JCSM Journal of Clinical Sleep Medicine

Volume 10, Number 1
January 15, 2014
Pages 1-116

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SCOPE
JCSM Journal of Clinical Sleep Medicine focuses on clinical sleep medicine. Its emphasis is publication of papers with direct applicability and/or relevance to the clinical practice of sleep medicine. This includes, clinical trials, clinical reviews, clinical commentary and debate, medical economic/practice perspectives, case series and novel/interesting case reports. In addition, the journal will publish proceedings from conferences, workshops and symposia sponsored by the American Academy of Sleep Medicine or other organizations related to improving the practice of sleep medicine.

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The American Academy of Sleep Medicine

American Academy of Sleep Medicine

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**Statement of Educational Purpose/Overall Education Objectives**
*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.

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*Journal of Clinical Sleep Medicine, Vol. 10, No. 1, 2014*
This issue of the Journal marks the beginning of its 10th year of publication. The Journal was “born” on March 19-20, 2004 at a meeting of the Academy’s board of directors to address a concern regarding insufficient publishing venues for clinical research in the field of sleep medicine. At that time, there were six journals focused on sleep, but one was a review journal, another was devoted to behavioral aspects of sleep medicine and two were perceived to be more basic research oriented. Thus, the Journal was launched in 2005 with the mandate to publish excellent science, but to be clinically relevant to sleep practitioners. As the founding Editor-in-Chief, I believe that this goal has been achieved.

The Journal has grown since those early days. The 1st issue was a blueprint for future issues. In addition to original clinical research papers and case reports, there was a Pro/Con Debate,1,2 a Sleep Medicine Pearl,3 a Board Review Cases,4,5 a Review Article,6 and two Special Articles.7,8 The Special Articles on the history of sleep medicine and a summary of the proceedings of a National Institutes of Health conference on health and quality of life with a forward by the Surgeon General of the United States were especially appropriate for the launch of a new journal focused on clinical sleep medicine.7,8 These sections of the Journal continue as they remain relevant today. Since that inaugural issue, the Journal has increased its publishing frequency from quarterly to monthly. It now processes over 400 submissions per year with the number continually increasing. They originate from all the permanently populated continents on earth. Although not a priority of the Journal, its initial impact factor was 3.232 in 2011, a highly respectable level. The number of indexed papers in PubMed is now approaching 1,000, and citations to articles published in the Journal exceed 2,200. Some papers have received considerable attention in the lay press.3,10 Thus, by any objective measure, the Journal has been quite successful in accomplishing its mission. However, more gratifying has been the verbal feedback from Academy members and other readers who have indicated that the Journal fills a void in their need for proceedings of ongoing medical education, and being informed regarding advances in clinical care and changes in the practice of sleep medicine.

With the advent of electronic publishing, smart phones and tablet computers the Journal has evolved from a traditional print venue to a multi-media platform. Starting in 2012, it became an online only publication with the option of print on demand and Kindle compatible issues for an additional fee. The Journal also is available in an easy to read electronic “magazine format”. For those who would rather have a summary of the editor’s pick of the most interesting papers, a monthly podcast is available for download. The Journal also offers the capability of incorporating videos and other recordings as an optional component of a published paper.

Over the past decade, the appearance of the Journal also has changed. Color schemes, tables and fonting have evolved to make the pages more visually appealing. In addition, a “Brief Summary” was added to each original research paper so that the reader could assimilate the essence of an article in less than a minute in order to determine whether it provoked his/her interest to read more. The “Brief Summary” is available in the electronic table of contents emailed to Academy members and subscribers with each issue as well.

What does the future hold for the Journal? Probably the greatest challenge is competition from other publications for excellent content in the field of clinical sleep medicine. As previously noted, 10 years ago, there were 6 sleep journals. Now, by my count there are 15, and perhaps others that I have overlooked. Virtually all of the new journals are “fee to publish” open access publications. Is there sufficient new clinical information to justify all of these new journals? Admittedly, the amount of new scientific information is growing rapidly, but it seems unlikely that it has expanded so rapidly that 9 new sleep journals are required. Nevertheless, it will be important that the Journal continue to attract high quality submissions to maintain its leadership in the field. The second challenge of the future will be to continue to evolve the Journal’s publication model to be relevant for the world of smartphones, tablets and social media. Information is now being disseminated in smaller “chunks” to facilitate learning. Determining how the Journal will accomplish this in the world of Twitter and Facebook remains to be determined. In reality, there are no crystal balls, but hopefully in the next decade, the Journal will remain nimble in the face of the ever evolving medical publishing landscape and the advances in the practice of clinical sleep medicine.

REFERENCES


CITATION

Periodic limb movements during sleep (PLMS) are associated with increased sympathetic nervous activity which may increase individual susceptibility to cardiac arrhythmia. The purpose of this study was to determine if cardiac arrhythmia was more common in individuals with PLMS.

**Study Impact:** The current finding that PLMS is associated with cardiac arrhythmia in subsets of older men with structural heart disease and those not taking certain anti-arrhythmic medications suggests that men with PLMS may have increased susceptibility to cardiac arrhythmia. Clinicians should be aware of this potential association between PLMS and cardiac arrhythmia, but at the present time additional investigation is needed in this area to make more concrete clinical inferences.
PLMS do not provoke arrhythmia but rather both of these entities arise from autonomic abnormalities.

To address whether PLMS are associated with cardiac arrhythmias, we analyzed data from the Outcomes of Sleep Disorders in Older Men Study (MrOS Sleep Study). The MrOS Sleep cohort is a large population-based sample of older men designed to examine multiple sleep related exposures and their potential association with cardiovascular outcomes. We hypothesized that the frequency of PLMS with and without arousal would be associated with increased rates of nocturnal ventricular and atrial arrhythmias and conduction delays. In addition, we explored whether the use of medications with anti-arrhythmic properties modified any relationship between PLMS and arrhythmias and examined data from men with prior myocardial infarction (MI) or CHF to determine if they, in particular, had increased associations of PLMS to cardiac rhythm disturbances.

**METHODS**

**Participants**

The MrOS Sleep Study was conducted between December 2003 and March 2005 and included a comprehensive sleep assessment in 3,135 elderly male participants of the parent Osteoporotic Fractures in Men (MrOS) Study cohort. The study involved 6 clinical centers (Birmingham, AL Minneapolis, MN; Palo Alto, CA; Pittsburgh, PA; Portland, OR; and San Diego, CA), a coordinating center (San Francisco Coordinating Center) and a Sleep Reading Center (Case Western Reserve University, Cleveland, OH). Study design and methods of recruitment have been previously published. Of the 3,135 men from the MrOS Sleep Study cohort, 179 refused polysomnography and an additional 45 had unusable data, resulting in 2,911 subjects who underwent home polysomnography. Men with missing polysomnographic data were more likely to be of minority race (p < 0.001), but were similar for all other characteristics examined. In addition, 118 men with pacemaker implantation were excluded from the analysis, leaving 2,793 men in the analytic sample. Protocols were approved by the institutional review board at each site, and all participants provided written informed consent.

**Polysomnography**

Unattended in-home polysomnography (PSG; Safiro, Compumedics, Inc., Melbourne, Australia) was conducted, with a recording montage that included: C1/A1 and C2/A2, electroencephalography, bilateral electrooculography, submental electromyography, thoracic and abdominal respiratory inductance plethysmography, naso-orbital thermistry, nasal pressure transduction, finger pulse oximetry, lead I EKG (sampled at 250 Hz) and bilateral anterior tibialis piezoelectric movement sensors. Home visits were performed by centrally-trained staff using procedures previously described. Data were scored by certified research polysomnologists at the central Sleep Reading Center using standardized criteria modified for use in large cohort studies, with established high levels of reliability. Apneas were identified by the near absence of airflow lasting ≥ 10 sec, while hypopneas were identified by ≥ 30% reduction of breathing amplitude lasting ≥ 10 sec as assessed by the summed abdominal and thoracic respiratory inductance signal or, when unclear, by the other respiratory signals. For this analysis, only apneas and hypopneas linked to ≥ 3% oxygen desaturation were included in the apnea-hypopnea index (AHI; i.e., total number of apneas and hypopneas per hour of sleep). Arousals were scored according to published guidelines and summarized as the total number of arousals per hour of sleep (arousal index).

Periodic limb movements were scored to be consistent with the AASM guidelines active at the time sleep studies in this cohort began. Individual leg movements were scored if there was a clear amplitude increase from baseline and the duration of movement was ≥ 0.5 sec and ≤ 5.0 seconds. To be considered periodic and for a final determination of PLMS, ≥ 4 movements needed to occur in succession no less and no more than 5 and 90 sec apart, respectively, according to the AASM criteria at the time of scoring. Leg movements following respiratory events were excluded unless they were part of a 4 (or more) movement cluster with ≥ 2 movements occurring independently of respiratory events. The periodic limb movement index (PLMI) was computed as the total number of periodic leg movements per hour of sleep and the periodic limb movement arousal index (PLMAI) was calculated as the total number of periodic leg movements per hour of sleep in which EEG arousal occurred within 3 sec of movement termination. An in-laboratory validation study conducted in 51 subjects in whom the PLMI was assessed concurrently in a blinded fashion using piezoelectric leg sensors scored using the original AASM criteria and using leg electromyography scored using the 2007 AASM criteria showed a correlation of r = 0.81. PLMI and PLMAI were examined as continuous variables in models.

**Outcome Data**

As part of the polysomnographic montage, single lead (Lead I) electrocardiography (EKG) was used to monitor heart rate and rhythm. EKG-specific software (Somte; Compumedics Ltd., Abbotsford, Victoria, Australia) was used by a trained scorer to manually annotate the EKG signals while blinded to leg movement and all other signals. Arrhythmia of uncertain category was arbitrated by a medical physician (RM). A physician also confirmed atrial fibrillation/flutter (AF) and complex ventricular ectopy (CVE) when identified by the polysomnologist. Arrhythmia outcomes identified by polysomnography were defined as described previously.

Ventricular arrhythmias annotated and summarized were: premature ventricular contractions (PVCs) ≥ 5/h, non-sustained ventricular tachycardia (NSVT: ≥ 3 consecutive ventricular ectopic beats with a mean rate of ≥100 beats/min) and complex ventricular ectopy defined as the occurrence of bigeminy, trigeminy, or quadrimeny or NSVT (CVE). Atrial arrhythmias were: premature atrial contractions (PACs) occurring ≥ 5 times per hour, AF (paroxysmal or continuous); supraventricular tachycardia (SVT). Conduction delay arrhythmias were: sinus pause with a duration ≥ 3 sec; first-degree atrioventricular (AV) block; second-degree AV block; and intraventricular conduction delay. For AV block identification, the PR interval was manually determined with the use of software-based calipers.
were performed when interactions were $p < 0.10$.

Categories using $\chi^2$ tests for categorical variables, ANOVA for normally distributed continuous variables, and Kruskal-Wallis tests for continuous variables with skewed distributions. Proportions of all outcomes by PLMI and PLMAI category were calculated, and a Chochran-Armitage test for trend was performed to examine an unadjusted linear trend across the categories.

Logistic regression was used to assess the association between PLMI or PLMAI and arrhythmia binary outcomes defined as occurrences (yes; no) of: NSVT, CVE, AF, supraventricular tachycardia, sinus pause, and first-degree AV block or of PVCs $\geq 5$/h and PACs $\geq 5$/h. Model results are presented as odds ratios (OR) with 95% confidence intervals (CI). Models were minimally adjusted for clinic, age, race, and BMI. These models were then further adjusted for smoking, alcohol use, physical activity, and AHI. The full multivariable model was further adjusted by covariates that could be on the intermediate pathway (prevalent hypertension, history of CHD, history of congestive heart failure [CHF], history of diabetes and use of $\beta$-blockers or calcium channel blockers).

Interactions were explored between PLMI or PLMAI and exposures that may modify arrhythmia susceptibility: (1) Use of $\beta$-adrenergic or calcium channel blocker medications due to a reduction in cardiac ectopy associated with these medications, and (2) Presence of structural heart disease as suggested by CHF or MI because of underlying increased susceptibility to sympathoexcitation. Stratifications by these parameters were performed when interactions were $p < 0.10$.

All significance levels reported were two-sided. Analyses were conducted using SAS version 9.2 (SAS Institute Inc, Cary, NC).

### RESULTS

#### Overall Characteristics

The sample of 2,793 men was predominantly Caucasian, with a mean age of 76.2 ± 5.5 years. Table 1 shows other baseline demographic characteristics of the overall cohort and the cohort stratified by PLMI and PLMAI categories. Almost one half of the sample had a PLMI $\geq 30$ (44.7%; $n = 1,248$). Having higher levels of PLMI was associated with older age, Caucasian race, coronary heart disease, as well as with a higher arousal index and lower AHI. Having higher levels of PLMAI was observed in almost 27% ($n = 750$) of the sample. Increasing PLMAI category was associated with older age, Caucasian race, coronary heart disease, higher AHI and arousal index and the use of $\beta$-blocker medications. Neither PLMI nor PLMAI were associated with diabetes, prevalent hypertension, BMI, smoking status, alcohol intake, or CHF.

#### Unadjusted Associations of Arrhythmia with PLMI and PLMA

Table 2 shows the distributions of the different arrhythmia types in the overall cohort and according to PLMI and PLMAI category. Of the ventricular arrhythmias, ventricular ectopy identified as PVCs at a rate $\geq 5$/h, was most common, observed in almost 42% of men. Complex ventricular arrhythmia was observed in 37.3% of men, while 3.2% were observed to have non-sustained ventricular tachycardia. Of the atrial arrhythmias, 60.0% had $\geq 5$ PACs/h, while 23.0% had supraventricular tachycardia and 4.8% had paroxysms or sustained periods of AF. Of the conduction delay arrhythmias, sinus pauses were observed in 13.3% of men, with periods of first and second degree AV block observed in 40.1% and 2.2% of men, respectively. Modest but significant increases in the frequencies of PVCs ($\geq 5$/h), NSVT, CVE, PACs ($\geq 5$/h), and AF were observed with increasing PLMAI category. In contrast, no association between PLMI category and conduction delays was observed. For increasing PLMAI category, significant increases were seen for frequencies of NSVT, CVE, PACs ($\geq 5$/h), sinus pause, and first degree AV block.

#### Adjusted Associations: Ventricular Arrhythmias

For ventricular arrhythmias including premature ventricular contractions, non-sustained ventricular tachycardia and complex ventricular ectopy, no significant associations were seen with PLMI or PLMAI after adjustment for multiple covariates (Table 3). For the outcome of NSVT, there were interactions between use of calcium channel/$\beta$-adrenergic blocking medication and both PLMI ($p = 0.08$) and PLMAI ($p < 0.01$). When considering the subset of men without $\beta$-adrenergic/calcium channel blocking medication usage ($n = 1,763$), after adjusting for clinic site, age, race, BMI, smoking, alcohol use, physical activity, AHI, prevalent hypertension, history of coronary heart disease, congestive heart failure, and diabetes, NSVT was associated with both PLMI (odds ratio of 1.30 per SD increase; 95% CI 1.00, 1.68) and PLMAI (odds ratio of 1.29 per SD increase; 95% CI 1.03, 1.62) (Figure 1).
Table 1—Distributions of participant characteristics by PLMI

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<th>Participant Characteristics</th>
<th>Overall Cohort (n = 2,793)</th>
<th>PLMI &lt; 5 (n = 821)</th>
<th>5 ≤ PLMI &lt; 30 (n = 724)</th>
<th>PLMI ≥ 30 (n = 1,248)</th>
<th>PLMAI &lt; 1 (n = 1,122)</th>
<th>1 ≤ PLMAI &lt; 5 (n = 921)</th>
<th>PLMAI ≥ 5 (n = 750)</th>
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<td>Age</td>
<td>76.2 ± 5.5</td>
<td>75.4 ± 5.1</td>
<td>75.9 ± 5.4</td>
<td>76.9 ± 5.6†</td>
<td>75.6 ± 5.2</td>
<td>76.1 ± 5.4</td>
<td>77.4 ± 5.7†</td>
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<tr>
<td>Caucasian race, n (%)</td>
<td>2,529 (90.6)</td>
<td>707 (66.1)</td>
<td>642 (88.7)</td>
<td>1,180 (94.6)‡</td>
<td>968 (86.3)</td>
<td>842 (91.4)</td>
<td>721 (95.9)†</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.2 ± 3.8</td>
<td>27.2 ± 3.9</td>
<td>27.2 ± 4.0</td>
<td>27.3 ± 3.7</td>
<td>27.2 ± 3.9</td>
<td>27.2 ± 3.7</td>
<td>27.3 ± 3.8</td>
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<td>Apnea-hypopnea index</td>
<td>17.0 ± 15.1</td>
<td>18.0 ± 15.3</td>
<td>16.5 ± 15.0</td>
<td>16.5 ± 15.1*</td>
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| Table 2—Distributions of cardiac arrhythmias by categories of periodic limb movements

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<td>≥ 5 premature ventricular contractions/h</td>
<td>1,153 (41.6)</td>
<td>323 (39.5)</td>
<td>279 (39.1)</td>
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<td>445 (40.1)</td>
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<td>Non-sustained ventricular tachycardia</td>
<td>88 (3.2)</td>
<td>21 (2.6)</td>
<td>16 (2.2)</td>
<td>51 (4.1)*</td>
<td>28 (2.5)</td>
<td>29 (3.2)</td>
<td>31 (4.1)*</td>
</tr>
<tr>
<td>Complex ventricular ectopy</td>
<td>1,043 (37.3)</td>
<td>283 (34.5)</td>
<td>265 (36.6)</td>
<td>495 (39.7)*</td>
<td>388 (34.6)</td>
<td>359 (39.0)</td>
<td>296 (39.5)*</td>
</tr>
<tr>
<td>Atrial arrhythmias</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 5 premature atrial contractions/h</td>
<td>1,664 (60.0)</td>
<td>473 (57.9)</td>
<td>397 (55.7)</td>
<td>794 (63.8)*</td>
<td>649 (58.4)</td>
<td>526 (57.6)</td>
<td>489 (65.2)*</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>134 (4.8)</td>
<td>31 (3.8)</td>
<td>30 (4.1)</td>
<td>73 (5.9)*</td>
<td>45 (4.0)</td>
<td>47 (5.1)</td>
<td>42 (5.6)</td>
</tr>
<tr>
<td>Supraventricular tachycardia</td>
<td>645 (23.1)</td>
<td>201 (24.5)</td>
<td>156 (21.6)</td>
<td>288 (23.1)</td>
<td>205 (22.3)</td>
<td>172 (22.9)</td>
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<tr>
<td>Conduction delay arrhythmias</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sinus pause (≥ 3 sec)</td>
<td>372 (13.3)</td>
<td>99 (12.1)</td>
<td>89 (12.3)</td>
<td>184 (14.7)</td>
<td>126 (11.1)</td>
<td>137 (14.9)</td>
<td>111 (14.8)*</td>
</tr>
<tr>
<td>First degree atroventricular block</td>
<td>1,120 (40.1)</td>
<td>320 (39.0)</td>
<td>285 (39.4)</td>
<td>515 (41.3)</td>
<td>434 (38.7)</td>
<td>348 (37.8)</td>
<td>338 (45.1)*</td>
</tr>
<tr>
<td>Second degree atrioventricular block Type 1</td>
<td>55 (2.0)</td>
<td>12 (1.5)</td>
<td>12 (1.7)</td>
<td>31 (2.5)</td>
<td>19 (1.7)</td>
<td>17 (1.9)</td>
<td>19 (2.5)</td>
</tr>
<tr>
<td>Second degree atrioventricular block Type 2</td>
<td>6 (0.2)</td>
<td>2 (0.2)</td>
<td>2 (0.3)</td>
<td>2 (0.2)</td>
<td>4 (0.4)</td>
<td>1 (0.1)</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>Intraventricular conduction delay</td>
<td>134 (4.8)</td>
<td>42 (5.1)</td>
<td>32 (4.4)</td>
<td>60 (4.8)</td>
<td>60 (5.4)</td>
<td>39 (4.3)</td>
<td>35 (4.7)</td>
</tr>
</tbody>
</table>

Data shown as mean ± SD unless specified. *p-values for continuous variables are from an ANOVA for normally distributed variables, a Kruskal-Wallis test for skewed data. p-values for categorical data are from a χ² test for homogeneity. **Coronary heart disease includes self report of a prior diagnosis of myocardial infarction, angina, bypass surgery, or angioplasty. BMI, body mass index; ChBlk, channel blocker; PASE, Physical Activity Scale for the Elderly; PLMAI, periodic limb movement arousal index; PLMI, periodic limb movement index.

Adjusted Associations: Atrial Arrhythmias
Among the atrial arrhythmias including premature atrial contractions, atrial fibrillation and supraventricular tachycardia, no significant associations were seen with PLMI or PLMAI after adjustment for multiple covariates (Table 3). For the outcome of AF, there were significant interactions between history of CHF or MI and both PLMI (p = 0.03) and PLMAI (p = 0.01); consequently stratification of the cohort by cardiac history was conducted. Among 532 men with CHF or myocardial infarction, after full adjustment there was a suggestion of association with AF and PLMI (OR = 1.29, 95% CI 0.96, 1.73 per SD increase; p = 0.09) and PLMAI (OR = 1.21, 95%
CI 0.94, 1.57 per SD increase; p = 0.14), although results did not reach statistical significance (Figure 2).

**Adjusted Analyses: Conduction Delay Arrhythmias**

Among the conduction delay arrhythmias, first degree AV block was associated with PLMAI in minimally and fully adjusted models such that for every SD increase in PLMAI, the odds of having first-degree AV block increased by 12% (OR 1.12, 95% CI 1.03, 1.21 per SD increase; Table 3). This association became statistically nonsignificant when subjects taking calcium channel or β-adrenergic blocking medication were excluded. For sinus pause arrhythmia, neither PLMI nor PLMAI was significantly associated with increased risk after minimal or full multivariable adjustment. There was a significant interaction between history of CHF or MI and PLMAI (p = 0.02). In the subset of men with CHF or MI, increases in PLMAI were associated with increasing odds of having sinus pauses (OR = 1.27, 95% CI 1.03, 1.58 per SD increase) after full multivariable adjustment.

**DISCUSSION**

In this community sample of older men, PLMS frequency with and without arousal was not associated with ventricular, atrial or conduction delay cardiac arrhythmia after considering a broad set of potential confounders. Because of the potential role of sympathetic hyperactivity on arrhythmia propensity, we explored interactions between PLMS with markers of both structural heart disease and use of calcium channel or β-adrenergic blocking medication. Among men without calcium channel/β-adrenergic medication usage, incremental increases in the PLMI or PLMAI were associated with a significantly increased odds ratio for NSVT. Among men with a history of CHF or prior MI, incremental increases in PLMI or PLMAI also were associated with increases in the odds of having AF, although the results only approached statistical significance. These findings, although based on subgroup analyses, suggest that PLMS are associated with AF among men with underlying structural heart disease and NSVT among men not using calcium channel or β-blocker medications. Overall, these findings are not consistent with association between PLMS and cardiac arrhythmia in all older men but there may be subsets of men, particularly those with structural heart disease and not on calcium channel or β-adrenergic medication, in which cardiac arrhythmia does seem to associate with PLMS.

In general, a normal cardiac rhythm is maintained by a tightly regulated balance of sympathetic and vagal tone. Ventricular arrhythmia is associated with increased sympathetic activity. Atrial arrhythmia and in particular atrial fibrillation may be triggered by vagal activation, although sympathetic
hyperactivity may be involved when there is structural heart disease. Both sympathetic and parasympathetic nervous activity are likely hyperactive in patients with PLMS. Typically, heart rate begins to accelerate 2-3 cardiac cycles before a PLM, peaks 4-5 cycles following a PLM, and falls below pre-association with AF and PLMI (OR = 1.29, 95% CI 0.96, 1.73 per SD increase; p = 0.09) and PLMAI (OR = 1.21, 95% CI 0.94, 1.57 per SD increase; p = 0.14), although results did not reach statistical significance. Adjusted for clinic site, age, race, BMI, smoking, alcohol use, physical activity, AHI, prevalent hypertension, history of coronary heart disease, history of diabetes, history of congestive heart failure. \(p\)-value < 0.05 NSVT, non-sustained ventricular tachycardia; OR, odds ratio; PLMAI, periodic limb movement arousal index; PLMI, periodic limb movement index; SD, standard deviation.

In subjects not taking β-adrenergic or calcium channel blocking medications, there was significantly increased odds of NSVT associated with PLMI (OR 1.30 per SD increase; 95% CI 1.00, 1.68) and PLMAI (OR 1.29 per SD increase; 95% CI 1.03, 1.62). Adjusted for clinic site, age, race, BMI, smoking, alcohol use, physical activity, AHI, prevalent hypertension, history of coronary heart disease, history of diabetes, history of congestive heart failure. \(p\)-interaction = 0.08

For those subjects with structural heart disease, CHF or MI, there was a suggestion of an association with AF and PLMI (OR = 1.29, 95% CI 0.96, 1.73 per SD increase; \(p\) = 0.09) and PLMAI (OR = 1.21, 95% CI 0.94, 1.57 per SD increase; \(p\) = 0.14), although results did not reach statistical significance. Adjusted for clinic site, age, race, BMI, smoking, alcohol use, physical activity, AHI, prevalent hypertension, history of coronary heart disease, history of diabetes, and β-blocker or calcium channel blocker use. CHF, congestive heart failure; OR, odds ratio; MI, myocardial infarction; PLMAI, periodic limb movement arousal index; PLMI, periodic limb movement index.

As the association of PLMS and arrhythmia was conducted on cross-sectional data, there is no information regarding directionality. It is tempting to assert that PLMS confers risk for arrhythmia and still certainly possible, but it is also conceivable that arrhythmia confers risk for PLMS or that both arrhythmia and PLMS arise from derangement in a similar system, like the autonomic nervous system. Justification for the first scenario is provided above. The middle scenario would likely make PLMS little more than a marker for cardiac disease. The last assumption that PLMS and arrhythmia arise from a similar abnormality is a very real possibility. It is clear that autonomic dysfunction in both sympathetic and parasympathetic arms of the nervous system increases risk for cardiac arrhythmia. The sympathetic nervous system extends from the thoracic to the lumbar spinal cord, while the parasympathetic system lies within the brainstem and sacral spinal cord. PLMS are also likely to arise from a spinal generator, and hyperexcitability within these spinal localizations could certainly result in abnormal limb movements as has been posited by previous investigators. 26-29

Sleep disordered breathing is an important potential confounding factor to discuss as it relates to PLMS and is an independent risk factor for cardiac arrhythmia. 26-30 Although the relationship between PLMS and sleep disordered breathing is not clear, PLMS is common among patients with obstructive sleep apnea. 31 Furthermore, increased upper airway resistance.
has been shown to coincide with PLMS.32 In our study, the apnea-hypopnea index was included in models as a covariate to control for potential confounding related to sleep apnea. If, however, there are features related to sleep disordered breathing such as increased airway resistance not reflected in the AHI, then such a statistical adjustment may not completely account for potential confounding. Unfortunately, analyses of participants with low AHI to further explore potential confounding by sleep disordered breathing could not be carried out secondary to low arrhythmia event rates in this subset of men.

Strengths of the current study include analysis of a large community-dwelling sample of elderly men, not chosen according to predilection for PLMS or cardiac disease, allowing generalizability to other samples of older men. Data were collected and scored using highly standardized criteria with scorers blinded to PLMS status. Adjustment for multiple potential confounders including cardiovascular risk factors and sleep related variables allowed for careful consideration of potential confounders and interactions. Limitations of the study include the cross-sectional nature of the study and the absence of multiple-day Holter monitoring data to fully describe patterns of cardiac arrhythmias. Piezoelectric sensors and not the standard anterior tibialis electromyography were used to measure PLMS. Finally, the most significant findings were observed in secondary analyses of groups identified to be potentially subject to different levels of susceptibility to altered sympathovagal balance. Although such findings could be spurious, they represent analyses derived from a priori hypotheses that are well supported by the known clinical and physiological associations between sympathetic nervous system activity and cardiac electrical activity and are internally consistent.

In summary, PLMS are not associated with cardiac arrhythmia in a general cohort of older men. PLMS are associated with arrhythmia in subsets of older men otherwise vulnerable to the cardiac electrical instability; i.e., those with underlying structural heart disease and those not using calcium channel/β-blocking medication. Although a causal role for PLMS in the pathogenesis of arrhythmias requires prospective and/or intervention studies, these results suggest that patients with underlying heart disease or not taking calcium channel/β-blocking medication may have increased rates of cardiac arrhythmias when PLMS are present.

REFERENCES


ACKNOWLEDGMENTS

Investigators in the Outcomes of Sleep Disorders in Older Men study (MoS Sleep): Coordinating Center (California Pacific Medical Center Research Institute and University of California, San Francisco): K.L. Stone (Principal Investigator...
Submitted for publication June, 2013
Submitted in final revised form September, 2013
Accepted for publication September, 2013

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DISCLOSURE STATEMENT

This was not an industry supported study. Funding Sources: The Osteoporotic Fractures in Men (MrOS) Study is supported by National Institutes of Health funding. The following institutes provide support: the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), the National Institute on Aging (NIA), the National Center for Research Resources (NCRR), and NIH Roadmap for Medical Research under the following grant numbers: U01 AR45580, U01 AR45614, U01 AR45632, U01 AR45647, U01 AR45654, U01 AR45583, U01 AG18197, U01 AG027810 and UL1 RR024140. The National Heart, Lung, and Blood Institute (NHLBI) provides funding for the MrOS Sleep ancillary study “Outcomes of Sleep Disorders in Older Men” under the following grant numbers: R01 HL071194, R01 HL070848, R01 HL070847, R01 HL070842, R01 HL070841, R01 HL070837, R01 HL070838, R01 HL070839. Dr. Mehra also receives additional funding from the Association of Subspecialty Professors (ASP)-CHEST Foundation Geriatrics Development T. Franklin Williams Research Award. Dr. Mehra serves on the medical advisory board for CareCore and is funded by the NIH: NHLBI R01 HL 103943, NHLBI HL101417-01 and R21 HL1032226. Dr. Ancoli-Israel serves on the scientific advisory board for Astra Zeneca, Ferring Pharmaceuticals Inc., GlaxoSmithKline, Hypnocore, Johnson & Johnson, Merck, NeuroVigil, Inc., Pfizer, Philips, Purdue Pharma LP and Sanofi-Aventis and is funded by the NIH: NIA AG08415. Dr. Redline has received a grant from the Resmed Foundation; her institution has received equipment for use in NIH funded studies and is supported by multiple NIH grants. The other authors have indicated no financial conflicts of interest.
Periodic Limb Movements Are Associated with Vasomotor Symptoms

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Study Objectives: Periodic limb movements (PLMs) are characterized by involuntary movements of the lower extremity during sleep. The etiology of PLM has been suggested to involve the dopaminergic system which, in turn, can be modulated by estrogen. It is currently unknown whether PLMs are associated with the menopausal transition and/or concomitant vasomotor symptoms. The aim of the present study was to examine if objectively diagnosed PLMs (with and without arousals) are more common in postmenopausal women or in women with vasomotor symptoms. A secondary aim was to analyze the influence of PLMs on self-reported HRQoL.

Methods: A community-based sample of 348 women underwent full-night polysomnography. PLMs (index > 15) and associated arousals (PLM arousal index > 5) were evaluated according to AASM scoring rules. Health-related quality of life was measured using the SF-36 questionnaire. The occurrence of peri- and postmenopausal symptoms were evaluated by a questionnaire and plasma levels of follicle stimulating hormone (FSH) were measured.

Results: After adjusting for confounding factors, vasomotor symptoms remained a significant explanatory factor for the occurrence of PLMs (adj. OR 1.86, 95% CI 1.03-3.37). In women with PLM arousals, adjusted OR for vasomotor symptoms was 1.61, 95% CI 0.76-3.42. PLMs did not seem to affect HRQoL.

Conclusion: We found that clinically significant PLMs, but not PLM with arousals, were more common among women with vasomotor symptoms, even after controlling for confounding factors. Menopausal status per se, as evidenced by FSH in the postmenopausal range, was not associated with PLMs.

Keywords: Periodic limb movements, women, menopause

Citation: Wesström J; Ulfberg J; Sundström-Poromaa I; Lindberg E. Periodic limb movements are associated with vasomotor symptoms. J Clin Sleep Med 2014;10(1):15-20.

BRIEF SUMMARY

Current Knowledge/Study Rationale: Sleep disturbances affect a substantial fraction of women during the menopausal transition, and female sex hormones are possibly involved in the origin of PLMs. It is currently unknown whether PLMs are associated with the menopausal transition and/or concomitant vasomotor symptoms.

Study Impact: This study shows an association between symptoms related to declining levels of estrogen, i.e. vasomotor symptoms, and PLMs. Future studies should address the possibility of using hormone replacement therapy in postmenopausal women with PLMD.

Periodic limb movements (PLMs) during sleep were first described in 1953 as “nocturnal myoclonus,” and were at that time thought to have similarities to nocturnal epilepsy.1 The pathophysiological mechanisms of PLMs are unclear, but abnormal hyperexcitability (or diminished inhibition) in the lumbosacral and cervical segments of the spinal cord have been hypothesized to be possible causes.2 PLMs are characterized by involuntary movements of the lower extremities, specifically the toes, ankle, knees, and hips, typically lasting between 0.5 and 10 seconds. The patient is usually unaware of the limb movements or the frequent sleep disruptions, and PLMs are often an incidental finding at polysomnography (PSG).3 PLMs may cause microarousals, leaving the affected patient fatigued the following day. Previously, it was assumed that PLMs were the cause of these arousals, but more recent studies have revealed that PLMs and arousals are associated in a more complex and non-unidirectional manner. Arousals can occur before, during, and after leg movements, indicating that the phenomenon is associated with an underlying arousal disorder.4

The exact prevalence of PLMs is unknown. They appear to be rare in children, to progress with advancing age, and to be more common in females than in males.5,6 In studies where PLMs have been objectively documented (PLM episodes/h of sleep > 5), the prevalence was 5% to 6% in younger adults, and 25% to 58% among elderly people.7 The diagnosis of periodic limb movement disorder (PLMD) is established when the affected individual also has insomnia and/or excessive daytime drowsiness. By subjective reports, the prevalence of PLMD has been estimated to be 3.9% in the general population.8

Restless legs syndrome (RLS) is a common sensory-motor disorder that produces uncomfortable sensations and a constant urge to move the lower limbs, and has a typical diurnal pattern with a peak of symptoms during rest periods in the evening and at night. RLS has also been reported to be associated with cardiovascular disease (CVD). In contrast to PLMs, the diagnosis of RLS is based on the patient’s subjective symptoms. PLMs are related to RLS, and the majority of patients with RLS display PLMs during sleep.9 Prior studies have discussed the relationship between PLMD and menopausal symptoms.
Another aim was to analyze the influence of PLMs on the hormonal status of the individuals. PLM associated with arousals from apneas, hypopneas, or respiratory effort related arousals (RERAs) were not scored. A rate > 15 PLM episodes per hour of sleep (PLM index) is considered clinically significant. 20

For the purposes of the present study, the diagnosis of PLM was made for women who had a PLM index > 15 (n = 93). In order to further examine the consequences of PLM arousals, women with PLM indexes > 15 and PLM arousal indexes > 5 were determined to be suffering from PLM arousals (n = 49). Two-hundred forty-three women with PLM indexes < 15 and PLM arousal indexes < 5 served as controls.

Questionnaires
The following questionnaires were filled out on the same evening as the polysomnographic recording:

RLS was diagnosed according to the International Restless Legs Syndrome Study Group standardized criteria (modified 2003). 21 The essential criteria for this syndrome were: (1) having an urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs; (2) experiencing the urge to move or unpleasant sensations beginning or worsening during periods of rest or inactivity, such as lying down or sitting; (3) having the urge to move or experiencing unpleasant sensations that are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues; (4) having the urge to move or experiencing unpleasant sensations that are worse in the evening or night than they are during the day, or which only occur in the evening or night. Each of these 4 criteria had to be met for the provisional study diagnosis of RLS in this study. Over time it has become clear that the positive predictive value of many RLS screening questionnaires may be low, and that many individuals who are identified as RLS sufferers by these screening questionnaires instead have other conditions that can mimic the features of RLS by satisfying the 4 diagnostic criteria. 22 In the current study however, RLS status was only used for adjustments, and the low positive predictive value of this measure was thus not considered to be problematic.

The Short Form Health Survey (SF-36) was used to evaluate each patient’s reported health. This instrument assesses an individual’s health-related quality of life across a range of patient populations with different medical conditions. SF-36 scores range from 1 to 100 for each attribute. A high score indicates a
better physical component summary (PCS) and mental component summary (MCS), indicating better overall reported health.

Alcohol dependency was defined as a subject’s having 2 positive answers on the 4-item CAGE (Cut down, Annoyed by criticism, Guilty about drinking, Eye-opener drinks) questionnaire.24

The subjects in the current report also completed a study-specific questionnaire that included questions on medical history, smoking, physical activity, medication, and hormonal status. In this questionnaire, subjects were asked if they had ever smoked regularly > 6 months and whether they were currently smokers or ex-smokers. The level of physical activity during leisure time was categorized into 4 groups, with a value of 1 for the lowest and 4 for the highest level of activity. The 4 values were dichotomized as low activity (levels 1 and 2) and high activity (levels 3 and 4). A low level of physical activity was defined as spending most of one’s time in front of the television, reading, or engaging in other sedentary activities. The highest level included regular physical activity such as swimming, jogging, tennis, aerobic exercise ≥ 3 h/week, or even more vigorous activities on a weekly basis. The categorization was adopted from a large population-based, prospective study on physical activity and mortality in women.25

Subjects were classified as having hypertension if they reported attending regular medical examinations for hypertension and/or answered “yes” to the question: “Do you have high blood pressure?” Similarly, those who answered “yes” to the question “Do you have diabetes?” and/or said that they attended regular medical examinations for diabetes were classified as having diabetes. Histories of previous myocardial infarction, heart failure, and stroke were also obtained by yes/no questions. Any type of regular medication was also documented.

Hormonal status was evaluated by the following questions: are you suffering from vasomotor symptoms (hot flushes and sweating)? How many menstruations have you experienced within the last 6 months or the last year? When did you experience your last menstruation? Are you currently being treated with any female steroid hormones? Have you been treated with female steroid hormones in the past? If so, when did you terminate treatment? For the purpose of the present study, only women who answered these questions were included.

### FSH and Hemoglobin Assays

A blood sample was taken from each subject in order to measure circulating levels of follicle stimulating hormone (FSH) and hemoglobin (Hb) using routine methods at the Department of Clinical Chemistry, Uppsala University Hospital. However, during the study period, the laboratory methods for FSH determination were altered; therefore, the FSH levels in this study were used merely to confirm menopausal status, using the reference intervals determined for each laboratory method. Because many women used HRT or intrauterine hormonal devices, it was assumed that FSH levels in the postmenopausal range would be a better indicator of postmenopausal status than amenorrhea.

### Statistics

Unpaired t-tests for numerical data and χ² tests for categorical data were used to analyze differences in characteristics, clinical and endocrine variables between subjects with PLMs index > 15, PLM arousals, and controls, respectively. Multiple logistic regression analyses were performed to estimate the risk, as approximated by the adjusted odds ratio (OR), of suffering from PLMs associated with vasomotor symptoms. The ORs, with 95% confidence intervals (CI), were calculated by means of multiple logistic regressions in order to determine the influence of potential confounding factors. The inclusion of confounding variables was based on significant findings in the bivariate analyses, with the exception of smoking and apnea-hypopnea index (AHI), which were forced into the model. The latter variable was included because of the oversampling of women with obstructive sleep disorder, which was categorized as having an AHI > 15. Measures of self-rated physical health, according to the SF-36-PCS, were categorized in quartiles, with subjects having scores in the highest quartile denoted as controls. A p-value < 0.05 was considered to be statistically significant. Statistical analyses were performed using IBM SPSS Statistics 20 (SPSS, Chicago, IL).

### RESULTS

Four hundred women were recruited for the study. Complete PSG recordings were obtained from all subjects. Due to technical difficulties, PLMs could not be scored in 7 women. In addition, 49 women did not complete the questionnaire concerning hormonal status and were excluded. Hence, 344 women were available for analysis. Of these, 243 women had a PLM index ≤ 15 and a PLM arousal index < 5 and were denoted as controls. Ninety-three women had a PLM index > 15 (women with PLM); of these, 49 also had a PLM arousal index > 5 (women with PLM arousals). Women with PLMs and PLM arousals were approximately 5 years older than controls. Women with PLMs were less likely than controls to be employed. There were no statistically significant differences in BMI, smoking habits, alcohol dependence, or degree of physical activity between the PLM groups and controls (Table 1).

As expected, women with PLMs and PLM arousals reported RLS more often than controls, and obstructive sleep apnea syndrome (evidenced by AHI > 15) tended to be more common in women with PLMs (Table 2). Women with PLM arousals reported hypertension more often (Table 2). Although chronic diseases and history of cardiovascular disease were rare in the study population, women with PLMs and PLM arousals had lower self-reported physical health (SF-36-PCS) than controls, respectively.

Wake time after sleep onset in women with PLMs was 71 ± 52 min, in women with PLM arousals 75 ± 52 min and in controls 64 ± 49 min in controls, p = 0.3 and p = 0.2 respectively. WASO in women with vasomotor symptoms was 73 ± 50 min and among those without vasomotor symptoms 63 ± 49 min, p = 0.1.

In our univariate analyses, FSH levels in the postmenopausal range and ongoing vasomotor symptoms were both associated with PLMs. Women with PLMs also reported the current use of hormonal replacement therapy more often than did controls, although this difference was not significant (p = 0.059; Table 3). A similar pattern was noted in women with PLM...
arousals, but none of the endocrine variables reached statistical significance (Table 3).

After adjusting for postmenopausal status (FSH in postmenopausal range), age, smoking, prevalence of RLS, prevalence of obstructive sleep apnea syndrome (AHI > 15), and self-rated physical health, vasomotor symptoms remained a significant explanatory factor for the occurrence of PLMs (adj. OR 1.86, 95% CI 1.03-3.37). Following adjustment for age, FSH in postmenopausal range did not remain a significant explanatory variable for the presence of PLMs. As expected, RLS was also significantly associated with PLMs (adj. OR 4.37, 95% CI 2.53-7.55; Table 4). A similar regression model was performed in women with PLM arousals, resulting in an adjusted OR for vasomotor symptoms of 1.61, 95% CI 0.76-3.42.

DISCUSSION

The main finding of the present study was that women with PLMs more often suffered from peri- and postmenopausal vasomotor symptoms, whereas postmenopausal status per se, following adjustment for age, did not remain a significant explanatory variable. These findings are in accordance with the results from a previous study in women with RLS, in which vasomotor symptoms during the menopausal transition, but not postmenopausal status, were associated with increased occurrence of RLS.15

The mechanisms by which the consequences of decreased ovarian function (vasomotor symptoms) are associated with PLMs, but not with menopause per se (increased FSH levels),
is not clear. The most straightforward explanation could be that women with PLMs have disturbed sleep and/or arousals, and thus might spend more time awake are more inclined to note vasomotor symptoms such as night sweats. In fact, we found a clear trend towards longer time awake after sleep onset in women with PLMs, PLM arousals and in women with vasomotor symptoms, but none of the results were significant. However, inferences about causal relationships between these sleep disturbing factors are not possible in this cross-sectional study design.

Vasomotor symptoms are considered to be indicative of estrogen deficiency, although no clear-cut relationship between serum concentrations of estrogen (or FSH) have been reported. It is thus possible that the loss of estrogen, which has multiple effects on neuronal function and neurotransmitter systems, might influence the propensity to develop PLMs. Estrogen receptors are expressed in brain areas responsible for sleep regulation. Estrogen signaling also increases the synthesis of acetylcholine, delays the turnover of serotonin, regulates serotonin transport and binding in the brain, and has both agonistic and antagonistic effects on the dopaminergic system. Long-term exposure to estrogen both increases dopamine uptake and decreases dopamine concentrations in dopaminergic areas in the brain. Of relevance to the study of PLM, it has been hypothesized that decreased estrogen levels worsen sleep movement disorders via decreasing the abundance of dopamine receptors or impacting catechol-O-methyltransferase (COMT) activity, the enzyme that degrades dopamine. However, it may be informative to point out that there is no evidence on a direct link between dopamine levels and hot flashes.

Emerging evidence also suggests that symptoms associated with sleep-related movement disorders may be associated with a low oxygenation of peripheral tissues. Remodeling of capillary geometry and a lower maximal oxygen uptake has been found in the tibialis anterior muscle of RLS patients. Estrogen has been shown to improve vascularization and to also, via increased nitric oxide production and vasodilatation, ultimately increase the oxygen supply. Nitric oxide has recently been reported to influence dopaminergic processes, promoting speculation on that the actions of this molecule may provide a link between the peripheral and central hypotheses of the origin of RLS/PLM. In addition, higher metabolism in the periphery during night sweats could lead to a build-up of lactic acid in the muscles, which leads to an increased excitability of nerve-muscle plates and to more frequent PLMs.

Although PLMs were significantly associated with vasomotor symptoms in the present study, no such association was found in women with PLM arousals. It is likely that the current study simply did not contain enough women with PLM arousals to reveal significant associations with menopause and/or vasomotor symptoms (indicating a type II error). With a larger sample of women with PLM arousals, it is possible that a positive association with vasomotor symptoms might have been revealed, but this remains to be established. On the other hand, arousals are common in women with PLMs, and spectral EEG may provide objective sleep measures indicating higher arousal levels in women with vasomotor symptoms. Our findings of an association between vasomotor symptoms and PLMs adds further complexity to the picture, and points to the fact that the mechanisms involved in arousals, whether associated with PLMs or vasomotor symptoms, remain insufficiently clarified.

In the current study, PSG recording were available for only a single night, which is an important limitation for the interpretation of our findings. Because of observed night to night variability of PLMs, particularly in RLS patients, it has been suggested that two consecutive full nights of PLM recordings may be necessary to make a valid estimate of the PLM index. However, this conclusion comes mostly from studies involving patients with sleep disorders such as RLS and PLMD.

Another limitation is that the cohort of women in this study was originally sampled for the evaluation of sleep disordered breathing. Therefore, the data in this study may not be used to estimate population-based prevalence rates of PLMs (or RLS) in women. However, for the associative analyses between vasomotor symptoms, menopause, and PLMs, the study design was considered reasonable. Furthermore, the prevalence of obstructive sleep apnea was adjusted for in the final regression analysis. The complex mechanisms underlying the association between OSA, RLS, and PLMs remain unclear. However, PLMs do not have an additive effect on the hypersomnia experienced by some sleep disordered breathing patients.

Even though RLS has been found to be associated with cardiovascular disease less is known about PLM and CVD. Due to the overall healthy population, this study did not add any information on the association between PLM and CVD.

We conclude that vasomotor symptoms are independently associated with PLMs and that ovarian steroids may play a role in the clinical manifestations of PLMs. At present, we may only speculate upon the biological mechanisms underlying this association; future studies should address the possibility of using hormone replacement therapy in postmenopausal women with PLMD.

**ABBREVIATIONS**

AASM, American Academy of Sleep Medicine
AHI, apnea-hypopnea index
BMI, body mass index

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**Table 4—Adjusted odds ratios and 95% confidence intervals for the explanatory variables of PLMs index > 15**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted odds ratio</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasomotor symptoms</td>
<td>1.86</td>
<td>1.03-3.37</td>
</tr>
<tr>
<td>FSH in postmenopausal range</td>
<td>1.22</td>
<td>0.57-2.61</td>
</tr>
<tr>
<td>Age</td>
<td>1.03</td>
<td>0.99-1.07</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.44</td>
<td>0.74-2.81</td>
</tr>
<tr>
<td>RLS</td>
<td>4.37</td>
<td>2.53-7.55</td>
</tr>
<tr>
<td>Apnea-hypopnea index &gt; 15</td>
<td>1.00</td>
<td>0.55-1.81</td>
</tr>
<tr>
<td>Self-rated physical health</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Highest quartile</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Intermediate quartiles</td>
<td>1.38</td>
<td>0.67-2.82</td>
</tr>
<tr>
<td>Lowest quartile</td>
<td>2.03</td>
<td>0.89-4.61</td>
</tr>
</tbody>
</table>

Odds ratios are adjusted for all variables in the table. FSH, follicular stimulating hormone; RLS, restless legs syndrome.
REFERENCES


ACKNOWLEDGMENTS

The authors thank Jan I flyer, of the Dalarna County Medical Research Center, for support with statistical calculations and Paul Murphy, of the Sleep Medicine Institute Mölndal, Sweden, for evaluating the polysomnographic recordings.

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication April, 2013
Submitted in final revised form August, 2013
Accepted for publication August, 2013
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DISCLOSURE STATEMENT

This was not an industry supported study. The study was supported by grants from the Swedish Heart Lung Foundation. The authors have indicated no financial conflicts of interest.
The Effects of Poor Sleep Quality on Cognitive Function of Patients with Cirrhosis

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1Division of Gastroenterology and Hepatology, Department of Internal Medicine University of Illinois at Chicago, Chicago, IL; 2Division of Biostatistics, Department of Health Sciences Research, and 3Department of Psychiatry and Psychology, Mayo Clinic, Rochester, MN

Objectives: This study was conducted to assess the ill-defined relationship between sleep quality and multiple, specific domains of cognitive function in patients with cirrhosis.

Methods: A comprehensive battery of neuropsychological tests (divided into six neurocognitive domains) and a standardized, validated measure of sleep quality (Pittsburgh Sleep Quality Index [PSQI]) were administered to patients with cirrhosis and without evidence of overt hepatic encephalopathy, recruited from liver transplant and advanced liver disease clinics (n = 34). An inflammatory bowel disease (IBD) control group (n = 23) was similarly recruited and evaluated to control for the secondary effect of a chronic illness on cognition. PSQI global and component scores were used to predict cognitive function in each neurocognitive domain, using linear regression

Results: Global PSQI scores were significantly higher (indicating poorer sleep quality) in the cirrhosis group (median [range] = 10 [1-19]) than in IBD controls = 5 (1-14); p = 0.002). After controlling for age and education, short duration of sleep was associated with impaired memory for patients with cirrhosis; the use of soporific agents was associated with poor visual-perceptual function in patients with IBD.

Conclusions: Poor sleep was associated with worsening of the already impaired cognitive function of patients with cirrhosis.

Keywords: Minimal hepatic encephalopathy, hepatic encephalopathy, poor sleep quality in cirrhosis, cognitive impairment and cirrhosis

Citation: Stewart CA; Auger R; Enders FTB; Felmlee-Devine D; Smith GE. The effects of poor sleep quality on cognitive function of patients with cirrhosis. J Clin Sleep Med 2014;10(1):21-26.

Up to 70% of individuals with cirrhosis (regardless of etiology) experience sleep disturbances.1,2 These disruptions commonly manifest as difficulty falling asleep and a shift in sleep schedule toward the latter part of the night, resulting in daytime sleepiness.2 Sleep deprivation has profoundly negative effects on cognition,3-10 which is already impaired in the majority of patients with cirrhosis.11,12 Hence, it is probable that sleep dysfunction from a circadian delay in patients with cirrhosis could have an additive effect on cognitive impairments.

In the general population, the psychomotor deficits associated with sleep deprivation are similar to those attributed to blood alcohol levels at or above the legal limit.10 Among patients with cirrhosis, deficits in sleep and cognition can have serious negative effects on their quality of life, safe driving, and workplace productivity.1,13-15

In previous work, actigraphy and a validated sleep questionnaire were used to evaluate sleep disturbances in patients with cirrhosis compared to a healthy volunteer group.1 The cirrhosis group was found to have greater difficulties falling asleep, more frequent awakenings, more difficulty awakening in the morning, and higher levels of daytime sleepiness. Underlying these findings was a circadian delay, as evidenced by the plasma melatonin peak in patients with cirrhosis and a healthy group.1 A correlation between severity of hepatic encephalopathy (using the Psychometric Hepatic Encephalopathy Score [PHES]) and sleep quality (as measured by Pittsburgh Sleep Quality Index [PSQI]) was not found; however, this study was limited in that individual cognitive domains were not examined.2

The objectives of our study were twofold: to evaluate differences in sleep quality between patients with cirrhosis and patients with another chronic disease (inflammatory bowel disease [IBD]); and in both groups, to test for an association between sleep quality and multiple specific domains of cognitive function. Sleep quality was assessed by a validated sleep questionnaire, the PSQI (global scores and individual component scores). Cognitive function was assessed by a comprehensive neuropsychological battery that evaluated specific neurocognitive domains, and therefore was expected to yield more accurate findings. We hypothesized that poorer sleep quality would be associated with more impaired cognitive function, and that this association would be stronger for patients with cirrhosis than for the IBD control group.
CA Stewart, R Auger, FTB Enders et al

Table 1—Neurocognitive domains and associated neuropsychological tests

<table>
<thead>
<tr>
<th>Domain</th>
<th>Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention/Concentration</td>
<td>WAIS-III Working Memory&lt;sup&gt;16&lt;/sup&gt;</td>
</tr>
<tr>
<td>Information processing speed</td>
<td>WAIS-III Processing Speed, Trails A &amp; B time&lt;sup&gt;16,21&lt;/sup&gt;</td>
</tr>
<tr>
<td>Learning</td>
<td>CVLT Total Learning,&lt;sup&gt;26&lt;/sup&gt; WMS-III Logical Memory I, Verbal Pairs-I,&lt;sup&gt;35&lt;/sup&gt;</td>
</tr>
<tr>
<td>Memory</td>
<td>CVLT-Long Delay,&lt;sup&gt;26&lt;/sup&gt; WMS-III Logical Memory II, Verbal Pairs-II&lt;sup&gt;15&lt;/sup&gt;</td>
</tr>
<tr>
<td>Visual perception</td>
<td>WAIS-III Perceptual Organization,&lt;sup&gt;16&lt;/sup&gt; Rey Figure Copy&lt;sup&gt;25&lt;/sup&gt;</td>
</tr>
<tr>
<td>Manual motor function</td>
<td>Grooved Pegboard, Dominant and Non-dominant hands&lt;sup&gt;21&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

CVLT, California Verbal Learning Test; WAIS, Wechsler Adult Intelligence Scale; WMS, Wechsler Memory Scales.

METHODS

Study Subjects

This study was approved by the Mayo Foundation Institutional Review Board. We recruited consecutive adult outpatients with a diagnosis of cirrhosis (based on histological, clinical, and radiological parameters) who were being treated in the liver transplant and advanced liver disease clinics at Mayo Clinic, Rochester, Minnesota, between May 2003 and June 2006. Patients were eligible for inclusion if they were English-speaking and abstinent from alcohol and other substances of abuse for at least 6 months. We excluded patients taking benzodiazepines or antipsychotic medicines, those with acute complications from liver disease, hepatic encephalopathy greater than grade 2, history of primary neurological disorders, and current uncontrolled psychiatric disorder.

Consecutive patients with inflammatory bowel disease (IBD) were recruited from the IBD clinics at Mayo Clinic, Rochester, Minnesota. The same inclusion and exclusion criteria used for patients with cirrhosis were employed, except patients with IBD who had liver disease or abnormal liver tests were excluded. All patients in the study were assessed with standardized neuropsychological tests and clinical evaluation during a single visit. The grade of hepatic encephalopathy for each patient was determined by a clinician on the basis of the West Haven Criteria within 24 h of neuropsychological testing. No patients were found to have overt hepatic encephalopathy.

Measures

Patients with cirrhosis and IBD control subjects completed the same set of neuropsychological and sleep measures, administered during a single clinic visit.

Neuropsychological Assessment

Participants were prospectively assessed with a standard pencil-and-paper neuropsychological battery as outlined in Table 1. Testing occurred under blinded conditions by the same trained neuropsychometrist. Results were interpreted by a single neuropsychologist.

All scores were transformed to age-adjusted standard scores (placed on a common z-score metric), such that negative scores represented poorer performance. Age adjustment was based on appropriate normative samples (i.e., the standardization samples for WAIS/WMS-III,<sup>16,17</sup> CVLT,<sup>16</sup> CPT-II,<sup>17,18</sup> Heaton,<sup>19</sup> norms for Trail Making,<sup>20</sup> Groove Pegboard,<sup>21</sup> Meyers norms for Rey-Osterrieth<sup>22</sup>). These standard scores were then organized into pertinent cognitive domains as reflected in Table 1. All domains included ≥ 2 measures in order to enhance the reliability of the estimated z-score in each domain. The score for each domain is the average age-adjusted z-score for all subtests in that domain.

Although each domain examines a different class of behaviors, they work in concert and are interdependent. In this study, attention/concentration refers to the ability of an individual to focus on selected sensory stimuli and ideas without being distracted by other stimuli. Information processing speed refers to the ability to rapidly process and respond to stimuli. The learning domain evaluates the ability to acquire new information. The memory domain samples recall or recognition of words and stories. Visual perception refers to the understanding of figural and spatial relationships and construction of designs. The motor domain involves tests of manual dexterity over a period of time.<sup>16,22</sup>

Pittsburgh Sleep Quality Index

The PSQI is easy to administer and interpret, and is widely used in sleep investigations. The questionnaire has 24 items; 19 are self-rated, and 5 are rated by the bed partner of the participants. The self-rated items are combined to form 7 component scores of subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction. Each of the 7 components is scored according to severity: a score of 0 = no difficulties for the component of interest; 1 = fairly good; 2 = bad; and 3 = very bad. These component scores are combined to generate a global PSQI score that reflects sleep quality and disturbances over a 1-month period. The global score ranges from 0 to 21, with higher scores indicative of poorer sleep quality.<sup>23</sup>

Using a cutoff of a global PSQI score > 5, the test demonstrated 89.6% sensitivity and 86.5% specificity in distinguishing between good and poor sleepers during an 18-month field trial. In our study, a PSQI score > 5 was considered consistent with the presence of poor sleep quality. We assessed both global PSQI and component scores, and determined their correlation with each of the neuropsychological domains.

Statistical Analysis

We compared cases and controls with respect to demographic predictors, using the Fisher exact test for binary variables and the Wilcoxon rank sum test for continuous variables. Unadjusted PSQI scores were compared between study groups with the Wilcoxon rank sum test for the global score and Fisher exact test for the subscores. Age was not tested as a confounder, because neuropsychological scores are already adjusted for age.

To assess the differential impact of PSQI scores on neuropsychological domain between cases and controls, we used the global PSQI score to predict neuropsychological domain scores using multiple linear regression. The outcome of the
neuropsychological domain was predicted by global PSQI, together with case-control status, and the interaction of global PSQI and case-control status. The interaction term was included to test for any differences in association of global PSQI with each neurocognitive domain between cases and controls. These models were also adjusted for age and education, as these variables proved different between the patients with cirrhosis and IBD. As a secondary analysis, we repeated these models, replacing the global PSQI score with each PSQI sub-score.

RESULTS

Participants

We enrolled 34 patients with cirrhosis and 23 IBD control subjects. The causes of cirrhosis included alcohol use (14/34, 41%) and cholestatic liver disease (4/34, 11.7%); the remainder (16/34, 47%) were uncharacterized. Median MELD score (range) was 11 (6-32). Gender distribution was similar in both groups (Table 2). Median age was greater for the cirrhosis group than the IBD control group (58 vs. 52 years; p = 0.028), whereas mean years of education was greater for IBD controls (15.5 vs. 14.3 years; p = 0.018).

Group Differences in Global and Component PSQI Scores

Global PSQI scores were significantly higher in the cirrhosis group (mean ± SD = 9.8 ± 4.9) than in IBD controls (5.6 ± 4.2; p = 0.002), indicating poorer sleep quality in patients with cirrhosis (Table 2). Patients with cirrhosis also reported higher scores (poorer sleep quality) than did the IBD control group for the following 4 PSQI components: sleep disturbance (p = 0.034), daytime dysfunction (p = 0.019), habitual sleep efficiency (p = 0.001), and sleep latency (p = 0.031). The groups did not differ significantly in their reported sleep duration, frequency of using soporific medications, or subjective sleep quality.

There were differences in PSQI component scores for patients with cirrhosis compared with IBD controls. With regard to sleep disturbance component scores, all patients with cirrhosis reported sleep disturbances (34/34), with 23/34 (68%) reporting scores ≥ 2 (i.e., greater than once weekly). In comparison, 22/23 (96%) IBD controls reported sleep disturbances, but only 9/22 (41%) had scores ≥ 2 (p = 0.034). Using the same method of comparison, daytime dysfunction was reported in 29/34 (85%) patients with cirrhosis, of whom 11/29 (38%) had scores ≥ 2. For daytime dysfunction, in comparison, 12/23 (52%) IBD controls reported difficulties, 5 (22%) of whom had scores ≥ 2 (p = 0.019). Poor sleep efficiency was reported by 25/34 (74%) patients with cirrhosis, 15 (44%) of whom had scores ≥ 2 (< 75% habitual sleep efficiency [HSE] versus 7/23 (30%) of IBD controls who reported impaired HSE, 4 (17%) of whom had scores ≥ 2 (p = 0.001). Finally, prolonged sleep latency was reported in 29/34 (85%) patients with cirrhosis, 19 (66%) of whom had scores ≥ 2, compared with 5/23 (22%) of subjects with IBD (p = 0.03; Table 2).

In the cirrhosis group, 76% (26/34) of patients had global PSQI scores > 5. There were no significant differences in age, gender, MELD scores, or etiology of disease between patients with cirrhosis who had high (> 5) versus low (< 5) PSQI scores (data not shown). In the IBD control group, 39% (9/23) of patients had a global PSQI score > 5. There was a statistically significant difference between the patients with low PSQI compared with those with high PSQI with respect to age (p = 0.025), but no relationship was seen with gender (data not shown).

Interaction of Sleep Quality and Cognitive Function with Disease Type

We performed a set of linear regression models to compare cirrhotic cases with IBD controls with respect to the impact of PSQI score on neuropsychological function. The association of the global PSQI score with the neuropsychological domain score did not differ significantly between cases and controls for any of the 6 neuropsychological domains (Tables 3A and 3B). For only one neuropsychological domain did either of the 2 potential confounders prove statistically significant: higher education level was positively associated with attention/
concentration after adjusting for age, global PSQI, and study group (p = 0.039).

When this analysis was repeated for each PSQI subscore, a few more specific associations became apparent. There was no association between sleep disturbance and learning in the IBD controls; but for patients with cirrhosis (cases), a greater sleep disturbance subscore was associated with higher functional learning (p = 0.04; Table 3A). There was no association between duration of sleep and better memory in controls, but in cases, better sleep duration (i.e., lower PSQI sleep duration subscore) was associated with better memory (p = 0.05; Table 3B). In controls, more use of sleep medications was significantly associated with poorer visual perceptual function; this association was not observed in the case group (p = 0.04; Table 3B).

Another important statistical outcome of these models was to identify strong differences between cases and controls in the association between PSQI and neuropsychological domain. To do this, we relied upon the linear regression coefficient and the coefficient of determination. The coefficient for global PSQI is on the same scale for all the neuropsychological domains, as the domain scores are adjusted z-scores. Unfortunately, none of the global PSQI interaction terms has a strong association with the neuropsychological domain, as the difference between cases and controls represents at most 0.06 SD in neuropsychological function, suggesting that the stronger coefficients of determination are driven by other variables in these models. The interaction coefficients in Tables 3A and 3B are also on the same scale for all the PSQI subscales. There was a 0.2 SD difference in the association between sleep disturbance and learning for cases and IBD controls. There was a 0.3 SD difference in the association of daytime dysfunction and visual perception for cases and IBD controls (other large effects for the visual perception domain were driven by associations within the control group, which were not as strong for cases). There was a 0.23 SD difference in the association of HSE and motor function between cases and controls.

Linear regression analyses to assess the association between neurocognitive function and sleep quality (global PSQI scores and separate composite scores) with neuropsychological assessment as continuous variables for patients with cirrhosis versus IBD controls revealed that sleep latency and time to bed were significantly associated with poor attention/concentration. However, after these variables were adjusted for age and educational level, only time to bed component was significantly associated with poor attention/concentration (p = 0.008; R² = 0.383).

## DISCUSSION

In this study we sought to determine the difference in sleep quality between patients with cirrhosis and a chronic illness control group of patients with IBD, and to assess whether poor sleep was associated with worsened cognitive function among the patients with cirrhosis.

Although sleep disturbances and cognitive impairment are both common among patients with cirrhosis, a definitive link between these two complaints has not been documented. If a specific association were found, greater clinical attention might...
be paid to sleep disorder screening (which is not routinely done in patients with cirrhosis and without overt hepatic encephalopathy), and to the testing of treatment strategies to ameliorate both sleep and cognitive dysfunction in these patients.

We found that patients with cirrhosis had significantly worse sleep quality than the control IBD group. Moreover, there was an association between poor sleep and cognitive impairment in both groups. Although a relationship between memory impairment and poor sleep has been documented in the general population, this is a new finding for patients with cirrhosis who have poor sleep.24 In general, a direct and multifaceted relationship exists between sleep and memory, such that sleep enhances recall performance on memory related tasks, and sleep is necessary for long-term memory consolidation. Sleep is important for newly acquired memory; declarative memory, a component of long-term memory, is dependent on sleep activity. The interdependency between sleep and memory has been substantiated by functional imaging of the brain, which has demonstrated decreased activity of the hippocampus, the area of the brain that is needed for memory functions, in individuals with poor sleep.24 This reduced hippocampus activity is associated with increased work of the individual to accomplish tasks. Overall, poor sleep leads to impaired learning and memory in the general population.25,26 Hence, the findings of this study are important for these sick patients, especially for patients with cirrhosis, most of whom are already cognitively impaired. The association between the use of soporific agents and visual perceptual impairment in patients with IBD is not surprising, since visual perceptual impairment is a known side effect of soporific agents.15,27-29 However, the surprising finding of improved learning with sleep disturbances in cirrhosis is very probably due to a type I error, as we are not aware of a biological explanation for this finding. The findings described herein are clinically significant, because they demonstrate that there is a high rate of self-reported difficulties with sleep among patients with cirrhosis, as has been shown by others.1,30,31 In addition, we found poor sleep quality is correlated with variable effects on cognitive function in this population in which diffuse neurocognitive deficits are pervasive, emphasizing the significant health burden that poor sleep has in the cirrhotic population. Sleep and circadian rhythm disorders are, however, treatable; therefore, there is a potentially reversible component of the cognitive deficits seen in patients with cirrhosis. Additionally, it is well known that the neurocognitive effects of these sleep disturbances have negative consequences on quality of life, workplace productivity, and safety,30 all of which could be addressed with accurate identification, characterization, and treatment of sleep disturbances in patients with cirrhosis. Hence, the identification of safe soporific agents could have a significant impact on the health of patients with cirrhosis, in whom metabolism of standard soporific agents is impaired by their diseased livers.32-34

This study is one of the few comparing sleep in cirrhosis to a sick control group using a validated sleep questionnaire, and it illustrates the need for larger studies to evaluate the association between sleep and cirrhosis. The findings suggest that intervening with efficacious treatment will be important for patients with cirrhosis who have poor sleep quality.


ACKNOWLEDGMENTS

The authors thank Drs. Anne Marie Weber-Main and Michael Howell for their critical review and editing of manuscript drafts.

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication September, 2012
Submitted in final revised form August, 2013
Accepted for publication August, 2013

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DISCLOSURE STATEMENT

This was not an industry supported study. The authors have indicated no financial conflicts of interest. Financial Support: NIH NIDDK 60018 to Dr. Stewart.
A growing body of evidence demonstrates that sleep promotes memory consolidation in healthy individuals. Numerous studies using various designs and memory tasks have consistently found that memory consolidation (i.e., improvement on a given memory task from initial training/test to retest) is significantly greater after a period of sleep than a period of wake. This is commonly referred to as sleep-dependent memory consolidation (SDMC). For example, improvements on a procedural finger-tapping task (FTT; procedural memory) and a word pair association task (WPT; declarative memory) and a finger-tapping task (FTT; procedural memory).

Studies examining declarative memory consolidation, such as with a word pair association task, also demonstrate improvements in performance after sleep. In addition to improvements in memory following overnight sleep, memory consolidation is also enhanced during naps as short as 45 minutes. Improvement in memory performance following sleep was lower with bedtime dosing of zolpidem-ER compared to placebo and middle-of-the-night dosing of zaleplon. There were no differences between placebo and zaleplon.

Introduction: Numerous studies have demonstrated that sleep promotes memory consolidation, but there is little research on the effect of hypnotics on sleep-dependent memory consolidation. We compared bedtime administration of zolpidem-ER 12.5 mg (6- to 8-h duration of action), middle-of-the-night administration of zaleplon 10 mg (3- to 4-h duration of action), and placebo to examine the effect of different durations of hypnotic drug exposure on memory consolidation during sleep.

Methods: Twenty-two participants with no sleep complaints underwent 3 conditions in a counterbalanced crossover study: (1) zolpidem-ER 12.5 mg (bedtime dosing), (2) zaleplon 10 mg (middle-of-the-night dosing), and (3) placebo. Memory testing was conducted before and after an 8-h sleep period, using a word pair association task (WPT; declarative memory) and a finger-tapping task (FTT; procedural memory).

Results: ANOVA revealed a significant condition effect for the WPT (p = 0.025) and a trend for the FTT (p = 0.067), which was significant when sex was added to the model (p = 0.014). Improvement in memory performance following sleep was significantly greater after a period of sleep than a period of wake. This study contributes to the research surrounding sleep-dependent memory and hypnotics, indicating that hypnotic exposure during most of the night may reduce sleep-dependent memory consolidation; whereas hypnotic exposure only during the second half of the night appears to have no effect.

Conclusions: The results suggest that in some circumstances hypnotics may have the potential to reduce the degree of sleep-dependent memory consolidation and that drug-free sleep early in the night may ameliorate this effect.

Keywords: Hypnotics, memory consolidation, sleep

Citation: Hall-Porter JM; Schweitzer PK; Eisenstein RD; Ahmed HAH; Walsh JK. The effect of two benzodiazepine receptor agonist hypnotics on sleep-dependent memory consolidation. J Clin Sleep Med 2014;10(1):27-34.
it is important to determine if memory consolidation during sleep is negatively affected by these drugs. Few studies have investigated the effect of hypnotics on sleep-dependent memory in humans. Melendez et al. reported no effect of either zolpidem immediate release (10 mg) or triazolam (0.25 mg) on SDMC in normal sleepers. However, subjects were trained to 100% on the memory tasks prior to the sleep period precluding a demonstration that the tests used were sensitive to SDMC with placebo. Other investigators found that zopiclone (7.5 mg), but not brotizolam (0.25 mg), impaired SDMC in normals. The small sample (N = 8) may have been insufficient to detect an effect with brotizolam. Finally, Morgan et al. reported significant impairment of sleep-dependent memory on a motor task with triazolam (0.375 mg), but not with zolpidem immediate release (10 mg). However, the dose of triazolam is rather high and the detected effect may be a direct influence of drug on motor performance during the morning testing period, rather than interference with SDMC. Additionally, the small sample (N = 12) may have provided insufficient power to detect an effect with the dose of zolpidem employed.

In sum, these studies provide some evidence that hypnotic drugs may impair SDMC, but further investigation is clearly needed to confirm these findings and assess possible contributing factors. One such factor may be duration of drug exposure. Given that memory consolidation improves after sleep periods (without medication) that are as brief as 1-2 hours, limiting drug exposure to a portion of the sleep period may result in less interference with SDMC, compared to drug exposure for the majority of the sleep period.

The objective of the present study was to determine the effect of different durations of hypnotic drug exposure on SDMC. To do this, we used hypnotics with different durations of action and administered them at different times of the night. We compared the effects of bedtime administration of zolpidem extended-release (zolpidem-ER) 12.5 mg, middle-of-the-night administration of zaleplon 10 mg, and placebo on procedural and declarative memory consolidation. The two hypnotics have similar mechanisms of action, both binding preferentially to the α-1 benzodiazepine receptor subunit, although their durations of action differ. Zolpidem-ER has an estimated duration of action of 6-8 h, with a t₁/₂ of 2.8 h and a tₘ₉ₗ of 1.5 h. In contrast, zaleplon has an estimated duration of action of 3-4 h due to rapid absorption and elimination, with t₁/₂ and tₘ₉ₗ both approximately one h. These doses were chosen because, at the time of study, they were the recommended therapeutic doses for treatment of insomnia. In addition, residual morning sedation has not been detected with either drug at these doses when administered at bedtime, or with zaleplon 10 mg when administered as little as 4 h before wake time (middle-of-the-night dosing). Normal subjects were studied to avoid potential influence of the inherent sleep disruption of insomnia patients.

We predicted that SDMC would be impaired following a period of sleep with drug activity during most or all of the night, but not after a period during which approximately half of the sleep is drug-free. Specifically, we hypothesized that bedtime administration of zolpidem-ER 12.5 mg would result in lower SDMC—measured as the percent change in memory performance from before sleep to after sleep—compared to placebo and middle-of-the-night zaleplon 10 mg. In addition we predicted that SDMC would not be lower following zaleplon 10 mg compared to placebo.

**METHODS**

**Subjects**

Healthy individuals with no sleep complaints were recruited via media advertisements and telephone contacts. Participants were required to have a Pittsburgh Sleep Quality Index (PSQI) global score ≤ 5 and report nightly total sleep time between 7 and 10 h with time in bed between 7 and 10.5 h. Exclusionary criteria included the presence of any clinically significant unstable medical condition; a DSM-IV axis-1 psychiatric disorder during the past 2 years; a prior diagnosis of, or symptoms suggesting risk for, sleep apnea, restless legs syndrome, or other sleep disorder; a history of substance abuse in the past year; use within the prior 2 weeks of prescription hypnotic medication, over-the-counter sleep aid, or any psychotropic medication; a history of adverse reaction to benzodiazepines or similar medications; and a body mass index ≥ 36. In addition, participants could not be night or rotating shift workers; consume ≥ 700 mg per day of xanthine-containing food or beverages; consume > 14 units of alcohol per week; or smoke ≥ 1 pack of cigarettes per day, use chewing tobacco > 3 times per day, or be unable to refrain from smoking or chewing without distress or discomfort while in the sleep laboratory. Female subjects could not be pregnant or nursing and were required to use adequate contraceptive procedures throughout the study.

**Experimental Design and Procedure**

The protocol was approved by the Institutional Review Board of St. Luke’s Hospital. All subjects provided written informed consent and were compensated for their participation. A randomized, counterbalanced, double-blind, placebo-controlled, crossover design was used to compare overnight memory consolidation during three drug conditions: (1) zolpidem-ER 12.5 mg (bedtime dosing), (2) zaleplon 10 mg (middle-of-the-night dosing), and (3) placebo (Figure 1). To provide blinding, capsules containing drug or placebo were administered twice each night: 30 min before bedtime and 3.5 h after bedtime during a brief experimental awakening. Thus placebo was given in the middle of the night during the zolpidem-ER condition, before bedtime in the zaleplon condition, and at both times in the placebo condition. Subjects were randomly assigned to a study condition sequence using a Latin Square design and had a 1- to 2-week interval between visits to allow for adequate wash-out.

Declarative memory and procedural memory tasks were administered 90 min before bedtime (60 min before drug administration) and 60 min after wake time, with the time between testing held constant at 10.5 h. The order of the tasks was counterbalanced within each study condition and held constant across conditions for each subject. Ninety minutes was chosen for the evening interval to allow time for memory testing and electrode placement prior to drug administration which occurred 30 min before bedtime. Sixty min was chosen for the morning interval so that testing occurred at a time when drug levels were undetectable or minimal. Thus
morning testing occurred 9.5 h after zolpidem-ER dosing and 5.5 h after zaleplon dosing which is approximately 1.5 h after drug should have been eliminated based on pharmacokinetic data.23,24 Both time intervals are consistent with prior studies of SDMC involving overnight sleep.5,6

Polysomnography (PSG) was conducted at each of the 3 overnight visits with bedtime at the subject’s reported typical bedtime and time in bed held constant at 8 hours. Sleep was recorded and scored according to standard criteria,30 using C3-A2 or C4-A1 EEG derivations by experienced staff blind to the experimental condition.

Subjects were instructed to cease caffeine consumption at 12:00 p.m., and to refrain from napping and consuming alcohol, on the days they were scheduled to arrive in the laboratory for overnight testing. In addition, use of nicotine products was prohibited while subjects were in the laboratory. Subjects were studied in private rooms without access to other subjects. During brief periods when testing was not conducted, subjects were permitted to engage in quiet activities such as reading or watching television. Breakfast was provided in the morning after awakening.

Double-blind study drug was prepared by a compounding pharmacy (Foundation Care, St. Louis, MO). Zolpidem-ER and zaleplon were over-encapsulated in identical #000-sized white opaque capsules and back-filled with an excipient (lactose). Identical placebo capsules contained only lactose. A dissolution test documented that there was less than a two-minute difference in dissolution of the outer capsule between the two active drug preparations.

**Dependent Measures**

Declarative memory was assessed with a word pair association task (WPT), modeled after that of Plihal and Born.31,32 Approximately 90 min prior to bedtime, 46 word pairs (23 related and 23 unrelated word pairs) were presented on a computer screen, one pair at a time for 3 sec each. Immediately following presentation of all 46 word pairs, an initial test of recall (WPT-Pre) was conducted. Participants were presented with the first (cue) word of each pair, one at a time and in a different order, and were asked to recall the second (target) word for each cue word. Immediately after each response, the correct word pairing—both cue word and target word—was displayed on the computer screen for 2 sec, regardless of whether the response was correct. Approximately 60 min after wake time, a second recall test (WPT-Post) was conducted during which subjects were again presented with the cue words, one at a time in yet a different order, and asked to recall the target words. Three unique versions of the test were utilized, with a different version administered during each of the 3 overnight conditions. Order of the test versions was randomly assigned and counterbalanced. SDMC was measured as the percent change in the number of correctly recalled word pairs from WPT-Pre to WPT-Post.

Procedural memory was assessed with a finger-tapping task (FTT), a test frequently used to demonstrate sleep-dependent memory.5,21 In this test, subjects are asked to type a 5-digit number sequence as quickly and as accurately as possible with the fingers of the nondominant hand by pressing 4 adjacent numeric keys on a standard computer keyboard. Subjects are instructed to look at the number sequence displayed on the computer screen while typing. No feedback on performance is given. Each test consists of twelve 30-sec tapping trials alternating with twelve 30-sec rest periods. The FTT was administered approximately 90 min prior to bedtime (FTT-Pre) and approximately 60 min after wake time (FTT-Post) using the same number sequence. Three versions of the test were utilized (2-4-3-1-2, 3-1-4-2-3, and 4-2-3-1-4), with a different version administered during each condition. Order of the test versions was randomly assigned and counterbalanced across conditions. SDMC was measured as the percent change in the number of correctly typed sequences from FTT-Pre (mean of the last 3 trials) to FTT-Post (mean of the first 3 trials).

Residual morning sedation was evaluated with the Digit Symbol Substitution Task (DSST), a measure of information processing, psychomotor performance, visuomotor coordination, and concentration. This test is commonly used as an indicator of psychomotor impairment and residual sedation following administration of hypnotics.33 The 90-sec test requires subjects to substitute digits (between 0 and 9) with different nonsense symbols according to a key which links symbols and
digits. The DSST was administered 60 min after wake time and just prior to the FTT-Post and WPT-Post. Three unique versions of the test were utilized, with a different version administered each morning and order randomly assigned and counterbalanced. The primary performance measure was the number of correct substitutions.

Statistical Analysis
Statistical analyses were conducted with SYSTAT 13, using repeated-measures ANOVAs followed by paired comparisons to examine condition differences. Age was used as a covariate for WPT analyses because it has been shown to affect declarative memory performance. $^{34,35}$ PSG measures were examined for the entire 8 h, the first 3.5 h of the night, and the last 4.5 h of the night.

RESULTS

Study Sample
Twenty-six individuals gave written informed consent and were randomized to the study. Two subjects withdrew due to scheduling conflicts, and 2 subjects were excluded from data analysis because of unusual sleep patterns while on placebo (one subject’s total sleep time was 263 min; one subject’s percent of REM sleep was 41%). The final sample (N = 22) consisted of 14 females and 8 males, with a mean age of 29.4 ± 6.7 years. Subjects had mean body mass index of 25.4 ± 4.3, and reported consuming an average of 1.0 ± 0.8 caffeinated beverages per day and 1.9 ± 1.7 alcoholic beverages per week. All but one of the subjects were nonsmokers; that subject consumed an average of 8 cigarettes per day and 1.9 ± 1.7 alcoholic beverages per week. All but one of the subjects were nonsmokers; that subject consumed an average of 8 cigarettes per day. Two extreme outliers (≥3 standard deviations from the mean) were noted on the WPT and excluded from analyses involving this task. This sample (N = 20) consisted of 14 females and 6 males, with a mean age of 30.1 ± 6.6 years.

Polysomnography
Polysomnography data in minutes and percents are shown in Table 1. Because time in bed was constant at 8 h, comparisons are similar for minutes and percents. Significant differences in the paired comparisons for both measures are presented in the table but data in minutes are reported here.

Comparing zolpidem-ER and placebo conditions, several predictable differences of minor magnitude reached statistical significance. For the entire night, zolpidem-ER had a shorter latency to persistent sleep (p = 0.007), less wake after sleep onset (WASO; p = 0.026) and stage 1 (p = 0.003), as well as more total sleep time (TST; p = 0.010), stage 2 (p = 0.012), and slow wave sleep (SWS; p < 0.001). Most of these differences occurred in the first 3.5 h, with zolpidem-ER demonstrating less WASO (p = 0.001), stage 1 (p = 0.001), and REM (p = 0.005), as well as more TST (p = 0.004), stage 2 (p = 0.035), and SWS (p = 0.001) during this time period. During the last 4.5 h the only difference was less stage 1 with zolpidem-ER (p = 0.015).

Sleep architecture was similar between the zaleplon and placebo conditions. Comparisons between these conditions showed only one significant difference, an increase (by 10.5 min) in SWS in the zaleplon condition for the entire night (p = 0.003). There were no other differences for the entire night, the first 3.5 h (when placebo was present during both conditions), or the last 4.5 h (following middle-of-the-night dosing).

Because zolpidem-ER was taken at bedtime and zaleplon was dosed in the middle of the night, we performed comparisons between these conditions for the entire night as well as the last 4.5 h. In addition, the first 3.5 hours were compared to demonstrate that the sleep architecture differences between zolpidem-ER and zaleplon conditions were parallel, as expected, to the differences between the first 3.5 h of the zolpidem-ER and placebo conditions. Comparisons between the two active drug conditions for the entire night demonstrated less WASO (p = 0.022) and stage 1 (p = 0.005), as well as more TST (p = 0.006) and stage 2 (p = 0.003) with zolpidem-ER compared to zaleplon. For the first 3.5 h when placebo was present in the zaleplon condition, zolpidem-ER had less WASO (p = 0.001), stage 1 (p = 0.001), and REM (p = 0.031), as well as more TST (p = 0.008), stage 2 (p = 0.023), and SWS (p = 0.004), consistent with the zolpidem-ER/placebo comparisons for the same time period. During the last 4.5 h, zolpidem-ER had more stage 2 (p = 0.016) than zaleplon.

DSST

The DSST means (number of correct substitutions) were: zaleplon = 67.4 ± 11.7, placebo = 68.0 ± 11.9, and zolpidem-ER = 64.5 ± 11.1. Repeated-measures ANOVA indicated a trend for a condition effect (F(2,20) = 3.095, p = 0.067. Follow-up paired comparisons showed lower DSST scores with zolpidem-ER compared to placebo (p = 0.029) and a trend for lower scores compared to zaleplon (p = 0.052). Correlational analyses were thus conducted to determine if residual sedation might be responsible for poorer SDMC in the zolpidem-ER condition. These analyses revealed no significant correlations between DSST and memory measures.

SDMC: Declarative

Pre-sleep learning (the number of correctly-recalled word pairs on the WPT-Pre) was similar among the conditions: zaleplon = 24.5 ± 8.9, placebo = 25.1 ± 6.9, and zolpidem-ER = 25.8 ± 8.1 (F(2,17) = 1.725, p = 0.208). There was evidence of an overnight improvement in memory for each condition, measured as raw score change in correctly recalled word pairs from WPT-Pre to WPT-Post (zaleplon: 4.15 ± 3.6, placebo: 4.20 ± 3.8, and zolpidem-ER: 3.35 ± 3.7). Repeated-measures ANOVA, including age as a covariate, demonstrated a significant effect of condition for the percent change from WPT-Pre to WPT-Post (F(2,17) = 4.619, p = 0.025; Figure 2). Pairwise comparisons revealed significantly lower overnight improvement on WPT in the zolpidem-ER condition compared to both the placebo (p = 0.015) and zaleplon (p = 0.031) conditions. There was no difference between zaleplon and placebo (p = 0.58).

SDMC: Procedural

Pre-sleep learning (the average number of correctly typed number sequences on the FTT-Pre) was similar among conditions: zaleplon = 19.3 ± 5.2, placebo = 20.0 ± 5.4, and zolpidem-ER = 20.2 ± 6.2 (F(2,20) = 1.52, p = 0.243). There was evidence of an overnight improvement in memory for each
condition, measured as raw score change in correctly typed sequences from FTT-Pre to FTT-Post (zaleplon: 2.77 ± 2.0, placebo: 2.59 ± 3.0, and zolpidem-ER: 1.53 ± 2.8). Repeated measures ANOVA showed a trend towards a condition effect for the percent change from FTT-Pre to FTT-Post (F(2,20) = 3.097, p = 0.067). Pairwise comparisons revealed significantly lower overnight improvement on FTT for zolpidem-ER compared to placebo (p = 0.035), a trend for less improvement with zolpidem-ER compared to zaleplon (p = 0.057), and no difference between zaleplon and placebo (p = 0.78). Because plots of the data indicated sex may have differentially affected performance on the FTT, we added sex to the ANOVA model for a secondary analysis of percent change. This analysis revealed a condition effect (F(2,19) = 5.446, p = 0.014) and a trend for a condition by sex interaction (F(2,19) = 3.028, p = 0.072). Pairwise comparisons revealed significantly lower overnight improvement on FTT for zolpidem-ER compared to both placebo (p = 0.014) and zaleplon (p = 0.012), and no difference between zaleplon and placebo (p = 0.88; Figure 3).

**Correlation between Sleep Parameters and SDMC**

Exploratory correlation analyses were conducted for each condition to determine if improvements in memory were related to specific all-night PSG measures (TST, Stage 1%, Stage 2%, SWS%, and REM%). In the placebo condition, WPT percent change was positively correlated with REM% (r = 0.520, p = 0.019) and FTT percent change was negatively correlated with stage 2% (r = -0.432, p = 0.044). In the zolpidem-ER condition, WPT percent change correlated negatively with SWS% (r = -0.524, p = 0.018).

**DISCUSSION**

The objective of the present study was to determine the effect of different durations of hypnotic drug exposure on SDMC. We compared bedtime administration of zolpidem-ER 12.5 mg (6- to 8-h duration of action) with middle-of-the-night administration of zaleplon 10 mg (3 to 4-h duration of action) and placebo. ANOVAs revealed a significant condition effect, measured as raw score change in correctly typed sequences from FTT-Pre to FTT-Post (zaleplon: 2.77 ± 2.0, placebo: 2.59 ± 3.0, and zolpidem-ER: 1.53 ± 2.8). Repeated measures ANOVA showed a trend towards a condition effect for the percent change from FTT-Pre to FTT-Post (F(2,20) = 3.097, p = 0.067). Pairwise comparisons revealed significantly lower overnight improvement on FTT for zolpidem-ER compared to placebo (p = 0.035), a trend for less improvement with zolpidem-ER compared to zaleplon (p = 0.057), and no difference between zaleplon and placebo (p = 0.78). Because plots of the data indicated sex may have differentially affected performance on the FTT, we added sex to the ANOVA model for a secondary analysis of percent change. This analysis revealed a condition effect (F(2,19) = 5.446, p = 0.014) and a trend for a condition by sex interaction (F(2,19) = 3.028, p = 0.072). Pairwise comparisons revealed significantly lower overnight improvement on FTT for zolpidem-ER compared to both placebo (p = 0.014) and zaleplon (p = 0.012), and no difference between zaleplon and placebo (p = 0.88; Figure 3).

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**Table 1**—Polysomnography data for each condition (N = 22)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Zaleplon (middle-of-the-night dosing)</th>
<th>Zolpidem-ER (bedtime dosing)</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Entire Night</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Latency to persistent sleep (min)</td>
<td>15.2 (14.6)</td>
<td>10.2 (8.2)</td>
<td>21.4 (15.4)*</td>
</tr>
<tr>
<td>Total sleep time (min)</td>
<td>434.6 (26.1)*</td>
<td>449.0 (15.4)</td>
<td>431.8 (23.9)*</td>
</tr>
<tr>
<td>Sleep efficiency (%)</td>
<td>90.6 (5.4)*</td>
<td>93.6 (3.2)</td>
<td>89.9 (5.0)*</td>
</tr>
<tr>
<td>Wake after sleep onset (min)</td>
<td>32.2 (20.4)*</td>
<td>22.0 (13.1)</td>
<td>31.8 (17.7)*</td>
</tr>
<tr>
<td>Stage 1 (min)</td>
<td>49.7 (16.9)*</td>
<td>37.0 (18.2)</td>
<td>50.9 (19.1)*</td>
</tr>
<tr>
<td>Stage 1 (%)</td>
<td>11.5 (4.1)*</td>
<td>8.3 (4.3)</td>
<td>11.9 (4.7)*</td>
</tr>
<tr>
<td>Stage 2 (min)</td>
<td>237.6 (26.4)*</td>
<td>264.8 (34.3)</td>
<td>244.7 (34.7)*</td>
</tr>
<tr>
<td>Stage 2 (%)</td>
<td>54.9 (7.2)</td>
<td>59.0 (6.0)</td>
<td>56.7 (7.6)*</td>
</tr>
<tr>
<td>SWS (min)</td>
<td>57.8 (31.6)</td>
<td>64.9 (39.1)</td>
<td>47.2 (28.2)*</td>
</tr>
<tr>
<td>SWS (%)</td>
<td>13.2 (7.2)</td>
<td>14.3 (8.5)</td>
<td>10.9 (6.3)*</td>
</tr>
<tr>
<td>REM (min)</td>
<td>89.5 (22.4)</td>
<td>82.3 (21.4)</td>
<td>80.0 (21.1)</td>
</tr>
<tr>
<td>REM (%)</td>
<td>20.5 (4.4)</td>
<td>18.3 (4.5)</td>
<td>20.5 (4.3)*</td>
</tr>
<tr>
<td><strong>First 3.5 hours</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total sleep time (min)</td>
<td>185.4 (17.0)*</td>
<td>194.9 (9.0)</td>
<td>183.8 (13.5)*</td>
</tr>
<tr>
<td>Wake after sleep onset (min)</td>
<td>21.0 (16.1)*</td>
<td>9.4 (5.6)</td>
<td>19.0 (11.1)*</td>
</tr>
<tr>
<td>Stage 1 (min)</td>
<td>22.5 (9.1)*</td>
<td>13.3 (6.0)</td>
<td>21.0 (9.4)*</td>
</tr>
<tr>
<td>Stage 1 (%)</td>
<td>12.3 (5.9)*</td>
<td>6.9 (4.3)</td>
<td>11.6 (5.5)*</td>
</tr>
<tr>
<td>Stage 2 (min)</td>
<td>97.6 (20.4)</td>
<td>108.8 (26.3)</td>
<td>100.9 (17.6)*</td>
</tr>
<tr>
<td>Stage 2 (%)</td>
<td>53.2 (13.1)</td>
<td>56.2 (15.0)</td>
<td>55.1 (9.9)</td>
</tr>
<tr>
<td>SWS (min)</td>
<td>44.6 (27.4)</td>
<td>57.6 (33.3)</td>
<td>38.6 (22.9)*</td>
</tr>
<tr>
<td>SWS (%)</td>
<td>23.5 (14.0)</td>
<td>29.2 (16.8)</td>
<td>20.8 (11.9)*</td>
</tr>
<tr>
<td>REM (min)</td>
<td>20.8 (11.9)</td>
<td>15.1 (9.1)</td>
<td>23.3 (10.7)*</td>
</tr>
<tr>
<td>REM (%)</td>
<td>10.9 (6.0)</td>
<td>7.7 (4.6)</td>
<td>12.5 (5.3)*</td>
</tr>
<tr>
<td><strong>Last 4.5 hours</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total sleep time (min)</td>
<td>248.9 (12.5)</td>
<td>250.4 (20.3)</td>
<td>247.7 (14.2)</td>
</tr>
<tr>
<td>Wake after sleep onset (min)</td>
<td>10.2 (7.2)</td>
<td>11.8 (10.5)</td>
<td>12.4 (10.3)</td>
</tr>
<tr>
<td>Stage 1 (min)</td>
<td>27.2 (10.4)</td>
<td>22.8 (12.3)</td>
<td>29.8 (12.5)*</td>
</tr>
<tr>
<td>Stage 1 (%)</td>
<td>11.0 (4.4)</td>
<td>9.3 (5.5)</td>
<td>12.2 (5.3)*</td>
</tr>
<tr>
<td>Stage 2 (min)</td>
<td>139.8 (17.1)*</td>
<td>153.9 (22.2)</td>
<td>143.7 (23.0)</td>
</tr>
<tr>
<td>Stage 2 (%)</td>
<td>56.2 (6.7)</td>
<td>61.6 (8.2)</td>
<td>57.9 (8.0)</td>
</tr>
<tr>
<td>SWS (min)</td>
<td>13.2 (5.2)</td>
<td>7.3 (11.0)</td>
<td>8.5 (8.8)</td>
</tr>
<tr>
<td>SWS (%)</td>
<td>5.2 (6.1)</td>
<td>2.8 (4.2)</td>
<td>3.5 (4.0)</td>
</tr>
<tr>
<td>REM (min)</td>
<td>68.7 (15.0)</td>
<td>66.4 (20.6)</td>
<td>65.6 (15.9)</td>
</tr>
<tr>
<td>REM (%)</td>
<td>27.5 (5.5)</td>
<td>26.3 (7.6)</td>
<td>26.4 (5.9)</td>
</tr>
</tbody>
</table>

Data are presented as mean (standard deviation). *p < 0.05, paired comparison vs. zaleplon. **p < 0.05, paired comparison vs. zolpidem-ER. 
effect for the WPT and a trend for the FTT, which was significant when sex was added to the model. The results suggest that bedtime administration of zolpidem-ER reduces the magnitude of SDMC while middle-of-the-night dosing with zaleplon does not.

One interpretation of these data is that the 3.5-h drug-free period of sleep prior to zaleplon ingestion was sufficient to allow SDMC to occur to the same degree as in the placebo condition, whereas having drug active in the brain for most of the sleep period, as in the zolpidem-ER condition, reduces SDMC. Observations from nap studies that as little as 45 minutes of sleep allows SDMC to occur is consistent with this interpretation.8,10 Our data do not address whether the timing of drug-free sleep is important. Similar results with zaleplon administered at bedtime (allowing a period of drug-free sleep in the latter part of the night) would suggest that some minimal period of drug-free sleep any time of night is sufficient to maximize SDMC. On the other hand, a decrement in SDMC in this circumstance would suggest that drug exposure early in the sleep period is a critical factor in diminishing SDMC.

Alternative explanations include differences specific to the two drugs or to the doses employed (affecting peak plasma and duration of action). Zaleplon and zolpidem-ER have different chemical structures. However, both are GABAA receptor agonists with preferential binding to the α-1 subunit, which is believed to be responsible for the drugs’ sedative properties as well as for anterograde amnestic effects.36

We do not believe residual sedation accounts for the reduced SDMC with zolpidem-ER 12.5 mg. since testing was done 9.5 hours post-dose and studies of this drug as a hypnotic indicate no residual sedation 8.5 to 9.5 hours post dosing.22,26,37 Although DSST scores with zolpidem-ER were slightly lower than those with zaleplon and placebo, follow-up correlational analyses between DSST and WPT/FTT performance showed no significant findings, indicating that any residual sedation present in the zolpidem-ER condition did not predict performance on the memory tests. We also visually examined the data to determine if residual sedation was more likely to occur in females, since the FDA has recently lowered the recommended dosage of zolpidem-ER for women based on reports that some women eliminate zolpidem more slowly than men.38 Our females did have lower DSST scores in the zolpidem-ER condition than in the other conditions, while males showed equivalent DSST scores in all three conditions. However, these scores were not correlated with WPT/FTT performance. In fact, males (in contrast to females) appeared to perform more poorly on the memory tests in the zolpidem-ER condition than in the other conditions.

It is important to note that although SDMC was reduced in the zolpidem-ER condition, memory improvement across the sleep period was present in all three conditions. The overnight percent change in FTT performance in the zaleplon and placebo conditions (14.4% to 15.4%) is similar to the improvement seen in published studies using the same test with overnight sleep ranging from 3.5 to 7.5 hours (14% to 18%).39 In comparison, the percent change with zolpidem-ER was only 8%. It is difficult to compare the WPT data (which show overnight improvements of 16% to 19%) with published studies because of variability of methodology, particularly in type and number of word pairs used in those studies. Nonetheless, these data suggest that sleep with a hypnotic does not prevent SDMC from occurring, but may reduce its magnitude.

Previous research has shown that certain aspects of sleep architecture may be associated with SDMC,41 although there is inconsistency among studies. In our exploratory analyses
Hypnotics and Sleep-Dependent Memory Consolidation

Our findings, if confirmed, may have implications for the treatment of insomnia. If hypnotics negatively affect SDMC, cognitive-behavioral treatment should be considered instead of or prior to pharmacological treatment of chronic insomnia, assuming no other compelling reasons to favor pharmacotherapy. When pharmacological treatment is considered, there may be an advantage for pro re nata treatment of insomnia, rather than prophylactic treatment in anticipation of sleep disturbance. In other words, taking a drug routinely to prevent insomnia might be less preferable than intermittent use so that SDMC can be optimized on nights when drug is not needed. Similarly, short-acting drugs, which allow some drug-free sleep to occur, may interfere less with SDMC than longer-acting drugs. Use of short-acting drugs or a drug with delayed release could be particularly advantageous for patients with sleep maintenance insomnia, the most frequent insomnia phenotype, with a population prevalence reported to be 16.1% to 23.5%.

However, a much better understanding of SDMC in insomnia patients is needed before making such recommendations. A modest amount of evidence suggests that SDMC may be impaired in primary insomnia. Whether use of hypnotic medication in this population worsens this impairment is unknown. The clinical significance of SDMC impairment, whether caused by insomnia, hypnotic use, or their combination must also be taken into consideration. Understanding the effects of hypnotics on SDMC in normal individuals without sleep problems or medical comorbidities is an important first step in this evaluation.

In conclusion, the findings of this study advance our knowledge of the effects of hypnotics on SDMC, an area with little research to date. The results suggest that in some circumstances hypnotics may have the potential to reduce the degree of SDMC and that drug-free sleep early in the night may ameliorate this effect. Future studies of SDMC would benefit from comparisons of specific drugs administered at different doses and times as well as study of drugs with different mechanisms of action in individuals with insomnia as well as normal controls.

ABBREVIATIONS

ANOVA, analysis of variance; statistical test
DSST, Digit Symbol Substitution Task
EEG, electroencephalogram
ER, extended-release drug
FTT, finger-tapping task
FTT-Pre, number of correctly-typed number sequences on the FTT test given before each sleep period
FTT-Post, number of correctly-typed number sequences on the FTT test given after each sleep period
PSG, polysomnography
SDMC, sleep-dependent memory consolidation; the improvement in memory from pre-sleep to post-sleep SWS, slow wave sleep
TST, total sleep time
WASO, wake after sleep onset
WPT, word pair task
WPT-Pre, number of correctly-recalled word pairs on the WPT test given before each sleep period
WPT-Post, number of correctly-recalled word pairs on the WPT test given after each sleep period

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Polysomnographic Findings in a Cohort of Chronic Insomnia Patients with Benzodiazepine Abuse

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Study Objectives: To evaluate sleep modifications induced by chronic benzodiazepine (BDZ) abuse.

Methods: Cohort study, comparison of sleep measures between BDZs abusers and controls. Drug Addiction Unit (Institute of Psychiatry) and Unit of Sleep Disorders (Institute of Neurology) of the Catholic University in Rome. Six outpatients affected by chronic BDZ abuse were enrolled, (4 men, 2 women, mean age 53.3 ± 14.8, range: 34-70 years); 55 healthy controls were also enrolled (23 men, 32 women, mean age 54.2 ± 13.0, range: 27-76 years). All patients underwent clinical evaluation, psychometric measures, ambulatory polysomnography, scoring of sleep macrostructure and microstructure (power spectral fast-frequency EEG arousal, cyclic alternating pattern [CAP]), and heart rate variability.

Results: BDZ abusers had relevant modification of sleep macrostructure and a marked reduction of fast-frequency EEG arousal in NREM (patients: 6.6 ± 3.7 events/h, controls 13.7 ± 4.9 events/h, U-test: 294, p = 0.002) and REM (patients: 8.4 ± 2.4 events/h, controls 13.3 ± 5.1 events/h, U-test: 264, p = 0.016), and of CAP rate (patients: 15.0 ± 8.6%, controls: 51.2% ± 12.1%, U-test: 325, p < 0.001).

Discussion: BDZ abusers have reduction of arousals associated with increased number of nocturnal awakenings and severe impairment of sleep architecture. The effect of chronic BDZ abuse on sleep may be described as a severe impairment of arousal dynamics; the result is the inability to modulate levels of vigilance.

Keywords: Abuse, arousal, benzodiazepines, cyclic alternating pattern, polysomnography, sleep

Citation: Mazza M; Losurdo A; Testani E; Marano G; Di Nicola M; Dittoni S; Gnoni V; Di Blasi C; Giannantoni NM; Lapenta L; Brunetti V; Bria P; Janiri L; Mazza S; Della Marca G. Polysomnographic findings in a cohort of chronic insomnia patients with benzodiazepine abuse. J Clin Sleep Med 2014;10(1):35-42.

Benzodiazepines (BDZs) are used as anxiolytics, hypnotics, anticonvulsants, muscle relaxants, and to induce anesthesia. Although guidelines emphasize that BDZs are not drugs of first choice and should only be used short term (recommended use should not exceed 4-6 weeks’ duration), their use beyond the licensed duration is common. Within weeks of chronic use, tolerance may occur, leading to unwanted dose increases, and withdrawal becomes apparent once the drug is no longer available: these conditions are both indicative of BDZ dependence. BDZs are also drugs of abuse, either on their own or in conjunction with opioids and stimulants. The diagnosis of addiction is made in presence of compulsive use of the drug despite negative consequences. Recently it has been suggested that specific psychological and situational factors differentiate benzodiazepine addicts from non-addicted benzodiazepine users; in particular, benzodiazepine addiction might be associated with higher neuroticism, introversion, less effective coping mechanisms, previous accumulation of adverse life events, and/or inadequate BDZ treatment. These drugs may initially lead to prolonged total sleep time as a desired effect. Acute and short-term usage of BDZs is usually associated with a reduction of nocturnal wake time, subjective improvements of quality and depth of sleep, as well as improved sleep continuity and total sleep time as reported by polysomnography.

Regarding the microstructure of sleep, BDZs lead to a reduction of slow frequencies and an increase of fast frequencies in the EEG. It has been demonstrated that BDZ users have less delta and theta activity than good sleepers. When compared to drug-free insomniacs, chronic BDZ users have less delta and theta activity only within the second sleep cycle. The effect of BDZs on sleep microstructure have been tested in a model of situational insomnia, i.e., a condition in which sleep is disrupted by exposing normal subjects to variable levels of noise. In this
model, BDZs (as well as other non-BDZ hypnotics) are able to reduce the instability of NREM sleep (CAP rate) and have a protective action against the perturbation induced by white noise. All hypnotic drugs, including BDZs, may determine a significant decrease in EEG arousals, as measured by CAP parameters. The intake of BDZs may have a negative long-term effect on sleep.8

The aim of the present study was to evaluate the sleep structure and the pattern of arousability in a cohort of patients with chronic abuse of BDZs. For this reason, we evaluated the macrostructure of sleep (by means of nocturnal polysomnographic recordings), EEG power spectral analysis, pattern of arousal (by means of the cyclic alternating pattern [CAP] analysis), and autonomic activity (by means of heart rate variability analysis).

MATERIALS AND METHODS

Patients

Six patients affected by chronic BDZ abuse were enrolled: 4 men and 2 women, mean age 53.3 ± 14.8 (range: 34-70 years). Patients were recruited consecutively from the Drug Addiction Unit of the Catholic University in Rome over 12 months (January to December 2012). Inclusion criteria was a diagnosis of by chronic BDZ abuse according to the criteria of the DSM-IV-TR,14 not associated with other drug or substance dependence or abuse. Exclusion criteria were: presence of other medical, neurologic, or psychiatric diseases; presence of heart disease, arrhythmias, intake of cardiovascular active drugs; diabetes; uncontrolled hypertension; severe obesity (BMI > 35 kg/m²); chronic respiratory disease; obstructive sleep apnea syndrome; restless legs syndrome; and thyroid diseases. All patients underwent a full psychiatric, medical, and neurological evaluation. The diagnosis of BDZ abuse was assessed on a clinical basis, according to DSM-IV-TR criteria.14 All patients were still taking BDZs at the time of the sleep study.

Control Group

Patients were compared with a control group of 55 healthy subjects, matched for age and sex: 23 men and 32 women, mean age 54.2 ± 13.0 (range: 27-76 years). Control subjects were healthy volunteers. Controls underwent a full medical and neurological evaluation and a hypnological interview to rule out present or previous history of sleep disorders. The same exclusion criteria were applied to patients and controls. To compare patients with controls of same age, we chose from the entire control group 3 subgroups, defined by age ranges: age 30-40 years (n = 12), age 50-60 years (n = 17), and age > 65 (n = 14). The study was approved by the local ethics committee; the study was designed according to the Helsinki Declaration of 1975. All patients and control subjects were fully informed, and all gave a written consent to participate.

Psychological Functioning Measures

All patient underwent a full clinical psychiatric evaluation, followed by a psychometric evaluation which included the following self-administered scales: Self-Administered Anxiety Scale (SAS#54),15 Beck Depression Inventory (BDI),16 Maudsley Obsessive Compulsive Inventory (MOCI),17 and Snaith-Hamilton Pleasure Scale (SHAPS).18

The SAS #54 is used in order to measure anxiety-related symptoms. It consists in a 4-point Likert-type scale, ranging from 1 to 4; higher scores correspond to higher levels of anxiety. The BDI is a 21-item validated instrument which measures characteristic attitudes and symptoms of depression. Scores range from 0 to 36; scores > 9 indicate mild to severe depression. The MOCI is a questionnaire with true-false format developed for evaluating obsessive-compulsive symptoms. The total score ranges between 0 (absence of symptoms) and 34 (maximum presence of symptoms). The SHAPS is a 14-item instrument that is used to measure hedonic capacity. Total scores range from 0 to 14; a higher total SHAPS score indicates higher levels of anhedonia.

Subjective Sleep Evaluation

Subjective evaluation of sleep quality was performed using the validated Italian version of the Pittsburgh Sleep Quality Index (PSQI).19 A global score > 5 was considered an indicator of poor sleep quality.20 The validated Italian version of the Epworth Sleepiness Scale (ESS)21 was used for the evaluation of excessive daytime sleepiness (EDS). A score > 9 was considered indicative of EDS. In all participants, patients and controls, an evaluation of the symptoms and clinical signs predictors of obstructive sleep apnea syndrome (OSAS) was performed by means of the Berlin Questionnaire.22 The clinical evaluation included the measure of neck circumference, body mass index (BMI), presence of habitual snoring, nocturia, morning headache, arterial hypertension, and apneas reported by the bed partner.

Polysomnography

Twenty-four hour ambulatory (home-based) polysomnography was recorded. This recording technique was chosen in order to allow the patients to sleep in their habitual home setting.23 Recording montage included EEG leads filled with electrolyte applied to the following locations: F4, C4, O2 or F3, C3 O1; reference electrodes applied to the contralateral mastoid (M1); 2 EOG electrodes applied to the outer ocular canthus and referred to the contralateral mastoid, surface EMG of submental muscles, and EKG. Patients were asked to indicate in a sleep log the times of lights-off and lights-on. Patients were not asked to keep a defined schedule, but were left free to follow their spontaneous sleep-wake cycle. Sleep recordings were analyzed on computer monitor, and sleep stages were visually classified according to the criteria of the American Academy of Sleep Medicine (AASM).24

In order to compare subjective sleep quality with results of PSG, in the morning after the PSG recording, all subjects were asked to make an estimate of their sleep latency, sleep duration, number of awakenings, and sleep quality (according to a visual analogue scale [VAS] ranging from 0 to 100). In order to quantify the degree of sleep misperception we calculated a misperception index (MI),25 which was computed using the following formula:

\[
MI = \frac{[\text{objective Total Sleep Time (oTST)} - \text{subjective Total Sleep Time (sTST)}]}{\text{objective Total Sleep Time (oTST)}}
\]
Sleep microstructure was evaluated by means of the detection of the fast-frequency EEG arousals and the analysis of CAP. Arousal were visually detected and quantified in accordance to the rules of the ASDA; separate arousal indexes (number of arousals/time) were calculated for the entire sleep period time, NREM sleep, and REM. To evaluate the dynamics of arousal, we quantified the arousal fluctuations during sleep by means of CAP. CAP scoring was performed visually, according to the criteria established by Terzano et al.27 We quantified, within NREM sleep stages, the percentage of NREM sleep occupied by CAP. This ratio (CAP duration/NREM sleep), referred to as CAP rate, is the expression of the percentage of NREM sleep spent in a state of arousal instability.

**Power Spectral Analyses**

Sleep EEG power spectral analysis was performed using a central monopolar scalp derivation (C4 or C3 referred to the contralateral mastoid M1 or M2). Recordings from leads placed centrally reflect EEG activity summed from both frontal and parietal regions and are considered the most sensitive for recording sleep related activity.28-31 Sleep power spectral analysis was performed on all NREM and REM stages. Each 30-sec epoch was visually screened for artifacts (EMG, temporary disconnect spikes, sweating, body movements), and epochs with artifacts were removed from further analysis. The remaining data were extracted from the scored sleep data file by a software program (Rembrandt SleepView, Medcare) and stored in separate ASCII file. Spectral analysis was performed on 1-sec windows with a frequency resolution of 0.5 Hz using a discrete Fourier transform algorithm. Four spectral bands (delta: 0.5-4 Hz, theta: 4.5-7.5 Hz, alpha: 8-13 Hz, beta: 13.5-30 Hz) were computed per 30-sec epochs for the entire recording period. These spectra were converted to data file for statistical analysis. To compensate for variability among subjects and across the night in EEG power, the spectra were normalized: values in each frequency band were expressed as percentage of the total power.

**Heart Rate Variability**

*Physiological Correlates of Heart Rate Variability Analysis*

Heart rate variability (HRV) analysis is the measure of the variations of the interval between consecutive heart beats. It is widely accepted that HRV represents a quantitative marker of autonomic activity.32,33 The variations in heart rate may be evaluated by time domain methods and frequency domain methods.

The time domain methods are based on the detection of the QRS in a normal EKG and on the determination of normal-to-normal (NN) intervals, which are all the intervals between adjacent QRS sinus complex. Time domain variables used in the present study were heart rate and heart rate standard deviation.

The frequency domain methods consist in the calculation of the power spectral density analysis of a plot of consecutive NN intervals, called the tachogram. The auto-regressive method used in this study allowed an accurate estimation of power spectral density even on a small number of samples on which the signal is supposed to maintain stationarity. Two major spectral components were computed: low-frequency (LF) and high-frequency (HF). The HF component of the spectrum is widely recognized as a measure of vagal activity; the significance of LF component is more debated and seems to reflect at the same time both vagal and sympathetic activity. Overall, the LF/HF ratio may provide a quantitative estimation of the balance of the 2 branches of the autonomic nervous system (sympathovagal balance). The power of LF and HF bands was expressed in normalized units (nu), and the LF/HF ratio was calculated. Normalization was performed according to the formula:

\[ Z = \frac{X - \mu}{\sigma} \]

where \( \mu = E[X] \) is the mean and \( \sigma = \sqrt{\text{Var}(X)} \) the standard deviation of the probability distribution of \( X \). A detailed description of HRV analysis, standards of measurement, physiological interpretation, and clinical use is available in the report of the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology.32,33

**Statistical Analysis**

Data obtained from the patient group were compared to those obtained from controls. The following sleep variables were compared: sleep latency (subjective and objective), total sleep time (subjective and objective), number of awakenings (subjective and objective), sleep efficiency, percentages of each sleep stage (N1, N2, N3, REM), sleep quality (subjective VAS), and CAP parameters. The HRV parameters considered were: HR, HR standard deviation, power of LF and HF bands in normalized units, and the LF/HF ratio. All sleep parameters and HRV measures were compared in these 2 groups by means of a nonparametric test (Mann-Whitney U-test). To avoid type I errors, a formal Bonferroni correction was applied to each family of comparisons. The threshold for significance was \( p = 0.05 \).

**RESULTS**

The mean duration of BDZ abuse was 3.5 years (range 2-6 years); BDZs used were lorazepam in 3 cases (mean daily dose: 7.8 mg), lormetazepam in 1 case (10 mg/day), alprazolam in 1 case (9 mg/day), and bromazepam in 1 case (31 mg/day). In all cases, BDZs were initially prescribed for the treatment of chronic insomnia.

**Psychometric and Subjective Sleep Evaluation**

All patients completed the study. In the subjective sleep evaluation, the mean PSQI score was 9.7 ± 4.1; all patients had PSQI ≥ 5, indicating poor subjective sleep quality. The ESS mean score was 3.7 ± 4.3; only one patient had ESS > 9, indicating excessive daytime sleepiness. As concerns the evaluation of anxiety symptoms, the mean SAS score was 48.7 ± 11.8 (2 patients were in the normal range, 3 had mild to moderate anxiety levels, 1 had a score indicating severe anxiety). Mean BDI was 5.5 ± 4.8: all patients but one were below the threshold indicating mild depression symptoms. The mean score of the MOCI was 12.7 ± 2.0; all patients had scores ≥ 10; these scores appear greater that those reported in literature for normal subjects.34 SHAPS scores were normal in all subjects. Results of psychometric and sleep quality tests are in Table 1.
Polysomnographic Scores

As concerns sleep macrostructure, BDZ abusers, compared to controls, had shorter SOL (patients: 14.8 ± 18.0 min, controls: 31.3 ± 23.7, U-test: 249, p = 0.042) and increased WASO (patients: 133.4 ± 54.9 min, controls: 54.3 ± 40.7 min, U-test: 49, p = 0.005); no differences were observed in sleep stage percentages. Three patients had negative MI (indicating underestimation of sleep duration), and 2 patients had positive MI (indicating overestimation of sleep duration). The most relevant differences between the groups were observed in sleep microstructure: BDZ abusers had lower indexes of fast-frequency EEG arousal in total sleep (patients: 7.0 ± 3.2 events/h, controls 13.6 ± 4.6 events/h, U-test: 292, p = 0.002), NREM (patients: 6.6 ± 3.7 events/h, controls 13.7 ± 4.9 events/h, U-test: 294, p = 0.002), and REM (patients: 8.4 ± 2.4 events/h, controls 13.3 ± 5.1 events/h, U-test: 264, p = 0.016). Moreover, BDZ abusers showed much lower levels of CAP time (patients: 46.5 ± 26.3 min, controls: 169.9 ± 49.5 min, U-test: 325, p < 0.001) and CAP rate (patients: 15.0% ± 8.6%, controls: 51.2% ± 12.1%, U-test: 325, p < 0.001). Results of polysomnographic and subjective sleep evaluations and the MI are in Table 2. Detailed results of sleep scoring and of CAP analysis are shown in Table 3 and Table 4. Sleep hypnograms of all patients enrolled are shown in Figure 1.

EEG Power Spectral Analysis

Relative spectral power analysis showed that abusers, as compared to controls, had more beta activity (patients 13.7% ± 11.3%, controls: 6.3% ± 5.7%, U-test: 44, p = 0.028) and less theta activity (patients 7.1% ± 4.4%, controls: 14.1% ± 4.0%, U-test: 179, p = 0.004), whereas no significant differences were measured in the relative amount of delta and alpha frequency bands. Detailed results of EEG power spectral analysis and comparison between patients and controls are shown in Figure 2.

HRV Analysis

No significant differences were measured between BDZ abusers and controls in HRV parameters, with the exception of an increased HF component (patients: 48.2 ± 12.2 nu, controls: 35.2 ± 20.2 nu, U-test: 84, p = 0.050). Results of HRV analysis and comparison are shown in Table 3.

DISCUSSION

The objective of the present study was to investigate the modification of sleep pattern in chronic benzodiazepine abusers. Our results, though obtained from a small cohort of patients, seem to indicate that chronic BDZ abuse is associated with a peculiar pattern of sleep modification involving all levels of sleep organization.

As concerns sleep macrostructure, all patients showed poor subjective sleep quality, and polysomnography showed a marked increase in wake after sleep onset, associated with a gross disruption of the ultradian NREM/REM cycle (Figure 1). Despite these modifications in sleep macrostructure, the most
relevant findings observed in the abuse cohort concerned microstructure: in particular, abusers, compared to controls had significantly lower indexes of EEG arousal in all sleep stages and lower indexes of NREM sleep instability, measured by CAP. It seems likely that also HRV modifications, and in particular an increased HF component (a marker of vagal tone) reflect the reduced activity of the autonomic branch of the arousal system.35

It has been reported that physiological fluctuations of the EEG arousal level influence cardiac autonomic activity in normal subjects during sleep.36

Arousal mechanisms comprise ascending networks projecting to the cerebral cortex, which stimulate cortical activation reflected as fast EEG activity, and descending networks project to the spinal cord, stimulating sensory-motor activation.37 Nevertheless, the role of arousal systems is not simply to induce and maintain wake and EEG activation. Arousal modulations act as a filter that gates the flux of information from the peripheral receptors to the cortex; anatomically, this filter is situated in the thalamocortical connections where the incoming signals are blocked or attenuated via synaptic inhibition.35 The major role in this mechanism is played by the thalamic reticular nucleus (TRN), which is a GABAergic nucleus placed between the thalamus and the cortex; it receives excitatory afferents from both cortical and thalamic neurons and sends inhibitory projections to nuclei of the dorsal thalamus. The TRN is involved in the regulation of bottom-up activities, including sensory gating and the transfer to the cortex of sleep spindles.38,39 This mechanism modulates the susceptibility of the cerebral cortex to all the activating stimuli. Seen in this view, the modulation of arousal levels during sleep have a complex role: that is, to allow prompt awakening from sleep, but at the same time, to allow processing of incoming

Table 3—Results of polysomnographic analysis, arousal and CAP scores, and HRV analysis in patients and controls, and statistical comparison

<table>
<thead>
<tr>
<th></th>
<th>Patients (n = 6)</th>
<th>Controls (n = 55)</th>
<th>Mann-Whitney U-test</th>
<th>Fisher exact test ( \chi^2 )</th>
<th>p</th>
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<tbody>
<tr>
<td>Gender</td>
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<tr>
<td>Gender</td>
<td>4M, 2W</td>
<td>23M, 32W</td>
<td></td>
<td></td>
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<tr>
<td>Age</td>
<td>53.3 14.8</td>
<td>54.2 13.0</td>
<td>124.0 0.248</td>
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<td>Sleep Parameters</td>
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<tr>
<td>Sleep onset latency</td>
<td>14.8 18.0</td>
<td>31.3 23.7</td>
<td>249.0 0.042</td>
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<tr>
<td>Time in bed</td>
<td>512.8 83.6</td>
<td>482.3 38.6</td>
<td>100.0 0.115</td>
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<td>Total sleep time</td>
<td>364.3 95.7</td>
<td>391.8 53.3</td>
<td>219.5 0.187</td>
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<td>Sleep period time</td>
<td>419.8 83.6</td>
<td>443.4 39.8</td>
<td>226.5 0.136</td>
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<td>Sleep efficiency index</td>
<td>86.2 8.5</td>
<td>92.0 5.3</td>
<td>242.0 0.062</td>
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<td>Wake after sleep onset</td>
<td>6.0 3.6</td>
<td>5.5 3.5</td>
<td>149.5 0.706</td>
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<td></td>
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<tr>
<td>REM</td>
<td>133.4 54.9</td>
<td>54.3 40.7</td>
<td>49.0 0.005</td>
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<td>N1</td>
<td>12.7 8.5</td>
<td>17.3 7.8</td>
<td>216.0 0.217</td>
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<tr>
<td>N2</td>
<td>5.6 3.1</td>
<td>10.8 8.3</td>
<td>246.0 0.050</td>
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<tr>
<td>N3</td>
<td>50.8 14.8</td>
<td>39.5 11.3</td>
<td>94.0 0.086</td>
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<td>Arousal index in sleep</td>
<td>17.2 13.6</td>
<td>20.7 10.5</td>
<td>180.0 0.716</td>
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<td>Arousal index in NREM</td>
<td>7.0 3.2</td>
<td>13.6 4.6</td>
<td>292.0 0.002</td>
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<td>Arousal index in REM</td>
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<td>13.7 4.9</td>
<td>294.0 0.002</td>
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<td>8.4 2.4</td>
<td>13.3 5.1</td>
<td>264.0 0.016</td>
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<td>51.2 12.1</td>
<td>325.0 &lt; 0.001</td>
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<td>Heart Rate Variability</td>
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<td></td>
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<tr>
<td>Heart rate</td>
<td>64.6 6.8</td>
<td>59.0 7.3</td>
<td>94.0 0.086</td>
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<td>LF (nu)</td>
<td>51.8 12.2</td>
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<tr>
<td>HF (nu)</td>
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<td>35.2 20.2</td>
<td>84.0 0.050</td>
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<td>2.9 2.9</td>
<td>221.0 0.175</td>
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<td>Heart Rate Variability NREM</td>
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<tr>
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<td>57.5 6.5</td>
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<td>219.5 0.187</td>
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<tr>
<td>HF (nu)</td>
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<td>242.0 0.062</td>
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<tr>
<td>LF/HF</td>
<td>0.7 0.5</td>
<td>0.6 0.6</td>
<td>226.5 0.136</td>
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<td>Heart Rate Variability REM</td>
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<tr>
<td>Heart rate</td>
<td>72.3 6.2</td>
<td>67.5 9.9</td>
<td>221.0 0.175</td>
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<tr>
<td>LF (nu)</td>
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<td>149.5 0.706</td>
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SD, standard deviation.
inputs and to define a threshold of intensity or relevance, above which the stimulus may cause awakening and below which the stimulus is dumped and sleep may go on.

Fluctuations of arousal, measured by CAP, constitute therefore an essential mechanism in sleep regulation. CAP acts as a constitutive element of sleep architecture, since arousal fluctuations are essential to allow the physiological balance between slow wave and desynchronized sleep (NREM/REM). Moreover, arousal fluctuations are also essential to dump the effect of incoming disruptive stimuli and to protect sleep from external perturbations.

Our patients, overall, did not show abnormal scores on tests of psychological measures, with the exception of the MOCI. MOCI score is a measure of obsessive-compulsive behaviors. Several data indicate a strong association between obsessive-compulsive disorder (OCD) and drug abuse. Obsessive-compulsive personality disorder (OCPD) has been reported as the most common personality disorder in hypnotic-dependent adults40; the co-occurrence of substance abuse in OCD is higher than in other psychiatric disorders41; and, in a neuroimaging study, orbitofrontal connectivity was reduced in both OCD and drug abusers, suggesting that the two conditions share important cognitive and neurobiological substrates.35,41 Anxious hyperarousability, a hallmark of Cluster C personality, and in particular of OCPD and avoidant features, is a sensitive risk marker for chronic insomnia, which was the initial reason for BDZ intake in all our patients.

Seen in this view, the effect of chronic BDZ abuse on sleep may be described as a severe modification of the thalamic gating of incoming stimuli and, consequently, of arousal dynamics. As result, abusers seem to have a reduced ability to elaborate afferent stimuli during sleep. Incoming stimuli in normal subjects can induce increased amount of arousal and CAP rate, without causing awakenings (as happens in the experimental model of noise-induced situational insomnia13,42). Conversely, in BDZ abusers, the chronic GABAergic stimulation makes the thalamic filter less adaptive: when exposed to stimuli, abusers either produce no response (and keep sleeping without arousal) or fully awaken. As a consequence, abusers have a marked reduction of arousals associated with increased number of nocturnal awakenings without relevant modifications of sleep macroarchitecture.

Study Limitations

The main limitation of the present study is the small number of patients enrolled. This is a consequence of the strict inclusion criteria: we decided to study sleep in a cohort of patients with pure BDZ abuse not associated with consumption of other drugs or substances. Moreover, the sleep study lasted 24 hours: this could have prevented evaluation of the circadian sleep-wake cycle and its variability.

Table 4—Results of polysomnographic analysis, arousal and CAP scores, and HRV analysis in patients and controls

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Controls 30-40 y (n = 12)</th>
<th>Patients 40-50 y (n = 17)</th>
<th>Patients Controls &gt; 65 y (n = 14)</th>
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<tr>
<td>Gender</td>
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<td>#5 Mean SD</td>
<td>#6 M</td>
<td>#2 M</td>
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<tr>
<td>Age</td>
<td>34 M</td>
<td>38 35.8 3.7</td>
<td>58 53 35.4 3.2</td>
<td>70 67 70.2 3.5</td>
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<tr>
<td>Sleep Parameters</td>
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<tr>
<td>Sleep onset latency</td>
<td>12.0</td>
<td>50.5 38.0 26.9</td>
<td>9.5 1.0</td>
<td>27.9 18.9 30.4 26.3</td>
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<td>Time in bed</td>
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<td>587.5 479.0 36.7</td>
<td>510.5 538.5 489.6 37.1</td>
<td>362.0 491.0 474.3 44.4</td>
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<td>Total sleep time</td>
<td>539.0</td>
<td>362.5 376.0 53.5</td>
<td>363.0 365.6 400.3 56.2</td>
<td>251.0 315.5 379.9 47.8</td>
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<td>Sleep period time</td>
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<td>428.5 434.2 33.2</td>
<td>397.5 431.0 451.9 38.8</td>
<td>350.0 340.0 440.9 42.0</td>
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<td>84.6 90.9 6.5</td>
<td>91.3 82.7 92.3 4.6</td>
<td>71.7 92.8 93.1 5.2</td>
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<td>Awakenings &gt; 1 min</td>
<td>11.0</td>
<td>9.0 6.1 3.3</td>
<td>3.0 2.0</td>
<td>5.9 4.5 7.0 4.0</td>
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<td>Wake after sleep onset</td>
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<td>174.5 65.1 57.7</td>
<td>138.0 181.0 46.3 40.0</td>
<td>106.0 164.5 62.8 34.8</td>
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<td>22.0</td>
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<td>21.4 2.8</td>
<td>15.7 6.0 10.1 15.9</td>
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<td>9.8</td>
<td>7.7 9.3 5.5</td>
<td>2.8 3.6</td>
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<td>59.8</td>
<td>49.6 39.4 8.2</td>
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<td>25.9 0.8</td>
<td>11.0 11.0 15.1 35.0</td>
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<td>Arousal index in sleep</td>
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<td>11.6 14.7 4.8</td>
<td>4.8 2.5</td>
<td>13.5 4.9 6.5 8.4</td>
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<td>Arousal index in NREM</td>
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<td>11.8 14.6 5.1</td>
<td>2.6 2.4</td>
<td>13.8 5.0 6.1 8.0</td>
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<td>Arousal index in REM</td>
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<td>12.0 5.0</td>
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<td>29.3</td>
<td>66.9 152.0 45.9</td>
<td>49.9 82.8</td>
<td>153.9 50.4 9.6 40.3</td>
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<tr>
<td>Heart rate</td>
<td>65.7</td>
<td>59.6 58.1 6.3</td>
<td>74.0 71.1 60.2 8.4</td>
<td>57.1 60.1 61.2 7.2</td>
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<td>1.7 2.8</td>
<td>3.5 2.0 13.0 6.0</td>
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<tr>
<td>LF (nu)</td>
<td>65.8</td>
<td>53.8 40.3 19.5</td>
<td>56.0 59.0</td>
<td>44.2 20.4 45.0 31.1</td>
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<tr>
<td>HF (nu)</td>
<td>34.2</td>
<td>46.2 36.2 21.4</td>
<td>44.0 41.0</td>
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<td>LF/HF</td>
<td>1.9</td>
<td>1.2 2.7 2.6</td>
<td>1.3 1.4</td>
<td>2.9 2.2 0.8 0.5</td>
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Control groups were obtained selecting patients for each age range from the total control group of 55. SD, standard deviation. Due to the low number of patients in each age subgroup, no statistical comparison was performed.
Figure 1—Twenty-four-hour sleep hypnograms in BDZ abusers

Figure 2—Histograms of relative power spectra in BDZ abusers and controls
REFERENCES


Clinical Usefulness of Watch-PAT for Assessing the Surgical Results of Obstructive Sleep Apnea Syndrome


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Objective: This study aimed to assess the accuracy and clinical efficacy of a wrist-worn device that is based on peripheral arterial tonometry (watch-PAT) to evaluate the surgical results of obstructive sleep apnea (OSA) syndrome subjects.

Study Design and Method: Thirty-five subjects who were diagnosed with OSA and underwent sleep surgeries such as septoplasty, tonsillectomy, or uvuloplasty to correct their airway collapse, participated in this study; the watch-PAT-derived respiratory disturbance index (RDI), apnea and hypopnea index (AHI), lowest oxygen saturation, and valid sleep time were measured after the sleep surgery.

Results: The present study showed that RDI (32.8 ± 10.7 vs 14.8 ± 7.5), AHI (30.3 ± 8.6 vs 13.4 ± 8.2 events/h), lowest oxygen saturation (78.2% ± 8.4% vs 90.5% ± 7.1%), and valid sleep time (329.1 ± 47.2 min and a postoperative value of 389.1 ± 50.1 min) recovered to within a normal range after surgery in 28 subjects. In addition, good agreement was found between watch-PAT-derived factors and visual analogue scales for changes in subjective symptoms, such as snoring, apnea, and daytime somnolence. Seven of the 35 subjects showed no improvement for their subjective symptoms and complained of snoring and apnea after surgery. We found that the RDI and AHI of those 7 subjects were not reduced, and the changes between pre- and postoperative values which were measured with watch-PAT were minimal. Their postoperative lowest oxygen saturation and valid sleep time were not elevated per the watch-PAT. The results support a strong correlation between the findings from watch-PAT and improved symptoms after surgical correction of an airway collapse.

Conclusions: Our study provides evidence that the factors measured by the watch-PAT might be reliable indicators of symptomatic changes in OSA subjects after sleep surgery and also shows that the watch-PAT is a highly sensitive portable device for estimating treatment results in OSA.

Keywords: Obstructive sleep apnea, watch PAT, sleep surgery, airway collapse

Citation: Park CY; Hong JH; Lee JH; Lee KE; Cho HS; Lim SL; Kwak JW; Kim KS; Kim HJ. Clinical usefulness of watch-PAT for assessing the surgical results of obstructive sleep apnea syndrome. J Clin Sleep Med 2014;10(1):43-47.
arterial pulse wave volume of the digit. Episodes of upper airway obstruction cause episodic vasoconstriction of digital vascular beds due to activation of the sympathetic nervous system, which results in attenuation of the PAT signal.6 The diagnosis of OSA is possible with this device using only five parameters: PAT signal, heart rate, oxyhemoglobin saturation, wrist activity without the conventional measurements of airflow, and respiratory effort. Some studies have attempted to assess the accuracy of the watch-PAT to diagnose and evaluate severity of OSA.7; although they had several limitations, the watch-PAT showed good concordance with PSG for diagnosing OSA. Also the watch-PAT had several advantages, such as inexpensive cost, wide accessibility, ease of use, lower risk, and few side effects. Some reports have shown that the watch-PAT might be useful in reassessing OSA patients for efficacy of CPAP treatment.6 However, there is controversy over whether the watch-PAT is able to evaluate the success rate of OSA improvement after surgical treatment.

In the present study, we analyzed the clinical efficacy of both pre- and postoperative, overnight, in-house watch-PAT use as a full PSG substitution to assess OSA surgical results.

MATERIALS AND METHODS

Subjects
Thirty-five adult subjects who had been diagnosed with moderate or severe OSA in Chung-Ang University Hospital (Seoul, Korea) participated in the study; all subjects gave informed consent. These patients were required to fill out our hospital’s sleep survey chart, which includes BMI, Epworth Sleepiness Scale (ESS), and visual analog scale (VAS) survey for snoring and apnea. Intrasal endoscopy, cephaleography, and drug-induced sleep endoscopy (DISE) were performed to evaluate airway narrowing and the exact site of airway collapse. All patients underwent DISE; among these patients, 25 showed severe narrowing (> 75%) of the nasopharynx and the retropalatal area. Of the remaining patients, 7 patients showed moderate narrowing (> 25%, < 75%) and 3 patients showed mild narrowing (< 25%) of the airway area. In cephaleography, the mean posterior air space (PAS) was 8.1 ± 2.3 mm (reference range 11 ± 2 mm) and mandible plane to hyoid (MPH) was 12.5 ± 3.7 mm (reference range 19 ± 2 mm). Septal deviation, redundant uvula, or tonsil hypertrophy were observed in the subjects, and OSA was finally diagnosed using the watch-PAT 200 (Itamar Medical Ltd, Caesarea, Israel). CPAP was recommended as a primary OSA treatment, but the subjects had refused to wear the unit due to the long treatment duration and related sleep discomfort. For primary treatment, all 35 subjects received septoplasty, 23 subjects received uvuloplasty, and 12 subjects received tonsillectomy to correct airway narrowing. Exclusion criteria were as follows: (1) history of peripheral vasculopathy or autonomic nervous system dysfunction and mild OSA; (2) cardiac problems, severe lung disease, and use of α-adrenergic receptor-blocking agents; and (3) finger deformity that might affect application of the watch-PAT probe. In addition, we did not include the subjects who showed narrowed airway at tongue base and glottis. The subject population consisted of 27 males and 8 females. The mean body mass index was 22.3 kg/m², and mean age was 50.7 years.

RESULTS

We recruited 35 subjects diagnosed with OSA and performed septoplasty, uvuloplasty, or tonsillectomy to resolve airway narrowing and to reduce airway collapse. Pre- and postoperative pAHI, pRDI, lowest oxygen saturation, and valid sleep time were evaluated. The mean pAHI for the 35 subjects was 30.3 ± 8.6 events/h when measured before sleep surgery using the watch-PAT, while the postoperative mean pAHI was 13.4 ± 8.2 events/h, showing a statistically significant reduction of pAHI after the sleep surgery (Figure 1A). The preoperative mean pRDI was 32.8 ± 10.7 events/h, while the postoperative mean pRDI was 14.8 ± 7.5 events/h; thus, postoperative pRDI was also significantly decreased after the sleep surgery (Figure 1B).

The pre-operative lowest oxygen saturation value was 78.2% ± 8.4% while the postoperative value was 90.5% ± 7.1%, a statistically significant improvement (Figure 1C). Also, there was a statistically significant improvement (p < 0.05) in valid sleep time, with a preoperative value of 329.1 ± 47.2 min and a postoperative value of 389.1 ± 50.1 min (Figure 1D).

These data show that surgical treatment for OSA is relatively successful when we analyze mean pAHI, pRDI, lowest oxygen saturation, and valid sleep time pre- and postoperatively using the watch-PAT. As a next step, we assessed the correlation between factors measured using the watch-PAT and the changes in subjective symptoms to determine whether the watch-PAT data were representative of an actual improvement in subjective symptoms after the sleep surgeries. Twenty-eight subjects showed good surgical results and were classified as the responder group. The VAS for snoring and apnea and the ESS scores for daytime somnolence were reduced after the sleep surgeries, and the pAHI, pRDI, lowest oxygen saturation, and valid sleep time from the watch-PAT were significantly improved. However, 7 of the 35 subjects who were classified as the non-responder group still complained of snoring, apnea, and daytime somnolence after the sleep surgery, and their pAHI, pRDI, lowest oxygen saturation, and valid sleep time from the watch-PAT had not significantly changed.

We then estimated the variability of pAHI, pRDI, lowest oxygen saturation, and valid sleep time and compared these

Study Design and Statistical Analysis
All subjects completed a pre- and postoperative research survey that included a visual analog scale (scale 1-10 where 10 was totally satisfied) for snoring and apnea, and an Epworth Sleepiness Scale was used to evaluate subjects’ daytime sleepiness.6 The watch-PAT was performed twice: once prior to the sleep surgery and 2 months after the surgery. The apnea-hypopnea index (pAHI), respiratory distress index (pRDI), lowest oxygen saturation, and valid sleep time were evaluated. To analyze the watch-PAT results, PAT studies were uploaded for automated analysis on a personal computer using the COMPACTFLASH reader provided with the PAT software (zzz_PAT version 1.5.44.7, Itamar Medical Ltd, Caesarea, Israel). Kendall tau-b was used to assess correlation and agreement between the surgical results and watch-PAT data. All analysis was performed with SPSS (version 18.0; SPSS Inc., Chicago, IL, USA) for Windows software. A p value < 0.05 was considered statistically significant.
changed values with the subjects’ VAS and ESS scores to investigate the factors measured using the watch-PAT. Figure 2 shows a scatter plot of change in pre- and postoperative snoring VAS score vs. change in pre- and postoperative pRDI. We found a high correlation ($r = 0.785$, $p < 0.05$) and good agreement between change in snoring VAS score and change in pRDI. Also, Figure 2 shows a scatter plot of change in pre- and postoperative snoring VAS score vs. change in pre- and postoperative pAHI. We found a high correlation ($r = 0.829$, $p < 0.05$) and good agreement between change in snoring VAS score and change in pAHI. In other words, if a subject’s apnea improved after sleep surgery, both pRDI and pAHI were reduced.

Figure 3 shows scatter plots of change in pre- and postoperative apnea VAS score vs. change in pre- and postoperative pRDI and pAHI. We found a high correlation ($r = 0.809$ for RDI, $r = 0.765$ for AHI, $p < 0.05$) and good agreement between these values. If a subject’s apnea improved after the sleep surgery, both pAHI and pRDI were reduced. In particular, the 7 subjects who did not show improvement in VAS for snoring or apnea also did not show much improvement in pRDI or pAHI.

We also evaluated the change in pre- and postoperative ESS score vs. change in pre- and postoperative pRDI and pAHI (Figure 4). We found a high correlation ($r = 0.774$ for RDI, $r = 0.758$ for AHI, $p < 0.05$) and high concordance between change in ESS score and pRDI and pAHI values. Again, the pRDI and pAHI values significantly decreased in subjects whose daytime somnolence was improved after the sleep surgery, but neither factor improved in subjects who still complained of daytime somnolence after sleep surgery.

**DISCUSSION**

In this study, we assessed the surgical results of OSA subjects using the watch-PAT and found that factors such as pRDI, pAHI, lowest oxygen saturation, and valid sleep time that were measured by watch-PAT appear to be well correlated with the improvement in a subject’s symptoms and reflect corrected airway narrowing.

The present accepted standard for OSA diagnosis is a full PSG in a sleep laboratory, and an overnight full PSG as a level I study is largely viewed as the most comprehensive. Full PSG involves 16 or more channels monitoring EEG, EKG, EOG, EMG, airflow oximetry, nasal pressure, esophageal pressure, body position, snoring sounds, and rib cage and abdominal movements. Full PSG should be performed in a hospital or sleep laboratory, with a sleep technologist and board certified
Portable PSG units were developed because of several recognized advantages over sleep-laboratory PSG, including sleep in a more familiar and flexible environment, fewer monitor leads, more convenience for patients with respect to transportation, probable reduced sleep disturbance, less technical complexity, and lower cost. The 1994 AASM practice standards ultimately concluded that there were some limitations to portable PSG for OSA assessment, and the efficacy of portable PSG was still controversial. Advances in the diagnosis and treatment of OSA have occurred largely based on data from full PSG, and portable PSG was assumed to not provide better or more reliable diagnosis of OSA or other sleep disordered breathing (SDB). Therefore, the AASM recommends that portable PSG should be used only in conjunction with a comprehensive sleep evaluation and must be supervised by a certified or eligible sleep medicine specialist.

Many portable monitoring devices for the diagnosis of OSA have been tested as an alternative to full PSG. Several studies pronounced the validation of portable PSG for the diagnosis of OSA or accordance with full PSG, and the clinical concordance of AHI, RDI, and oxygen desaturation between portable and full PSG has been suggested.

A portable PSG that uses pulsatile arterial tonometry, the watch-PAT might be accurate in identifying moderate-to-severe SDB. The watch-PAT device is unique since it allows for diagnosis of OSA through the detection of episodic vasoconstriction of the digital vascular beds rather than conventional measures of airflow and chest/abdominal excursion such as the PSG. The watch-PAT is a level III sleep study that detects peripheral arterial tonometry, making possible at-home testing. Also,
the accuracy of watch-PAT in the diagnosis of OSA and related sleep factors between watch-PAT and full PSG have been assessed in various studies. Bar et al. reported that the PAT AHI and PSG AHI were in high concordance with each other across a wide range of AHI values. Similarly, a study performed by Pittman et al. compared PSG scoring data and watch-PAT data and showed a high correlation between PSG AHI and PAT AHI values. Due to the portability and low cost of the watch-PAT, sleep study may be conveniently and efficiently performed prior to and after CPAP therapy. The watch-PAT device is easy to use for home sleep studies, with a low failure rate and minimal technical effort when compared with PSG. However, there have been a few studies in which the surgical results assessed after correcting airway narrowing using watch-PAT did not correlate well with the subjects’ reported symptoms.

In the present study, we performed a sleep study using a watch-PAT both before and after sleep surgeries in order to diagnosis OSA and also evaluated the effect of surgical correction for airway collapse. We found that the mean values of the watch-PAT-derived parameters, such as pAHI, PRDI, lowest oxygen saturation, and valid sleep time were significantly improved after the sleep surgeries, and the watch-PAT appears to provide useful clinical information about the efficacy of sleep surgery and success or failure in correction for airway collapse.

Twenty-eight subjects were divided into responder groups after sleep surgery and showed an improvement in subjective symptoms such as snoring, apnea, and daytime somnolence. Their postoperative watch-PAT results showed a significant decrease in pAHI and PRDI values. In addition, oxygen saturation and valid sleep time were improved along with their reported subjective symptoms. These data suggest good correlation and agreement between a subject’s symptoms and important parameters of the watch-PAT after surgical correction for airway collapse in OSA subjects. In particular, for the seven subjects who reported having no subjective improvement in snoring, apnea, or daytime somnolence, the watch-PAT also showed no significant change in pAHI, PRDI, lowest oxygen saturation, or valid sleep time, resulting in high correlation to the subjects’ symptoms. We conclude that the watch-PAT might be a convenient portable device for evaluating surgical results, and the parameters of watch-PAT could compensate for the disadvantages of full PSG.

The present study did not validate the concordance between overnight PSG and the watch-PAT for measuring the sleep factors. However, many studies have reported the good agreement between the two devices, and our main goal was to determine the usefulness of the watch-PAT before and after surgical treatment in order to simply diagnosis and assess OSA results rather than focusing on the concordance between the PSG and the watch-PAT.

OSA is a condition that can greatly affect a person’s quality of life and may also result in serious medical disease. Therefore, accurate diagnosis and early treatment are essential for OSA patients. The watch-PAT is easy to use for home sleep studies, with a low failure rate and minimal technical effort. The results of watch-PAT can be interpreted more simply than full PSG and provide useful information about the efficacy of sleep surgeries. This study demonstrates that the watch-PAT may be efficiently applied not only to the diagnosis of OSA, but also to accurately assess treatment results of sleep surgeries.

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Submitted for publication May, 2013
Submitted in final revised form July, 2013
Accepted for publication August, 2013
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DISCLOSURE STATEMENT

This was not an industry supported study. The authors have indicated no financial conflicts of interest.
Impact of Dronabinol on Quantitative Electroencephalogram (qEEG) Measures of Sleep in Obstructive Sleep Apnea Syndrome

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Study Objectives: To determine the effects of dronabinol on quantitative electroencephalogram (EEG) markers of the sleep process, including power distribution and ultradian cycling in 15 patients with obstructive sleep apnea (OSA).

Methods: EEG (C4-A1) relative power (% total) in the delta, theta, alpha, and sigma bands was quantified by fast Fourier transformation (FFT) over 28-second intervals. An activation ratio (AR = \([\text{alpha} + \text{sigma}] / [\text{delta} + \text{theta}]\)) also was computed for each interval. To assess ultradian rhythms, the best-fitting cosine wave was determined for AR and each frequency band in each polysomnogram (PSG).

Results: Fifteen subjects were included in the analysis. Dronabinol was associated with significantly increased theta power (\(p = 0.002\)). During the first half of the night, dronabinol decreased sigma power (\(p = 0.03\)) and AR (\(p = 0.03\)), and increased theta power (\(p = 0.0006\)). At increasing dronabinol doses, ultradian rhythms accounted for a greater fraction of EEG power variance in the delta band (\(p = 0.04\)) and AR (\(p = 0.03\)). Females had higher amplitude ultradian rhythms than males (theta: \(p = 0.01\); sigma: \(p = 0.01\)). Decreasing AHI was associated with increasing ultradian rhythm amplitudes (sigma: \(p < 0.001\); AR: \(p = 0.02\)). At the end of treatment, lower relative power in the theta band (\(p = 0.02\)) and lower AHI (\(p = 0.05\)) correlated with a greater decrease in sleepiness from baseline.

Conclusions: This exploratory study demonstrates that in individuals with OSA, dronabinol treatment may yield a shift in EEG power toward delta and theta frequencies and a strengthening of ultradian rhythms in the sleep EEG.

Keywords: Dronabinol, sleep, quantitative EEG, ultradian rhythms, OSA

Citation: Farabi SS; Prasad B; Quinn L; Carley DW. Impact of dronabinol on quantitative electroencephalogram (qEEG) measures of sleep in obstructive sleep apnea syndrome. J Clin Sleep Med 2014;10(1):49-56.

Obstructive sleep apnea (OSA) is associated with increased sleep fragmentation, decreased sleep efficiency and reduced slow wave sleep. These changes in the sleep process undermine sleep quality and are hypothesized to be an important source of excessive daytime sleepiness, the dominant symptom of OSA. Still, despite decades of investigation, the mechanisms linking sleep, disordered breathing, daytime sleepiness, and cognitive dysfunction in OSA remain poorly defined. This knowledge gap has hindered efforts to develop effective OSA drug treatments. We previously demonstrated that oral dronabinol decreased apnea hypopnea index (AHI) in subjects with OSA. Interestingly, although overall sleep stage percentages did not change with treatment, daytime sleepiness decreased significantly. Here, we hypothesized that simple sleep stage distributions may be insensitive to important aspects of sleep architecture contributing to improved alertness with dronabinol treatment. In comparison to visually assigned sleep stages, quantitative changes in EEG power spectra may provide more sensitive markers of sleep depth, structure, and continuity. Further, cannabinoid drugs such as dronabinol have been shown to alter EEG power spectra both in animals and humans.

Ultradian cycling between light and deep sleep and between NREM and REM sleep is another highly characteristic component of normal sleep that can be disrupted in subjects with OSA and is not directly assessed by sleep stage distributions, sleep bout durations, arousal indexes, sleep stage transition frequencies, and similar statistics. Such disruption may play a role in the excessive daytime sleepiness seen in people with OSA. Effects of cannabinoid drugs on ultradian rhythms during sleep have not been systematically studied.

The aims of the present study were to quantify the effects of dronabinol on EEG power distributions and ultradian cycling of EEG power in subjects with OSA.

Methods: Details of the underlying proof of concept trial have been published previously, and are summarized here.
Subjects
Seventeen adults (ages 21 to 64 years) with moderate to severe OSA (AHI ≥ 15) were enrolled. Individuals working night or rotating shifts, taking medications with known effects on sleep architecture, with clinically significant and uncontrolled or progressive medical comorbidity or any other primary sleep disorder were excluded. Individuals treated by positive airway pressure discontinued treatment ≥ 7 days prior to enrolling in the study. Two of the 17 subjects initially enrolled discontinued prior to completing the study and were not included in the analysis. Table 1 summarizes baseline characteristics for the 15 subjects included in the present analysis.

Dose Escalation Protocol
Following a baseline overnight polysomnogram (PSG), which also served as the final screening to document OSA severity, subjects were started on oral dronabinol, 2.5 mg/day 30 min before bedtime, for 1 week. If this dose was well-tolerated, the dose was increased to 5 mg/day during week 2, and again as tolerated to 10 mg/day during week 3. Repeat PSGs were performed at the end of each treatment week. As outlined in Table 2, a total of 8 subjects were fully escalated and received 10 mg/day dronabinol during the third treatment week. One PSG was technically inadequate at this dose and was not included in the analysis. Five subjects maintained 5 mg/day dronabinol during the final treatment week, and 2 subjects remained at a dose of 2.5 mg/day throughout. There were no statistically significant differences in baseline characteristics, reported in Table 1, between those subjects that escalated fully and those that did not tolerate escalation.

Power Spectrum Analysis
Polysomnographic data were sampled (256/s) and stored to disk using Alice 5 hardware (Philips Respironics). Fast Fourier transformation (FFT) was applied to contiguous 4-s segments, and periodograms from 7 successive segments were averaged to obtain relative power (% total power) once every 28 s for the delta (≥ 0.5 to 3.5 Hz), theta (≥ 3.5 to 8 Hz), alpha (≥ 8 to 12 Hz), and sigma (≥ 12 to 16 Hz) frequency bands of the central (C4-A1) electroencephalogram (EEG). To determine the balance of high versus low frequency activity in the EEG power spectrum, an activation ratio (AR) was computed as the sum of alpha + sigma power divided by the sum of delta + theta power for each 28-s epoch. Determinations of band definitions and widths, electrode derivations and formation of AR were all fixed prior to data analysis based on common practice reported in the literature. The means and standard deviations of each band and the AR were computed over the entire night and separately for the first and second 4-h recording intervals. Within subjects ANOVA was conducted to determine the effects of treatment dose on relative power in each band as well as on the AR.

Ultradian Analysis
We also investigated the effect of dronabinol on the ultradian structure of EEG power. For this purpose, the best-fitting cosine wave was determined for each frequency band and the AR for each PSG recording. Because the period of any underlying biological ultradian rhythm could not be known in advance and may have differed between individuals and across dronabinol doses, for each PSG recording we successively fitted cosines with periods ranging from 60 to 150 min in 6-min increments by least-squares regression. In each case the cosine with the highest Pearson product-moment correlation coefficient was selected as the best overall fit. Regression analyses were performed to determine the effects of AHI, dose, weight, age, and gender on each parameter (amplitude, period, phase, and R^2) of the best-fitting cosine wave for the AR and each EEG band.

In order to determine the sensitivity of this approach to meaningfully estimate the underlying period of the biological rhythm, we performed a sensitivity analysis. As shown in Figure 1, with respect to the “best fit” cosine wave, shifting the period by 6 min resulted in an average decrease of R^2 ≥ 20%, suggesting that the regression procedure realistically identified a meaningful best fit, even when the correlation coefficient was low. In fact, paired t-tests demonstrated statistically significant differences (p < 0.0005) in R^2 between the best fit cosine and cosines with periods ± 6 minutes (Figure 1).

RESULTS

Power Spectrum Analysis
As depicted in Figure 2, within subjects ANOVA revealed significant differences among doses for AR (p = 0.03) in the first 4 h of the night. Figure 3 demonstrates that this effect was driven primarily by dose dependent changes in theta (p = 0.0006) and sigma (p = 0.03) power. The dose-dependent effect remained significant for the full 8-h period for relative theta power (p = 0.002). Similar trends were seen for the full 8-h period for AR and relative sigma power, but these did not reach statistical significance (Table 3).

### Table 1—Summary of subject characteristics (mean ± SD)

<table>
<thead>
<tr>
<th>Parameter</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Gender (M/F)</td>
<td>6/9</td>
</tr>
<tr>
<td>Age</td>
<td>51.7 ± 7.9</td>
</tr>
<tr>
<td>BMI</td>
<td>35.1 ± 7.1</td>
</tr>
<tr>
<td>AHI</td>
<td>44.5 ± 22.8</td>
</tr>
<tr>
<td>Minutes at SpO₂ &lt; 90%</td>
<td>30.7 ± 49.46</td>
</tr>
<tr>
<td>Arousal Index</td>
<td>42.67 ± 22.76</td>
</tr>
</tbody>
</table>

### Table 2—Summary of dose escalation protocol: values indicate the number of subjects (recordings) at each dose by treatment week, available for final analysis

<table>
<thead>
<tr>
<th></th>
<th>0 mg</th>
<th>2.5 mg</th>
<th>5 mg</th>
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<tbody>
<tr>
<td>Baseline</td>
<td>15</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Week 1</td>
<td>0</td>
<td>15</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Week 2</td>
<td>0</td>
<td>3</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Week 3</td>
<td>0</td>
<td>2</td>
<td>5</td>
<td>7*</td>
</tr>
</tbody>
</table>

*One subject escalated to 10 mg/day for week 3, but PSG recording was technically inadequate for analysis.
Ultradian Analysis

Figure 4 provides an illustration of ultradian fluctuations in AR for a single subject at dronabinol doses of 0 mg (baseline recording) and 10 mg per day. Characteristics for the parameters of ultradian rhythm for each frequency band and the AR are summarized in Table 4. Consistent with Figure 4, the group-wise data show that as the dronabinol dose increased, ultradian fluctuations accounted for an increasing fraction of the overall variance in the AR (p = 0.03). Table 5 shows correlation coefficients between best-fit ultradian cosine parameters (R², phase, period, and amplitude) and potential explanatory variables including AHI, dose, weight, age, and gender. At increasing dronabinol doses, ultradian rhythms accounted for a higher fraction of total variance in the delta (p = 0.04), alpha (p = 0.06), and sigma (p = 0.07) bands and, as previously noted, the AR (p = 0.03). Females had higher amplitude ultradian rhythms than males in
the theta (p = 0.01) and sigma (p = 0.01) bands. Decreasing AHI was associated with increasing amplitude of ultradian rhythms in the sigma frequency band (p < 0.001) and the AR (p = 0.02). In view of the exploratory nature of this analysis, p-values reported in Table 5 were not corrected for multiple comparisons.

**Sleep Stage Analysis**

Table 6 reports the effects of dronabinol on sleep architecture, based on sleep stage analysis using 30-s epochs. There were no statistically significant changes in the expression of stages 1, 2, slow wave (SWS; stage 3 + stage 4), or REM as a percentage of total sleep time. Similarly, the mean bout durations for stage 1, SWS, and REM remained unchanged, suggesting that sleep fragmentation was not improved by dronabinol. In fact, the mean bout duration for stage 2 was decreased slightly by dronabinol.

**DISCUSSION**

This exploratory study demonstrates effects of dronabinol on quantitative EEG measures of the sleep process in patients with obstructive sleep apnea and suggests possible mechanisms by which dronabinol reduces daytime sleepiness in this population. Specifically, increasing doses of dronabinol were associated with a shift in EEG power toward delta and theta frequencies and strengthening of ultradian rhythms in the sleep EEG. This suggests that oral dronabinol may have improved restorative aspects of the sleep process, contributing to the observed decrease in daytime sleepiness, despite the absence of changes in overall sleep stage percentages or sleep efficiency. Previous investigations have reported a wide variety of cannabinoid effects on sleep architecture in humans. The most consistent finding is a decrease of REM sleep following cannabinoid administration. Some studies report increased stage 2 sleep with decreased stage 4 sleep, while others report an increase in stage 4 sleep. These inconsistent findings may reflect differences in agents, formulations, routes of administration, concentrations, durations of exposure, ages, populations studied, and other factors. As previously reported and shown in Table 6, we observed no significant changes in overall sleep stage distribution associated with dronabinol administration at
doses up to 10 mg/day in our subjects with OSA. Table 6 also illustrates that the mean bout durations for SWS and REM sleep were not increased by dronabinol, suggesting that sleep fragmentation, as measured by sleep stage analysis, was not improved. The present analysis revealed, however, that oral dronabinol shifted EEG power toward lower frequencies, reducing the AR (Figures 2, 3; Table 3). Although cannabinoids have been shown to affect sleep EEG power distributions in both animals and healthy humans, the previously reported effects on theta and sigma band power are inconsistent, and the doses employed were typically higher than in the present study. This is the first report to define the possible impact of oral dronabinol on sleep EEG power distribution in individuals with OSA.

The observed effects were more apparent during the first half of the night after oral administration of dronabinol. A statistically significant decrease in relative sigma power with a concomitant increase in relative theta power was evident during the first 4.5 hours after oral dronabinol dosing. These effects remained statistically significant for relative theta power but were less evident and not statistically significant for relative sigma power when considering the full 8-hour PSG recording period. This temporal pattern could be expected based on the pharmacokinetics of the drug, as the first-compartment plasma elimination half-life of oral dronabinol is 2 to 3 hours, and with daily dosing, plasma concentrations return to or near to baseline levels within 4 to 5 hours of drug administration.

Although the decrease in relative sigma power and increase in relative theta power were small, the change in activation ratio (AR) at the end of treatment was much larger and may have more biological significance, as AR is a more integrative measure of the EEG power distribution.

Figure 2 suggests the possibility of a minimum effective dose of dronabinol somewhere between 5 mg/day and 10 mg/day, for reducing AR. However, Figure 3 illustrates that even 2.5 mg/day of dronabinol exerts a significant effect on EEG power in the theta band. This suggests that the net effects of dronabinol on AR may reflect a more complex set of interactions, and not a simple threshold phenomenon. For example, Figure 3 also depicts that the dose effect of dronabinol on theta and sigma power is not monotonic. This may reflect the fact that dronabinol has multiple and potentially interacting sites of action.
action in the central nervous system. Further, the effects of dose and time-on-treatment remain confounded due to the dose escalation study design. In addition, the fact that doses were escalated only in subjects who experienced no ongoing side effects may have introduced a selection bias, such that higher doses were made available only to those subjects who were “less sensitive” to the drug.

A similar redistribution of sleep EEG power toward lower frequencies has been reported to accompany institution of continuous positive airway pressure treatment for OSA. In contrast, hypnotic agents exhibit varying effects on sleep EEG. For example, zolpidem suppresses theta and slow-alpha activity (5-10 Hz) and enhances sigma activity—effects opposite to those reported here for dronabinol. In contrast, gaboxadol enhances both delta and theta activity, similar to the dronabinol effects we observed. To examine whether the observed shift toward lower frequency EEG power may at least partially account for the decreased sleepiness reported by our subjects with OSA, we performed a correlation analysis between qEEG measures, AHI, and change in sleepiness from baseline to end of treatment, assessed using the 7-point Stanford Sleepiness Scale. Figure 5 illustrates that after 21 days of dronabinol treatment, relative theta power during sleep was positively associated with change in sleepiness from baseline to end of treatment (r = 0.61; p = 0.02). That is, dronabinol increased relative theta power, and those subjects with the highest theta power at the end of treatment showed the least improvement in sleepiness. Indeed, subjects in whom theta represented > 30% of the total EEG power tended to exhibit increased sleepiness at the end of treatment.

Sedation is a well-recognized side of effect of cannabinoid use, and it is possible for this sedation to carry over to the following day. For example, Nicholson et al. reported that healthy subjects experience increased subjective sleepiness the day after evening oral cannabinoid administration. Thus, we anticipated that, acting independently, dronabinol might cause sedation/sleepiness during the daytime with daily dosing. Conversely, we found that subjects reported decreased daytime sleepiness while taking oral dronabinol. Although not conclusive, these data are consistent with the possibility that the shift toward lower sleep EEG frequencies, and in particular the observed increase of relative theta power, reflects a direct CNS effect of dronabinol, and therefore a potential biomarker of its sedating properties.

As depicted in Figure 6, AHI at the end of treatment also was significantly related to change in sleepiness (r = 0.54, p < 0.05). In this case, dronabinol treatment consistently decreased AHI, and the lower the AHI at the end of treatment, the more sleepiness improved with treatment. As we have previously reported, the most probable site of dronabinol action for reducing sleep related breathing disorder is cannabinoid receptors in the peripheral nodose ganglia of the vagus nerves. Thus, the balance between potential alerting and sedating effects of dronabinol may reflect a balance between peripheral and central activity of the drug.

To date, there is virtually no literature regarding the effects of cannabinoids on ultradian rhythms in the sleep EEG. These

<table>
<thead>
<tr>
<th>Parameter</th>
<th>0 mg</th>
<th>2.5 mg</th>
<th>5.0 mg</th>
<th>10.0 mg</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1%</td>
<td>13.72 ± 13.37</td>
<td>18.48 ± 13.01</td>
<td>16.49 ± 10.67</td>
<td>18.41 ± 7.29</td>
<td>0.67</td>
</tr>
<tr>
<td>Stage 2%</td>
<td>61.89 ± 11.85</td>
<td>59.90 ± 11.03</td>
<td>60.28 ± 12.18</td>
<td>60.61 ± 11.33</td>
<td>0.96</td>
</tr>
<tr>
<td>SWS%</td>
<td>7.44 ± 6.36</td>
<td>6.02 ± 5.94</td>
<td>4.77 ± 4.17</td>
<td>7.55 ± 7.76</td>
<td>0.55</td>
</tr>
<tr>
<td>REM%</td>
<td>16.67 ± 6.70</td>
<td>15.61 ± 5.87</td>
<td>18.49 ± 8.01</td>
<td>13.44 ± 6.20</td>
<td>0.33</td>
</tr>
<tr>
<td>Stage 1 bout durations, min</td>
<td>1.18 ± 0.45</td>
<td>1.10 ± 0.45</td>
<td>1.08 ± 0.25</td>
<td>1.33 ± 0.67</td>
<td>0.55</td>
</tr>
<tr>
<td>Stage 2 bout durations, min</td>
<td>7.47 ± 3.22</td>
<td>5.19 ± 2.82</td>
<td>5.11 ± 2.21</td>
<td>4.11 ± 1.88</td>
<td>0.02*</td>
</tr>
<tr>
<td>SWS bout durations, min</td>
<td>5.5 ± 10.97</td>
<td>3.14 ± 4.11</td>
<td>1.75 ± 1.56</td>
<td>1.76 ± 1.03</td>
<td>0.32</td>
</tr>
<tr>
<td>REM bout durations, min</td>
<td>14.74 ± 8.32</td>
<td>11.80 ± 9.65</td>
<td>12.18 ± 10.83</td>
<td>10.24 ± 9.78</td>
<td>0.72</td>
</tr>
</tbody>
</table>

Stage percentages are % total sleep time. *p < 0.05.
exploratory results are, to the best of our knowledge, the first demonstration that oral dronabinol improves ultradian cycling in subjects with OSA. Further, this effect was dose-dependent, with ultradian rhythms accounting for a greater fraction of total EEG power at higher dronabinol doses. From the present data, we cannot determine whether this reflects a direct effect of the drug, an indirect effect of reducing AHI, or a combination of both effects. It is possible that dronabinol, by decreasing the frequency of sleep state transitions, led to an improvement in ultradian cycling. However, this does not appear to have been the case given that dronabinol did not decrease sleep fragmentation assessed by arousal index or sleep bout durations (Table 6). It is also possible that the reduction in apneas and hypopneas due to oral dronabinol allowed ultradian cycling to become more evident by reducing an apnea-related masking of ultradian rhythms.

Decreasing AHI was also associated with increasing amplitude of ultradian rhythms (Table 5). This suggests that apneas are not just adding noise to the ultradian rhythms but that apneas are also decreasing the amplitude of ultradian cycling. The potential mechanisms linking disordered breathing events to ultradian rhythm amplitude cannot be determined from the present results. Dronabinol may impact ultradian rhythms by acting directly on sleep homeostatic pathways or indirectly by reducing disordered breathing events. Oral dronabinol may improve breathing stability during sleep by acting peripherally at the nodose ganglia to disinhibit upper airway dilator muscles. Conversely, by decreasing the rapidity or number of state transitions, dronabinol could have improved the stability of sleep and decreased the occurrence of apneas. Again, this does not seem to be a primary mechanism given the lack of evidence for reduced sleep fragmentation at the dronabinol doses tested. At present, there are no published reports documenting improved ultradian sleep structure following institution of any form of treatment for OSA, but this should be further investigated in future clinical trials.

Women exhibited higher amplitude ultradian rhythms in all EEG frequency bands, and this achieved statistical significance for the theta and sigma bands (Table 5). Gender effects on sleep EEG have been previously reported, but the observations are mixed. Fukuda et al. reported that middle-aged and elderly females had larger amounts of spectral power in the delta band than males. In contrast, Latta et al. reported that older women have lower delta amplitude than men. In another study, adolescent females had lower delta power than males. These inconsistent results may arise from varying methods of data collection, participant age, or other factors. This exploratory analysis is the first to report a possible gender difference in the amplitude of ultradian rhythms of the sleep EEG in individuals with sleep apnea. This gender difference did not appear to be influenced by dronabinol administration, as dronabinol dose did not influence the amplitude of ultradian rhythms (Table 5).

We also observed that slower ultradian oscillations (longer periods) were associated with increased sleepiness at the end of the 3-week treatment period: delta ($r = 0.74; p = 0.003$); theta ($r = 0.53; p = 0.05$); alpha ($r = 0.57; p = 0.04$); sigma ($r = 0.19; p = 0.51$); average period ($r = 0.70; p = 0.006$). The impact of cannabinoids on ultradian periods of the sleep EEG has not been previously studied, and we found no effect of dronabinol on the period in any frequency band. It seems likely, therefore, that the correlation between ultradian period and sleepiness may reflect some combination of underlying biological factors, rather than a drug effect. Indeed, van Hilten et al. reported that prolonged periods in the ultradian rhythm of sleep EEG in patients with myotonic dystrophy correlated with increased daytime sleepiness.

It should be noted that the findings of this study and their generalizability are limited by the small sample size. Additionally, subjects followed a dose escalation paradigm in...
which only 8 of the subjects reached the full dose of 10 mg/day of dronabinol. Although we cannot rule out the possibility of an important time-on-treatment effect, we were able to identify significant dose effects despite the small sample size. Longer duration, larger clinical studies will be needed to fully delineate both the dose and the time-on-treatment effects of dronabinol in OSA.

In summary, this exploratory study demonstrates that in individuals with OSA, dronabinol treatment yields a shift in EEG power toward delta and theta frequencies and a strengthening of ultradian rhythms in the sleep EEG. In particular, ultradian rhythms became stronger with increasing doses of dronabinol and their amplitudes increased as AHI decreased. These effects suggest that oral dronabinol may have improved restorative aspects of the sleep process, contributing to the observed decrease in daytime sleepiness, despite the absence of changes in overall sleep stage percentages or sleep efficiency previously reported. Larger scale studies will be needed to confirm and elaborate these effects, and to dissect the potentially interacting influences of dose and time-on-treatment.

REFERENCES


SUBMISSION & CORRESPONDENCE INFORMATION
Submitted for publication July, 2013
Submitted in final revised form September, 2013
Accepted for publication September, 2013
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DISCLOSURE STATEMENT
This study was supported by a grant from Pier Pharmaceuticals and involved investigational use of dronabinol in subjects with obstructive sleep apnea syndrome. Dr. Carley is an inventor on patents and patent applications disclosing the use of dronabinol as a treatment for obstructive sleep apnea. All rights to these patents and applications have been assigned to the University of Illinois. Dr. Carley previously served as a consultant to and member of the board of directors of Pier Pharmaceuticals, which has been acquired by Cortex Pharmaceuticals. The other authors have indicated no financial conflicts of interest.
Influence and Predicting Variables of Obstructive Sleep Apnea on Cardiac Function and Remodeling in Patients without Congestive Heart Failure

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Study Objective: Obstructive sleep apnea syndrome (OSAS) has been considered to be an important predisposing factor for cardiovascular disease. This study aims to investigate the impact of OSAS on cardiac function and remodeling in patients without congestive heart failure.

Methods: A total of 79 patients with sleep disordered breathing, preserved systolic function, and normal pro-brain natriuretic peptide level were enrolled. Sixty-five patients were classified to have moderate to severe OSAS (apnea-hypopnea index [AHI] ≥ 15/h), while the other 14 patients with mild or no OSAS (AHI < 15/h) served as control subjects. Baseline clinical and polysomnographic variables as well as tissue Doppler imaging and three-dimensional echocardiographic parameters were obtained.

Results: The body mass index, neck circumference, Epworth Sleepiness Scale, desaturation index, arousal index, and snoring index were significantly higher in patients with moderate to severe OSAS than those without (p < 0.05). The left atrial size, mitral A-wave velocity, and left ventricular end-diastolic volume were significantly larger, while E/A ratio was lower in patients with moderate to severe OSAS than those without (p < 0.05). Notably, AHI in REM sleep was significantly correlated with the aortic root size, E/A ratio, left ventricular volume, and stroke volume. In addition, the area under the receiver operator characteristic curve for AHI in REM sleep ≥ 32.3/h was 0.647 (95% CI [0.525, 0.769]) in predicting the development of left ventricular diastolic dysfunction. AHI in REM sleep ≥ 32.3/h was the only independent variant in predicting diastolic dysfunction after adjusting the variables including age, gender, hypertension, and body mass index.

Conclusions: Patients with moderate to severe OSAS tend to have cardiac dysfunction revealed by echocardiography. High AHI in REM sleep is significantly associated with cardiovascular remodeling and ventricular diastolic dysfunction, and may be a potential variable to predict cardiac dysfunction.

Keywords: Echocardiography, sleep apnea syndrome, diastolic dysfunction, cardiovascular remodeling.

Citation: Chen YL; Su MC; Liu WH; Wang CC; Lin MC; Chen MC. Influence and predicting variables of obstructive sleep apnea on cardiac function and remodeling in patients without congestive heart failure. J Clin Sleep Med 2014;10(1):57-64.
high-sensitivity C-reactive protein (hs-CRP) and N-terminal pro-brain natriuretic peptide (NT-proBNP) have been well defined techniques to investigate cardiac structural and functional remodeling and to predict patients with a high risk of cardiovascular mortality and morbidity. In spite of the fact that these tools are widely available and frequently introduced in clinical settings, the structural and functional remodeling studied by utilizing TDI and RT3D has rarely been conducted in patients with OSAS to evaluate their cardiac function. In addition, the frequent coexistence of OSAS and congestive heart failure in clinical scenarios make it difficult to clearly define the exact impact of OSAS on cardiac remodeling and function, and vice versa. In order to answer these unresolved issues regarding the impact of OSAS itself on cardiac structure and function, it is crucial to conduct a study enrolling subjects exclusively without clinical symptoms of heart failure.

This study tested the hypothesis that significant OSAS may be associated with enlarged left ventricle and ventricular dysfunction. Accordingly, we measured the echocardiographic parameters by TDI and RT3D echocardiography in sleep disordered breathing patients with preserved systolic function and without significant congestive heart failure (normal NT-proBNP level), and we aimed to identify important parameters in predicting the development of cardiovascular remodeling and ventricular dysfunction in patients with sleep disordered breathing.

**METHODS**

**Patient Population**

Patients with symptoms of sleep disordered breathing referred to our sleep center for sleep study between June 2009 and September 2011 were enrolled in this study. The following were exclusion criteria: (1) unwillingness or inability to perform the testing procedures; (2) systolic dysfunction defined as left ventricular ejection fraction < 50% and with marked symptoms or signs of congestive heart failure; (3) cardiac murmur revealed by physical examination or significant valvular stenosis or regurgitation documented by echocardiography; (4) evidence of ischemic heart disease; (5) any documented bradycardia, tachycardia, or aborted cardiac death; (6) diabetes mellitus and other metabolic disorders; (7) renal function impairment, defined as serum creatinine > 1.2 mg/dL; and (8) history of malignancy. Echocardiography measurements and blood tests were routinely performed in all patients before the polysomnographic study to minimize investigation bias. The study protocol was approved by the Institutional Review Committee for Human Research at our institution (98-0769B). Written informed consents were obtained from all subjects prior to the study.

**Polysomnography**

All patients enrolled in this study underwent an overnight polysomnographic study. Prior to the sleep study, body height, body weight, body mass index (BMI), and neck size were measured. The tendency to fall asleep during various situations, and subjective sleepiness was assessed simultaneously by using a validated questionnaire, the Epworth Sleepiness Scale (ESS). The overnight polysomnographic study was conducted using a standardized commercial suite (Sandman Elite, Mallinckrodt Inc., St. Louis, MO) set in our sleep center. Sleep parameters were then recorded and analyzed, and the respiratory events were identified by experienced technicians according to the standard criteria. Respiratory events were classified as either obstructive or central on the basis of presence or absence of respiratory effort. Respiratory events were defined as apnea when there was a cessation of oronasal airflow ≥ 10 seconds. Hypopnea was defined as a decrease ≥ 30% in oronasal airflow ≥ 10 seconds, associated with a fall in arterial oxygen saturation (SpO2) > 4% of the baseline level or associated with an arousal. Mean nighttime SpO2, minimum SpO2 (lowest values recorded during sleep), desaturation index, and percentage of time with SpO2 < 90% on oximetry were computed as indexes of nocturnal oxygen saturation. Moderate to severe OSAS was defined as apnea-hypopnea index (AHI) ≥ 15/h with associated symptoms, such as excess daytime sleepiness and witnessed apneas during sleep.

**Echocardiography**

Transthoracic two-dimensional (2D) echocardiography, TDI, and RT3D echocardiography were performed using a Sonos 7500 (Live 3D Echo; Philips Medical Systems, Andover, MA) with an S3 transducer, and iE-33xMATRIX Echocardiography System (Philips Medical Systems, Andover, MA), following our previous echocardiography protocol. The left atrial and ventricular dimensions, aortic root size and septal-to-posterior wall motion delay (SPWMD) were determined with conventional M-mode echocardiography. Pulsed-wave Doppler was used for the measurement of myocardial performance index (MPI), an index combining systolic and diastolic myocardial performance, and the aortic time-velocity integrals.

Tissue Doppler imaging was conducted using standard apical views for long-axis motion of the ventricle, as previously described. At least 3 consecutive beats were stored with digital loops for offline analysis using a validated software, QLAB version 8.1 (Philips Medical Systems). Times to peak systolic velocity (Ts) and early diastolic velocity (Te) were determined for each of the 12 non-apical segments. Synchronicity was assessed by calculating the standard deviation of Ts (Ts-SD) and Te (Te-SD) of all 12 non-apical segments.

The details of RT3D measurements have been reported in our previous studies. In brief, the RT3D echocardiography obtained a pyramidal volume in real time using an X4 matrix transducer. QLAB version 8.1 was also used for quantitative analysis. The RT3DE data sets were used for time-volume analysis for the determination of global and segmental left ventricular volumes. The systolic dyssynchrony index was measured; a higher systolic dyssynchrony index indicated increased intra-ventricular dyssynchrony.

**Statistical Analysis**

There were two well-trained echocardiologists performing the echocardiogram in our study. Eight study subjects were selected for assessment of inter-rater and intra-rater reliability. The intraclass correlation coefficient for intraobserver agreement was 0.913, 0.982, and 0.974 for systolic dyssynchrony index, A-wave velocity, and myocardial performance index, respectively. The interclass correlation coefficient
for interobserver agreement was 0.896, 0.937, and 0.963 for systolic dyssynchrony index, A-wave velocity, and myocardial performance index, respectively. Data were expressed as mean ± SD unless stated otherwise. Differences in continuous variables were analyzed using Mann-Whitney-Wilcoxon test and categorical variables by $\chi^2$ test or Fisher exact test. The correlation between AHI in REM sleep or NREM sleep and all echocardiographic parameters were analyzed with Pearson correlation test. Areas under the receiver operator characteristic curve were constructed for the sensitivity and specificity of AHI to predict the development of left ventricular diastolic dysfunction in patients with sleep disordered breathing. Multiple stepwise logistic regression analysis was utilized for independent predictors of diastolic dysfunction which defined as E/A ratio ≤ 1. Statistical analysis was performed using commercial statistical software (SPSS for Windows, version 13; SPSS Inc., IL, USA). A two-sided p-value < 0.05 was considered statistically significant.

### RESULTS

#### Baseline Characteristics of the Study Patients

Eighty- four consecutive patients were screened during the study period. Five patients were subsequently excluded due to obvious valvular regurgitation, stenosis, or left ventricular systolic dysfunction. A total of 79 patients thus completed this study. After an overnight polysomnographic study, 65 patients were classified as having moderate-to-severe OSAS (AHI ≥ 15/h), while the other 14 patients with mild or no OSAS (AHI < 15/h) served as control subjects. Table 1 lists the baseline clinical characteristics and laboratory data of the studied patients with and without moderate-to-severe OSAS. There was no significant difference in age, gender, prevalence of hypertension, dyslipidemia, or systolic or diastolic blood pressures between the 2 groups. In addition, serum levels of the hs-CRP, NT-proBNP, creatinine, and sodium, as well as the heart rate, PR interval, QRS duration, and QRS axis measured by 12-lead surface electrocardiography did not differ significantly between the 2 groups. Polysomnographic variables obtained from both groups are shown in Table 2. The BMI, ESS, the lowest oxyhemoglobin saturation, desaturation index, arousal index, and snoring index were significantly higher in patients with moderate-to-severe OSAS than those without (all $p < 0.05$). There was no significant difference in REM sleep and NREM sleep percentage.

#### Echocardiographic Parameters of Study Patients

Table 3 shows the echocardiographic parameters of patients with and without moderate to severe OSAS. Between the 2 groups there was no significant difference in the thickness of interventricular septum and left ventricular posterior wall, left ventricular end-diastolic and end-systolic diameters, left ventricular ejection fraction, myocardial performance index, time-velocity integral at left ventricular outflow tract, E-wave velocity, deceleration time, tricuspid regurgitation pressure gradient, left ventricular end-systolic volume, left ventricular stroke volume, and global left ventricular ejection fraction by RT3D echocardiography, as well as mechanical dyssynchrony indices, such as septal-to-posterior wall motion delay by M-mode echocardiography, Ts-SD and Te-SD by TDI, and systolic dyssynchrony index by RT3D echocardiography.

Nevertheless, the left atrial size, mitral A-wave velocity, and left ventricular end-diastolic volume by RT3D echocardiography were significantly larger in patients with moderate to severe OSAS than those without (all $p < 0.05$). The E/A ratio was significantly lower in patients with moderate to severe OSAS than in those without ($p < 0.05$).

### Table 1—Baseline characteristics and laboratory data of all patients with sleep disordered breathing

<table>
<thead>
<tr>
<th>Variables</th>
<th>OSAS group</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
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<td>14</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>49 ± 10</td>
<td>47 ± 8</td>
<td>0.426</td>
</tr>
<tr>
<td>Male gender</td>
<td>83.1% (54)</td>
<td>64.3% (9)</td>
<td>0.113</td>
</tr>
<tr>
<td>Hypertension</td>
<td>49.2% (32)</td>
<td>50.0% (7)</td>
<td>0.958</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>26.2% (17)</td>
<td>28.6% (4)</td>
<td>1.000</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.9 ± 3.6</td>
<td>24.1 ± 3.4</td>
<td>0.007</td>
</tr>
<tr>
<td>Neck circumference, cm</td>
<td>38.4 ± 3.2</td>
<td>36.2 ± 3.7</td>
<td>0.053</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>139 ± 16</td>
<td>133 ± 19</td>
<td>0.913</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>79 ± 11</td>
<td>80 ± 13</td>
<td>0.639</td>
</tr>
<tr>
<td>hs-CRP, mg/dL</td>
<td>2.40 ± 3.03</td>
<td>1.95 ± 2.02</td>
<td>0.572</td>
</tr>
<tr>
<td>NT-proBNP, pg/mL</td>
<td>37.56 ± 30.37</td>
<td>31.18 ± 22.11</td>
<td>0.554</td>
</tr>
<tr>
<td>Serum creatinine, mg/dL</td>
<td>0.94 ± 0.20</td>
<td>0.92 ± 0.18</td>
<td>0.792</td>
</tr>
<tr>
<td>Serum sodium, mEq/L</td>
<td>141.6 ± 1.7</td>
<td>140.6 ± 2.0</td>
<td>0.077</td>
</tr>
<tr>
<td>Heart rate, beats per minute</td>
<td>76 ± 21</td>
<td>70 ± 9</td>
<td>0.176</td>
</tr>
<tr>
<td>PR interval, ms</td>
<td>157 ± 28</td>
<td>152 ± 20</td>
<td>0.282</td>
</tr>
<tr>
<td>QRS duration, ms</td>
<td>92 ± 15</td>
<td>91 ± 7</td>
<td>0.814</td>
</tr>
<tr>
<td>QRS Axis</td>
<td>47 ± 32</td>
<td>42 ± 34</td>
<td>0.521</td>
</tr>
</tbody>
</table>

Data expressed as mean ± SD or % (n) of patients. hs-CRP, high-sensitivity C-reactive protein; NT-pro BNP, N-terminal pro-brain natriuretic peptide. Obstructive sleep apnea syndrome (OSAS) group is defined as apnea-hypopnea index (AHI) ≥ 15/h, while control group is defined as AHI < 15/h.
Correlation between AHI and Echocardiographic Parameters

In order to explore the impact of OSAS on cardiac function, the association between AHI (both in REM and NREM sleeps) and all echocardiographic parameters measured by M mode, 2D and RT3D echocardiography and TDI were further analyzed.

Table 2—Polysomnographic variables of all patients with sleep disordered breathing

<table>
<thead>
<tr>
<th>Variables</th>
<th>OSAS group</th>
<th>Control group</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>65</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Epworth sleepiness scale</td>
<td>11.2 ± 5.3</td>
<td>7.6 ± 2.3</td>
<td>0.010</td>
</tr>
<tr>
<td>AHI, per hour</td>
<td>45.4 ± 19.5</td>
<td>8.6 ± 3.8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>AHI in REM phase, per hour</td>
<td>48.3 ± 18.8</td>
<td>18.0 ± 15.3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>AHI in NREM phase, per hour</td>
<td>44.9 ± 21.3</td>
<td>6.4 ± 3.5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Lowest SpO₂, %</td>
<td>75.5 ± 11.4</td>
<td>85.2 ± 6.7</td>
<td>0.002</td>
</tr>
<tr>
<td>Desaturation index, per hour</td>
<td>33.1 ± 22.1</td>
<td>3.3 ± 3.2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Arousal index, per hour</td>
<td>40.9 ± 24.1</td>
<td>11.6 ± 6.7</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Snoring index, per hour</td>
<td>324.6 ± 212.5</td>
<td>150.1 ± 171.5</td>
<td>0.005</td>
</tr>
<tr>
<td>REM phase, %</td>
<td>14.5 ± 6.6</td>
<td>15.8 ± 4.3</td>
<td>0.365</td>
</tr>
<tr>
<td>NREM, %</td>
<td>85.4 ± 6.7</td>
<td>84.2 ± 4.3</td>
<td>0.400</td>
</tr>
</tbody>
</table>

Data expressed as mean ± SD. AHI, apnea-hypopnea index; SpO₂, oxyhemoglobin saturation. Obstructive sleep apnea syndrome (OSAS) group is defined as apnea-hypopnea index (AHI) ≥ 15/h, while control group is defined as AHI < 15/h.

Table 3—Echocardiographic parameters of all patients with sleep disordered breathing

<table>
<thead>
<tr>
<th>Variables</th>
<th>OSAS group</th>
<th>Control group</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>65</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>2D echocardiography</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left atrial size, mm</td>
<td>34.7 ± 4.7</td>
<td>31.1 ± 5.3</td>
<td>0.023</td>
</tr>
<tr>
<td>Aortic root size, mm</td>
<td>31.6 ± 3.6</td>
<td>29.2 ± 4.0</td>
<td>0.058</td>
</tr>
<tr>
<td>Thickness of IVS, mm</td>
<td>11.6 ± 1.8</td>
<td>10.9 ± 1.9</td>
<td>0.265</td>
</tr>
<tr>
<td>Thickness of LVPW, mm</td>
<td>9.7 ± 2.0</td>
<td>8.7 ± 2.9</td>
<td>0.207</td>
</tr>
<tr>
<td>LVEDD, mm</td>
<td>49.2 ± 4.7</td>
<td>47.8 ± 6.2</td>
<td>0.601</td>
</tr>
<tr>
<td>LVESD, mm</td>
<td>30.8 ± 4.4</td>
<td>30.5 ± 4.7</td>
<td>0.794</td>
</tr>
<tr>
<td>LVEF, mm</td>
<td>67.1 ± 8.2</td>
<td>64.9 ± 8.8</td>
<td>0.437</td>
</tr>
<tr>
<td>SPWMD, mm</td>
<td>1.5 ± 46.5</td>
<td>-10.2 ± 38.4</td>
<td>0.319</td>
</tr>
<tr>
<td>MPI</td>
<td>0.323 ± 0.115</td>
<td>0.348 ± 0.087</td>
<td>0.252</td>
</tr>
<tr>
<td>TVI at LVOT, cm</td>
<td>22.4 ± 6.2</td>
<td>22.4 ± 4.5</td>
<td>0.704</td>
</tr>
<tr>
<td>E-wave velocity, cm/sec</td>
<td>74.3 ± 18.6</td>
<td>74.8 ± 14.5</td>
<td>0.957</td>
</tr>
<tr>
<td>A-wave velocity, cm/sec</td>
<td>71.0 ± 16.7</td>
<td>60.2 ± 11.0</td>
<td>0.026</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1.1 ± 0.3</td>
<td>1.3 ± 0.3</td>
<td>0.025</td>
</tr>
<tr>
<td>DT, msec</td>
<td>175.5 ± 39.1</td>
<td>169.5 ± 34.5</td>
<td>0.461</td>
</tr>
<tr>
<td>TRPG, mm Hg</td>
<td>19.7 ± 6.3</td>
<td>19.4 ± 6.2</td>
<td>0.802</td>
</tr>
<tr>
<td>3D echocardiography</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SDI, %</td>
<td>2.02 ± 1.29</td>
<td>2.60 ± 2.14</td>
<td>0.272</td>
</tr>
<tr>
<td>LVEDV, mL</td>
<td>96.4 ± 23.6</td>
<td>81.9 ± 15.8</td>
<td>0.041</td>
</tr>
<tr>
<td>LVESV, mL</td>
<td>41.5 ± 12.5</td>
<td>35.8 ± 9.3</td>
<td>0.138</td>
</tr>
<tr>
<td>LVSV, mL</td>
<td>54.9 ± 13.8</td>
<td>46.1 ± 10.4</td>
<td>0.053</td>
</tr>
<tr>
<td>Global LVEF by RT3DE imaging, %</td>
<td>57.2 ± 6.0</td>
<td>56.2 ± 7.5</td>
<td>0.476</td>
</tr>
<tr>
<td>Tissue Doppler Echocardiography</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ts-SD, msec</td>
<td>21.7 ± 15.6</td>
<td>14.4 ± 7.3</td>
<td>0.075</td>
</tr>
<tr>
<td>Te-SD, msec</td>
<td>23.1 ± 10.0</td>
<td>25.1 ± 7.3</td>
<td>0.162</td>
</tr>
</tbody>
</table>

Data expressed as mean ± SD. 2D, two-dimensional; 3D, three-dimensional; DT, deceleration time; IVS, interventricular septum; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVESV, left ventricular end-systolic volume; LVPW, left ventricular posterior wall; LVSV, left ventricular stroke volume; MPI, myocardial performance index; SDI, systolic dyssynchrony index; SPWMD, septal-to-posterior wall motion delay; Te-SD, standard deviation of time to early diastolic velocity; TRPG, tricuspid regurgitation pressure gradient; Ts-SD, standard deviation of time to peak systolic velocity; TVI at LVOT, time-velocity integral at left ventricular outflow tract. Obstructive sleep apnea syndrome (OSAS) group is defined as apnea-hypopnea index (AHI) ≥ 15/h, while control group is defined as AHI < 15/h.
Notably, only AHI in REM sleep but neither AHI in NREM sleep nor total AHI was significantly associated with the aortic root size, E/A ratio, left ventricular end-diastolic volume, left ventricular end-systolic volume, and left ventricular stroke volume (Table 4).

Discriminant analysis was performed to identify the AHI in REM sleep in predicting the development of left ventricular diastolic dysfunction (E/A ≤ 1) in patients with sleep disordered breathing. The area under the receiver operator characteristic curve for the cutoff value ≥ 32.3/h was 0.647 (95% CI [0.525, 0.769], p = 0.032; Figure 1).

Multivariate Logistic Regression Analysis of Predictors for Left Ventricular Diastolic Dysfunction

Multiple stepwise logistic regression analysis of the variables, including age, gender, hypertension and AHI in REM sleep showed that AHI in REM ≥ 32.3/h was the only independent predictor of left ventricular diastolic dysfunction (E/A ≤ 1; Table 5).

**DISCUSSION**

In this study we used echocardiographic methods to investigate the impact of marked OSAS on cardiac function and structural remodeling in sleep disordered breathing patients without symptoms of congestive heart failure. We found that patients with moderate to severe OSAS have an increased size of left atrium, larger A-wave velocity and left ventricular end-diastolic volume and lower E/A ratio compared with patients with mild or no OSAS, and this is independent of the presence of hypertension. In addition, the aortic root size, E/A ratio, left ventricular end-diastolic volume, left ventricular end-systolic volume, and left ventricular stroke volume were strongly associated with AHI in REM sleep but not in NREM sleep. This suggests that high AHI in REM sleep could be a potential polysomnographic variable for predicting ventricular dysfunction and cardiovascular structural remodeling in patients with sleep disordered breathing who are without clinical symptoms of congestive heart failure.

OSAS has been reported to cause hypertension and has been associated with the development of variable cardiovascular disease and probably, congestive heart failure. In patients with OSAS, nocturnal intermittent hypoxemia and arousals from sleep increase sympathetic activity and induce acute hemodynamic changes. Increased negative intrathoracic pressure due to upper airway collapse increases transmural cardiac pressure, ventricular wall tension, and afterload. Both increased venous return and increased pulmonary arterial

---

**Table 4**—Correlation between AHI and echocardiographic parameters

<table>
<thead>
<tr>
<th>Variables</th>
<th>AHI</th>
<th>AHI in REM</th>
<th>AHI in NREM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>p</td>
<td>r</td>
</tr>
<tr>
<td>Aortic root size</td>
<td>0.113</td>
<td>0.326</td>
<td>0.228</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>-0.116</td>
<td>0.147</td>
<td>-0.324</td>
</tr>
<tr>
<td>LVEDV</td>
<td>0.181</td>
<td>0.109</td>
<td>0.316</td>
</tr>
<tr>
<td>LVESV</td>
<td>0.181</td>
<td>0.111</td>
<td>0.305</td>
</tr>
<tr>
<td>LV SV</td>
<td>0.145</td>
<td>0.201</td>
<td>0.260</td>
</tr>
<tr>
<td>Left atrial size</td>
<td>0.214</td>
<td>0.060</td>
<td>0.122</td>
</tr>
<tr>
<td>A-wave velocity</td>
<td>0.166</td>
<td>0.147</td>
<td>0.170</td>
</tr>
<tr>
<td>Ts-SD</td>
<td>0.086</td>
<td>0.463</td>
<td>-0.036</td>
</tr>
</tbody>
</table>

AHI, apnea-hypopnea index; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVSV, left ventricular stroke volume; Ts-SD, standard deviation of time to peak systolic velocity.

**Table 5**—Multivariate logistic regression analysis of predictors for left ventricular diastolic dysfunction

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHI in REM ≥ 32.3/h</td>
<td>4.422</td>
<td>1.334-14.666</td>
<td>0.015</td>
</tr>
</tbody>
</table>

CI, confidence interval.

**Figure 1**—Receiver operator characteristic curve for the cutoff value of apnea-hypopnea index (AHI) in predicting E/A ratio ≤ 1 (an index of ventricular diastolic dysfunction)

The area under curve (AUC) for the cutoff value of AHI ≥ 32.3/h was 0.647. 95% CI: 0.525-0.769. p = 0.032.
pressures caused by hypoxemia may elevate right ventricular pressure, resulting in a leftward shift of the interventricular septum.20,21 Such hemodynamic changes may cause left ventricular dys synchrony, and either diastolic or systolic heart failure. On the other hand, patients with congestive heart failure have also been reported in association with OSAS, with the reported prevalence up to a range of 11% to 37%.21,22 Upper airway soft tissue edema caused by congestive heart failure, and consequently increased airway resistance, may result in increased inspiratory force and upper airway collapse, which may lead to an increased risk of the development of OSAS. The frequent coexistence of congestive heart failure and OSAS may therefore make it difficult to dichotomize the impact of OSAS on cardiac dysfunction in patients with congestive heart failure.

It has been believed that OSAS has a profound negative effect on the cardiovascular system and induces a high cardiovascular event rate in the long run. Several cardiovascular biomarkers have been measured and have been shown to be associated with the severity of OSAS. However, the definite mechanisms of how OSAS causes cardiovascular diseases remain incompletely elucidated. Our study showed that patients with moderate-to-severe OSAS and preserved systolic function have cardiac remodeling with dilated left atrial size, decreased E/A ratio, increased A-wave velocity, and enlarged left ventricular end-diastolic volume when compared to those with mild or no OSAS. These changes could be induced by the repetitively and abruptly increased transmural gradients across the atria,34-45 ventricles, and aorta,46-49 caused by the very substantial negative intrathoracic pressure (possibly approaching -65 mm Hg) during pharyngeal collapse.50

This study showed a novel finding in that AHI in REM sleep, but not NREM sleep, was significantly associated with cardiac remodeling (dilated aortic root size by 2D echocardiography, increased left ventricular end-diastolic volume, left ventricular end-systolic volume, and left ventricular stroke volume by 3D echocardiography) and ventricular diastolic dysfunction (high A-wave velocity and low E/A ratio). The severity of OSAS becomes greater during REM sleep, partly due to a decreased respiratory muscle tone.51,52 Sympathetic activity is typically higher with intermittent discharge surges in REM sleep than in NREM sleep, and is further exacerbated with recurrent upper airway obstruction and hypoxemia.53 This increased sympathetic output in REM sleep may underlie the relationship between sleep disordered breathing, insulin resistance, and glucose intolerance.54,55 Moreover, there may be more pronounced neuroendocrine perturbations and cytokine release during REM sleep caused by apnea and hypopnea, as compared to NREM sleep.56-59 All these pathophysiological changes may be the underlying mechanisms to explain why the AHI in REM sleep, but not the AHI in NREM sleep, was significantly associated with cardiovascular remodeling and ventricular diastolic dysfunction in this study. It is also possible that muscular compensatory ability decreases significantly in patient with occult cardiac dysfunction. The decreased respiratory muscular compensation along with the decreased muscle tone in REM sleep results in a higher AHI. As a result, higher AHI in REM sleep might serve as a surrogate predicting variable for cardiovascular diseases. By receiver operator characteristic curve, we identify the cutoff value ≥ 32.3/h in AHI during REM sleep in predicting the development of left ventricular diastolic dysfunction in patients with OSAS. This suggests that in patients with severe OSAS, particularly those with an AHI greater than 30/h, their cardiovascular function should be surveyed. Treatment of OSAS might reverse these adverse effects on the cardiovascular system.

Limitations

There are some limitations in the study. Although this study demonstrated the novel finding of high AHI in REM sleep, but not AHI in NREM sleep, being significantly associated with cardiovascular remodeling and ventricular diastolic dysfunction. Further research should investigate the complete mechanisms or pathways regarding OSAS contributing to cardiovascular diseases. In addition, the subject number in the control group was limited and normal non-snoring subjects were not enrolled. Due to our facility shortage and long waiting list, only patients with symptoms of sleep disordered breathing could receive the polysomnographic studies during the study period. Instead, we separated patient groups by their AHI of 15/h, which has been commonly introduced for defining significant OSAS. Furthermore, the effects of OSAS treatment should be investigated in order to further clarify the mechanisms of OSAS influencing cardiac function.

CONCLUSIONS

By using echocardiography, we found that patients with moderate to severe OSAS have a higher incidence of cardiovascular remodeling and ventricular diastolic dysfunction than those without. In addition, high AHI in REM sleep is significantly associated with cardiovascular remodeling and ventricular diastolic dysfunction and might be a potential variable to predict cardiac dysfunction and remodeling. Occult cardiac dysfunction may be present in most patients with significant OSAS, and they thus require further detailed evaluation and management.

REFERENCES


YL Chen, MC Su, WH Liu et al
Carotid Artery Stiffness and Obstructive Sleep Apnea: Implications for Cardiovascular Disease Risk Prediction

We found that increased carotid-femoral pulse wave velocity was independently associated with an increased risk of obstructive sleep apnea syndrome.

Mean carotid-femoral pulse wave velocity was increased in those with obstructive sleep apnea syndrome compared with controls. The difference in pulse wave velocity was independent of age, sex, body mass index, waist circumference, and estimated glomerular filtration rate.

This study suggests that increased carotid-femoral pulse wave velocity is an independent risk factor for obstructive sleep apnea syndrome.

References


ACKNOWLEDGMENTS

Yung-Lung Chen, M.D. and Mao-Chang Su, M.D. contributed equally to this paper. Meng-Chih Lin, M.D. and Mien-Cheng Chen, M.D. contributed equally to this paper. The authors thank the Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Kaohsiung, Taiwan for financially supporting this research under Contract number (CMRPG880771-880772).

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication March, 2013
Submitted in final revised form September, 2013
Accepted for publication September, 2013

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DISCLOSURE STATEMENT

This was not an industry supported study. This study was supported by program grants from the Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Kaohsiung, Taiwan (CMRPG880771-880772). The authors have indicated no financial conflicts of interest.
Spinal cord injury (SCI) affects a large number of adults worldwide, with an estimated incidence rate of 15 to 40 cases per million populations. The prevalence of SCI in the United States is estimated to exceed 250,000 people, with approximately 11,000 new cases of SCI each year. Most SCIs occur during the second or third decade of life, leading to a major impact on young individuals in the community. Respiratory complications secondary to ineffective cough, poor airway clearance, infections and respiratory failure are major causes of morbidity and mortality in patients with SCI, particularly at cervical levels. In a longitudinal study from Norway, respiratory failure and ineffective mucous clearance were the main complications after SCI and respiratory causes of death were increased twofold as expected for their age. While advances in acute care have resulted in improved survival for the first year after SCI, there is minimal change in survival when the injury becomes chronic after few years.

Patients with SCI are also at increased risk of sleep disordered breathing (SDB), with a prevalence ranging from 27% to 62%. A longitudinal study in the first year after cervical SCI found that 60% of patients with cervical SCI developed SDB within 2 weeks of injury, peaked at 13 weeks and returned back to 60% after a one-year follow-up. It is of note that both SDB and chronic SCI are associated with increased adverse cardiovascular consequences. Hence it is plausible that SDB may contribute to increased cardiovascular mortality in SCI patients. The majority of SCI survivors have symptomatic SDB and poor sleep that may be missed if not carefully assessed. Decreased V02 and increased P02-CO2 during sleep in patients with cervical SCI relative to thoracic SCI suggests that sleep related hypventilation may contribute to the pathogenesis SDB in patients with chronic cervical SCI.

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**Study Objectives:** Spinal cord injury (SCI) is associated with 2-5 times greater prevalence of sleep disordered breathing (SDB) than the general population. The contribution of SCI on sleep and breathing at different levels of injury using two scoring methods has not been assessed. The objectives of this study were to characterize the sleep disturbances in the SCI population and the associated physiological abnormalities using quantitative polysomnography and to determine the contribution of SCI level on the SDB mechanism.

**Methods:** We studied 26 consecutive patients with SCI (8 females; age 42.5 ± 15.5 years; BMI 25.9 ± 4.9 kg/m2; 15 cervical and 11 thoracic levels) by spirometry, a battery of questionnaires and by attended polysomnography with flow and pharyngeal pressure measurements. Inclusion criteria for SCI: chronic SCI (> 6 months post injury), level T6 and above and not on mechanical ventilation. Ventilation, end-tidal CO2 (PETO2), variability in minute ventilation (V02-CV) and upper airway resistance (RUA) were monitored during wakefulness and NREM sleep in all subjects. Each subject completed brief history and exam, Epworth Sleepiness Scale (ESS), Pittsburgh Sleep Quality Index (PSQI), Berlin questionnaire (BQ) and fatigue severity scale (FSS). Sleep studies were scored twice, first using standard 2007 American Academy of Sleep Medicine (AASM) criteria and second using new 2012 recommended AASM criteria.

**Results:** Mean PSQI was increased to 10.3 ± 3.7 in SCI patients and 92% had poor sleep quality. Mean ESS was increased 10.4 ± 4.4 in SCI patients and excessive daytime sleepiness (ESS ≥ 10) was present in 59% of the patients. Daytime fatigue (FSS > 20) was reported in 96% of SCI, while only 46% had high-risk score of SDB on BQ. Forced vital capacity (FVC) in SCI was reduced to 70.5% predicted in supine compared to 78.5% predicted in upright positions (p < 0.05). Likewise forced expiratory volume in first second (FEV1) was 64.9% predicted in supine compared to 74.7% predicted in upright positions (p < 0.05). Mean AHI in SCI patients was 29.3 ± 25.0 vs. 20.0 ± 22.8 events/h using the new and conventional AASM scoring criteria, respectively (p < 0.001). SCI patients had SDB (AHI > 5 events/h) in 77% of the cases using the new AASM scoring criteria compared to 65% using standard conventional criteria (p < 0.05). In cervical SCI, V02 decreased from 7.2 ± 1.6 to 5.5 ± 1.3 L/min, whereas P02-CO2 and V02-CV, increased during sleep compared to thoracic SCI.

**Conclusion:** The majority of SCI survivors have symptomatic SDB and poor sleep that may be missed if not carefully assessed. Decreased V02 and increased P02-CO2 during sleep in patients with cervical SCI relative to thoracic SCI suggests that sleep related hypventilation may contribute to the pathogenesis SDB in patients with chronic cervical SCI.

**Keywords:** Sleep, spinal cord injury, tetraplegia, central apnea

**Citation:** Sankari A; Bascom A; Oomman S; Badr MS. Sleep disordered breathing in chronic spinal cord injury. J Clin Sleep Med 2014;10(1):65-72.
Unfortunately, SDB in SCI patients remains underdiagnosed and undertreated. Furthermore, there are insufficient data on the type of SDB, mechanism of disease, and predictors for the increased prevalence and the relationship to level of injury.

The purposes of this study were (1) to characterize the sleep disturbances in the SCI population using standardized questionnaires and the associated physiological abnormalities using quantitative polysomnography with pharyngeal pressure catheter; (2) to determine the contribution of SCI level on the SDB mechanism (obstructive vs. central); and (3) to determine the magnitude of the fall in ventilation during sleep in chronic SCI patients. To this end, we measured pressure and ventilatory parameters during wake and sleep in addition to apnea-hypopnea index (AHI). Results of this study have previously been reported in the form of abstracts.17

**METHODS**

**Subjects**

The Human Investigation Committee of Wayne State University and the VA Medical Center approved the experimental protocol. An informed written consent was obtained and subjects had a screening polysomnography. We studied adults (> 18 years old) with chronic SCI if they fit the inclusion and exclusion criteria.

Inclusion criteria were as follows: non-ventilator dependent subjects with chronic SCI (> 6 months post-injury), American Spinal Injury Association grade A, B, C, or D, spanning the spectrum from cervical to thoracic levels (T6 and above).

Participants were excluded from the study for any of the following: (1) < 18 years of age; (2) pregnant or lactating females; (3) currently ventilator dependent or with tracheotomy tube in place; (4) history of cardiac disease including heart failure, peripheral vascular disease or stroke; (5) history of head trauma resulting in neurological symptoms or loss of consciousness; (6) advanced lung, liver or chronic kidney disease; (7) extreme obesity, defined for this protocol as BMI > 38 kg/m2 (to avoid the effect of morbid obesity on pulmonary mechanics and ventilatory control); or (8) other illness that would interfere with completion of the study in the investigators’ judgment.

The participants were recruited from the local and regional spinal cord injury care centers including the Detroit VA Medical Center and the Rehabilitation Institute of Michigan. Additional mailings were sent local electronic database of patients with International Classification of Disease (ICD-9) codes corresponding to paraplegia or quadriplegia (344.0 or 344.1). Letters were sent to area physicians soliciting referrals of appropriate patients. In addition, SCI patients were contacted through publications on the internet by contacting SCI support groups.

**Measurements**

Every subject who agreed to enroll had brief history and exam and completed the following questionnaires: Epworth Sleepiness Scale (ESS), Pittsburgh Sleep Quality Index (PSQI), Berlin questionnaire and fatigue severity scale (FSS). All subjects had baseline spirometry (forced vital capacity (FVC), forced expiratory volume in the first second (FEV1), and FEV1/FVC ratio) and respiratory muscle forces (maximal inspiratory and expiratory pressure MIP and MEP, respectively) in upright and supine position to assess positional effect on respiratory function. In addition to standard polysomnography including EEG and chin EMG, nasal airflow was measured by a pneumotachometer (Hans Rudolph, inc., Model 3700A, Shawnee, KS) connected to a tight-fitting nasal mask. Tidal volume (\(V_t\)) was obtained by integrating the pneumotachograph flow signal. End-tidal carbon dioxide (\(P_{\text{ETCO}_2}\)) was measured with a gas analyzer (VacuMed, Model 17515, Ventura, CA). Supraglottic pressure was measured with a pressure tipped catheter (Millar Instruments, Houston, TX), positioned in the hypopharynx.

**Data Analysis**

The best effort of the baseline spirometry and respiratory muscle forces were reported in each participant (in both absolute and % of predicted) on the same night of the sleep study, which were then summarized as mean ± SD. Baseline wake and sleep monitoring: sleep, ventilation and noninvasive blood pressure were monitored in each subject to assess the effect of SCI during wakefulness and sleep. Periods of 2 min from wakefulness and stable NREM sleep were measured to assess baseline ventilation (\(V_t\), \(V_T\), \(F_{\text{CO}_2}\), \(T_{\text{ET}}\), \(P_{\text{ETCO}_2}\), \(O_{2\text{Sat}}\)), and minute ventilation coefficient of variation (\(V_t\)-CV), which were then summarized as mean ± SD. \(V_t\)-CV was calculated for \(V_t\) by the following formula: \(CV\% = (SD/\text{mean})*100\).

Standard polysomnography (PSG) was performed according to AASM standards and respiratory events were scored by the 2007 standard (the only scoring criterion accepted by Medicare)18 and by the 2012 AASM recommended scoring criterion.19 The standard scoring criterion for respiratory hypopnea was ≥ 30% reduction in nasal flow signal for ≥ 10 sec associated with ≥ 4% desaturation from pre-event baseline. In 2012, the recommended scoring criterion for respiratory events as hypopnea was modified to 30% reduction in nasal flow for ≥ 10 sec associated with ≥ 3% desaturation from pre-event baseline or arousal.19

Supraglottic pressure was used to differentiate the central from obstructive apneas by identifying the absence or presence of effort as described previously.20 Sleep disordered breathing was identified if the calculated AHI was ≥ 5 events/h of sleep. Central SDB was defined as \(AIH\) ≥ 5 events/h of sleep and central apnea index (CAI) > 5 events/h sleep. Cheyne-Stokes respiration (CSR) was defined as ≥ 3 consecutive cycles of cyclical crescendo and decrescendo change in breathing amplitude and at least one of the following: (1) ≥ 5 central apneas or hypopneas/h of sleep, (2) cyclical crescendo and decrescendo change in breathing lasting ≥ 10 consecutive minutes.19 The cycle duration ≥ 40 sec was not implemented in the definition of CSR, as SCI patients did not have heart failure. Periodic breathing (PB) was defined as cyclical increases in the rate and depth of breathing (hyperpnea) alternating with either a reduction by 50% (hypopnea) or complete cessation (apnea) of nasal airflow and respiratory effort lasting ≥ 10 seconds.21,22 We excluded obstructive patterns when defining periodic breathing. For hypopneas, we identified periodic breathing if there was decreased effort by supraglottic pressure and belts.

**Statistical Analysis**

All data were assessed for normal distribution. An unpaired t-test was used to compare the mean values of all demographic...
parameters. A paired t-test or adequate nonparametric test such as Wilcoxon signed rank test (when normal distribution failed) was used to compare the group values of each ventilatory data between wake and sleep (V<sub>T</sub>, V<sub>P</sub>, F<sub>VO</sub><sub>2</sub>, T<sub>Ti</sub>, P<sub>ET</sub>CO<sub>2</sub>, O<sub>2</sub>Sat, and V<sub>I</sub>-CV). Paired t-test was used to compare the mean values of PSG data scored using conventional AASM scoring criteria and new recommended criteria. Chi-square analysis was used to compare the proportions of SDB in SCI (defined as AHI > 5) using conventional AASM scoring criteria and new recommended criteria. Analysis of variance (ANOVA) was used for subgroups comparisons of thoracic vs. cervical effect on the ventilatory data between wake and sleep. To assess the relationship between the self-reported questionnaires (ESS, PSQI, and FSS) and objectively measured tests (AHI, sleep efficiency, and arousal index) a Spearman correlation analysis was used. Multiple linear regression models were used to identify if ESS, PSQI, and FSS or NC can be independent predictors of AHI.

**RESULTS**

We studied 26 chronic SCI patients including 15 with cervical (C4-C7) and 11 with thoracic (T2-T6) levels who had similar demographics. Poor sleep quality and fatigue were noted, as evidenced by a high mean PSQI score 10.3 ± 3.7 in 26 SCI patients; 92% had poor sleep quality (PSQI score > 5 indicates poor nocturnal sleep). The mean score of the sleepiness scale (ESS) was 10.4 ± 4.4 in SCI patients and daytime sleepiness (ESS ≥ 10) was present in 59% of the patients. Daytime fatigue (FSS > 20) was reported in 96% those with SCI, while 46% had high-risk scores for OSA on Berlin questionnaire. Table 1 summarizes the demographics, sleep quality, and daytime symptoms in these participants using the PSQI, ESS, FSS, and Berlin questionnaires.

Baseline spirometry on the day of the assessment revealed that forced vital capacity (FVC) in SCI was 70.5% predicted in supine compared to 78.5% predicted in upright positions (Figure 1; p < 0.05). Likewise, FEV<sub>1</sub> was 64.9% predicted in supine compared to 74.7% predicted in upright positions (p < 0.05). Mean maximal inspiratory pressure (MIP) was 83.6% and 85.9% predicted in supine and upright positions, respectively (p = NS). Mean maximal expiratory pressure (MEP) was 42.2% and 47.5% predicted in supine and upright positions, respectively (p < 0.05). Table 2 summarizes the upright and supine pulmonary function and respiratory muscle strengths measures in both cervical and thoracic SCI categories. It is of note that the effect of body position on PFTs was different in thoracic SCI versus cervical SCI. FEV<sub>1</sub>/FVC and MEP decreased in the supine position in cervical SCI but not in thoracic SCI patients. Despite significant drops in FVC, FEV<sub>1</sub>,

**Table 1**—SCI Patient characteristics and sleep quality

<table>
<thead>
<tr>
<th></th>
<th>Cervical</th>
<th>Thoracic</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>15</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>44.8 ± 16.5</td>
<td>39.4 ± 17.2</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>24.5 ± 4.4</td>
<td>27.8 ± 5.2</td>
<td>NS</td>
</tr>
<tr>
<td>Gender (F/M)</td>
<td>3/12</td>
<td>4/7</td>
<td></td>
</tr>
<tr>
<td>NC (cm)</td>
<td>38.9 ± 3.4</td>
<td>39.7 ± 5.0</td>
<td>NS</td>
</tr>
<tr>
<td>Time since injury (year)</td>
<td>11.1 ± 7.3</td>
<td>13.0 ± 6.4</td>
<td>NS</td>
</tr>
<tr>
<td>Use of narcotics (%)</td>
<td>33.0 ± 49.0</td>
<td>18.0 ± 40.0</td>
<td>NS</td>
</tr>
<tr>
<td>ESS (points)</td>
<td>11.2 ± 4.5</td>
<td>9.2 ± 4.1</td>
<td>NS</td>
</tr>
<tr>
<td>PSQI (% &gt; 5 points)</td>
<td>87.0 ± 35.0</td>
<td>100.0 ± 0.0</td>
<td>NS</td>
</tr>
<tr>
<td>FSS (% &gt; 2 points)</td>
<td>93.0 ± 26.0</td>
<td>100.0 ± 0.0</td>
<td>NS</td>
</tr>
<tr>
<td>Berlin Q (% high risk)</td>
<td>47.0 ± 52.0</td>
<td>50.0 ± 53.0</td>
<td>NS</td>
</tr>
</tbody>
</table>

All data mean ± SD. NC, neck circumference; BMI, body mass index; ESS, Epworth Sleepiness Scale (0-24); PSQI, Pittsburgh Sleep Quality Index (> 5 abnormal); FSS, Fatigue Severity Scale (> 2 abnormal); Berlin Q, Berlin Questionnaire for sleep apnea (Low, Intermediate, or High risk).

**Figure 1**—Mean values of (% predicted) forced vital capacity (FVC), FEV<sub>1</sub>, and FEV<sub>1</sub>/FVC of 26 SCI participants during upright (gray bars) and supine (white bars) positions.

*p < 0.05.

**Table 2**—Baseline pulmonary function and muscle forces

<table>
<thead>
<tr>
<th></th>
<th>Cervical</th>
<th>Supine</th>
<th>Thoracic</th>
<th>Supine</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>15</td>
<td>15</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt; (%)</td>
<td>74.3 ± 19.4</td>
<td>65.3 ± 15.0 *</td>
<td>75.2 ± 12.3</td>
<td>64.4 ± 12.3 *</td>
</tr>
<tr>
<td>FVC (%)</td>
<td>74.7 ± 24.0</td>
<td>71.1 ± 18.9</td>
<td>79.9 ± 14.6</td>
<td>71.3 ± 15.4 *</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;/FVC</td>
<td>82.9 ± 6.7</td>
<td>77.1 ± 8.7 *</td>
<td>77.6 ± 6.2</td>
<td>76.6 ± 10.5</td>
</tr>
<tr>
<td>FEF 25-75 (%)</td>
<td>68.2 ± 19.5</td>
<td>59.2 ± 18.9 *</td>
<td>69.6 ± 19.9</td>
<td>56.6 ± 18.3 *</td>
</tr>
<tr>
<td>MIP (%)</td>
<td>75.3 ± 26.4</td>
<td>77.5 ± 22.0</td>
<td>100.2 ± 48.1</td>
<td>91.4 ± 35.5</td>
</tr>
<tr>
<td>MEP (%)</td>
<td>54.3 ± 22.6</td>
<td>36.3 ± 12.0 *</td>
<td>41.6 ± 16.4</td>
<td>50.4 ± 21.8</td>
</tr>
</tbody>
</table>

All data mean ± SD (% predicted). FEV<sub>1</sub>, forced expiratory volume 1<sup>st</sup> second; FVC, forced vital capacity; FEF 25-75, forced expiratory flow 25-75; MIP, maximal inspiratory pressure; MEP, maximal expiratory pressure. *p value < 0.05 Supine vs. Upright.
and FEV1/FVC from upright to supine positions (6.4 ± 12.1, 14.3 ± 13.2, and 5.7% ± 9.5%, respectively; p < 0.05), there was no correlation between positional FVC change and measured maximal inspiratory pressure in either position.

Table 3—Characteristics of sleep and polysomnography data

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cervical</th>
<th>Thoracic</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>15</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>TST (minutes)</td>
<td>169.8 ± 65.4</td>
<td>153.0 ± 76.2</td>
<td>NS</td>
</tr>
<tr>
<td>Stage N1 (%)</td>
<td>25.1 ± 20.5</td>
<td>25.1 ± 27.3</td>
<td>NS</td>
</tr>
<tr>
<td>Stage N2 (%)</td>
<td>50.8 ± 16.8</td>
<td>46.7 ± 17.8</td>
<td>NS</td>
</tr>
<tr>
<td>Stage N3 (%)</td>
<td>19.8 ± 19.5</td>
<td>22.7 ± 19.7</td>
<td>NS</td>
</tr>
<tr>
<td>REM sleep (%)</td>
<td>4.4 ± 5.8</td>
<td>5.6 ± 10.9</td>
<td>NS</td>
</tr>
<tr>
<td>Sleep Efficiency (%)</td>
<td>60.6 ± 12.6</td>
<td>70.9 ± 25.6</td>
<td>NS</td>
</tr>
<tr>
<td>Mean AHI (recommended) (event/h)</td>
<td>20.7 ± 18.7</td>
<td>10.9 ± 20.5</td>
<td>NS</td>
</tr>
<tr>
<td>AHI (% &gt; 5 events/h)</td>
<td>93.0 ± 26.0*</td>
<td>55.0 ± 52.0</td>
<td>0.02</td>
</tr>
<tr>
<td>AHI (% &gt; 15 events/h)</td>
<td>80.0 ± 41.0*</td>
<td>27.0 ± 47.0</td>
<td>0.006</td>
</tr>
<tr>
<td>ARI (% &gt; 5 events/h)</td>
<td>86.0 ± 36.0</td>
<td>55.0 ± 52.0</td>
<td>NS</td>
</tr>
<tr>
<td>ODI (% &gt; 5 events/h)</td>
<td>57.0 ± 51.0</td>
<td>27.0 ± 47.0</td>
<td>NS</td>
</tr>
<tr>
<td>CAI (% &gt; 5 events/h)</td>
<td>40.0 ± 51.0</td>
<td>18.0 ± 40.0</td>
<td>NS</td>
</tr>
<tr>
<td>OAI (% &gt; 5 events/h)</td>
<td>33.0 ± 49.0</td>
<td>18.0 ± 40.0</td>
<td>NS</td>
</tr>
<tr>
<td>CSR (%)</td>
<td>27.0 ± 48.0</td>
<td>9.0 ± 30.0</td>
<td>NS</td>
</tr>
<tr>
<td>PB (%)</td>
<td>60.0 ± 51.0</td>
<td>27.0 ± 47.0</td>
<td>NS</td>
</tr>
</tbody>
</table>

All data mean ± SD. TST, total sleep time; AHI, apnea-hypopnea index; ODI, oxygen-desaturation index; ARI, respiratory related arousal index; CAI, central apnea index; OAI, obstructive apnea index; CSR, Cheyne-Stokes Respiration; PB, periodic breathing. *p value < 0.05 cervical vs. thoracic.

Table 3 summarizes the characteristics of sleep and polysomnography data. In-laboratory polysomnography studies (PSG) with pharyngeal catheter and pneumotachometer revealed that 77% of SCI patients had sleep disordered breathing (AHI > 5). Mean AHI in SCI patients was 29.3 ± 25.0 vs. 20.0 ± 22.8 events/h using the new and conventional AASM scoring criteria, respectively (p < 0.001). The majority of SCI patients (77%) had SDB (AHI > 5) using the new AASM scoring criteria compared to 65% using standard conventional criteria (p < 0.05). It is of note that 9 of 15 (60%) cervical SCI patients demonstrated evidence of central SDB manifesting as central apnea or periodic breathing. Four of the 9 (44%) had Cheyne-Stokes respiration pattern (CSR) as shown in Figure 2. In sub-analysis conducted after excluding individuals who were using opioids (6 cervical and 3 thoracic), it was found that 89% of cervical and 50% of thoracic SCI cases had SDB, with AHI ≥ 5 events/hour. One-third of those with cervical SCI vs. 13% of those with thoracic SCI had central sleep apnea with CAI > 5/h (Table 4).

The sleep state was associated with significant changes in ventilation and gas exchange. Median minute ventilation decreased from 7.2 L/min during wakefulness to 5.5 L/min during stable NREM sleep (p < 0.05) as shown in Figure 3. In addition, patients with cervical SCI demonstrated substantial respiratory variability and hypoventilation after transitioning to sleep as evidenced by increased coefficient of variation of $V_t$, lower $SpO_2$, and higher $P_{ET CO_2}$ relative to thoracic SCI patients (Figure 4). Baseline ventilation and oxygen saturation were similar between cervical and thoracic SCI patients during wakefulness (Table 5).

Both AHI and respiratory related arousal index correlated positively with daytime sleepiness (ESS score) ($r = 0.40$).
and 0.39, respectively; p < 0.05) but not with PSQI or FSS (p = NS). AHI also correlated with neck circumference and age (r = 0.52 and 0.43, respectively; p < 0.05), but not with BMI (p = NS). Using multiple linear regression model to predict AHI from the following correlating variables (ESS, NC, and age), ESS score was the only independent predictor of AHI (p < 0.05).

**DISCUSSION**

The major findings of this study were that (1) 77% of SCI survivors have symptomatic SDB and poor sleep quality better detected by new AASM scoring criteria; (2) the level of SCI (cervical versus thoracic) affected the prevalence of SDB and type of respiratory events (more central SDB noted in cervical SCI) and PFT findings; (3) decreased ventilation (VT) in the cervical level (VT dropped 21%) compared to thoracic (11% drop) between wakefulness and sleep indicates the importance of hypoventilation during sleep in the mechanism of SDB in chronic cervical SCI.

This is the first study to assess sleep disordered breathing and ventilation changes comparing two different levels of SCI (cervical vs. thoracic). Ventilation decreased significantly more in those with cervical SCI than those with thoracic SCI, as evidenced by the greater drop in tidal volumes and the rise in end-tidal CO₂ seen in cervical versus thoracic SCI cases indicating the occurrence of alveolar hypoventilation during sleep.

We noted that sleep quality was very poor in the majority of SCI patients regardless of their level of injury or severity of sleep disordered breathing. SCI patients screening revealed excessive daytime fatigue and sleepiness. We considered several possibilities to explain poor sleep quality and daytime function in patients with SCI. Medication use may be implicated; however, less than one-third of those with SCI were receiving narcotic medications and there was no correlation

**Table 4**—Characteristics of sleep and polysomnography data after excluding patients using opioids

<table>
<thead>
<tr>
<th></th>
<th>Cervical</th>
<th>Thoracic</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>TST (minutes)</td>
<td>161.2 ± 69.9</td>
<td>144.6 ± 82.3</td>
</tr>
<tr>
<td>Stage N1 (%)</td>
<td>31.3 ± 22.9</td>
<td>29.2 ± 29.2</td>
</tr>
<tr>
<td>Stage N2 (%)</td>
<td>48.7 ± 16.8</td>
<td>41.8 ± 16.5</td>
</tr>
<tr>
<td>Stage N3 (%)</td>
<td>16.0 ± 12.4</td>
<td>23.8 ± 22.1</td>
</tr>
<tr>
<td>REM sleep (%)</td>
<td>4.9 ± 5.5</td>
<td>5.1 ± 11.6</td>
</tr>
<tr>
<td>Sleep Efficiency (%)</td>
<td>62.6 ± 9.0</td>
<td>77.7 ± 19.9</td>
</tr>
<tr>
<td>AHI (% &gt; 5 events/h)</td>
<td>89.0</td>
<td>50.0</td>
</tr>
<tr>
<td>AHI (% &gt; 15 events/h)</td>
<td>78.0*</td>
<td>25.0</td>
</tr>
<tr>
<td>AI-res (events/h)</td>
<td>29.4 ± 23.1</td>
<td>15.2 ± 20.1</td>
</tr>
<tr>
<td>CAI (% &gt; 5 events/h)</td>
<td>33.0</td>
<td>13.0</td>
</tr>
<tr>
<td>OAI (% &gt; 5 events/h)</td>
<td>33.0</td>
<td>25.0</td>
</tr>
<tr>
<td>CSR (%)</td>
<td>22.0</td>
<td>0.0</td>
</tr>
<tr>
<td>PB (%)</td>
<td>56.0</td>
<td>25.0</td>
</tr>
</tbody>
</table>

All data mean ± SD. TST, total sleep time; AHI, apnea-hypopnea index; ODI, oxygen-desaturation index; AI-res, respiratory related arousal index; CAI, central apnea index; OAI, obstructive apnea index; CSR, Cheyne-Stokes respiration; PB, periodic breathing. *p value < 0.05 cervical vs. thoracic.
between daytime symptoms and medication use. Melatonin deficiency has also been reported in patients with SCI; this may affect sleep quality and daytime function. In a small sample of SCI individuals it was found that melatonin level does not increase at night in cervical SCI (tetraplegia) compared to those with thoracic SCI and controls. However, melatonin deficiency does not explain poor sleep in thoracic SCI, as melatonin levels increased similar to the able body group. Accordingly, we attribute poor daytime function to increased indices of SDB rather than non-respiratory factors.

Our study revealed a higher prevalence of SDB (defined by AHI > 5; 93% of cervical and 55% of thoracic SCI) than what has been reported in the literature. However, screening tools were inadequate to identify patients with SDB. For example, the Berlin questionnaire suggested that only 50% of SCI patients (thoracic and cervical equally) were at high risk for sleep apnea. High prevalence of OSA has been reported in many previous studies—up to 60%, particularly in the tetraplegic group. High prevalence of OSA has been reported in many previous studies—up to 60%, particularly in the tetraplegic group. High prevalence of OSA has been reported in many previous studies—up to 60%, particularly in the tetraplegic group. High prevalence of OSA has been reported in many previous studies—up to 60%, particularly in the tetraplegic group. High prevalence of OSA has been reported in many previous studies—up to 60%, particularly in the tetraplegic group. High prevalence of OSA has been reported in many previous studies—up to 60%, particularly in the tetraplegic group.

Our findings are consistent with the study by Dicpinigaitis et al., which revealed a muscarinic receptor bronchial hyperresponsiveness in cervical SCI patients, as evidenced by the presence of methacholine hyperresponsiveness that is reversible with inhaled ipratropium bromide. The combination of decreased post-hyperventilation hypocapnia (hypocapnic type) below a highly sensitive “apneic threshold.” Central apnea rarely occurs as isolated events but as cycles of apnea or hypopnea alternating with hyperpnea, a reflection of the negative feedback closed-loop cycle that characterizes ventilatory control; this is often described using the engineering concept of “loop gain,” which is the net ventilatory change for a given perturbation, combining the response of the ventilatory system to changing P\textsubscript{ET CO\textsubscript{2}}, the controller, and the effectiveness of the lung/respiratory system in lowering P\textsubscript{ET CO\textsubscript{2}} in response to hyperventilation (the plant). Changes in either parameter would change the requisite hypocapnia to reach central apnea. In addition, sleep state instability, manifested by recurrent arousals, might trigger or exacerbate breathing instability due to rapid fluctuation in chemoreflex sensitivity or upper airway patency.

Repetitive arousals may also contribute to the breathing instability by augmenting the ventilatory response to a given perturbation and periodic breathing. Sleep fragmentation might be very relevant to tetraplegic patients, who are already known to have increased occurrences of spasticity, pain and periodic leg movements. As a result of these alterations between sleep onset and arousal, repetitive perturbations in ventilatory control can occur throughout sleep. Subtle autonomic arousals, without EEG changes may also contribute to the genesis of unstable breathing and poor sleep quality.

Our study corroborated previous studies documenting decreased VC, especially in the supine position, indicative of a restrictive defect in SCI patients. Interestingly, there was no significant difference between the two groups. Patients with cervical SCI only demonstrated reduced FEV\textsubscript{1}/FVC ratio in the supine relative to the upright position. The etiology of this finding is unclear but may be due to a combination of decreased lung volumes and the interruption of the sympathetic innervation of the lung by cervical spine injury, leaving the parasympathetic innervation unopposed. Our findings are consistent with the study by Dicpinigaitis et al., which revealed a muscarinic receptor bronchial hyperresponsiveness in cervical SCI patients, as evidenced by the presence of methacholine hyperresponsiveness that is reversible with inhaled ipratropium bromide. The combination of decreased

### Table 5—Ventilatory parameters (N = 26)

<table>
<thead>
<tr>
<th></th>
<th>Cervical</th>
<th>Sleep</th>
<th>Thoracic</th>
<th>Sleep</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Wake</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V\textsubscript{i} (L/min)</td>
<td>7.2 ± 1.6</td>
<td>5.5 ± 1.3*</td>
<td>6.6 ± 2.2</td>
<td>5.5 ± 1.8*</td>
</tr>
<tr>
<td>V\textsubscript{c} (L)</td>
<td>0.53 ± 0.16</td>
<td>0.40 ± 0.11*</td>
<td>0.38 ± 0.10</td>
<td>0.34 ± 0.09*</td>
</tr>
<tr>
<td>F\textsubscript{E} (breath/min)</td>
<td>14.4 ± 3.4</td>
<td>14.2 ± 2.5</td>
<td>17.4 ± 3.2</td>
<td>16.6 ± 3.4*</td>
</tr>
<tr>
<td>T\textsubscript{i} (sec)</td>
<td>1.9 ± 0.5</td>
<td>1.9 ± 0.5</td>
<td>1.5 ± 0.3</td>
<td>1.6 ± 0.3</td>
</tr>
<tr>
<td>T\textsubscript{o} (sec)</td>
<td>2.6 ± 0.7</td>
<td>2.5 ± 0.6</td>
<td>2.1 ± 0.4</td>
<td>2.2 ± 0.6</td>
</tr>
<tr>
<td>T\textsubscript{i} / T\textsubscript{TOT} (sec)</td>
<td>0.43 ± 0.05</td>
<td>0.44 ± 0.07</td>
<td>0.43 ± 0.03</td>
<td>0.43 ± 0.07</td>
</tr>
<tr>
<td>P\textsubscript{ET CO\textsubscript{2}} (mm Hg)</td>
<td>39.7 ± 3.8</td>
<td>41.3 ± 4.6*</td>
<td>37.2 ± 4.2</td>
<td>37.5 ± 4.1</td>
</tr>
<tr>
<td>O\textsubscript{2} Sat (%)</td>
<td>96.2 ± 1.2</td>
<td>95.3 ± 1.3*</td>
<td>96.9 ± 1.0</td>
<td>96.9 ± 1.2</td>
</tr>
<tr>
<td>V\textsubscript{c}-CV (%)</td>
<td>21.7 ± 11.9</td>
<td>38.1 ± 22.7*</td>
<td>13.4 ± 4.7</td>
<td>23.8 ± 19.2</td>
</tr>
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<tr>
<td>V\textsubscript{i} (L/min)</td>
<td>7.2 ± 1.6</td>
<td>5.5 ± 1.3*</td>
<td>6.6 ± 2.2</td>
<td>5.5 ± 1.8*</td>
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<tr>
<td>V\textsubscript{c} (L)</td>
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<td>0.40 ± 0.11*</td>
<td>0.38 ± 0.10</td>
<td>0.34 ± 0.09*</td>
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<td>F\textsubscript{E} (breath/min)</td>
<td>14.4 ± 3.4</td>
<td>14.2 ± 2.5</td>
<td>17.4 ± 3.2</td>
<td>16.6 ± 3.4*</td>
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<td>T\textsubscript{i} (sec)</td>
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<td>T\textsubscript{i} / T\textsubscript{TOT} (sec)</td>
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<td>0.44 ± 0.07</td>
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All data mean ± SD. V\textsubscript{i}, inspiratory minute ventilation; V\textsubscript{c}, tidal volume; F\textsubscript{E}, breathing frequency; T\textsubscript{i}, inspiratory time; T\textsubscript{o}, expiratory time; P\textsubscript{ET CO\textsubscript{2}}, end-tidal CO\textsubscript{2}; O\textsubscript{2} Sat, oxygen saturation; V\textsubscript{c}-CV, minute ventilation coefficient of variation. *p value < 0.05 Cervical vs. Thoracic.
expiratory flow and decreased MEP may contribute to retained secretions and contribute to the development of episodic hypoxia and sleep fragmentation.

We found that FVC and FEV1 were decreased and became lower in the supine position compared to the upright position, which may play a role in predisposing SCI patients for sleep disordered breathing by more collapsible airway and hypoventilation under smaller lung volumes in supine position. Contrary to our findings, previous studies have reported that FVC and FEV1 in tetraplegia patients tended to be larger in supine than seated positions.33,34 Our study measured forced, not slow, vital capacity in upright and supine positions on the day of the sleep study. The changes in spirometric measurements in SCI patients were found previously to be dependent on injury level in complete injuries. Incomplete SCI had less effect on FVC in cervical levels, which may explain the higher FVC values in our study, as most injuries were incomplete and low cervical.

Methodological Considerations

Several considerations may influence the interpretation of the findings. First, our design does not allow us to address the prevalence of SDB in patients with SCI. However, we included all consecutive subjects who qualified for enrolment independent of the presence of sleep symptoms. Second, the use of invasive measurements and the small sample size may have affected sleep continuity and generalizability of the findings. Third, our findings do not allow us to isolate the independent effect of SCI on ventilation given the concomitant use of medications and the presence of comorbid conditions. Fourth, although the cervical and thoracic SCI body mass indexes were not statistically different, thoracic SCI individuals were more overweight, which could play a role in the increased obstructive SDB disorders compared to cervical group.

Clinical Implications

Our findings have significant implications regarding the diagnosis and treatment of sleep apnea in patients with SCI: (1) Positive screening questionnaires in our study may lack the discriminatory power to inform further diagnostic evaluation and may be superfluous given the high prevalence of SDB in this population; (2) Many studies in chronic SCI patients have used type III or IV devices, which have not been validated beyond the diagnosis of OSA in patients with a high index of suspicion. Conventional “qualitative” polysomnography may also fail to detect hypopneas if oxyhemoglobin desaturation is mild, or if arousal threshold is elevated, a potential consequence of narcotics administration. In fact, the diagnosis of SDB may be missed if type IV devices using ODI are used for the diagnosis. We propose that all SCI patients should undergo full polysomnography either as an in-lab (type I) or home polysomnography (type II) studies. Limited recordings may fail to accurately detect and classify SDB in patients with SCI; (3) Nearly all SCI patients have poor sleep quality (increased PSQI) and daytime fatigue (increased FSS), but these do not predict SDB severity. Excessive daytime sleepiness, measured by ESS score, is the only independent predictor of SDB severity; (4) Cervical SCI patients manifest as central SDB more commonly than thoracic injuries, which require special consideration in diagnosis and treatment; (5) Therapeutic methods that target hypoventilation during sleep in cervical SCI may play important role in the treatment of SDB.

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ACKNOWLEDGMENTS

The authors thank Nicole Nickert, Sukanya Pranathiageswaran, Lola Adekanmbi, and Anita D’Souza for technical assistance. Author contributions to the study: conception and design: Abdulghani Sankari and M. Safwan Badr; analysis and interpretation: Abdulghani Sankari, Amy Bascom, Sowmini Oomman, and M. Safwan Badr; drafting the manuscript for important intellectual content: Abdulghani Sankari and M. Safwan Badr.

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Submitted for publication May, 2013
Submitted in final revised form September, 2013
Accepted for publication September, 2013
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DISCLOSURE STATEMENT

This was not an industry supported study. The study was funded by the Department of Veterans Affairs (Award Number I01BX007080 from the Biomedical Laboratory Research & Development Service of the VA Office of Research and Development). The authors have indicated no financial conflicts of interest.
Monitoring Sound To Quantify Snoring and Sleep Apnea Severity Using a Smartphone: Proof of Concept


Subjects
The subjects included 50 patients who underwent diagnostic polysomnography (PSG), of which the data of 10 patients were used for developing the program and that of 40 patients were used for validating the program. A smartphone was attached to the anterior chest wall over the sternum. It acquired ambient sound from the built-in microphone and analyzed it using a fast Fourier transform on a real-time basis. Snoring time measured by the smartphone highly correlated with snoring time measured by PSG (r = 0.93). The top 1 percentile value of sound pressure level (L1) determined by the smartphone correlated with the ambient sound L1 during sleep determined by PSG (r = 0.92). Moreover, the respiratory disturbance index estimated by the smartphone (smart-RDI) highly correlated with the apnea-hypopnea index (AHI) obtained by PSG (r = 0.94). The diagnostic sensitivity and specificity of the smart-RDI for diagnosing OSA (AHI ≥ 15) were 0.70 and 0.94, respectively.

Conclusions: A smartphone can be used for effectively monitoring snoring and OSA in a controlled laboratory setting. Use of this technology in a noisy home environment remains unproven, and further investigation is needed.

Keywords: Snoring, home monitoring, obstructive sleep apnea, smartphone

Citation: Nakano H; Hirayama K; Sadamitsu Y; Toshimitsu A; Fujita H; Shin S; Tanigawa T. Monitoring sound to quantify snoring and sleep apnea severity using a smartphone: proof of concept. J Clin Sleep Med 2014;10(1):73-78.

METHODS

Study Objectives: Habitual snoring is a prevalent condition affecting 22% to 44% of middle-aged males and 13% to 28% of middle-aged females. It is a key symptom suggesting the possibility of obstructive sleep apnea (OSA). Moreover, it has been suggested that snoring can be a vascular risk. Primary snoring is readily affected by body position; it may decrease or increase with loss or gain in body weight. Decrease in snoring reduces the risk of sleep disordered breathing. Therefore, self-monitoring of snoring is considered to be a useful tool for maintaining good health among the general population. However, no device is currently available for home monitoring of snoring. Recently, smartphones with various sensors and signal processing capabilities have been used as tools for home healthcare (for example, as a pedometer, an exercise pulse rate monitor, and an advisory service for dietary control). Moreover, a growing body of biomedical engineering research demonstrated that snoring characteristics carry very useful information about OSA severity. We attempted to develop a snoring sound monitor consisting of a smartphone alone. The system was designed for quantifying snoring as well as OSA severity.

Subjects
The subjects included 50 patients who underwent diagnostic PSG for suspected sleep apnea. The study was approved by our institutional review board, and all patients gave their written informed consent.

Smartphone
An ordinary smartphone in Japan (SH-12C, Sharp Corp., Osaka, Japan) was used as the snoring sound monitor. It was attached to the anterior chest wall over the sternum using adhesive tape. The opening of the built-in microphone was directed toward the neck.

Acquisition of Sounds
The smartphone operated on the Android system (version 2.3.3). A custom-made program on the smartphone acquired ambient sounds from the built-in microphone and analyzed it on a real-time basis. The procedure of signal processing was as follows: the system acquired sound data for approximately 0.1 s (11025-Hz sampling frequency, 1024 points, Hanning
window), calculated power spectra using a fast Fourier transform, and stored these on the memory of the smartphone; this process was repeated every 0.2 s. Although this procedure discards half the data, it seems sufficient for the acquisition of snoring sound. The sound acquisition procedure was identical to that developed for tracheal sound monitoring to detect OSA.15

**Analysis of the Sounds**

**Sound Intensity**

The program was calibrated once using a reference sound pressure level (94 dB [0 dB = 20µPa], 1 kHz) during its development. A sound calibrator (SC-2120A; Ono Sokki, Yokohama, Japan) was connected to the smartphone at the opening of the built-in microphone using a custom-made attachment to ensure a sealed connection. The program calculated the top 1 percentile sound pressure level (L1) and the equivalent sound pressure level (Leq) in dB from the all-night data as variables of snoring sound intensity.16

**Detection of Snoring Sound**

Recorded spectra of the 10 development group subjects were displayed as spectrograms (Figure 1), from which the segments with features characteristic of snoring were selected to determine the spectral parameters for snoring detection. These parameters were adjusted to maximize the association between snoring time measured with the smart phone and that taken from PSG tracheal sounds.

**Detection of Respiratory Events**

Sound power (in dB, 50-2000 Hz) time series data were generated and low-pass filtered (cutoff frequency 0.05 Hz), from which we detected sound power dips fulfilling the following criteria (Figure 1): the sound power dip was defined as a dip in more than a given threshold value in the time series, lasting ≤ 90 s, with the descending and ascending portions steeper than the threshold value per 18 s. The dip was assumed to correspond to a respiratory event.15 We defined the smart-RDI as the number of sound power dips per hour of examination. The optimal threshold for the dip was determined from the 10 development group patients’ data, based on the value that maximizes the association between the smart-RDI and PSG-AHI.

**Polysomnography**

The sensors for PSG along with the smartphone were fixed by technicians, but the sensors were not monitored after the start of the recording. PSG was recorded using a polygraph system (EEG7414; Nihon Kohden, Tokyo, Japan). Nasal airflow was monitored with a nasal prong pressure transducer (PTAF; Pro-Tec, Mukilteo, WA, USA). Thoracic and abdominal respiratory movements were monitored with respiratory inductive plethysmography (Q-RIP; Braebon Medical Corp., Kanata, Ontario, Canada). Oxyhemoglobin saturation was monitored using a pulse oximeter (OLV-3100; Nihon Kohden, Tokyo, Japan) at the fastest response mode.

Tracheal sound was recorded from an air-coupled microphone (ECM-PC60, SONY, Tokyo, Japan) attached on the neck.

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**Figure 1**—Representative trace showing relationship between polysomnograph signals and smartphone-acquired sounds

(A) Polysomnography signals. One obstructive apnea (OA) and 3 obstructive hypopnea (OH) events are detected during the 5 minutes data. Tracheal sound spectrogram shows snoring (indicated by red color) predominantly during hypopnea events. (B) Smartphone-acquired sounds. The parameters for detection of snoring (total power, peak power spectral density) and respiratory events (filtered total power time series) are shown. Arrows indicate the sound power dips detected at a threshold of 3 dB (see text).
over the trachea. The recording system of tracheal sound was calibrated using a reference sound pressure level (94 dB) in the same way as the smartphone system. Tracheal sounds were digitized by the sound system incorporated in a personal computer (PC) at a sampling frequency of 11025 Hz. To evaluate snoring sound intensity, ambient sound pressure was also recorded using a sound level meter (LA1200; Ono Sokki, Yokohama, Japan). The microphone of the sound level meter was suspended 1.2 m above the surface of the patient’s bed. The ambient sound intensity was measured as an A-weighted sound pressure level with a time constant of 125 ms. The measured sound pressure level was inputted to the polygraph system as an analogue signal and digitized simultaneously with the other PSG signals.

The recording by PSG and the smartphone were started simultaneously. Sleep stages were scored manually according to standard criteria. Apnea was defined as cessation of airflow lasting ≥ 10 s. Hypopnea was defined as an episode of airflow amplitude reduction (≥ 50%) lasting ≥ 10 s and associated with ≥ 3% oxygen desaturation or an arousal. The apnea-hypopnea index (AHI) was calculated as the number of apnea and hypopnea events per hour of sleep. Snoring was detected from the tracheal sound data automatically using the criteria in which a peak value of power spectral density ≥ 70 dB/Hz, which means a power spectrum of about 80 dB at the frequency resolution of 10.8 Hz (11025-Hz sampling and 1024 points window), within the frequency bandwidth of 100-300 Hz was defined as snoring. Thereafter, we examined the whole overnight sound spectrogram and excluded body movement sounds and voice sounds from the automatically detected segments. As a variable of snoring sound intensity, we calculated the L1 and Leq during sleep from tracheal sound spectra data recorded every 0.2 s during PSG. In addition, the L1 and Leq during sleep were calculated from the ambient sound level data, because variables from the tracheal sounds were found to suffer a ceiling effect in patients with loud snoring.

Analysis

The subjects were divided into the development group (n = 10) and the validation group (n = 40). The spectral parameters for detecting snoring and the threshold for detecting sound power dips were determined using data from the development group subjects. Comparisons between the snoring time using the smartphone and that using PSG tracheal sounds and between the smart-RDI and AHI were performed using data from the validation group subjects. The L1 and Leq values determined by the smartphone were compared with those of tracheal sounds and ambient sounds determined by PSG in all subjects. All variables from PSG were calculated for total sleep time (TST) with denominator of TST, while the compared variables from smartphone were calculated for entire examination time with denominator of examination time. The smartphone data were analyzed using a custom-made PC program, which can be implemented on a smartphone, and no manual editing was made.

RESULTS

Characterization of Subjects

Of the 50 subjects, 42 were males and 8 were females. The mean age of the subjects was 47.9 years (SD 13.7 years), and the mean body mass index was 26.4 (SD 6.1). The mean AHI was 27.3 (SD 26.1). Eleven patients were not apneic (AHI < 5), 10 patients had mild OSA (AHI 5-14.9), 12 patients had moderate OSA (AHI 15-29.9), and 17 patients had severe OSA (AHI ≥ 30).

Snoring Sound

The L1 value using the smartphone correlated with the tracheal sound L1 (r = 0.75) and ambient sound L1 (r = 0.92) during sleep using PSG (Figure 2, n = 50). The Leq value
using the smartphone correlated with the tracheal sound Leq ($r = 0.72$) and ambient sound Leq ($r = 0.82$) during sleep using PSG (Figure 3; $n = 50$).

The parameters for detecting snoring were determined by the data of the development group subjects. Consequently, the following 3 parameters were determined: power spectral peak density > 35 dB/Hz, which means a power spectrum of about 45 dB at the frequency resolution of 10.8 Hz (11025-Hz sampling and 1024 points window), and between 50 and 300 Hz; total power exceeding the lowest level during the preceding 5 s by > 6 dB; and continuing for 0.4-3.0 s. If a data segment fulfilled all 3 conditions, it qualified as snoring.

Snoring time (% examination time) measured using the smartphone and based on the above criteria highly correlated with the snoring time (% TST) determined using PSG in the validation group (Figure 4; $r = 0.93$, $n = 40$).

**Apnea and Hypopnea**

The data from the development group subjects were divided into 80 1-h segments. The number of sound power dips detected by the smartphone at various thresholds and that of
apnea-hypopnea events detected by PSG were compared in each segment. The correlation between both numbers was highest at a threshold of 3 dB, which was adopted as the threshold for the validation of the smart-RDI.

Comparison of the smart-RDI and AHI in all 40 subjects of the validation group revealed a high correlation (Figure 5; \( r = 0.94 \)). Bland-Altman analysis showed that the mean difference between the smart-RDI and AHI was -6.0 and the limit of agreement was -25.0 to 13.1 (Figure 6). The diagnostic sensitivity and specificity of the smart-RDI in the validation group are shown as receiver operating characteristic curves (Figure 7). The sensitivity was moderate and the specificity was relatively high.

**DISCUSSION**

We attempted to use a smartphone for monitoring snoring and OSA. The smartphone program to detect snoring and OSA events was developed using data from 10 patients and validated using data from the other 40 patients and proved to be considerably effective in detecting snoring and OSA events.

Many screening tools based on questionnaires use snoring as a key symptom of OSA. However, it may be difficult for a single adult to answer these questionnaires accurately because most snorers are unaware of their snoring. Objectively measured snoring intensity is known to correlate with pleural pressure swing amplitude and OSA severity. A study in rabbits demonstrated that exposure to vibrations induced carotid artery endothelial dysfunction in a vibration energy dose-dependent manner, suggesting the importance of snoring intensity. We reported that ambient sound \( L_1 \) during sleep is related to sleepiness and daytime blood pressure independent of obesity and OSA. We therefore suggest that a simple method using a smartphone to measure snoring is useful not only for screening OSA but also for evaluating snoring as a detrimental symptom.

The present study has limitations that have to be addressed. First, the subjects were patients with symptoms suggestive of OSA. It is therefore necessary to test the method in the general population. Second, the recording was performed in a single room for polysomnography. In the presence of a bed partner, measurement of snoring and OSA may be affected by various sounds, including the bed partner’s snoring. Third, the performance of the monitor should be dependent on the characteristics of the smartphone. Therefore, the parameters to detect snoring and OSA events need to be tuned appropriately to each individual.
specific smartphone. Finally, the results suggest that the correlation between the smart-RDI and AHI was not as good for subjects with an AHI less than 30. Therefore, the smartphone program may have insufficient diagnostic accuracy for use as a screening tool to rule out milder forms of OSA.

The present study presents the concept that a smartphone can be used for monitoring snoring and OSA. This method cannot be used as a substitute for the type 4 OSA monitor because the reliability of the method depends on the environment and the device. However, it may be a very useful tool for individuals to check the status of their snoring and OSA daily when attempting various behavioral modifications, e.g., changes in sleeping posture or decrease in body weight. Further studies under practical conditions are warranted.

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SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication June, 2013
Submitted in final revised form August, 2013
Accepted for publication August, 2013
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DISCLOSURE STATEMENT

This was not an industry supported study. This study was supported by a grant from a Health and LaborSciences Research Grant (22110201), Ministry of Health, Welfare and Labor. The authors have indicated no financial conflicts of interest.
Obstructive sleep apnea (OSA) has serious cardiovascular and neurocognitive consequences, and the vibrations of snoring alone may contribute directly to atherosclerosis. Despite these detrimental effects, one of the more common motivations for treatment is some variation of “My snoring is bothering my spouse.” Snoring, which can be louder than a vacuum cleaner at a 1 meter distance (~70 decibels), affects the sleep quality of bed-partners, but at least may prompt evaluation of the snorer. Unfortunately, by itself, snoring is not specific for OSA, and further testing is usually required. However, in this issue of *JCSM* Nakano and colleagues report a breakthrough to simplify this problem: they have used snoring sounds alone to measure OSA severity, and have done so using no more specialized equipment than a “smartphone.”

In their study, respiratory sounds were monitored using a smartphone placed on the chest while patients were simultaneously assessed for snoring and sleep apnea severity in a controlled laboratory setting. Respiratory sounds have a characteristic frequency profile (e.g. in musical terms a particular bass, mid and treble) that provides for ready analysis. To quantify snoring, the authors used the smartphone to measure the peak (top 1%) sound pressure in a low frequency range (bass: 50-300 Hz), which was tightly associated with the peak (top 1%) sound pressure level measured at the trachea and at a microphone 1.2 m from the patient. Moreover, the hypopneic/apneic periods of OSA were identified, paradoxically, by relative peace despite often vigorous efforts to breathe and hypoxemia. It is the accompanying “dips” in total sound pressure level (in the bass and mid frequency range of 50-2000 Hz) that were assessed quantitatively: transient 3 decibel dips in sound pressure (halving of sound power level) were shown to identify respiratory events with impressive accuracy when compared to gold standard polysomnography (PSG). In theory, any modern smartphone could be used in this fashion.

We applaud their efforts. If future research confirms their results, the advance by Nakano and colleagues paves the way for widespread screening for OSA. There is a desperate need for methods to screen patients for OSA, for example, before surgery, and current methods and questionnaires lack specificity. Although home testing with portable monitoring has made impressive advances, they are still nowhere near as ubiquitous and portable as smartphones. Their work also allows for the ongoing real-time home monitoring of OSA in patients already diagnosed with OSA, something not currently possible given the limited access to sleep laboratories and portable monitors for repeated assessments. Accurate home monitoring would enable patients to take control of their disease, similar to blood glucose monitoring for diabetes (rather than hemoglobin A1c measurements every 3 months). Patients could use such technology to observe a progressive reduction in OSA severity with weight loss, providing essential motivation for adhering to a strict weight-loss regimen. Conversely, the effects of weight gain or alcohol intake on their OSA severity may help patients avoid behaviors that adversely affect health. Combined with accelerometry (available on most smartphones) the effects of position therapy could also easily and conveniently be assessed. Perhaps a smartphone with accelerometer could alert patients with supine-dependent OSA to roll onto their side, preempting loud snoring, and the unhappy bed-partner’s inevitable elbow?

Of course, additional research is needed before this technology is ready for home use. A noisier home environment, or multiple snorers (“He/she snores louder than me!”) may overwhelm the technology; a second smartphone nearer to the bed-partner may be needed to subtract this interference. Quieter forms of sleep apnea, such as central or mixed apnea, may go undetected by sound analysis. We encourage the authors to validate and refine their technology for use outside the controlled laboratory environment.

More broadly, these impressive preliminary results emphasize that techniques for OSA diagnosis are now far ahead of our understanding of OSA pathophysiology and treatments for OSA. Put another way—what will we do with all of the patients that we might diagnose with OSA using such technology? CPAP is likely to be refused by many, and thus new treatments are desperately needed. Identifying why an individual patient has OSA (their “phenotype”) is highly likely to help direct treatment. Just as the field is moving away from PSGs for OSA diagnosis, we are now discovering that they contain a wealth of quantitative physiological information that can be used to measure OSA phenotypic traits. For example, the overshoot-undershoot airflow patterns can reveal the ventilatory control (“loop gain”) contribution to OSA, a phenotype that may be amenable to treatment with acetazolamide or oxygen. Frequent but mild oxygen desaturation and a greater proportion of wake and stage N1 sleep may indicate a low arousal threshold or “sleep state instability” that is amenable to treatment with...
sedatives. In the future, we envision the use of mobile technology for providing similar clues as to the underpinnings of OSA in an individual. Do snoring frequency profiles identify the site of airway narrowing? Does a faster, more regular “cycling” of obstructive events reveal a major ventilatory control contribution to OSA? Advances in both understanding OSA pathophysiology and monitoring technology could eventually allow us to use our smartphones not only to diagnose and monitor OSA, but to make smart treatment plans.

CITATION

Sands SA; Owens RL. Does my bed partner have OSA? There’s an app for that! J Clin Sleep Med 2014;10(1):79-80.

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Submitted for publication November, 2013
Accepted for publication November, 2013
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DISCLOSURE STATEMENT

Dr. Sands is supported by a National Health and Medical Research Council of Australia Early Career Fellowship (1053201) and R.G. Menzies award. Dr. Owens is supported by the National Institutes of Health (K23 HL105542). He serves as a consultant for Philips Respironics.
Effect of Body Position and Sleep State on Obstructive Sleep Apnea Severity in Children with Down Syndrome

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Study Objectives: To investigate the influence of sleep position and sleep state on obstructive sleep apnea (OSA) severity in children with Down syndrome (DS).

Design: Retrospective review.

Setting: Sleep disorders laboratory of a tertiary medical center.

Participants: Children with Down syndrome and typically developing children matched for age, gender, apnea-hypopnea index (AHI), and year of polysomnogram.

Measurements and Results: Sleep variables from baseline polysomnography. Sensor-recorded position (supine, prone, lateral) was expressed as the percentage of total sleep time. The AHI was calculated in each sleep state (NREM, REM), position, and position-sleep state combination. Of 76 DS subjects (55% male) the median age and AHI were 4.6 years (range 0.2-17.8 years) and 7.4 events/h (range 0-133). In all subjects, AHI was higher in REM than NREM (p < 0.05); however, the NREM AHI was higher in DS subjects than controls (p < 0.05). Compared to controls, the percentage of prone sleep was greater in DS subjects (p < 0.05), but the percentage of supine or non-supine (prone plus lateral) sleep was no different. For DS subjects alone, NREM AHI was higher in supine than non-supine sleep (p < 0.05).

Conclusion: In DS and non-DS children alike, respiratory events are predominantly REM related. However, when matched for OSA severity, children with DS have a higher NREM AHI, which is worse in the supine position, perhaps indicating a positional effect compounded by underlying hypotonia inherent to DS. These findings illustrate the clinical importance of NREM respiratory events in the DS population and implications for treatment options.

Keywords: Down syndrome, sleep position

Citation: Nisbet LC; Phillips NN; Hoban TF; O’Brien LM. Effect of body position and sleep state on obstructive sleep apnea severity in children with Down syndrome. J Clin Sleep Med 2014;10(1):81-88.

Dow[n syndrome (DS), or Trisomy 21, is the most common chromosomal disorder and is associated with multiple coexisting medical conditions affecting the cardiovascular, respiratory, neurological, gastrointestinal, and hormonal systems. One such disorder is obstructive sleep apnea (OSA), which has a reported prevalence of 45% to 79% in children with DS. In striking contrast, OSA has a prevalence of 1% to 5% in the general pediatric population. Several clinical characteristics present in DS heighten the risk of OSA and additional sleep disturbance, including hypotonia, overweight, an underdeveloped midface and narrow nasopharynx, occurring in conjunction with relative macroGLOSSIA as a function of a normal sized tongue within a small pharynx. In addition, the pharynx is frequently crowded by both lymphoid hyperplasia and a more posterior location of the tongue, further compounded by a reduction in pharyngeal muscle tone.

OSA is the more severe form of a spectrum of disorders known as sleep disordered breathing (SDB), the hallmark of which is snoring. OSA in children is characterized by frequent prolonged partial obstruction or intermittent complete collapse of the upper airway. The pediatric ramifications of OSA are vast, including adverse cardiovascular outcomes such as elevated blood pressure, autonomic dysfunction, and neurocognitive and behavioral deficits. The gold-standard method to diagnose OSA is overnight polysomnography (PSG), from which OSA severity is typically defined using the apnea-hypopnea index (AHI)—the total number of respiratory events per hour of sleep.

It has long been known in adults that both body position during sleep and sleep state can affect OSA severity in adults although findings conflict in the pediatric literature. Although highly prevalent in children with Down syndrome, the effects of body position and sleep state on OSA severity have received little attention despite that consideration of both may impact interpretation of polysomnography and subsequent treatment modality.

Study Impact: When matched for severity of OSA, children with Down syndrome have worse OSA in NREM sleep compared to typically developing children. While the effect of sleep position on OSA severity was similar in both groups of children, those with Down syndrome had worse NREM OSA severity in the supine position. For the clinician, these findings highlight the importance of NREM sleep contribution to OSA severity in children with Down syndrome.
compared to supine position.\textsuperscript{23-25,28,29} More recently, a significant effect of body position on OSA severity has emerged in pediatric studies, although findings are conflicting; some studies observed an improvement in OSA severity in the supine position\textsuperscript{30}; others reported a worsening when supine\textsuperscript{31,32}; and some found no positional difference.\textsuperscript{33-35} Furthermore, the long-held conviction that pediatric OSA is a REM-related disorder\textsuperscript{11,35,36} has also been challenged; while the majority of children do exhibit a higher AHI in REM sleep\textsuperscript{37,38} a considerable minority of children (30\% in one study),\textsuperscript{38} were found to have predominantly NREM-related OSA.

Despite the astoundingly high prevalence of OSA in children with DS,\textsuperscript{1,4} the effects of body position and sleep state on OSA severity in the DS population have received little attention. Knowing the effects of these factors on OSA severity is important, as previously the validity of a diagnosis or classification of OSA severity based on PSG has been questioned in those who had inadequate supine and/or REM sleep, as these factors may result in an understimation of severity.\textsuperscript{32} There are multiple reasons why the effects of body position and sleep state on OSA severity may be different in the DS population compared to patterns reported in typically developing children or adults with OSA. Positional effects may differ as a function of the etiology of OSA, considering the physical characteristics of DS (relative macroglossia, posterior tongue position, etc.); sleep state effects may also vary as a result of the generalized hypotonia commonly associated with DS and also due to alterations in sleep architecture, notably decreased amounts of REM sleep.\textsuperscript{39} We therefore aimed to investigate the effects of body position and sleep state on OSA severity, as measured by AHI, in children with DS in comparison to typically developing children matched for age, gender, OSA severity (total AHI), and year of PSG. We hypothesized that, in general, the influence of position and sleep state on OSA severity may be different in the DS population compared to patterns reported in typically developing children or adults with OSA. Positional effects may differ as a function of the etiology of OSA, considering the physical characteristics of DS (relative macroglossia, posterior tongue position, etc.); sleep state effects may also vary as a result of the generalized hypotonia commonly associated with DS and also due to alterations in sleep architecture, notably decreased amounts of REM sleep.\textsuperscript{39} We therefore aimed to investigate the effects of body position and sleep state on OSA severity, as measured by AHI, in children with DS in comparison to typically developing children matched for age, gender, OSA severity (total AHI), and year of PSG. We hypothesized that, in general, the influence of position and sleep state on OSA severity would differ between DS and non-DS subjects. Specifically, we hypothesized that compared to controls, changes in position would have less effect on OSA severity in DS subjects, such that AHI in the non-supine position would be higher in DS subjects than controls. We also hypothesized that while overall OSA would still be predominantly REM related in DS subjects, it would be to a lesser extent compared to controls, such that the NREM AHI would be higher in DS subjects than in controls.

**METHODS**

**Subjects and Study Protocol**

Ethics approval for this retrospective case-control chart review was granted by the University of Michigan Health System Institutional Review Board. Subjects were children aged 0 to < 18 years, with or without SDB, who were referred to the University of Michigan Pediatric Sleep Disorders Clinic or Pediatric Multidisciplinary Behavioral Sleep Clinic for suspected SDB. All subjects subsequently underwent baseline polysomnography (PSG) between August 2008 and January 2013. Index cases were identified as children with a diagnosis of “Down Syndrome,” “Down’s Syndrome,” or “Trisomy 21.” Children with DS were excluded if their baseline PSG was conducted as a split-night PSG involving a period of continuous positive airway pressure (CPAP) titration. Cases were then matched for age, gender, AHI, and year of PSG with control subjects who did not have DS or other major medical conditions (including craniofacial abnormalities). Subjects with adenotonsillectomy (AT) or other upper airway surgery prior to baseline PSG were not excluded, as this is a common clinical SDB treatment pathway for children both with and without DS.

All subjects (cases and controls) underwent standard clinical overnight PSG using a commercially available PSG system. This included 6-channel electroencephalograms (F3-A2, F4-A1, C3-A2, C4-A1, O1-A2, O2-A1 of the 10-20 international system for electrode placement), electro-oculogram (right and left outer canthi), submental and bilateral anterior tibialis surface electromyograms, 3-lead electrocardiogram, thoracic and abdominal excursion (piezoelectric strain gauges), oronasal airflow (thermocouples and nasal pressure), and finger oximetry. As this was a retrospective study, body position during sleep was entirely up to the individual. Position was identified by a calibrated position sensor, located midline on the anterior aspect of the thoracic belt of each subject. Body posture during sleep was recorded as supine, prone, left lateral, and right lateral positions based on the truncal position as detected by the position sensor. Head and neck positions were not recorded.

**Data Analysis**

Demographic variables were reported alongside standard sleep and respiratory PSG parameters for each subject. Height and weight measured on the night of PSG were used to calculate body mass index (BMI) in subjects ≥ 2 years, which was converted to a BMI z-score according to age and gender.\textsuperscript{20} Sleep staging was performed in 30-s epochs and followed standard criteria.\textsuperscript{20} The percentage of total sleep time (TST) spent in each sleep state (NREM and REM) was calculated in each subject, along with the percentage of TST spent in each body position (supine, prone, right lateral, left lateral). Durations of sleep in the prone, right lateral, and left lateral positions were combined and termed non-supine sleep, and similarly expressed as a percentage of TST in each subject. Additionally, the percentages of TST spent in both supine and non-supine positions in NREM and REM sleep were calculated separately. Respiratory events ≥ 2 respiratory cycles in duration were scored as obstructive apneas, hypopneas, RERAs, or central apneas according to pediatric criteria recommended by the American Academy of Sleep Medicine (AASM) in 2007.\textsuperscript{20} Obstructive apnea was defined as cessation of thermocouple-derived airflow, or decrement > 90\% from previous baseline, with continued chest and abdominal movement. Hypopnea was defined as a decrease in oronasal airflow, thoracic, or abdominal excursion ≥ 50\% when followed by a decrease in oxyhemoglobin saturation ≥ 4\% or an EEG arousal ≥ 3 seconds. The AASM-2007 apnea-hypopnea index was calculated as the number of apneas and hypopneas per hour of sleep, and the AASM-2007 respiratory disturbance index (RDI) was calculated similarly, with the addition of RERAs.\textsuperscript{20} The mean oxygen saturation (SpO\textsubscript{2}) during sleep was reported for each subject. Sleep efficiency was calculated as the percentage of time asleep following lights out. The arousal index was calculated as the number of arousals per hour of TST, the periodic leg movement index (PLMI) as the number of periodic
leg movements per hour of TST, and the periodic leg movement with arousal index as the number of periodic leg movements per hour of TST that were associated with an arousal.

In addition to the total AHI, the AHI was calculated separately in NREM sleep, REM sleep, and again in each body position (supine, prone, right lateral, left lateral, collective non-supine). Finally, the AHI in supine and non-supine NREM and REM sleep was calculated. There exist no accepted description of positional sleep apnea in children; therefore, 2 methods were used to describe the effect of body position. Firstly, “positional patients” were defined as those in whom the AHI was at least twice as high in one body position as another. For example, “supine positional” meant that the AHI in the supine position was at least twice that of the non-supine position. This description is similar to that used previously in adults and children, although we used non-supine instead of lateral to incorporate the prone position. Secondly, positional patients were identified simply by the absolute numeric majority of AHI for either supine or non-supine sleep in each child.

Medical records were reviewed, and the number of subjects who underwent a successful CPAP titration study following the baseline PSG were recorded. The difference in total AHI, NREM AHI, and REM AHI from baseline to titration was expressed as a percentage of the relevant baseline AHI.

Statistical Analysis

Statistical analysis was performed using SPSS (Version 20, IBM SPSS, Armonk, NY, USA). Data were first tested for normality and equal variance. Normality could not be achieved through log transformation; hence, demographic and sleep characteristics were compared between DS and control subjects using the Wilcoxon-signed rank test. The predominance of respiratory events in REM sleep (termed REM predominance index, REM PI) was calculated to reflect the ratio of REM to NREM events, using an adjustment factor (0.5) added to the AHI values to allow inclusion of zero values in analysis. The equation used was REM PI = log(REM AHI + 0.5) – log(NREM AHI + 0.5), equivalent to log(REM AHI + 0.5 / NREM AHI + 0.5). The REM PI was subsequently compared with a value of 0 (no difference between REM and NREM AHI) using the Wilcoxon-signed rank test. Within DS subjects as a whole and again within control subjects, the Wilcoxon-signed rank test was used to compare the effects of sleep state (NREM, REM) on AHI, of body position (supine, non-supine) on total AHI, and of body position (supine, non-supine) on NREM AHI as well as REM AHI. As infancy and/or puberty may influence the effects of body position and/or sleep state on AHI, analyses were repeated in a subsample of subjects aged ≥ 2 years and < 13 years. The proportion of subjects in each of the DS and control groups with a REM PI < 0 was compared using χ² analysis, as were the proportion of positional patients (supine positional, non-supine positional, non-positional), for both methods of categorization of “positional patients.” Statistical significance was taken at p < 0.05, and data were expressed as the median and interquartile range.

RESULTS

A total of 76 children with DS were compared with 76 control subjects matched for age, sex, total AHI, and year of PSG.

<p>| Table 1—Demographic and basic polysomnographic characteristics of DS and control subjects |
|-----------------|-----|-----|-----|</p>
<table>
<thead>
<tr>
<th>N</th>
<th>DS</th>
<th>Control</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male n (%)</td>
<td>42 (55%)</td>
<td>42 (55%)</td>
<td>–</td>
</tr>
<tr>
<td>Age, years</td>
<td>4.6 (2.8, 8.4)</td>
<td>5.1 (1.9, 8.8)</td>
<td>NS</td>
</tr>
<tr>
<td>BMI z-score</td>
<td>1.32 (0.04, 1.91)</td>
<td>1.36 (0.09, 1.96)</td>
<td>NS</td>
</tr>
<tr>
<td>TST, min</td>
<td>430 (391, 468.5)</td>
<td>442.5 (406, 474)</td>
<td>0.03</td>
</tr>
<tr>
<td>NREM AHI, %TST</td>
<td>83.7 (78.5, 90.4)</td>
<td>82.3 (77, 86.2)</td>
<td>NS</td>
</tr>
<tr>
<td>REM AHI, %TST</td>
<td>16.3 (9.6, 21.8)</td>
<td>17.7 (13.7, 23)</td>
<td>NS</td>
</tr>
<tr>
<td>Total AHI, events/hour</td>
<td>7.4 (4.1, 14.9)</td>
<td>7.5 (3.5, 14.7)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Sleep efficiency, %</td>
<td>83 (73.8, 88.4)</td>
<td>87.7 (79.7, 91.7)</td>
<td>0.002</td>
</tr>
<tr>
<td>Mean SpO2, %</td>
<td>96 (95, 97)</td>
<td>97 (96, 98)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>SpO2 nadir, %</td>
<td>86 (83, 90)</td>
<td>88 (84, 91)</td>
<td>0.05</td>
</tr>
<tr>
<td>Arousal index, events/hour</td>
<td>11.3 (7.4, 15.3)</td>
<td>12.2 (8.3, 20.1)</td>
<td>0.05</td>
</tr>
<tr>
<td>PLMI, events/hour</td>
<td>0.3 (0, 2.1)</td>
<td>1.1 (0, 5.8)</td>
<td>0.04</td>
</tr>
<tr>
<td>PLM arousal index, events/hour</td>
<td>0 (0, 1.1)</td>
<td>0.1 (0, 0.7)</td>
<td>NS</td>
</tr>
<tr>
<td>NREM AHI, events/hour</td>
<td>5.6 (2.5, 12.4)</td>
<td>5.3 (2.3, 11.4)</td>
<td>0.03</td>
</tr>
<tr>
<td>REM AHI, events/hour</td>
<td>13.6 (5.3, 33.6)</td>
<td>12.6 (5.4, 21.3)</td>
<td>NS</td>
</tr>
<tr>
<td>REM PI</td>
<td>0.56 (-0.05, 1.33)</td>
<td>0.69 (0.11, 1.3)</td>
<td>NS</td>
</tr>
</tbody>
</table>

1 n = 57 case-control pairs. *p < 0.05 compared to NREM AHI of the same group. Data presented as median (25th percentile, 75th percentile). DS, Down syndrome; BMI, body mass index; TST, total sleep time; NREM, non-rapid eye movement; REM, rapid eye movement; AHI, apnea-hypopnea index; SpO2, oxygen saturation; PLMI, periodic leg movement index; PLM, periodic leg movement; NS, not significant; REM PI, REM predominance index.

Effect of Sleep State on Apnea-Hypopnea Index

The NREM AHI was significantly higher in DS subjects than control counterparts (p < 0.05), but there were no differences in the percentage of TST spent in either NREM or REM sleep. Despite matching for severity of SDB, the total AHI was significantly higher in DS subjects than control counterparts (p < 0.05). Sleep efficiency, mean oxygen saturation, and the oxygen saturation nadir were significantly lower in DS subjects than controls (p < 0.05 for all). There was no difference in arousal index or PLM arousal index between DS and control subjects, although subjects with DS had a lower PLMI than controls (p < 0.05).
the REM AHI was significantly higher than the NREM AHI (p < 0.001 for both). The REM PI was significantly greater than 0 in both DS and control groups (p < 0.001 for both), further indicating an overall predominance of events in REM sleep. However, the REM PI was not different between DS and control subjects. A REM PI < 0 was seen in 28% of DS subjects, indicating a predominance of NREM events in these subjects, in comparison to 20% of control subjects, although the proportion of subjects with an REM PI < 0 was not different between groups (p = 0.22).

### Body Position during Sleep

The percentage of TST spent in each body position (supine, prone, right lateral, left lateral, and total non-supine) in both DS and control subjects is shown in Table 2. Compared to controls, DS subjects spent a significantly larger percentage of sleep in the prone position and a smaller percentage of time in the right lateral position (p < 0.05 for both). However, overall there were no differences between DS and control subjects in the percentage of time spent asleep in the non-supine position, or in the supine position.

### Effect of Body Position on Apnea-Hypopnea Index

Figure 1 compares the AHI in DS and control subjects for each position of sleep. There were no significant differences in the AHI between DS and control subjects for supine or any non-supine sleep position. In DS subjects overall, and similarly in control subjects as a whole, the AHI was not significantly different in the supine compared to the non-supine position, although numerically the AHI appeared to be higher during supine sleep.

DS and control subjects were categorized as “positional patients” using the “twice as high” rule, as shown in Table 3. Categorization was not possible in 18 DS subjects and 5 control subjects, as they had not slept in either the supine or non-supine position, precluding calculation of an AHI in both positions. Of the DS subjects, 48% were found to be “positional patients”; 33% of subjects had an AHI twice as high in the supine position, and 15% of subjects had an AHI twice as high in the non-supine position. The proportion of positional patients was not significantly different between the DS and control groups.

According to absolute numerical majority, there were no differences between the DS and control groups in the proportion of subjects with either a higher supine AHI or a higher non-supine AHI (Table 4). In DS subjects, AHI was higher in the supine position in 53%, in the non-supine position in 42%, and was equal in supine and non-supine positions in 5% of subjects.

### Effect of Body Position on Apnea-Hypopnea Index in Each Sleep State

The percentage of TST spent in the supine or non-supine position in both NREM and REM sleep is shown in Table 5. There were no differences between DS and control subjects in the percentage of non-supine NREM sleep, supine NREM sleep, non-supine REM sleep, or supine REM sleep. The AHIs in each of the respective body position and sleep state combinations
were not different between control and DS subjects. In DS subjects as a whole, the AHI of NREM sleep was significantly higher in the supine than the non-supine position (p < 0.05); however, in control subjects this positional difference was not observed. The AHI of REM sleep was not significantly different in the supine and non-supine position in either the DS or control group separately.

**Effect of Age on the Sleep State and Positional Influences on Apnea-Hypopnea Index**

As the subject age range was wide, analyses were repeated in a subsample of children aged ≥ 2 and < 13 years to exclude the possible effects of infancy and puberty. A total of 51 subjects with DS with a median age of 6.0 years and AHI of 7.5 events/h (range 0-61.3) were compared with 51 matched controls. Results of the effects of sleep state, body position, and the combination of sleep state and body position on AHI were similar to findings with children of all ages (data not shown).

**Changes in Apnea-Hypopnea Index with Continuous Positive Airway Pressure**

In order to determine the distribution of respiratory events in NREM and REM sleep, we reviewed charts of a subsample of DS subjects who underwent successful CPAP titration (n = 10). Four subjects had a greater percentage improvement in NREM AHI than in REM AHI. Although not statistically significant, a greater improvement in total AHI was observed in those with a greater improvement in NREM AHI than those who had a greater improvement in REM AHI (median change in total AHI 87% [interquartile range 74% to 96%] compared to 76% [37% to 87%]; data not shown).

**DISCUSSION**

The present study is the first to investigate both the effects of sleep state and body position on OSA severity in children with DS. Previous studies have assessed these factors, often as a secondary aim, in only a small number of children with DS and have not always included a comparison group of children.42,43 The main findings of this study were that, in comparison to typically developing children with OSA of a similar severity, children with DS similarly exhibited a REM predominance of respiratory events, with a minority of individuals demonstrating a preponderance of NREM-related events; and the DS children had a higher NREM AHI, despite being matched for total AHI and having a similar percentage of sleep time in NREM. Notably, children with DS exhibited a higher NREM AHI in the supine position compared to the non-supine position—a finding not observed in the control children or during REM sleep in either group. While the children with DS spent a greater amount of time sleeping prone, overall the amount of non-supine sleep (prone plus lateral) was not different.

In children with and without DS alike, we found respiratory events to be predominantly, although not exclusively, present in REM sleep. This pattern is not surprising and has been reported previously in typically developing children with OSA.37-38 Verginis and colleagues found that a significant subset of children (30%) exhibit a NREM predominance of obstructive events.38 In our DS population, we similarly found 28% of children to have NREM-predominant OSA, illustrating that consideration of sleep state distribution is just as important in individuals with DS. While numerous studies have investigated the prevalence of OSA in children with DS, few have assessed the effects of either sleep state or body position on OSA severity. Two studies provided in-depth descriptions of respiratory events in children with DS but did not report positional or sleep state-specific AHI.42,44 Another study, of 33 children with DS aged 0-19 years, found the REM AHI to be three times higher than the NREM AHI and to be associated with the lowest oxygen saturation recorded.3 The present study introduced another element by comparing AHI with typically developing children. Interestingly, we found that in children of similar overall OSA severity, the NREM AHI was significantly higher in children with DS. Together, these findings suggest a heightened importance of the NREM sleep contribution to OSA in DS subjects, even in the context of REM-predominant OSA.

We observed an increased proportion of sleep time in the prone position in children with DS compared to controls, although when grouped into supine or non-supine sleep, the two groups of children were similar. A previous study of 17 children with DS, aged 2-18 years, found a tendency for an increased proportion of supine sleep compared to controls of similar age, gender and AHI, but no difference in the amount of prone sleep.42 Aside from differences in sample size, findings may differ from the present study due to a lower OSA severity (median total AHI of 4.3 events/h compared to present study AHI of 7.4 events/h). Other studies in children with DS have reported a higher number of changes in position during sleep45,46 and an increased amount of sleep time in the “leaning forward” position42 in comparison to controls; however, we did not measure either of these variables. Our findings suggest
that children with DS and moderately-severe OSA generally exhibit positional preferences during sleep similar to those of typically developing children of similar OSA severity. Interestingly, studies of small cohorts of children with OSA have found that the supine position is highly prevalent throughout the night, such that the sleeping positions of children are altered by the presence of OSA. A larger study determined that when compared to children without OSA, children with OSA spent more time in the supine position and less time in the lateral position, while obese children with OSA were more likely to sleep prone. The adoption of the prone position in the presence of obesity suggests that the supine or lateral positions may increase the risk for more severe respiratory disturbance when OSA and obesity coexist. It is likely that a similar pattern exists in DS, which could be further augmented not just by the presence of obesity but by other physical characteristics which may act to increase the risk of respiratory difficulty in certain positions. The contention that OSA affects positional sleeping preferences is further supported by the findings of increased supine time, reduced lateral time, and reduced prone time in a relatively overweight group of children with OSA following adenotonsillectomy. The positional preferences of children with DS but without OSA are yet to be elucidated.

We observed no difference between DS and non-DS children in relation to the positional effects of OSA severity over the night as a whole. In each position, the AHI was similar in DS and control children despite possible differences in OSA etiology, including contributions of physical characteristics. The only previous study to measure positional AHI in children with DS similarly reported no difference between DS and control groups in the various positions. We did not detect a difference in AHI between the supine and non-supine positions in either DS or control children, although OSA severity appeared to be increased in supine sleep. In typically developing children, OSA severity is reportedly worsened when supine or not affected by position, depending on the study. In our cohort of DS subjects, 53% had a numerically higher supine AHI than non-supine AHI, and 33% of subjects had an AHI twice as high in the supine position. The proportion of subjects in these “positional” categories was not different from proportions seen in our typically developing control children. Supine positional OSA is more common in adults with OSA, accounting for 50% to 60% of individuals. Our findings suggest a heterogeneous effect of position on overall OSA severity in children with DS.

We subsequently examined the effect of supine and non-supine sleep on OSA severity specific to each sleep state and found that children with DS were different from controls in one aspect alone; during NREM sleep the AHI was significantly higher in the supine position compared to the non-supine position. This difference was not found in the control children or in either group during REM sleep, suggesting that the effects of position are more overt in NREM sleep in those with DS. In view of the hypotonia inherent to DS, we contend that the gravitational effect on airway patency associated with supine sleep is possibly augmented by increased pharyngeal muscle hypotonia, which would not normally be seen during NREM sleep in typically developing children. It fits that during REM sleep, a degree of hypotonia occurs regardless of position in children with and without DS alike, hence reducing the positional difference on OSA severity in this state. Therefore, the combination of sleep state and position merits consideration when both interpreting PSG and guiding treatment choices for children with DS.

In typically developing children, the effect of position on OSA severity can vary not only with obesity but also with age; however, we did not find this to be the case in children with DS. Our findings were similar both when all subjects were included, aged from 2 months to less than 18 years, and when restricted to those aged 2 years to less than 13 years. While we could not characterize the positional and sleep state effects during infancy or puberty due to small numbers of subjects of these ages, for the majority of pre-pubescent children with DS, to the best of our knowledge it appears that the positional effects remain the same in children with DS irrespective of age.

Knowledge of the positional and sleep state effects on OSA severity may be important for optimizing treatment in children with DS as a whole, but also on an individual level. We demonstrated in a small subsample of children that improvement in total AHI was greater in children who had a larger change in NREM AHI than in REM AHI. This occurred in spite of a REM predominance of respiratory events. Thus consideration of the sleep state distribution of respiratory events should be an important factor when interpreting PSGs and formulating management plans in children with DS. As recently reported by Eiseman in adults with OSA, it is important to consider “conditional” AHI values when position and/or sleep state dependent OSA is evident on PSG, as there is a clear risk for potential misclassification of disease presence or severity. As suggested in both that study and by our findings, routine PSG interpretation should include the frequency of respiratory events by both sleep state and body position, values that may have particular importance for the DS population.

On an individual level, consideration of therapies which treat OSA preferentially in one sleep state or which make a bigger improvement in a certain position may prove helpful. For example, a study in adults with non-positional OSA found uvulopalatopharyngoplasty to produce a much greater decrease in the lateral RDI than in supine RDI. Indeed, knowledge of the positional and sleep state distribution of events would allow clinicians to estimate the range of OSA severity that could occur, for example, from presumably the most severe in cases where a child has the majority of sleep in the supine position, to the least severe where the child is mostly in the lateral/prone positions. One night in the sleep laboratory may not be representative of the child’s typical sleep in his/her own environment, particularly in regard to position and sleep state distribution, and so the ability to extrapolate data as described is likely to result in improved individual treatment recommendations. It follows that consideration of the OSA pattern may prove beneficial in OSAT patients, DS and non-DS alike.

This study is not without limitations. Despite matching, total AHI was statistically higher in children with DS than controls. However, this statistical difference is unlikely to be clinically significant, as paired values were consistently of the same OSA severity grouping as defined clinically; moreover, median total AHI values of each group differed by only 0.1 events per hour. It is possible that the difference in NREM AHI between groups is a result of the statistical difference in total AHI between...
groups; however, as the median, 25th and 75th percentile values of NREM AHI were all consistently higher in the DS group, this effect is less likely. As this was a retrospective review of the positional effects of OSA, we did not control sleeping positions, and thus not all subjects slept in all positions. However, in doing so, it permitted us to compare the preference for sleep positions in our subjects, albeit in a clinical laboratory setting. For analysis of AHI according to each sleep state-position combination, prone and lateral sleep durations were grouped together as non-supine sleep in order to maximize the number of subjects contributing to the findings. Furthermore, we do not have record of head or neck flexion or rotation during sleep, or of upper airway examination in our subjects. Children in the prone or lateral position can have flexion of their neck, which may lead to increased upper airway collapsibility.46-51 Using rigid video endoscopy, a study of typically developing children with OSA determined that the positional effects varied as a function of the type of upper airway narrowing; the supine position was preferable to lateral in those with only adenoidal hypertrophy; however, in the case of hypertrophic tonsils and adenoids, breathing was worse in the supine position.33 Their findings support a gravitational component of OSA in children, even if the level of obstruction is typically at the adenoids, breathing was worse in the supine position.33 Their findings support a gravitational component of OSA in children, although is a potential area for future research. Despite these limitations, the present study has nonetheless provided important insights into factors which affect OSA severity in DS, highlighting areas for future focus and for clinical consideration.

CONCLUSION

The present study found that in DS and typically developing children of similar age and OSA severity, respiratory events are predominantly REM related but can be related to NREM sleep or the supine position in significant subset of individuals. When matched for total AHI, children with DS have a higher NREM AHI. The effect of position on total AHI is similar in DS and control children, however in children with DS, NREM AHI worsened in the supine position, perhaps indicating a positional effect compounded by underlying hypotonia inherent to DS. These findings illustrate the importance of the NREM sleep contribution to OSA severity in the DS population. Consideration of both sleep state and position warrant attention when interpreting OSA severity and choosing treatment modalities.

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SUBMISSION & CORRESPONDENCE INFORMATION
Submitted for publication May, 2013
Submitted in final revised form August, 2013
Accepted for publication September, 2013
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DISCLOSURE STATEMENT
This was not an industry supported study. Dr. O’Brien was partially supported by grants from the National Heart, Lung, and Blood Institute (K23 HL085739, R21 HL089918, and R21 HL087819). She receives equipment support from Philips Respironics Inc., has received sleep-related NIH grant funding, and has received honoraria for speaking on the topic of sleep disordered breathing. The other authors have indicated no financial conflicts of interest.
The Impact of Gender on Timeliness of Narcolepsy Diagnosis

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Study Objectives: To examine the impact of gender in narcoleptic patients on timeliness of diagnosis, symptomology, and health and lifestyle impairment

Methods: This is a cross-sectional study of 109 consecutive patients (68 women) with newly diagnosed narcolepsy with and without cataplexy, from a University sleep disorders center. Consecutive patients were administered an 8-page questionnaire at the time of their diagnosis regarding sleep habits, medications, and medical conditions, lifestyle impairments, as well as details regarding narcolepsy-related symptoms.

Results: Men and women presented with remarkably similar narcolepsy related symptoms, yet women were more likely to be delayed in diagnosis; 85% of men were likely to be diagnosed by 16 years after symptom onset, compared to 28 years in women. More women were likely to remain undiagnosed at any given time point after symptom onset (hazard ratio for diagnosis of men compared to women 1.53; 95% CI 1.01-2.32; p = 0.04). Men and women reported similar degree of subjective sleepiness as measured by the Epworth Sleepiness Scale (mean 16.2 ± 4.5; p = 0.18), though women demonstrated significantly more severe objective sleepiness on multiple sleep latency testing (MSLT) (mean sleep latency in women = 5.4 min (± 4.1), in men 7.4 min (± 3.5); p = 0.03). Despite being more objectively sleepy, women were less likely to report lifestyle impairments in the areas of personal relationships (71% men, 44% women, p = 0.01) and physical activity (36% men, 16% women, p = 0.02), but were also more likely to self-medicate with caffeine (63.4% men, 82.4% women; p = 0.03).

Conclusions: Narcolepsy impacts men and women’s health and lifestyle differently, and may cause delays diagnosis for women.

Keywords: Narcolepsy, gender, sex, sleep, hypersomnia, diagnosis, women

Citation: Won C; Mahmoudi M; Qin L; Purvis T; Mathur A; Mohsenin V. The impact of gender on timeliness of narcolepsy diagnosis. J Clin Sleep Med 2014;10(1):89-95.

Sleep disorders affect women and men differently. This is well described, for example, in sleep disordered breathing, insomnia, and restless leg syndrome. In these common sleep disorders, there are notable sex differences in disease prevalence, manifestation, health effects, and social consequences,¹⁰ as well as sex-related discrepancies in diagnosis and health care delivery.¹⁰ There is some evidence from animal models and genetic studies to suggest sex differences in the susceptibility and manifestation of narcolepsy.¹¹-¹³ However, sex differences in narcolepsy remain understudied in humans, and there is little scientific information regarding the clinical significance and consequences of the diagnosis of narcolepsy in women. Therefore, this study aimed to compare clinical presentations of narcolepsy in men and women from an academic sleep center, and to identify potential sex differences affecting recognition, diagnosis, and treatment of this disorder. This is the first study dedicated to addressing clinical gender differences in narcolepsy.

MATERIAL AND METHODS

Study Population
One-hundred twenty-five consecutive patients with newly diagnosed narcolepsy from 2007 to 2010 were identified from the Yale Center of Sleep Medicine. All patients completed polysomnography (PSG) and multiple sleep latency test (MSLT), and a structured interview by an independent sleep specialist. Patients were administered a standardized 8-page questionnaire within 4 weeks of their narcolepsy diagnosis. Sixteen patients did not complete the questionnaire or had missing data, and were excluded. The study was approved by the Yale Institutional Review Board.

Questionnaire
The standardized questionnaire, in addition to other sleep disorder symptoms, sleep history and habits, current medications, and social, psychological, psychiatric, surgical, and

BRIEF SUMMARY

Current Knowledge/Study Rationale: There have been descriptions of sex differences in several sleep disorders such as obstructive sleep apnea and restless leg syndrome, however, the impact of sex in narcolepsy has not been previously explored. This study was performed to assess whether narcolepsy clinically presents and affects women differently than men.

Study Impact: This study suggests there are critical differences between men and women in the clinical care and outcomes of patients with narcolepsy. This study supports the necessity for consideration of sex in narcolepsy research.
medical conditions, contained detailed questions about sleepiness, the Epworth Sleepiness Scale (ESS), naps, cataplexy, hypnagogic and hypnopompic hallucinations, sleep paralysis, and disrupted nocturnal sleep. The cataplexy section of the questionnaire explored the following conditions: sudden episodes of loss of muscle function in response to emotion, ranging from slight weakness (such as sagging of the jaw and facial muscles, nodding of the head, closure of the eyes, double vision, buckling of the knees, dropping of the arms, weakness of the hands, and loss of speech or slurred speech) to complete body collapse. With regard to hypnagogic or hypnopompic hallucinations, patients were asked whether they have ever experienced vivid dream-like scenes, or tactile, auditory or visual hallucinations upon awakening or falling sleep. For sleep paralysis the questionnaire asked for transient inability to move partially or completely upon awakening from nocturnal sleep or naps.

The questionnaire asked binary questions, followed by open-ended questions regarding the impact of narcolepsy in the following areas: (1) work or school, (2) social activities, (3) personal relationships, and (4) exercise and physical activity. Questionnaire responses were scored and recorded by a single blinded researcher.

Polysomnography

Nocturnal PSG and MSLT were performed after a sleep diary confirmed a patient’s regular sleep habits with ≥ 6 h of nocturnal sleep per night during the 2 weeks preceding the evaluation. Patients discontinued any wake-promoting medications 2 weeks before the sleep study. Antidepressants were tapered off 2 weeks prior to the sleep study in subjects who were considered psychiatratically stable and who were willing to come off these medications. For those with obstructive sleep apnea, MSLT was performed after a night on therapeutic positive airway pressure therapy and apnea-hypopnea index (AHI) was < 5 events per hour. PSG and MSLT were standardized, and performed and scored according to American Academy of Sleep Medicine guidelines.14,15

Statistical Analysis

All tests of significance were two-sided. For univariate analysis, continuous variables were reported as means and standard deviations (SD) if they were normally distributed, and student’s t-tests were used to do comparisons between two groups. Otherwise they were reported as medians and 25% to 75% quartiles (Q) and were analyzed using nonparametric Wilcoxon method. For categorical variables, frequencies and percentages were reported. Chi-square tests or Fisher exact tests were used to compare differences in proportions of patients as appropriate. Logistic regression was performed to obtain the odds ratios (ORs) of cataplexy with sleep paralysis as the predictor. Association between time to diagnosis and age at symptom onset was assessed by Spearman correlation coefficient. Cox proportional hazards regression survival model were performed by gender with time to diagnosis from symptom onset as the independent variable of interest, and initial ESS, BMI, presence of cataplexy, and age at symptom onset as predictors. Hazard ratio (HRs) and 95% CIs for the incidence of diagnosis were calculated. Cumulative incidence of diagnosis for each gender group was estimated using the Kaplan-Meier method and compared with the log-rank test for patients with age at symptom onset < 15 years old. Analyses were carried out with the use of SAS software (SAS Institute Inc, Cary, NC). P values of less than 0.05 were considered to indicate statistical significance.

RESULTS

Patient Characteristics

Among 109 patients with narcolepsy, 68 (62.4%) of participants were women. The patients in this study were predominantly younger (mean [SD] = 30.4 [10.9] years), and their ages ranged between 14 and 62 years. The characteristics of the patients are shown in Table 1. Obesity (BMI ≥ 30 kg/m²) was common, affecting 27.8% of patients, with no gender differences observed. There was a bimodal pattern of age distribution in symptom onset (Figure 1). A peak in symptom presentation occurred during the age period of 10-15 years with diminishing

### Table 1—Characteristics of narcolepsy patients by gender

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Men</th>
<th>Women</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants, n (%)</td>
<td>41 (37.6)</td>
<td>68 (62.4)</td>
<td>0.19</td>
</tr>
<tr>
<td>Age at diagnosis, years, mean (SD)</td>
<td>28.6 (11.8)</td>
<td>31.4 (10.2)</td>
<td>0.19</td>
</tr>
<tr>
<td>Race White, n (%)</td>
<td>20 (48.8)</td>
<td>33 (48.5)</td>
<td>0.98</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>26.3 (4.4)</td>
<td>27.2 (6.5)</td>
<td>0.41</td>
</tr>
<tr>
<td>BMI ≥ 30 kg/m², n (%)</td>
<td>10 (24.4)</td>
<td>20 (29.9)</td>
<td>0.54</td>
</tr>
<tr>
<td>Caffeine, n (%)</td>
<td>26 (63.4)</td>
<td>56 (82.4)</td>
<td>0.03*</td>
</tr>
<tr>
<td>Nicotine, n (%)</td>
<td>5 (12.2)</td>
<td>16 (23.5)</td>
<td>0.15</td>
</tr>
<tr>
<td>Alcohol, n (%)</td>
<td>12 (29.3)</td>
<td>16 (23.5)</td>
<td>0.51</td>
</tr>
<tr>
<td>Sleep paralysis, n (%)</td>
<td>5 (12.2)</td>
<td>13 (19.2)</td>
<td>0.35</td>
</tr>
<tr>
<td>Current prescribed medications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychiatric, n (%)</td>
<td>19 (46.3)</td>
<td>30 (44.1)</td>
<td>0.82</td>
</tr>
<tr>
<td>Stimulants, n (%)</td>
<td>4 (9.8)</td>
<td>5 (7.4)</td>
<td>0.73</td>
</tr>
<tr>
<td>Hypnotics, n (%)</td>
<td>1 (2.4)</td>
<td>8 (11.8)</td>
<td>0.15</td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypersomnia, n (%)</td>
<td>41 (100)</td>
<td>67 (98.5)</td>
<td>0.44</td>
</tr>
<tr>
<td>Sleep disruption, n (%)</td>
<td>8 (19.5)</td>
<td>14 (20.6)</td>
<td>0.89</td>
</tr>
<tr>
<td>Cataplexy, n (%)</td>
<td>15 (36.6)</td>
<td>38 (55.9)</td>
<td>0.05</td>
</tr>
<tr>
<td>Hallucination, n (%)</td>
<td>31 (75.6)</td>
<td>58 (85.3)</td>
<td>0.21</td>
</tr>
<tr>
<td>Sleep paralysis, n (%)</td>
<td>20 (48.8)</td>
<td>40 (58.8)</td>
<td>0.31</td>
</tr>
<tr>
<td>Initiation insomnia (SOL &gt; 60 min), n (%)</td>
<td>10 (27.0)</td>
<td>14 (21.9)</td>
<td>0.56</td>
</tr>
<tr>
<td>Reported nightly sleep hours, mean (SD)</td>
<td>7.3 (1.6)</td>
<td>7.7 (2.3)</td>
<td>0.36</td>
</tr>
<tr>
<td>Initiation insomnia (SOL &gt; 60 min), n (%)</td>
<td>10 (27.0)</td>
<td>14 (21.9)</td>
<td>0.56</td>
</tr>
<tr>
<td>Daily naps, n (%)</td>
<td>25 (62.5)</td>
<td>44 (66.7)</td>
<td>0.66</td>
</tr>
<tr>
<td>Family history of a sleep disorder, n (%)</td>
<td>10 (24.4)</td>
<td>12 (17.6)</td>
<td>0.40</td>
</tr>
</tbody>
</table>
frequency with increasing age and a second slight increase in presentation between the ages of 35-40 years. We did not observe a gender difference in the bimodal character of age at which symptoms presented. Twenty-four percent of men and 22% of women (p = 0.78) associated the onset of hypersomnia with a discreet event. The most common events described by women included head trauma (n = 5), infection (e.g., Lyme disease, mononucleosis, viral infection) (n = 4), and childbirth (n = 2). The most common preceding event reported by men was infection (e.g., Lyme disease, mononucleosis, encephalitis) (n = 5).

There was a high prevalence of self-reported anxiety (32.1%) and depression (56.0%) in both men and women, and greater than 40% of men and women were taking psychiatric medications at the time of diagnosis. As shown in Table 2, the prevalence of attention deficit hyperactive disorder (ADHD); in men, 19.5%, in women, 2.9%; p = 0.006) and autoimmune disorders (in men, 0%, in women, 10.3%; p = 0.03) differed in similar gender trends as those observed in the general population.16 Autoimmune disorders included 4 women with rheumatoid arthritis, 2 women with lupus and/or antiphospholipid syndrome, and one woman with Hashimoto thyroiditis.

Neurologic conditions were reported more frequently in women (men, 14.6% vs. women, 42.6%; p = 0.002), with the most common condition being headaches or migraines (82%). The prevalence of cardiovascular disease was similar for both men and women (17%), and consisted mostly of hypertension (67%). Other cardiovascular diagnoses included arrhythmias (reported by 3 men) and a patent foramen ovale reported by one woman.

Objective sleepiness as measured by mean sleep latency on MSLT was more severe in women (women 5.7 [4.1]; men 7.4 [3.5] min; p = 0.03) despite significantly longer total sleep time and sleep efficiency, and fewer respiratory events during the preceding night’s sleep (Table 3). The mean sleep latency was not affected by cataplexy status: 5.7 (4.6) min in women with cataplexy vs 5.8 (3.3) min in women without cataplexy, (p = 0.9), compared to 6.6 (3.2) min in men with cataplexy vs 7.8 (3.6) min in men without cataplexy, (p = 0.3).

There were 17 women and 11 men diagnosed with narcolepsy despite lack of initial MSLT findings of mean sleep latency (MSL) < 8 min and ≥ 2 SOREMPs. For 7 of these women and 9 of these men, narcolepsy was diagnosed despite negative MSLT findings, based on a history of clear-cut cataplexy. For 14 women and 8 men diagnosed with narcolepsy (there was overlap with the cataplectic group mentioned above), the lack of ≥ 2 SOREMPs on their initial MSLT was attributed to active antidepressant use at the time of the study.

Gender differences were not apparent in the subgroups of narcoleptics with and without cataplexy, with two notable exceptions. Those with cataplexy were more overweight than their non-cataplectic counterparts (BMI 28.0 [6.7] kg/m² vs 25.7 [4.7] kg/m²; respectively; p = 0.04), and those with cataplexy

**Figure 1—Age of symptom onset**

(A) Age of symptom onset of narcolepsy for all subjects. (B) Age of symptom onset by gender. In both genders, there was a peak of onset between the ages of 10-15 years, with decreasing frequency with age and a slight increase in onset during the ages of 35-40 years.

**Table 2—Comorbid disorders**

<table>
<thead>
<tr>
<th>Sleep disorders</th>
<th>Men (N = 41)</th>
<th>Women (N = 68)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>OSA</td>
<td>10 (24.4)</td>
<td>12 (17.6)</td>
<td>0.40</td>
</tr>
<tr>
<td>UARS</td>
<td>7 (17.0)</td>
<td>5 (7.5)</td>
<td>0.13</td>
</tr>
<tr>
<td>RLS</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>NA</td>
</tr>
<tr>
<td>PLMD</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>NA</td>
</tr>
<tr>
<td>RBD</td>
<td>0 (0.0)</td>
<td>2 (2.9)</td>
<td>0.53</td>
</tr>
<tr>
<td>Bruxism</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>NA</td>
</tr>
<tr>
<td>Paroxysmal sneeze</td>
<td>6 (14.6)</td>
<td>15 (22.1)</td>
<td>0.34</td>
</tr>
</tbody>
</table>

Cardiovascular disorders

- Anxiety
- Depression
- ADHD
- Endocrine disorders
- Fibromyalgia or chronic pain
- Autoimmune disorders

OSA, obstructive sleep apnea (AHI ≥ 5); UARS, upper airways resistance syndrome (respiratory disturbance index ≥ 10); RLS, restless leg syndrome; PLMD, periodic limb movement disorder (periodic limb movement index > 15); RBD, REM behavior disorder; ADHD, attention deficit hyperactivity disorder.

COHOP was not be able to perform calculations.
were more likely to use nicotine than those without cataplexy (32.1% vs 7.1%; p = 0.001). ESS were similar in those with and without cataplexy (16.0 [5.0] vs. 16.5 [4.0]; p = 0.5).

**Time to Diagnosis**

Multivariable Cox proportional hazards model showed men were diagnosed earlier than women, and more women remained undiagnosed at any given time point after symptom onset (male hazards ratio [HR] 1.53; 95% CI 1.01-2.32; p = 0.04). Among men, 85% were likely to be diagnosed by 16 years after symptom onset, compared to 28 years in women. Patients achieved a sooner diagnosis if their symptoms started at an older age (HR 1.06; 95% CI 1.04-1.08; p < 0.0001). Patients with greater BMI also experienced sooner time to diagnosis (HR 1.05; 95% CI 1.01-1.09; p = 0.02). The presence of cataplexy did not impact timing of diagnosis (HR 0.70; 95% CI 0.47-1.04; p = 0.08; *Table 4*).

**Impact on Lifestyle**

The majority of men and women (90%) reported having trouble at work and/or school due to narcolepsy, and specifically due to excessive sleepiness (*Figure 2*). More men reported their narcolepsy-related symptoms negatively affected their personal relationships, with the main reason being excessive sleepiness and not cataplexy or other REM-intrusive symptoms. More men were also likely to reduce their physical activity and exercise due to symptoms associated with narcolepsy. Up to a third of both men and women reported having to reduce their social activities due to excessive sleepiness. Patients generally reported oversleeping or feeling too tired to engage in social activities, and 2 patients reported cutting back on social activity because of concerns about driving. Seven patients ascribed drug abuse to sleep problems, with 4 patients abusing stimulants such as amphetamines and cocaine, and the remaining 3 using alcohol to assist with sleep. More than 40% of narcoleptic men and women reported at least one incident of falling asleep while driving.

**DISCUSSION**

Gender differences in the presentation and manifestation of common sleep disorders are well recognized. However, aside from few animal and genetic data, there is a paucity of data regarding potential gender differences in the clinical presentation and manifestation of narcolepsy. Given the relevance of sex hormones and/or gender roles on other sleep disorders such as sleep disordered breathing and restless leg syndrome, the potential for gender differences in narcolepsy—a disease commonly emergent during adolescence and young adulthood17,18—necessitates further investigation.
It has been reported that a diagnosis of narcolepsy is commonly delayed on the order of 10 years, and it is important to understand the impact of gender on these delays since narcolepsy may be associated with significant morbidity. Patients in this study were also delayed in their diagnosis by a median of 8 years (25% to 75% range: 2-15 years) from the time of symptom onset. Gender seemed to impact the timeliness of diagnosis with women being more likely to be delayed despite women reporting more occurrences of cataplexy and having greater objective sleepiness on MSLT. This held true even after considering age of symptom presentation, presence of cataplexy, and ESS.

Interestingly, we observed a bimodal pattern of age distribution in symptom onset, similar to that which has been described in previous studies.21-23 We observed a peak in symptom presentation during the age period of 10-15 years with diminishing frequency with age and a second slight increase in presentation between the ages of 35 and 40 years. We did not observe a gender difference in the bimodal character of age at which symptoms presented, and therefore could not explain its contribution to the observed gender difference in time to diagnosis.

We were able to ascertain occupational history and found at the time of diagnosis, three women were homemakers, 17 were students (ranging from undergraduate to graduate or professional students), and the remainder were employed. Examples of female occupations include teachers, research assistants, waitresses, secretaries, nurses, and financial consultants. Two men did not work due to retirement and disability, 19 were students, and the remainder were employed. Men also varied widely in their occupations, and examples include teachers, auto mechanics, bankers, and engineers. There were significantly more male students compared to female students (46% vs 25%, respectively, p = 0.02). However, student status was not found to contribute to gender differences in the delay to diagnosis. Our cohort may represent a greater proportion of adult students compared to those seen at other sleep centers, and likely reflects the association of this sleep center to a large university.

Narcolepsy is a relatively rare disorder and presents with nonspecific complaint of daytime sleepiness, and therefore requires a high index of suspicion for the diagnosis. The diagnosis is often readily made by sleep specialists, and we assume a delay in referral to a sleep specialist likely contributes to the delay in diagnosis. This delay in referral may reflect either delay in recognition by the referring provider or delay in seeking medical help by the patient. When looking at referral patterns, 53% of women and 58% of men were referred to the sleep center by their primary care providers. The next most common referring provider was a neurologist (n = 13) then a psychiatrist (n = 8) for women, and a neurologist (n = 6) and an ENT (n = 4) for men. Geriatricians, pediatrics, endocrinologists, rheumatologists, and pulmonologists referred fewer than 3 patients each of men or women. We did not observe differences in time to diagnosis between the referring provider specialties; however, there were small numbers in each group.

We suggest one possible reason for the gender difference in time to diagnosis may be that women are less forthcoming with their symptoms, opting to self-medicate, or because they are less affected in their daily lives than men. Although men and women had similar ESS scores and similar narcolepsy related symptoms, men were more likely to report problems with personal relationships and more likely to experience a negative impact on their physical activity. Interestingly, greater impairments were reported by men even while women had more severe findings on MSLT. It is possible that women are delayed in their diagnosis due to underestimating their subjective sleepiness on the Epworth Sleepiness Scale and/or underestimating their degree of impairments. Alternatively, women may cope with narcolepsy symptoms differently allowing for different lifestyle implications. For example, women demonstrated more self-medicating behavior with greater proportion of women reporting use of daily caffeinated beverages. We ascertained daily caffeine use by asking subjects on average the number of cups of caffeinated coffee consumed per day, number of caffeinated sodas consumed per day, and number of power drinks consumed per day. We analyzed the percentage of subjects reporting daily caffeine use rather than comparing amount of caffeine intake because we assumed the former was more indicative of self-medicating behavior while the amount of caffeine per day is more reflective of caffeine response. Our study also showed greater percentage of women using over-the-counter stimulants and nicotine; however, these were not statistically significant. It should be noted that in both men and women, the vast majority reported impairments in work/school, social, and intimate relationships, confirming narcolepsy is a debilitating disease for the majority of patients. These discrepancies may not be specific to narcolepsy per se, and may represent a general pattern of gender effect on chronic disease. It is important to understand these implications in narcolepsy, however, because current treatments are directed at symptom management and improving quality of life. Understanding the impact of narcolepsy on lifestyle allows us to interpret treatment efficacy and affect important outcomes such as depression and obesity.

Obesity predicted a sooner narcolepsy diagnosis, and it may have been that obese individuals were more likely to be referred to sleep specialists for concerns of the more commonly recognized sleep disorder, sleep apnea, and in this process were diagnosed with narcolepsy. Patients whose symptoms started in childhood (age < 15 years old) were more likely to be delayed in their diagnosis (p = 0.61, p < 0.001); gender differences were apparent in this group as well. The median time for women with childhood onset symptoms (n = 23) was 15 years (13-23; 25% to 75% range) compared to men (n = 15) who had a median time of 11 years (9-13; 25% to 75% range; p = 0.04). Those with childhood narcolepsy were also more likely to have acquired psychiatric diagnoses (p = 0.045), suggesting that children with narcolepsy may have been more likely to be misdiagnosed with a psychiatric disorder, or that they are at greater risk for psychiatric comorbidities. It should be noted that these patients were from an adult sleep clinic, and therefore reflect adult patients who escaped diagnosis as children and are different from children with narcolepsy who are diagnosed accurately during childhood.

There were remarkably very little differences in the clinical presentation of men and women with narcolepsy, with the exception of a trend toward greater cataplexy in women. We suspect because of the elusive nature of cataplexy, the observed difference reflects a complex gender-influenced interaction between the patient’s ability to recognize and communicate cataplexy symptoms, and the clinician’s ability to diagnose cataplexy.
Epidemiologic studies on narcolepsy have not consistently found a gender difference, and prevalence and incidence rates in both men and women differ by ethnicities and with changing narcolepsy definitions. Hypocretin deficiency, which is tightly associated with cataplexy, has not been described to be influenced by gender, although studies addressing this specific question have not been rigorously performed. The possibility of a true gender difference, however, should not be discounted. For example, greater rates of HLA DQB1 genotype has been described in Mexican women compared to men, suggesting greater susceptibility for cataplexy in women in this specific ethnic group.

The lack of a gender difference in the prevalence of cardiovascular disease and obstructive sleep apnea (defined as AHI ≥ 5)—diseases otherwise typified by male predominance—were unexpected, and raised the question of whether narcolepsy could be a risk factor for these diseases in women. We found an overall high prevalence of OSA in narcolepsy (> 20%) akin to that described by Sansa et al. (28% for AHI ≥ 10). While obesity was predictive of OSA in women with narcolepsy, women were not more likely to be obese than men. This suggests perhaps being female is not protective for OSA in patients with narcolepsy. Hypocretin-deficient mouse models such as the preprohypocretin knockout and orexin/atxin-3 transgenic mice have shown greater levels of serum leptin and greater leptin resistance in female than male mice. Leptin is known to be a ventilatory stimulant whose levels are elevated in OSA and decrease with CPAP use, and thus leptin has been hypothesized to be partially pathogenic in OSA.

Being female was also not protective of cardiovascular disease in this predominantly premenopausal sample of narcoleptics. In this group of patients, the occurrence of cardiovascular disease was independent of OSA status. Cardiovascular risk factors such as obesity and insulin resistance have been described in narcolepsy. Metabolic derangements are hypothesized to arise from perturbations in feeding and energy expenditure as well as sleep fragmentation, and hypocretin and leptin have been shown to directly impact cardiovascular function. It has been suggested that estrogen provides women cardiovascular protection through a hypocretin-mediated pathway, and our findings are supportive of the hypothesis that hypocretin-deficiency may reduce a woman's protective advantage against cardiovascular disease.

Limitations of the Study

There were 17 women and 11 men diagnosed with narcolepsy despite lack of initial MSLT findings of MSL < 8 minutes and 2 or more SOREMPs. These patients were diagnosed with narcolepsy based on highly suggestive clinical features such as cataplexy, and their MSLTs interpreted within their clinical context. For 14 women and 8 men, the lack of 2 or more SOREMPs on initial MSLT was attributed to REM suppressing medication use at the time of the study. Our MSLT positivity findings are consistent with the Aldrich study, in which they describe 2 or more SOREMPs occurring in approximately 80% of narcoleptic subjects during an initial diagnostic MSLT. They also reported 93% of those with cataplexy and 97% of narcoleptics without cataplexy had MSL < 8 minutes, a finding similar to our cohort. They concluded that while the MSLT is highly sensitive and specific for narcolepsy when narcolepsy is clinically suspected, exclusive reliance on MSLT for the diagnosis of narcolepsy may lead to misdiagnosis or non-diagnosis. It is recommended if there is a high clinical suspicion for narcolepsy without cataplexy that MSLT be repeated when initial results are non-diagnostic. Unfortunately in many of our cases it was felt unsafe or patients refused to be discontinued off confounding medications for a repeat MSLT. Because we do not have repeat MSLT data, we concede it is possible that up to 27% of our study group may represent alternative diagnoses such as idiopathic hypersomnia. However, there were no clinical or demographic differences between those that did and did not meet strict International Classification of Sleep Disorders 2 edition criteria for narcolepsy.

The results of this study represent a cohort of patients from a single academic adult sleep center, and thus its application to narcoleptics from other centers is limited. Hypocretin levels were not measured thus the role of hypocretin deficiency was speculative. While hypocretin deficiency is ubiquitous in cataplexy, its role in narcolepsy without cataplexy is heterogeneous and unpredictable. Sixteen patients otherwise qualifying for the study were not included in the analysis due to pertinent missing data. Thirteen of these 16 patients were women. While selection bias may have affected results, we were reassured by similar demographic and polysomnographic findings in this excluded group. Finally, since many of the symptoms and disease history depended on self-reporting, we are not able to exclude gender-influenced recall bias.

CONCLUSION

This is the first study dedicated to addressing gender differences in the clinical presentation of narcolepsy, and to investigate the impact of the diagnosis in women. There are many studies to suggest gender impacts disease differently across a spectrum of common sleep conditions. Likewise, we have shown that men and women with narcolepsy despite similar symptom severity and profile have important differences in health care, health risks, and lifestyle impairments. This study substantiates the need for further research on the influence of gender on narcolepsy, and emphasizes the importance of thoughtfulness to gender in future research on narcolepsy.

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Gender and Narcolepsy

Submitted for publication May, 2013
Submitted in final revised form September, 2013
Accepted for publication October, 2013
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DISCLOSURE STATEMENT
This was not an industry supported study. The authors have indicated no financial conflicts of interest.
A 2-year-old girl underwent resection of a fourth ventricle anaplastic ependymoma through a posterior fossa approach at age 1. Prior to the craniotomy, the patient had neither apneas nor snoring. She required postoperative tracheostomy placement, which was removed 2 weeks prior to presentation. After tracheostomy removal the mother reported breathing pauses followed by gasping at night. The patient was admitted for observation and placed on high-flow oxygen. The sleep medicine team was consulted. The patient did not have any other past medical or surgical history.

On physical exam while awake, her blood pressure was 125/88, her heart rate 126, and her respiratory rate 24. Physical exam while awake revealed horizontal nystagmus. Her tongue showed fine fasciculation without atrophy or tongue deviation. Palate elevation was normal bilaterally. Tonsil size was 2+. Breathing was labored with increased oral secretions but no drooling or choking. She appeared to have partial airway obstruction while awake. Flexible laryngoscopy revealed an enlarged adenoid pad, normal vocal cord movements bilaterally, and airway patency. Lung exam was normal with transmitted upper airway sounds. Physical exam while asleep revealed mouth breathing, loud snoring with increased upper airway sounds secondary to secretions, and increased use of accessory breathing muscles with prolonged apneas.

Laboratory work up including comprehensive metabolic panel and complete blood count were normal. A barium swallow X-ray study showed delay in the oral and pharyngeal phase of swallowing. Diagnostic polysomnogram (PSG) was performed without high-flow oxygen at the start of the recording. Without high-flow oxygen the oxygen saturation was > 95% during wakefulness. After sleep onset, sleep disordered breathing emerged and the oxygen saturation dropped to 25% to 30%; high-flow oxygen was resumed early during the study. PSG revealed a total sleep time (TST) of 459 minutes, sleep efficiency of 93%, sleep latency of 12 minutes, and a TST apnea-hypopnea index of 66 events/h of sleep, all obstructive with no evidence of hypoventilation noted. The minimum oxygen saturation on high-flow oxygen during NREM sleep was 50%, and during REM sleep was 33% (Figure 1A).

The patient underwent tonsillectomy–adenoidectomy. After extubation the patient continued to exhibit severe oxygen desaturation with labored breathing and witnessed apneas during sleep. The patient was re-intubated. Magnetic resonance imaging (MRI) of the brain revealed post-surgical changes of the left cerebellar hemisphere associated with posterior approach to the fourth ventricle and deformation of the dorsal-lateral medulla (Figure 1B).

Tongue fasciculation and severe sleep disordered breathing with difficulty clearing secretions and delayed swallowing phase on barium swallow contributed to decide the best treatment option consisted on repeat tracheostomy. The labored breathing and witnessed apneas resolved with normalization of oxygen saturation.

**Discussion**

The mechanism of obstructive sleep apnea in children has been almost exclusively linked to peripheral obstruction due to tonsillar or adenoid hypertrophy, however the patency of the airway in both children and adults, depends on the tonic and phasic activation of muscles of the tongue and pharynx supplied by pontomedullary cranial nerves.1 Obstructive sleep apnea (OSA) is common in children with neurologic deficits from cerebral palsy, spina bifida, Chiari malformation, and achondroplasia. Compression of these cranial nerves at the foramen magnum level has been postulated...
as a contributing mechanism of OSA in patients with Chiari malformation or achondroplasia.\textsuperscript{2,3}

The hypoglossal nerve (HN) arises from the hypoglossal nucleus in the medulla just off the midline, below the floor of the fourth ventricle and exits the medulla between the pyramid and the inferior olive. The HN innervates the genioglossus muscle (GM), considered the main tongue protruder and main pharyngeal dilator.\textsuperscript{4}

HN motor neurons receive serotonergic and noradrenergic activation during wakefulness. This input is decreased at sleep onset and completely withdrawn during REM sleep, contributing to decreased GM activity and airway vulnerability during this sleep stage.\textsuperscript{5}

Nerve conduction studies and electromyography studies have shown hypoglossal mononeuropathy in adult patients with OSA, suggesting that loss of hypoglossal axons may predispose to pharyngeal collapse and OSA.\textsuperscript{6} In addition, HN stimulation has been shown to improve the severity of OSA.\textsuperscript{7}

In our patient, postoperative medullary insult with hypoglossal nerve (HN) damage may have resulted in centrally mediated severe obstructive sleep apnea with tongue fasciculation, which was not evident while the patient was on chronic tracheostomy. The main criteria for decannulation in patients with chronic tracheostomy are resolution of the initial insult or injury that prompted the tracheostomy; and the patient’s ability to maintain a safe and adequate airway without the tracheostomy.\textsuperscript{8} Polysomnography is useful in the evaluation of these children prior to decannulation. In our patient, pharyngeal muscle weakness, presence of large adenoidal pad and enlarged tonsils could have contributed to worse OSA during REM sleep as seen in the hypnogram.

Management strategies for our patient included tonsillectomy-adenoidectomy, continuous positive airway pressure, or tracheostomy. After tonsillectomy-adenoidectomy, the family opted for tracheostomy. The patient underwent tracheostomy and remains stable.

**REFERENCES**


**SUBMISSION & CORRESPONDENCE INFORMATION**

Submitted for publication August, 2013
Submitted in final revised form September, 2013
Accepted for publication September, 2013
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**DISCLOSURE STATEMENT**

This was not an industry supported study. The authors have indicated no financial conflicts of interest.
Obstructive sleep apnea (OSA) is a highly prevalent medical condition in obese children and is associated with significant neurocognitive, cardiovascular and metabolic derangements. Monogenic forms of obesity resulting from disruption of the leptin-melanocortin pathways have become more notable in recent years and distinguish between various obese phenotypes. However, the association of such disorders with OSA is not well established in children or adults. In this report, we describe a 23-month-old female with morbid obesity and OSA, who was found to carry a defect in the melanocortin-4 receptor (MC4R) pathway. This report emphasizes the genetic basis of obesity related to MC4R deficiency and OSA in children. Keywords: Melanocortin 4 receptor (MC4R) deficiency, monogenic obesity, OSA, polysomnography.

Monogenic forms of obesity could result from disruptions of the leptin-melanocortin pathway. The most common causes are those associated with mutations in the melanocortin-4 receptor (MC4R). These are found in 2.5% of children with early onset obesity and in 6% of obese adults.1 The MC4R is expressed largely in the hypothalamus and closely involved in appetite regulation, autonomic and endocrine functions, and insulin resistance.

Obstructive sleep apnea (OSA) is one of the most deleterious consequences of childhood obesity and carries significant cardiovascular, neurocognitive, and metabolic morbidities. However, the association of MC4R deficiency and OSA in children is not well established, and may possibly affect a significant number of children with obesity in our society.

REPORT OF CASE

A 23-month-old obese Hispanic female presented to the Sleep Disorders Center at The Children’s Hospital at Montefiore in April 2012 for evaluation of OSA. She was born at term weighing 2.7 kg (10th centile) to non-consanguineous parents. At 4 months, she was noted to have excessive appetite. At 6 months her weight was 13.6 kg (>> 97th centile), and by 13 months she weighed 28 kg (>> 97th centile). Other diagnoses included: asthma, chronic rhino-sinusitis, anemia, hypertension (treated with amlodipine), and mild pulmonary hypertension. Developmental milestones were appropriate for age.

Family history was significant for obesity in her siblings, parents, uncles and grandparents. In addition, there was a strong family history of diabetes mellitus, hypertension, stroke, and early deaths secondary to cardiovascular disease.

On examination her vital signs were normal. Her weight was 37 kg and height was 94 cm with a BMI of 41.8 and BMI Z-score of 7.1 (Figure 1). She was noted to have noisy, heavy breathing when awake, with 2+/4 tonsils and a crowded oropharynx. Laboratory tests were significant for HbA1C of 5.7% (normal = 4.7-6.4), elevated triglycerides 190 mg/dL (normal = 35-110) and elevated fasting insulin of 169 IU/mL (normal = 2.7-24.9). Thyroid profile and cortisol levels were normal.

Figure 1—Subject propped up in sleeping position prior to adenotonsillectomy due to severe OSA in supine posture
Figure 2—Hypnogram of the overnight sleep study demonstrating severe REM (red horizontal bars) related obstructive events (green vertical lines) with severe desaturations to 60% (red line)
DISCUSSION

To our knowledge this is the first report of OSA confirmed by polysomnography in a child or an adult identified to be homozygous for MC4R deficiency. We did find a single report in the form of “letter to the editor” describing anesthetic management of a child with MC4R deficiency undergoing adenotonsillectomy. Considering the prevalence of MC4R gene mutations, it is possible that the association with OSA is under reported, especially since genetic testing for MC4R is seldom performed in these patients.

The association between early onset obesity and mutations in the MC4R gene was first described in 1998. The prevalence of MC4R deficiency in the general population is high and is estimated to be 1:2000. Homozygous individuals develop early onset symptoms that include: hyperphagia, morbid obesity, tall stature, increased lean body mass, and hyperinsulinemia. History of consanguinity increases the risk of homozygous MC4R mutations, and the earlier reports of MC4R deficiency are mostly from consanguineous parents.

Obesity increases the risk of OSA in children by more than fourfold. Previous studies have reported a 12% increase in severity of OSA for every unit increase in BMI above the mean for age and gender. Though it is likely that the morbid obesity in our patient contributed to the severity of the OSA, what is not clear is the role (if any) of melanocortin in the pathogenesis of OSA. It has been postulated that high leptin levels may serve as an adaptive mechanism to provide ventilatory stimulation that is suppressed in obese individuals. The high insulin levels in the patient in discussion could have resulted from a combination of morbid obesity, severe OSA, and mutation of MC4R pathway.

A recent study reports a high prevalence of ADHD in subjects with MC4R deficiency. Obesity and ADHD are highly heritable conditions, possibly sharing a common link involving the dopamine receptor. Even though the mechanisms of association between MC4R related obesity and ADHD are unclear it could very well be related to underlying, untreated OSA.

Currently, there are no specific treatment guidelines for MC4R deficiency other than weight management, exercise, and lifestyle modifications. In addition, we treated our patient with adenotonsillectomy and noninvasive ventilation during sleep to address the important morbidities associated with OSA.

In summary, this report emphasizes that early obesity may not only be linked to OSA but could suggest a specific mutation in the MC4R gene. With the growing epidemic of obesity, it is important that pediatricians and sleep physicians be aware of this genetic disorder. Finally, future research may provide more information on the possible links between MC4R and OSA.

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SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication June, 2013
Submitted in final revised form August, 2013
Accepted for publication August, 2013
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DISCLOSURE STATEMENT

This was not an industry supported study. Funding: National Institutes of Health grants: HD-053693 and HL-105212. The authors have indicated no financial conflicts of interest.
Sleep disordered breathing (SDB) is a term used to describe nocturnal breathing and ventilatory problems. SDB includes obstructive sleep apnea, which is defined as partial or complete closure of the upper airways and central sleep apnea, which describes apneic events due to lack of respiratory effort.\(^1\) The severity of SDB is measured by the number of apneas and hypopneas per hours of sleep, the apnea-hypopnea index (AHI).

SDB has been associated with 2-3 times higher risk of incident stroke in several large well-designed prospective studies.\(^2,5\) Moreover, a recent meta-analysis concludes that SDB with an AHI > 5 events/hour is seen in 72% and with AHI > 20 events/hour in 38% of all stroke or transient ischemic attack (TIA) patients.\(^5\) The highest prevalence of SDB is seen among male patients, patients with recurrent strokes, and those with stroke of unknown etiology. The underlying mechanisms explaining a high prevalence of SDB among stroke and TIA patients remain to be established, but the hypothesized mechanisms behind a deleterious effect of SDB on stroke incidence and prognosis include hypertension, endothelial damage, cardiac arrhythmias, variability in cerebral blood flow, and oxygen desaturation.\(^7,9\)

Two previous reviews have found that SDB in stroke patients leads to poorer outcomes and increased risk of recurrent stroke.\(^10,11\) Another review is inconclusive about the benefits from treatment of SDB after stroke.\(^12\) The relationship between stroke and SDB is being increasingly discussed in the scientific literature,\(^12,13\) and we aimed to systematically evaluate serious adverse outcomes in stroke and TIA patients related to SDB. This review differs from previous reviews by focusing exclusively on the effects of SDB after stroke, and by reviewing the literature systematically. The systematic design ensures that all relevant studies are included regardless of outcome, which is necessary to draw conclusions about the state of the art of current literature.

Continuous positive airway pressure (CPAP) can be applied to patients with obstructive SDB. The rationale is that the closure of the upper airway can be prevented by the applied airway pressure when given overnight. CPAP treatment has been shown to reduce the severity of SDB in stroke patients from an AHI > 30 events/hour to 10 events/hour or less.\(^14,15\) The ability of CPAP to reduce recurrent events and death in stroke patients is still uncertain due to small and, in some cases, methodologically weak intervention studies.\(^16,17\)

The objective of the present study is to systematically review the literature on how SDB affects the probabilities of recurrence and death among patients diagnosed with stroke or TIA. A secondary objective is to evaluate how treatment of SDB with CPAP affects the risk of recurrence and death in these patients. A secondary objective was to evaluate how treatment of SDB with continuous positive airway pressure (CPAP) affects the risk of recurrence and death in these patients.

**Study Objectives:** The primary objective was to systematically review the literature on how sleep disordered breathing (SDB) affects recurrence and death among stroke or transient ischemic attack (TIA) patients. A secondary objective was to evaluate how treatment of SDB with continuous positive airway pressure (CPAP) affects the risk of recurrence and death in these patients.

**Methods:** Adults (18+) with a stroke or TIA diagnosis were eligible for inclusion. Case groups consisted of patients with a sleep disorder. The outcomes of interest were all-cause mortality, recurrent vascular events, and case fatality.

**Results:** Ten articles covering 1,203 stroke and TIA patients were included in the review. The results generally support a dose-response relationship between severity of SDB and risk of recurrent events and all-cause mortality in stroke and TIA patients. Three small-scale articles with substantial risk of bias evaluated the effects of CPAP therapy, and the results are inconclusive. Data on case fatality is too sparse to be conclusive.

**Conclusions:** Existing studies provide sufficient data to establish obstructive SDB as a negative predictor of all-cause mortality and recurrent vascular events following stroke or TIA. The ability of CPAP treatment to lower the risk of serious adverse outcomes after stroke remains controversial because of substantial risk of bias identified in most of the eligible studies addressing this relation. Additional studies are needed.

**Keywords:** Stroke, sleep apnea, transient ischemic attack, outcome, systematic review, continuous positive airway pressure, sleep disorders

**Citation:** Birkbak J; Clark AJ; Rod NH. The effect of sleep disordered breathing on the outcome of stroke and transient ischemic attack: a systematic review. J Clin Sleep Med 2014;10(1):103-108.
METHODS

Initially, a review protocol specifying the criteria of the review was developed. The protocol was changed once when the area of interest was restricted to only include stroke and TIA in order to get a reasonable number of studies for the qualitative analysis. The protocol can be assessed by contacting the corresponding author.

The eligibility criteria for inclusion were: adults (18+) with stroke or TIA diagnosed by qualified personnel (in an emergency department, stroke center, department of neurology, or a similar unit). Case groups had to consist of patients with a sleep disorder (e.g., obstructive or central sleep apnea, Cheyne-Stokes respiration). In order to comprehensively review the literature on sleep and stroke outcomes, our initial protocol included no restrictions on sleep disorder measurements, and patients suffering from sleep impairment (e.g., long/short sleep, snoring, nightmares, poor sleep, and insomnia) were also eligible for inclusion into the review. However, no relevant articles on sleep impairment and adverse outcomes of stroke and TIA were identified, and assessment of these associations was therefore omitted from the review.

The outcomes of interest were serious adverse events, including case fatality (death within 28 days), all-cause mortality, and recurrent vascular events. Experimental studies and observational studies were eligible for inclusion (i.e., cohort design, case-control design, cross-sectional studies, and case-studies with ≥ 10 cases).

A systematic search of articles using MEDLINE, EMBASE, PsycINFO, and The Cochrane Library was conducted using the following search terms: Sleep; sleep apnea; sleep disorders; insomnia; nightmare AND stroke; transient ischemic attack AND prognosis; disease progression; recurrence; case fatality. The searches were conducted in the total time span available in the respective databases with no language restrictions. In order to identify unpublished data, we contacted the corresponding authors of all included studies.

Database searches were conducted on March 5, 2012, and updated on November 28, 2012. The study selection process is illustrated in Figure 1. Eight articles met the eligibility criteria and two additional articles were identified and included by screening reference lists of the full-text articles and reviews on adjacent topics found by a search in The Cochrane Library. Thus, a total of 10 studies were included in the review. During the selection process, studies were excluded on the grounds of: not performing a sleep study in all patients, mixing stroke or TIA patients with other diagnoses without performing separate analyses, and not investigating the outcomes of interest.

As we wanted to include all types of sleep disorders and sleep impairment, we did not make any restrictions about sleep exposure and sleep exposure measurements. However, all studies that met the eligibility criteria focused on obstructive or central sleep apnea or habitual snoring, which is included in the term SDB. The severity of SDB (the AHI) was measured with sleep study recorders of different brands, henceforth known as partial polysomnography (PSG), in all studies except two:
Good et al. used overnight oximetry,16 and Mansukhani et al. used a questionnaire.20

The literature search and the screenings of headings and abstracts were made by JB. Data on methods, participants, exposure, outcome, and results was extracted using a data extraction sheet developed by inspiration of The Cochrane Consumers and Communication Review Group’s data extraction template.21 The data extraction sheet template used is available from the corresponding author upon request. The extraction of data and the assessment of bias were done by JB. AC read all 41 full-text articles that were assessed for eligibility and verified all data extraction sheets. If consensus was not achieved, NR was included for a final decision.

The risk of bias was systematically evaluated in each eligible study. This included limitations related to study design and study population, randomization to treatment, proportion lost to follow-up, degree of adequate compliance, adjustment for potential confounding factors, and possible conflicts of interest. We found great differences in the characteristics of the eligible studies regarding measurements of outcome, assessment of sleep exposure, eligibility criteria for participants, and follow-up time. This lack of comparability between the studies was expected; thus we focused on qualitative analyses rather than conducting a meta-analysis.

### RESULTS

#### SDB and Serious Adverse Events in Stroke and TIA Patients

We identified eight studies on SDB and serious adverse events in stroke and TIA patients. Study characteristics and main results for these are presented in Table 1. Six studies were European22-27 and two were North American.19,20 The sample sizes were small, ranging from 47 to 174 stroke or TIA patients. The study designs included seven prospective cohort studies19,26,23-27 and one cross-sectional study.22 Two studies presented stroke recurrence as a primary outcome,22,23 five studies addressed all-cause mortality as primary outcome,19,20,23,26,27 and one study evaluated both fatal and nonfatal cardiovascular events.22 Two studies had case-fatality as secondary outcomes.20,22 The definition of SDB varied from AHI of 5 events/hour to 20 events/hour. An apnea episode was defined as ≥ 10 seconds. In most cases, the hypopnea had to be discernible22,23 or > 75%22,23,26,27 or a discernible23 or clear23 reduction in airflow or thoraco-abdominal amplitude for ≥ 10 seconds. In most cases, the hypopnea had to be associated with a 3% to 4% oxygen desaturation.22-27

<table>
<thead>
<tr>
<th>Study ID, Country</th>
<th>N (% male)</th>
<th>Age (SD)</th>
<th>Study design (Follow-up)</th>
<th>Interval: stroke to sleep study</th>
<th>Outcome</th>
<th>Groups N patients</th>
<th>Adjustments</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mansukhani 2011, USA</td>
<td>174 stroke pts. (48)</td>
<td>71 (14)</td>
<td>Cohort (262 d)</td>
<td>N/A</td>
<td>All-cause mortality, Case fatality</td>
<td>High risk: 105 Low risk: 69</td>
<td>Age, NIHSS score</td>
<td>High risk of OSA insignificantly increased risk of mortality (OR = 1.8; [0.9-3.6]); but had no impact on risk of case fatality (RR = 1.15; [0.35-3.78])</td>
</tr>
<tr>
<td>Rola 2008, Poland</td>
<td>91 stroke pts. incl. 22 TIA pts. (87)</td>
<td>65 (10)</td>
<td>Cohort (2 y)</td>
<td>≤ 7 d</td>
<td>Recurrent stroke or TIA, Case fatality</td>
<td>AHI ≤ 5: 30 AHI &gt; 5: 61</td>
<td>No adjustments</td>
<td>SDB increased risk of recurrent stroke or TIA (OR = 1.52; [1.06-2.14]); SDB did not significantly increase risk of case fatality</td>
</tr>
<tr>
<td>Turkington 2004, UK</td>
<td>120 stroke pts. (42)</td>
<td>79 (11)</td>
<td>Cohort (6 mo)</td>
<td>≤ 24 h</td>
<td>All-cause mortality</td>
<td>AHI &gt; 10: 61%</td>
<td>Age, sex, BMI, DM, hypertension, Bartheil index, SSS score, stroke subtype, GCS score, limb weakness, previous stroke, neck circumference, oxygen saturation</td>
<td>OSA predicted increased mortality rate, OR = 1.07; [1.03-1.12] for each additional unit of AHI</td>
</tr>
<tr>
<td>Parra 2004, Spain</td>
<td>161 stroke pts. incl. 39 TIA pts. (51)</td>
<td>72 (9)</td>
<td>Cohort (22.6 mo)</td>
<td>48-72 h</td>
<td>All-cause mortality</td>
<td>AHI &lt; 10: 45 AHI &gt; 10: 116</td>
<td>Age, sex, BMI, DM, hypertension, nicotine, IHD, cardiac arrhythmia, cardiac insufficiency, COPD, alcohol abuse, dyslipidemia, Bartheil index, Canadian scale score, antiplatelet and anticoagulant therapy</td>
<td>AHI carried a HR of 1.05; [1.01-1.08] for each additional unit of AHI</td>
</tr>
<tr>
<td>Sahlin 2008, Sweden</td>
<td>132 stroke pts. (41)</td>
<td>75-80</td>
<td>Cohort (10 y)</td>
<td>23 (8) d</td>
<td>All-cause mortality</td>
<td>AHI &lt; 15: 79 AHI ≥ 15: 51</td>
<td>Age, sex, BMI, DM, hypertension, nicotine, minimal effort hyperventilation, Mini-Mental State Examination score, Barthel index</td>
<td>OSA was associated with an increased risk of death: AHI &gt; 15: HR = 1.76; [1.05-2.95]; AHI &gt; 5: HR = 1.47; [0.88-2.47]; CSA was not associated with risk of death: HR = 1.07; [0.65-1.76]</td>
</tr>
<tr>
<td>Martinez-Garcia 2012, Spain</td>
<td>166 stroke pts. (59)</td>
<td>73 (11)</td>
<td>Cohort (7 y)</td>
<td>2 mo</td>
<td>Fatal and nonfatal CVE</td>
<td>AHI &lt; 20: 70 AHI ≥ 20: 68</td>
<td>Age, sex, BMI, DM, hypertension, nicotine, IHD, atrial fibrillation, hypercholesterolemia, fibrinogen levels, carotid stenosis, Bartheil index, previous stroke or TIA</td>
<td>AHI ≥ 20 + non-tolerance to CPAP treatment carried a fatal HR of 1.76 [1.12-2.68] and a nonfatal HR of 2.87 [1.11-7.71]</td>
</tr>
<tr>
<td>Good 1999, USA</td>
<td>47 stroke pts. (55)</td>
<td>69 (-)</td>
<td>Cohort (1 y)</td>
<td>11-76 d</td>
<td>All-cause mortality</td>
<td>DI &lt; 10: 32 DI &gt; 10: 15</td>
<td>No adjustments</td>
<td>Death by 1 year correlated with mean SaO2 (r = 0.37, p = 0.01) and percentage of time spent at &lt; 90% SaO2 (r = -0.41, p = 0.004)</td>
</tr>
<tr>
<td>Dziewas 2005, Germany</td>
<td>102 stroke pts. (67)</td>
<td>65 (14)</td>
<td>Cross-sectional</td>
<td>≤ 3 d</td>
<td>Recurrent stroke</td>
<td>AHI ≤ 10: 42 AHI ≥ 10: 60</td>
<td>Age, sex, BMI, DM, hypertension, neck circumference, hypercholesterolemia, NIHSS score</td>
<td>AHI ≥ 10 and AHI ≥ 50 carried an OR of 3.5; [1.10-11.20] and 9.7; [1.60-58.34] for stroke recurrence, respectively.</td>
</tr>
</tbody>
</table>
Two cohort studies and one cross-sectional study found SDB to be associated with higher risk of recurrent events.\textsuperscript{24,25} The study by Rola et al. included 91 stroke patients and found a higher risk of recurrent stroke or TIA after 24 months of follow-up (odds ratio [OR], 1.52; 95% confidence interval [CI], 1.06-2.14).\textsuperscript{24} They defined SDB as AHI > 5, which is markedly lower than any in the other included studies. The mean AHI in patients with SDB was 20.8 ± 15.8 compared with 1.7 ± 1.4 in patients without SDB (p < 0.05). The relatively low cut-point for SDB could have overestimated the fraction of patients with SDB and consequently underestimated the effect. The study by Martinez-Garcia et al. included 166 stroke patients; they found that an AHI ≥ 20 and intolerance to CPAP treatment carried a hazard ratio (HR) of 2.87 (95% CI, 1.11-7.71) for a recurrent nonfatal cardiovascular event.\textsuperscript{24} In a cross-sectional study, Dziewas et al. showed a dose-response relation between the severity of SDB and the risk of stroke recurrence.\textsuperscript{22}

Six cohort studies have addressed the relationship between SDB and fatal cardiovascular events.\textsuperscript{24} Three of these studies found an exposure-dependent relationship between the severity of SDB and risk of death, within six months,\textsuperscript{22} two years,\textsuperscript{23} and 10 years\textsuperscript{23} follow-up. Martinez-Garcia et al. found an increased risk of premature death among stroke patients with AHI ≥ 20 and intolerance to CPAP treatment carried a hazard ratio (HR) of 2.87 (95% CI, 1.11-7.71) for a recurrent nonfatal cardiovascular event.\textsuperscript{24} In a cross-sectional study, Good et al. found nocturnal oxygen desaturations to be associated with mortality after a one year follow-up.\textsuperscript{19} In a similar vein, Mansukhani et al. showed a nonsignificant association between SDB assessed by a questionnaire and mortality (OR, 1.8; 95% CI, 0.9-3.6) after 262 days follow-up.\textsuperscript{20} In summary, despite differences in study designs, definition of SDB, and length of follow-up, all of the included studies supported a higher risk of mortality among stroke and TIA patients with SDB.

Two studies included analyses on case fatality.\textsuperscript{20,25} Mansukhani et al. found no clear association between SDB and case fatality based on 11 cases (relative risk [RR], 1.15; 95% CI, 0.35-3.78).\textsuperscript{20} Rola et al. found that SDB was related to a nonsignificant higher occurrence of case fatality based on six cases.\textsuperscript{25}

The study by Sahlin et al. found no association between central SDB and increased risk of death (HR, 1.07; 95% CI, 0.65-1.76).\textsuperscript{26} There was, however, limited statistical power to assess this association. In the study by Parra et al., 39% of the participants had central SDB, but they were not analyzed separately in the study.\textsuperscript{23}

### How CPAP Affects Stroke and TIA Outcome in Patients with SDB

The three studies, which addressed the effect of CPAP on adverse outcomes in stroke and TIA patients with SDB are summarized in Table 2. All 3 studies were European, involving 376 participants in total.\textsuperscript{24,26,29} The definition of SDB varied from an AHI of 10 events/hour in combination with excessive daytime sleepiness to 20 events/hour. Compliance rates varied from 11%\textsuperscript{29} to 72%,\textsuperscript{24} with a mean of 37%.

Parra et al. contributed with the only randomized controlled trial identified on this topic. They found no significant impact of CPAP treatment on all-cause mortality after two years of follow-up (HR, 0.62; 95% CI, 0.11-3.46).\textsuperscript{29} The two other intervention studies are cohort studies with follow-up between five and seven years.\textsuperscript{24,28} The study by Martinez-Garcia et al. concludes that patients with an AHI ≥ 20 and adequate CPAP compliance had hazard ratios that were not different from patients with an AHI < 20 in terms of both fatal and nonfatal cardiovascular events.\textsuperscript{24} In the final intervention study by Bassetti et al., only eight of 70 intervention patients had adequate compliance, leaving limited strength to assess the association.\textsuperscript{28}

### DISCUSSION

#### Summary of Evidence

Based on this systematic review of the literature SDB is identified as a risk factor for recurrence and mortality following stroke or TIA. Central SDB is only seen in few cases and its impact on recurrence and mortality following stroke remains controversial. The evidence suggests that there is a dose-response relationship between the severity of obstructive SDB and the risk of serious adverse outcomes in stroke and TIA patients. The presented data are too sparse to draw conclusions about the risk of case fatality.

In terms of CPAP treatment, the only randomized controlled trial showed no protective effect of CPAP usage among stroke patients with SDB.\textsuperscript{29} Martinez-Garcia et al. found that adequate...
CPAP treatment neutralized the excessive risk of cardiovascular events associated with SDB. The cohort study by Bassetti et al. did not prove any benefit of CPAP treatment in stroke patients with SDB. The evidence is too sparse to draw conclusions. Low compliance rates, mainly because of discomfort with the machine, are a major problem even when the patients in the worst mental and physical conditions are left out. Further studies are needed to clarify the role of CPAP treatment among stroke patients with SDB.

Risk of Bias within Studies

Six of the included studies were well adjusted for baseline characteristics and known cardiovascular and cerebrovascular risk factors; one study adjusted for only age and stroke severity; three studies investigated for differences in the distribution of confounding factors among the study groups, but made no adjustments (Tables 1 and 2). In studies with insufficient adjustments cerebrovascular risk factors such as hypertension, smoking, obesity, and arrhythmias could be distributed unevenly among the study groups and potentially introduce confounding.

None of the studies used full PSG to measure SDB in all patients. Instead, different validated partial PSG systems were used. Good et al. used a simple overnight oximetry to calculate the desaturation index (DI) on basis of episodes with ≥4% desaturation from baseline and time with \( \text{SpO}_2 < 90\% \). The authors recognize that the fraction of patients having SDB could be underestimated. In the Mansukhani study SDB was assessed by the Berlin Sleep Questionnaire, which has previously been validated to have a positive predictive value between 89% and 96% in identifying patients with sleep apnea. While the use of alternatives to full PSG might be an economic necessity when classifying SDB, low diagnostic agreement with full PSG may lead to misclassification of some SDB patients and probably underestimate the associations.

The time interval from stroke onset until sleep study varied significantly among the studies - from 24 hours to 76 days. The previously mentioned meta-analysis by Johnson et al. found no difference in SDB frequency related to the timing of the sleep study in a review of 29 studies. A few studies have found spontaneous remission of SDB, and we cannot exclude that the variations in time interval could possibly influence the findings.

Two studies included both stroke and TIA patients, but the results were not subdivided by these diagnoses. There is no indication that stroke and TIA differ in risk of serious adverse outcomes in relation to SDB, but a separation of patient types would have been preferable. Few studies included both central and obstructive SDB, with up to 39% of the patients having central SDB without conducting separate analyses. If central SDB is not a predictor of serious adverse outcomes, as the Sahlin study suggests, these studies potentially underestimate the deleterious effects of obstructive SDB.

Risk of Bias Related to CPAP Studies

In terms of bias associated with study design, the two non-randomized intervention studies had control groups consisting of patients who did not tolerate CPAP treatment. Even though the groups were adjusted for potential cerebrovascular confounders, it is likely that patients who tolerated CPAP had better mental, cognitive, or social status, and potentially a better prognosis before treatment, thus introducing selection bias. This could have led to an overestimation of the protective effect of CPAP treatment.

Low compliance rates caused substantial risk of bias in most of the intervention studies. When a great deal of the intervention group, and most likely those in the worst condition, is left out of the analyses, the beneficial effect of treatment is likely to be overestimated.

The only potential conflicts of interest declared in the included studies were related to Bassetti, who is member of the medical advisory board of ResMed, the company that produced the CPAP device used in the study. The role of this relationship is unknown, however, the results of the study did not show any beneficial effects of CPAP treatment in stroke patients with SDB.

Risk of Bias across Studies

The AHI score used to classify SDB was very variable, and while some studies found a higher risk of adverse outcomes even at low cut points for SDB, other studies only found an effect in the more severe cases of SDB. The definitions used to classify apneas and hypopneas and the partial PSG recorders differed slightly across the studies. Such variations and their possible influence on the results are inevitable. No studies used placebo CPAP, also known as sham CPAP, though this is available. The major impact on daily living associated with CPAP usage, long-term trials with placebo CPAP could very well be considered unethical, though a demand for these trials is proposed by many authors.

Patients with a diagnosis of previous stroke are expected to have a worse prognosis than first-time stroke victims. However, four studies screened for and included patients with previous stroke at baseline, and two studies did not assess the occurrence of previous stroke in their baseline characteristic.

It is well known that positive results are more likely to be published than negative results, especially in terms of small studies as the ones included in this review. By making a broad search in different electronic databases, and by contacting authors of eligible studies, we did our utmost to assess all existing relevant studies, but the existence of publication bias cannot be fully excluded.

In summary, based on this systematic and comprehensive review of the literature, we conclude that existing studies provide sufficient data to establish obstructive SDB as a negative predictor of serious adverse outcomes following stroke or TIA in terms of all-cause mortality and recurrent vascular events. The evidence on central SDB is insufficient, and additional studies are needed to address this relationship. The present data on case fatality are also very sparse and inconclusive. The ability of CPAP treatment to lower the risk of serious adverse outcomes after stroke remains controversial because of substantial risk of bias identified in most of the eligible studies addressing this relation. Intolerance to CPAP treatment among stroke patients is high, and alternative ways of treating SDB should be considered including, for example, positional therapy, which has been shown to reduce SDB by changing sleeping position, and usage of therapeutic pillows. In relevant cases, weight loss intervention should be considered as a way to reduce SDB severity and cerebrovascular risk. Given the results of this systematic review, we suggest
that SDB should be recognized as a predictor of worse outcome among stroke patients, but further studies are necessary in order to recommend an appropriate intervention for these patients.

ABBREVIATIONS

AHI, apnea-hypopnea index
CI, confidence interval
CPAP, continuous positive airway pressure
DI, desaturation index
HR, hazard ratio
OR, odds ratio
PSG, polysomnography
RR, relative risk
SDB, sleep disordered breathing
TIA, transient ischemic attack

REFERENCES


DISCLOSURE STATEMENT

This was not an industry supported study. The authors have indicated no financial conflicts of interest.
A 4-year 10-month-old female was referred to the pediatric sleep clinic for intermittent snoring with periods of observed gasping. She underwent adenoidectomy at 3 years 11 months, after which nasal congestion, snoring, and increased nighttime awakenings again recurred. Parents reported neck hyperextension, frequent mouth breathing, and daytime sleepiness, in addition to restless sleep. She frequently came to sleep in parents’ bed, and mother noted intermittent episodes of hyperextension of arms and legs with associated tremors but not tonic-clonic activity.

She was diagnosed with autism spectrum disorder after a developmental evaluation for delayed social skills. She was born full term via C-section without complications due to breech presentation. She has no history of seizures or other neurological disorders nor a family history of seizures. However family history was significant for snoring in parents and half-brother with learning disability and tic disorder. Prior trials of antihistamines resulted in daytime sedation, and steroidal nasal sprays were associated with behavior issues.

Examination showed a cooperative quiet girl with height and weight appropriate for age. She was noted to have frequent mouth breathing. On oropharyngeal exam, tonsils were graded 2-3+. Moderate nasal congestion without obvious turbinate hypertrophy was noted. Cardiorespiratory and neurologic exam were normal.

Patient underwent an overnight polysomnogram. Evaluation of the respiratory component noted mild supine dependent sleep apnea, with an RDI of 4.6, and supine RDI of 8.4 with lowest oxygen saturation of 96%. On the accompanying EEG, the following was noted (see Figure 1).

**QUESTION:** What do the findings on the EEG (Figure 1) represent?

![Figure 1— 30-second epochs prior to and after sleep onset](image)

(A) 30-second epoch showing EEG abnormality in the right central lead prior to sleep onset. (B) 30-second epoch soon after sleep onset with increased frequency of spike discharges in right central region during NREM sleep. LEOG AND REOG, left and respectively right outer canthus electro-oculography electrodes; F3-M2, C3-M2 and O1-M2, left frontal, central and respectively, occipital electroencephalography electrodes; F4-M1, C4-M1 and O2-M1, right frontal, central and respectively, occipital electroencephalography electrodes; Chin EMG, submental electromyography signal; ECG II, one standard electrocardiogram lead; TFLOW, the airflow via nasal/oral thermocouples; PFLOW, the airflow via nasal air pressure transducer; CHEST and ABDO, chest and respectively abdominal walls motion via inductive plethysmography; SpO2, the pulse oximetry by finger probe; PLETH, plethysmographic waveform; POSITION, S = Supine.
DISCUSSION

Epileptiform discharges are found in 1% to 2% of pediatric polysomnograms, and incidence may be higher in those with sleep disordered breathing.1,4 Additionally, children with autism spectrum disorders are at an increased risk of seizures with epileptiform abnormalities reported on EEG in 10% to 50% of cases.2 Centrotemporal spikes seen on EEG in children between 3 and 13 years of age is typical of BRE. Peak age of onset for BRE is 5-8 years with a male predominance. Seizures in BRE present with unilateral facial or oropharyngeal muscle involvement, hypersalivation, speech arrest and sometimes tonic-clonic activity. They are usually brief, lasting for 1-2 minutes often occurring during sleep or just before awakening, but may become secondarily generalized.3 Remission is usually within 2-4 years of onset and often by adolescence. The overall total number of seizures is also small, with the majority of patients having less than 10 seizures; 10% to 20% have only a single seizure.4 Some patients may not have seizures, and this case study emphasizes the need for EEG findings to be correlated with clinical history.

EEG evaluation is the primary tool for diagnosis with unilateral or bilateral centro-temporal spikes, seen during wakefulness but markedly accentuated by NREM sleep. The EEG evaluation should include an overnight EEG, prolonged daytime EEG to capture sleep, or a polysomnogram with additional bilateral EEG electrodes for a definitive diagnosis. Only those with cognitive impairment, very frequent epileptiform discharges on EEG, and history of generalized seizures are generally treated.3 Such patients should undergo neurological evaluation.

CLINICAL PEARLS

1. Epileptiform discharges are found in 1% to 2% of pediatric polysomnograms and are seen at a markedly higher frequency in autism spectrum disorders.

2. Focal centro-temporal spike wave discharges on the EEG are suggestive of benign rolandic epilepsy.

3. Neurological evaluation is recommended in patients with non-sleep related nocturnal paroxysmal events.

4. Polysomnography with an extended EEG montage along with video recording is recommended for evaluation of paroxysmal nighttime awakenings that may be seizure related.3

REFERENCES

In a recent publication in *JCSM*,1 Drs. Cartwright and Guilleminault suggest that spectral analysis of the sleep EEG can be used to support a defense of sleepwalking in criminal cases. In particular the authors point to 3 publications that concluded that the sleep of sleepwalkers is defined by frequent arousals during SWS (slow wave sleep) as well as—or as a result of—a lower percentage of SWS (slow wave activity).2-4 However, the authors of the study most often referred to have themselves concluded that spectral analysis of the sleep EEG in sleepwalkers is not suitable for forensic use. Gadreau and colleagues2 write: “Given the likelihood that results of our study could be used in medico-legal settings, it is worth noting that the presence or absence of a decrease of SWS early in the night and of awakenings from SWS in a given individual does not conclusively establish or refute a tendency toward sleepwalking” (pages 4-5).

The issue of frequent arousals and changes in SWS% in sleepwalkers as forensic evidence has also been previously reviewed in detail and was the subject of a series of letters to the editor of *Sleep Medicine Reviews* between Drs. Cartwright and Pressman in 2007-8 that readers might find of interest.6-9

As noted by Drs. Cartwright and Guilleminault, establishing a current diagnosis of sleepwalking for a defendant is not the same as establishing that the defendant was sleepwalking during the commission of a crime. Nevertheless, this article suggests that spectral analysis of sleep recorded months or years after the incident offense can be used to support such a sleepwalking defense. There are 3 scientific publications currently available that conclude that arousals from SWS sleep and hypersynchronous delta waves are not diagnostic for sleepwalking.10-12 These published scientific studies analyzed arousals and SWS using standard visual methods and have reported a lack of statistical sensitivity and especially specificity as diagnostic markers. Further, there are now more than 7 published studies that report arousals indexes for patients with sleepwalking (see Table 1 in ref. 10). While they are often elevated compared to normal controls there is significant intersubject variability and there is no specific cutoff statistically or otherwise to assist in making the diagnosis. Additionally, the results of a CAP analysis have failed to differentiate between sleepwalkers and patients with a diagnosis of upper airway resistance syndrome (UARS).11 Because of these methodological problems, the clinical diagnosis of sleepwalking does not require an objective PSG finding.

Drs. Cartwright and Guilleminault state that spectral analysis is a reliable method and cite 3 published studies.14,16 However, none of the cited studies were performed in patients with a diagnosis of sleepwalking. In 2 of 3 cited studies, there is high reliability only for consecutive nights of sleep, 2 and 5 nights, respectively.14,15 In the third study, PSGs were performed on non-consecutive nights with the younger group (x age = 22 years) undergoing PSG studies with a median interval of 11 days.16 Sleep studies performed as part of a forensic evaluation are most often performed months and even years after the date of the criminal act. In the case described by the authors, almost 9 months elapsed between the index incident and the conduct of the sleep study. There is no scientific evidence that spectral analysis of sleep of sleepwalkers or any other group produces characteristic and reliable EEG findings over this length of time. In many criminal cases, defendants spend months in prison before sleep studies are conducted. Sleep in prison often results in significantly different sleep/wake schedules and patterns, sleep durations, absence of drug and alcohol effects, and weight loss. Arousals scored in sleepwalkers are sensitive to sleep deprivation and not always reversed in the expected direction. Guilleminault and colleagues have reported that 36 hours of sleep deprivation as well as 2 days with total sleep time limited to 2 hours reduced sleep fragmentation and complex behaviors in clinically diagnosed sleepwalkers.17 As noted by the authors, the occurrence of sleepwalking is episodic, suggesting that even if these features are present they are likely not related to the actual occurrence of sleepwalking.

Drs. Cartwright and Guilleminault repeatedly state in their article that sleep specialists have been warned not to testify in criminal cases presenting sleepwalking defenses.18,19 This does not reflect the actual content of the articles cited. Mahowald and colleagues make it quite clear in their recent publications that their criticism of expert sleep witnesses in court is directed at those experts who have based their testimony on out-of-date
and unreliable sleep science, usually labeled junk science. We are in the era of Evidence-Based Medicine. Diagnostic methods and treatments now require proof that they are objectively effective, valid and reliable. Scientific evidence in court must also be based on generally accepted and reliable science.

Drs. Cartwright and Guilleminault describe a recent criminal case as an example of how CAP and spectral analysis might be used to establish a diagnosis of sleepwalking and assist the sleepwalking defense. Before discussing legal approaches to scientific evidence we wish to make clear that we are in no way suggesting anything improper occurred in this case. The presiding judge is the absolute gatekeeper for scientific evidence and may allow, limit, or exclude scientific evidence or expert testimony. The judge did decide to admit the spectral analysis data as evidence. However, the defense also had much to recommend it other than spectral analysis. The defense attorney in this case was highly experienced and had won an acquittal in another sleepwalking defense case. Dr. Cartwright is a well-known sleep and sleepwalking expert. Further, based on the description in this article and newspaper reports the defendant was clearly in an altered or confused state. This was evident to the victim who initially did not wish to proceed with criminal charges. We cannot know just how much weight the jury placed on the scientific evidence such as spectral analysis as opposed to other evidence. Studies of scientific evidence and expert witnesses in court often suggest jurors do not understand or consider complex scientific evidence. If and how spectral analysis influenced jury deliberation and the final judgment cannot be determined.

Although the judge is the absolute arbiter of what scientific evidence the triers of fact (the jury) are permitted to hear from expert witnesses, all jurisdictions in the United States, both state and federal, have laws related to expert witnesses and scientific evidence. The case described by the authors occurred in the state of Illinois. Expert witness qualifications as well as admissibility of scientific evidence are determined in this state by the Illinois Rule of Evidence 702. Admissibility of scientific evidence in this state follows the rules of Frye v. United States, 1923 – the standard used in 18 states in the United States. Illinois Rule of Evidence 702 reads as follows:

“If scientific, technical, or other specialized knowledge will assist the trier of fact to understand the evidence or to determine a fact in issue, a witness qualified as an expert by knowledge, skill, experience, training, or education, may testify thereto in the form of an opinion or otherwise. Where an expert witness testifies to an opinion based on a new or novel scientific methodology or principle, the proponent of the opinion has the burden of showing the methodology or scientific principle on which the opinion is based is sufficiently established to have gained general acceptance in the particular field in which it belongs.” (emphasis added)

Tests of any sort performed months or years after the index crime can tell us nothing about whether or not the criminal defendant was sleepwalking during commission of the crime act.

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Submitted for publication November, 2013
Accepted for publication November, 2013
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DISCLOSURE STATEMENT

This was not an industry supported study. The authors have indicated no financial conflicts of interest.

CITATION

LETTER TO THE EDITOR

We thank the editor for the opportunity to respond to the letter by Pressman et al. This is a critique of the article by Cartwright and Guilleminault recently published in the Journal of Clinical Sleep Medicine. We address the salient points their letter raised:

1. The aim of our article

This was clearly stated in the abstract: “To test whether laboratory-based research differentiating sleepwalkers (SW) from controls (C) can be applied in an uncontrolled forensic case as evidence the alleged crime was committed during an arousal from sleep in which the mind is not fully conscious due to a SW disorder.” This aim was restated in more specific terms: “The objective of this study is to test the SWA in a forensic case to determine if it was significantly low in the first NREM cycle and if that indicated the presence of a predisposing condition and possibly a sleep problem which could be treated.” (p.723). Thus the aim was to test if this lab-based finding could be replicated in an uncontrolled setting and not to use “spectral analysis…to support a defense of sleep walking in criminal cases” in general.

Pressman et al. quote a cautionary statement from Gaudreau et al. that a significantly low slow wave activity (SWA) in the first NREM cycle “does not conclusively establish or refute a tendency toward sleepwalking.” We agree that this is not in itself sufficient evidence to support a SW diagnosis nor would it establish that it was the cause of an event which took place at an earlier date. However the Pressman et al. letter did not include the two sentences prior to the one quoted which puts the Gaudreau et al. admonition in a significantly different light. “Our results suggest that spectral analysis of SWA across NREM cycles can contribute to our understanding of the disorders of arousal. Delineating patterns of SWA associated with various parasomnias could help clarify their underlying pathophysiology.” Our aim was to encourage just this—enhancing the understanding of the pathophysiology of NREM sleep arousal disorders.

2. Was the method appropriate?

We based the method for our study on the hypotheses proposed by Espa et al. as the conditions necessary to precipitate an occurrence of a SWS parasomnia. “The occurrence of SWS parasomnia requires not only a SWS pressure increase but also SWS arousal enhancement.” This is the push/pull model that Pressman argued was a theory that only Cartwright held in the debate he refers the reader to review. He argued forcefully and repeatedly that SW only occurred with an increase of SWS and that this was the accepted wisdom. In fact the two variable model was stated earlier by Broughton et al. in describing the Ken Parks case. “These typical polysomnographic features of sleepwalkers suggest the coexistence of both pressure for deep sleep (SWS) and of heightened arousal causing inability to sustain such sleep.” This opposite pressure model was used in the Pilon et al. study which succeeded in eliciting sleepwalking events in the laboratory by combining increasing pressure for SWS by a prior period of sleep deprivation and increasing arousals from sleep by delivering auditory tones during the recovery sleep. Neither of these manipulations was successful when applied singly. It was this opposite pressure model that we tested in the case study reported in our recent paper.

The evidence presented in court supported both pressures were present in the defendant on the night of the event (he had a period of prior sleep deprivation and excessive caffeine intake during the day before the event). Thus the conditions for a SW event were present. Furthermore we pointed out that “the additional history of snoring and a mild breathing disorder validated in the PSG may be a contributing cause of his low SWA, high CAP rate and arousal into non-conscious acts when sleep deprived and over-caffeinated.”

Pressman et al. raise the question whether a low SWA in the first NREM cycle, measured after the fact (not months or years) but specifically in this case eight months after the incident, can be a reliable marker of a predisposition to SW. The authors of the critique point out that the studies showing high reliability within subjects of the profile of the
spectral analysis sleep EEG wave forms, were not conducted on SW subjects and have not been shown to be stable over the extended period that usually occurs between an event that results in a criminal charge and a subsequent sleep study. However the several studies showing night-to-night reliability of delta power within normal individuals\textsuperscript{11-14} even under sleep deprivation conditions, along with the several studies showing the significantly lower SWA in SW groups than in C even when no SW events occurred\textsuperscript{3,4,15} makes a low SWA a strong candidate to be a manifestation of the genetic vulnerability to abnormal delta arousals\textsuperscript{16-19} and therefore likely to be a stable characteristic of sleep. Our article was one small step to encourage research needed to test stability of this within SW subjects over time.

3. Should sleep experts testify in forensic cases?

Pressman et al.\textsuperscript{20} deny that Mahowald et al.\textsuperscript{2} discourage sleep experts from acting in forensic cases or from conducting research. The reference cited for this statement includes these quotes: “the expert witness can inform all parties there is absolutely no after-the-fact polysomnographic evidence that could possibly have any relevance as to whether the accused was sleepwalking at the time of the event.” And later “attempts to ‘stimulate’ sleepwalking in the sleep laboratory (by sleep deprivation, medication administration, or alcohol ingestion) are completely worthless and totally inappropriate.” However these authors add “there may be a future role for utilizing PSG evaluations in forensic sleepwalking cases for ruling out, or greatly minimizing the probability, that the accused is in fact a sleepwalker.” Sleep science should inform both sides in an adversarial trial.

4. Other mistaken implications re: Cartwright and Guilleminault

The data presented in support of this case did not rely on the visual scoring of SWS% and made no mention hypersynchronous delta (HSDWA) which Pressman et al.\textsuperscript{1} note have not contributed to diagnosis of SW.

Another mistaken implication is that a sleep study conducted after a defendant has spent many months in prison would not reflect their prior sleep. Our case did not serve any time before his sleep study was run. This was carried out while awaiting his trial, during which time he lived at home.

5. Conclusion

Finally, we disagree with the last sentence of the Pressman et al. letter: “Tests of any sort performed months or years after the index crime can tell us nothing about whether or not the criminal defendant was sleepwalking during commission of the crime act.” For someone who puts such emphasis on science, the first author sells short the promise of new technology to advance our ability to do appropriate testing; for example the use of home video monitoring. Mweng et al.\textsuperscript{10} conducted a long term study of a SW comparing two nights of lab based video-polysomnography to thirty-six nights of home video monitoring over three months in three different locations. They found no significant difference in the frequency or duration of the SW events captured in the lab and at home. The one difference that was highly significant was that under home video monitoring conditions the events were significantly more complex than those in the laboratory. If home polysomnography were added to the video monitoring, we would be able to test whether low SWA was stable over extended time.

Having reviewed this critique carefully we remain in support of our concluding statement: “There is, for example, a strong need for research involving larger samples to clarify disparate findings between studies with small samples.”

Properly credentialed sleep medicine professionals who are approached to serve as experts in forensic cases need to view this as an opportunity for a “field study” to collect new observations and evaluate these against whether or not they are supported by the state-of-the-art sleep research and whether further sleep testing would be useful in clarifying the question of guilt. That is the role of the expert. It also requires judgment as is reflected in the wording of the oath concerning “reasonable doubt.” Science is our method to test beliefs. It is constantly evolving and on occasion enough evidence accumulates to require a “paradigm shift.” We may be at that point where dogma about the type of study needed in forensic cases and role of the sleep expert must give way to a new approach.

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Letter to the Editor


DISCLOSURE STATEMENT

The authors have indicated no financial conflicts of interest.