Sleep Medicine 24 (2016) 24–31

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Original Article

Sleep remains disturbed in patients with obstructive sleep apnea treated with positive airway pressure: a three-month cohort study using continuous actigraphy

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ARTICLE INFO

Article history:
Received 5 January 2016
Received in revised form 20 May 2016
Accepted 4 July 2016
Available online 16 August 2016

Keywords:
Obstructive sleep apnea
Residual sleepiness
Positive airway pressure
Actigraphy

ABSTRACT

Objective: Some patients with obstructive sleep apnea (OSA) remain sleepy despite positive airway pressure (PAP) therapy. The mechanisms by which this occurs are unclear but could include persistently disturbed sleep. The goal of this study was to explore the relationships between subjective sleepiness and actigraphic measures of sleep during the first three months of PAP treatment.
Methods: We enrolled 80 patients with OSA and 50 comparison subjects prior to treatment and observed them through three months of PAP therapy. PAP adherence and presence of residual respiratory events were determined from PAP machine downloads. Epworth Sleepiness Scale (ESS), Functional Outcomes of Sleep Questionnaire (FOSQ), and actigraphic data were collected before and at monthly intervals after starting PAP.
Results: Patients with OSA were sleepier and showed a greater degree of sleep disruption by actigraphy at the baseline. After three months of PAP, only ESS and number of awakenings (AWAKE#) normalized, while wake after sleep onset and sleep efficiency remained worse in patients with OSA. FOSQ was improved in patients with OSA but never reached the same level as that of comparison subjects. ESS and FOSQ improved slowly over the study period.
Conclusions: As a group, patients with OSA show actigraphic evidence of persistently disturbed sleep and sleepiness-related impairments in day-to-day function after three months of PAP therapy. Improvements in sleepiness evolve over months with more severely affected patients responding quicker. Persistent sleep disruption may partially explain residual sleepiness in some PAP-adherent OSA patients.
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1. Introduction

By providing a patent airway during sleep, positive airway pressure (PAP) therapy mitigates the recurrent obstructive respiratory events and associated oxygen desaturations and arousals that are characteristic of obstructive sleep apnea (OSA) [1]. In doing so, PAP has been shown to improve the quality of life, cognitive function, and excessive daytime sleepiness (EDS) in the affected patients [2–4]. However, some treated patients still complain of being excessively sleepy. Since Guillemninault and Philip [5] first reported that some PAP-treated patients remain sleepy, questions have lingered about the causes and frequency of persistent sleepiness and even about its existence as a problem unique to these individuals [6]. The proportion of treated patients affected by persistent sleepiness is reported to be as high as 13% [7], but different methods of assessing sleepiness yield different results. Weaver et al. [8] showed that while about 20% of patients averaging eight hours of nightly PAP use for three months were excessively sleepy as indexed by subjective measures such as the Epworth Sleepiness Scale (ESS), nearly half had objective evidence of sleepiness on the multiple sleep latency test (MSLT). Timing of sleep assessment is another potential factor. Sleepiness has been shown to improve within two weeks using MSLT [9] and driving simulator outcomes [10], while subjective improvement occurs more slowly [11,12]. Finally, the nature of the residual symptoms may depend on how it is perceived by the patient; many complain of persistent fatigue, inattention, or lack of a sense of well-being rather than “sleepiness” per se [13].

Intermittent hypoxia-induced cellular injury to basal forebrain and brainstem wake-promoting centers has been demonstrated in mice [14], and similar injury in humans with OSA could explain some cases of persistent sleepiness. However, a more likely explanation for the majority of PAP-treated patients is inadequate adherence to PAP therapy. Weaver et al. [8] demonstrated a dose–response

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http://dx.doi.org/10.1016/j.sleep.2016.07.008
1389-9457/Published by Elsevier B.V.

relationship between hours of use and normalization of sleepiness; fewer hours of use were associated with a greater probability of persistent sleepiness. Patients may also remain sleepy because of residual respiratory events due to PAP under-titration or mask leaks, other coexisting sleep disorders (such as central sleep apnea and periodic leg movements), and depression [15]. Poor sleep hygiene and insufficient sleep are common in the general population and are likely to cause sleepiness in some patients with treated OSA. Moreover, there is evidence that nearly half of the treated patients continue to have poor quality sleep as indexed by an elevated Pittsburgh Sleep Quality Index (PSQI) [16].

Sleep duration, timing, and disruptions in sleep–wake patterns resulting in a perception of poor quality sleep are usually determined by a subjective patient report, but a more objective method of determining these is with the use of actigraphy. Actigraphy has been shown to be a reliable and valid method of assessing sleep–wake patterns in normal subjects, although its validity has been questioned in patients with highly fragmented sleep, such as those with OSA [17]. On the contrary, Gagnadoux [18] and Wang [19] reported close agreement between actigraphically derived sleep metrics and polysomnography (PSG) in treated and untreated OSA. Otake et al. [20] demonstrated short-term improvements in sleep quality assessed by actigraphy in patients after introduction of PAP, suggesting that actigraphy may be a useful means of indexing sleep duration and quality in treated patients.

The primary goals of this study were to explore the relationships between subjective sleepiness and actigraphically derived measures of sleep duration and quality in patients with OSA treated with PAP and to identify aspects of sleep recorded over an extended course of treatment, which potentially predict residual sleepiness. To do so, we studied patients with a wide spectrum of OSA severity over three months, making monthly assessments of self-reported sleepiness, and relating these reports to data from continuously acquired actigraphy. Subjective indices included ESS and Functional Outcomes of Sleep Questionnaire (FOSQ). Objective indices included total sleep time (TST), sleep fragmentation including number of awakenings (AWAKE#) and wake minutes after sleep onset (WASO), and sleep efficiency (SE). The secondary goals were to characterize the time course of changes in subjective sleepiness and sleep quality as measured by actigraphy from before to three months after introduction of PAP and to examine factors that predicted those changes. We characterized individual differences in initial status and rates of change through monthly assessments of subjective sleepiness. Quantitative indices of sleep quality from actigraphy were summarized to correspond to the timing of data collection in subjective indices. We considered several factors as predictors of post-PAP improvements in both subjective and objective sleepiness, including pre-PAP disease severity, body mass index (BMI), and PAP use. We elected to base recruitment of subjects solely on whether they met the accepted clinical and polysomnographic criteria for the diagnosis of OSA rather than constraining the populations to subjects with predetermined levels of sleepiness based upon ESS scores. This strategy ensured that the populations we studied were representative of what may be encountered in clinical practice.

2. Materials and methods

2.1. Subjects

Eighty patients with OSA (53 males) and 50 comparison subjects (32 males) participated in a study of real-world driving safety and PAP use. Patients with OSA were recruited from the University of Iowa (UI) and the Iowa City Veterans Affairs Medical Center located in eastern Iowa. Patients with OSA were newly diagnosed, met ICSD-2 clinical criteria for OSA [1], and had not previously been treated with PAP. Comparison subjects were recruited from the general community surrounding Iowa City through local newspapers and public service announcements. The comparison group was matched to patients with OSA at the group level on average age (within five years) and education (within two years), with similar distributions for the season of year. The comparison subjects were screened with the same procedures as those for patients with OSA. Inclusion criteria for all participants included at least 10 years of driving experience, driving a primary vehicle at least 100 miles or two hours per week, and primary vehicle being a make of 1996 or later.

Exclusion criteria included (a) history of a neurological disorder or sleep disorder besides OSA, (b) acute illness or active, confounding medical conditions (eg, chronic pulmonary disease requiring medical or supplemental oxygen therapy, congestive heart failure, dementia, major psychiatric and vestibular diseases, alcoholism, or other forms of drug addiction), (c) using stimulants, antihistamines, sedating antidepressants, narcotics, anxiolytics, anticonvulsants, and other major psychoactive medications, (d) consumption of ≥7 cups of caffeinated beverages daily [21], (e) an irregular sleep–wake pattern, working nights/rotating shifts, or a habitual sleep duration of <6 or >9 hours [22], (f) no longer driving, (g) having visual field defects defined by Humphrey perimetry [23], and (h) diseases of the optic nerve, retina, or ocular media coupled with a corrected visual acuity of less than 20/50.

The UI Institutional Review Board approved the study and written informed consent was obtained after full explanation of the study procedures. Subjects received $500 for compensation.

2.2. Polysomnography

Patients with OSA attended in-laboratory PSG prior to recruitment, which was scored by one of two registered PSG technologists and interpreted by a board-certified sleep medicine physician (JT). PSGs were scored according to the accepted protocols and criteria [24]. Measures of apnea–hypopnea index (AHI), respiratory disturbance index (RDI), and minimum oxygen saturation (SpO2 nadir) constituted disease severity indices in the analyses. Hypopneas were scored when associated with a ≥4% oxygen desaturation. The RDI was calculated as the sum of all apneas, hypopneas, and respiratory effort-related arousals divided by the TST. Comparison subjects underwent unattended type-II PSGs performed in the UI Clinical Research Unit, which were scored similarly to the in-laboratory PSGs. Patients with OSA had an RDI >15 in keeping with other studies of PAP usage and daytime sleepiness (8), while controls had an RDI < 5. Results from the unattended studies were used only to screen potential control subjects and were not included in subsequent analyses.

2.3. PAP therapy

Patients with OSA were started on PAP either as part of a "split-night" study or during a dedicated titration study with pressures titrated to a minimum "adequate" level [25] using a fixed pressure. The interpreting physician was responsible for the decision to use continuous positive airway pressure or bi-level positive airway pressure.

2.4. Procedure

Participants completed questionnaires two weeks before beginning PAP therapy and at monthly intervals during the post-PAP phase [26]. Scheduling contingencies introduced significant variability when anticipated "monthly" ratings were actually obtained in both patients with OSA and comparison subjects. Duration of study was not extended when patients with OSA did not commence PAP in the anticipated timeline. Participants were given wrist actigraphy (Actiwatch Spectrum Plus, Philips Respironics, Murrysville, PA) at