school to form a partnership in clinical, educational, and research activities and to include the longitudinal collection and analysis of outcome measures. We believe that the unique scope of practice for physicians and dentists can be preserved and business success achieved. Implementation of the model across the country will require a significant and novel commitment of dental schools to educate students in the field of sleep medicine and to demonstrate how the dentist can play a significant role in the success of oral appliance therapy by working closely with sleep physician colleagues.1

The Care-Under-One-Roof Concept

Since fragmentation of care and limited communication have been major stumbling blocks to comprehensive care, we propose a care-under-one-roof (“one sandbox”) concept allowing sleep physicians to be in face-to-face contact with dental sleep faculty for discussion of patient care issues pertaining to diagnosis, treatment, follow-up, and to provide the necessary dental care that must be delivered prior to rendering dental appliance treatment. We anticipate that co-treatment of patients in the same facility would raise expectations and clinical successes within the facility and improve patient care. Care-under-one-roof would effectively minimize patient travel from office to office. This would ensure that patients are treated, that patients receive follow-up care and post-treatment evaluation, and that all medical caregivers receive communication on the patient’s treatment plan. This approach has been well validated in other disease models and has been shown to improve outcomes.10,11

A care-under-one-roof model also provides a ready venue for the practitioners to effectively collaborate. For example, the current AADSM-approved protocol for oral appliance therapy for sleep disordered breathing in adults (http://www.aadsm.org/PDFs/TreatmentProtocolOAT.pdf) includes the possibility of combining positive airway pressure and oral appliances for patients who have a subtherapeutic response to oral appliances alone.12,14 However this therapy is rarely offered to patients because of the lack of a setting in which the dental (oral appliance and its titration) and medical (PAP and its titration) components can be implemented together or the lack of business plan to bill insurance companies for the combined service. The care-under-one-roof model offers a means to overcome these limitations as well as the venue for the conduct of much needed clinical research on combination therapy.

Preliminary Organizational Structure and Personnel

Any integrative and collaborative model should adhere to accreditations standards set by the AASM. Sleep disorders centers should comply with AASM practice parameters including comprehensive assessment of patients by, or under the supervision of, a board certified sleep specialist (http://www.aasmnet.org/accred_centerstandards.aspx). The Medical Director of the
center is ultimately responsible for maintaining the standards and assuring quality delivery of all aspects of care. We propose that a faculty member of the dental school who is a diplomate of the (ABDSM) serve as the dental sleep expert at the sleep disorders center. This individual would be expected to develop and streamline dental treatment and assessment while taking into consideration center-specific infrastructure and patient management procedures. However, unlike in the existing separate office model of care, the dental sleep expert would be available on a scheduled basis to consult with patients during their visits to the sleep disorders center and advise on their candidacy for oral appliance therapy. In addition, the dental sleep expert would participate in multidisciplinary staff conferences during which treatment plans for the more difficult-to-manage patients are generated (see Figure 1).

Potential candidates for oral appliance therapy would complete a battery of questionnaires and receive a standardized orofacial and dental examination within the comprehensive sleep disorders center. Impressions and records would be taken for fabrication of the dental appliance (see 2 in Figure 1). In the nearby dental facility, dental radiographs would be taken as necessary to complete the evaluation.

The patient would return to the sleep disorders center for fitting of the appliance and post-insertion instructions on its use, cleaning, and titration. For the latter, the patient would increase the extent of jaw advancement on a set schedule until his symptoms were eliminated or wear of the appliance became uncomfortable. Titration protocols can be home based, in which titration is done based on patient and family feedback. This technique can take several weeks and has a potential of resulting in incomplete treatment of OA. Because elimination of symptoms does not necessarily guarantee normalization of the apnea-hypopnea index (AHI), out-of-center sleep testing (OCST) or in-lab polysomnography may guide additional advancement of the jaw. OCST may be considered in patients for whom OCST is appropriate, as described by AASM practice parameters. The use of OCST is also recognized in the current AADSM approved protocol for oral appliance therapy for sleep disordered breathing in adults (http://www.aadsm.org).

Figure 1—Schematic diagram of the proposed care-under-one-roof model for integrating dental sleep medicine and sleep medicine within the university-based sleep disorders center.

Research components are indicated by dashed lines (see 1R and 4R).
the care-under-one-roof model (see org/PDFs/TreatmentProtocolOAT.pdf). Thus, in the proposed model the patient would be scheduled for administration of OCST by the sleep disorders center or in-lab polysomnography at the sleep disorders center, once adjustments in the appliance to eliminate the patient’s symptoms had been made. Published studies have shown that a higher proportion of patients can be treated effectively if the custom-fabricated oral appliance is adjusted during an overnight sleep study.17,20,21

Patients who respond to OAT with AHI normalized as determined during OCST or polysomnography reevaluation, would be seen for routine follow-up in the sleep center in 6 months, 12 months, and yearly intervals thereafter in accordance to recommendations of the AASM practice parameters (see 3 in Figure 1).4 On the yearly visits, the patient would be seen by the dental team and the sleep center healthcare professional, who would evaluate compliance with therapy and assure continuity of medical care.

Patients whose sleep disordered breathing could not be corrected solely with an OAT would be reevaluated for CPAP or surgical procedures (see 4 in Figure 1) or undergo CPAP titration while wearing the dental appliance (see 4R in Figure 1). Because the jaw is stabilized in a forward and upward position, the effective pressure may be less than that required without an appliance, thereby decreasing pressure-related patient complaints.13,14 Moreover, support for nasal pillows or a mask can be obtained directly from the appliance, eliminating all straps and contact with the patient’s face except for the nasal or perinasal region. There are other advantages to patient care of an integrated care-under-one-roof delivery model. There is growing interest in determining which patients are good candidates for oral appliance therapy prior to treatment. Cephalometric measurements may help predict patients who may benefit from OA.23

Alternatively, in-lab “prognostic” titration has been shown not only to produce rapid results but can also be helpful in predicting patient response.24-27 During the titration study, the teeth are engaged by upper and lower layers of impression material that can be slid apart manually or by remote control to advance the mandible. The goal is to determine if the patient’s sleep disordered breathing can be alleviated by jaw advancement and to estimate the extent of advancement required. The procedure is anticipated to be particularly important in the assessment of patients who have failed CPAP repeatedly and who have been considered poor candidates for oral appliance therapy based on other factors such as a high BMI.28 The authors are already investigating this newly validated approach to patient care and have included it as a research component for select patients in the care-under-one-roof model (see 1R in Figure 1).

Patients may also be offered a trial of jaw advancement using a less expensive boil and bite appliance, before a custom-fabricated appliance is suggested.29 We feel that prognostic sleep studies and temporary oral appliances can be successfully used to determine the efficacy of jaw advancement and acceptance by a segment of patients before ordering a more expensive permanent appliance. For example, temporary appliances are indicated for patients who are undergoing dental treatments over an extended period of time. However, custom-fabricated appliances have been shown to be more efficacious and compliance is higher.29,30

Safety and Compliance Monitoring

Safety and compliance monitoring would be conducted every 4-6 weeks after an appliance is delivered until treatment efficacy and patient adherence have been established. In addition to compliance, patient adverse effects would be documented and addressed by the attending dental sleep expert. Noncompliance (compliance being defined as ≥ 4 h use for ≥ 70% the nights) or failure due to intolerance of oral appliance therapy would trigger an alternative treatment strategy in consultation with the sleep specialist. These might include hybrid therapy, PAP therapy, or surgical intervention in select cases. A sleep specialist would manage any concomitant sleep disorders, which a patient may have to avoid overlap of visits. Cardiovascular and cognitive markers would be recorded for outcome data analysis and quality control.

Outcomes Measures

We recommend outcome measures form the backbone of the proposed model’s care of patients with obstructive sleep apnea. Outcome measures would serve as benchmarks for quality assurance and improve our understanding of the natural history of the disease with different interventions. Several outcome measures would be evaluated for quality assurance including compliance (patient-reported until reliable low-cost objective measures can be obtained), post intervention reductions in the AHI and excessive daytime sleepiness (e.g., Epworth Sleepiness Scale) and improvements in scales of neurocognitive functioning (e.g., psychomotor vigilance testing). Recently, mouth temperature-sensing compliance-monitoring chips embedded in oral appliances have been shown to be useful in recording hours per night and nights per week of therapy.31 This technology will provide oral appliance data similar to compliance monitoring of positive airway pressure therapy. Long-term follow-up and monitoring of blood pressure, cardiac and cerebrovascular events, and mortality would be undertaken, so that the benefits of oral appliance and positive airway pressure therapies can be compared. A concomitant surveillance of adverse effects (both short-term and long-term) would be documented.

Educational Activity

The integrated care-under-one-roof model provides educational opportunities at all levels consistent with the mission of the medical and dental schools of the faculty working at the sleep disorders center. The weekly multidisciplinary conferences would provide a forum for cross-training of medical and dental personnel as well as other healthcare professionals present (e.g., otorhinolaryngology and pulmonary medicine). Dental school residents (particularly those in general practice residency programs, advanced education in general dentistry programs, and orofacial pain residency programs) would be given the opportunity to rotate in the sleep disorders center to practice the dental sleep medicine skills taught at the dental school by both medical and dental faculty. Fellows at the sleep disorder center and the dental residents would present clinical cases during ground round presentations with literature reviews. It is anticipated that sleep medicine education would eventually be incorporated into the pre-doctoral M.D. and D.D.S. curricula. Opportunities would develop for continuing education of physician and dentists in private practice, as well as for sleep tech-
nologists and respiratory technicians providing CME, CDE, and CEU credits, as appropriate.

Research
The establishment of a strong and productive integrated care-under-one-roof program would naturally motivate research activities. The collection and analysis of outcome measures for oral appliance therapy from short-term efficacy to long-term compliance and impact on medical comorbidities of untreated OSA would be most vital. Clinical trials on combined oral appliance/positive airway pressure therapies are needed and would be made readily possible with a single healthcare visit. Depending on infrastructure and support, we suggest that research from outcome measures, prospective trials on combined therapies, and therapy compliance be a mission of the integrated care-under-one-roof program.

Maintaining Defined Scopes of Practice
There are specific Medical and Dental Licensing Laws and Practice Acts, which dictate the scope of practice for physicians and dentists (http://www.aasmnet.org/resources/pdf/AADSMJointOSApolicy.pdf). As per individual state law, laws only a licensed physician can make a diagnosis and treatment plan for sleep disordered breathing. Similarly, a dentist’s scope of practice includes evaluating the candidacy of patients for oral appliance therapy as well as construction and fitting of the appliances. The proposed “care-under-one-roof model” will be structured within the practice parameters established by the AASM. Updated practice parameters are currently being prepared by the AASM for publication.

Responsibilities of staff dental sleep expert:
1. Evaluate patients for dental sleep medicine therapies.
2. Discuss treatment options (mandibular advancement splints, combination MAS/PAP therapy, tongue retaining device, maxillofacial surgery, etc.).
3. Manage coexistent dental disorders, such as bruxism.
4. Counsel on dental hygiene and daily maintenance of oral appliances.
5. Follow-up patients every 4-6 weeks until treatment efficacy and patient adherence to therapy have been established.
6. Review compliance and manage potential complications or adverse effects of therapy.
7. Maintain communication with sleep physician specialist for outcome measures monitoring.
8. Assess the need for change in treatment, or repeat PSG for either re-titration or resolution of sleep disordered breathing.
9. Establish protocols at the sleep disorders center on oral device titration, technician training, consent procedure, off-hour call coverage issues.
11. Provide ongoing and routine patient follow-up care.

Business Model
Sustainability of the integrated care-under-one-roof model would depend on development of a business model that can successfully address the financial challenges faced by many dentists today who provide oral appliance therapy. Ideally, the sleep clinic administration would negotiate contracts with medical insurance companies for the dental providers in much the same way the physicians are enrolled to deliver contracted services and are credentialed as providers. The clinic office would ideally handle preauthorization and file insurance claims for the dental component of the patient’s evaluation and treatment. A single, unified electronic medical record (EMR) system would be used by all providers. Financial sustainability would be made possible, in part, by the efficiency of care delivery and the quantity of care delivered. The dental sleep expert may be able to bill for his services provided to the patient at the sleep disorders center even if seen on the same day as the sleep specialist, as services provided are different and performed by two different specialists.

The care-under-one-roof model raises legal concerns that would need to be addressed to comply with individual state and federal laws. For example, dentists in some states are bound by a “corporate practice” doctrine, which prevents non-dentists from owning any part of the dental practice. Moreover, compliance with the federal Stark laws also require that the referring physician have no financial interest in any business that provides positive airway pressure (CPAP provider) or oral appliance (dentist), as both are viewed as durable medical equipment (DME) providers by the Centers for Medicare and Medicaid Services. However, several large hospitals and institutions now have DME services and can provide integrated care-under-one-roof with appropriate safeguards. Due to these limitations, we believe that this model is best suited initially for use in an academic/institutional setting with a community-based model evolving from the experience of these centers.

Community-Based Non-Academic Model
Although the above model is proposed with academic institutions in mind, this model can be adapted for non-academic
centers. We propose that this collaboration take place in AASM-accredited sleep disorders centers. Board-certified sleep physicians at the center should form alliance with dedicated dental practitioners who have adequate training in sleep medicine and are motivated to serve this population. The dental expert should have scheduled clinic hours at the sleep center where a comprehensive dental evaluation may be performed. Dentist “chair” is a small investment which the sleep center or the dentist has to make (a refurbished chair can be obtained for around $3,000.00). The use of radiographs is essential to the treatment decision (http://www.aadsm.org/PDFS/TreatmentProtocolOAT.pdf), but these can be obtained from the patients’ general dentists. Many dentists have digital offices and therefore are able to email the radiographs upon patients’ permission. This will all be done in conjunction with a comprehensive dental exam, periodontal screening, muscle evaluation, TMJ evaluation, and review of medical history.

From a business perspective, the sleep center charges the dental sleep expert for renting space and equipment. The dental sleep expert, by his presence and expertise, determines which patients are good candidates for OA. The dentist utilizes the center’s expertise to titrate patients either by OCST or in-lab titration, and in long-term follow-up.

Oral appliances for OSA are considered durable medical equipment, so several models out in the real world can exist. Under one model, the sleep center provides DME, and the dentist is contracted to provide under the DME services of that group. This model allows the DME company to bill on behalf of the dentist for those services. Other models have the dentist with their own DME, then provide services and bill for their services. The advantage of the dentist contracting under the sleep center DME is that most of the DME companies already have insurance contracts in place to provide CPAP, another DME item. It is then easy for the contracts to be extended to oral appliances.

While the reimbursement for OA is varied, it is a covered benefit to most patients with private insurance. Medicare has also come on board in reimbursing for these appliances with fairly strict coverage and mandating delivery by a dentist.

We feel this model will not only improve patient care and comfort, but it is also financially viable and professionally satisfying.

CONCLUSION

Integrating oral appliance therapy into the delivery of care for obstructive sleep apnea syndrome has been a challenge and few effective models exist so far. It is imperative that the sleep medicine community develops a realistic and effective model of this underutilized but promising treatment modality. We believe that the best structure is to integrate dental sleep medicine with the sleep disorders program via a care-under-one-roof concept. Training, communication, education, marketing, and evaluating outcome data are vital. Such centers of excellence at academic institutions are best suited to lay this foundation. These institutional centers can provide care in their community as well as serve as a model of integrated care delivery for sleep medicine throughout the country in nonacademically based sleep centers.

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A 57-year-old woman presented with difficulty in falling asleep and occasional perceived lack of sleep for the entire night despite taking sleeping pills every night for more than ten years. Prior to then, for no obvious causes, she gradually had difficulty falling asleep at night, daytime fatigue, sleepiness, and no energy. Afterwards, the insomnia symptoms gradually worsened. She then began to be very anxious about sleep and often sought medical assistance. After seeing her first physician, she began using 0.4–0.8 mg of alprazolam with inconsistent results—sometimes she felt better, sometimes not. Since the initial prescription of alprazolam, in attempts to get a better night’s sleep, she frequently sought help from neurologists and psychiatrists, and was even hospitalized twice. This led to a variety of prescriptions including fluoxetine, paroxetine, sertraline, trazodone, mirtazapine, quetiapine, zolpidem, zopiclone, and eszopiclone. None of these medications significantly improved her sleep, and she felt that alprazolam was more helpful for her sleep than the other drugs. Therefore, she continued taking alprazolam and had gradually increased the dosage to 1.2 to 2.0 mg per night. She had also been diagnosed as having hypertension and had routinely taken antihypertensive medications for approximately six years. When we ran a symptom check for a sleep breathing disorder, we found that she had loud snoring and could truly fall asleep during the day, but did not know whether she had breathing pauses during sleep. No special findings were obtained in the routine medical examination and laboratory results. Her BMI was 23.42 kg/m², neck circumference was 36 cm, and she had a normal looking chin. Her total score on the Epworth Sleepiness Scale (ESS) was 22, which reflected her subjective severe excessive daytime sleepiness. Scores for the Hamilton depression and anxiety scales were 17 and 24, respectively, suggesting that she had had mild to moderate severity depression and anxiety.

Examination and Management at Sleep Laboratory
We arranged an overnight polysomnographic (PSG) examination followed by a multiple sleep latency test (MSLT). As shown in the top panel of Figure 1, the patient had 7.4 h of total sleep, but had 367 obstructive apneas and 162 episodes and hypopneas, central, and mixed apnea/hypopnea. Her apnea/hypopnea index (AHI) was 72/h. There were marked recurrent reductions of oxygen saturation throughout the full night recording (see Figure 1). She had N2 time over 60% and no slow wave sleep (N3). However, when we asked her for her subjective sleep time after the examination, she said that she had no sleep during the entire night because she did not take alprazolam. The mean sleep latency on MSLT was only 2.3 min (Figure 2), and she also had one episode of REM during her third nap. This indicated that she had objective severe excessive daytime sleepiness.

A few days later, the patient was scheduled to receive auto nasal continuous positive airway pressure (CPAP) titration followed by MSLT. As shown in the center panel of Figure 1, she had 9.1 h of total sleep, and AHI was successfully reduced to 7/h. N1 and N2 time and number of awakenings and brief arousals were markedly reduced, whereas N3 and REM time were increased considerably. Associated with the improvement in overnight sleep, the mean sleep latency on MSLT the day following CPAP titration increased from 2.3 min to 9.9 min (Figure 2). When we asked her subjective feelings regarding overnight sleep and daytime functioning, she said that she had not had such wonderful sleep over the past ten years and that her energy during the day appeared be similar to that she had twenty years ago. She immediately began to receive CPAP therapy (ResMed, S8 Auto Set Spirit). Since that time, she has had much improved subjective overnight sleep and completely discontinued taking alprazolam after a week of CPAP treatment.

Nine months after she began to receive CPAP therapy, she was recalled for a follow-up evaluation. The memory card of the CPAP machine indicated that average usage was from 8 to 9 h per night, and that the average AHI was 6.1/h. As shown in the bottom panel of Figure 1, during CPAP pressure titration at this time, AHI was further reduced to 1.5/h; total sleep time, N3, and REM time were considerably reduced; and N2 time was increased more than twofold, compared to during the first CPAP pressure titration. The perception of sleep (calculated as
The mean sleep latency on the MSLT was also prolonged to 14.6 min (Figure 2). The scores on ESS and Hamilton depression and anxiety scales were also back in normal ranges. She also unexpectedly reported that she had stopped taking antihypertensive medications a few months after she began CPAP, due to her blood pressure normalizing.

**Figure 2**—Multiple sleep latency test following CPAP pressure titration nights

[subjective TST / objective TST * 100] was 102%. The mean sleep latency on the MSLT was also prolonged to 14.6 min (Figure 2). The scores on ESS and Hamilton depression and anxiety scales were also back in normal ranges. She also unexpectedly reported that she had stopped taking antihypertensive medications a few months after she began CPAP, due to her blood pressure normalizing.

**QUESTION: What is your diagnosis?**
DISCUSSION

There is little doubt that the patient had a severe obstructive sleep apnea (OSA)-induced sleep perception problem presenting as a subjective type of insomnia. The fact that she had little to no perceived sleep appeared to be related to poor quality of sleep (N1, 22%; N2, 61%; and no N3) induced by very frequent apnea events. The cause and effect relationship between severe sleep apnea and insomnia was clearly reflected in the considerable improvement in both subjective and objective overnight sleep after CPAP treatment. The nine month follow-up evaluation further indicated a cause and effect relationship.

OSA-related insomnia was first reported in the early 1970s, and recent studies suggest that possibly 25% to 50% of patients have both OSA and insomnia. However, a high percentage of these patients have mild to moderate severity of apnea and do not fully comply with CPAP therapy; therefore, they do not receive much benefit with respect to perceived sleep. Due to the poor compliance with CPAP therapy, current opinion holds that it is very challenging to treat patients with OSA and insomnia. But, the successful diagnosis and treatment in this case illustrated that, at least for some patients, particularly for severe apnea related insomnia, CPAP therapy may produce a dramatic improvement in both subjective and objective overnight sleep, and in both subjective and objective daytime functioning.

The DSM-IV states that “most individuals with breathing-related sleep disorder have obstructive apnea that can be distinguished from primary insomnia by a history of loud snoring, breathing pauses during sleep and excessive daytime sleepiness.” This patient had at least two symptoms (snoring and daytime sleepiness); however, she mainly complained of severe insomnia and was never aware that her snoring might be associated with her insomnia. Thus, she never mentioned severe snoring to any physicians during her clinic visits. No family member witnessed her apnea. Most importantly, no physicians considered possible OSA and did not run any symptom check for OSA, even though she was hospitalized twice. This misdiagnosis led to her using 1.2-2.0 mg of alprazolam per night, which may have considerably aggravated her apnea and daytime sleepiness. In particular, since she had a history of hypertension, the misdiagnosis and the continual use of alprazolam could increase her life risk.

The fact that a variety of antidepressants were persistently prescribed over a long period, even with little improvement for her subjective sleep, suggests that neurologists and psychiatrists normally pay great attention to depression and anxiety in insomnia patients, but lack adequate awareness of OSA-related insomnia. This may be particularly true for countries such as China, where the training system for sleep disorder specialists has not been well established. Even in the United States, which has the most well-developed training system in sleep disorders, restrictions for reimbursement from medical health insurance companies, may make physicians reluctant to call for an overnight study to detect potential OSA-related insomnia.

On follow-up, we unexpectedly learned that her blood pressure was normalized after a few months of CPAP treatment, although she had taken antihypertensive medications for six years. Though benzodiazepines may not worsen mild to moderate of OSA, their influence in severe OSA has not been experimentally documented. We believe that both the immediately successful treatment of her sleep breathing issue and the successful discontinuation of the relatively high dosage of alprazolam could have contributed to the normalization of her blood pressure.

CLINICAL PEARLS

1. Physicians may need to routinely run a brief symptom check in their insomnia patients to distinguish possible OSA patients, at least for the symptoms mentioned in the DSM-IV, including snoring, witnessed breathing pauses during sleep, and excessive daytime sleepiness.
2. Most individuals with OSA and insomnia comorbidities may not fully comply with CPAP therapy. But, at least for some severe apnea related insomnia, CPAP therapy may produce a dramatic improvement and may lead to discontinuation of sleeping pills.
3. In patients with hypertension and OSA-induced insomnia, reduction or normalization of blood pressure may occur after CPAP treatment, even in patients who have taken antihypertensive medications over a long period.

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