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JCSM Journal of Clinical Sleep Medicine

Volume 8, Number 5
October 15, 2012
Pages 467-626

Official publication of the American Academy of Sleep Medicine

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JCSM Journal of Clinical Sleep Medicine (Online 1550-9397; Website: www.aasmnet.org/jcsm) is published on-line 6 times per year: February, April, June, August, October, and December by the American Academy of Sleep Medicine, 2510 North Frontage Road, Darien, IL, 60561-1511, phone (630) 737-9700 and fax (630) 737-9790.

ANNUAL SUBSCRIPTION RATES: Subscription rates for Volume 8, 2012: Individual Online (US and International): $75.00; Institutional Online (US and Internationally): $140.00. Mid-year subscriptions are not available. Subscriptions begin with the February issue of the current year. Renewals should be secured as early in the year as possible to avoid uninterrupted service. Questions about subscriptions (including payments, billing procedures, or policy matters) should be directed to the AASM office at (630) 737-9700.

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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.

The following articles in this issue may be read for CME credit:

Effects of Positive Airway Pressure Treatment on Clinical Measures of Hypertension and Type 2 Diabetes
Objective: Understand that positive airway pressure treatment of sleep apnea has a beneficial effect on blood pressure control in men with hypertension.

Beginning page #

Sleep Quality, Short-Term and Long-Term CPAP Adherence
Objective: Understand the relationship between the quality of sleep at the time of titration and CPAP adherence.

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In this issue, Drs. Owens, Kothare, and Sheldon with Dr. Gozal engage in a healthy debate regarding the necessity of accreditation standards for centers that diagnose and treat pediatric sleep disorders.1-2 In their editorial, Drs. Owens, Kothare, and Sheldon express concern that my editorial on the Future of Sleep Medicine did not specifically mention pediatric sleep medicine. The conclusion that the American Academy of Sleep Medicine (AASM) is therefore ignoring our youngest patients could not be farther from the truth. Pediatric sleep medicine is included at all levels in the activities of the AASM: education of sleep specialists is a high priority and insuring the best possible care for children with sleep disorders is of utmost concern.

In just the past year the AASM undertook the following initiatives related to pediatric sleep medicine:

- Achieved acceptance of a two separate pediatric Polysomnography CPT codes that recognize and reimburse the additional effort needed to obtain high quality sleep studies in children.
- Developed a pediatric sleep medicine course, which be held in Fall 2012 in conjunction with a pediatric sleep research course sponsored by the Sleep Research Society.
- Invested in the development of standards of practice documents for respiratory and non-respiratory pediatric sleep disorders.

Further, the AASM has supported pediatric sleep medicine more broadly. For example, pediatric sleep specialists, including authors on both sides of this debate, are integral members of task forces that drafted practice parameters related to pediatric sleep medicine and are involved in updates to critical sleep medicine texts such as the International Classification of Sleep Disorders 3rd Edition and the upcoming revision of The AASM Manual for the Scoring of Sleep and Associated Events. In addition, the AASM Board has physicians with specific expertise in pediatric sleep medicine as Directors and there is a dedicated section for pediatrics where ideas and thoughts are shared among colleagues. Further, the AASM has always supported the inclusion of pediatric training for sleep specialists; in fact, the Accreditation Council for Graduate Medical Education (ACGME) syllabus requires exposure to pediatric sleep medicine in its curriculum and the American Board of Medical Specialties (ABMS) includes pediatric sleep medicine questions in its examination. Several lectures on pediatric sleep medicine are included in the AASM’s Board Review for the Sleep Specialist course. Also, the Education Committee has produced several excellent products focused on pediatrics, including a 3-CD set of informative slides and accompanying text.

In his editorial,2 Dr. Gozal makes a salient point that is the crux of this debate: there is a dearth of appropriately trained specialists to treat pediatric patients with sleep disorders. According to the American Board of Pediatrics (ABP) website, there are 216 physicians certified in sleep medicine by the ABP through December 2011. With more than 2,600 sleep disorders centers accredited by the AASM, there is an obvious need for additional fellowship programs and physicians trained in pediatric sleep medicine to meet the present reality and future demands. As the AASM continues to support efforts related to pediatric sleep, it is incumbent on us as individual clinicians to serve as advocates for sleep medicine and promote pediatric sleep medicine opportunities to medical students and our colleagues.

Building on the consideration of an inadequate number of pediatric-trained sleep physicians, another astute point Dr. Gozal articulates is the inability of accredited sleep disorders centers to fully and fairly implement standards specific to pediatric patients. In assessing this debate, it is important to remember that the AASM Standards for Accreditation of Sleep Disorders Centers presently include provisions for pediatric sleep medicine.

The AASM Standards for the Accreditation of Sleep Disorders Centers are not simply a checklist of requirements—the standards require compliance with published AASM practice parameters and guidelines. The introduction states that “Accredited sleep facilities must adopt and follow the standards in all active AASM Practice Parameter papers. In addition, it is recommended that accredited sleep facilities adopt and follow all active AASM Clinical Guidelines.” The inclusion of this language insures that evidenced-based standards of care, as they evolve and are included in AASM publications, are always a part of the requirements for accreditation. Further, these policies insure that accreditation encourages compliance with the most up-to-date evidence available and assures consistency among the publications of the AASM and in clinical practice. As evidence for pediatric diagnoses and treatments coalesce, practice parameters and guideline papers published by the AASM automatically update accreditation standards.

The standards require that “the signals collected and the equipment used for comprehensive polysomnography must be in compliance with The AASM Manual for the Scoring of Sleep and Associated Events.” For pediatric patients, this means that sleep studies must include transcutaneous or end-tidal CO₂.
monitoring. In addition, The AASM Manual for the Scoring of Sleep and Associated Events requires that pediatric sleep studies provide the data necessary to diagnose hypoventilation, and this requires CO₂ monitoring. Further, the manual requires the use of this rule with patients less than 13 years of age. Accreditation standards require that centers have written protocols for patient acceptance, which must include the ages of patients seen in the center. When site visitors encounter sleep centers that study children, appropriate equipment for CO₂ monitoring is required. Site visitors review protocols for pediatric sleep studies and insure that the environment is appropriate for the ages studied.

Accreditation standards also require that pediatric sleep studies are interpreted using the separate rules for pediatric sleep staging and respiratory events scoring in The AASM Manual for the Scoring of Sleep and Associated Events. Gaining experience with these rules and evaluating competence in the scoring of pediatric sleep studies may be difficult to obtain. In response, the AASM is in the early stages of developing a pediatric section for the Inter-scorer Reliability Program, currently used by more than 2,800 scorers. The program provides standard sample recordings that are scored by a committee of expert “gold standard” scorers and provides immediate feedback to users. Users are able to compare their scores to the scores of all users. An instructive monthly video review of contentious epochs provides an enriched learning experience. This will certainly be a valuable educational resource on the scoring of pediatric sleep studies.

An area of complete agreement with Dr. Owens and colleagues is that pediatric sleep studies require a family oriented approach. Input from a spouse or a bed partner is helpful in adult sleep medicine; input from parents or caregivers is critical in pediatric sleep medicine. The article by Zaremba⁷ has been incorporated into many AASM courses and forms the basis for the popular “Making Sleep Studies Child Friendly” DVD. This resource is highly recommended viewing for center physicians and technical staff when pediatric patients are studied. Accreditation standards also require a quality improvement plan. This often includes assessment of patient (or parental) satisfaction and is intended to form the basis for a feedback loop leading to optimization of pediatric sleep study procedures and environment. Appropriate patient follow-up is also a key element of accreditation standards.

The AASM is highly sensitive to access to care issues. Accreditation standards are carefully weighed to determine the burden they place on community sleep specialists. The balance is to require a standard of care without placing excessively harsh restrictions that might lead a specialist to turn patients away. Because an increasing number of pediatric sleep patients will present with symptoms consistent with obstructive sleep apnea, recognition, correct diagnosis, and appropriate treatment of these patients should be a standard part of every sleep specialist’s training. Recognition of less common pediatric sleep disorders and, at a minimum, a plan for referral for treatment is also expected. Within this framework, the AASM leadership welcomes evidence-based recommendations for additional standards of care.

Finally, recognition of the field of sleep medicine was a hard-fought battle that required demonstrating that a unique body of knowledge and training existed that was not present in any other medical specialty. The American Medical Association, AC-GME, and the ABMS came to support this proposition and our field is stronger with this recognition. Fragmentation of sleep medicine into sub-disciplines runs the risk of eroding this support. A focus of the AASM has always been inclusion of the pediatric expertise in standards of care, publications, courses, and educational products. Our goal is to educate sleep specialists in the care of pediatric sleep disorders patients, thereby making integrated sleep medicine programs truly comprehensive.

REFERENCES


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Submitted for publication May, 2012
Submitted in final revised form May, 2012
Accepted for publication May, 2012
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DISCLOSURE STATEMENT

This was not an industry supported study. Dr. Fleishman has indicated no financial conflicts of interest.
Recently, the leadership of the American Academy of Sleep Medicine has called for the development of innovative approaches to better enable the field to meet the challenges of anticipated changes in healthcare delivery, to weather the realities of the current economic climate and tightening cost-containment measures, and to ultimately shift the focus of clinical sleep medicine from an emphasis on diagnostic testing to a comprehensive approach in the future to the treatment of children with sleep disorders is both striking and highly disappointing to those of us who care for these pediatric sleep patients and their families. On the one hand, the current lack of standardization with these important and timely efforts, the absence of any support our adult sleep medicine colleagues in moving forward with sleep disorders is substantial.

While we applaud these developments and enthusiastically support our adult sleep medicine colleagues in moving forward with these important and timely efforts, the absence of any mention whatsoever of the need to establish accreditation standards for children or to develop a similarly comprehensive and integrated approach in the future to the treatment of children with sleep disorders is both striking and highly disappointing to those of us who care for these pediatric sleep patients and their families. On the one hand, the current lack of standardization for conducting pediatric sleep diagnostic services and providing comprehensive evaluation and treatment of pediatric sleep disorders in “mixed” adult and pediatric sleep centers greatly increases the risk of delivery of “second class” or substandard care for children, a situation which is clearly unacceptable. On the other hand, if future accreditation standards for the field of sleep medicine are truly to address the needs of all patients and incorporate a developmental “life cycle” perspective, then neglecting to include the fundamental, unique, and complex needs of children and families in the model is tantamount to a failure to achieve those goals.

Based on this assumption that a “double standard” in the clinical care of adult and pediatric sleep patients currently exists, we propose that the AASM should take the lead in rectifying the situation. We believe that including pediatric standards in the AASM accreditation of sleep centers as a means of achieving parity in the delivery of sleep medicine services is not only necessary and important, but urgent. The specific rationale for this proposal is outlined below:

1) Demand for pediatric sleep diagnostic services is likely to increase.

The AASM 2011 Practice Parameters on Respiratory Indications for PSG in Children recommends that all children undergo adenotonsillectomy for sleep disordered breathing have a diagnostic sleep study to establish the diagnosis and determine severity. Currently, it is estimated that fewer than 10% of children have a sleep study prior to surgery. The practice parameters further recommend that repeat sleep studies be conducted in clinical situations in which residual SDB is likely to be present (e.g., obesity, severe baseline SDB, craniofacial anomalies); the percentage of high risk children currently undergoing postoperative PSG is not known, but likely to be similarly small. In addition, it is anticipated that increased awareness among pediatric healthcare providers of SDB and its potential consequences will result in increased demand. As more studies linking pediatric OSAS with adverse behavioral and cognitive outcomes are published and disseminated, mental health providers, educators, and parents are also likely to become more active in the referral process. Thus, the potential need for expansion of sleep diagnostic services to appropriately evaluate and treat SDB in children is substantial.

At the same time, we acknowledge that there is clearly a significant “service gap” posed by the relative lack of facilities around the country which provide specialized pediatric sleep medicine services, especially in non-academic and non-urban settings. Currently there are only 28 “titled” pediatric sleep centers accredited by the AASM, according to the 2012 AASM Roster of Accredited Sleep Centers. This results in a total of only 1.8% of all accredited sleep centers. Eighty-two percent of
accredited sleep disorders centers report accepting children 13 years of age or older. Only 47% of all accredited centers report acceptance of patients 5 years of age or younger and less than one-third of centers will accept children less than 3 years of age.

2) At the same time, demand for in-lab testing in adults is likely to decrease.

As portable monitoring increasingly becomes the standard for adults with uncomplicated sleep apnea,1 sleep labs will face increasing competition for inpatients. Given the complexity of conducting sleep studies in children, it is not expected that home studies will also become the standard of care, at least in individuals under 12. The financial incentive for adult labs to study children has also increased due to the recent CPT Editorial Panel approval of increased reimbursement for pediatric sleep studies (age less than 6 years) (http://www.ama-assn.org/resources/doc/cpt/summary-of-panel-actions-feb2012.pdf). While this change is an acknowledgment of such child-specific variables as the increased time and effort required to score and interpret pediatric studies and the need for a high sleep technologist to patient ratio (1:1) in many pediatric patients, it may have the unintended consequence of encouraging unequipped and ill-prepared adult facilities to market their services to the child population.

One probable result of this situation of increased demand and enhanced incentives is that more adult sleep programs will consider expanding their services to include diagnosing and treating children. Recognizing this reality and acknowledging that pediatric sleep centers are currently inadequate in number and geographical distribution to meet the demands, we would argue that the need to establish clear standards for conducting and interpreting pediatric sleep diagnostic tests in non-pediatric settings now is imperative and that incorporation of those standards into accreditation requirements for mixed labs in the near future is mandatory.

3) Inappropriate or substandard pediatric sleep testing drives up healthcare costs.

In this era of tighter healthcare budgets, increasing scrutiny of health expenditures and uncertainty regarding the future of federal healthcare programs, any perceived unnecessary or wasteful spending for diagnostic procedures will be closely examined and challenged. We contend that pediatric sleep studies which are inappropriately conducted, interpreted, or scored by sleep medicine providers inadequately trained in pediatrics may result in excessive healthcare costs due to the need to repeat studies, delays in treatment, and unnecessary or over-treatment. Requiring specialized pediatric accreditation standards would substantially reduce this risk.

4) Conducting, scoring, and interpreting sleep studies in children require specialized training of both healthcare providers and technologists.

There are a myriad of specific and unique challenges to providing at the very least a minimum standard of diagnostic sleep services for children. First, both healthcare providers and technologists need to possess a knowledge base regarding pediatric respiratory pathophysiology and neurophysiology, normal developmental changes in sleep architecture and cognitive/motor/language/social developmental milestones. Required technical skills in conducting and scoring pediatric sleep studies necessitate initial specialized training, ongoing education, and exposure to an adequate volume of patients. For example, most adult sleep labs have little experience with ETCO2 monitoring, which is considered the standard of care in performing pediatric sleep studies. Sleep staging and respiratory scoring in children in particular, are quite different from those in adults (i.e., sleep architecture findings unique to children such as hypnogogic hypersynchrony, required duration of apneic/hypopneic events,). Moreover, implementation of specific diagnostic procedures such as the multiple sleep latency test, and therapeutic interventions such as PAP therapy in the child population, requires both specialized knowledge and technical expertise, as well as application of principles of behavioral sleep medicine.7

We would argue that many, if not most, sleep centers contemplating expanding their services to include children, as well as some “mixed” labs currently seeing children, do not currently have the knowledge, skill, and expertise to do so. There are a number of reasons for this situation. While ABMS sleep medicine fellowship trained physicians are required spend a minimum percentage of their training seeing children (40 pediatric sleep studies), this may not be sufficient to ensure adequate quality of care, especially for non-pediatric specialties. The relative dearth of specialized pediatric sleep centers available for training sleep medicine fellows also is likely to result in variability in amount and quality of exposure to pediatric sleep medicine across programs. Moreover, non-fellowship trained sleep physicians may have had minimal to no pediatric training. Finally, sleep technologists are not required to have any specific pediatric exposure or to learn appropriate skills during their training.

Therefore, we would propose that a minimum requirement for mandatory training in pediatric sleep medicine for physicians and other healthcare providers and sleep technicians/technologists be developed and included in the AASM accreditation standards for all labs intending to study patients under the age of 16 years. Previously accredited labs would be required to meet these specialized pediatric accreditation standards, including demonstration of pediatric proficiency of technologists in data acquisition and scoring, at the time of re-accreditation.

5) Family-centered care is a mandatory component of pediatric sleep diagnostic and treatment services.

Conducting sleep studies in children requires specific accommodations to the physical space (sleeping accommodations for parents, cribs), to the emotional and physical needs of children across a range of ages and their caregivers, and the implementation of pediatric-specific procedures to insure comfort and safety.4,9-10 For example, lab hours may need to be extended to accommodate young patients, and age-appropriate toys and books need to be made available. Tours of the lab prior to the testing date should be offered and instructions regarding lab procedures should be sent in advance to families. Recognizing that caregivers are an integral component of pediatric care, sleep programs should have specific policies which provide family-centered and child-friendly care. This is currently not required for accreditation. We contend that minimum standards
for the children in the sleep lab environment should be established and child-specific policies and procedures should be included in pediatric accreditation requirements.

6) Appropriate triaging of pediatric patients is fundamental to successful integration of pediatric sleep services.

While triaging by age is straightforward and feasible, appropriate screening mechanisms to exclude children with significant medical, psychiatric, and neurodevelopmental comorbidities, or children with severe sleep disorders are also needed. Inadequate screening potentially results in poor diagnostic yield and suboptimal care in these special populations and may pose situations which are safety threats. Thus, patient acceptance and referral procedures, and triage parameters and guidelines should be included in pediatric accreditation standards. However, recognizing that, at best, screening procedures are imperfect and that children may present to the sleep lab with unexpected medical, cognitive, or behavioral challenges, the sleep lab personnel, environment, and policies must be prepared to accommodate a wide range of clinical situations. Policies and procedures specific to caring for children with special needs should be included in accreditation standards.

7) Comprehensive clinical care, including follow-up care for pediatric sleep patients undergoing diagnostic procedures, and evaluation and management of children with the full range of sleep disorders is a necessary component of an integrated sleep medicine program.

Accreditation of “free-standing” sleep labs, without wrap-around full-service clinical sleep medicine services, is no longer offered by the AASM. Furthermore, no accredited adult sleep lab would be allowed to limit their scope of services solely to testing for sleep disordered breathing. Similarly, accredited sleep labs which provide services to children should not only offer the full range of diagnostic testing and treatment procedures, but also make available the corresponding appropriate follow-up and comprehensive clinical care. Current lab accreditation standards stipulate that no more than 80% of patients referred for sleep testing be direct referrals; this means that at least 20% of pediatric sleep study patients should be accommodated and seen in an affiliated clinical sleep program before or after their sleep study.

A high percentage of children referred to sleep clinics have diagnoses other than sleep disordered breathing, which include behavioral insomnia, RLS/PLMD, partial arousal parasomnias, and circadian rhythm disturbances, the evaluation and treatment of which may differ substantially from that for similar diagnostic entities in adults. Moreover, a substantial proportion (up to 40%) of children referred for overnight sleep studies for a suspicion of SDB have at least one, and frequently multiple, additional sleep diagnoses. Therefore, a comprehensive evaluation for the range of sleep disorders is a necessary component of standards of care.

Finally, our field is rapidly moving to a conceptualization of sleep disorders as chronic health conditions frequently necessitating long-term care. If anything, this paradigm shift is even more salient for children, for whom both the short- and long-term consequences of sleep disorders such as OSAS are often profound and wide-ranging. There is a substantial need for ongoing medical and psychosocial management of chronic sleep disorders in children and adolescents such as narcolepsy or delayed sleep phase disorder in order to prevent poor health and functional outcomes. Conversely, early identification and rapid treatment of sleep disorders such as SDB may result in significantly improved outcomes.

8) Adequate evaluation, treatment, and follow-up of pediatric sleep disorders, including sleep disordered breathing, may not be available in the community.

A number of studies have substantiated the observation that primary care pediatricians, medical subspecialists (neurology, pulmonary), and mental health practitioners caring for children are often poorly trained in the diagnosis and management of children with sleep disorders. Therefore, the assumption that pediatric providers in the community appropriately screen for and refer patients with sleep disorders may be erroneous, and reliance on these providers to subsequently appropriately manage children diagnosed with sleep disorders may be misguided. Therefore, accreditation standards should states that the provision of sleep diagnostic services for children must be accompanied by access to appropriate follow-up care.

9) Ultimately, failure to include special considerations for the pediatric population in planning for the future of sleep medicine would represent the loss of a major opportunity to improve the health of children and advance the field.

There is increasingly compelling evidence for the negative impact of an insufficient quantity and/or quality of sleep on children’s physical and mental health, cognitive function, behavior, and academic success, consequences for which children from racial/ethnic minorities and those living in poverty may be at even higher risk. There are a large number of cross-sectional and prospective studies which have consistently shown associations between sleep problems and a host of adverse health outcomes in children and adolescents, including increased obesity risk, higher rates of motor vehicle accidents and accidental injuries, adverse cardiovascular outcomes, and depression and suicidal ideation. By mandating accreditation standards for the delivery of sleep services for children, the AASM would be sending a clear message that the field acknowledges the profound impact that sleep disorders have on children’s health and recognizes that optimal diagnosis and management of pediatric sleep disorders in the clinical setting represents a key strategy to reduce adverse outcomes. Adoption of pediatric accreditation standards would make practical, real and sustainable progress towards achieving those goals.

Finally, the future of sleep medicine will depend in large part upon the development of innovative approaches to care delivery such as telemedicine, the emergence and validation of new and existing sleep technologies, the development of more sophisticated techniques such as biomarkers, and the incorporation into practice settings of tools like clinical registries to assess outcomes and quality of care. In order for any of
these innovations to be truly progressive and to ultimately have an impact on the health of all Americans, we would contend that the inclusion of the pediatric perspective is both necessary and timely.

CITATION


REFERENCES

There is no doubt that the ability to summon extraordinary eloquence during a debate provides a compelling tendency for endorsement of any reasonably valid argument in which opposite and contradictory opinions on certain details are discussed. Furthermore, we routinely tend to side with the “underdog,” and will more willingly support minority opinions, especially when such opinions deal with a sector of our population for whom we are genetically and evolutionarily conditioned to protect, namely our children. In their rendering of an opinion on integrated sleep centers, Owens et al. demonstrate in a superlative manner the persuasive nature of such skills and circumstances. However, in spite of an almost relentless inner drive to cede to my esteemed colleagues, I will try to delineate some of the drawbacks of the proposal they so eloquently formulate.

Access to Care

Under the auspices of the most recent consensus focused on indications for PSG in children with respiratory symptoms, and similar guidelines originating from different countries and medical disciplines over the last decade, and with the ever increasing awareness among pediatricians and primary care physicians on the importance of healthy sleep in children’s well-being, it is indeed predictable that a progressive increase in the utilization of sleep services will occur in the pediatric age range. The major problems with this proposition are that access to pediatric sleep specialists is quite limited in the US, and even further restricted in other countries around the world. As such, the access to care will be further compromised particularly considering that only a very small number of pediatricians are formally trained in sleep medicine on a yearly basis. Therefore, although relying on a different perspective of medical practice, I will wholeheartedly agree with Owens et al. that demand will definitively increase for pediatric clinical services. What remains unclear is whether such services will require in-laboratory PSG, or whether similar to the current trends in adult sleep medicine, we will witness a progressive transition to alternative diagnostic methods relying on polygraphic respiratory recordings at home or on innovative urine biomarkers. Such uncertainties are likely to dampen any “business-oriented” initiatives to expand the current capacity of sleep laboratories. However, the increased demand in a setting of declining activity around adult patients will, at least temporarily, shift the current trends to increase the current proportion of children being evaluated in sleep medicine centers around the country. Under such circumstances, there is no doubt that the accrediting bodies will have to incorporate improved methods for ascertaining the adequacy of resources and capabilities embedded in the accreditation process of sleep laboratories and centers that evaluate and manage children. In other words, the accreditation process is not in need of change, but rather the specific content as it relates to children will need to gain more specific attention during the accreditation and reporting process.

Medical Home Concept

The conceptual framework of patient centered care and medical home is not novel but has received more recent attention in the context of the emerging radial changes in the delivery of healthcare in our country. As part of this trend, the AASM has indeed fostered a vibrant discussion process that is still in its initial operational implementation stages. Under such conceptual framework, there is clearly a need for revising the current accreditation standards and implementing a new revised set of well-validated and standardized definitions and metrics for assessing health outcomes, in the context of the full spectrum of sleep disorders. There is no doubt that lack of inclusion of any specific constituent into the overall operational set of guidelines may have detrimental effects and result in substandard care for patients. However, the concepts enunciated are not exclusive of children or geriatric patients or any other specific patient group, and therefore, we need to operate as collaboratively as possible to ascertain that the common goals are fulfilled and that specific differences pertaining to any special group of patients or diseases are addressed. Efforts in this direction have clearly been implemented in many of the practice guidelines documents emanating from the AASM, whereby pediatric experts have consistently been included and have contributed to the content and specific items prescribed in such guidelines.

The Multidisciplinary Aspects of Sleep Medicine

The most attractive characteristic of our field of sleep medicine is the fact that we operate in a multidisciplinary contextual setting, whereby the classic specialties are incorporated into the overarching umbrella of sleep. A potential consequence of requiring specific and distinctly separate sets of operational guidelines and accreditation standards in the context of pediatric patients could create a domino effect, whereby all the “silo”
subspecialties represented in AASM may see as pertinent the need to segregate and formulate separate documents and rules. In other words, do we need then specific sub-accreditations for a sleep program or center, if patients with neurological, psychiatric, psychological, cardiovascular, pulmonary, etc… diseases are evaluated and treated in such center? I firmly believe that the AASM, as the leading organization responsible for establishing professional guidelines in sleep medicine, should merge all of these silos and provide a set of standard guidelines for accreditation that are operationally sound, protect the welfare of the patient, promote optimized outcomes, and overall improve health. If any specific unpredictable adverse consequences result from such efforts in the context of the continuous self-critical evaluation and appraisal process that is implemented as part of such efforts, then, and only then, specific corrections will be needed.

Before I address each of the 7 arguments enunciated as being detrimental to the outcomes of pediatric patients, I will have to point out that none of such arguments relies on objective data that have been critically assessed, and as such, they are more akin to a “gut feeling” rather than being based on specific facts and figures.

(1) Inappropriate or substandard pediatric sleep testing drives up healthcare costs.

Owens et al. contend that if pediatric sleep studies are inappropriately conducted, interpreted, or scored by sleep medicine providers inadequately trained in pediatrics, then excessive healthcare costs will result, and that therefore the implementation of specialized pediatric accreditation standards would substantially reduce this risk. The problem with this statement is that there is absolutely no evidence to support this contention. For example, ~90% of all children with habitual snoring are currently undergoing evaluation and treatment by Ear Nose and Throat specialists in the absence of any evaluation by Sleep Medicine physicians. However, there are no studies documenting that the outcomes of such pediatric patients are worse than similar patients being evaluated in pediatric sleep centers. Furthermore, there is no evidence that habitually snoring children referred by pediatricians to either sleep centers or ENT practices present with significant differences in the prevalence of PSG-diagnosed sleep apnea. In addition, I could contend that implementation of PSG in the US alone to establish the definitive diagnosis of OSA among the estimated 500,000 habitually snoring children undergoing adenotonsillectomy each year, would not only be unfeasible when considering the current number of sleep centers that are proficient in pediatric sleep issues, but would also undoubtedly and excessively delay access to treatment, potentially aggravating end-organ morbidity, and furthermore increasing the already elevated healthcare costs among these children. One could further propose that increased access to the existing large network of accredited adult sleep laboratories in the US could markedly reduce the current resistance to include a PSG as part of the diagnostic process, and thus overall favorably impact the outcomes in the pediatric population.

(2) Conducting, scoring, and interpreting sleep studies in children require specialized training of both health care providers and technologists.

There is no doubt that the statements regarding the difficulties and challenges regarding delivery of optimal sleep medicine services to pediatric populations are correct and point out the formidable barriers that will need to be overcome. Most, if not all of the arguments advanced regarding the training experience acquired during fellowship and the scarcity of comprehensive pediatric sleep centers available as well as the high degree of variability in experience by physicians and technologists encompass likely contributions to the less than optimal standard performances by most sleep centers that are not extensively engaged in pediatrics. However, requesting specific accreditation standards that can not be pragmatically implemented due to the lack of appropriate training opportunities will not change the current reality. Instead, a more realistic evolutionary process that implements a set of desirable performance milestones and quality control supervision by the AASM might provide a more tangible solution and resolve some of the more acute problems in this area.

(3) Family-centered care is a mandatory component of pediatric sleep diagnostic and treatment services.

In this area, reason and extensive experience in pediatrics clearly mandate the implementation of requirements to enable adequate facilities and accommodations to the family unit during diagnostic and treatment phases of children. Although the current prescriptive requirements for accreditation do not mandate a detailed set of guidelines, there is no doubt that most of these requirements should be easily delineated and could become rapidly enforceable in sleep programs aiming to expand their pediatric scope of clinical activities.

(4 and 5) Appropriate triaging of pediatric patients is fundamental to successful integration of pediatric sleep services. Comprehensive clinical care, including follow-up care for pediatric sleep patients undergoing diagnostic procedures, and evaluation and management of children with the full range of sleep disorders is a necessary component of an integrated sleep medicine program.

The premise that accredited adult sleep labs would be allowed to restrict the scope of clinical services to exclusively testing for sleep disordered breathing is not a viable proposition. However, we could contemplate the option that many of the screening and post-test functions could be assumed by physicians with expertise in pediatrics, whereby the lab unit performing the test would be responsible for providing a “dry assessment and interpretation” of the test, rather than integrating the test results into the conglomerate of complexities associated with each individual patient. This approach alone could clearly reduce the substantial bottleneck and waiting periods associated with pediatric diagnostic ad treatment services. One could further argue that the training and certification of sleep physicians has clearly endorsed the view of sleep as a continuum from prematurity to geriatrics, and that therefore we should believe that medicine is not practiced by professional associations, but is rather practiced by individual physicians, such that the burden of responsibility and accountability falls on the sleep specialists to deliver the best possible care and ascertain optimal outcomes. Thus, one could easily view the evolution and emergence of hierarchically structure sleep programs, in which the degree of complexity in both the diagnosis and management would enable provision of different levels of service.
Of course, such service structure may not be ideal and will likely evolve over time. However, improved timely access to diagnosis is the first step of the process, and one that, as discussed earlier, is markedly deficient in pediatric settings.

(6) Adequate evaluation, treatment, and follow-up of pediatric sleep disorders, including sleep disordered breathing, may not be available in the community.

It is not only evident that both primary care pediatricians and other specialists are deficiently trained in the diagnosis and management of children with sleep disorders, but it is further disappointing that the vast majority of such physicians do not adhere to the existing professional guidelines. Therefore, before we blame those who wish to help children in “adult-oriented” facilities, we first need to fix things at home.

(7) Ultimately, failure to include special considerations for the pediatric population in planning for the future of sleep medicine would represent the loss of a major opportunity to improve the health of children and advance the field.

Mandating accreditation standards for the delivery of sleep services for children by the AASM will not solve the extreme shortages in well-trained pediatric sleep specialists, and the unique disparities to access to care that are pervasively engrained in our society and healthcare systems.

The future of pediatric sleep medicine is dependent on those of us who will assume the leadership roles of promoting Sleep Medicine to our students, our colleagues, and our own pediatric professional organizations, through stringent demonstration of evidence and progress across the translational planes. If we believe that children are our future, then it is on us to make sure that those of us who have chosen the path of caring for children will build and prepare their future as best as we can. In this regard, I am confident that the AASM will prove to be a valuable and worthy partner in such efforts.

CITATION


REFERENCES


ACKNOWLEDGMENTS

Dr. Gozal is supported by National Institutes of Health grants RO1 HL-065270, RO1 HL-086662, and 5P50HL107160.

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication May, 2012
Submitted in final revised form May, 2012
Accepted for publication May, 2012
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DISCLOSURE STATEMENT

This was not an industry supported study. Dr. Gozal has indicated no financial conflicts of interest.

Pro/Con Debate
Effects of Positive Airway Pressure Treatment on Clinical Measures of Hypertension and Type 2 Diabetes

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Purpose: Mechanistic and observational studies support an independent increase in risk of hypertension and abnormal glucose metabolism associated with obstructive sleep apnea (OSA). However, the specific populations and outcomes that improve with treatment of OSA in clinical practice are not established. We examined the effectiveness of OSA treatment on clinical blood pressure and diabetes control measures in men with preexisting systemic hypertension or type 2 diabetes.

Methods: A retrospective cohort of veterans (n = 221) with new diagnosis and treatment of OSA was identified using administrative databases and clinical records. Outcomes were changes in blood pressure (BP; mean of 3 highest recordings; systolic and diastolic) and glycemic control (mean of 3 highest fasting glucose and hemoglobin A1C values) at 3-6 months (T1) and 9-12 months (T2) following treatment compared to pretreatment. A generalized estimating equation model was used with adjustment for potential confounders: demographics, body mass index (BMI), OSA severity, Charlson comorbidity index, and pharmacologic treatment for hypertension and diabetes. Sustained independent effects of OSA treatment (mean change [95% CI]) were noted in both systolic BP (T1; -7.44 [-10.41 to -4.47] and T2; -6.81 [-9.94 to -3.67]) and diastolic BP (T1; -3.14 [-4.99 to -1.29] and T2; -3.69 [-5.53 to -1.85]). Diabetes control measures did not change with OSA treatment.

Conclusions: Treatment of OSA improves office blood pressure in hypertensive men. Prospective studies are necessary to better characterize specific populations with OSA that benefit from treatment with respect to progression of hypertension and type 2 diabetes.

Keywords: Effectiveness, OSA, hypertension

Citation: Prasad B; Carley DW; Krishnan JA; Weaver TE; Weaver FM. Effects of positive airway pressure treatment on clinical measures of hypertension and type 2 diabetes. J Clin Sleep Med 2012;8(5):481-487.

Considerable evidence from observational studies implicates obstructive sleep apnea (OSA) as an independent risk factor for systemic hypertension1 and abnormal glucose metabolism.2 The results of experimental studies evaluating effects of OSA treatment in hypertension reveal modest benefits,3,4 and the data regarding improvement in glucose homeostasis in type 2 diabetics from small clinical trials are inconsistent.5,6 This discrepancy is partly due to the size and type of cohorts examined or the specific outcomes assessed.7 Several studies examined populations with differential baseline characteristics (presence or absence of preexisting hypertension/diabetes) or variable OSA disease severity.7-12 Additional sources of variability relate to duration of follow-up and levels of treatment adherence.13 However, frequently the outcomes examined are not routinely available in clinical practice, and the applicability of these findings to usual care settings is unclear.

The objective of this study was to examine the effectiveness of treatment of OSA on routine clinical measures of hypertension and diabetes control in a primary care practice setting. We examined the long-term effects of OSA treatment on diurnal office BP, fasting glucose, and hemoglobin A1C (HbA1C) in veterans with newly diagnosed OSA and comorbid systemic hypertension and/or type 2 diabetes.
identified by ICD9 codes. New diagnosis of OSA with initiation of treatment was defined as: (1) a CPT code for a diagnostic sleep procedure (polysomnography; PSG or unattended level 3 portable monitoring, Stardust II, Philips-Respirronics; PM) followed by an ICD-9 code for OSA within 3 months; (2) prosthetics records indicating CPAP or APAP device provision within 6 weeks of the diagnostic procedure; (3) no OSA ICD-9 code in administrative and clinical records for 6 months prior to the diagnostic procedure date. The exclusion criterion was CPT codes for or history of surgical or dental device treatment for OSA. Subjects received either laboratory titrated fixed-CPAP treatment (Remstar Pro, Philips-Respirronics, Inc; Murrysville, PA, USA) or APAP device treatment set at 4 to 20 cm H2O upon initiation (Remstar Auto with C-Flex, Philips-Respirronics). The veterans with both fixed CPAP and APAP treatments had similar outpatient follow-up with sleep medicine physicians, and the APAP device pressure was adjusted to ≥ 90th percentile after treatment initiation at the treating physician’s discretion. This study was approved by the institutional review board at both participating facilities.

**Analysis**

The index date for the study was the date of CPAP or APAP device distribution. Three months preceding the index date was defined as the baseline period (T0), 3-6 months following the index date as T1 (first follow-up), and 9-12 months following the index date as T2 (second follow-up). The outcomes assessed (final cohort, n = 221) at T1 and T2 were: (1) Outpatient office visit systolic and diastolic BP (from the same recordings) in the subjects diagnosed with hypertension. For conservative treatment-related effect estimates, an average of the highest 3 values was taken to represent the systolic and diastolic BP within each time interval. (2) Outpatient fasting glucose values extracted from clinical records. If multiple values were noted, the last value within each time interval (T0, T1, and T2) was recorded. If the lab did not specifically indicate fasting glucose in the remarks, an outpatient blood draw that occurred between 07:00 to 08:30 was considered a fasting sample. (3) Outpatient hemoglobin A1C (HbA1C) extracted from clinical records. If multiple values were noted, the last value within each time interval (T0, T1, and T2) was recorded.

Several potential confounders were assessed, including: demographic data (age, race, BMI), concurrent medical illnesses per ICD9 codes, drug treatment of hypertension and diabetes, objective OSA treatment adherence (SmartCard download to EncorePro software), and self-reported daytime sleepiness documented in clinician notes. Demographic, comorbid medical disorders, and pharmacy data were extracted from administrative records. Data regarding vital signs, OSA disease severity, OSA treatment adherence, and symptom of sleepiness were extracted from clinical records. OSA disease severity was defined by the apnea hypopnea index (AHI) per published criteria for PSG.14 For both PSG and PM, the criterion for hypopnea was ≥ 50% airflow reduction and ≥ 3% desaturation (or associated arousal for PSG). The Charlson comorbidity index (CCI) was calculated and used to indicate general health status.15 The pharmacy data provided the total number and dosage of medications used for treatment of hypertension and diabetes. Three pharmacologic treatment measures were considered as covariates: changes in number of drugs, changes in dose of drugs, and adherence to drugs. Adherence to medications for hypertension and diabetes was defined by the medication possession ratio (MPR).16 MPR calculation results in a ratio < 1.0 if there are lapses in prescription refilling. The MPR was truncated at the maximum value of 1.0 (indicating potentially perfect adherence). An MPR was calculated for each 90-day interval (T1 and T2) and for each drug. The mean MPR for each drug class (antihypertensive and oral plus injectable hypoglycemics) within T1 and T2 individually were used as a measure of adherence to pharmacologic treatment. Total number of antihypertensive and antihyperglycemic medications as well as dose changes was recorded. Change in total number of medications during each follow up interval compared to baseline was coded as -3 to +3 (0 being no change in number of medications). Change of medications within the same class (e.g., ACE inhibitors) and replacement of one drug with another was not considered. Dose changes of individual medications was recorded categorically: none (0), increase (+1), and decrease (-1).

**Statistical Analysis**

Comparisons of sociodemographic characters of the final cohort to those lost to follow-up (Figure 1) were performed with χ² or t-tests. Primary outcomes were examined for treatment-related changes in outcomes at T1 and T2 using the generalized estimating equation (GEE) model, where the final model was adjusted for time and the potential covariates described above. OSA disease severity was treated as a categorical variable with 2 levels: mild (AHI or RDI 5-15) and moderate to severe (AHI or RDI > 15). Daytime sleepiness symptom was coded as a categorical variable (yes/no/missing). Multicollinearity amongst
the covariates was checked with variance inflation factor (VIF, < 5 accepted). In the stratified analyses (by type of treatment; CPAP vs. APAP and by race; European Americans vs. African Americans), similar adjusted GEE model was used with added variables of groups as defined above and time-group interaction terms. Adherence to OSA device treatment (CPAP or APAP) was treated as a continuous variable (average nightly use in hours and minutes). Due to significant missing data, adherence to OSA treatment was excluded as a covariate in the final GEE model. The effect of adherence to OSA treatment on individual outcomes was separately examined with general linear regression. All analyses were performed using SAS 9.2, and a p-value ≤ 0.05 was considered significant.

RESULTS

Cohort Lost to Follow-Up (Figure 1)
As total of 650 veterans were diagnosed with OSA, but only 302 were identified as receiving treatment (CPAP or APAP device) within 6 weeks of diagnosis. Veterans who did vs. did not receive treatment were not different by race (p = 0.81), marital status (p = 0.54), or age (p = 0.57).

Baseline Measurements (Table 1)
Ninety-four percent of participants had a diagnosis of hypertension, while 40% had type 2 diabetes. Approximately one-fourth had mild sleep apnea, and more than half reported no daytime sleepiness. A third of the subjects were treated with APAP long-term in the autoadjusting mode. Compared to those treated with CPAP, the APAP treated subjects had higher BMI (33.9 ± 6.3 vs. 35.9 ± 5.7, p = 0.02) and were more frequently ethnic minorities (28% vs. 68%, p < 0.0001). The preponderance of African Americans veterans among those treated with APAP reflects the practice patterns at the 2 study sites (i.e., the urban VAMC utilizes APAP more frequently). Due to this difference of treatment modality with regards to race, we examined the effect of race on baseline characteristics of the cohort. African Americans (AA) compared to European Americans (EA) and Hispanics/other were not different in OSA disease severity, self-reported sleepiness, or the prevalence of hypertension or diabetes at baseline. However, AA veterans were younger (59.5 ± 10.9 vs. 64.7 ± 10.5, p = 0.007), more obese (BMI 36.5 ± 5.9 vs. 33.9 ± 6.3, p = 0.004), and had lower adherence to pharmacologic treatment (MPR) for hypertension (0.96 ± 0.09 vs. 0.98 ± 0.03, p = 0.01) and diabetes (0.93 ± 0.13 vs. 0.97 ± 0.05, p = 0.05).

Effects of OSA Treatment (Table 2): Primary Outcomes
Both systolic and diastolic BP decreased significantly with initiation of OSA treatment at both T1 and T2. No significant change in fasting glucose or HbA1C was noted at either T1 or T2 after initiation of PAP treatment. Of the other factors (explanatory variables) considered in the model, age was significant with regard to BP outcomes. Specifically, increasing age was associated with a greater reduction in both systolic BP (p = 0.04) and diastolic BP (p < 0.0001). A second significant factor was change in dose of antihypertensive medications. An increase in dose of antihypertensive medications was related to less reduction in diastolic BP (p = 0.03; systolic not significant at p = 0.08), likely reflecting a response rather than a causal effect.

For glucose control measures, OSA treatment had no independent effect on fasting glucose or HbA1C. Of the other predictors considered for fasting glucose, a greater reduction in fasting glucose was seen in older veterans (p = 0.05). Medical comorbidity (measured by CCI) was the only significant predictor of HbA1C, where a higher number of diagnosed medical conditions was associated with an increase in HbA1C over time (p = 0.001).

Notably, large standard deviations were noted for reductions in both systolic and diastolic BP over time (5.94 to -3.67 at T1), indicating a heterogeneity of treatment effects (HTE) within the cohort. To examine potential explanatory variables for this HTE (Table 3), we examined changes in systolic and diastolic BP outcomes by type of treatment (CPAP vs. APAP) and by race (EA vs. AA). Systolic and diastolic BP improved in veterans with either CPAP or APAP. African Amer-

Table 1—Baseline characteristics of cohort (N = 221)

<table>
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<tr>
<th>Characteristic</th>
<th>Count</th>
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<td><strong>Demographics</strong></td>
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<tr>
<td>Age</td>
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<td>Body mass Index</td>
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<td>CCI</td>
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<td>Race</td>
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<tr>
<td>European American</td>
<td>135 (61%)</td>
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<tr>
<td>African American</td>
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<tr>
<td>Hypertension</td>
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<tr>
<td>Type 2 diabetes</td>
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<td><strong>OSA severity (AHI or RDI)</strong></td>
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<tr>
<td>Mild (≤ 15/h)</td>
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<td><strong>Daytime sleepiness</strong></td>
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<td><strong>Diagnosis</strong></td>
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<td>PSG</td>
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<td>PM</td>
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<td><strong>Treatment</strong></td>
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</tr>
<tr>
<td>APAP</td>
<td>75 (34%)</td>
<td></td>
</tr>
<tr>
<td><strong>Baseline BP</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline Systolic BP</td>
<td>138.75 (14.65)</td>
<td></td>
</tr>
<tr>
<td>Baseline Diastolic BP</td>
<td>77.76 (6.68)</td>
<td></td>
</tr>
<tr>
<td>Baseline HbA1C</td>
<td>7.04 (1.49)</td>
<td></td>
</tr>
<tr>
<td>MPR Hypertension</td>
<td>0.98 (0.06)</td>
<td></td>
</tr>
<tr>
<td>MPR Diabetes</td>
<td>0.95 (0.13)</td>
<td></td>
</tr>
</tbody>
</table>

Mean (SD), mean (standard deviation); AHI, apnea hypopnea index; RDI, respiratory disturbance index; PSG, polysomnography; PM, portable monitoring; CPAP, fixed continuous positive airway pressure; APAP, autoadjusting positive airway pressure; CCI, Charlson comorbidity index; MPR, medication possession ratio; BP, blood pressure; HbA1C, Glycosylated hemoglobin.
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noted significant reductions in both systolic and diastolic BP comparatively lower adherence to pharmacologic treatment, we of device (CPAP and APAP) used for treatment. Despite their of hypertension and diabetes control in a real-world setting. In veterans with type 2 diabetes on clinically utilized glucose homeostasis markers: fasting glucose and HbA1c.

We failed to discern any independent effects of OSA treatment in veterans with type 2 diabetes on clinically utilized glucose homeostasis markers: fasting glucose and HbA1c. Published evidence largely supports a causal association between OSA and elevated blood pressure,17,18 and OSA is recognized as a treatable cause of hypertension.19 Efficacy studies support modest beneficial effects of fixed-CPAP and APAP treatments on blood pressure.5,20 This effect may be more robust on 24-hour and nocturnal BP, which are better predictors of cardiovascular risk.21 Clinical trials and meta-analyses indicate that populations with higher levels of obesity (BMI) and severity of OSA with preexisting systemic hypertension, and those receiving antihypertensive pharmacologic therapy maybe more likely to benefit from CPAP treatment.25,26 The magnitude of systolic and diastolic BP reduction noted in this study is higher than has been previously reported with CPAP treatment.13,27 Studies that recruited participants without hypertension may have encountered floor effects. Other characteristics of this naturalistic cohort, which may explain these findings include; older men (mean age 61-63 years), with a high prevalence of moderate-severe OSA (60% to 80% with AHI/RDI > 15/h) and obesity, a large proportion with resistant hypertension28 (use of ≥ 3 antihypertensive medications; 59/209, 28%) and multiple cardiovascular comorbidities (more than half had at least one of the following: heart failure, atrial fibrillation, hypertensive heart disease). These population characteristics have individually been associated with higher therapeutic effects of CPAP on BP.4,20,29,30 Age and OSA interact as risk factors for hypertension31: the importance of age as an effect modifier of treatment response is illustrated in this study; that is, older men showed greater OSA treatment-related response in both systolic and diastolic BP. The effect size (Cohen’s d for repeated measures) when considered by type of treatment and race varied from small to large, indi-

**DISCUSSION**

This is the first study to our knowledge to examine the effectiveness of treatment of OSA on routine clinical measures of hypertension and diabetes control in a real-world setting. In this cohort of hypertensive men on drug therapy, we found OSA treatment was associated with improvement in diurnal office systolic and diastolic blood pressure up to 1 year after initiation of PAP treatment. The finding was not related to the type of device (CPAP and APAP) used for treatment. Despite their comparatively lower adherence to pharmacologic treatment, we noted significant reductions in both systolic and diastolic BP among African Americans, while among the European Americans, only systolic BP showed a statistically significant change.

As expected in a naturalistic dataset, we encountered missing data (39% at T1 and 54% at T2) with regards to OSA treatment adherence. Missing data for adherence to OSA treatment was not significantly different by age, race, OSA severity, or symptoms at T1. In the subset of the cohort where adherence to OSA treatment data was available, adherence was objectively assessed for each time interval (SmartCard reports extracted in average daily hours of use). The adherence was stable over time (T1; mean ± SD = 4.90 ± 1.59, T2; mean ± SD = 4.44 ± 1.57, p = 0.15). Adherence to OSA treatment did not correlate with adherence to pharmacologic treatment (MPR for hypertension; p = 0.77 or MPR for diabetes; p = 0.67). Examination of the effect of adherence to OSA treatment on primary outcomes at T1 with general linear regression showed results consistent with previous reports, i.e., adherence to OSA treatment was significantly associated with lower diastolic BP, HbA1C, and fasting glucose (Figures 2A-C).

**Table 2**—Changes in outcomes with OSA treatment at Time 1 and Time 2

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Difference T1-T0, Mean (CI)</th>
<th>p-value*</th>
<th>Difference T2-T0, Mean (CI)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP</td>
<td>-7.14 (-10.41, -4.47)</td>
<td>&lt; 0.0001</td>
<td>-6.81 (-9.94, -3.67)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>-3.14 (-4.99, -1.29)</td>
<td>0.0009</td>
<td>-3.69 (-5.53, -1.85)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>10.08 (-12.33, 32.49)</td>
<td>0.38</td>
<td>2.54 (-18.83, 23.92)</td>
<td>0.81</td>
</tr>
<tr>
<td>HbA1c</td>
<td>0.10 (-0.47, 0.68)</td>
<td>0.71</td>
<td>-0.08 (-0.67, 0.83)</td>
<td>0.83</td>
</tr>
</tbody>
</table>

Difference T1, change in outcome from T0 to T1; Difference T2, change in outcome from T0 to T2; T0, 3 months preceding OSA treatment; T1, 3-6 months after OSA treatment; T2, 9-12 months after OSA treatment; Mean (CI), mean (confidence interval); BP, blood pressure; HbA1c, glycosylated hemoglobin. *Adjusted p-value for covariates.

<table>
<thead>
<tr>
<th>Type of Treatment</th>
<th>Race</th>
<th>Outcomes</th>
<th>CPAP</th>
<th>APAP</th>
<th>EA</th>
<th>AA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Systolic BP</td>
<td>Mean (SE)</td>
<td>p-value*</td>
<td>Mean (SE)</td>
<td>p-value*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diastolic BP</td>
<td>Mean (SE)</td>
<td>p-value*</td>
<td>Mean (SE)</td>
<td>p-value*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Systolic BP</td>
<td>-7.14 (1.85)</td>
<td>0.0001</td>
<td>-8.21 (2.38)</td>
<td>0.0006</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diastolic BP</td>
<td>-2.45 (1.04)</td>
<td>0.02</td>
<td>-5.26 (1.77)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Change in outcome presented is from T0 to T1; T0, 3 months preceding OSA treatment; T1, 3-6 months after OSA treatment; Mean (SE), mean (standard error); CPAP, laboratory titrated fixed continuous positive airway pressure treatment; APAP, auto-adjusting positive airway pressure; EA, European Americans; AA, African Americans; BP, blood pressure. *Adjusted p-value for covariates.

ics exhibited significant reductions in both systolic and diastolic BP, while among the European Americans, only systolic BP showed statistically significant change.

**Adherence to OSA Treatment**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Type of Treatment</th>
<th>Race</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CPAP</td>
<td>EA</td>
</tr>
<tr>
<td></td>
<td>APAP</td>
<td>AA</td>
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<tr>
<td></td>
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</tbody>
</table>
cating that type of treatment and race may also be significant determinants of HTE. For systolic BP changes the effect size were; CPAP = 0.49, APAP = 0.56, European Americans = 0.39, and African Americans = 0.80. For changes in diastolic BP observed, the effect size were; CPAP = 0.28, APAP = 0.50, European Americans = 0.27, and African Americans = 0.67.

The duration of treatment effect of OSA on BP is unknown, with most studies examining outcomes at a few weeks. We noted a sustained response of BP in this cohort to OSA treatment up to 12 months of follow-up. These results are consistent with a recent randomized trial of CPAP in a population with coexistent OSA and systemic hypertension. Barbe et al., reported significant but comparatively modest therapeutic effects of CPAP on systolic (-1.89 mm Hg) and diastolic BP (-2.19 mm Hg). Less than half of the participants in this study were on any drug treatment and all were asymptomatic, while the average number of antihypertensive medications per subject in this cohort was 2.67, and 40% reported daytime sleepiness.

Small efficacy studies indicate the cardiovascular risk reduction with use of APAP devices for treatment may not be equivalent to fixed-CPAP treatment. Moreover, due to lack of data, the use of APAP therapy in populations with comorbid cardiorespiratory illnesses is not recommended. The current cohort included subjects with comorbid conditions—known chronic obstructive pulmonary disease (45/221; 20%), congestive heart failure (20/221; 9%), and stroke (12/221; 5%)—were included, a previously understudied group. Our results indicate reduction in systemic BP with both APAP and CPAP treatments. These data provide a rationale to prospectively test the effectiveness of APAP treatment for titration and long-term therapy in a broader population, particularly as this technology advances.

A third of this cohort was African American, a population that suffers a higher burden of hypertension and in whom treatment of OSA is recommended as adjunctive therapy. We found significant effects on both systolic and diastolic BP that are clinically highly significant. Such treatment-related effects, if prospectively confirmed in a similar population, would have a considerable impact on cardiovascular disease.

Our data do not support the effectiveness of OSA treatment in improving clinical glycemic control indices in type 2 diabetes. This may be related to sample size or inability to adequately control for adherence in this cohort. Despite the demonstrated independent detrimental effect of OSA on the full spectrum of abnormal glucose homeostasis, data from a single randomized sham-CPAP controlled trial of CPAP (mean CPAP adherence 3.6 h nightly) in subjects with OSA and diabetes are negative. In contrast, studies with a less robust design in a similar population demonstrate a therapeutic effect of CPAP on HbA1C at 3-4 months post-treatment, suggesting an important modification of effects of CPAP on glucose homeostasis by level of adherence.

The impact of OSA treatment adherence on intermediate cardiovascular risk markers noted in this study is consistent with published reports. Nevertheless, sizable missing data on device treatment adherence limit conclusions in this study. Prospective examination of the effect modification of OSA treatment adherence on systemic BP and glucose metabolism by objective and unobtrusive measurement is crucial. A second limitation of this study pertains to selection bias (Figure 1), where the final cohort assessed for OSA treatment effects is about half of all eligible veterans. The veterans who did not follow-up at the study sites were not different with regard to available sociodemographic data, i.e. race, age, or marital status. However, there are other potential uncontrolled sources of bias that limit our results. In addition, the retrospective design imposed a burden of attrition of sample size due to missing data for key variables.

CONCLUSIONS

OSA treatment lowers blood pressure in a clinical population of men with hypertension. This study extends the known effi-
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cacy to real-world effectiveness of OSA management on hypertension. Prospective effectiveness research examining changes in cardiovascular outcomes with treatment interventions for OSA is necessary to confirm these findings, to identify traits associated with a positive therapeutic response, and to inform clinical practice.

REFERENCES


ACKNOWLEDGMENTS

The authors thank Dr. Samuel Kuna for his review and valuable advice during the preparation of this manuscript. Work for this study was performed at Center for Management of Complex Chronic Care, Hines, Edward J Hines Jr. VAMC and University of Illinois at Chicago. Funding was provided by Center for Management of Complex Chronic Care, Edward Hines Jr. VA Hospital

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication February, 2012
Submitted in final revised form April, 2012
Accepted for publication May, 2012
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DISCLOSURE STATEMENT

Disclaimer: The findings of this research do not reflect the policy of the Department of Veterans Affairs. This was not an industry supported study. Dr. Terri Weaver has received equipment for research from Philips Respironics, Inc., grant support from Cephalon, Inc., and remuneration for consultation from Apnex Medical, Inc. She also has FOSQ license agreements with Nova Som, Apex Medical, Inc., GlaxoSmithKline, Philips Respironics, Inc., Cephalon, Inc., and Innovaderm Research, Inc. The other authors have indicated no financial conflicts of interest.
untreated obstructive sleep apnea/hypopnea syndrome (OSAHS) significantly affects quality of life and cardio-vascular/cerebrovascular morbidities and mortality. CPAP therapy has been shown to be effective in treating sleep disordered breathing (SDB) by reducing the apnea/hypopnea index (AHI) and by reducing excessive daytime somnolence (EDS). Despite this, CPAP acceptance and adherence are disappointingly low. A significant number of patients (ranging from 30% to 80% in various studies) demonstrate an average CPAP usage of less than 4 hours per night. Several reviews have emphasized the need to identify patients who are at the greatest risk for non-adherence, with the goal of developing techniques to maximize overall adherence. Studies have suggested that CPAP adherence can be correlated to characteristics of patients at baseline, such as the severity of OSAHS, the level of EDS, and anatomical factors (smaller nasal cross-sectional area, reduced nasal volume, and high nasal resistance), but the strength of these correlations has been weak. However, it has been shown that patients whose sleep efficiency on the CPAP titration night improved most had the greatest CPAP compliance at 47 days. More recently, studies using social cognitive theory and health behavior models demonstrate that psychological factors (e.g., outcome expectations, self-efficacy, risk perception) significantly influence CPAP adherence. Interventions such as education (centered around OSAHS, CPAP treatment, and machine management), supportive phone calls, group sessions, and frequent office visits, as well as technologies aimed at reducing pressure intolerance (auto-titrating devices, bilevel CPAP, and expiratory pressure reduction), have all been
inconsistent in improving long-term adherence. Nevertheless, the consistent observation has been that early adherence and acceptance of CPAP has a relatively significant predictive value for long-term adherence.2,3,29,30

The purpose of the present study was to evaluate the utility of measures of sleep architecture and continuity on the CPAP titration study as predictors of both short-term and long-term CPAP adherence. In addition to traditional metrics of sleep such as total sleep time, sleep efficiency, and time in sleep stages and wake, we also examined sleep continuity using survival (of sleep) analysis, which has been shown to be useful in characterizing sleep in OSAHS.31 These data were collected as part of a larger research study examining the relationship of SDB to daytime function, in which patients with OSAHS underwent standardized evaluation and management of their SDB, objective monitoring of CPAP adherence, and evaluation of daytime outcomes.

Journal of Clinical Sleep Medicine, Vol. 8, No. 5, 2012

METHODS

For the present study, 106 patients (72 male/34 female; > 18 years of age) were prospectively recruited from all patients seen at the NYU Sleep Disorders Center between 2006 and 2009 who presented with complaints of EDS and/or snoring and were all eligible for a clinical trial of CPAP based on usual medical criteria. All patients had a primary diagnosis of OSAHS or upper airway resistance syndrome. In 99 patients, the respiratory disturbance index (RDI; see definition in data analysis) was > 10/h from an in-laboratory full-night diagnostic nocturnal polysomnography (NPSG). In 7 patients, RDI was < 10/h, but these patients had long periods of inspiratory flow limitation and snoring, EDS, or REM-related or supine RDI > 15/h, and were prescribed a therapeutic CPAP trial. We excluded subjects who were pregnant, had medically unstable conditions, congestive heart failure, change in medications during the trial, recent or confirmed history of alcohol or recreational drug abuse, inability to provide informed consent, or inability to perform the psychomotor vigilance test (PVT). Ninety-three (61 male/32 female) of 106 recruited patients completed the initial recruitment protocol that included the CPAP titration study and objective evaluation of CPAP adherence. Six patients did not return for the CPAP titration study; CPAP adherence data were not available in 3 patients due to technical problems with the CPAP machine; 3 patients withdrew from the study after their CPAP titration; one patient was removed from the protocol due to the patient’s inability to follow instructions. This protocol was approved by NYU School of Medicine Institutional Review Board, and all patients signed informed consent.

Protocol Summary

The study was divided into 3 phases: diagnostic evaluation, titration, and follow-up. First, all patients underwent a full clinical evaluation for sleep disorders, which included a sleep-specific interview and a physical exam performed by a sleep physician at the NYU Sleep Disorders Center. Following this, all patients underwent a full in-laboratory diagnostic NPSG, including objective and subjective assessment of sleepiness and a separate standard in-laboratory CPAP titration study. On the morning after CPAP titration, patients filled out a questionnaire assessing their subjective response to the CPAP therapy. Patients were then given a custom CPAP machine (Fisher & Paykel HealthCare, NZ) to use at home with enhanced adherence monitoring capability (see below). A follow-up NPSG at therapeutic CPAP and concurrent daytime testing were repeated at the end of an average of 9 weeks of CPAP use (range 6 weeks- 3 months). Adherence to CPAP use in the home was assessed using data from the CPAP machine download over 2 distinct 14-day periods. The short-term (ST) adherence was evaluated in the 14-day period immediately following dispensing the CPAP machine; 6 subjects did not return for the CPAP titration study; one patient was removed from the protocol due to the patient’s inability to follow instructions. This protocol was approved by NYU School of Medicine Institutional Review Board, and all patients signed informed consent.

Procedures

In-Laboratory Polysomnography (NPSG)

All in-laboratory NPSGs were performed according to AASM guidelines and included full sleep and respiratory mon-
tages. During the Diagnostic NPSG, respiratory airflow was assessed with a nasal cannula connected to a pressure transducer (Protech PTAF2) and an oral thermistor, whereas during CPAP titration NPSG respiratory airflow was assessed from the CPAP analog output.

The CPAP titration study was performed manually by an experienced sleep technician according to AASM guidelines during a separate full-night NPSG. Pressure was raised until all SDB events (including obstructive apneas, hypopneas, and runs of inspiratory flow limitation) were eliminated. A single optimal pressure was identified for each patient following review of the study by a physician. Per protocol, patients were educated about the function, purpose, and maintenance of CPAP and given a custom CPAP machine (Fisher & Paykel Healthcare) that was capable of continuously recording theraw signals of delivered airflow and pressure at 50 Hz on a portable USB memory card for prolonged periods. This machine provided heated humidification but did not provide bilevel pressure, expiratory pressure relief, or a pressure ramp. Using this CPAP machine, data were collected and downloaded, after which the raw tracings could be visualized and manually scored for respiratory events. The device could also be programmed to change pressure at a predetermined date and time. All patients had a scheduled return visit with the research coordinator after 2 weeks on CPAP, during which time CPAP use was reviewed and problems with the equipment or mask fitting were addressed. Patients then used the CPAP machine set at their fixed therapeutic pressure for the remainder of the study. Follow-up thereafter consisted of a phone call once a month by the research coordinator to discuss CPAP use and schedule additional visits. Patients were encouraged to call the research coordinator at any time during the study period if they experienced problems with therapy.

In 74 patients, the CPAP device was programmed to deliver CPAP in a sequence that began with an initial period of 2 nights at the prescribed therapeutic pressure. This was followed by multiple nights at fixed pressures covering a total range of 2–3 cm H2O above and below the prescribed therapeutic pressure. Pressures were changed every 2 days over 2 weeks in a sequence that alternated increases or decreases of pressure with a return to prescribed therapeutic pressure. In 12 patients, the initially prescribed pressure was low, and hence pressures below therapeutic were not tested. Data files containing the CPAP pressure and airflow were downloaded and reviewed. From these, we confirmed or modified the prescription of CPAP based on the efficacy of each pressure to obtain an optimal setting, which was used thereafter. ST adherence was evaluated over the entire 2-week period (during which time pressures were varying). In 19 patients, only one pressure (optimal determined by physician) was used for the entire 2-week period due to unavailability of the CPAP device with programming capabilities. CPAP adherence was defined as the total time that airflow was observed visually at the prescribed pressure.

In a minority of patients (n = 14), side effects such as improper fitting of mask, dryness requiring humidification, or travel preventing CPAP use needed to be addressed, and collection of ST data was initiated only after these complaints were addressed. Despite the fact that pressure fluctuated around the optimal pressure, “ST adherence” was defined as the average hours of use from all nights, regardless of pressure, including nights in which the patient chose to not use CPAP. In order to evaluate the effect of varying CPAP pressure across nights in a patient (in those subjected to these changes), we also calculated the hours of use at each separate pressure. Figure 2 plots hours of use against the deviation from the optimal pressure and shows there was no trend for an effect of pressure on CPAP adherence. This allowed us to pool these data, providing a single value per subject over all pressures to define ST adherence. After ST data collection, patients were switched to a commercial CPAP generator (with conventional adherence monitoring) set to the therapeutic CPAP pressure, and no further changes were made in CPAP pressure delivered.

LT adherence was obtained in only 56 patients due to the design of the parent study, which was intended to evaluate for follow-up only those patients who showed adequate ST CPAP use. Patients without LT adherence data collected include one patient who withdrew from the study, 2 patients who underwent bariatric surgery and 34 patients who were excluded because they showed zero hours of use (13 patients) or < 2 h average use per night (21 patients) on the ST adherence monitoring. Towards the end of the study enrollment period, these criteria were relaxed, and 4 patients with ST adherence < 2 h average per night were restudied at LT. All statistical tests were run with and without these 4 patients included, with no effect on the results. All of the LT data reported in the results section includes the 4 patients.

Measurement of Sleepiness

Subjective assessment of sleepiness consisted of the Epworth Sleepiness Scale (ESS), and the Functional Outcomes of Sleep Questionnaire (FOSQ). Objective tests consisted of a 20-min psychomotor vigilance task (PVT) and the multiple sleep latency test (MSLT). The objective tests were administered 4
times across the day at 2-h intervals beginning at 09:00. Average PVT lapses (transformed as √lapses + √(lapses + 1) and mean sleep latency were calculated as the average from the 4 tests.

Data Analysis

Sleep stages, arousals, periodic leg movements, and respiratory events (apneas, hypopneas, respiratory effort-related arousals [RERAs]) were scored by a single technician (in order to minimize interscorer variability) using American Academy of Sleep Medicine guidelines. In particular, hypopnea was defined by the “preferred” AASM definition: airflow reduction > 30% of baseline and associated with a 4% drop in oxygen saturation. AHI4% was defined as the sum of apneas and hypopneas divided by the total sleep time (TST). RDI was defined as the sum of apneas, hypopneas, and RERAs divided by the TST. Summary data included conventional methods for quantifying the quality of sleep (e.g., TST, sleep efficiency, time and %TST spent in sleep stages and wake). We also evaluated sleep continuity using the survival analysis technique described by Nor- man et al. and calculated the average run length of continuous sleep defined as the time (in minutes) between the first occurrence of stage 1 and the return to stage wake or stage 1 (if stage N2 sleep was observed).

Comparisons between diagnostic, titration, and follow-up NPSG parameters were made using paired t-tests. ST and LT adherence were compared by Pearson correlation analysis. Significance of this relationship was tested at the 0.05 level, as it was the primary predetermined variable of the study.

For other continuous variables, we examined the relationship between each variable and ST adherence, and similarly each variable and LT adherence, using Pearson correlation coefficients. In addition, the 93 patients who underwent ST assessment were divided into 3 groups as per usual clinical practice based on the average ST hours of CPAP use (< 2 h, 2-4 h, > 4 h) and compared using ANOVA. Data are presented as mean ± standard deviation and data analyses were conducted using SPSS 17. The patients who underwent LT adherence assessment were divided into 2 groups (< 4 h and > 4 h), as there were only 4 patients with LT adherence < 2 h, and differences between groups were examined using independent sample t-tests. We applied χ2 tests to compare frequencies and proportions. For all comparisons (other than between ST and LT adherence), we used a significance level of < 0.005 due to the large number of variables examined. The term “trend” is used when the p values were between 0.05 and 0.005.

The total data set (n = 93) consisted of 61 male and 32 female patients, with body mass index (BMI mean ± SD): 35.7 ± 9.6 kg/m², age: 47.9 ± 11.7 years (range = 56). Racial breakdown was as follows: 40% of patients were White, 27% Black, 7% Asian, and 26% not reported/other. Ethnicity was 19% Hispanic.

RESULTS

Table 1 shows summary data for the entire group for SDB indices and sleep architecture variables obtained from the diagnostic, CPAP titration (before short-term compliance assessment) and final follow-up (after long-term compliance assessment) laboratory NPSG on therapeutic CPAP. As expected, SDB and sleep architecture variables improved significantly from the baseline diagnostic NPSG to the CPAP titration NPSG. In addition, from the CPAP titration NPSG to the final CPAP NPSG, AHI4% and RDI decreased and changes were observed in %N2 and %N3 sleep. We did not analyze TST or change in TST among the 3 NPSGs, as this variable is confounded by the design of our protocol: on the CPAP titration NPSG patients were allowed to leave as early as 07:00 (at their discretion), whereas on the diagnostic and final follow-up CPAP NPSG, they were encouraged to sleep ad libitum because they were.
expected to remain in the laboratory for daytime testing. Thus, any prolongation of TST on the final NPSG could have reflected the longer time in bed than the CPAP titration night.

Table 2 and Figure 3A show average ST CPAP adherence data in the 93 patients. The average ST adherence was 3.2 ± 2.3 h (range = 8.6 h). Thirteen of these patients had zero hours of short-term use. Average ST adherence excluding these 13 patients was 3.9 ± 1.1 h/night. The number of days on which CPAP was used (> 0 h) was correlated (r = 0.73, p < 0.001) to the average hours of use per day, supporting the use of the latter as our metric of adherence. Subjects with poor (< 2 h), moderate (2-4 h), or adequate (> 4 h) CPAP usage did not differ in age, BMI, gender, race, or level of therapeutic CPAP.

Table 2 and Figure 3B also show average LT CPAP adherence in the 56 patients who completed this part of the protocol. The average LT adherence was 4.8 ± 2.1 h (range = 8.6 h). For these same 56 patients, the ST adherence...
had been 4.4 ± 1.8 hours. Subjects with moderate (< 4 h) and adequate (> 4 h) CPAP usage did not differ in age, BMI, or gender.

Table 3A shows data from the initial diagnostic NPSG and the concurrent daytime assessments. Groups of poor, moderate, and adequate ST users did not show statistically significant differences in SDB, sleep architecture, or daytime outcome variables. Moderate and adequate LT CPAP users are compared in Table 3B. Although no statistically significant differences (assessed at p < 0.005) were seen for SDB, sleep architecture, or daytime outcome variable, an interesting trend (p = 0.03) suggests that poor LT adherence was associated with shorter TST and lower RDI (p = 0.04) on the diagnostic laboratory NPSG.

Tables 4A and 4B show data from the titration NPSG for poor, moderate, and adequate CPAP user groups in the short-term, and moderate and adequate user groups in the long-term, respectively. These data show there was no difference between the groups in TST on the titration NPSG, despite the differences in their home usage, suggesting that under supervision all patients were able to use CPAP therapy similarly, and that this did not clearly reflect variation in their usage in the home. However,
there was a statistically significant difference observed between the adherence groups for %time in stage N2 sleep (p = 0.002) on the titration NPSG. There was also a trend for adequate CPAP users to have a higher %time in REM sleep (p = 0.008) on the titration NPSG.

Table 4B shows the same titration NPSG data broken down when the patients were grouped by their long-term CPAP usage. Differences between LT adherent groups in %Stage N2 (p = 0.005) and in %REM sleep (p = 0.003) on the titration NPSG are still evident. Sleep continuity (mean duration to arousal) on the titration NPSG was greater in the adequate LT adherence group than the moderate adherence group, but this did not reach statistical significance (p = 0.061). All results were unchanged when the ST adherence data were analyzed combining poor and moderate ST adherence groups (n = 54) compared to subjects with adequate CPAP use (n = 39).

Thirty-six of the 93 subjects were on medications that could have affected sleep architecture (SSRIs, β-blockers, anti-psychotic agents, and anti-epileptic agents), particularly the duration of REM sleep. However, we found no difference between the 3 ST adherence groups, in the number of subjects who were on medications (46%, 36%, and 36%, respectively, p = 0.45). Interestingly, and contrary to our expectation, we also found no significant differences in any sleep variables between the subjects with or without medications on the diagnostic and titration NPSGs (data in supplement Tables S2A and S2B). The only medication-related significant finding in our data was that those subjects on medication had a worse FOSQ score than those without medications. Despite our inability to show a difference in sleep architecture related to medication use, we did re-analyze our data excluding the 36 subjects who were on medications; for the remaining 57 subjects we showed the same findings (or trends) in sleep percentages between ST adherence groups (lower %N2 and trend for higher %REM, higher sleep efficiency and sleep continuity on the CPAP titration night in
Figure 4

(A) The graph shows the ST adherence grouped by subject responses to the question “How would you rate your sleep after using CPAP?” the morning after the titration study. No significant differences were seen between groups. (B) The graph shows the ST adherence grouped by subject responses to the question “How would you rate your CPAP treatment?” the morning after the titration study. No significant differences were seen between groups. (C) The graph shows the ST adherence grouped by subject responses to the question “Would you like to continue to use CPAP therapy at home?” The group that answered “yes” had a significantly (p < 0.001) higher CPAP adherence that the group who answered “No/Not Sure.” The graphs shows the mean and SD of ST CPAP adherence in each group.

Figure 5

Graph shows short-term CPAP adherence (x-axis) plotted against long-term adherence (y-axis) (r = 0.81, p < 0.001). Each data point represents one subject.

the adequate users compared to the poor CPAP users data in supplement Tables S3A and S3B).

Figure 4 examines the impact of subjective patient assessment of satisfaction with CPAP on the morning after the CPAP titration on ST CPAP adherence in the 85/93 patients who filled out the morning questionnaire. ST CPAP adherence was not different when patients were separated into groups by their answers to 2 questions “How would you rate your sleep after using CPAP?” and “How would you rate your CPAP treatment?” However, answering “yes” to “Would you like to continue to use CPAP therapy at home?” was associated with higher ST CPAP adherence (4.0 ± 2.1 h/night vs. 2.1 ± 2.2 h/night, p < 0.001). When subjects were grouped based on response to this question (Tables S4A and S4B in supplement) no differences were observed in demographics or on the diagnostic NPSG. Those subjects who reported willingness to use CPAP also had significantly longer TST, greater %REM, and better sleep efficiency on the CPAP titration NPSG. Figure 5 shows that the better short-term CPAP users tended to continue on to become better long-term users; i.e., there was a significant correlation between ST and LT home CPAP adherence (r = 0.81, p < 0.001). Because this correlation was performed including subjects with zero CPAP usage, we repeated the analysis with these subjects excluded and were still able to show a significant relationship (r = 0.61, p = 0.05; not shown on figure).

In order to assess the relationship between CPAP adherence and the change in sleep parameters from diagnostic to titration NPSG (Δ = titration NPSG value minus diagnostic NPSG value), we examined these for each CPAP adherence group. In the ST data, no Δvariable was significantly different between groups, although ΔSleep_Efficiency showed a trend (−6.2% ±
16.4% for < 2-h adherence, +2.5% ± 16.4% for 2- to 4-h adherence, +2.1% ± 11.7% for > 4-h adherence, p = 0.045). In the LT data, only Δ%REM (+1.5% ± 10.0% for < 4 h, +10.4% ± 9.8% for > 4 h, p = 0.002) was significantly different between groups, with the adequate users showing a bigger change in %REM between diagnostic and titration NPSG.

We also examined the strength of a linear regression model predicting ST and LT adherence from all sleep and SDB variables obtained on the titration NPSG. We found that the %N2 sleep on the titration NPSG had a significant correlation to both ST adherence (r = 0.32, p = 0.002) and LT adherence (r = 0.38, p = 0.001), and addition of other variables did not improve the fit beyond that of a model with %N2 alone. We further examined models using the Δ in sleep variables between titration and diagnostic NPSGs. No significant models could be found that adequately predicted ST adherence. A model combining ΔSleep_Continuity (r = 0.29) and ΔSleep_Efficiency (r = 0.23) predicted LT adherence (r² = 0.17, p = 0.006), although it did not satisfy the null-hypothesis α limit of 0.005 for significance.

## DISCUSSION

Our data confirm that there is a significant relationship between short-term and long-term CPAP adherence, and that short-term CPAP use observed in the first two weeks at home is largely predictive of long-term adherence. Importantly, we were able to demonstrate a new finding: variables addressing aspects of sleep architecture (%N2 and %REM) on the titration NPSG were correlated to short-term and long-term CPAP home use. Sleep continuity on the titration NPSG did not correlate with either ST or LT adherence. However, in subjects with LT adherence data, a regression model combining change in sleep continuity and change in sleep efficiency between the diagnostic and titration nights was predictive of LT adherence (r² = 0.17, p = 0.006). These findings are in accord with and supplement published findings, which demonstrate that characteristics of sleep, even on the CPAP titration NPSG, can help predict long-term adherence.

Despite observing the expected improvement in SDB and all sleep parameters on CPAP, the overall mean ST adherence was 3.2 h and the LT adherence (which excluded most of the patients with ST adherence < 2 h) was 4.8 hours. Although these values are slightly lower than average adherence in some studies, they are in the same range as most studies reporting CPAP adherence.

The only differences we found between adequate and poor ST CPAP adherents was that the good users had lower %N2 sleep and higher %REM sleep on the titration laboratory NPSG. At the present time there is no consensus as to the underlying purpose of sleep, and thus it is difficult to define “better” sleep quality without assessing a behavioral outcome. In the sleep literature it is often assumed that increases in %REM and %N3 sleep, even within the normal range, may suggest “better” sleep. Both REM disruption and a reduction in %REM and %N3 sleep are generally seen in diseases that reduce the well-being of a subject through sleep-disrupting mechanisms, with corresponding increases in other stages of sleep. This pattern has been invoked as a measure of poor sleep quality in aging and insomnia literature, and also when describing the “first-night” effect in the laboratory. Furthermore in CPAP-treated OSA, increases in %REM and/or %N3 sleep are generally interpreted as indicating a beneficial effect of CPAP on sleep. The effect of CPAP on %REM sleep was seen in our own data (Table 1 comparing CPAP NPSGs to the diagnostic NPSG). The average %REM sleep on the titration CPAP night was within the normal range, but was highest in the subjects with the highest ST CPAP adherence. We interpret this as consistent with the idea that these particular subjects may have had better sleep on CPAP than those who eventually showed lower CPAP adherence.

With the above assumptions about sleep quality, our data suggest “better sleep” on the titration night is related to better home CPAP adherence, but this observation is consistent with at least two interpretations: (1) Subjects with a “better” first night on CPAP may be more likely to continue using CPAP because of the good quality of their first exposure to CPAP (or, stated conversely, poor initial sleep caused by CPAP discomfort during early use limits CPAP adherence). Alternatively, (2) Subjects with better sleep pre-CPAP may be less susceptible to the discomfort of CPAP use (or, stated conversely, preexisting poor sleep limits CPAP adherence). Because we cannot separate the impact of CPAP on quality of sleep from CPAP’s effect on the underlying SDB, our data do not allow us to distinguish between these two possible explanations. Only knowing the patients’ quality of sleep prior to their having SDB would directly address this issue.

Our findings are in agreement with the Drake et al., who reported that a patient’s initial experience with CPAP (and the degree of improvement in sleep efficiency on the titration) was a significant predictor of future CPAP adherence. Lewis et al., also showed that those patients who reported problems on the first night of CPAP showed worse CPAP adherence. In support of the hypothesis that better sleep on the titration night predicts better adherence, Colleen et al., and Lettieri et al., showed that use of a sedative hypnotic on the titration study night was associated with longer TST and higher sleep efficiency on that night and was also a significant predictor of higher short-term CPAP adherence. These authors suggest that “medication use may improve the patients’ overall experience in the sleep laboratory setting.”

Previous studies have produced conflicting data about the relationship of age, gender, degree of sleepiness, and severity of SDB with short or long-term CPAP use. Our data, which include subjects with a wide range of SDB severity and sleepiness as well as wide ranging racial and gender distribution, are in agreement with studies that showed no relationship between these demographic variables and short-term or long-term CPAP use. In our dataset with 27% Black subjects, we failed to show a difference in ST CPAP adherence based on race (Black subjects: 3.2 ± 2.0 h/night vs White subjects: 3.2 ± 2.4 h/night, p = 0.99). Other studies have showed significantly reduced CPAP adherence in black subjects, although most of these studies did not report socioeconomic status, which has been shown to be an independent predictor of CPAP adherence regardless of race.

In our dataset, patients who stated that they would not or were not sure they would use CPAP following their titration night had significantly lower ST adherence: adherence in these subjects was almost 50% less than in those who stated that they would use CPAP (2.1 vs. 4.0 h/night). Of note, these same patients had significantly lower TST and sleep efficien-
cy on the titration laboratory NPSG (sleep efficiency 71% ± 14% for “no/not sure” vs. 83% ± 13% for “yes,” p < 0.001). These data show that the initial subjective, as well as objective, experience with CPAP (positive or negative) is associated with subsequent adherence. The questionnaire responses may be related to the domain of self-efficacy and our finding is in keeping with some recent studies examining psychological factors that include patient’s beliefs and perceptions of OSA and CPAP (risk perception, outcome expectancies, and self-efficacy) that have been shown to explain up to 25% of the variance in CPAP adherence. However, we are not able to distinguish whether poor sleep while on CPAP caused poor adherence or a patient’s preconception against CPAP caused both poor sleep on the titration night and poor adherence. One potential implication of the relationship between sleep quality on the CPAP titration night and CPAP adherence is that home CPAP titration might produce “better” sleep and therefore enhance CPAP adherence. However, there are conflicting results regarding whether CPAP adherence is higher or lower when home titration is performed compared to in-laboratory titration,50–52 and the present data do not allow us to address this issue directly.

The strengths of our study are that data were obtained in a group of subjects with a wide range of severity of SDB, with objective monitoring of both the efficacy of the pressure and of usage. All subjects were given comprehensive education about their need for CPAP and were encouraged to use it with intense usage. All subjects were given comprehensive education about objective monitoring of both the efficacy of the pressure and of usage. The questionnaire responses may be related to the domain of self-efficacy and our finding is in keeping with some recent studies examining psychological factors that include patient’s beliefs and perceptions of OSA and CPAP (risk perception, outcome expectancies, and self-efficacy) that have been shown to explain up to 25% of the variance in CPAP adherence. However, we are not able to distinguish whether poor sleep while on CPAP caused poor adherence or a patient’s preconception against CPAP caused both poor sleep on the titration night and poor adherence. One potential implication of the relationship between sleep quality on the CPAP titration night and CPAP adherence is that home CPAP titration might produce “better” sleep and therefore enhance CPAP adherence. However, there are conflicting results regarding whether CPAP adherence is higher or lower when home titration is performed compared to in-laboratory titration,50–52 and the present data do not allow us to address this issue directly.

Second, LT data were not collected in all patients due to the study design of the parent protocol. However, there were no differences in demographic or diagnostic NPSG data between those subjects who did not have LT data and those who were studied long term (see supplemental data Table S1A and S1B). On the titration night, there was also a trend to worse sleep (more %N2 and less %REM) in those who did not complete the LT data collection; this would be consistent with our adherence result if all of these ST dropout subjects went on to be poor LT users (as opposed to just not being restudied).

Although we show a statistically significant correlation of adherence to sleep variables on the titration NPSG, the proportion of explained variance of this finding is small (5% to 15%). Thus, adherence to CPAP appears to be driven primarily by additional factors beyond those seen on the PSG. This is in accord with work on adherence to other medical therapies, suggesting that physiological disease may be less important in determining adherence to therapy than psychosocial factors.56 It is difficult to say from our data whether good sleepers become good CPAP users or whether initial CPAP tolerance and good sleep on the titration night promotes LT adherence. If therapeutic interventions to improve adherence are to be considered, separating these causal pathways to CPAP adherence has implications beyond making a prediction of LT adherence. In the second scenario, an intervention could be targeted at improving sleep during the titration night (e.g., giving sedatives or anxiolytics), whereas in the former, the goal would be to improve sleep independent from the CPAP intervention (e.g., by treating insomnia itself, as by using CBT prior to a CPAP trial or to rescue poor CPAP users). In either case, the close correlation between ST and LT adherence and the difficulty in predicting who will be poorly compliant before the first exposure to CPAP suggests that improvements to CPAP adherence are most likely to come from interventions before, rather than after a patient identifies him/herself as poorly adherent. This, of course, does not apply to interventions aimed at specific conditions related to CPAP discomfort that appear when therapy is initiated (e.g., mask fit, nasal congestion), but, by the above reasoning, the data we and others have collected suggest that interventions after the first exposure to CPAP may not be the only method to impact on LT CPAP adherence.

**ABBREVIATIONS**

OSAHS, obstructive sleep apnea hypopnea syndrome  
SDB, sleep disordered breathing  
AHI, apnea hypopnea index  
EDS, excessive daytime somnolence  
CPAP, continuous positive airway pressure  
NPSG, nocturnal polysomnogram  
RDI, respiratory disturbance index  
AI, apnea index  
N1, sleep stage N1  
N2, sleep stage N2  
N3, sleep stage N3  
WASO, wake after sleep onset  
ESS, Epworth Sleepiness Scale  
FOSQ, Functional Outcomes of Sleep Questionnaire  
PVT, psychomotor vigilance test
MSLT, multiple sleep latency test
TST, total sleep time
ST, short-term
LT, long-term
BMI, body mass index

REFERENCES


Sleep Quality, Short Term and Long Term CPAP

ACKNOWLEDGMENTS

The authors acknowledge the technical assistance of Rakhil Kanevskaya and Ming Chen. Support for this study was provided by NIH grants R01HL81310, 1 UL1RR029893, and grants from the Foundation for Research in Sleep Disorders.

DISCLOSURE STATEMENT

This was not an industry supported study. Dr. Norman holds multiple US and foreign patents covering techniques and analysis algorithms for the diagnosis of OSAHS and techniques for administering CPAP. Several of these have been licensed to Biologics, Fisher & Paykel Healthcare, Advanced Brain Monitoring and Tyco (Health C’Aire). Dr. Rapoport has received support for research from Fisher & Paykel Healthcare, Ventus Medical; speaking and consulting engagements for Fisher & Paykel Healthcare. He holds multiple US and foreign patents covering techniques and analysis algorithms for the diagnosis of OSAHS and techniques for administering CPAP. Several of these have been licensed to Biologics, Fisher & Paykel Healthcare, Advanced Brain Monitoring and Tyco (Health C’Aire). Dr. Indu Ayappa has received support for research Fisher & Paykel Healthcare and Ventus Medical. She holds multiple US and foreign patents covering techniques and analysis algorithms for the diagnosis of OSAHS and techniques for administering CPAP. Several of these have been licensed to Fisher & Paykel Healthcare and Advanced Brain Monitoring. The other authors have indicated no financial conflicts of interest.
Background: Obstructive sleep apnea (OSA) is prevalent in the surgical population, and it has been suggested that preoperative patients should be screened and treated for OSA. However, it remains unclear whether patients diagnosed with OSA in the preoperative period adhere to prescribed CPAP therapy.

Objective: Our aim was to objectively quantify CPAP adherence, investigate predictors of poor CPAP adherence, and to establish an optimal CPAP setting in a cohort of presurgical patients diagnosed with OSA as part of the preoperative work-up.

Methods: In a retrospective observational study, we collected data on all adult presurgical patients seen by the Anesthesia Perioperative Medicine Clinic (APMC) who screened positive for OSA on the STOP-Bang questionnaire and underwent an in-laboratory diagnostic polysomnogram (PSG) before surgery. CPAP was offered to patients with moderate or severe OSA. Objective CPAP adherence was recorded during the perioperative period. Factors associated with reduced CPAP adherence were delineated. Patient characteristics were compared between those with STOP-Bang scores of 3-4 and those with higher scores (STOP-Bang score ≥ 5).

Results: During a 2-year period, 431 patients were referred and 211 patients completed a PSG. CPAP therapy was required in 65% of patients, and the optimal level was 9 ± 2 cm H2O. Objective CPAP adherence was available in 75% of patients who received CPAP therapy; median adherence was 2.5 h per night, without any significant difference between the STOP-Bang subgroups. African American race, male gender, and depressive symptomatology were independent predictors of reduced CPAP adherence. Severe OSA was significantly more prevalent in patients with a STOP-Bang score ≥ 5 than those whose score was 3-4 (55.1% versus 34.4%, p = 0.005). However, optimum CPAP pressure levels and adherence to therapy did not differ between the 2 STOP-Bang groups.

Conclusions: Adherence to prescribed CPAP therapy during the perioperative period was extremely low. African American race, male gender, and depressive symptoms were independently associated with reduced CPAP usage. Further research is needed to identify and overcome barriers to CPAP acceptance and adherence in the perioperative setting.

Keywords: Obstructive sleep apnea, continuous positive airway pressure, CPAP, adherence, compliance, perioperative, STOP-Bang

Citation: Guralnick AS; Pant M; Minhaj M; Sweitzer BJ; Mokhlesi B. CPAP adherence in patients with newly diagnosed obstructive sleep apnea prior to elective surgery. J Clin Sleep Med 2012;8(5):501-506.
METHODS

Between March 2009 and February 2011, adult presurgical patients who were identified at high risk for OSA by the STOP-Bang screening survey administered during their visit to the Anesthesia Perioperative Medicine Clinic (APMC) were recommended to undergo a diagnostic in-laboratory PSG prior to elective surgery. Patients with prior diagnosis of OSA were excluded from our cohort. The STOP-Bang surveys were completed by the patients; APMC medical assistants measured the neck circumference, weight, and height, and the body mass index (BMI) was calculated by the preoperative computerized program used by the APMC. A request for an expedited in-laboratory PSG was submitted by the APMC staff to the sleep laboratory, and an appointment for the PSG was made within 3 days of the initial APMC visit as long as the patient was willing to undergo the PSG. In order to avoid any delay in surgery, split-night PSGs (first half of the study to establish diagnosis and the second half dedicated to CPAP titration) were performed on those patients who demonstrated at least moderate OSA (AHI ≥ 15). Given the long wait times in the sleep clinic and in order to avoid delaying surgery, the patients were not evaluated by a sleep physician preoperatively. However, patients were seen in consultation by a sleep physician 6 to 8 weeks after surgery.

PSGs were staged and scored according to the 2007 American Academy of Sleep Medicine Manual for the Scoring of Sleep and Related Events. Hypnopneas were scored if the magnitude of ventilation signal decreased by ≥ 50% of the baseline amplitude of the nasal pressure transducer ≥ 10 sec and were associated with either ≥ 3% drop in oxygen saturation as measured by finger pulse oximetry, or an electroencephalographic microarousal. The 3% oxygen desaturation index (ODI) indicated the number of 3% desaturations per hour of sleep. A patient was considered not to have OSA if the AHI was < 5, to have mild OSA if the AHI was 5-14, moderate OSA if the AHI was 15-29, and severe OSA if the AHI was ≥ 30. CPAP titration was considered successful if, on optimal CPAP pressure, the residual AHI was < 5 and included supine REM sleep. The sleep studies were reviewed by sleep specialists the day after the PSG, and those with moderate or severe OSA were prescribed and received an auto-titrating CPAP device. The pressure range of the auto-titrating device was determined based on the optimal CPAP level obtained during the titration portion of the PSG. As an example, if the optimal CPAP pressure was 9 cm H2O, the minimum pressure setting of the auto-CPAP device would be set at 2 cm H2O below the optimal pressure and the maximum pressure would be set at 3 cm H2O above the optimal pressure (e.g., 7 to 12 cm H2O). The patients were systematically educated by a trained respiratory therapist on the importance of adherence to therapy during the perioperative period, underwent appropriate mask fitting, and were instructed on how to use their auto-titrating CPAP device. Patients received the auto-titrating CPAP devices the day after the in-laboratory PSG and were instructed to bring their auto-CPAP devices with them on the day of surgery. All patients were contacted by a sleep physician the day after the sleep study to briefly discuss the findings of the polysomnogram and the importance of adhering to CPAP therapy before and after surgery. There were no additional communications between the sleep laboratory staff and the patient until the sleep clinic consultation 6-8 weeks after surgery.

RESULTS

Over a 2-year period, 431 patients who screened at high risk for OSA were referred for an in-laboratory PSG. Of the 431 referred patients, 211 scheduled and completed the in-laboratory PSG. The remainder of the patients did not show up for the scheduled polysomnogram (Figure 1). Our population of patients who had a PSG included those undergoing elective orthopedic surgery (29%), genitourinary surgery (18%), general surgery (12%), vascular surgery (8%), head and neck surgeries (7%), gynecologic surgery (5%), thoracic surgery (3%), and all other surgeries (18%). None of the patients underwent a sleep consultation prior to the diagnostic polysomnogram.

Statistical Analyses

Means or proportions of all variables were calculated for the entire cohort and then separately for those with STOP-Bang scores of 3-4 and those with STOP-Bang scores ≥ 5. The distribution of each continuous variable was examined. Continuous variables that were normally distributed were summarized as mean ± standard deviation (SD) and were compared using Student’s t-test. Continuous variables that were not normally distributed were summarized as median and interquartile range (IQR) and were compared using the Mann-Whitney nonparametric test. Differences in proportions were tested using the χ2 test. We performed a linear regression model to adjust for possible confounding variables in order to identify independent predictors of CPAP adherence. Differences were considered statistically significant when p value was ≤ 0.05. All analyses were performed using PASW Statistics (v.18.0, SPSS, Inc., Chicago, IL).
Of the 211 patients who screened high risk for OSA and underwent a diagnostic PSG, 6% did not have OSA, 20% had mild OSA, 28% had moderate OSA, and 46% had severe OSA. However, the prevalence of severe OSA increased from 36% in patients with STOP-Bang score of 3 to 79% in patients with STOP-Bang scores of 7-8 (Figure 2). We divided the cohort into 2 STOP-Bang subgroups with similar sample sizes. Among the 211 patients who underwent PSG, we compared 93 patients (44%) with STOP-Bang scores of 3-4 to 118 patients (56%) with STOP-Bang scores of 5-8 (Tables 1, 2). Severe OSA was significantly more prevalent in patients with a STOP-Bang scores of 5-8 (55.1% vs. 34.4, p = 0.005) (Table 1). The group with STOP-Bang scores of 5-8 included a significantly higher proportion of men and had a larger neck circumference, higher BMI, and more severe indices of OSA as measured by AHI, ODI, and percent of total sleep time below oxygen saturation of 90% (T90) (Table 2, Figure 3).

CPAP therapy was required and provided to a total of 138 out of 211 patients (65%). On average, patients were started on CPAP therapy 4 days before the date of surgery. Not surprisingly, a higher proportion of patients with STOP-Bang scores ≥ 5 required CPAP therapy (73% vs. 56%, p = 0.01). However, among patients who underwent CPAP titration in the 2 groups, there was no significant difference in the CPAP levels required to optimally treat OSA (Table 2). Objective CPAP adherence data during the first 30 days of therapy was available in 104 of the 138 patients who received CPAP therapy (75%). There was no significant difference in the proportion of patients with CPAP adherence data available in the 2 STOP-Bang categories (p = 0.15). CPAP adherence was quantified as a continuous variable (mean daily usage over 30 days of therapy) as well as a categorical variable (percentage of patients using CPAP ≥ 4 h/night). The overall median adherence to CPAP during the first 30 days of therapy was quite suboptimal at 2.5 h/night (interquartile range of 0.7-4.5 h/night), and there was no significant difference in CPAP adherence between the 2 STOP-Bang categories. Based on this distribution, only 25% of patients prescribed CPAP therapy were using their CPAP devices for ≥ 4.5 h/night. As expected, adherence was also poor when examined as a categorical variable since only 33% of patients used CPAP ≥ 4 h/night (Table 2). In a fully adjusted linear regression model, African American race, male gender, and the presence of depressive symptomatology were each independently associated with approximately 1 h less of CPAP adherence.

**Table 1**—Prevalence of OSA severity in the two STOP-Bang categories

<table>
<thead>
<tr>
<th>OSA Severity</th>
<th>All patients (n = 211)</th>
<th>STOP-Bang 3-4 (n = 93)</th>
<th>STOP-Bang ≥ 5 (n = 118)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No OSA, n (%)</td>
<td>13 (6.2)</td>
<td>10 (10.8)</td>
<td>3 (2.5)</td>
</tr>
<tr>
<td>Mild OSA, n (%)</td>
<td>42 (19.9)</td>
<td>23 (24.7)</td>
<td>19 (16.1)</td>
</tr>
<tr>
<td>Moderate OSA, n (%)</td>
<td>59 (28.0)</td>
<td>28 (30.1)</td>
<td>31 (26.3)</td>
</tr>
<tr>
<td>Severe OSA, n (%)</td>
<td>97 (46.0)</td>
<td>32 (34.4)</td>
<td>65 (55.1)</td>
</tr>
</tbody>
</table>

*p = 0.005 by χ² comparing all OSA severity categories between STOP-Bang 3-4 and STOP-Bang ≥ 5.
use per night after adjustment for OSA severity, STOP-Bang category, hypersomnolence, and education level (Table 3).

We also found that the majority of patients were optimally treated with CPAP pressure of 9 ± 2 cm H$_2$O, and there was no

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**Table 2—Patient characteristics**

<table>
<thead>
<tr>
<th>Variables</th>
<th>All patients (n = 211)</th>
<th>STOP-Bang 3-4 (n = 93)</th>
<th>STOP-Bang ≥ 5 (n = 118)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>61.9 ± 11.0</td>
<td>61.7 ± 12.4</td>
<td>62.1 ± 10.0</td>
<td>0.8</td>
</tr>
<tr>
<td>Men, %</td>
<td>61.6</td>
<td>53.8</td>
<td>67.8</td>
<td>0.037</td>
</tr>
<tr>
<td>African American, %</td>
<td>56.5</td>
<td>60.8</td>
<td>53.0</td>
<td>0.26</td>
</tr>
<tr>
<td>Education level ≥ high school, %</td>
<td>59.0</td>
<td>58.0</td>
<td>58.0</td>
<td>0.98</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>80.0</td>
<td>77.4</td>
<td>82.2</td>
<td>0.41</td>
</tr>
<tr>
<td>Type 2 diabetes, %</td>
<td>31.8</td>
<td>36.6</td>
<td>28.0</td>
<td>0.29</td>
</tr>
<tr>
<td>Epworth Sleepiness Scale</td>
<td>8.9 ± 4.3</td>
<td>8.5 ± 4.2</td>
<td>9.2 ± 4.5</td>
<td>0.3</td>
</tr>
<tr>
<td>Epworth Sleepiness Scale ≥ 10, %</td>
<td>40.0</td>
<td>39.0</td>
<td>40.0</td>
<td>0.88</td>
</tr>
<tr>
<td>CES-D depression scale ≥ 16, %</td>
<td>30.0</td>
<td>29.0</td>
<td>31.0</td>
<td>0.88</td>
</tr>
<tr>
<td>Neck size, inches</td>
<td>16.3 ± 1.6</td>
<td>15.6 ± 1.4</td>
<td>16.9 ± 1.5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>BMI, kg/m$^2$</td>
<td>33.5 ± 8.1</td>
<td>30.7 ± 7.3</td>
<td>35.7 ± 8.1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>AHI, events/h</td>
<td>27.0 (12-45)</td>
<td>21.0 (10.5-33.5)</td>
<td>30.0 (19.0-52.3)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>SpO$_2$ nadir</td>
<td>84.5 ± 6.6</td>
<td>85.5 ± 6.6</td>
<td>83.7 ± 6.5</td>
<td>0.06</td>
</tr>
<tr>
<td>ODI, events/h</td>
<td>19.0 (8.0-42.5)</td>
<td>14.0 (6.0-32.0)</td>
<td>27.0 (10.0-55.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>T90</td>
<td>3.0 (1.0-10.0)</td>
<td>2.0 (0.0-6.0)</td>
<td>5.0 (1.0-20.0)</td>
<td>0.003</td>
</tr>
<tr>
<td>Received CPAP therapy, n (%)</td>
<td>138.0 (65)</td>
<td>52.0 (56)</td>
<td>86.0 (73)</td>
<td>0.01</td>
</tr>
<tr>
<td>Final CPAP pressure, cm H$_2$O</td>
<td>8.8 ± 2.0</td>
<td>8.6 ± 1.6</td>
<td>8.9 ± 2.2</td>
<td>0.22</td>
</tr>
<tr>
<td>CPAP adherence data available, n (%)</td>
<td>104.0 (75)</td>
<td>43.0 (83)</td>
<td>61.0 (71)</td>
<td>0.15</td>
</tr>
<tr>
<td>CPAP adherence, hours/night</td>
<td>2.5 (0.7-4.5)</td>
<td>2.3 (0.6-4.2)</td>
<td>2.8 (0.7-4.6)</td>
<td>0.69</td>
</tr>
<tr>
<td>CPAP use ≥ 4 h/night, n (%)</td>
<td>34.0 (33)</td>
<td>14.0 (33)</td>
<td>20.0 (33)</td>
<td>0.98</td>
</tr>
</tbody>
</table>

Normally distributed data are presented as mean ± SD and compared using t-students. Not normally distributed data are presented as median (25th-75th interquartile range) and compared using Mann-Whitney nonparametric test. Categorical values were tested using $\chi^2$. Epworth Sleepiness Scale is a validated 8-item questionnaire with a scale of 0 to 24 in which a score ≥ 10 is suggestive of hypersomnolence. CES-D, Center for Epidemiologic Studies Depression Scale is a validated 20-item questionnaire with a scale of 0 to 60 in which scores ≥ 16 are suggestive of depressive symptomatology. AHI, Apnea-hypopnea index; BMI, Body mass index; SpO$_2$, Lowest oxygen saturation during sleep; ODI, number of 3% oxygen desaturations per average hour of sleep; T90, % of total sleep time with oxygen saturation below 90%; CPAP, Continuous positive airway pressure.

**Figure 3—Box plots showing the distribution of and differences in 3% oxygen desaturation index (ODI 3%) and percent of total sleep time below oxygen saturation of 90% (T90) across the two STOP-Bang categories**

Lower and upper boundaries of the box indicate 25th and 75th percentages. A solid line within the box marks the median, and vertical lines indicate the 10th and 90th percentages. Circles are outliers. ODI 3% and T90 were significantly higher in patients with STOP-Bang scores of 5-8 (p = 0.001 and p = 0.003, respectively).
significant difference in the optimal CPAP pressure between the 2 STOP-Bang groups.

**DISCUSSION**

Our study demonstrates that in an urban tertiary care academic medical center, a high proportion of presurgical patients that underwent polysomnographic evaluation had severe OSA. Overall CPAP adherence during the first 30 days of perioperative period was extremely low compared to known CPAP adherence at our institution, as well as reported national averages of 4.7 hours/night.\textsuperscript{19-23} Indeed, only a third of patients were using CPAP at least 4 hours/night. Moreover, African American race, male gender, and the presence of depressive symptoms were significant predictors of reduced CPAP adherence. These are novel findings that have not been previously investigated in this patient population.

Further investigation into why perioperative patients are less adherent to CPAP and interventions to overcome noncompliance is needed if successful therapy is desired. While we have previously reported that OSA patients seen by sleep physicians are more adherent to CPAP therapy,\textsuperscript{19} none of the patients underwent a sleep consultation prior to the diagnostic polysomnogram. It remains to be elucidated whether a sleep consultation in the preoperative period would lead to improvement in CPAP adherence. In a recent study, 88 patients identified as having OSA who received CPAP therapy during the preoperative period were surveyed with a mailed questionnaire two years after surgery to assess “subjective” CPAP adherence.\textsuperscript{13,25} Although the study reported 45% of patients being adherent with therapy, the findings were limited by not having objective CPAP adherence data, as well as lack of information about the more immediate perioperative CPAP use. It is important to recognize that CPAP adherence is frequently overestimated by patients.\textsuperscript{20,22} Notwithstanding these limitations, the study reported that patients adherent with CPAP therapy experienced greater symptomatic benefit.\textsuperscript{24} Although long-term CPAP non-adherence is associated with increased cardiovascular morbidity and mortality,\textsuperscript{4,9} the impact of CPAP non-adherence in the perioperative period has not been evaluated in a systematic fashion.

We also found that despite removing administrative barriers and ensuring that there would be full availability of resources from the sleep laboratory to obtain a confirmatory in-laboratory PSG in a timely fashion without delaying surgery, a large proportion of patients were unable or unwilling to undergo a PSG. It is noteworthy that others have also reported a low patient acceptance rate of in-laboratory PSG in either a clinical or research setting.\textsuperscript{11,28} Our study was not designed to elucidate the reasons for which patients refused or deferred a PSG. However, we speculate that the inconvenience of an overnight in-laboratory PSG, cost, under-appreciation of the implications of OSA, lack of understanding of the consequences of untreated OSA or unwillingness to use CPAP may have all contributed.

Our data also demonstrate that the average CPAP level required to optimally treat patients is approximately 9 ± 2 cm H\textsubscript{2}O. Therefore an auto-titrating CPAP device with a minimum pressure setting of 7 cm H\textsubscript{2}O and a maximum pressure setting of 12 cm H\textsubscript{2}O adequately treated the vast majority of our patients. In practice, we have noted that some anesthesiologists at our institution start empiric CPAP at 5 cm H\textsubscript{2}O in the postoperative period in patients with suspected OSA. Most likely, this treatment approach will not give full resolution of upper airway obstruction; based on our findings, higher pressure needs to be prescribed for successful treatment. This is an important finding, given that the vast majority of patients with OSA are not typically diagnosed preoperatively, but can be suspected to have OSA based on patient characteristics, by using the STOP-Bang screening tool, or by nocturnal oximetry.\textsuperscript{26-28}

Our study has several limitations. Although we objectively measured CPAP adherence, we were unable to obtain adherence data on all the patients. However, objective CPAP adherence data were available in 75% of patients who received CPAP therapy. There is a possibility of a selection bias leading to a high proportion of patients having moderate or severe OSA in our study. Patients with more severe symptoms may have been more willing to undergo a PSG. We cannot calculate sensitivity or specificity for the STOP-Bang cutoffs used in our study, since we did not systematically test patients who screened at low risk for OSA on the questionnaire (scores below 3). Given that overall serious postoperative complications due to OSA are rare, our study was neither powered nor designed to ascertain rates of postoperative complications between patients with higher and lower STOP-Bang scores or between patients that were adherent and non-adherent to CPAP therapy. Finally, the findings in our inner-city urban cohort may not be applicable to other populations. As such, further studies are needed to confirm our findings.

In summary, the willingness of patients who screen at high risk for OSA to submit to an in-laboratory PSG during the immediate preoperative period is low. However, those identified as high risk by STOP-Bang scores of 5-8 have a high likelihood of moderate-severe OSA. The adherence to prescribed CPAP therapy in the perioperative period in our population was extremely low. Further research is needed to identify barriers to CPAP adherence in this patient population, or efforts directed towards diagnosis are likely to be wasted. Ultimately, large multicenter randomized trials with clinically important and relevant end points are needed to test the validity and cost-

### Table 3—Significant predictors of mean CPAP adherence over the first 30 days of therapy in minutes from a fully adjusted multiple linear regression model\textsuperscript{*}

<table>
<thead>
<tr>
<th>Regression Coefficient (Minutes)</th>
<th>95% CI (Minutes)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>African American race -68</td>
<td>(-126, -10)</td>
<td>0.021</td>
</tr>
<tr>
<td>Depressive symptoms -65</td>
<td>(-123, -6)</td>
<td>0.030</td>
</tr>
<tr>
<td>Men -61</td>
<td>(-119, -3)</td>
<td>0.041</td>
</tr>
</tbody>
</table>

\*The model is fully adjusted for race (African American vs. non-African American), gender, education (greater than high school vs. high school or less), OSA severity (moderate vs. severe), STOP-Bang score (≥ 5 vs. 3-4), hypersomnolence (Epworth Sleepiness Scale score ≥ 10 vs. Epworth Sleepiness Scale < 10), depressive symptoms (CES-D ≥ 16 vs. CES-D < 16). Non-significant covariates in this model included: education category, OSA severity, STOP-Bang category, and presence of hypersomnolence.
effectiveness of various approaches in diagnosing and treating OSA in the perioperative setting.

REFERENCES

Sleep Disordered Breathing, Insomnia Symptoms, and Sleep Quality in a Clinical Cohort of US Hispanics in South Florida

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Study Objectives: There is a paucity of information on the epidemiology of sleep disorders among US Hispanics. This study describes the frequency of sleep disordered breathing (SDB) risk, insomnia complaints, poor sleep quality, and daytime somnolence in a clinical cohort of ethnically diverse US Hispanics living in South Florida.

Methods: We explored the presence of sleep disorders in a cohort of Hispanics seen at primary care, pulmonary, and sleep clinics at the University of Miami and Miami Veterans Affairs Medical Center. Participants completed validated questionnaires, evaluating risk of SDB, presence of insomnia symptoms, sleep quality, and daytime sleepiness. Polysomnography was completed on the majority of the sleep clinic participants.

Results: Participants (N = 282; 62% male; mean age 54 ± 15 years; mean BMI 31 ± 6 kg/m²) included Hispanics of Cuban, Puerto Rican, Central/South American, and Caribbean heritage. Excessive daytime sleepiness was noted by 45% of participants. Poor sleep quality was reported by 49%; 76% screened high risk for SDB, and 68% had insomnia symptoms. Sleep disorders were more commonly reported in sleep clinic participants; however, 54% of non-sleep clinic participants were high risk for SDB, 35% had insomnia complaints, 28% had poor sleep quality, and 18% reported daytime sleepiness.

Conclusions: Sleep disorders (including SDB) are common in clinical samples of Hispanics in South Florida. These findings highlight the urgent need for linguistically relevant and culturally responsive screening, awareness and education programs in clinical sleep medicine among US Hispanics.

Keywords: Sleep disordered breathing, insomnia, sleep quality, excessive daytime somnolence, Hispanic, ethnicity, epidemiology

Citation: Shafazand S; Wallace DM; Vargas SS; Del Toro Y; Dib S; Abreu AR; Ramos A; Nolan B; Baldwin CM; Fleming L. Sleep disordered breathing, insomnia symptoms, and sleep quality in a clinical cohort of US Hispanics in South Florida. J Clin Sleep Med 2012;8(5):507-514.

Hispanics in the United States (US) are a diverse population originating from Mexico, Puerto Rico, Cuba, and countries in Central, South America, and the Caribbean. Several studies have documented increased rates of disorders traditionally associated with sleep disordered breathing (SDB), including diabetes,1,2 obesity,3,4 and cardiovascular disease5,6 among US Hispanics. Acculturation to the American diet and lifestyle, in addition to lower socioeconomic status, decreased access to health care, and increased stress associated with migration may all contribute to the increased prevalence of these disorders.3,5,7 Similar to other ethnic groups, cardiovascular disease is the leading cause of death in US Hispanics.10

A significant body of literature points to the roles that sleep quality (SQ) and sleep duration play in normal metabolism, immune function, mood, and cognitive functioning.11-14 In particular, SDB has been associated with an increased risk of stroke, hypertension, atrial fibrillation, myocardial infarction, worsening diabetes, and all-cause mortality.15-19 Given the relationship between sleep disorders and cardiovascular disease, sleep health is likely to play a significant role in the overall health and healthcare utilization of US Hispanics.15,20,21 As the largest and fastest growing minority population in the US, Hispanics will continue to have considerable social, economic, and political impact, with unique healthcare requirements that need to be recognized and addressed. Despite significant research in recent years on the prevalence and health impact of sleep disorders, there is a relative paucity of data on sleep disorders among eth-

BRIEF SUMMARY
Current Knowledge/Study Rationale: Despite significant research in recent years on the prevalence and health impact of sleep disorders, there is a relative paucity of data on sleep disorders among ethnically diverse US Hispanics. This study describes the frequency of sleep apnea risk, insomnia complaints, poor sleep quality, and daytime somnolence in a clinical cohort of ethnically diverse US Hispanics living in South Florida.

Study Impact: Our study increases the awareness that risks for sleep apnea, insomnia symptoms, poor sleep quality, and excessive daytime sleepiness are common in a clinical cohort of US Hispanics and highlights the need for increased screening and awareness by healthcare providers.
nically diverse US Hispanics. This study describes the frequency of SDB risk, insomnia complaints, poor sleep quality, and daytime somnolence in a clinical cohort of ethnically diverse US Hispanics living in South Florida. We hypothesized that Hispanic participants recruited from sleep clinics would have higher prevalence of sleep complaints than those participants from non-sleep clinics.

**METHODS**

**Subjects**

We enrolled consecutive adult (age ≥ 18 years), self-identified Hispanic patients referred to the University of Miami (UM) sleep, primary care (general internal medicine), and pulmonary clinics, and the Miami Veterans Affairs (VA) Medical Center sleep clinics from September 2009 to November 2010. Participants were excluded if they were unable to read English or Spanish at a fifth-grade level. Participants in the general internal medicine or pulmonary clinics had chief complaints unrelated to a primary sleep disorder. The reasons for primary care visits ranged from routine well visits to the renewal of prescription medications, monitoring chronic health conditions (diabetes, hypertension), and new patient visits. The pulmonary clinic participants were seen for follow-up of common respiratory conditions including cough, dyspnea, asthma, and emphysema. The University of Miami and the Miami VA Administrative Panel on Human Subjects in Medical Research approved the protocol, and all participants signed a written informed consent prior to enrollment.

**Study Variables**

Demographic characteristics and medical history were obtained from patient interview and a review of medical records. Depression and anxiety were determined by the following single question asked at the time of enrollment, “Have you ever been told by a doctor that you have depression or anxiety?” Anthropometric measures (height, weight, and neck circumference) were obtained on the day of enrollment. All participants completed validated questionnaires (available in both English and Spanish) to determine risk for SDB, insomnia symptom severity, sleep quality (SQ), and daytime somnolence. We screened for increased risk of sleep apnea using the STOP BANG questionnaire. A recently validated measure to determine SDB risk, the STOP BANG compares favorably to the Berlin sleep index. The validated insomnia severity index (ISI) was used to measure insomnia symptomatology. Sleep quality was evaluated using the Pittsburgh Sleep Quality Index (PSQI). A global PSQI score > 5 yields a diagnostic sensitivity of 89.6% and specificity of 86.5% in distinguishing good from poor sleepers. We evaluated subjective daytime sleepiness using the Epworth Sleepiness Scale (ESS). The internal consistency, concurrent validity, and sensitivity to clinical improvements of these questionnaires are well established.

**Polysomnography**

Both sleep and non-sleep clinic participants were encouraged to undergo in-laboratory video polysomnography (PSG), with most of the participants recruited from the sleep clinics agreeing to do so. We conducted PSG in accordance with the standards established by the American Academy of Sleep Medicine. Records were scored using standardized techniques and the recommended scoring rules for hypopneas. The oro-nasal thermistor and nasal pressure transducer channels were used to score apneas and hypopneas, respectively. An apnea-hypopnea index ([AHI], number of apneas and hypopneas/h of sleep) ≥ 5 was used to diagnose SDB.

**Data Analysis**

We report means and standard deviations (SD), medians and interquartile ranges (IQR) and frequencies. Participants were divided into 2 groups (sleep clinic, and non-sleep clinic participants); differences in study variables were compared using the χ2 test statistic, Fisher exact test, Student t-test, or Mann Whitney U tests. Given the small number of participants recruited from pulmonary clinics (n = 22), we have provided summary statistics for the general medicine and pulmonary clinic subgroups (non-sleep clinic group), but we did not perform comparisons between subgroups. High risk for SDB was calculated as the proportion of individuals with a STOP BANG score ≥ 3. The presence of insomnia symptoms was calculated as the proportion of individuals with ISI score ≥ 8. The frequency of poor SQ was calculated as the proportion of individuals with a PSQI ≥ 5. Excessive daytime sleepiness (EDS) was defined as proportion of participants with ESS ≥ 10. We used multivariable modeling to adjust results for gender, age, body mass index (BMI), presence of diabetes, anxiety, and depression. We accepted a 2-tailed p-value < 0.05 as statistically significant for all analyses. We analyzed data using SPSS for Windows, version 17.0 statistical software package (SPSS; Chicago, IL).

**RESULTS**

**Characteristics of Study Participants**

We enrolled 282 participants (174 sleep clinic, 108 non-sleep clinic), 62% male with a mean age of 54 ± 15 years and mean BMI 31 ± 6 kg/m² (Table 1). At the UM enrollment sites, Spanish was the preferred language for communication and completion of study questionnaires for 77% of participants, with 44% expressing discomfort with speaking English in day-to-day life. Cuban Americans, the largest Hispanic group in this study, constituted 35% of participants, with Puerto Ricans being the next largest group at 22%. There was a statistically significant difference in age and BMI between sleep clinic and non-sleep clinic subgroups, with the sleep clinic subjects being younger and heavier. Sleep clinic participants were more likely to be male, diabetic, and to suffer from anxiety or depression, with no other differences in comorbidities noted (Table 1).

**Risk of Sleep Disordered Breathing and its Prevalence on Polysomnography**

An increased risk of SDB using the STOP BANG measure was noted in 76% of all participants. Sleep clinic subjects were more likely to be at high risk for SDB (90% vs. 54%, p < 0.001). Baseline PSG was available for 56% of all participants; 81% of
participants completing PSG had objective SDB with median AHI of 20.2 (IQR 136.7), 63% of whom had moderate to severe disease (AHI ≥ 15). Sleep apnea syndrome (SAS), defined as AHI ≥ 5 and sleepiness (ESS ≥ 10) was found in 83% of the sleep clinic population.

**Insomnia Symptomatology and Severity**

Symptoms suggestive of clinical insomnia (ISI ≥ 8) were reported in 68% of the group as a whole, with a significantly higher frequency in the sleep clinic participants (87% vs. 35%, p < 0.001). The mean ISI for all participants was 11.6 ± 7.8 (Table 2), indicating mild clinical insomnia in this population. There were significant group differences seen in the ISI scores with the non-sleep clinic participants reporting lower ISI scores (6.2 ± 6.4 vs.14.9 ± 6.6, p < 0.001). This difference remained significant after adjustment for age, gender, BMI, presence of diabetes, and mood disorders. The results for insomnia symptoms and severity are provided in Table 2.

**Sleep Quality and Excessive Daytime Sleepiness**

The mean PSQI for all participants was 8.8 ± 4.9, indicating poor SQ; however, the non-sleep clinic group had significantly better SQ than sleep clinic subjects (6.3 ± 4.6 vs. 10.2 ± 4.5, p < 0.001) (Table 2). These comparisons remained significant between groups after adjustment for age, gender, BMI, presence of diabetes, anxiety, and depression.

When queried about sleep during the previous month, 56% of all subjects reported having nighttime arousals and 46% reported loud snoring or coughing during sleep ≥ 3 times a week. A quarter of the participants required medication (prescription or over-the-counter) ≥ 3 times a week to help initiate and/or maintain sleep. Only 10% of participants ranked their overall SQ as very good, while 49% reported fairly to very bad SQ in the previous month. Sleep clinic subjects were significantly more likely to report nighttime arousals (73% vs. 39%, p < 0.001) and loud snoring or cough (57% vs. 26%, p < 0.001) ≥ 3 times a week. Only 1% of the sleep clinic participants and

### Table 1—Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All (N = 282)</th>
<th>Sleep Clinic Participants (N = 174)</th>
<th>Non Sleep Clinic Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Gen Med (N = 86)</td>
<td>Pulmonary (N = 22)</td>
</tr>
<tr>
<td>Age, yrs*†</td>
<td>54 ± 15</td>
<td>50 ± 13</td>
<td>61 ± 16</td>
</tr>
<tr>
<td>Gender, male, n (%) †</td>
<td>175 (62)</td>
<td>147 (85)</td>
<td>21 (24)</td>
</tr>
<tr>
<td>BMI, kg/m²*†</td>
<td>31 ± 6</td>
<td>32 ± 6</td>
<td>29 ± 5</td>
</tr>
<tr>
<td>Neck circumference, cm* †</td>
<td>41 ± 4</td>
<td>43 ± 4</td>
<td>38 ± 3</td>
</tr>
<tr>
<td>Country of Origin, n (%) †</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cuba</td>
<td>99 (35)</td>
<td>59 (34)</td>
<td>33 (38)</td>
</tr>
<tr>
<td>Puerto Rico</td>
<td>63 (22)</td>
<td>54 (31)</td>
<td>9 (11)</td>
</tr>
<tr>
<td>Mexico</td>
<td>4 (1)</td>
<td>2 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Caribbean (Dominican, Haiti)</td>
<td>9 (3)</td>
<td>8 (5)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Central America</td>
<td>35 (12)</td>
<td>20 (12)</td>
<td>13 (15)</td>
</tr>
<tr>
<td>South America</td>
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<td>20 (23)</td>
</tr>
<tr>
<td>Other</td>
<td>23 (8)</td>
<td>9 (5)</td>
<td>9 (11)</td>
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<tr>
<td>Marital status, n (%) †</td>
<td></td>
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</tr>
<tr>
<td>Married/partner</td>
<td>157 (56)</td>
<td>107 (61)</td>
<td>42 (49)</td>
</tr>
<tr>
<td>Single</td>
<td>101 (36)</td>
<td>62 (36)</td>
<td>34 (40)</td>
</tr>
<tr>
<td>Other</td>
<td>24 (9)</td>
<td>5 (3)</td>
<td>10 (11)</td>
</tr>
<tr>
<td>Education, n (%) †</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ Grade 8</td>
<td>29 (10)</td>
<td>2 (1)</td>
<td>22 (26)</td>
</tr>
<tr>
<td>Some high school or diploma</td>
<td>77 (27)</td>
<td>46 (26)</td>
<td>24 (28)</td>
</tr>
<tr>
<td>Some college or college degree</td>
<td>135 (48)</td>
<td>100 (57)</td>
<td>29 (34)</td>
</tr>
<tr>
<td>Professional degree</td>
<td>32 (11)</td>
<td>23 (13)</td>
<td>6 (7)</td>
</tr>
<tr>
<td>Unknown</td>
<td>9 (3)</td>
<td>3 (2)</td>
<td>5 (6)</td>
</tr>
<tr>
<td>Employment, n (%) †</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Employed</td>
<td>137 (49)</td>
<td>93 (53)</td>
<td>36 (42)</td>
</tr>
<tr>
<td>Unemployed</td>
<td>29 (10)</td>
<td>24 (14)</td>
<td>4 (5)</td>
</tr>
<tr>
<td>Other (retired, disability, housewife)</td>
<td>116 (41)</td>
<td>57 (33)</td>
<td>46 (53)</td>
</tr>
<tr>
<td>Comorbidities, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>36 (13)</td>
<td>23 (13)</td>
<td>10 (12)</td>
</tr>
<tr>
<td>Stroke</td>
<td>16 (6)</td>
<td>7 (4)</td>
<td>7 (8)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>181 (64)</td>
<td>116 (67)</td>
<td>54 (63)</td>
</tr>
<tr>
<td>Diabetes †</td>
<td>65 (23)</td>
<td>46 (26)</td>
<td>19 (22)</td>
</tr>
<tr>
<td>Lung disease</td>
<td>73 (26)</td>
<td>47 (27)</td>
<td>13 (15)</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>27 (10)</td>
<td>16 (9)</td>
<td>11 (13)</td>
</tr>
<tr>
<td>Anxiety and/or depression †</td>
<td>119 (42)</td>
<td>82 (47)</td>
<td>29 (34)</td>
</tr>
</tbody>
</table>

*Mean ± SD; Numbers are rounded and may not add to 100%; Gen Med = General Medicine Clinics; †p < 0.001 for the comparison between sleep clinic and non-sleep clinic groups; ‡p < 0.05 for the comparison between sleep clinic and non-sleep clinic groups
25% of the non-sleep clinic participants reported very good SQ in the preceding month. Overall, participants reported a mean 6 ± 2 h sleep per night, with a self-reported sleep onset latency of 31 ± 34 minutes. There was a significant difference in sleep duration between groups, with sleep clinic participants reporting shorter mean sleep duration.

EDS was reported by 45% of all participants. Among sleep clinic patients, the rate was 62%, while 18% of the non-sleep clinic participants reported EDS. The median Epworth score for the entire study population was 9 (IQR = 11), with a statistically significant difference noted between groups that remained significant after adjustment for age, gender, BMI, presence of diabetes, anxiety, and depression. The results for EDS are displayed in Table 2.

### Table 2—Sleep Questionnaires

<table>
<thead>
<tr>
<th>Metric</th>
<th>All</th>
<th>Sleep Clinic Participants (N = 174)</th>
<th>Non Sleep Clinic Participants</th>
<th>Gen Med (N = 86)</th>
<th>Pulmonary (N = 22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESS, median (IQR)†</td>
<td>9.0 (11)</td>
<td>11.0 (8)</td>
<td>3.0 (7)</td>
<td>5.0 (9)</td>
<td></td>
</tr>
<tr>
<td>High Risk For SDB, n (%)†</td>
<td>215 (76)</td>
<td>157 (90)</td>
<td>45 (52)</td>
<td>13 (59)</td>
<td></td>
</tr>
<tr>
<td>Global PSQI‡</td>
<td>8.8 ± 4.9</td>
<td>10.2 ± 4.5</td>
<td>5.9 ± 4.4</td>
<td>8.0 ± 5.1</td>
<td></td>
</tr>
<tr>
<td>Sleep Quality in the Preceding Month, n (%) ‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very good</td>
<td>28 (10)</td>
<td>2 (1)</td>
<td>24 (28)</td>
<td>2 (9)</td>
<td></td>
</tr>
<tr>
<td>Fairly good</td>
<td>93 (33)</td>
<td>48 (26)</td>
<td>35 (41)</td>
<td>10 (46)</td>
<td></td>
</tr>
<tr>
<td>Fairly bad</td>
<td>77 (27)</td>
<td>58 (33)</td>
<td>13 (15)</td>
<td>6 (27)</td>
<td></td>
</tr>
<tr>
<td>Very bad</td>
<td>63 (22)</td>
<td>53 (30)</td>
<td>8 (9)</td>
<td>3 (14)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>21 (7)</td>
<td>13 (7)</td>
<td>6 (7)</td>
<td>1 (5)</td>
<td></td>
</tr>
<tr>
<td>Self-Reported Sleep Latency, min*</td>
<td>30.6 ± 33.7</td>
<td>28.5 ± 29.7</td>
<td>30.2 ± 30.8</td>
<td>49.7 ± 61.0</td>
<td></td>
</tr>
<tr>
<td>Self-Reported Sleep Duration, h*</td>
<td>6.2 ± 1.7</td>
<td>5.7 ± 1.7</td>
<td>7.0 ± 1.5</td>
<td>6.5 ± 1.8</td>
<td></td>
</tr>
<tr>
<td>Global ISI‡</td>
<td>11.6 ± 7.8</td>
<td>14.9 ± 6.6</td>
<td>5.5 ± 6.1</td>
<td>9.0 ± 7.0</td>
<td></td>
</tr>
<tr>
<td>No insomnia, n (%)</td>
<td>89 (32)</td>
<td>21 (12)</td>
<td>58 (67)</td>
<td>10 (46)</td>
<td></td>
</tr>
<tr>
<td>Sub-threshold/mild insomnia, n (%)</td>
<td>81 (29)</td>
<td>59 (34)</td>
<td>16 (19)</td>
<td>8 (27)</td>
<td></td>
</tr>
<tr>
<td>Moderate insomnia, n (%)</td>
<td>65 (23)</td>
<td>55 (32)</td>
<td>6 (7)</td>
<td>4 (18)</td>
<td></td>
</tr>
<tr>
<td>Severe insomnia, n (%)</td>
<td>41 (15)</td>
<td>37 (22)</td>
<td>3 (4)</td>
<td>1 (5)</td>
<td></td>
</tr>
<tr>
<td>Unknown, n (%)</td>
<td>6 (2)</td>
<td>2 (1)</td>
<td>3 (4)</td>
<td>1 (5)</td>
<td></td>
</tr>
</tbody>
</table>

*Mean ± SD; Numbers are rounded and may not add to 100%; †p < 0.001 for the comparison between sleep clinic and non-sleep clinic groups. ESS, Epworth Sleepiness Score; PSQI, Pittsburgh Sleep Quality Index; ISI, Insomnia Severity Index; IQR, Interquartile range.

According to 2010 US census data, there are over 50 million Hispanics in the United States (16% of the US population) comprising the largest single minority group, yet little is known about the sleep disturbances experienced by this growing segment of our population. Our findings indicate that subjectively reported SDB, insomnia symptoms, poor sleep quality, and daytime somnolence are common among an ethnically diverse sample of Hispanics living in South Florida who were seen in clinical settings. The presence and range of sleep disorders among our Hispanic sleep clinic patients suggest the potential for poorer health outcomes and higher health care costs relevant to sleep-associated comorbidities. We have reviewed the limited existing general population studies on sleep disorders in Hispanics and in mixed population primary care settings. Direct comparisons between studies are difficult due to the variability in measurement tools and population comorbidities. We present these data to provide a framework for the state of the knowledge to date. Table 3 summarizes the main sleep related findings in our clinical sample and places them in the context of reports from the literature as discussed below.

### Sleep Disordered Breathing

Snoring is a focal sign of obstructive sleep apnea. Self-reported snoring rates in our study were 55% in the entire cohort, with 43% of women and 62% of men reporting loud snoring. These numbers are higher than previous reports and may reflect our recruitment strategy. One-third of the participants recruited from our non-sleep clinics reported loud snoring, including 37% of women and 22% of men, suggesting that snoring is prevalent in our Hispanic clinical group with no specific sleep complaints. Notably, elevated rates of snoring alone among Hispanic children and adults have been reported elsewhere. Reasons for this increased rate among Hispanics are not known. Further studies are needed given this consistent finding to determine if culture, lifestyle, physiognomy or other factors play a role.

Over two-thirds of our participants were found to be at high risk for SDB using the STOP BANG measure, including over half of the non-sleep clinic patients. Studies in multi-ethnic office based settings suggest that the prevalence of SDB in patients seen in primary care clinics is higher than general population estimates. This may be due to the increased frequency of diabetes and obesity in these settings. Netzer et al. surveyed 40 primary care offices and clinics in United States (n = 3915) and Europe (Germany and Spain [n = 2308]) using the Berlin questionnaire to determine SDB risk. The risk for SDB was higher in US (35.8%) than European primary care populations (26.3%). The SDB risk prevalence in two Florida primary care settings included in this survey ranged from 36.4% to
In their study of a family practice clinic in Cleveland Ohio, Senthilvel et al. surveyed 101 patients (11% Hispanic) using several standardized sleep questionnaires, including Berlin and STOP questionnaires. High risk for SDB was found in 33% (Berlin) and 34% (STOP) of participants.

Comparisons between different studies are difficult due to the variability in measurement tools, ethnic diversity of the population studied, and differing comorbidities that increase the risk for sleep apnea. However, the high frequencies of snoring and overall risk of SDB in the non-sleep clinic group in our study suggest the need for an increased awareness of SDB in this population and for routine screening during patient encounters using appropriately Spanish translated measures at relevant reading and comprehension levels.

The actual prevalence of objectively diagnosed SDB in Hispanics is not well known. Kripke performed home sleep oximetry in 355 subjects, including 44 Hispanics, and estimated that 16.3% of Hispanics and other racial minorities had ≥ 20 desaturation events per hour (comparable to moderate to severe SDB), compared to 4.9% of non-Hispanic whites. Bouscoulet et al. performed home portable respiratory monitoring during sleep in 188 subjects from Mexico City and found the prevalence of moderate sleep apnea was as high as 23.5%. We report much higher estimates in our cohort of sleep clinic patients. This may be due to our use of PSG as the gold standard of SDB diagnosis, selection bias noted in sleep clinics, or may reflect a true increase in risk. Preliminary data from two ongoing population- and community-based NIH sponsored studies suggested higher estimates.

### Table 3—Reported Prevalence of Sleep Disorders in Hispanics

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Hispanics</th>
<th>Total Study N</th>
<th>Design</th>
<th>Measure Used</th>
<th>Prevalence Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sleep Disordered Breathing (moderate to severe)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1) Kripke et al.39</td>
<td>44</td>
<td>355</td>
<td>Survey in San Diego</td>
<td>Overnight oximetry</td>
<td>16.3%</td>
</tr>
<tr>
<td>2) Bouscoulet et al.40</td>
<td>188</td>
<td>188</td>
<td>Random sample in Mexico city</td>
<td>Simplified respiratory polygraphy</td>
<td>10.1%</td>
</tr>
<tr>
<td>3) Sleep Health and Knowledge, San Diego41</td>
<td>168</td>
<td>363</td>
<td>Random sample in San Diego</td>
<td>Portable Home PSG</td>
<td>16.1% moderate SDB, 26.8% severe SDB</td>
</tr>
<tr>
<td>4) Baldwin et al.44</td>
<td>265</td>
<td>5237</td>
<td>Cross-sectional, Multi-center</td>
<td>Portable Home PSG</td>
<td>17%</td>
</tr>
<tr>
<td>5) Current Study</td>
<td>158</td>
<td>158</td>
<td>Cross-sectional, Single center, clinical sample</td>
<td>In lab PSG</td>
<td>63%</td>
</tr>
<tr>
<td><strong>Insomnia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1) Baldwin et al.44</td>
<td>265</td>
<td>5237</td>
<td>Cross-sectional, Multi-center</td>
<td>SHQ from SHHS</td>
<td>36%</td>
</tr>
<tr>
<td>2) Ram et al.45</td>
<td>737</td>
<td>6139</td>
<td>2005–2006 National Health and Nutrition Examination Survey</td>
<td>Question: difficulty falling asleep, staying asleep</td>
<td>42%</td>
</tr>
<tr>
<td>3) Bouscoulet et al.40</td>
<td>4533</td>
<td>4533</td>
<td>Population survey in 4 Latin American cities</td>
<td>Question: “difficulty in falling asleep during the previous 6-month period ≥ 2 nights a week”</td>
<td>34.7% (33.3% to 36%)</td>
</tr>
<tr>
<td>4) Current Study</td>
<td>282</td>
<td>282</td>
<td>Cross-sectional, Single center, clinical sample</td>
<td>ISI</td>
<td>68% All subjects, 35% Non sleep clinic subjects</td>
</tr>
<tr>
<td><strong>Poor Sleep Quality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1) NSF Poll46</td>
<td>250</td>
<td>1007</td>
<td>Random digit dialing, national phone survey</td>
<td>Question: “how often you had a good night’s sleep”</td>
<td>29% reported a few nights a month to never having good sleep</td>
</tr>
<tr>
<td>2) Current Study</td>
<td>282</td>
<td>282</td>
<td>Cross-sectional, Single center, clinical sample</td>
<td>PSQI</td>
<td>49% All subjects, 28% Non sleep clinic subjects</td>
</tr>
<tr>
<td><strong>Excessive Daytime Sleepiness (EDS)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1) Baldwin et al.44</td>
<td>265</td>
<td>5237</td>
<td>Cross-sectional, Multi-center</td>
<td>ESS</td>
<td>24%</td>
</tr>
<tr>
<td>2) Bouscoulet et al.40</td>
<td>4533</td>
<td>4533</td>
<td>Population survey in 4 Latin American cities</td>
<td>Question: “Is it difficult for you to stay awake during the daytime, at least 3 days a week”</td>
<td>16.4% (15.3 -17.5%)</td>
</tr>
<tr>
<td>3) Current Study</td>
<td>282</td>
<td>282</td>
<td>Cross-sectional, Single center, clinical sample</td>
<td>ESS</td>
<td>45% All subjects, 18% Non sleep clinic subjects</td>
</tr>
</tbody>
</table>

ESS, Epworth Sleepiness Score; PSQI, Pittsburgh Sleep Quality Index; ISI, Insomnia Severity Index; SHQ, Sleep Habits Questionnaire; SHHS, Sleep Heart Health Study; PSG, Polysomnography; NSF, National Sleep Foundation.
gest that the numbers for SDB among Hispanics is higher than the general population estimates often quoted for non-Hispanic whites,\(^3\) highlighting the trend for higher rates of SDB among Hispanics that mirrors our findings.

**Insomnia Symptoms**

Very little is known about the prevalence of insomnia symptoms among US Hispanics. Overall, our study participants had significant (moderate to severe) insomnia complaints (38%), in keeping with the SHHS estimates for Hispanics who were primarily of Mexican heritage.\(^4\) Self-reported insomnia symptoms were particularly high among our patients with objective findings of SDB. The NHANES data suggest that 13.4% of Hispanic respondents had trouble falling asleep, 13.7% would wake up during the night with difficulty returning to sleep, and 14.7% would wake up early in the morning.\(^4\) More than a third (33%) of our general medicine subgroup reported insomnia symptoms. This is comparable to Senthilvel’s multi-ethnic primary care office-based study, in which 32% of participants had symptoms suggestive of insomnia.\(^38\)

**Sleep Duration and Quality**

The data on sleep duration in Hispanics are variable and may reflect the impact of factors other than ethnicity on sleep duration. In the National Sleep Foundation (NSF) 2010 survey,\(^46\) Hispanics reported an average of 6 hours and 34 minutes of sleep during workdays. They slept longer than African Americans but less than Asians and non-Hispanic whites. In the 1990 National Health Interview Survey,\(^47\) non-Mexican Hispanics had an increased risk for short sleep duration compared to non-Hispanic whites. The 2005-2006 National Health and Nutrition Examination Survey (NHANES) of 6139 individuals (12% Hispanic), however, reported that Hispanics (6.9 h) and Whites (7.0 h) had longer mean sleep duration than Blacks (6.5 h).\(^48\) Our data demonstrate shorter sleep duration among participants with sleep complaints seen in sleep clinics, but is consistent with the NHANES data for those individuals seen in non-sleep clinics.

Restricted or impaired sleep has a significant economic burden with conservative estimates at $107 billion.\(^49\) In our study participants reported poor SQ and even among persons without a specific sleep complaint or diagnosis, only 25% reported very good SQ. In 2010, the National Sleep Foundation (NSF) conducted a phone survey of Americans (25% Hispanic) to determine their sleep habits and knowledge.\(^46\) Nearly 40% of respondents, including 38% Hispanic, said they get a good night’s sleep every night or almost every night. Rarely or never having a good night’s sleep was reported by 14% of Hispanics. Although this survey is not directly comparable to our results, it corroborates our findings that many Hispanics are not satisfied with some aspect of their SQ, and very good sleep is experienced at best by less than half of those surveyed regardless of the method of evaluation.

**Excessive Daytime Sleepiness**

Nearly half of our study participants reported significant daytime sleepiness, a known risk factor for vehicular crashes and impaired work performance.\(^49\)\(^50\) In the multicenter, population-based SHHS, 23% of Hispanic participants had EDS.\(^44\) Bouclet et al.\(^4\) determined EDS prevalence to be 16.4% (95% CI 15.3-17.5) among adults ≥ 40 years old, living in 4 large Latin American cities, using a single question “Is it difficult for you to stay awake during the daytime at least 3 days a week?” Our non-sleep clinic participants were seen in clinic for routine primary care or pulmonary follow-ups; the 18% EDS noted in this group is within the range of previous estimates (Table 3) and highlights a need to address this sleep complaint in Hispanics in primary care and pulmonary clinics. The impact of EDS on overall health, social, and economic domains among Hispanics has yet to be determined.

**Limitations**

Our study has several limitations. We are unable to make direct comparisons to other ethnic groups (non-Hispanic whites, African Americans, and Asians), as we studied Hispanic patients only. Our study cannot provide true population prevalence estimates, as we did not use randomized sampling techniques, but instead relied on a convenience sample of patients in sleep and non-sleep clinics. However, our non-sleep clinic group had no sleep disorders diagnosed at the time of enrollment and were not actively seeking help for sleep complaints. We provide data for the pulmonary and general medicine subgroups in Tables 1 and 2. However, due to the small sample size in pulmonary clinics, we refrained from subgroup analyses. Finally, SDB diagnosis was based on PSG only in the sleep clinic subjects. PSG was offered to all participants; however, the non-sleep clinic and some of the sleep clinic subjects declined testing due to lack of daytime symptoms, a belief that they did not have sleep apnea, lack of desire to use positive airway pressure therapy should the baseline tests prove to be positive, or lack of insurance coverage.

**Summary**

Despite these limitations, our study reports the frequency of several sleep disorders in a diverse group of US Hispanics seen in clinical settings and highlights the need for increased awareness and screening by healthcare providers. Sleep and its associated disorders play an important role in health, wellness, disease, and quality of life. Hispanics are a rapidly growing segment of US society with ever growing healthcare needs. Social, socioeconomic, sociopolitical, lifestyle, cultural, or physiological characteristics may predispose Hispanic patients to an increased prevalence of sleep disorders, including sleep apnea, snoring, and poor sleep quality. Language and cultural barriers may widen health disparities. Our study increases the awareness that risk for SDB, insomnia symptoms, poor sleep quality, and excessive daytime sleepiness are common in a clinical cohort of US Hispanics living in South Florida and highlights the need for further research and education in this area.

**REFERENCES**

Sleep Disorders in US Hispanics


ACKNOWLEDGMENTS

All authors had access to the data and contributed substantially to the design, acquisition, and analysis of data, and writing of manuscript. The work was completed at University of Miami and Miami VA Health Care System. Dr. Shafazand was supported by a grant from the American Sleep Medicine Foundation. Dr. Fleming was supported in part by the European Union ERDF Funding to the ECEHH (University of Exeter).
Obstructive Sleep Apnea in a Danish Population of Men and Women Aged 60-80 Years with Nocturia

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Introduction and Hypothesis: The aim of the present study was in a case-control design to evaluate the association between nocturia and obstructive sleep apnea, in men and women who had nocturia ≥ 2 per night (nocturics) compared to those without nocturia (controls).

Methods: Participants were randomly selected among respondents in a population study of 4000 elderly individuals. Nocturia was assessed using the validated Nocturia, Nocturnal Enuresis, and Sleep-interruption Questionnaire (NDES-Q). Nocturia (≥ 2 voids/night) or control (< 1 void/night) status was assessed by a 3-day frequency volume chart (FVC). Furthermore, all participants completed an overnight ambulatory polygraphic recording to identify obstructive sleep apnea (OSA).

Results: Of 1111 eligible individuals, a total of 75 nocturics and 75 controls (13.5%) were included. Overall, the prevalence and severity of OSA among nocturics and controls was not significantly different. In a sub-analysis we found that 22 nocturics with OSA (69%) had nocturnal polyuria. This led to a significantly increased risk of having OSA (OR 2.8, 95% CI: 1.1-7.3, p < 0.05) when having nocturnal polyuria compared to other pathophysiological causes of nocturia (polyuria, low bladder capacity, a combination of nocturnal polyuria/low bladder capacity, and neither nocturnal polyuria/low bladder capacity).

Conclusions: Nocturia twice or more was not significantly associated with OSA. However, nocturics with nocturnal polyuria had a significantly higher risk of having OSA than nocturics with other pathophysiologicals.

Keywords: Case-control study, elderly, nocturia, nocturnal polyuria, obstructive sleep apnea.

Citation: Bing MH; Jennum P; Moller LA; Mortensen S; Lose G. Obstructive sleep apnea in a danish population of men and women aged 60-80 years with nocturia. J Clin Sleep Med 2012;8(5):515-520.

BRIEF SUMMARY

Current Knowledge/Study Rationale: Nocturia and OSA are common conditions in the elderly population. Is there an association between the two conditions in the general population?

Study Impact: The study showed no overall difference in prevalence of OSA among nocturics and controls. However, nocturics having nocturnal polyuria, had a significant increased risk of having OSA.

Nocturia, defined as waking up at night to void, is highly prevalent in the elderly population. The pathophysiological causes of nocturia are polyuria, nocturnal polyuria, low bladder capacity, sleep disorders, or combinations of these. Age-related changes in the lower urinary tract (including prostatic disease) may cause nocturia, but factors unrelated to the lower urinary tract may also play a role. Factors like excessive fluid before bedtime, alcohol, caffeine, diuretics, and pathological conditions such as hypertension, congestive heart failure, diabetes mellitus, neurological diseases, and OSA may be involved.

Data regarding nocturia and OSA emerging from a general population are sparse; however, such data might elucidate the overall risk of having OSA in nocturics. This might support the clinician in selecting individuals with nocturia who should be referred for further work-up in a sleep clinic.
The aim of the present study was in a case-control design to evaluate the association between nocturia and obstructive sleep apnea by comparing men and women who had nocturia ≥ 2 per night (nocturics) to those without nocturia (controls).

**MATERIALS AND METHODS**

Nocturia was defined as waking up at night to void. Nocturnal polyuria was defined as nocturnal urine volume larger than 33% (in the elderly) of the total 24-h urine volume. All definitions were in accordance with ICS terminology.

Nocturia was assessed in a population study using the new and validated Nocturia, Nocturnal Enuresis, and Sleep-interruption Questionnaire (NNES-Q). The ESS is designed to provide a measurement of an individual’s general level of daytime sleepiness. Respondents are asked to rate on a scale of 0-3 how likely they would be to doze off or fall asleep in 8 situations, based on their usual way of life in recent times. Except for gender-specific items (e.g., deliveries, hormonal treatment, prior gynecological surgery, prior prostate surgery) the questionnaire as a whole, was similar to all. The total number of items in the questionnaire was 98 for women and 94 for men.

Participants were randomly recruited among respondents in a population study of 4000 men and women aged 60-80 years. Details from this study have previously been reported. The inclusion criterion was if participants had completed a question on nocturia. Exclusion criteria were night shift work, severe physical disability, or mental impairment (dementia) and inability to follow instructions. Eligible for inclusion were participants who confirmed nocturic or control status by using a 3-day frequency volume chart (FVC), which recorded volumes and time of each micturition over 3 representative days. Voids that occurred between the time recorded for initiation of nighttime sleep and wake time in the morning were considered nocturia episodes; all other voiding was diurnal. Based on the FVC findings, individuals were categorized as nocturics if they had an average ≥ 2 nocturia episodes/night; controls had an average < 1 nocturia (less than one) episode/night over a 3-day period. Participants were asked to report urinary incontinence episodes in FVCs (Figure 1).

Medical history was obtained through semi-structured interviews. Physical examination was performed, and height and weight measured. All participants completed an overnight ambulatory polygraphic recording identifying chest and abdominal movements, airflow through the nose, and pulse oximetry (Embletta PDS, Flaga, Iceland), which is a valid standard method of screening for SDB.

Participants were given oral and written instructions on how to use the polygraphic equipment on the day of the sleep study. The sleep recording equipment was returned within 1-2 days and data downloaded. Sleep data was evaluated for technical quality; if insufficient, the study was repeated.

Data analysis was performed by initial automatic scoring, supervised by an experienced polygraphic technician and lastly evaluated by one of the authors (PJ) who was blinded for knowledge of nocturic or control status. Technically adequate recordings of ≥ 5 h sleep were required for the recording to be scored. When scoring the sleep recordings the following conventional definitions were used: Apnea was defined as the cessation of airflow through the nose ≥ 10 sec, and hypopnea was defined as the reduction in airflow ≥ 50% associated with a decrease in the pulse oximetry reading (desaturation) ≥ 4%. The severity of obstructive sleep apnea was described by number of apneas and
hypopneas per hour of sleep (apnea-hypopnea index [AHI]). A central apnea event occurred if no abdominal movements were registered during an apnea event. OSA was defined as an AHI ≥ 5, and we defined OSAS as an AHI ≥ 5 and excessive daytime sleepiness (ESS score > 12).

Statistical Analysis
A total of 46 participants in each group were needed to detect a difference ≥ 20% in frequency of OSA, with a statistical power of 80% and a 2-tailed type 1 error rate of 0.05. Fisher exact test or χ² test was used to compare frequency data. Unpaired t-test or Wilcoxon rank sum test were used to compare continuous data. A logistic regression model was used to analyze the question regarding nocturia, thereby becoming potential candidates for participation in the study. Further, we included 50 women in each group; however, we were only able to include 25 men within the time period from January 2003 to January 2005. Thus, a total of 75 nocturics and 75 controls (13.5%) were included. Median age was 71 years (range: 60-82) in nocturics and 66 years (range: 60-82) in controls (Table 1). Participants in this study were slightly younger (median age 67 years [range: 60-82]) than participants in the population study (median age 70 years [range: 60-80]).

Frequency Volume Charts
Mean (95% CI) number of nocturia episodes in nocturics was 2.5 (2.3-2.6), and in controls 0.2 (0.1-0.2), with no significant difference between genders (Table 2). Frequency of individuals having nocturnal polyuria was 55% in nocturics vs. 20% in controls (p < 0.0001).

Obstructive Sleep Apnea
Eleven initial sleep recordings (7.3 %) required repeated evaluation. Two participants with apneas/hypopneas had missing oxygenation recording even after repeated measurements; however they were classified according to their AHI. Further, more women nocturics had oxygen desaturation < 90% compared to controls (Table 2), whereas there was no difference in men. As seen in Figure 2 and Table 2, mean AHI in women was significantly higher in nocturics than controls, whereas no difference in men was observed. In terms of the Epworth Sleepiness Scale, score no significant difference between nocturics and controls was observed.

In nocturics and controls, no significant difference in prevalence and severity of OSA was observed (Table 3). In women, 34% of nocturics had AHI ≥ 5 vs. 24% of controls; in men 56% of nocturics had AHI ≥ 5 vs. 60% of controls. With a more strict definition of OSA based on AHI ≥ 15, the prevalence among nocturics dropped to 16% of nocturics vs. 4% of controls (women) and 32% of nocturics vs. 32% of controls (men). Only one nocturic had OSAS, and this patient had been previously diagnosed with narcolepsy.

Overall, no significant association between OSA and nocturia in general was demonstrated (OR 1.4, 95% CI: 0.7-2.9; Table 4).
One participant had both OSA and central apnea events, and one had predominantly central apnea events. Exclusion of these participants did not change the result. Among those with nocturnal polyuria, there was no significant association between OSA in nocturics vs. controls (OR 1.3 [95% CI: 0.4-4.3]).

In a sub-analysis among nocturics only, we found that 22 individuals with OSA (69%) had nocturnal polyuria. This gives a significant increased risk of having OSA (OR 2.8, 95% CI: 1.1-7.3) when a nocturic had nocturnal polyuria compared to other pathophysiological causes of nocturia (polyuria, low bladder capacity, a combination of nocturnal polyuria/low bladder capacity, or neither nocturnal polyuria/low bladder capacity). In addition, only 7 controls with OSA (27%) had nocturnal polyuria, and there was no significant increased risk of having OSA when nocturnal polyuria occurred in controls (OR 1.9, 95% CI: 0.6-6.0).

We found no significant difference in the prevalence of potential confounders such as hypertension, cardiac disease, neurological disease, use of hypnotics, diabetes, or alcohol intake.

Table 2—Nocturia, Epworth Sleepiness Scale (ESS) score, and sleep variables in participants

<table>
<thead>
<tr>
<th>Variable</th>
<th>Nocturics (n = 25)</th>
<th>Controls (n = 25)</th>
<th>p</th>
<th>Nocturics (n = 50)</th>
<th>Controls (n = 50)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nocturia episodes, mean (95% CI)</td>
<td>2.4 (2.1-2.6)</td>
<td>0.2 (0.1-0.3)</td>
<td>***</td>
<td>2.5 (2.3-2.7)</td>
<td>0.2 (0.1-0.2)</td>
<td>****</td>
</tr>
<tr>
<td>% nocturnal/24 h urine vol., mean (95% CI)</td>
<td>39.2 (34.8-43.6)</td>
<td>24.6 (21.3-28.0)</td>
<td>****</td>
<td>37.5 (34.5-40.6)</td>
<td>26.2 (24.1-28.3)</td>
<td>****</td>
</tr>
<tr>
<td>Epworth Sleepiness Scale, mean (95% CI)</td>
<td>4.8 (3.5-6.1)</td>
<td>5.0 (3.8-6.3)</td>
<td>NS</td>
<td>5.2 (4.2-6.1)</td>
<td>3.8 (2.8-4.8)</td>
<td>NS</td>
</tr>
<tr>
<td>AHI, mean (95% CI)</td>
<td>13.8 (7.1-20.5)</td>
<td>11.8 (5.1-18.5)</td>
<td>NS</td>
<td>6.1 (3.5-8.8)</td>
<td>3.2 (1.5-5.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Oxygen desaturations &lt; 90% (no.), mean (95% CI)</td>
<td>35.0 (13.5-56.6)</td>
<td>29.5 (8.9-50.1)</td>
<td>NS</td>
<td>24.4 (13.1-35.8)</td>
<td>10.1 (1.3-21.5)</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS, nonsignificant; *p < 0.05; ****p < 0.0001; unpaired t-test; Wilcoxon rank sum test.

Figure 2—AHI index in relation to nocturic and control status in men (A) and women (B)

The solid line is the median, the box the interquartile range, the bars the 10th and 90th percentile and the points the outliers.

Table 3—Obstructive sleep apnea (OSA) distribution according to nocturic or control status, stratified by gender

<table>
<thead>
<tr>
<th>Variable</th>
<th>Gender</th>
<th>Normal, 0-4</th>
<th>Mild OSA, 5-14</th>
<th>Moderate OSA, 15-29</th>
<th>Severe OSA, ≥ 30</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nocturics</td>
<td>Women (n = 50)</td>
<td>66%</td>
<td>18%</td>
<td>10%</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>Women (n = 50)</td>
<td>76%</td>
<td>20%</td>
<td>4%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Nocturics</td>
<td>Men (n = 25)</td>
<td>44%</td>
<td>24%</td>
<td>20%</td>
<td>12%</td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>Men (n = 25)</td>
<td>40%</td>
<td>28%</td>
<td>20%</td>
<td>12%</td>
<td></td>
</tr>
</tbody>
</table>

*χ² test.

Table 4—Nocturics vs. Control Crude OR (95% CI) Adjusted OR (95% CI)*

<table>
<thead>
<tr>
<th>Nocturics vs. Control</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men and Women</td>
<td>1.4 (0.7-2.7), NS</td>
<td>1.4 (0.7-2.9), NS</td>
</tr>
<tr>
<td>Men</td>
<td>1.7 (0.5-5.4), NS</td>
<td>1.8 (0.5-7.1), NS</td>
</tr>
<tr>
<td>Women</td>
<td>1.3 (0.6-2.8), NS</td>
<td>1.4 (0.6-3.8), NS</td>
</tr>
</tbody>
</table>

Logistic regression model of OSA in nocturics vs. controls, crude and adjusted odds ratios (nocturics: n = 25 men, 50 women; controls: n = 25 men, n = 50 women). NS, nonsignificant. *Adjusted for BMI, smoking, and time in bed.
between nocturics and controls (Table 1). Only time spent in bed differed between the groups. BMI and smoking differed only between women nocturics and controls (Table 1).

DISCUSSION

Our study assesses the association between nocturia and OSA in an unselected elderly population of nocturics and controls. We used the validated Nocturia, Nocturnal Enuresis and Sleep-interruption Questionnaire (NNES-Q) for assessing nocturia; nocturia was defined according to the International Continence Society and OSA according to the American Academy of Sleep Medicine Task Force. Assessing voiding and sleep related respiratory variables within the same sample, selected from a general population have only been addressed in few studies. These studies demonstrated that older adults with severe sleep disordered breathing have an increased number of nocturia episodes. Most previous studies have been performed in patients attending sleep clinics. The protocol included an intensive examination program, which may partly explain the low participation rate (13.5%). It is likely that the subgroup studied represents a more mobile and healthier population than the total population, which may limit the external validity of the study.

Except from time spent in bed, and BMI, and smoking in women, the frequency of potential confounders did not differ between nocturics and controls (Table 1). This is in contrast with results from our earlier population study, which showed that several morbidities were associated with increasing nocturia severity. It has previously been demonstrated that time spent in bed differed between nocturics and controls, which was confirmed in our study, and we thus adjusted for this effect in the analyses (Table 4).

Frequency Volume Charts

We found that significantly more nocturics than controls had nocturnal polyuria (p < 0.0001), with no difference between genders. This finding corresponds with studies by Swithinbank et al. (women), Rembratt et al. (men and women), and Massolt et al. (incontinent women) who found a markedly higher frequency of nocturnal polyuria in subjects having nocturia (≥ 2 voids) compared to no nocturia.

Obstructive Sleep Apnea

We found no significant association between nocturia per se and obstructive sleep apnea (Table 4). An explanation could be that the association between nocturia and OSA is only found in severe OSA as previously described in a study of community-dwelling elderly. Further, a type II error may influence the results. The finding of nocturnal polyuria in the vast majority of nocturics with OSA emphasizes the importance of elucidating the pathophysiology of nocturia in the individual person with nocturia twice or more. The present study shows that AHI was significantly higher in women with nocturia (Table 2); however, the AHI level was relatively low in both nocturics and controls, and the clinical impact of this gender difference remains unclear.

In a cross-sectional study of community older adults, Endeshaw et al. observed that elderly with an AHI of 25 or greater had significantly more nocturia episodes. This finding agreed with reports on sleep clinic patients. Endeshaw et al. noted that subjects were not randomized, which could have biased the results.

OSA may be associated with increased renal sodium and water excretion mediated by plasma atrial natriuretic peptide (ANP) levels. However, whether ANP level is associated with nocturnal polyuria in the elderly remains unclear. In a recent study by Svatikova et al., the effect of moderate-to-severe OSA (AHI ≥ 20) on plasma ANP levels was examined. The authors concluded that acute untreated OSA and subsequent treatment with CPAP significantly altered the levels of ANP. Among contributing factors to nocturnal polyuria may be an age-related reduction in the diurnal variation in the secretion of plasma arginine vasopressin (AVP), AVP is often undetectable in elderly with nocturia. However, studies of elderly persons have failed to find any correlation between nocturnal polyuria and AVP levels.

Mechanisms other than those mentioned above may be involved in the pathogenesis of nocturia. Sagaya et al. studied biochemical and body composition differences between elderly with nocturia ≥ 2 with young and elderly control groups. The main finding was that in elderly persons with nocturia, a sleep disorder related to a decrease of melatonin may be considered, and a sleep disorder may decrease the threshold for awakening by the desire for voiding.

The above studies demonstrate that the mechanism explaining the association between nocturia and obstructive sleep apnea in the elderly remains unclear.

In conclusion, nocturia twice or more was not significantly associated with OSA in the present study. However, female nocturics had significantly higher AHI and more desaturations < 90% than female controls, indicating a trend towards women having more severe obstructive sleep apnea if they had nocturia. Furthermore, nocturics with nocturnal polyuria had a significantly higher risk of having OSA than nocturics with other pathophysiology.

REFERENCES


ACKNOWLEDGMENTS

This study was financially supported mainly by Lions Club (Scandinavia), Augustinus Foundation, Director Jacob Madsen and Olga Madsens Foundation, AP Moeller Foundation and Ferring Pharmaceuticals. Research Centre for Prevention and Health, Glostrup County Hospital, Denmark has contributed with advice regarding design of the study and layout of the questionnaire, and technical support.

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication September, 2011
Submitted in final revised form February, 2012
Accepted for publication April, 2012

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DISCLOSURE STATEMENT

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

MH Bing, P Jennum, LA Moller et al
Study Objectives: Red blood cell distribution width (RDW) is a newly recognized risk marker for various diseases. We evaluated the value of RDW in predicting the severity of obstructive sleep apnea syndrome (OSAS).

Methods: From retrospective analyses of 526 patients admitted to our sleep laboratory for polysomnography between January 2010 and July 2011, 108 patients with complete medical records and hemogram analyses were evaluated.

Results: The study population consisted of 108 patients (age: 49.16 ± 11.1 [range 16-76] years; 72 [66.7%] males). In the overall population, the mean RDW was 14.04 (± 2.37), and 31 patients (28.7%) had RDW > 15. RDW increased significantly with increased severity of OSAS (p = 0.046) and was positively correlated with the apnea-hypopnea index (p = 0.002, r = 0.300), even in the non-anemic group (p = 0.013, r = 0.291). The apnea-hypopnea index was significantly higher in the group with high RDW (> 15; p = 0.046). RDW was negatively correlated with sleep time (p = 0.028, r = 0.217), average oxygen saturation of hemoglobin (p = 0.003, r = -0.239), and minimum desaturation value (p = 0.016, r = -0.235).

Conclusions: In patients referred with a clinical diagnosis of OSAS, RDW may be a marker for the severity of the condition. As RDW is usually included in a complete blood count, it could provide an inexpensive tool for triaging OSAS patients for polysomnography evaluation.

Keywords: Apnea-hypopnea index, red blood cell distribution width, obstructive sleep apnea syndrome, hemogram

Citation: Sökücü SN; Karasulu L; Dalar L; Seyhan EC; Altın S. Can red blood cell distribution width predict severity of obstructive sleep apnea syndrome? J Clin Sleep Med 2012;8(5):521-525.
Demographic and health behavior-related data, including age, gender, body mass index (BMI), and age-associated medical conditions, as well as medical histories regarding sleep habits and cardiovascular disease were collected from patient records. A respiratory function test, posteroanterior chest x-ray, and electrocardiography performed before PSG were evaluated, and complete blood counts were analysed. Patients known to have cardiovascular, renal, or hepatic diseases were excluded. Patients diagnosed with obesity hypoventilation, overlap syndrome, complex sleep apnea, central sleep apnea, Cheyne-Stokes sleeping disorder, or REM-induced OSAS were excluded from the PSG results. These patients were excluded because these diseases have comorbidities that could cause inflammation, such as morbid obesity, COPD, cardiovascular disease. Also in REM-induced OSAS there are other severity criteria other than AHI. According to these criteria, of 526 consecutive patients, 108 met inclusion criteria and had medical records included and analysed. Based on the AHI, patients were grouped into three OSAS severity categories: mild (AHI 5-15), moderate (AHI 15-30), and severe (AHI > 30). None of the patients had an AHI ≤ 4. Patients were also grouped by BMI, according to the WHO classification: < 20, 20-24.9, 25-29.9, 30-34.9, 35-44.9, 45-49.9, and > 50. Anemia was diagnosed as a hemoglobin value < 13 in men and < 12 in women.

**Measurement of RDW and Laboratory Parameters**

Morning blood samples were drawn from participating patients after an overnight fast > 12 h, and analyzed. RDW, hemoglobin level, white blood cell count, and mean corpuscular volume (MCV) were determined using an ABX Pentra 120 analyzer, with a differential count included as part of the complete blood cell count.

**Polysomnography**

Overnight polysomnography was performed using an Embla A-10 data acquisition and analysis system (Medcare Flaga, Reykjavik, Iceland) in the attended setting at a sleep laboratory under baseline conditions. The following physiological parameters were monitored: brain electrical activity by electroencephalography (EEG; with electrode placements at C4-A1, C3-A2, O2-A1, and O1-A2); eye movements by electro-oculography (EOG); submental muscle activity by electromyography (EMG); ribcage and abdominal effort by respiratory inductive plethysmography (RIP; XactTrace, Medcare Flaga); body position, by a calibrated sensor; snoring sounds by a piezoelectric sensor; oronasal flow, by a nasal pressure cannula (Medcare Flaga); oxygen saturation of hemoglobin (SpO2) by pulse oximetry (8000J; Nonin Medical, Plymouth, MN, USA) with the averaging time set at 3 s; and electrical activity of the heart by electrocardiography (ECG; lead II) sampled at 512 Hz. Sleep stages and arousals were scored according to standard criteria by a skilled pulmonary physician (LK) using the Somnologica Studio software package (Medcare Flaga). Apnea was defined as a cessation of airflow ≥ 10 s and was classified as obstructive in the presence of continued movement on RIP or central in the absence of movement on RIP. Hypopnea was defined as a reduction ≥ 50% in oronasal flow amplitude ≥ 10 s, accompanied by ≥ 3% desaturation and/or arousal. Hypopnea was classified as obstructive when there was evidence of upper airway resistance, such as snoring, paradoxical motion in the respiratory bands, or inspiratory flow limitation indicated by nasal pressure signals.

**Statistical Analysis**

All variables were tested for normality of distribution using the Kolmogorov-Smirnov test. Continuous variables with normal distributions are expressed as mean ± standard deviation (SD). Continuous variables with non-normal distributions are summarized as medians (interquartile range, IQR). Categorical variables are expressed as numbers (percentage). RDW was normally distributed, and comparisons between independent groups were made using the Mann-Whitney U test. Correlations between RDW and nonparametric variables were analysed using Spearman correlation. Correlations between RDW and parametric variables were analysed using Pearson correlation. ANOVA was used for comparisons.

**RESULTS**

The study population consisted of 108 patients (mean age: 49.16 ± 11.1 [range 16-76] years; 72 (66.7%) males). Most patients (92.6%) were under 65 years of age. Fifteen patients (13.9%) were anemic.

Mean recording time was 451.1 ± 38.0 (269-507) min, with a mean sleep time of 353.6 ± 70.6 (127-485) min. Mean average oxygen saturation during sleep was 91.4% ± 6.6% (63%-98%) (Table 1).

In the overall population, the mean RDW was 14.04 (± 2.37), and 31 patients (28.7%) had an RDW > 15. Sixteen patients (14.8%) had mild OSAS, 19 (26.9%) had moderate OSAS, and 31 patients (28.7%) had an RDW > 15. Sixteen patients (14.8%) had mild OSAS, 19 (26.9%) had moderate OSAS, and 31 patients (28.7%) had severe OSAS. Mean RDW values in each group are shown in Table 2.

RDW was not correlated with age or gender. Among other hematological variables, RDW showed an inverse correlation

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Sex</th>
<th>Age (y)</th>
<th>Anemia</th>
<th>Recording time (min)</th>
<th>Sleep time (min)</th>
<th>Average saturation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>72 male/36 female</td>
<td>49.16 ± 11.1</td>
<td>15 anemic/93 nonanemic</td>
<td>451.1 ± 38.0</td>
<td>353.6 ± 70.6</td>
<td>91.4 ± 6.6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>OSAS classification</th>
<th>Severity</th>
<th>Number of patients</th>
<th>Ratio</th>
<th>RDW (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5-15 Mild</td>
<td>16</td>
<td>14.8%</td>
<td>13.15 ± 1.7</td>
</tr>
<tr>
<td></td>
<td>15-30 Moderate</td>
<td>19</td>
<td>26.9%</td>
<td>13.10 ± 2.3</td>
</tr>
<tr>
<td></td>
<td>&gt; 30 Severe</td>
<td>63</td>
<td>58.3%</td>
<td>14.67 ± 2.5</td>
</tr>
</tbody>
</table>

Table 1—Properties of the study cases

Table 2—RDW values by OSAS classification of the study cases
with MCV (86.4 [31.7-108] fL; p = 0.022, r = −0.221). RDW was also correlated with platelet number (p = 0.013, r = 0.239).

**Polysomnographic Parameters**

Platelet number, BMI, AHI, and oxygen desaturation index (ODI) were positively correlated with RDW; whereas MCV, average oxygen saturation of hemoglobin (average SpO2), minimum oxygen saturation of hemoglobin (minimum SpO2), and sleep time were negatively correlated with RDW. After correction for anemia, RDW was still positively correlated with AHI and ODI and negatively correlated with average SpO2, minimum SpO2, and sleep time. Correlations between RDW and the sleep parameters are shown in Table 3.

The AHI was significantly higher in the group with high RDW values (> 15; p = 0.046). Significant positive relationships between RDW and hemoglobin, MCV, platelet count, and AHI were seen in the groups with normal RDW and high RDW values (Table 4, Figure 1).

Based on one-way ANOVA after corrections, RDW increased significantly as the severity of OSAS increased (p = 0.046). The relationships between mild OSAS and moderate OSAS, mild OSAS and severe OSAS, and moderate OSAS and severe OSAS were p = 0.812, p = 0.005, and p = 0.006, respectively (Figure 2).

**DISCUSSION**

This retrospective study is one of only a few studies examining the relationship between RDW and AHI in OSAS. Although preliminary, the results support a correlation between RDW and the severity of OSAS.

RDW has been shown to be a strong independent predictor of morbidity and mortality in patients with chronic heart failure or newly diagnosed symptomatic heart failure and in patients with coronary artery disease. In addition, RDW has been a strong predictor of all-cause mortality in population cohorts. RDW was not only associated with cardiovascular disease, but also predicted mortality from acute pulmonary embolism and community-acquired pneumonia. These findings suggest that the pathophysiology leading to increased RDW may affect the outcomes in chronically ill patients, regardless of anemia status.

Chronic inflammation is also present in OSAS patients, as a part of this multisystem disease. There is evidence that inflammatory processes leading to endothelial dysfunction play a pivotal role in the pathogenesis of cardiovascular complications in OSAS. Various studies have demonstrated elevated

### Table 3—Correlations of RDW with other parameters

<table>
<thead>
<tr>
<th>Parameters</th>
<th>All patients</th>
<th>Non-anemic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r value</td>
<td>p value</td>
</tr>
<tr>
<td>WBC (10³/mm³)</td>
<td>0.015</td>
<td>0.878</td>
</tr>
<tr>
<td>Hb (g/dL)</td>
<td>-0.062</td>
<td>0.526</td>
</tr>
<tr>
<td>Plt (10³/mm³)</td>
<td>0.239</td>
<td>0.013*</td>
</tr>
<tr>
<td>MCV (µm³)</td>
<td>-0.221</td>
<td>0.022*</td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.086</td>
<td>0.496</td>
</tr>
<tr>
<td>BMI</td>
<td>0.213</td>
<td>0.030*</td>
</tr>
<tr>
<td>Recording time (min)</td>
<td>-0.064</td>
<td>0.509</td>
</tr>
<tr>
<td>Sleep time (min)</td>
<td>-0.217</td>
<td>0.028*</td>
</tr>
<tr>
<td>REM duration (min)</td>
<td>0.013</td>
<td>0.895</td>
</tr>
<tr>
<td>AHI</td>
<td>0.300</td>
<td>0.002*</td>
</tr>
<tr>
<td>Average SpO₂ (%)</td>
<td>-0.239</td>
<td>0.013*</td>
</tr>
<tr>
<td>ODI</td>
<td>0.295</td>
<td>0.008*</td>
</tr>
<tr>
<td>Minimum SpO₂ (%)</td>
<td>-0.235</td>
<td>0.016*</td>
</tr>
</tbody>
</table>

BMI, weight/height²; AHI, apnea hypopnea index; ODI, oxygen desaturation index; *p < 0.05.

### Table 4—Evaluation of parameters between groups with normal RDW and higher RDW

<table>
<thead>
<tr>
<th>Parameters</th>
<th>RDW &lt; 15 (n = 77)</th>
<th>RDW ≥ 15 (n = 31)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>49.27 ± 11.61</td>
<td>48.90 ± 9.91</td>
<td>NS</td>
</tr>
<tr>
<td>Sex</td>
<td>51 male (66.23%)</td>
<td>21 male (67.74%)</td>
<td>NS</td>
</tr>
<tr>
<td>WBC (10³/mm³)</td>
<td>7.57 ± 2.03</td>
<td>7.60 ± 1.86</td>
<td>NS</td>
</tr>
<tr>
<td>RBC (10³/mm³)</td>
<td>4.88 ± 0.52</td>
<td>4.94 ± 0.83</td>
<td>NS</td>
</tr>
<tr>
<td>Hb (g/dL)</td>
<td>14.45 ± 1.47</td>
<td>13.54 ± 2.59</td>
<td>0.023</td>
</tr>
<tr>
<td>MCV (µm³)</td>
<td>87.94 ± 8.25</td>
<td>82.54 ± 6.23</td>
<td>0.001</td>
</tr>
<tr>
<td>Plt (10³/mm³)</td>
<td>237.07 ± 61.47</td>
<td>284.61 ± 70.00</td>
<td>0.001</td>
</tr>
<tr>
<td>BMI</td>
<td>31.70 ± 6.48</td>
<td>32.14 ± 7.85</td>
<td>NS</td>
</tr>
<tr>
<td>Recording time (min)</td>
<td>450.58 ± 41.28</td>
<td>452.25 ± 28.61</td>
<td>NS</td>
</tr>
<tr>
<td>Sleep time (min)</td>
<td>358.78 ± 67.28</td>
<td>341.07 ± 78.04</td>
<td>NS</td>
</tr>
<tr>
<td>REM duration (min)</td>
<td>18.30 (12.6-25.8)</td>
<td>17.70 (12.3-20.6)</td>
<td>NS</td>
</tr>
<tr>
<td>AHI</td>
<td>33.3 (21.0-57.2)</td>
<td>58 (32.5-71.4)</td>
<td>0.046</td>
</tr>
<tr>
<td>OSAS classification</td>
<td>Mild:13</td>
<td>Mild:3</td>
<td>0.030</td>
</tr>
<tr>
<td></td>
<td>Moderate:25</td>
<td>Moderate:4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severe:39</td>
<td>Severe:24</td>
<td></td>
</tr>
<tr>
<td>Average SpO₂ (%)</td>
<td>91.87 ± 6.38</td>
<td>90.34 ± 7.26</td>
<td>NS</td>
</tr>
<tr>
<td>ODI</td>
<td>10 (4-32)</td>
<td>25 (8.3-63.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Minimum SpO₂ (%)</td>
<td>77.53 ± 14.61</td>
<td>74.38 ± 15.66</td>
<td>NS</td>
</tr>
</tbody>
</table>

p > 0.05 were nonsignificant (NS); BMI, weight/height²; AHI, apnea hypopnea index; SpO₂, oxygen saturation of hemoglobin measured by pulse oximeter; ODI, oxygen desaturation index; n, number of patients.
inflammatory marker levels in OSAS patients compared with matched controls, with a significant fall after effective treatment with continuous positive airway pressure.\textsuperscript{11} In addition to inflammation, intermittent hypoxia and sleep deprivation may also explain the relationship between RDW and AHI in OSAS. Intermittent hypoxia in OSAS results in the activation of pro-inflammatory transcription factors, which promote the activation of various inflammatory cells, particularly lymphocytes and monocytes.\textsuperscript{12} Thus, hypoxia also triggers inflammation in OSAS patients.

Our results revealed a positive association between RDW and AHI. This relationship was previously reported in a study involving a small number of patients.\textsuperscript{13} However, in contrast to that study, our study found that the relationship remained after adjusting for anaemia, an important confounding factor. Our finding is consistent with previous reports suggesting that the inflammatory mechanism in OSAS may not be directly linked to hemoglobin levels, as RDW was only modestly correlated with serum hemoglobin.\textsuperscript{8} Thus, our study demonstrates a relationship between severity of OSAS and RDW that is dependent on inflammation and intermittent hypoxia and independent of anemia.

We also found a negative association of RDW with average and minimum oxygen saturation during sleep, which could be explained by the effect of hypoxia on RDW. Intermittent hypoxia is a major trigger for the cardiovascular and metabolic alterations associated with OSAS.\textsuperscript{12,14} Recurrent pharyngeal collapse during sleep can lead to repetitive sequences of hypoxia-reoxygenation, which induce immuno-inflammatory alterations and cardiovascular complications.\textsuperscript{12,14} A positive relationship between RDW and the oxygen desaturation index may also indicate the severity of OSAS. On the other hand, we found only a weak negative correlation between sleep time and RDW, although effects of sleep deprivation and shorter sleep duration on metabolic processes have been reported.\textsuperscript{15,16}

One of the weaknesses of our study is that because it is a retrospective study, we do not have markers of inflammation which could affect RDW values, thus we could not evaluate their correlation. Also, although RDW could not be used as a screening tool for general population depending on this study results because it could be affected by various independent variables, it could be used in sleep laboratories with long waiting lists to give earlier appointment so these patients could able to reach earlier treatment options.

In conclusion, the present study demonstrated a positive relationship between RDW at presentation and the AHI in patients evaluated for OSAS, even in non-anemic patients. The study of anisocytosis may provide important pathophysiological insights into OSAS. The retrospective evidence of an association between elevated RDW and the severity of OSAS in the present study suggests the clinical usefulness of RDW values. As RDW is usually included in a complete blood count, it could provide an inexpensive tool for triaging OSAS patients for polysomnography evaluation. Patients with severe OSAS could be identified based on RDW at the first examination and given priority for testing and treatment. Prospective studies with larger populations, using different severity criteria and excluding other inflammatory causes, are needed to confirm RDW as a useful severity assessment tool in OSAS.

REFERENCES

Detection of Sleep Disordered Breathing and Its Central/Obstructive Character Using Nasal Cannula and Finger Pulse Oximeter

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1Center for Sleep and Wake Disorders, Institute of Medicine, University of Gothenburg, Sweden; 2Institute for Monitoring, Diagnosis and Assistance (IMDA), SRH University of Applied Science Heidelberg, Germany; 3Institute of Biomedical Engineering, Karlsruhe Institute of Technology (KIT), Karlsruhe, Germany

Study Objective: To assess the accuracy of novel algorithms using an oximeter-based finger plethysmographic signal in combination with a nasal cannula for the detection and differentiation of central and obstructive apneas. The validity of single pulse oximetry to detect respiratory disturbance events was also studied.

Methods: Patients recruited from four sleep laboratories underwent an ambulatory overnight cardiorespiratory polygraphy recording. The nasal flow and photoplethysmographic signals of the recording were analyzed by automated algorithms. The apnea hypopnea index (AHI\text{auto}) was calculated using both signals, and a respiratory disturbance index (RDI\text{auto}) was calculated from photoplethysmography alone. Apnea events were classified into obstructive and central types using the oximeter derived pulse wave signal and compared with manual scoring.

Results: Sixty-six subjects (42 males, age 54 ± 14 yrs, body mass index 28.5 ± 5.9 kg/m²) were included in the analysis. AHI\text{manual} (19.4 ± 18.5 events/h) correlated highly significantly with AHI\text{auto} (19.9 ± 16.5 events/h) and RDI\text{auto} (20.4 ± 17.2 events/h); the correlation coefficients were r = 0.94 and 0.95, respectively (p < 0.001) with a mean difference of -0.5 ± 6.6 and -1.0 ± 6.1 events/h. The automatic analysis of AHI\text{auto} and RDI\text{auto} detected sleep apnea (cutoff AHI\text{manual} ≥ 15 events/h) with a sensitivity/specificity of 0.90/0.97 and 0.86/0.94, respectively. The automated obstructive/central apnea indices correlated closely with manually scoring (r = 0.87 and 0.95, p < 0.001) with mean difference of -4.3 ± 7.9 and 0.3 ± 1.5 events/h, respectively.

Conclusions: Automatic analysis based on routine pulse oximetry alone may be used to detect sleep disordered breathing with accuracy. In addition, the combination of photoplethysmographic signals with a nasal flow signal provides an accurate distinction between obstructive and central apneic events during sleep.

Keywords: Central sleep apnea, finger photoplethysmography, home sleep test, obstructive sleep apnea, sleep disordered breathing

Citation: Sommermeyer D; Zou D; Grote L; Hedner J. Detection of sleep disordered breathing and its central/obstructive character using nasal cannula and finger pulse oximeter. J Clin Sleep Med 2012;8(5):527-533.
D Sommermeyer, D Zou, L Grote et al

However, distinction between obstructive and central events using oximetry alone is an issue that remains to be solved, especially in patients with chronic heart failure.15

Intrathoracic pressure changes during spontaneous breathing are mirrored in the peripheral pulse wave.16 Whether this feature can be used to distinguish obstructive and central apnea events has not been tested. We have developed a novel finger photoplethysmography pulse oximeter sensor for the assessment of cardiovascular risk in patients with suspected OSA.17 Several parameters including oxygen saturation, pulse rate and a finger pulsatile wave signal can be derived from the oximeter sensor. In the current study, we aimed to validate an automatic algorithm using signals derived from the oximeter probe and nasal cannula to detect and differentiate obstructive and central apnea. In addition, the accuracy of the oximeter sensor signal for quantification of SDB was evaluated alone or in combination with a nasal airflow signal.

METHODS

Study Subjects

Seventy-six subjects with suspected SDB were recruited from the sleep laboratory at Sahlgrenska University Hospital, Gothenburg, Sweden (n = 46) and 3 German sleep centers in Ulm, Berlin, and Nuernberg (n = 30). Subjects were informed regarding their participation in the study.

Sleep Study

All patients underwent an ambulatory overnight cardiorespiratory polygraphy recording (SOMNOcheck2, WEINMANN, Germany) including nasal airflow, thoracic and abdominal respiratory effort, heart rate, oxygen saturation (SpO₂) and body position. Patients received oral/written instructions for proper application during the sleep clinic visit. The device was self-applied by the patients at home before bedtime.

Sleep related respiratory events were manually scored by sleep technicians who were blind to the study. In brief, an apnea was scored as ≥ 90% flow reduction compare to baseline ≥ 10 seconds. An obstructive apnea was classified by continued/ increased inspiratory effort during the event and a central apnea was characterized by absent inspiratory effort during the event. A hypopnea was defined by ≥ 50% flow reduction compared to baseline for ≥ 10 sec together with ≥ 3% oxygen desaturation. AHI_manual was calculated as the total number of apnea/hypopnea events divided by the recording time.

Automatic Algorithm Description

Signal Handling

A subset of the polygraphic channels (pulse oximeter and optional nasal cannula) was applied for autonomic analyses. The pulse wave signal was extracted from the oximeter recording. Pulse wave amplitude (PWA) and pulse rate were calculated from the pulse wave signal.

A minimum ≥ 3-h artifact-free analysis periods of the flow signal were considered acceptable for computation of validity data in the study. In general, a signal decomposition algorithm based on a dictionary of time-frequency atoms (matching pursuit method)18 was modified in order to analyze specific patterns in the oximeter signals (see appendix for further detail of method). Thus, well-defined template functions were correlated through the original signals and the template functions with the highest correlation coefficient were saved for further analysis. The forms of these template functions were predefined by designed mathematical functions which reflect the typical patterns of interest (e.g., desaturations). These functions were then fitted to the particular, real signal pattern by varying function parameters to generate the best fit in terms of amplitude and frequency characteristics. By doing this, chronological coherences as well as morphological parameters of the used signals were considered in the calculation process. Separate algorithms were applied to automatically quantify respiratory disturbance index (RDI_auto), AHI_auto, obstructive apnea index (OAI), and central apnea index (CAI).

Autonomic Arousal Detection

An autonomic arousal, which indicates an activation of the autonomic nervous system, was used to confirm the sleep disrupting character of mild respiratory events like hypopneas. It was defined as: (1) pulse rate increase ≥ 20% compared to baseline; or (2) PWA attenuation ≥ 40% compared to baseline; or (3) PWA attenuation ≥ 35% with pulse rate increase ≥ 15% compared to baseline.

Respiratory Event Detection

RDI_auto was calculated based on oximeter signal alone. SpO₂, pulse rate, and PWA were used to classify respiratory disturbance events. The definition of an automatically scored respiratory disturbance event was: (1) SpO₂ drop ≥ 4% or (2) SpO₂ drop ≥ 3% with an autonomic arousal. RDI_auto was calculated as the number of automatically scored respiratory disturbance events divided by the recording time.

AHI_auto was automatically calculated using nasal flow and oximeter signals. The definition of an automatically scored apnea was: (1) ≥ 90% drop in the flow amplitude compare to baseline; (2) duration of the event ≥ 10 sec; (3) > 90% of the event’s duration met the amplitude reduction criteria for apnea. The definition of an automatically scored hypopnea was: (1) ≥ 50% drop in the flow amplitude compared to baseline together with 3% oxygen desaturation or an autonomic arousal; (2) duration of the event ≥ 10 sec; (3) more than 90% of the event’s duration met the amplitude reduction criteria for hypopnea, which conforms to the alternative criteria of the AASM scoring manual.19 AHI_auto was calculated as the number of automatically scored apnea/hypopnea events divided by the recording time.

Obstructive/Central Apnea Differentiation

Identification of apneas as well as determination of their duration was based on the assessment of the inspiratory and expiratory phases of the nasal flow signal. The type of the apnea (obstructive vs. central) was determined by analysis of the pulse waveform. In detail, respiratory effort was derived by analyzing fluctuations of the PWA signal caused by intrathoracic pressure changes during spontaneous breathing cycles. The PWA signal was derived from the photoplethysmographic pulse wave signal by computing and plotting subsequently the amplitude value of each pulse wave for the duration of each single pulse wave...
Obstructive/Central Apnea Distinction from PWA

(Figure 1). In order to detect the presence or absence of respiratory effort, baseline drifts of the PWA signal were eliminated as a first analysis step. Next, the signal power in the typical frequency band of breathing (0.15-0.4 Hz) was determined during the apnea phase and compared with the signal power of the same frequency range 15 sec before the apnea event (Figure 2). An *effort ratio* index was defined as:

\[
\text{effort\_ratio} = \frac{\text{signal\_power\_pwa\_periodic\_During\_Apnea}}{\text{signal\_power\_pwa\_periodic\_Before\_Apnea}}
\]

Since the intrathoracic pressure changes may increase during obstructive events, effort ratios > 1.0 are possible. An effort ratio < 0.56 was required for classification of a central event.

**Post Hoc Analysis On Flow Signal Quality**

In order to evaluate the influence of signal quality to the algorithms, flow data quality was rated according to the proportion of recording time with an offset signal, mouth leak, or reduced signal amplitude (positioning of the sensor). A 3-level scale was used with cutoff of more than 80%, 60% to 80%, and < 60% of artifact-free recording time.

**Statistical Analysis**

Pearson correlation analysis was used to assess the association between \( \text{AHI}_{\text{manual}} \) and \( \text{AHI}_{\text{auto}}/\text{RDI}_{\text{auto}} \). The intraclass correlation coefficient (ICC) was used to assess the overall agreement between \( \text{AHI}_{\text{manual}} \) and \( \text{AHI}_{\text{auto}}/\text{RDI}_{\text{auto}} \). Differences between the methods were analyzed using the Bland-Altman plot. Receiver operator characteristic (ROC) curves were applied to assess the diagnostic accuracy of the algorithm using different AHI cutoff points. Sensitivity and specificity, positive predictive value (PPV), negative predictive value (NPV), as well as positive and negative likelihood ratio were calculated. The data were presented as mean and standard deviation. A p-value of 0.05 or less was considered statistically significant.

**RESULTS**

Ten of 76 subjects were excluded due to poor data quality (7 with poor flow or effort signals, 3 with insufficient recording time due to loss of finger sensor signal). Sixty-six subjects (42 males, age 54 ± 14 years, body mass index 28.5 ± 5.9 kg/m², recording time 6.9 ± 1.2 h) were included in the final analysis. The most frequent comorbidities included hypertension (46%) and diabetes (14%). See Table 1 for patient characteristics.

**Table 1—Patient characteristics of the study cohort**

<table>
<thead>
<tr>
<th>Mean (SD)</th>
<th>Number (percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (yrs)</strong></td>
<td>54 (14)</td>
</tr>
<tr>
<td><strong>Body mass index (kg/m²)</strong></td>
<td>28.5 (5.9)</td>
</tr>
<tr>
<td><strong>Heart rate (bpm)</strong></td>
<td>68.2 (10.3)</td>
</tr>
<tr>
<td><strong>Systolic BP (mm Hg)</strong></td>
<td>133.6 (25.3)</td>
</tr>
<tr>
<td><strong>Diastolic BP (mm Hg)</strong></td>
<td>78.2 (12.1)</td>
</tr>
<tr>
<td><strong>Apneahypopnea index (events/h)</strong></td>
<td>19.3 (18.5)</td>
</tr>
<tr>
<td><strong>Apnea index (events/h)</strong></td>
<td>10.4 (15.4)</td>
</tr>
<tr>
<td><strong>4% oxygen desaturation index (events/h)</strong></td>
<td>19.3 (17.2)</td>
</tr>
<tr>
<td><strong>ESS</strong></td>
<td>10 (5)</td>
</tr>
<tr>
<td><strong>Subjects</strong></td>
<td>66</td>
</tr>
<tr>
<td><strong>Males</strong></td>
<td>42 (63%)</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>30 (46%)</td>
</tr>
<tr>
<td><strong>Post myocardial infarction</strong></td>
<td>7 (11%)</td>
</tr>
<tr>
<td><strong>Congestive heart failure</strong></td>
<td>5 (8%)</td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td>3 (5%)</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>9 (14%)</td>
</tr>
<tr>
<td><strong>COPD</strong></td>
<td>4 (6%)</td>
</tr>
</tbody>
</table>
In total, 8,804 apnea/hypopnea events (4,715 apneas) were manually scored, and 9,055 apnea/hypopnea events were detected by the autonomic algorithm. Among 2,260 hypopnea events automatically detected, 74% were based on 3% oxygen desaturation criteria and 26% were based on autonomic arousal criteria (approximately 9 events per subject, generating an index of 1.4/h). There was a very good agreement between AHImanual and AHIauto (r = 0.94, ICC 0.93, p < 0.001). The mean difference between the methods was -0.5 ± 6.6 events/h (Figure 3A). The correlation between the AHImanual and the oximeter based RDIauto was r = 0.95 (p < 0.001). The Bland-Altman analysis showed a mean difference between the methods of -1.0 ± 6.1 events/h (Figure 3B); the ICC was 0.94. The variability of the AHI/RDI differences suggested an underestimation of the automated algorithm in some patients with higher AHImanual. Flow signal quality analysis showed that 36 of the 66 recordings contained > 80% artifact-free time. An additional 20 recordings were in the 60% to 80% range. Finally, 10 recordings showed < 60% of recording time without artifacts. The correlation between AHImanual and AHIauto in the 3 categories was 0.98, 0.90, and 0.88, respectively, indicating that flow signal quality strongly influenced the agreement between the methods.

Accuracy of the Automated Obstructive/Central Apnea Scoring Algorithm

The analysis of the algorithm for differentiation of obstructive (n = 3,673) and central (n = 1,042) apneas was made on the complete data set irrespective of the flow signal quality. Mixed apnea in the manual scoring was classified as obstructive apnea in the comparison. The correlation coefficients between manually and automatically scored CAI and OAI were 0.95 and 0.87, respectively. The mean difference between the methods for central apnea and obstructive apnea detection was 0.3 ± 1.5 and -4.3 ± 7.9 events/h, respectively. BMI did not systematically influence the accuracy of the detection algorithm, although only a limited number of subjects (n = 6) had BMI > 35 kg/m² (data not shown). Some of the obstructive apnea events were scored as hypopnea in the algorithm. The difference between manually and automatically scored hypopnea indices was 4.1 ± 7.2 events/h. A case-by-case comparison in subjects with central apnea index ≥ 3 events/h is shown in Figure 4.

Diagnostic Accuracy

Different cutoff values were used to validate the diagnostic capacity of the AHIauto. The sensitivity, specificity, positive and negative predictive values (PPV, NPV), positive and negative likelihood ratios (+LR, -LR), and the area under the ROC curve value for identification of sleep apnea are shown in Table 2.

The AHIauto based on photoplethysmography and flow signals, showed a sensitivity of 0.90 and a specificity of 0.86 when the AHI cutoff of 15 was used. The area under the ROC curve was 0.96. When the assessment was purely based on the pulse oximetry derived RDI, the sensitivity and specificity were 0.97 and 0.94, respectively, with the area under the ROC curve of 0.98 (Figure 5).
Obstructive/Central Apnea Distinction from PWA

When using CAI_{manual} ≥ 5 events/h as the diagnostic cutoff for patient with a component of CSA (n = 6), the automated algorithm detected CSA patients with sensitivity, specificity, PPV, NPV, +LR, -LR, and area under the ROC curve of 0.83, 0.98, 0.83, 0.83, 25, 0.17, and 0.98, respectively.

DISCUSSION

The current study demonstrated for the first time that a novel computer algorithm based on a combination of nasal air flow and photoplethysmographic pulse wave signals may be used to accurately detect and differentiate obstructive and central sleep apnea events. In addition, an algorithm based on the pulse oximeter signal alone provided a good quantitative estimate of SDB severity.

OSA, the most common type of SDB, has been associated with cardiovascular, metabolic, and pulmonary comorbidities. In the light of a growing need for diagnosis and treatment of SDB patients, unattended home sleep studies using portable monitoring devices have been widely applied in the clinical setting. For instance, ambulatory cardiorespiratory polygraphy have been used for CSA/Cheyne-Stokes respiration detection in heart failure patients.22 According to the AASM, a minimum of heart rate, oxygen saturation, and respiratory analysis (e.g., by airflow or peripheral arterial tone) is required for out-of-center sleep testing.22 Finger PWA derived from peripheral arterial tone has been used for respiratory disturbance event detection in combination with a pulse oximeter at home.23 In this study, we were interested in the combination of airflow and signals derived from a common pulse oximeter sensor, including PWA. Recently, we were able to derive a PWA signal from pulse oximetry and evaluated its relevance for cardiovascular risk assessment.17 Thus, we wanted to further test the validity of such a signal for SDB diagnostics in the ambulatory setting. The diagnostic capacity was tested in two separate conditions: One included application of a nasal cannula and the other was based on signals derived from the pulse oximeter sensor alone.

It is known that respiratory movements cause variation in the peripheral circulation. Changes in intrathoracic pressure modulate central venous pressure and alter venous return to the heart which can be detected by photoplethysmographic sensor attached to skin.16 The respiratory induced frequency component of the photoplethysmographic signal has been closely associated with respiratory volume.24 Although the underlying physiological mechanisms are not fully understood, intrathoracic pressure changes and autonomic nervous activity oscillations seem to play a role in this variation.24,25 Central apnea is characterized by an absence of inspiratory effort during airflow cessation which is associated with lower signal power in the 0.15-0.40 Hz frequency band of the PWA signal. This was indeed the case in our finger PWA signal analysis which provided a possibility to distinguish between obstructive and central apnea. We also found that in subjects with dominant central apneas, the algorithm tended to slightly underestimate the number of central events. In cases with mixed apneas, which were classified as “obstructive apnea” in the analysis, there was a trend towards overestimation of the central events, and the degree depended on the length of the central apnea component.

The pathogenesis of CSA and OSA is different, but there may be similar clinical complications in terms of cardiovascular morbidity and mortality. In a large community-based cohort, increments of obstructive and central apnea indices were both associated with increased incidence of cardiovascular events.26 In patients with congestive heart failure, severe SDB provided a 2-fold increase risk for death compared with those without severe SDB.27 In the post hoc analysis comparing severe and mild SDB groups, mortality was only significantly higher in the group with predominant CSA but not in those with predominant OSA. Hence, the distinction between different types of respiratory events may have important implications for the

<table>
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<tr>
<td>AHI</td>
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<tr>
<td>≥ 5/h</td>
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<tr>
<td>≥ 10/h</td>
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<tr>
<td>≥ 15/h</td>
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<tr>
<td>≥ 20/h</td>
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<td>≥ 30/h</td>
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Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (+LR), negative likelihood ratio (-LR), and area under the ROC curve (AUC) of AHI_{auto} using different cutoff values of AHI_{manual}.

Figure 5—Receiver operator characteristic curve of RDI_{auto} and AHI_{manual} (cut-off AHI_{manual} ≥ 15), AUC = 0.98
classification and treatment of patients with SDB. According to the AASM guidelines, the preferred technique for detection of respiratory effort is either esophageal manometry, or calibrated or uncalibrated inductance plethysmography. However, both methods provide an obvious limitation in terms of applicability during unattended recordings in the home environment. To the best of our knowledge, the current available diagnostic instruments using nasal flow and pulse oximeter can detect apnea/hypopnea events but are unable to differentiate obstructive versus central apnea event. In the current study we have shown that our automatic algorithm can differentiate central/obstructive events with high accuracy. Hence, the algorithm may provide an important additional benefit in screening programs, particularly in populations with high likelihood of central events (e.g., patients with heart failure, stroke, or opioid intake).

Using AHI ≥ 15 as the diagnostic cutoff, oximeter combined with nasal cannula has been shown to detect sleep apnea with a high accuracy. However, when AHI ≥ 5 was applied as the cutoff, high sensitivity but low specificity of the automatic analysis was found in the current study. This was not unexpected, as previous studies using similar signals and cutoff levels showed comparable results.\(^8\)\(^,\)\(^11\) Hence, limited-channel devices may be sensitive to rule in SDB patients but seem to be less robust to rule out patients, especially when lower thresholds are applied. The diagnostic accuracy of these devices could be improved if recordings are manually reviewed. A study comparing automatic analysis to manual scoring from a limited channel device found an increase in specificity from 0.6 to 0.87 when a cutoff AHI ≥ 5 was used.\(^12\)

The quantification of RDI using information derived from oximeter yielded also a good agreement with the manually scored AHI. The diagnostic accuracy of using oximeter signal alone was found to be similar to nasal cannula/oximeter combination in this cohort. One explanation could be that there were few respiratory disturbance events based on 3% desaturation and autonomic arousal in the analyzed material (~2.5 events/h). On the other hand, finger pulse wave attenuations reflecting sympathetic nervous activity have been shown to associate in all the cases.

Several study limitations need to be addressed. In order to reflect the clinical setting, unattended ambulatory recordings were applied in the study. However, we did not use PSG as the comparator which limited the capacity for scoring arousals and may, in some patients (delayed sleep onset or low sleep efficiency), lead to overestimation of the validity of the algorithm. Inter- and intra-score variability testing was not conducted prior to the analysis and event-by-event concordance was not performed. Nasal flow, but not oronasal thermistor, was used to classify an apnea event; this is not in accordance with current AASM guidelines as remaining mouth flow may be left undetected.\(^30\) The hypopnea event definition in the study was adapted from the alternate AASM guidelines, but automatic arousal was used rather than arousal determined in electroencephalographic (EEG) recording. Although the number of hypopnea events detected solely by the autonomic arousal criterion was low in the current study, we consider that these events may provide novel information on apnea/hypopnea related autonomic activation and it is important to maintain it in the algorithm. PWA attenuations and pulse rate accelerations were used to classify autonomic arousal events instead of changes in electroencephalography activity used for standard arousal classification. It has been shown that a drop of PWA is a sensitive marker for changes in cortical activity during sleep.\(^31\) Acoustically induced arousal from NREM sleep could induce biphasic changes of finger PWA fall and an increase of heart rate.\(^32\) Indeed, the reduced PWA alone or in combination with an increase in heart rate was found to be closely correlated with PSG-scored electroencephalographic arousals.\(^33\) In the current study, we did not use a separate nasal airflow and oximeter device for comparison with the polygraphic recording. Rather, we tested the algorithm using signals derived from the polygraphic recording itself. Hence, the reproducibility of such algorithms in a two-channel screening device for SDB recognition remains to be determined. Study subjects were selected among patients referred to the sleep laboratory. Although the cohort included some patients with predominantly central apneas, the study population was not ideally balanced in terms of proportion of central or obstructive sleep apnea. The applicability of the algorithms to identify high risk SDB patients in the general population needs also to be further studied. Finally, the classification of mixed apneas as “obstructive” apneas might not be accurate in all the cases.

CONCLUSIONS

There is an unmet need for simple diagnostic devices with documented accuracy for the differentiated classification of SDB. This study describes a novel automated algorithm that uses a combination of nasal flow and different features of the photoplethysmographic signals to detect and differentiate obstructive and central apneas. It was also demonstrated that information from the finger pulse oximeter alone could be used for more advanced SDB diagnostics. This finding has a potential implication in the era of shift from attended laboratory monitoring towards ambulatory home testing.\(^35\)

REFERENCES


ACKNOWLEDGMENTS

This work was supported by the German Ministry for Education and Science (BMBF), the Swedish Heart and Lung Foundation and the Royal Society of Arts and Science in Göteborg.

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication July, 2011
Submitted in final revised form February, 2012
Accepted for publication March, 2012
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DISCLOSURE STATEMENT

This study was supported by a research grant from Weinmann GmbH. Dr. Sommermeyer was an employee of MCC which was under contract to Weinmann GmbH. Dr. Grote has served as a medical advisor of Weinmann and has participated in clinical studies sponsored by MSD, Philips Respironics, Weinmann and Mundipharma. Dr. Hedner has participated in clinical trials sponsored by MSD, Philips Respironics and Weinmann. The other author have indicated no financial conflicts of interest.
Study Objectives: Serious morbidity may be linked to sleep disordered breathing (SDB) among children with sickle cell disease (SCD). We investigated the stability of polysomnography (PSG) results among children not having acute complications of SCD.

Methods: Two PSGs were performed on a subsample of 63 children 4 to 18 years of age from the Sleep and Asthma Cohort Study. All had HbSS or HbSβ disease. Two PSGs were compared for 45 subjects. Excluded from comparison were 18 children who had begun transfusions or hydroxyurea, had an adenotonsillectomy between the PSGs, or had a pain crisis or behavioral problems may be due to sleep disruption by pain, treatment, or stroke. In addition, preliminary results suggest that more than 20% of SCD patients with sleep disordered breathing do not have habitual snoring.

PSG is considered the “gold standard” test for evaluating SDB. However, it can be burdensome and its clinical value has been debated, because of a lack of data on the stability and interpretability of the findings. We investigated whether classification of SDB status changes 1 year or more after an initial PSG in a group of SCD patients who were clinically stable at between PSGs was 581 ± 119 days (19.1 ± 3.9 months). Ten of 45 changed from ≥ 2 events per hour to < 2; 3 of 45 from < 2 to ≥ 2; 7 of 45 had ≥ 2 on both nights. Six of 45 changed from ≥ 5 to < 5, 2 of 45 from < 5 to ≥ 5, and 1 had ≥ 5 on both nights (McNemar χ², p = 0.09, and p = 0.29).

Conclusions: In the absence of acute SCD complications, overnight PSG usually remains stable or improves over a 12- to 30-month period. Only 6.7% subjects, or fewer, had AHI on a subsequent PSG that would re-classify the child as having SDB not identified in the earlier PSG.

Keywords: Sickle cell disease, polysomnography, obstructive sleep apnea

Citation: Mullin JE; Cooper BP; Kirkham FJ; Rosen CL; Strunk RC; DeBaun MR; Redline S; Kemp JS. Stability of polysomnography for one year and longer in children with sickle cell disease. J Clin Sleep Med 2012;8(5):535-539.

BRIEF SUMMARY

Current Knowledge/Study Rationale: Particularly serious morbidity is associated with sleep-disordered breathing among patients with sickle cell disease. We investigated whether polysomnography results would change in otherwise stable patients.

Study Impact: Over an 18 month interval, in the absence of worsening of symptoms due to sleep-disordered breathing or sickle cell disease, polysomnography results were stable among patients 4 to 18 years old.
METHODS

Institutional review board approval was obtained at Washington University in St. Louis, Missouri, and Case Medical Center, Cleveland, Ohio.

Participants

Participants were excluded from this study if they met any of the following criteria: chronic blood transfusion at time of enrollment, comorbidities such as Pierre-Robin sequence, craniostenosis, neuromuscular disease, serious preexisting lung disease, or use of continuous positive airway pressure therapy. Participants were not excluded if they had adenotonsillar hypertrophy or prior adenoid or tonsil surgery. A PSG was performed upon enrollment for all patients, provided they were free of pain or symptoms of a respiratory infection. A second PSG was performed later on a convenience sample of 63 patients willing to undergo a second study enrolled at 2 of the 3 SAC sites (St. Louis and Cleveland), when they were free of pain or symptoms of a respiratory infection. Participants were ≥ 4 and ≤ 18 years old with sickle cell disease: Hemoglobin SS or Hemoglobin HbSβ* Thalassemia (Hb SS or HbSβ*). Participants who were prescribed hydroxyurea, or had an adenoidectomy, tonsillectomy, or adenotonsillectomy before studies underwent the second PSG but were excluded from this analysis. Any participant requiring supplemental oxygen during a PSG, as determined by clinician’s judgment, was excluded from the analysis. Medical records were reviewed to determine which participants were hospitalized for vaso-occlusive pain events or acute chest syndrome within 3 months of a PSG, which participants were hospitalized for respiratory symptoms within 2 weeks of a PSG, and which participants were started on chronic blood transfusion between PSGs. These participants were also excluded from the analysis. None were excluded because of worsening symptoms of OSA between PSGs—snoring, behavioral disturbances, daytime sleepiness, etc. Analgesic drugs were routinely prescribed for as needed use. Frequencies of narcotic use or prescription refills were not analyzed.

Polysomnography

Each patient underwent 2 nocturnal PSGs in the sleep laboratories at St. Louis Children’s Hospital/Washington University in St. Louis or the clinical research unit at University Hospital–Case Medical Center, Cleveland, Ohio. The PSGs were performed using a standardized protocol and centrally scored at a reading center by research polysomnologists who were blinded to any clinical data, per the SAC protocol as described in detail elsewhere. Inter- and intra-scorer reliability were monitored across clinical data, per the SAC protocol as described in detail elsewhere by research polysomnologists who were blinded to any data. Other PSG indices analyzed included total sleep time (TST), percent of TST in REM sleep, percent of TST in the supine position, AHI, and average SpO2% during sleep. Study 1 and Study 2 group-mean differences were compared using unpaired t tests or the Mann-Whitney rank-sum test. The within-subject differences of key variables were compared between nights using paired t tests for normally distributed variables and Wilcoxon signed-rank test for variables that were not distributed normally. Difference values were calculated by subtracting Study 1 values from Study 2. All point estimates are presented with 95% confidence intervals unless otherwise indicated.

Further analysis was conducted for the primary metric of AHI. Participants were classified as having SDB using both thresholds (≥ 2 and ≥ 5 events/h) and were classified into 4 groups based on congruency of classification from Study 1 to Study 2: no SDB on both nights, SDB on study 1 only, SDB on study 2 only, and SDB on both nights. Analysis of variance (ANOVA) was conducted on all 4 groups to compare the groups on the basis of age at date of first study, number of days between studies, BMI, time spent in REM sleep, time spent supine, and difference in time spent in REM sleep and in time spent supine. Chi-square analyses were used to compare all 4 groups on the basis of site and gender, using Fisher exact test when appropriate. McNemar test for changes was used to quantify the significance of changes in category (SDB vs. no SDB) from night 1 to night 2, using both ≥ 2 and ≥ 5 event thresholds.

RESULTS

Patient Characteristics

Sixty-three children had 2 PSGs performed an average of 581 [544.7, 616.4] days apart (range: 322-987 days or 10.6 to 32.4 months). Forty-five participants met the inclusion criteria for analysis of both PSGs in this study. Eighteen were excluded because they had begun transfusions (8), hydroxyurea (4), or nighttime supplemental oxygen (1), had an adenotonsillectomy between PSGs (1), or had a pain crisis or acute chest syndrome (4) within 3 months before the second PSG. Five participants were taking hydroxyurea at the time of both PSGs, and were included in the final analysis. Mean age at time of first study was 12.3 [11.1, 13.5] years (range: 4.6-18.7), and 49% were male. Mean BMI on night of study 1 was 18.2 [17.3, 19.2] kg/
Comparison of Group Mean PSG Parameters between Study 1 and Study 2

Table 1—Group mean results for sleep and respiratory parameters for PSG nights 1 and 2

<table>
<thead>
<tr>
<th>Sleep variables</th>
<th>Night 1</th>
<th>Difference night 2 – night 1</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Sleep Time (min)</td>
<td>473.4 [451.0, 495.8]</td>
<td>45.4 [22.4, 68.4]</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>REM (%TST)</td>
<td>19.2 [17.2, 21.2]</td>
<td>1.4 [-1.0, 3.7]</td>
<td>0.226</td>
</tr>
<tr>
<td>Supine position (%TST)</td>
<td>47.3 [40.3, 54.3]</td>
<td>3.0 [-5.1, 11.2]</td>
<td>0.453</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Respiratory variables</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>AHI</td>
<td>1.2 [0, 35.2]*</td>
<td>-1.45 [-3.2, 0.3]</td>
<td>0.154</td>
</tr>
<tr>
<td>Average SpO2% during sleep</td>
<td>94.5 [93.6, 95.5]</td>
<td>0.4 [-0.5, 1.3]</td>
<td>0.487</td>
</tr>
</tbody>
</table>

*Median and Range values, respectively.

Polysomnographic classification of SDB remained consistent for both thresholds

The relationship between difference in AHI (night 2 – night 1) and mean AHI (for night 1 plus night 2) for each subject is depicted in Figure 1. One participant with a mean AHI of 7 had 7 more events on night 2 than on night 1. All other participants with large differences had fewer events on night 2 (Figure 1).

Table 2—AHI threshold of 2 events/hour

<table>
<thead>
<tr>
<th>Night of Study 1</th>
<th>Night 2</th>
<th>&lt; 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 2</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>&lt; 2</td>
<td>10</td>
<td>25</td>
</tr>
</tbody>
</table>

Table 3—AHI threshold of 5 events/hour

<table>
<thead>
<tr>
<th>Night of Study 1</th>
<th>Night 2</th>
<th>&lt; 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 5</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>&lt; 5</td>
<td>6</td>
<td>36</td>
</tr>
</tbody>
</table>

Table 2—AHI threshold of 2 events/hour

Table 3—AHI threshold of 5 events/hour

Among the 18 subjects who had 2 PSGs but whose results were excluded from the group comparisons, 6 of 18 (33%) had AHI ≥ 2 on study night 1, and 2 of 18 (11%) had AHI ≥ 5. On study night 2, 1 of 18 (6%) had AHI ≥ 2 and none had AHI ≥ 5. Though not explored in detail, this reduction in SDB sever-
ity on the second exam is consistent with the more aggressive treatment for SCD these children received.

**DISCUSSION**

Because of severe morbidity associated with SDB, an argument could be made to do routine second PSGs as screening tests on children with SCD, even in the absence of progression of symptoms of SDB or abnormalities on the first PSG. Our study showed that among children studied when free of acute illness and not receiving specific treatment for SDB or more aggressive SCD therapy, classification of SDB changed little over an average of 1.5 years. Specifically, using either of two alternative definitions of SDB, most children who were not classified with SDB on the first PSG also were free of SDB later. In contrast, despite an insignificant increase in BMI and without surgical intervention, when the PSG was abnormal on night of study 1, 59% to 86% subsequently had results below the threshold on night of study 2 (<2 or <5 events/h, 10 of 17, or 6 of 7, respectively).

The question of which children with SCD to study with PSG, and the frequency of study, is unsettled. In any child with a chronic health condition, changes in overall health, medication use, lung function, nasal congestion, and body weight and other factors all may influence the measured severity of SDB at any given point in time. Furthermore, interpreting PSG in children with SCD can be challenging due to underlying abnormalities in lung function and in oxyhemoglobin saturation, which can obscure the identification of hypopneas among subjects whose hemoglobin has less affinity for oxygen than Hgb A. The results of the current study suggest that a PSG performed when children with SCD were free of acute illness provided an estimate of SDB severity that changes little over 1.5 years. In particular, very few children whose first PSG results were below recognized thresholds for SDB developed new SDB over this period of time. On the other hand, some children with AH1 above SDB threshold values were measured to have lower AHIs at a later point. This may be due to a reduction in SDB severity with growth in children (reflecting a relative increase in airway size over tonsillar mass) or could reflect a “regression to the mean.” However, even with the latter reclassification, the overall mean change in AH1 as well as other PSG parameters were modest, suggesting that for research purposes, a single PSG performed under the appropriate conditions may provide reliable estimates of SDB in children not undergoing interventions that could alter SDB severity.

How less inconvenient or labor-intensive proxies for full PSG might be used in children with SCD deserves attention. However, as noted above, particular caution must be taken when applying methods to assess hypopnea primarily based on SpO₂% in patients whose hemoglobin may have unpredictable affinity for oxygen.

Other caveats seem important to the prudent use of our findings. Although less frequently than in children without SCD, habitual snoring, labored breathing, and apnea are associated with SDB among children with SCD; and thus a worsening in these symptoms should prompt consideration to repeat the PSG. Even though our findings showed little progression of disease within subjects who did not undergo adenotonsillectomy, these findings should not alter current approaches that demand that progression of symptoms of SDB warrants re-evaluation of SDB.

There are several other limitations. First the subjects were a convenience sample from the Sleep and Asthma Cohort. Second, we excluded from analysis patients receiving chronic transfusion therapy and those begun on hydroxyurea between the PSG. Our results are thus most pertinent to patients with less severe SCD and to those who may be using hydroxyurea but not recently begun on this agent. Finally, we did not compare symptoms of SDB before Study 1 to the appearance or progression of symptoms before Study 2. However, of 18 children excluded from comparison, only 1 was excluded because of an adenotonsillectomy between PSGs. Furthermore, only 4.4% to 6.7% of those with a normal PSG on Study 1 surpassed either threshold for SDB on Study 2. This suggests that even if more subjects were snoring or sleepy or had behavioral disturbances that a new classification as SDB would be unlikely.

Most studies on the reproducibility of PSG results in diagnosing OSA have focused on short-term variability. Studies in healthy adults have shown some modest night-to-night variability when the PSGs were performed at intervals < 28 days. Reproducibility of PSG results in children has been assessed in a small number of studies. In one study of children who snorled, subjects had PSGs performed 7 to 28 days apart. The classification of OSA or primary snoring remained the same for all 30 participants.

We did not examine the short-term variability, or reproducibility, of PSG in children with SCD. Rather, we have shown the longer-term stability of PSG in children with SCD who were free of vaso-occlusive crises or the acute chest syndrome for 3 months. In the absence of progression of pulmonary hypertension or new stroke, among children with SCD who are otherwise clinically stable, our results indicate that a second PSG 1 to 3 years after one that is normal is unlikely to show worsening sleep disordered breathing.

**REFERENCES**


ACKNOWLEDGMENTS

Support for this study provided by the National Heart, Lung, Blood Institute, HL079937.
Sickle cell anemia (SCA) remains one of the most common inherited diseases, with the major burden of disease in sub-Saharan Africa, where iron deficiency is also common. Determinants of the wide variation in the clinical expression of SCA are being investigated; current candidates include hemolytic rate and hemoglobin oxygen desaturation, both of which may be modified by iron status through effects on red cell count and mean cell hemoglobin concentrations (MCHC), thus affecting red cell oxygen carrying capacity. Iron deficiency, if severe enough, should contribute to the level of anemia in SCA and also decrease mean cell volume and MCHC. However, there is some evidence that in SCA, higher iron status is associated with increased hemolysis, lower hemoglobin, but higher MCHC. Higher MCHC may cause increased sickling rates as the propensity of sickle hemoglobin (HbS) to polymerize increases with concentration of HbS. Reduced MCHC in co-inherited α-thalassemia is a proposed mechanism for some beneficial effects in SCA. Thus red cell indices are affected by co-inherited α-thalassemia and iron status, but overall effects on hemoglobin oxygen saturations are unknown.

The prevalence of nocturnal hemoglobin oxygen desaturation is increased in SCA and is associated with complications including frequent painful crisis and vascular dysfunction. The underlying mechanisms of hemoglobin oxygen desaturation are poorly understood but likely involve anemia and red cell physiology. Reduced lung function in children with SCA does not appear to be an important factor, but interactions with cardiac function are likely in view of the high prevalence of elevated pulmonary pressures, with the potential for right-to-left shunting, as well as diastolic dysfunction.

Limited data on iron status in SCA populations exist, partly because determination of iron status is complex due to inflammation increasing ferritin independently of iron status. Transferrin saturation may be reduced in inflammation, but values < 16% have been reported to be sensitive to response to iron supplementation in SCA. Iron deficiency may be underestimated in children with SCA and may be particularly common in sub-Saharan Africa. Low or absent iron stores within the bone marrow have been reported, especially in non-transfused patients.

In children from the general population undergoing adenotonsillectomy, anemia and markers suggestive of iron deficiency are poorly understood but likely involve anemia and red cell physiology. Reduced lung function in children with SCA does not appear to be an important factor, but interactions with cardiac function are likely in view of the high prevalence of elevated pulmonary pressures, with the potential for right-to-left shunting, as well as diastolic dysfunction. Limited data on iron status in SCA populations exist, partly because determination of iron status is complex due to inflammation increasing ferritin independently of iron status. Transferrin saturation may be reduced in inflammation, but values < 16% have been reported to be sensitive to response to iron supplementation in SCA. Iron deficiency may be underestimated in children with SCA and may be particularly common in sub-Saharan Africa. Low or absent iron stores within the bone marrow have been reported, especially in non-transfused patients.
ciency are reported to be common.\(^{15}\) We therefore investigated the relationship between transferrin saturation, α-thalassemia genotype, and nocturnal oximetry in pediatric SCA patients with the hypothesis that those with evidence of iron deficiency would have lower SpO\(_2\).

**PATIENTS AND METHODS**

Ethical permission was granted by the Muhimbili University of Health & Allied Sciences ethics committee (MU/RP/AECNoI.XII/77). Written informed consent was obtained from parents or guardians in their own language and where appropriate, children’s assent obtained. Data were collected between the 9 March and 19 June 2009.

**Patients**

Children (< 16 y) were recruited from confirmed HbSS patients enrolled in a cohort study at Muhimbili National Hospital, Dar-es-Salaam\(^1\) during a routine clinic visit when clinically well. All cohort children are routinely prescribed folate supplementation (5 mg/day) and prophylactic chloroquine. None of the children were receiving hydroxyurea or routine blood transfusions.

**Nocturnal Pulse Oximetry**

Motion-resistant pulse oximetry was sampled in the day at rest and over a single night using a 2-sec averaging time and 1 Hz sampling rate (Masimo Radical, Artemis UK). Sleep diaries were kept by the attending parent or guardian during the night. Data analysis was performed with Download 2001 software (Stowood Scientific, Oxford UK). Poor perfusion, low signal identification and quality, movement artifact data, and periods of wakefulness as recorded in the sleep diary were excluded manually. Only studies with a minimum of 4 h of artifact-free data were included. Analysis software yielded standard measures including mean and minimum SpO\(_2\) and desaturation index ≥ 3% from baseline.

**Hematology and Iron Status Measurements**

Averaged steady-state values for hemoglobin and other red cell indices from full blood pictures (Pentra 60, Horiba ABX, Kyoto, Japan) conducted at routine clinic visits in the previous year were calculated. Blood samples were collected between 08:00 and 10:00. Serum iron and total iron binding capacity were measured in stored samples (Architect C8000, Abbott, New York, USA) meeting steady-state criteria: temperature ≤ 37.4°C, negative malaria rapid test, and absence of pain or hospital admission within 90 days. Transferrin saturation was calculated from serum iron and total iron binding capacity.

**Data Analysis**

Variables were inspected for normality and multivariable linear regression was used (STATA 11-IC; StataCorp, College Station, TX, USA). No differences were observed with log-transformed or non-transformed variables with mild positive skew, thus results of non-transformed data are presented. P values < 0.05 were considered significant.

**RESULTS**

Out of 50 children with SCA in whom nocturnal oximetry was conducted, 32 (mean age 8.0 [SD 3.3; range 3.6-15.3] years, 16 boys (50%) also had transferrin saturation assessed. Descriptive statistics for transferrin saturation, averaged steady-state hematology, and pulse oximetry data are given in Table 1. There were no significant differences in age, sex, hematologic, or pulse oximetry data between those who had transferrin saturation data available and those who did not (data not shown). Data from 3 (1 boy, 1 with α-thalassemia; mean age 7.0 [SD 1.4; range 5.7-8.3] years) were excluded because there were < 4 h of artifact-free data. There were no differences between transferrin saturation in those who were included (mean 22.2%, SD 10.9) and excluded (mean 17.3%, SD 3.8). Twenty-eight percent (9/32) had low transferrin saturation (< 16%) indicating probable iron deficiency (Table 1), a similar proportion to all SCA patients with data available (25%,

**Table 1**—Iron status, steady-state hematology, and daytime and nocturnal pulse oximetry data in 32 Tanzanian children with sickle cell anemia

<table>
<thead>
<tr>
<th>Variable</th>
<th>Iron status</th>
<th>Hematology</th>
<th>Pulse oximetry</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median steady-state transferrin saturation (%)</td>
<td>19.1 (IQ range 13.6 – 29.3)</td>
<td>Mean averaged steady-state Hb* (g/dL)</td>
<td>96.5 (SD 3.0) (range 89.1 – 99.9)</td>
</tr>
<tr>
<td>Mean serum iron (μmol/L)</td>
<td>11.8 (SD 4.8) (range 3.1 – 22.1)</td>
<td>Mean averaged steady-state RCC x10**</td>
<td>88.0 (IQ range 83.0 – 90.5)</td>
</tr>
<tr>
<td>Mean serum TIBC (μmol/L)</td>
<td>50.8 (SD 9.9) (range 34.6 – 70.7)</td>
<td>Mean averaged steady-state MCHC* (g/dL)</td>
<td>3.85 (IQ range 1.21 – 5.67)</td>
</tr>
<tr>
<td>Mean averaged steady-state MCV* (fL)</td>
<td>80.4 (SD 8.0) (range 62.0 – 94.6)</td>
<td>Mean minimum overnight SpO(_2) (%)</td>
<td>9.5 (SD 2.2) (range 4.5 – 13.8)</td>
</tr>
</tbody>
</table>

*Mean of multiple measurements made at routine steady-state (no fever, malaria parasites or antigens, or admission within 90 day period) routine clinic visits preceding sleep study.

\(\text{Hb}\) = hemoglobin; \(\text{RCC}\) = red cell count; \(\text{MCHC}\) = mean corpuscular hemoglobin concentration; \(\text{MCV}\) = mean corpuscular volume; \(\text{SpO}\(_2\)\) = oxygen saturation; \(\text{TIBC}\) = total iron binding capacity; \(\alpha\)-thalassemia;
N = 212/836, unpublished data, Cox et al.) but lower than in non-SCA Tanzanian control children (32/66, 48%). No SCA patients had high transferrin saturation (> 55%) which might indicate iron overload. Twenty-five patients (78%) had never received a blood transfusion. The remaining patients had received one (5 patients) or two (2 patients) blood transfusions in their lifetime. There was no association between transferrin saturation and age, sex, nutritional status (body mass index z-score), or blood transfusion history. Thirty of the 32 children with transferrin saturation data available had genotypes for the 3.7 α-thalassemia deletion: 11 (37%) were heterozygous and 1 was homozygous (3.3%). There were no statistically significant associations between transferrin saturation and steady-state averaged hemoglobin, red cell count, or mean cell volume in these children (data not shown). Presence of the 3.7 α-thalassemia deletion was associated with a 56% increase in transferrin saturation (p = 0.034), but was not significantly associated with any of the hematology variables in this study population (data not shown).

**Associations with Nocturnal Hemoglobin Oxygen Saturation**

Differences in nocturnal SpO2 and in the number of SpO2 dips per hour in SpO2 > 3% according to age, transferrin saturation status (≥ or < 16%) and α-thalassemia 3.7 deletion genotype, unadjusted for age are shown in Table 2. The results of multivariable linear regression analyses of the associations between nocturnal oximetry data and transferrin saturation, averaged steady-state hematology measures and α-thalassemia 3.7 deletion using linear regression, adjusted for age as indicated (N = 32, unless otherwise stated)

**DISCUSSION**

In this study we report that nocturnal hemoglobin oxygen desaturation is associated with higher levels of transferrin saturation independently of the presence of the 3.7 α-thalassemia deletion in SCA, although levels were not suggestive of iron overload (unlikely in our non-transfused population). Although

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**Table 2**—Nocturnal mean SpO2 (%) and number of SpO2 dips > 3%/h according to iron status and α-thalassemia genotype.

<table>
<thead>
<tr>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean overnight SpO2 (%)</td>
<td>96.0 (SD 2.75)</td>
<td>98.0 (SD 3.31)</td>
<td>97.8 (SD 1.96)</td>
<td>95.4 (SD 3.42)*</td>
</tr>
<tr>
<td>Median overnight SpO2 dips &gt; 3%/h</td>
<td>0.40 [IQ range 0.33-0.47]</td>
<td>0.29 [IQ range 0.18-0.41]</td>
<td>0.32 [IQ range 0.27-0.40]</td>
<td>0.41 [IQ range 0.29-0.56]</td>
</tr>
</tbody>
</table>

*p < 0.05.

**Table 3**—Relationships between nocturnal oximetry data and transferrin saturation, averaged steady-state hematology measures and α-thalassemia 3.7 deletion using linear regression, adjusted for age as indicated (N = 32, unless otherwise stated).

<table>
<thead>
<tr>
<th>Dependent variable</th>
<th>Regression coefficient [95% CI]</th>
<th>p-value</th>
<th>r²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean overnight SpO2*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>-0.36 [-0.67 / -0.06]</td>
<td>0.022</td>
<td>0.13</td>
</tr>
<tr>
<td>Transferrin saturation %</td>
<td>-0.14 [-0.22 / -0.06]</td>
<td>0.001</td>
<td>0.39</td>
</tr>
<tr>
<td>Transferrin saturation &lt; 16%</td>
<td>2.17 [0.04 / 4.31]</td>
<td>0.045</td>
<td>0.27</td>
</tr>
<tr>
<td>MCHC (g/dL)</td>
<td>-0.80 [-1.70 / -0.09]</td>
<td>0.075</td>
<td>0.20</td>
</tr>
<tr>
<td>α-thalassemia genotype**</td>
<td>-2.63 [-4.65 / -0.60]</td>
<td>0.013</td>
<td>0.27</td>
</tr>
<tr>
<td>Mean overnight SpO2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>-0.34 [-0.62 / -0.07]</td>
<td>0.016</td>
<td></td>
</tr>
<tr>
<td>Transferrin saturation %</td>
<td>-0.11 [-0.20 / -0.03]</td>
<td>0.013</td>
<td></td>
</tr>
<tr>
<td>α-thalassemia genotype**</td>
<td>-1.48 [-3.51 / -0.56]</td>
<td>0.147</td>
<td>0.41</td>
</tr>
<tr>
<td>Minimum overnight SpO2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Red Blood Cell count x10⁶</td>
<td>7.94 [0.89 / 15.0]</td>
<td>0.029</td>
<td>0.12</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>4.69 [0.40 / 8.98]</td>
<td>0.033</td>
<td>0.11</td>
</tr>
<tr>
<td>Number of overnight SpO2 dips &gt; 3%/h</td>
<td>0.045 [0.0125 / 0.0778]</td>
<td>0.008</td>
<td>0.19</td>
</tr>
</tbody>
</table>

*Estimated effect of explanatory variables adjusted for independent effect of age. **N = 30, presence of α-thalassemia 3.7 deletion coded as 1, absence as 0 (only 1 homozygote for 3.7 deletion).
this relationship was unexpected and is counter to our prior hypothesis, it is in line with data from adults with obstructive sleep apnea (OSA) from the general population, in whom higher ferritin levels were associated with lower minimum overnight SpO2.16 Although this prior observation could have resulted from OSA associated inflammation as a confounding factor, in our study chronic inflammation would be expected to decrease transferrin saturation and is therefore unlikely to be a confounder.

We can think of theoretical mechanisms by which higher iron availability could result in lower nocturnal SpO2 (Figure 2), but the most parsimonious explanation is that of reverse causality involving an effect of desaturation on iron metabolism through the hypoxic-inducible factors (HIF-1 and HIF-2).17 Hemoglobin oxygen desaturation causes upregulation of HIF-1 and HIF-2 levels, the downstream effects of which include increased erythropoietin, decreased hepcidin (a negative regulator of iron absorption and release from the reticuloendothelial system), and increased transferrin, increasing iron absorption and mobilization for erythropoiesis and thus higher transferrin saturation.17 The levels and exposure to chronic intermittent and sustained desaturation required to induce HIF in humans and in SCA remain to be determined. However, existing evidence from cell cultures and mouse models suggest chronic intermittent hypoxemia is a stronger and more long lasting stimulus than chronic hypoxemia.18

In patients with SCA, whose hemoglobin polymerizes on deoxygenation, any decrease in mean nocturnal SpO2 or presence of significant dips in SpO2 is likely to have clinical relevance. In London children with sickle cell disease, an increase of one unit in mean nocturnal SpO2 was associated with an average fall of 0.83 in the number of days of pain per year requiring hospital treatment (p < 0.001), and the presence of any dips in SpO2 was

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**Figure 1**—Association between transferrin saturation and mean nocturnal SpO2 showing the regression line and the 95% confidence interval.

**Figure 2**—Potential mechanisms underlying the negative association between transferrin saturation and mean nocturnal SpO2.
Iron deficiency appears associated with higher SpO₂ and erythropoiesis, with the paradoxical consequence that hemoglobin oxygen desaturation, which upregulates iron absorption and erythropoiesis, was associated with higher transferrin saturation. The primary driver is probably high average numbers of days admitted to hospital for pain.7

In conclusion, we have demonstrated in SCA that sustained nocturnal hemoglobin oxygen desaturation and the number of dips per hour > 3% from baseline in SpO₂ were associated with higher transferrin saturation. The primary driver is probably high average numbers of days admitted to hospital for pain.7

The long-term effects of hemoglobin oxygen desaturation on iron status in children with SCA warrant further investigation in view of the clinical evidence of a link with unfavorable clinical course.

**ABBREVIATIONS**

SCA, sickle cell anemia
Hb, hemoglobin
SpO₂, hemoglobin oxygen saturation
OSA, obstructive sleep apnea
HIF, hypoxic-inducible factor

**REFERENCES**


**ACKNOWLEDGMENTS**

The authors warmly thank the patients and staff of MNH and MUHAS, Dar-es-Salaam, Tanzania who made this work possible. We also thank David Roberts and Charles Newton for reading the draft manuscript, the staff in the clinical chemistry unit at MNH central pathology laboratory for clinical chemistry and transferrin saturation analyses and Josephine Mgaya and Harvest Maniki for the hematology analyses and sample archiving. This research was supported by Wellcome Trust, UK: project grant 080205 to Dr. Cox, personal fellowship 072064; 084538 to Dr. Makani and a WT Student Elective Fellowship to Dr. L’Esperance 50331115.

Authorship contributions: Drs. Kirkham, Cox, and Hill conceived and designed the study; Dr. L’Esperance conducted the sleep studies, including manual processing of sleep data and contributed to data analysis; and Drs. Makani, Soka, and Cox collected the remaining data. Dr. Cox conducted the statistical analyses and wrote the paper. All authors contributed to critical evaluation and final drafting of the manuscript.

**ETHICS APPROVAL:** Ethical permission was granted by the Muhimbili University of Health & Allied Sciences ethics committee (Ref: MU/RPI/ECNol.XII/77).

**DISCLOSURE STATEMENT**

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

**REFERENCE**

Sleep Misperception in Healthy Adults: Implications for Insomnia Diagnosis

Matt T. Bianchi, M.D., Ph.D., M.M.Sc.,1,2 Wei Wang, Ph.D.,1,2 Elizabeth B. Klerman, M.D., Ph.D.,1,2

1Sleep Division, Neurology Department, Massachusetts General Hospital, Boston, MA; 2Division of Sleep Medicine, Brigham and Women’s Hospital & Harvard Medical School, Boston, MA

Study Objectives: Time estimation is a complex cognitive task that is especially challenging when the time period includes sleep. To determine the accuracy of sleep duration perception, we investigated 44 healthy subjects participating in multi-day inpatient sleep protocols during which they had extended nighttime and short daytime sleep opportunities but no time cues or knowledge of time of day.

Methods: The first sleep opportunity was at habitual sleep time and duration. The subsequent 3, 4, or 11 days had 12-h nighttime sleep opportunities and 4-h daytime nap opportunities, potentially creating an experimentally induced “insomnia” with substantial time awake during scheduled sleep.

Results: Subjective sleep duration estimates were accurate for the first (habitual) sleep opportunity. The subjective reports following nighttime 12-h sleep opportunities significantly underestimated objective sleep duration, while those following daytime 4-h sleep opportunities significantly overestimated objective sleep duration. Misperception errors were not explained by poor sleep efficiency, which was lower during 4-h (~39%) than 12-h opportunities (~71%). Subjective sleep estimates after 4-h opportunities correlated with the percentage of REM and N3 sleep. Subjective sleep estimates following 12-h opportunities were, unexpectedly, negatively correlated with NREM stage 2 sleep.

Conclusion: The estimation of sleep duration in the absence of time cues may depend on length of sleep opportunity and/or time of day. The results have implications for understanding sleep state misperception, which is an important consideration in patients with insomnia.

Keywords: Insomnia, subjective sleep estimation, time perception, time cues


The clinical diagnosis and management of insomnia rests largely upon the subjective self-report of patients describing difficulty with sleep onset or sleep maintenance.1 It has long been recognized, however, that subjective reports may differ from objective measurements of sleep using physiological criteria.2-6 In particular, patients with insomnia may underestimate their actual sleep times and overestimate their wake times. This mismatch has implications for both diagnosis and treatment of patients with insomnia.

Perception of time as it relates to sleep is a particularly challenging topic. The subjective experience of wake may differ for the time elapsed preceding sleep onset compared to the time elapsed during mid-sleep awakenings. Also, mid-sleep awakenings may be associated with variable levels of alertness, which may affect perception. These issues become clinically important when considering the manifold forms of insomnia, and how the fragmentation of sleep and neurophysiological hyperarousal7,8 may affect time estimation. Current theories of insomnia pathophysiology include the issue of hyperarousal, as evidenced by increased high-frequency EEG activity as well as increased metabolism.9 The extent to which hyperarousal contributes to the failure to register what appears to be sleep by physiological criteria is an area of ongoing investigation.10 Because the diagnosis and management of insomnia each rely profoundly on patient self-report, it is critical that physicians and patients improve their understanding of subjective-objective mismatch in sleep duration, or sleep misperception.

The extent to which sleep misperception may be a “trait” present in certain patients with sleep disorders, or a “state” that varies night to night, remains uncertain. In this study, we investigated self-reported sleep-wake estimates in healthy adults undergoing multiple days of inpatient assessments. Subjects had no time cues during the protocol, including not knowing the scheduled length of their sleep or wake opportunities, and had extended sleep opportunities during the day and at night, which caused an experimental form of insomnia due to excess time in bed. We hypothesized that the perception of sleep duration would be altered in this setting, and would relate to the degree of sleep fragmentation.
MT Bianchi, W Wang, and EB Klerman

Table 1—Subject characteristics

<table>
<thead>
<tr>
<th></th>
<th>Younger</th>
<th>Older</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>32</td>
<td>12</td>
</tr>
<tr>
<td>Age (years) mean</td>
<td>22.0</td>
<td>68.0</td>
</tr>
<tr>
<td>95% CI of mean</td>
<td>20.0-23.3</td>
<td>64.8-71.2</td>
</tr>
<tr>
<td>Range</td>
<td>16-32</td>
<td>60-76</td>
</tr>
<tr>
<td>M:F</td>
<td>16:16</td>
<td>5:7</td>
</tr>
<tr>
<td>Habitual sleep time (hours) mean</td>
<td>8.6</td>
<td>8.0</td>
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<tr>
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<td>8.2-8.9</td>
<td>7.6-8.4</td>
</tr>
<tr>
<td>Range</td>
<td>6.1-10.3</td>
<td>7.0-8.9</td>
</tr>
<tr>
<td>Owl-Lark Score mean</td>
<td>48.9</td>
<td>62.5*</td>
</tr>
<tr>
<td>95% CI of mean</td>
<td>46.0-51.9</td>
<td>55.4-69.6</td>
</tr>
<tr>
<td>Range</td>
<td>33.0-65.0</td>
<td>39.5-76</td>
</tr>
</tbody>
</table>

*p < 0.05 by ANOVA, with Bonferroni correction.

METHODS

Population

Healthy younger and older adults were pre-screened to rule out sleep and circadian disorders and prescription or elicit drug use. Subjects were healthy based on history, physical examination, electrocardiogram, routine blood and urine screens, and a polysomnogram to exclude those with sleep apnea and periodic limb movements.11,12 None had performed night shift work within 3 years or crossed more than one time zone in the previous 3 months. The age of the population was bi-modal, with a “younger” cohort (ages 18-32 years; n = 32) and an older cohort (ages 60-76; n = 12). Chronotype was assessed by the Horne and Ostberg method,13 described here as the Owl-Lark score.

Protocol

The protocol was approved by the Partners Healthcare Institutional Review Board. Actigraphy and diary monitoring for 3 weeks at home during habitual sleep behavior was followed immediately by the inpatient portion of study. During the home and inpatient portions, subjects abstained from medications, supplements, caffeine, tobacco, and alcohol. Subjects then spent 10-13 days and nights in the Brigham and Women’s Hospital General Clinical Research Center, in single occupancy suites with no windows and no information about time. Subjects were not informed of the exact length of their scheduled sleep or wake opportunities; the consent documents stated “You will be assigned to one of four groups which have different patterns of sleep and wake times.” The inpatient portion of the protocol was designed to evaluate the response to sleep deprivation for a separate study; some data from this protocol have been previously reported.11,12 The inpatient portion began with an initial sleep opportunity at one of four groups which have different patterns of sleep and wake opportunities. The consent documents stated “You will be assigned to one of four groups which have different patterns of sleep and wake times.” The inpatient portion of the protocol was designed to evaluate the response to sleep deprivation for a separate study; some data from this protocol have been previously reported.11,12 The inpatient portion began with an initial sleep opportunity at each subject’s habitual sleep time and duration, followed by 3-8 consecutive days with 12-h nocturnal sleep opportunities (centered at the same time as habitual sleep) and 4-h daytime nap opportunities (centered 12 h opposite the 12-h nocturnal sleep period). For some subjects, a sleep deprivation occurred after these 3-8 days (random assignment stratified by age and sex); only the data from before the sleep deprivation and the final 8-h sleep period of the inpatient protocol after three 24-h days of recovery from the sleep deprivation are used for these analyses. The last sleep period was 8 h in duration, centered at the same time as the 12-h sleep period. This last period was not included in most of the Results analysis, unless specifically stated. During waking periods, subjects were not allowed to lie in bed. During sleep opportunities, which occurred in darkness, subjects were required to remain inactive in bed.

Subjective and Objective Recordings

Sleep was recorded on Viatport digital recorders (Temec, The Netherlands) using standard EEG, EMG, and EOG montage, and scored in 30-sec increments according to Rechtschaffen and Kales criteria14 by experienced technicians. For this report, NREM stages 3 and 4 were analyzed separately and as a combined stage to yield stage N3, to align with recent changes in scoring criteria. After each sleep opportunity, subjects were asked to record their estimate of sleep latency, total sleep time (TST), and number of awakenings for the prior sleep period. The errors in these estimates were calculated as “subjective – objective,” such that negative values represent underestimation errors. Latency to persistent sleep (LPS) was defined as latency until the start of 20 consecutive epochs (10 min) of any stage of sleep. Wake after persistent sleep onset (WAPSO) was defined as the amount of wake occurring between the end of 20 consecutive epochs of sleep (LPS) and the final awakening. Objective criteria for number of awakenings was pre-specified to be ≥ 2 consecutive epochs (1 min) scored as wake after persistent sleep (as defined above) was achieved.

Analysis

Group comparisons for basic demographics, TST errors, and sleep efficiency were performed with either ANOVA with Bonferroni correction for multiple comparisons, or, in cases of non-Gaussian distributions, with nonparametric Kruskal-Wallis testing (with Dunn multiple comparisons test). Correlation analysis was conducted using the Spearman nonparametric method. For 12-h and 4-h sleep opportunities, each subject contributed multiple data points, and the number was not the same for all subjects due to the protocol (see supplemental material, Figure S1). Group analysis and correlation analysis were conducted by first taking the median of all 12-h or 4-h blocks for each subject, so that each subject contributed only one data point to the analysis.

RESULTS

Baseline Subject Characteristics

Table 1 contains the baseline characteristics of this population (n = 44), divided into older and younger groups. There were approximately equal numbers of males and females. The average habitual sleep durations overall were 8.4 ± 0.9 h (mean ± SD; range of 6.1 to 10.3 h). The habitual sleep durations were not statistically different between age groups, while the chronotype scores were different (ANOVA, p < 0.05), with older groups having more early-morning tendency.

The first inpatient night began at each individual’s habitual bedtime and lasted for their habitual sleep duration. We label this first night sleep period as “FNH.” The baseline sleep stage...
findings on this first night are shown in Table 2. The results with subgrouping by age or sex are reported in the supplemental material. Similar sleep time estimation patterns were observed for males and females. Although misperception showed a trend toward being more evident in younger than in older subjects, the differences were not significant. Thus, for the remaining analyses below, all 44 subjects were analyzed as a group.

Changing Patterns of Sleep Stages across the Protocol
As expected, sleep efficiency was highest (> 90%) during the FNH night of the experimental protocol. Sleep efficiency was significantly decreased for the enforced nighttime 12-h sleep opportunities (Figure 1A); this is not surprising, given the excess time in bed compared with habitual sleep durations, which averaged ~8 h. Efficiency was lowest for the 4-h opportunities (Figure 1A) that occurred during the daytime. The distribution of sleep stages during the different sleep opportunities differed in the percentage of REM sleep (smaller in 4-h compared to FNH and 12-h), and in the percentage of NREM stage 1 sleep (larger in 4-h compared to FNH and 12-h) (Figure 1B). The temporal pattern of sleep efficiency demonstrates 2 tendencies: (i) gradually decreasing efficiency over successive days in the protocol, and (ii) systematically lower efficiency in the 4-h compared to the 12-h sleep opportunities (Figure 1C). The final sleep opportunity (8-h sleep opportunity) showed partial return towards the sleep efficiency of FNH.

Subjective Versus Objective Sleep-Wake Durations
Figure 1D shows that the subjective estimates following 12-h opportunities were significantly lower than those for the habitual duration, and that estimates for 4-h opportunities were significantly lower than those for either 12-h or FNH opportunities (p < 0.05, Kruskal-Wallis). Figure 1E shows for comparison the objective TST values for the FNH, 12-h, and 4-h sleep opportunities; the objective TST for 4-h periods was significantly smaller than the other periods (p < 0.05, Kruskal-Wallis). Subjective TST estimates were accurate for FNH, with a median error of -9.1 min (quartiles of -43.5 to 51.3 min), not significantly different from zero error (Figure 2A). Negative values indicate underestimation (subjective minus objective TST minutes). Subjects significantly underestimated their TST for 12-h sleep opportunities, and overestimated their TST for 4-h sleep opportunities (Figure 2A). The median TST error was -109.4 min (quartiles of: -227.2 to -47.4) after 12-h opportunities and 58.3 min (quartiles of: -0.2 to +142.4) after 4-h opportunities (Figure 2A).

Sleep latency estimations were accurate for FNH and 4-h sleep opportunities, but were slightly but significantly underestimated for 12-h sleep opportunities (Figure 2B). The number of reported awakenings within sleep was significantly underestimated compared to objective criteria for FNH and 12-h sleep opportunities, while the number reported for 4-h opportunities was accurate (Figure 2C).

To illustrate the temporal stability of the systematic under- and overestimations of TST, Figure 2D shows the errors for each sleep period: the alternating pattern for 12-h and 4-h sleep periods of errors persists throughout the protocol. The final sleep opportunity (SP17) was an 8-h opportunity at the habitual sleep time and shows resumed accuracy, although the variance was larger than on the first night. Similar patterns were observed when we compared male versus female subjects, and old versus young subjects (Figure S2).

Correlates of Subjective TST Estimation
We next conducted correlation analysis to determine whether the degree of TST error was related to sleep consolidation in

| Table 2—Sleep characteristics on the first night of habitual time and duration |
|-----------------------------|---------------------|---------------------|
|                            | Younger             | Older               |
| TST (h)                    | 7.9 ± 0.8           | 6.7 ± 0.8           |
|                            | (5.8 - 9.7)         | (6.4 - 8.0)         |
| Latency NREM stage1 (min)  | 10.9 ± 8.7          | 8.0 ± 4.2           |
|                            | (1 - 36)            | (2.5 - 14.5)        |
| Latency NREM stage2 (min)  | 17.0 ± 10.3         | 14.7 ± 11.0         |
|                            | (3.5 - 36.5)        | (3 - 40)            |
| Latency REM (min)          | 95.2 ± 45.3         | 89.2 ± 32.9         |
|                            | (56 - 246.5)        | (43.5 - 176.5)      |
| Latency SWS (min)          | 31.4 ± 13.3         | 36.8 ± 24.5         |
|                            | (11.5 - 65.5)       | (8 - 70)            |
| Latency PS (min)           | 14.0 ± 10.1         | 16.7 ± 14.0         |
|                            | (1 - 37.5)          | (2.5 - 51.5)        |
| NREM stage 1 (min)         | 44.3 ± 21.4         | 51.1 ± 27.2         |
|                            | (6.5 - 104.5)       | (18 - 106)          |
| NREM stage2 (min)          | 248.7 ± 36.1        | 212.7 ± 22.9        |
|                            | (177.5 - 318.5)     | (167 - 240.5)       |
| NREM stage3 (min)          | 31.5 ± 17.0         | 39.4 ± 25.3         |
|                            | (10 - 72.5)         | (0 - 93)            |
| NREM stage4 (min)          | 40.5 ± 27.0         | 18.4 ± 21.5         |
|                            | (0 - 92)            | (0 - 52.5)          |
| N3 (min)                   | 71.9 ± 27.3         | 57.8 ± 41.8         |
|                            | (10 - 117.5)        | (0 - 126)           |
| REM (min)                  | 109.5 ± 33.1        | 79.3 ± 64.2         |
|                            | (36 - 184.5)        | (40 - 117)          |
| WAPSO (min)                | 24.7 ± 24.9         | 64.2 ± 31.5*        |
|                            | (3.5 - 107.5)       | (7 - 138.5)         |
| %NREM stage1               | 8.9 ± 4.4           | 11.0 ± 6.0          |
|                            | (1.4 - 21.4)        | (4.4 - 23.9)        |
| %NREM stage2               | 50.0 ± 7.0          | 45.8 ± 4.3          |
|                            | (38.7 - 73.0)       | (40.6 - 52.5)       |
| %NREM stage3               | 6.4 ± 3.4           | 8.3 ± 4.8           |
|                            | (2.3 - 15.7)        | (0 - 17.7)          |
| %NREM stage4               | 8.1 ± 5.4           | 3.9 ± 4.7           |
|                            | (0 - 16.7)          | (0 - 12.4)          |
| %N3                        | 14.5 ± 5.6          | 12.2 ± 8.5          |
|                            | (2.3 - 24.5)        | (0 - 24.2)          |
| %REM                       | 21.8 ± 5.6          | 17.1 ± 4.9          |
|                            | (7.8 - 36)          | (8.8 - 28.2)        |
| %WAPSO                     | 4.8 ± 4.6           | 13.8 ± 7.0          |
|                            | (0.1 - 14.9)        | (1.7 - 29.5)        |
| Efficiency %               | 92.6 ± 5.3          | 83.6 ± 7.3          |
|                            | (80.5 - 98.8)       | (69.0 - 97.4)       |
| # wakes (total)            | 4.4 ± 3.3           | 9.2 ± 3.2           |
|                            | (0 - 12)            | (2 - 13)            |

Mean ± SD; *p < 0.05 by Kruskal-Wallis with Dunn multiple comparison test. Parentheses show range values (minimum to maximum).
Figure 1—Sleep stages and relation to total sleep time errors

(A) Overall sleep efficiency in the different sleep opportunity durations. Brackets indicate significant differences with p < 0.05 by Kruskal-Wallis test with Dunn post-test. The median sleep efficiency value within individuals was used, such that each subject contributed one point for each sleep period. The first (FNH) opportunity and subsequent 12-h and 4-h opportunities are shown. (B) Sleep stage composition in FNH, 4-h, and 12-h conditions. In each group, the values were averaged within subject for 12-h and 4-h periods, such that each subject contributes one point to the group data for each sleep period. *Significant difference from FNH and 12-h (p < 0.05; ANOVA with Bonferroni post-test). (C) Sleep efficiency across each sleep period of the protocol; brackets indicate significant differences (p < 0.05; ANOVA with Bonferroni post-test). Note that (i) SP1 is the first, habitual night (FNH, variable length), SP2 (and subsequent even numbers) are 12-h nocturnal sleep periods; SP3 (and subsequent odd numbers) are 4-h daytime nap periods. The final opportunity, SP17, is an 8-h sleep period centered at habitual time; (ii) the number of subjects contributing values to each sleep period decreased after SP8 due to the protocol design (n = 39-42 for SP 1-7, n = 32 for SP 8, n = 26 for SP 9, n = 11-12 for SP 10-16, and n = 12 for SP17). (D) Subjective TST estimate values according to the duration of sleep opportunity. In the box-and-whisker plots, the boxes show the median as well as 25% and 75% boundaries, while the whiskers show the 90% confidence range (5% to 95%). The * symbols indicate the mean value. Brackets indicate significant differences (p < 0.05; Kruskal-Wallis test, with Dunn post-test). In each group, the median value was taken across 12-h and 4-h periods, such that each subject contributes one point to the group data. (E) Objective TST values according to the duration of sleep opportunity. Box-and-whisker plots as in panel D. Brackets indicate significant differences (p < 0.05; Kruskal-Wallis test, with Dunn post-test).
the prior sleep period. There were no significant correlations between the TST error for a given 12-h or 4-h sleep opportunity and the sleep efficiency of the preceding 4-h or 12-h sleep periods, such that each subject contributes one point to the group data. The error metric is derived from subtracting the objective value from the subjective value, such that negative values represent subjective underestimation. Brackets indicate significant differences by Kruskal-Wallis (in panel B and C, with Dunn post-test; p < 0.05). (D) The distribution of TST errors is shown over successive sleep periods. SP1 is the first, habitual night (FNH, variable length), SP2 (and subsequent even numbers) are 12-h nocturnal sleep periods; SP3 (and subsequent odd numbers) are 4-h daytime nap periods. SP17 is an 8-h sleep period centered at habitual time. Note that (i) SP1 is the first, habitual night (FNH, variable length); SP2 (and subsequent even numbers) are 12-h nocturnal sleep periods; n = 39-42 for SP 1-7, n = 32 for SP 8, n = 26 for SP 9, n = 16 for SP 10-16, and n = 12 for SP17. Brackets indicate significant differences between adjacent sleep periods (p < 0.05; ANOVA with Bonferroni correction).

Surprisingly, TST estimates were negatively correlated with the percentage of NREM stage 2 sleep.

For the 4-h sleep periods, TST estimates were positively correlated with the percentage of stages N3 and REM sleep (Table 3). Similar correlations were found for individual NREM stages 3 and 4 sleep, when considered separately (data not shown).

The above analysis considered the subjective estimation of TST, regardless of accuracy. We finally turn to investigation of correlations with the magnitude of the error in TST estimation (Table 4). Given that our calculation of TST error yields negative values for underestimation, positive correlation mean "the higher the value of variable X, the less the..."
Table 3—Correlation with TST estimate

<table>
<thead>
<tr>
<th></th>
<th>12-h</th>
<th>4-h</th>
</tr>
</thead>
<tbody>
<tr>
<td>%NREM stage 1</td>
<td>-0.06</td>
<td>-0.29</td>
</tr>
<tr>
<td>%NREM stage 2</td>
<td><strong>-0.38</strong> (&lt; 0.02)</td>
<td>0.03</td>
</tr>
<tr>
<td>%N3</td>
<td>0.28</td>
<td><strong>0.40</strong> (&lt; 0.007)</td>
</tr>
<tr>
<td>%REM</td>
<td>0.22</td>
<td><strong>0.41</strong> (&lt; 0.005)</td>
</tr>
<tr>
<td>%WAPSO</td>
<td>-0.04</td>
<td>-0.17</td>
</tr>
<tr>
<td># wakes (≥ 1 min)</td>
<td>-0.23</td>
<td>0.17</td>
</tr>
</tbody>
</table>

Spearman correlations; significant values are bolded.

Table 4—Correlation with TST error

<table>
<thead>
<tr>
<th></th>
<th>12-h</th>
<th>4-h</th>
</tr>
</thead>
<tbody>
<tr>
<td>LPS</td>
<td>-0.12</td>
<td>-0.06</td>
</tr>
<tr>
<td>LPS error</td>
<td>-0.01</td>
<td>-0.11</td>
</tr>
<tr>
<td>%NREM stage 1</td>
<td>-0.11</td>
<td>-0.03</td>
</tr>
<tr>
<td>%NREM stage 2</td>
<td><strong>-0.34</strong> (&lt; 0.03)</td>
<td>-0.08</td>
</tr>
<tr>
<td>%N3</td>
<td>0.24</td>
<td>0.25</td>
</tr>
<tr>
<td>%REM</td>
<td>0.01</td>
<td>0.26</td>
</tr>
<tr>
<td>%WAPSO</td>
<td><strong>0.43</strong> (&lt; 0.003)</td>
<td>0.04</td>
</tr>
<tr>
<td># wakes (≥ 1 min)</td>
<td>-0.05</td>
<td>-0.03</td>
</tr>
</tbody>
</table>

Spearman correlations; significant values are bolded.

Table 5—Correlation with objective TST

<table>
<thead>
<tr>
<th></th>
<th>12-h</th>
<th>4-h</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST estimate</td>
<td>0.26</td>
<td><strong>0.31</strong> (&lt; 0.04)</td>
</tr>
<tr>
<td>LPS</td>
<td>-0.22</td>
<td><strong>-0.33</strong> (&lt; 0.03)</td>
</tr>
<tr>
<td>LPS error</td>
<td>0.15</td>
<td>0.10</td>
</tr>
<tr>
<td>%NREM stage 1</td>
<td>-0.12</td>
<td><strong>-0.38</strong> (&lt; 0.01)</td>
</tr>
<tr>
<td>%NREM stage 2</td>
<td>-0.07</td>
<td>-0.07</td>
</tr>
<tr>
<td>%N3</td>
<td>0.00</td>
<td>0.27</td>
</tr>
<tr>
<td>%REM</td>
<td><strong>0.30</strong> (&lt; 0.05)</td>
<td><strong>0.72</strong> (&lt; 3×10^-3)</td>
</tr>
<tr>
<td>%WAPSO</td>
<td><strong>-0.76</strong> (&lt; 3×10^-4)</td>
<td><strong>-0.55</strong> (&lt; 0.0001)</td>
</tr>
<tr>
<td># wakes (≥ 1 min)</td>
<td><strong>-0.32</strong> (&lt; 0.03)</td>
<td><strong>0.56</strong> (&lt; 9×10^-4)</td>
</tr>
</tbody>
</table>

Spearman correlations; significant values are bolded.

TST underestimation.” Regarding 4-h sleep opportunities, we found no significant correlations between sleep-wake stage percentages, efficiency, or number of awakenings and the TST error (Table 4), including when NREM stages 3 and 4 were analyzed separately (not shown).

Of note, the objective TST was not significantly correlated with the subjective estimate of TST during 12-h sleep opportunities (r = 0.26; p > 0.05). Objective TST during 12-h sleep opportunities was, however, positively correlated with REM% (r = 0.30; p < 0.05), and inversely correlated with WAPSO% (r = -0.76; p < 3×10^-3) and the number of awakenings (r = -0.32; p < 0.03) (Table 5). Objective TST during 4-h sleep opportunities was correlated positively with the subjective TST estimate (r = 0.31; p < 0.04), as well as the REM% (r = -0.72; p < 3×10^-3), while it was inversely correlated with LPS (r = -0.33; p < 0.03), NREM stage 1% (r = -0.38; p < 0.01), and WAPSO% (r = -0.55; p < 0.0001). Unexpectedly, the objective TST was positively correlated with the number of awakenings during 4-h sleep opportunities (r = -0.56; p < 3×10^-7) (Table 5).

Regarding 12-h opportunities, TST errors were not correlated with sleep latency errors, arguing against a “general” error of time perception. This suggested that retrospective self-report of sleep onset and total sleep time involve distinct cognitive processes. Contrary to expectations, TST error was positively correlated with WAPSO (lower WAPSO correlated with greater underestimation) and negatively correlated with the proportion of NREM stage 2 sleep (higher N2% correlated with greater underestimation). The direction of these relationships was unexpected, given the working hypothesis that errors are increased by sleep fragmentation. Two potential explanations were entertained. One is that larger errors are theoretically possible when more objective sleep (and less WAPSO) occurs and N2 comprises the majority of objective TST. The other possibility relates to the fact that the TST error is calculated directly from the objective TST, which is itself positively correlated with time spent in NREM stage 2 sleep and negatively correlated with time spent awake. To evaluate the potential for spurious correlations of TST error with sleep stage percentages due to this “embedded” correlation, we undertook additional analysis (supplemental material). This analysis shows how sleep architecture associations with TST error are confounded by the fact that the objective TST is both used in the calculation of the error and itself has correlations with sleep architecture components. This embedded correlation may lead to incorrect conclusions about TST error in relation to sleep stage percentages.

DISCUSSION

The main finding of this study is that healthy adults without evidence of sleep misperception on the baseline habitual night of sleep within an inpatient experimental facility exhibit substantial sleep misperception under subsequent conditions of (i) absence of time cues and (ii) extended time in bed per 24 hours. The inpatient extended sleep opportunity resulted in decreased sleep efficiency and thus a form of experimental insomnia. The misperception of sleep duration was bi-directional: overestimation of sleep following 4-h daytime nap opportunities, and underestimation of sleep following 12-h nocturnal sleep opportunities. Contrary to our working hypothesis, neither the subjective TST estimates nor the extent of their accuracy was correlated with commonly accepted indices of sleep fragmentation, such as NREM stage 1 sleep or the number of awakenings.

Time Perception during Sleep and Wake States

Retrospectively estimating sleep duration involves, among other things, time cues common to daily life, such as looking at the time just before bed, natural sunlight variations, and waking to an alarm in the morning. Systematic removal of time cues may compromise accuracy in retrospective time estimation. The use of auxiliary cues is not surprising, since sleep is a state of altered consciousness, and presumably an individual cannot directly assess a sense of time passage while asleep. For patients with insomnia, the existing data do not support the hypothesis that general time perception is abnormal. For example,
Sleep Stage Correlates of Sleep Misperception

Errors in TST underestimation are most clinically relevant for insomnia patients, who often demonstrate a component of sleep misperception. Underestimation errors were observed specifically for 12-h nighttime sleep opportunities, whereas overestimation was observed for 4-h daytime sleep opportunities. TST errors were related to NREM stage 2 sleep in an unexpected direction: the less of this stage, the higher the subjective TST estimate. The basis of this finding is uncertain, though it is worth mentioning that the percent of NREM stage 2 sleep was inversely related to the percentage of REM and N3 sleep. Thus the apparent correlation may be spurious (see supplemental material) and reflect its relation to these other stages of sleep, which themselves did not reach significance in correlations with TST estimates, possibly due to greater variance compared to the dominant NREM stage 2 sleep percentages. Similarly, the apparent correlation of TST error with the percentage of WAPSO was likely related to the strong inverse correlation of WAPSO with objective TST (see Table 5).

Regarding the potential importance of sleep stages, there is literature supporting the restorative and cognitive roles of REM and slow wave sleep, although a variety of opinions on the role of particular sleep stages exist. Here, REM and slow wave sleep only showed significant correlations with TST estimates following 4-h sleep opportunities. The relationship is clearly complex, since TST was overestimated for 4-h sleep opportunities, despite less REM sleep in these daytime naps. Although we expected that the degree of fragmentation evidenced by increased WAPSO% would influence the perception of sleep, clearly this is not a simple causal relationship, as the TST errors following 12-h periods were larger when WAPSO% was smaller, and there was no correlation of WAPSO% with errors following 4-h periods. In addition, TST errors for 4-h periods were overestimated despite the markedly decreased sleep efficiency. One might predict that this overestimation was in fact related to sleep inertia when awakening from slow wave sleep. Despite a correlation of TST estimate following 4-h sleep opportunities with the N3%, there was no correlation of TST error for 4-h sleep periods with the absolute or relative amount of slow wave sleep whether it was considered as NREM stages 3 and 4 sleep separately or combined as stage N3 sleep. In fact, the magnitude of TST error for 4-h periods was not correlated with any other sleep-wake metrics. Therefore, misperception is not strictly related to the degree of fragmentation or WAPSO. The difference between subjective estimates and the extent to which they are incorrect (i.e., the TST error) suggest that the subjective experience of sleep has complex dependencies, only a portion of which relates to the sleep-wake stage content of the sleep opportunity.

In summary, subjective sleep estimates demonstrated correlation with sleep stage amounts. The magnitude of misperception errors, however, showed no clear mechanistic link to the amounts of individual sleep stages. The potential roles for circadian phase in sleep perception could not be assessed in these protocols, but could represent an important factor in how we process time perception. We also cannot address whether subjects inferred either the time of day or the expected sleep duration based on the repeating alternation of 12-h and 4-h sleep opportunities, despite not being informed of this pattern. The extent of misperception was nevertheless substantial, even if unaccounted for heuristics were involved.

Clinical Implications of Misperception

Despite the extensive literature documenting the occurrence of misperception in various sleep disorders, the issue of perception is not typically addressed in epidemiological studies that depend on self-reported sleep. Many reports utilize subjective reports of latency, efficiency, and total sleep time in insomnia interventions. Although the patient’s subjective perception is a justifiable endpoint for assessing the effectiveness of interventions, from a mechanistic standpoint and from the perspective of possible feedback to re-align subjective-objective mismatch, understanding the degree to which this phenomenon occurs in insomnia patients remains an important goal.

Clearly the misperception of sleep times was a “state” rather than a “trait” phenomenon in this study of healthy adults. Patients with insomnia could, in principle, demonstrate a trait of misperception, independent of the sleep stage amounts on a particular night, in which case pharmacological management takes on a perspective other than increasing the amount of sleep obtained. Other patients may demonstrate fluctuations in their sleep stage amounts and consolidation from night to night, and thus their degree of misperception may also fluctuate as a reversible state. Determining where on this spectrum a particular patient resides may have important implications for insomnia management.

Limitations

This study has several limitations. First, the experimental setting was highly controlled, and thus may not have external validity with respect to the sleep-wake patterns of patients with insomnia. Although excess time in bed is a maladaptive behavior adopted by some patients with insomnia, absence of time cues and other experimental restrictions on activity do not occur clinically. The variance in misperception among individuals with insomnia accounted for by excess time in bed is unknown. Moreover, the habit of clock-watching may actually exacerbate insomnia. Second, the form of insomnia observed here is entirely attributed to excess time in bed, whereas clinical insomnia is often multifactorial. Third, healthy subjects presumably do not have the hyperarousal that is hypothesized to be a major pathophysiological aspect of chronic insomnia. The extent to which hyperarousal contributes to misperception is incompletely understood, but cortical hyperarousal is a plausible (and testable) potential etiology. Finally, we cannot distinguish possible contributions of circadian factors (i.e., time of day or night) or sleep opportunity duration (4-h or 12-h) as potential causes of the differences in misperception between the two types of sleep period using these data.

REFERENCES


ACKNOWLEDGMENTS

The authors thank Drs. Andrew Phillips and Catherine Chu-Shore for valuable discussions. Funding: Department of Neurology, Massachusetts General Hospital, Center for Integration of Medicine and Innovative Technology, and the Clinical Investigator Training Program: Harvard/MIT Health Sciences and Technology – Beth Israel Deaconess Medical Center, in collaboration with Pfizer, Inc. and Merck &Co. (MTB); NIH P01-AG009975, NSBRI HFP01603, NIH RC2-HL101340, K02-HD045459, and NIH K24-HL105664 (EBK); and NCRR-GCRC-M01-RR02635 to the BWH GCRC.

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication October, 2011
Submitted in final revised form April, 2012
Accepted for publication April, 2012
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DISCLOSURE STATEMENT

This was not an industry supported study. Dr. Bianchi has a patent pending on a home sleep monitoring device that may be used in the future for insomnia patients. Dr. Klerman has received support from Respironics and Sony Corporations. The other author has indicated no financial conflicts of interest.
The treatment of central sleep apnea (CSA) continues to lack a universally recognized standard of care.1 Variable etiologies of CSA and the presence of concomitant disorders influence the choice of therapy. Thus, therapeutic options have varied markedly from positive airway pressure (PAP) devices, including continuous positive airway pressure (CPAP),2-6 bilevel positive airway pressure therapy (BPAP),7-9 and adaptive servoventilation,10-13 to supplemental O2,14-17 carbon dioxide,1,22 and/or pharmacologic agents.23-25,29,30 The outcomes of therapy have also varied considerably, with limited evidence to establish the effectiveness of any therapy for CSA.24,26-31,32 The majority of published literature has focused on the treatment of CSA secondary to congestive heart failure (CHF),2,11,13,15-22,26,29 with very little data on patients with “primary” CSA21,24 or CSA secondary to causes other than CHF.33 In addition, there is very little data on the treatment of CSA related to opioid use and CSA that is concomitant with OSA.13,35 The latter entities are of increasing importance in the US veteran population due to the increased use of prescription opioid drugs for chronic pain control and the risk for opioid related deaths.34

Central apnea (CA), defined as the cessation of breathing with an absence of respiratory effort, occurs as cycles of apnea alternating with hyperpnea. The ventilatory overshoot in the recovery period leads to hypocapnia and recurrent apneas. Treatment strategies primarily focus on preventing the “overshoot.”
Central Sleep Apnea Titration Protocol

The CSA treatment protocol was designed as a technologist-driven protocol that was utilized in all patients with CSA, regardless of its etiology or the presence of concomitant OSA. The protocol was developed prior to the wide availability of ASV, which was not attempted if the above protocol was successful. Positive pressure titration was initiated at CPAP 4-5 cm H₂O and titrated upward to 10-14 cm H₂O. If frequent central apneas persisted at CPAP pressures of 10-14 cm H₂O, then CPAP was not increased further, in order to avoid further hypoinflation and hypocapnia. Instead, supplemental O₂ was added at 2 liters per minute (L/min) to dampen the post- apneic ventilatory overshoot, and increased by 1 L/min to maintain oxygen saturation ≥ 93%, keeping CPAP at the same level. Oxygen saturation was maintained at ≥ 93%, to ensure that it was consistently > 90% even if apnea occurred, and allowing for a 2% device error. Supplemental oxygen at above goal was continued for ≥ 20 minutes. If central apneas persisted despite the addition of adequate supplemental O₂ for ≥ 20 min, CPAP was switched to BPAP while maintaining oxygen saturation ≥ 93%. Initial BPAP setting was adjusted to keep the inspiratory positive airway pressure setting (IPAP) 2-3 cm H₂O higher, and the expiratory positive airway pressure setting (EPAP) 2 cm H₂O lower than the previous CPAP setting. These were adjusted upward if hypopneas and obstructive apneas in addition to CA appeared, but keeping the IPAP-EPAP difference low (4-6 cm H₂O) to prevent further hypocapnia and central apneas. The usual laboratory protocol was to achieve optimal titration in both supine and lateral positions. Eighty-four patients underwent a second or third night study for an initial or repeat PAP titration according to the above treatment protocol.

Data Analysis

A cross-sectional analysis of the data was performed on consecutive patients identified as having CSA by chart review for the period between January 2006 and June 2009, who received the diagnosis of CSA during an overnight baseline PSG or the diagnostic portion of a split-night PSG study. Patients with PAP-emergent CSA (CAI < 5/h on the diagnostic portion of the PSG but ≥ 5/h during the titration phase of full-night PAP titration study or a split-night study) were not included in this analysis, as this was not the objective of the study. Moreover, the natural history of PAP-emergent CSA is that these resolve spontaneously over time. Demographics and medical history data that could influence the presence of CSA and hypoxia were extracted, including age, gender, body mass index (BMI), Epworth Sleepiness Scale (ESS) score, medical history of heart failure (CHF), coronary artery disease (CAD), atrial fibrillation, hypertensive HTN, diabetes (DM), stroke, chronic obstructive pulmonary disease (COPD), and the use of opioid drugs. In addition, from the sleep study reports and charts we recorded the type of sleep study (baseline full-night or split-night PSG study), AHÍ, CAI, minimum oxygen saturation, the presence or absence of Cheyne-Stokes breathing/periodic breathing, and when available, transthoracic cardiac echocardiogram (ECHo) reports for ejection fraction (EF) and the presence or absence of diastolic dysfunction. Following initial variations in protocol implementation during the technologist training period, the protocol was followed more consistently and patients underwent titrations using the protocol on either the first night or a repeat study night. For the purpose of data analysis, an optimal response was defined as CAI ≤ 5/h and an AHÍ < 10/h. If the
Table 1—Demographics and baseline characteristics

<table>
<thead>
<tr>
<th>Group characteristics</th>
<th>Entire group (n = 162)</th>
<th>CPAP (n = 72)</th>
<th>CPAP+O2 (n = 38)</th>
<th>BPAP+O2 (n = 17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>59.0 ± 11.5</td>
<td>56.4 ± 11.8*</td>
<td>62.5 ± 8.9</td>
<td>62.0 ± 9.1</td>
</tr>
<tr>
<td>Males</td>
<td>159 (98)</td>
<td>72</td>
<td>37</td>
<td>16</td>
</tr>
<tr>
<td>BMI</td>
<td>33.5 ± 7.1</td>
<td>34.0 ± 7.1</td>
<td>32.9 ± 7.5</td>
<td>35.0 ± 6.2</td>
</tr>
<tr>
<td>ESS</td>
<td>11 ± 6</td>
<td>11 ± 6</td>
<td>11 ± 6</td>
<td>12 ± 6</td>
</tr>
<tr>
<td>Opioid use</td>
<td>47 (29)</td>
<td>25 (35)</td>
<td>16 (42)</td>
<td>7 (41)</td>
</tr>
<tr>
<td>History of CHF</td>
<td>32 (20)</td>
<td>9 (13)</td>
<td>8 (21)</td>
<td>6 (35)</td>
</tr>
<tr>
<td>Systolic dysfunction†</td>
<td>23 (14)</td>
<td>10 (14)</td>
<td>9 (24)</td>
<td>4 (24)</td>
</tr>
<tr>
<td>Diastolic dysfunction¶</td>
<td>25 (15)</td>
<td>11 (15)</td>
<td>8 (21)</td>
<td>6 (35)</td>
</tr>
<tr>
<td>CAD</td>
<td>39 (24)</td>
<td>12 (17)</td>
<td>13 (34)</td>
<td>4 (24)</td>
</tr>
<tr>
<td>HTN</td>
<td>115 (71)</td>
<td>44 (61)</td>
<td>28 (74)</td>
<td>16 (94)*</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>20 (12)</td>
<td>3 (4)</td>
<td>10 (26)*</td>
<td>3 (18)</td>
</tr>
<tr>
<td>Stroke/TIA</td>
<td>10 (6)</td>
<td>4 (6)</td>
<td>0 (0)</td>
<td>4 (24)*</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>8 (5)</td>
<td>4 (6)</td>
<td>2 (5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>DM</td>
<td>60 (37)</td>
<td>26 (36)</td>
<td>15 (39)</td>
<td>8 (47)</td>
</tr>
<tr>
<td>COPD</td>
<td>21 (13)</td>
<td>5 (7)</td>
<td>5 (13)*</td>
<td>5 (29)*</td>
</tr>
<tr>
<td>Baseline AHI</td>
<td>68.9 ± 29.8</td>
<td>66.8 ± 30.4</td>
<td>64.8 ± 28.8</td>
<td>70.7 ± 20.3</td>
</tr>
<tr>
<td>Baseline CAI</td>
<td>28.0 ± 25.6</td>
<td>23.8 ± 21.9</td>
<td>31.0 ± 32.6</td>
<td>21.6 ± 19.1</td>
</tr>
<tr>
<td>Baseline minimum SpO2</td>
<td>82.0 ± 6.2</td>
<td>82.3 ± 5.2</td>
<td>82.7 ± 7.7</td>
<td>80.2 ± 7.0</td>
</tr>
</tbody>
</table>

Numbers in parenthesis are percentages of the number of patients in that group, rounded to the nearest integer. †Systolic cardiac dysfunction with estimated left ventricular ejection fraction < 55% (by 2-D echocardiogram, ECHO). ¶Diastolic cardiac dysfunction with normal systolic function of ejection fraction > 55% (2-D ECHO). The treatment groups were overall similar in characteristics to the entire “parent” group and to one another, except for the ones annotated; €p < 0.05 vs. entire group, *p < 0.05 vs CPAP, §p < 0.05 vs CPAP+O2.

RESULTS

CSA was diagnosed in 162 patients following 41 full-night diagnostic/baseline and 121 split-night overnight attended PSG studies. The protocol was completed appropriately in 151 patients. Concomitant OSA was present in 149 of the 151 patients. The baseline characteristics of the patients are given on Table 1. Prescription opioid drug use was the most com-
Stage 1 was markedly reduced, but not in the “normal” range.

Optimal response in all 3 groups (Journal of Clinical Sleep Medicine, Vol. 8, No. 5, 2012 S Chowdhuri, A Ghabsha, P Sinha et al).

The time interval noted in each therapeutic group, thus establishing the presence of an optimal response to therapy. The time interval when apneas and hypopneas still persisted, prior to optimal response; however, on optimal PAP/PAP+O2 therapy, stage 1 was only 13%, with 87% of time with optimal response being stage N2/N3 and REM sleep (also see Figure 2 as example). This along with the improvement in the arousal index indicates an improvement in sleep continuity with optimal CPAP or optimal PAP+O2 combination therapy.

Periodic breathing pattern was observed in 41 patients during their respective baseline study periods. The remaining patients experienced repetitive central apneas but without a crescendo-decrescendo periodic breathing pattern. Of the individuals with oscillatory periodic breathing pattern, echocardiography was available in 28 and showed that 14 (50%) had diastolic function by echocardiography. The periodic breathing index (see Data Analysis) decreased significantly with CPAP (n = 25, 30.9 ± 24.9/h vs. 0.4 ± 1.4/h, p < 0.001), CPAP+O2 (n = 16, 27.2 ± 17.3 vs. 1.1 ± 3.5/h, p < 0.001) and BPAP+O2 (n = 5, 42.2 ± 31.5 vs. 1.0 ± 2.3/h, p = 0.04), respectively.

### Table 2—Numbers of individuals with optimal response to the protocol

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>CPAP</th>
<th>CPAP+O2</th>
<th>BPAP+O2</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients, n = 151</td>
<td>127 (84)</td>
<td>72 (48)</td>
<td>38 (25)*</td>
<td>18 (11)*</td>
</tr>
<tr>
<td>Opioid users, n = 41</td>
<td>36 (89)</td>
<td>22 (54)</td>
<td>11 (27)#</td>
<td>4 (10)*</td>
</tr>
</tbody>
</table>

Optimal response was defined as CAI < 5/h and AHI < 10/h (responders). Numbers in parenthesis are percentages rounded to the nearest integer. No significant differences in outcomes between the entire vs. opioid user groups. Among the 3 interventions, significantly higher number of responders was noted with CPAP alone.*p < 0.01 vs CPAP, p = 0.02 vs CPAP, *p < 0.01 vs CPAP+O2.

### Table 3—Comparison of sleep parameters for all patients at baseline and on therapy

<table>
<thead>
<tr>
<th></th>
<th>(1) Baseline</th>
<th>(2) CPAP therapy</th>
<th>(3) CPAP+O2 therapy</th>
<th>(4) BPAP+O2 therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST, minutes</td>
<td>131.7 ± 90.3</td>
<td>273.6 ± 61.9*</td>
<td>274.8 ± 92.0*</td>
<td>215.2 ± 114.8*</td>
</tr>
<tr>
<td>SE %</td>
<td>63.4 ± 18.4</td>
<td>77.4 ± 15.1*</td>
<td>74.5 ± 19.4*</td>
<td>72.1 ± 21.0</td>
</tr>
<tr>
<td>Stage N1, %</td>
<td>52.9 ± 25.7</td>
<td>23.6 ± 12.8*</td>
<td>27.6 ± 13.4*</td>
<td>36.6 ± 23.1</td>
</tr>
<tr>
<td>Stage N2, %</td>
<td>37.9 ± 21.4</td>
<td>53.0 ± 14.8*</td>
<td>52.7 ± 11.2*</td>
<td>47.8 ± 18.2</td>
</tr>
<tr>
<td>Stage N3, %</td>
<td>5.5 ± 10.5</td>
<td>8.3 ± 10.7*</td>
<td>5.7 ± 8.5</td>
<td>4.2 ± 5.9</td>
</tr>
<tr>
<td>Stage R, %</td>
<td>4.1 ± 7.2</td>
<td>14.6 ± 9.1*</td>
<td>14.1 ± 11.3*</td>
<td>11.4 ± 10.4*</td>
</tr>
<tr>
<td>Total arousal index, per hr at baseline and on optimal therapy§</td>
<td>63.2 ± 27.1</td>
<td>3.8 ± 5.1*</td>
<td>3.6 ± 4.5*</td>
<td>4.2 ± 6.3*</td>
</tr>
</tbody>
</table>

Treatment group vs. baseline values, *p < 0.05, p = 0.001; 1CPAP vs. BPAP+O2, p < 0.05. Remaining group comparisons were not significantly different.

Lower baseline TST values are due the fact that both full-night and the diagnostic portion of split night studies are included in the analysis. TST, total sleep time; SE, sleep efficiency; N1, N2, N3 are stages of NREM sleep; stage R, REM sleep. The sleep stages percentages are given for the entire study duration for the baseline diagnostic period and for the entire PAP/PAP+O2 titration periods, respectively. §The arousal index was averaged for the baseline period and for the final PAP/PAP+O2 therapy setting that produced an optimal response. See text for a definition of optimal response.

A common risk factor for CSA (29%, 47 of 162 patients), even more common than the history of CHF (20%) or stroke (6%). All patients were naïve to CPAP at the time of titration, except one individual who had returned for a repeat split-night study and had CSA on the baseline portion of the study that resolved on CPAP alone. There was an optimal response in 127 of the 151 (84.1%) patients following the protocol (Table 2). In addition, the most common therapeutic modality that was effective was CPAP in 48% of individuals (Table 2). Significant reduction in AHI and CAI to AHI < 10/h and CAI < 5/h, respectively (Figure 1A-C), was achieved on final optimal settings with a concomitant significant increase in maximum oxygen saturation noted in each therapeutic group, thus establishing the presence of an optimal response to therapy. The time interval between the initiation of supplemental oxygen and the resolution of CSA in the CPAP+O2 group was 97.8 ± 79 min (median 78 min, range 0 to 285 min; Figure 2). Finally, in 12 patients, the addition of oxygen did not eliminate CA adequately (CAI > 5/h) despite attaining adequate oxygen saturation. A significantly higher percent of this non-responder group compared to the entire sample had underlying systolic cardiac dysfunction (25% vs 10%, p < 0.01), while other baseline characteristics were similar. Table 3 provides an assessment of sleep architecture on each therapeutic modality that produced an optimal response. The overall sleep architecture was improved compared with baseline but was not significantly different among the 3 therapy groups. The arousal index was elevated at baseline. Compared to baseline values, the arousal index was markedly reduced on the PAP/PAP+O2 therapy settings that produced an optimal response in all 3 groups (Table 3). The percentage of stage 1 was markedly reduced, but not in the “normal” range for the overall titration duration which included an initial titration period when apneas and hypopneas still persisted, prior to optimal response; however, on optimal PAP/PAP+O2 therapy, stage 1 was only 13%, with 87% of time with optimal response being stage N2/N3 and REM sleep (also see Figure 2 as example). This along with the improvement in the arousal index indicates an improvement in sleep continuity with optimal CPAP or optimal PAP+O2 combination therapy.

Subgroup of Opioid Users with Optimal Response

Forty-seven patients (29%) were on prescribed opioid therapy for chronic pain control. The prescribed opioid drugs included hydrocodone (n = 19), oxycodone (n = 10), morphine (n = 7), methadone (n = 6), codeine (n = 3), oxymorphone (n = 1), propoxyphene (n = 1), buprenorphine (n = 1), and tramadol (n = 7). The exact dosing of opioid therapy was available from the medical record in 44 patients. The 24-h morphine sulfate equipotency dosing for the group was 93 ± 102 mg, with a median dose of 40 mg and maximum dose of 363 mg. The characteristics of the opioid users were not significantly differ-
ent from the parent group: 94% males, BMI 33.9 ± 7.4 kg/m², AHI 77.4 ± 33.1/h, CAI 37.6 ± 28.9/h, minimum O₂ saturation 80.5% ± 5.5%, ESS score 13 ± 5. However, the opioid user subgroup was younger, 53.7 ± 11.5 vs 59.0 ± 11.5 yrs, p < 0.01; only 6 individuals had a concomitant history of CHF, with 5 patients with EF < 55%; the proportion of individuals with CHF in opioid users was similar to that in the entire group, (13% vs 20%, p = ns). The titration protocol was fully implemented in 41 patients, with optimal response noted in 36 (89%). CPAP was the most effective treatment (Table 2) followed by PAP with oxygen supplementation. There were also significant improvements in AHI, CAI, and oxygen saturation, compared with baseline values in this subgroup (Figure 3) with the titration protocol.

**DISCUSSION**

To date, only small studies15-19 conducted mostly in patients with underlying CHF, have demonstrated the effectiveness of adding O₂ for the management of CSA. However, no study has evaluated the effectiveness of a combination therapy of PAP and supplemental oxygen on the evolution of central apneas in an unselected population of patients with a mix of etiologies for CSA.

**Summary of Findings**

This study revealed several important findings: (1) CPAP therapy was effective in 50% of the study population, affirming that CPAP remains the initial therapeutic option when CSA is observed on a sleep study. (2) Supplemental O₂ therapy with PAP was effective in an additional 35% of cases, regardless of the etiology of CSA. These therapies reduced CSA with an improvement in sleep continuity and periodic breathing. (3) Narcotic use is very common in patients with CSA, and these results may be applicable to patients and of importance to practitioners outside of the VA system. We found that narcotic use was a more common risk factor for CSA than heart failure. (4) PAP with adjunctive oxygen therapy was effective in CSA with opioid drug use and may be considered as alternative therapy when central apneas are not eliminated by CPAP alone.

**Potential Mechanisms of Action**

Evidence supports the salutary effect of nasal CPAP in the treatment of central sleep apnea, with the strongest evidence obtained from studies of patients with central apnea in relation to heart failure. The therapeutic effects of nasal CPAP could be due to restoring upper airway patency and stabilization of the respiratory control system. Central apnea rarely occurs as a single event, but as cycles of apnea/hypopnea alternating with hyperpnea, often in association with obstructive events. Once apnea occurs, several factors promote further instability. Central apnea results in pharyngeal airway narrowing or occlusion; therefore, resumption of spontaneous breathing requires opening an occluded airway, overcoming tissue adhesion force and perhaps gravitational forces. Furthermore, based on prior data, there is an “inherent inertia of the ventilatory control system” that prolongs a central apnea and only allows resumption of respiratory activity after the arterial PCO₂.
is 4-6 mm Hg above eupnea. The prolongation of apnea leads to variable asphyxia (hypoxia and hypercapnia) and transient arousals, resulting in ventilatory overshoot, subsequent hypocapnia, and further apnea/hypopnea.

The aforementioned sequence may explain the reported therapeutic effects of nasal CPAP in the treatment of central apnea. First, nasal CPAP restores upper airway patency, resulting in dampening of ventilatory overshoot, and mitigation of subsequent hypocapnia. CPAP increases nocturnal PaCO₂, perhaps by dampening ventilatory overshoot and hypocapnia, as well as by increased lung volume. Edwards et al. have shown that CPAP stabilizes chemoreflex control of the respiratory system in the newborn lamb, via increased lung volume and decreased loop gain. In addition, improvement in the cardiac output with improved circulation time may contribute to stable breathing in individuals with CHF. However, the response to PAP in non-CHF patients indicates that the decreased propensity to central apnea may also be due to improved oxygenation, mitigation of intermittent hypoxia, increased lung volume, restoration of upper airway patency, and unloading of respiratory muscles. Our data do not allow us to ascertain the relative contribution of each potential mechanism.

We noted that the timeline for resolution of central apnea after initiation of supplemental oxygen was inconsistent with a peripheral chemoreceptor inhibition. While the duration of time required to reach SpO₂ of 93% may determine the time taken to eliminate the central apneas, in majority of the patients, resolution of central apnea required more than 5 minutes after reaching the goal SpO₂ level, indicating that the response was a central phenomenon and not a peripheral chemoreceptor response, since a peripheral chemoreceptor response would have occurred within a few breaths of adding oxygen. Therefore, we interpret our findings as a consequence of central stimulatory effect rather than peripheral inhibitory effect of hyperoxia. The present study corroborates our previous study demonstrating that sustained levels of oxygen at FiO₂ 0.40 to 0.70 mitigates the susceptibility to hypocapnic central apnea in healthy adults during sleep. Likewise, there is evidence that adding oxygen at FiO₂ as low as 30% for 30 minutes resulted in increasing minute ventilation by 21% above room air levels. Thus, sustained hyperoxia is a ventilatory stimulant. Specific

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**Figure 2**—The hypnogram from an individual patient undergoing a night study demonstrates an “optimal response” upon adding supplemental O₂ to CPAP

Position channel: B, back; R, right; L, left; S, side. Therapy channel: numbers indicate CPAP (cm H₂O) while the horizontal dark blue line indicates time period when supplemental O₂ was added to the circuit, starting from the arrow (↓), initially at 2 Lpm and then increased to 3 Lpm. On the respiratory event channel, the light blue, red, pink, and green bars represent central apneas, obstructive apneas, mixed apneas, and hypopneas, respectively. Respiratory events channel: numbers indicate duration of event in seconds; LM, leg movements. The clock time is indicated on the top border of the figure. Both obstructive and central events were at present at baseline and were partially resolved with CPAP; whereas the residual central apneas were completely eliminated by the addition of supplemental oxygen; (↓) denotes addition of O₂. Following an increase in the supplemental O₂ to 3 Lpm there was an optimal response (see text for definition). The sleep architecture also improved significantly on the optimal setting of CPAP plus oxygen at 3 Lpm, with maximum percentage of TST on this setting being stage N2 followed by stage R sleep. The salutary effect of supplementary O₂ was noted 25 min after adding supplemental O₂, or approximately 10 min (horizontal arrow, ←→), after reaching 93% SpO₂, represented by the elimination of central apneas.
mechanisms of hyperoxic hyperventilation include increased brain tissue PCO₂ via cerebral vasoconstriction,⁴⁹ the Haldane effect,⁵⁰ or a direct stimulatory effect on chemosensitive respiratory neurons⁵¹ via production of reactive oxygen species. The net effect of hyperoxia is alveolar hyperventilation, decreased plant gain, and increased CO₂ reserve, thus stabilizing respiration⁶ during sleep.

The aforementioned discussion is applicable to post-hyperventilation central apnea. Nevertheless, it is unclear if the same mechanisms apply to CSA due to opioid use, given the uncertainty regarding the underlying mechanisms. It is possible that increased oxygen level increases chemoreceptor output⁶⁰ in this scenario too, while increased upper airway collapsibility may be countered by PAP, however, the latter explanation is speculative and needs further exploration in experimental settings.

**Methodological Considerations**

Several methodological issues should be considered for proper interpretation of our findings. First, our protocol does not allow us to test the effects of adaptive servo-ventilation (ASV) on central apnea, which was not included in the main pathway, as it was not available when this protocol was initiated in our facility. ASV may contain features that combine the mechanical effects of CPAP with dampening of ventilatory overshoot. A small study in patients with CSR compared the effects of CPAP vs. BPAP vs. ASV vs. O₂ alone, however CPAP plus O₂ was not included as a comparison group.²⁰ Another study¹¹ that included CPAP plus O₂ in a small group patients (n = 7) noted a decline in CSA; however, the majority (> 60%) had CPAP-emergent or “complex-CSA,” unlike the population described in our study. A randomized study with direct comparisons of CPAP plus O₂ with ASV is required to assess the relative effects of each approach as well as relative cost-effectiveness. While BPAP with oxygen did produce an optimal response, a spontaneous mode of BPAP without a back-up rate was used, which is a limitation of this study. We recommend that future studies compare the efficacy of BPAP and oxygen, both in the spontaneous and spontaneous-timed modes. Second, our study was limited by the retrospective design, the predominance of males (because of the study location in a VA medical center), and the lack of longitudinal comparisons among different treatment arms. Third, the presence of REM sleep could have eliminated the central events during the latter portion of the PAP titration; however, the majority of sleep time was in NREM sleep with REM occupying only 8% to 14% of the TST. Fourth, we referred to the AASM scoring manual¹² for a qualitative definition of Cheyne-Stokes/predicating breathing pattern. However, proper quantification of periodic breathing cycles requires concomitant measurement of esophageal or supraglottic pressure for accurate classification of central and obstructive events, especially hypopnea. Finally, given the retrospective nature of the study we were unable to confirm the actual ingested dose of opioid medications. However, we expect that the patients were regularly ingesting the prescribed dosing of opioid for treatment of chronic pain. In addition, it was not possible to retrospectively determine the exact etiology triggering CSA in each patient. However, our primary goal at the outset of the study was to simulate real clinical situations where CSA coexists with comorbid conditions and to determine the role of O₂ supplementation as a simple and easily accessible measure in this patient group.

**Significance**

Our study included a population of patients referred from multiple VA medical centers, with many underlying etiologies of CSA, and not just limited to patients with CSA due to heart failure or “primary” CSA. The recently published AASM Practice Parameters⁶⁴ provide guidance for the treatment of CSA in several clinical settings, and supports the use of CPAP alone or supplemental oxygen alone for the treatment of CSA. However, the document does not address the use of combination therapy of PAP plus supplemental oxygen because such studies are lacking. Moreover, there is very limited evidence for the management of CSA due to opioid use⁵³, as noted in the practice parameter⁶⁴. The practice parameter also highlighted the absence of a large series evaluating the role of “dead space” and recognized that carbon dioxide is not universally available and is difficult to administer.⁶⁴ While ASV is now available, the cost of these devices is much greater than the cost of CPAP, and the latter may be sufficient in half of the patients with CSA. Additionally, ASV is not used as first line treatment for CSA, and alternative therapies are required for the management of CSA that persists on CPAP. The current study contributes to the available literature by providing a real-life scenario where OSA frequently coexists with CSA in both patients with CHF and prescription opioid medication users. To our knowledge, this is also the largest series of patients with CSA associated with prescription opioid use that describes the effect of the three different therapeutic modalities, in contrast to prior studies.⁵³ These results are of great relevance in the US veteran popula-
This study purports to simplify the management of CSA in a step-wise fashion in a sleep clinic-based population with underlying co-morbidities and prescription opioid use. The results show that in individuals who fail initial CPAP during a titration study, a majority of residual CSA can be eliminated effectively by using oxygen adjunctively with PAP. Prospective comparative efficacy and cost-effectiveness trials using different treatment modalities are needed to expand on these findings.

**REFERENCES**


63. The Hopkins Opioid Program, last accessed 5/07/12.


ACKNOWLEDGMENTS

Dr. Chowdhuri has received funding from VHA Career Development Award-2 and Dr. Badr from VHA Merit Review Award. The authors acknowledge the assistance of Gregory Koshorek, B.Sc.

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication December, 2011
Submitted in final revised form July, 2012
Accepted for publication July, 2012
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DISCLOSURE STATEMENT

This was not an industry supported study. The authors have indicated no financial conflicts of interest.
Multimodality Therapy for Sleep Apnea Syndromes

Commentary on Chowdhuri et al. Treatment of central sleep apnea in US veterans.

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The fixation on unimodal approaches to management of “sleep apnea” defies biological reality. Perhaps the incredible success of continuous positive airway pressure (CPAP) for obstructive sleep apnea is at least partially to blame, but the increasing evidence for sleep apnea phenotypes has not resulted in a meaningful translation to patient care. Taking obstructive sleep apnea, studies compare CPAP with an oral appliance, or with weight loss, or placebo, depending on the precise scientific question and the desire to show “equivalence” or at least clinical effectiveness (e.g., hypoglossal nerve stimulation, Provent) for aid to marketing and FDA approval.1

However, sleep apnea in a wider sense is the end result of interactive pathophysiological processes. These include sleep fragmentation propensity, upper airway obstruction, and respiratory chemoreflex under- or over-responsiveness.2,3 Then why is it that there is so little data on combination therapies? Was there ever a clinical trial of myocardial infarction or congestive heart failure comparing unimodal therapies? Typically a pathophysiology-driven “basic cocktail” is tested against a new add-on. The need for improved management strategies for sleep apnea syndromes is evident—not more than 50% compliance/adherence for an apparently gold standard treatment that almost always shows sleep laboratory effectiveness, in patients seeking help for debilitating symptoms, should raise the possibility that maybe our gold is a metal of lesser worth. The clinical challenge is even greater in those with central or complex apnea and hypoventilation syndromes, where advanced modes of ventilation are being evaluated as stand-alone therapies, such as adaptive ventilation in congestive heart failure-associated periodic breathing.4 If there is one condition where sleep fragmentation, obstructive elements, and respiratory decontrol interact, it is in heart failure patients.

The paper by Chaudhuri et al.5 in this issue of the journal is an important one. Though not randomized, it seems to reasonably support the beneficial effect of supplemental oxygen in improving sleep-respiration in those with significant central sleep apnea, using a threshold of a central apnea index ≥ 5/hour of sleep. The delay in response is intriguing and likely reflects an interaction of sleep state effects (REM, stable NREM rebound) and direct biological effects of oxygen, including plausibility changes in redox state. Looking closely at the data shows that stage N1 remains high, and some important information about the characteristics of the “optimal response” are missing (duration, sleep stage, and state). The definition of the optimal response also leaves something to be desired: is getting the CAI under 5/hour really a valid biological target? Other limitations of the paper include not scoring respiratory effort related arousals and hypopneas that do not have a 50% signal reduction. During titration, getting rid of major discrete events is relatively easier than normalizing sleep-breathing, and use of the alternate criteria when supplemental oxygen is added (thus directly modifying one of the scoring tags) can overestimate efficacy. Though periodic breathing was recognized, using the 10-minute criterion (which has no specific biological basis) will exclude shorter bursts of periodic breathing that are common in those with mixed apnea and have been well described at high altitude, the quintessential chemoreflex-induced sleep apnea model. Nevertheless, the study is a very important contribution to the literature and was just begging to be done.

Table 1 lists some of the options available to target the different pathophysiological processes in sleep disordered breathing syndromes. The therapies available to overcome obstruction are relatively straightforward, and some combinations are logical (weight loss + CPAP). However, the oral appliance vs. CPAP story has taken a gladiatorial color—what about combined therapy, especially those who have high pressure requirements? Most centers probably offer this on a case-by-case basis, as we do, but there may be additional potential benefits of minimizing mouth breathing and preventing an oronasal mask from pushing the jaw backwards during sleep. Positive pressure + a sedative are a logical approach to the anxious patient and those with severely fragmented sleep, and a subset of patients could benefit over the long term. The sedative could also improve blood pressure dipping,6 which is frequently abnormal in sleep apnea patients. In hypoventilation syndromes and in those with pulmonary pathology affecting gas exchange such as chronic obstructive lung disease, supplemental oxygen could be a useful adjunct to bilevel ventilation by allowing targeting both CO2 and O2 end-points; adding O2 is commonly done in clinical practice, but is there an advantage to keep the saturations closer to 98% vs. 90%? The latter target results in vulnerability to significant desaturations with changes in body position, sleep stage, mask or mouth leak, and minor respiratory events. Part of the effectiveness of Provent may relate to minimizing hypocapnia.7

The approach to management of various hyperresponsive chemoreflex syndromes (central and complex sleep apnea, peri-
Table 1—Targeting therapy to pathology in sleep apnea management

<table>
<thead>
<tr>
<th>Pathophysiologic target</th>
<th>Modality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper airway obstruction</td>
<td>Positive pressure (various), oral appliance, various soft tissue and bone-based surgeries, Provent, oral negative pressure, hypoglossal nerve stimulation, weight loss including bariatric surgery, body positioning (non-supine), lower body negative pressure</td>
</tr>
<tr>
<td>Sleep fragmentation propensity</td>
<td>Sleep hygiene, treating circadian phase abnormalities, sedatives</td>
</tr>
<tr>
<td>Hyporesponsive respiratory chemoreflex</td>
<td>Bilevel ventilation, volume-target pressure support ventilation, acetazolamide, weight loss including bariatric surgery, O₂</td>
</tr>
<tr>
<td>Hyperresponsive respiratory chemoreflex</td>
<td>Adaptive ventilation, sedatives, acetazolamide, O₂, CO₂ based approaches including dead space, body positioning, Provent (?), cardiac pacing, lower body negative pressure (?)</td>
</tr>
<tr>
<td>Disordered integration (opiates, brain stem pathologies)</td>
<td>Adaptive ventilation, O₂, CO₂ modulation</td>
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Scoring event-by-event introduces a strong bias in the direction of obstruction, as flow-limitation is common in periodic breathing sequences. The update of respiratory scoring criteria have made a real effort to aid us in characterizing central hypopneas, yet leave it optional—why should anything considered important be optional? If it is assumed, as stated in the article, that “separation of hypopneas into central or obstructive is not clinically indicated in the majority of patients,” then we are never going to accurately phenotype sleep apnea. It is likely that there was far more “central” disease both before and after treatment in these patients than that quantified by a central apnea count. Using a 10-minute threshold to tag periodic breathing minimizes the recognition of this pattern; the new criteria more readily enable identifying periodic breathing. The REM vs. NREM severity difference is blurred when global apnea-hypopnea or respiratory-disturbance indices are computed; NREM dominance is characteristic of strong respiratory chemoreflex effects. The bimodality of NREM sleep, where periods of stable breathing can occur during N2, can result in the premature declaration of CPAP success in NREM-dominant sleep apnea syndromes. Second, we should have greater expectations from the definition of success. In fact, the end point of success should be the same for obstruction or central sleep apnea syndromes—elimination of all respiratory events including respiratory effort related arousals, normalizing sleep quality, and optimal clinical outcomes (e.g., daytime sleepiness and fatigue, blood pressure dipping). In the Chaudhuri study, stage N1 remained markedly elevated—in all probability, there was significant residual sleep apnea subthreshold to the scoring criteria used. Equally possible is that these patients have an increase in sleep fragmentation propensity independent of sleep apnea, as has been noted in complex apnea and congestive heart failure. A “sleep stabilizer” (aka sedative) would be a logical addition here.

Hypopnea driven respiratory instability is the most important factor in central apnea syndromes—rebreathing approaches and acetazolamide are logical adjuncts, even to adaptive ventilation. The sad part is that much of the above may well remain devoid of high levels of evidence—there is little incentive to study these systematically, never mind the enormous cost and little return to the use of freely available generic drugs. Sedatives have been traditionally abhorrent entities in sleep apnea management. Perhaps it is time to revisit this dogma, given:

1. the availability of sedatives with acceptable impact on respiration
2. the recognition of the role of arousals in amplifying sleep apnea severity
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CITATION


REFERENCES


ACKNOWLEDGMENTS

Work for this study was performed at Beth Israel Deaconess Medical Center, Boston.

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication September, 2012
Accepted for publication September, 2012
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DISCLOSURE STATEMENT

Dr. Thomas is a patent holder of an approach to use adjunctive CO₂ added to positive airway pressure for treatment of central and complex sleep apnea; co-patent holder/license (To MyCardio, LLC) for technology using the ECG to detect and quantify sleep apnea phenotypes. Off-label use: Multimodality approaches to sleep apnea treatment involve off-label use of FDA approved products (masks) and drugs (e.g., acetazolamide, sedatives).
Adaptive Servoventilation in Patients with Central or Complex Sleep Apnea Related to Chronic Opioid Use and Congestive Heart Failure

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Study Objectives: Adaptive servoventilation (ASV) is often used to treat central sleep apnea (CSA) and complex sleep apnea syndrome (CompSAS). Both CompSAS and CSA may occur in the setting of CHF and with the use of chronic opioids. We hypothesized that ASV would be less successful in treatment of CSA and CompSAS secondary to opioid use than in CHF patients.

Methods: Consecutive patients were studied between January and December 2009 who underwent ASV titration for CSA or CompSAS due to CHF (defined as EF < 45%, or > 50% with evidence for diastolic dysfunction on echocardiogram) and chronic opioid users (defined by the use of opioids > 6 months).

Results: Study included one hundred and eight patients with 77 males (71.3%) and 31 females (28.7%). Subjects had severe sleep apnea at baseline (AHI 45.6 ± 27.4) and inadequate control of sleep disordered breathing on CPAP (AHI 50.0 ± 32.2, CAI 36.6 ± 32). No significant differences were found between the groups in overall ASV success, defined as AHI < 10/h (p = 0.236). ASV was successful in 28 (59.6%) of those in the opioid group, compared to 43 (70.5%) of those in the CHF group. When ASV success was defined as AHI < 5/h at optimum EEP, there was again no significant difference between the groups (p-value = 0.812). Logistic regression showed unit increases in BMI, unit increases in HCO₃, and presence of CSR were each associated with decreased likelihood of ASV success.

Conclusion: We did not find a statistically significant difference in the effectiveness of ASV between CHF patients and chronic opioid users, with the overall success rate approaching 70%, as defined by an AHI < 10/h.

Keywords: Adaptive servoventilation, central sleep apnea, complex sleep apnea, chronic opioid use, congestive heart failure

Commentary: A commentary on this article appears in this issue on page 577.

Citation: Ramar K; Ramar P; Morgenthaler TI. Adaptive servoventilation in patients with central or complex sleep apnea related to chronic opioid use and congestive heart failure. J Clin Sleep Med 2012;8(5):569-576.

BRIEF SUMMARY

Current Knowledge/Study Rationale: Based on its internal proprietary algorithm, we hypothesized that adaptive servoventilation (ASV) might function better in the presence of a highly regular and periodic central sleep disordered breathing (such as Cheyne-Stokes respiration (CSR) in the setting of CHF) compared to the non-periodic (such as irregular or ataxic/Biot breathing patterns in chronic opioid users) central sleep disordered breathing.

Study Impact: ASV was as effective in the treatment of central and complex sleep apnea in chronic opioid users as it is in patients with CHF, with the overall success rate of 70% as defined by an AHI ≤ 10/hour. Lower body mass index, but higher bicarbonate values and absence of CSR, were predictors for ASV success in both groups.
Adaptive servoventilation (ASV) is a pressure preset, volume or flow cycled form of closed-loop mechanical ventilator that monitors the patient’s breathing pattern over a certain period of time. It uses an internal algorithm to provide breath-by-breath dynamic adjustment of inspiratory pressure support with a back-up respiratory rate to normalize breathing patterns by-breath dynamic adjustment of inspiratory pressure support that monitors the patient’s breathing pattern over a certain period. The studies in these two studies were small (5 and 22 patients, respectively). In addition, there are no studies to date that compare the effectiveness of ASV between the CHF and opioid users. This study compares the efficacy of ASV in the treatment of CSA and CompSAS secondary to opioid use with those secondary to CHF.

Overview and Study Design
The study was approved by the Mayo Clinic Institutional Review Board (IRB Application #:11-007500). Retrospectively, we screened consecutive patients referred to our sleep center who underwent ASV titration between January and December 2009. Patients were selected if their baseline diagnostic polysomnography (PSG) showed an AHI ≥ 5/h and subsequent continuous positive airway pressure (CPAP) titration showed control of obstructive events but a residual AHI > 5/h or the persistence of CSA and/or CSR on CPAP. All of our patients were identified based upon split-night studies. They were allotted in the CHF group if they had a transthoracic echocardiogram that showed an ejection fraction (EF) ≤ 45%, or if they had an EF > 50% but had documentation of heart failure with preserved EF (diastolic dysfunction). The chronic opioid group included those who had been treated with opioid medications > 6 months. Patients were excluded from analysis if they did not meet our definition for CHF or chronic opioid use.

Setting and Participants
One hundred and eight patients were found eligible based on the above screening criteria. Patient records from 2009 contained data on the titration study to assess the optimum AHI at the prescribed end-expiratory pressure (EEP) on ASV titration. EEP was also titrated to a maximum of 15 cm of water, if needed.

Clinical records of consults and follow-up visits were reviewed, and data were collected including age, gender, body mass index (BMI), EF from echocardiogram, and presence or absence of atrial fibrillation. Polysomnographic data on both the diagnostic and titration studies were also collected as stated below. The main reason for the use of chronic opioids was for chronic pain syndrome.

Polysomnography
Polysomnography (PSG) was performed using a digital polygraph (Nicolette, San Diego, CA). We used the electroencephalogram ([EEG] 2 channels), electrocugulogram ([EOG] 2 channels), and electromyogram ([EMG] 1 channel) montage as described in the recent scoring manual of the American Academy of Sleep Medicine.16 Airflow and respiratory effort were monitored using oronasal thermocouple and nasal pressure transducer, respiratory inductive plethysmography (RIP) during the diagnostic study, and, during titration, using the flow channel from the CPAP and bilevel positive airway pressure (BPAP) plus RIP. Sleep staging and arousals were scored.

An apnea was defined as cessation of inspiratory flow (> 90% reduction in airflow signal) ≥ 10 sec. An obstructive apnea was defined as the absence of airflow in the presence of rib cage and abdominal excursions. A central apnea was defined as the absence of airflow with absence of rib cage and abdominal excursions. Hypopnea was defined as a 50% reduction in airflow signal lasting ≥ 10 sec associated with ≥ 4% drop in oxygen saturation. We defined CSA to be present if the central apnea index (CAI) was > 5/h and the CAI was ≥ 50% of the AHI. CSA due to CSR was considered to be present based on the interpreting physician’s report or consult note; CSR was defined by the presence of ≥ 3 consecutive cycles of cyclical crescendo and decrescendo breathing consisting of apneas, hypopneas, hypoapneas, and hypopneas, with each cycle lasting ≥ 45 sec, and a central apnea index ≥ 5/h. Complex sleep apnea (CompSAS) was considered present if the diagnostic PSG demonstrated findings consistent with obstructive sleep apnea, but CPAP titration sufficient to alleviate obstruction left residual central apneas and/or periodic breathing with hypopneas sufficient to produce an AHI ≥ 5/h.

Standard protocols for our sleep laboratory were used to titrate for CPAP and ASV. Different masks were used based on patient’s preference, comfort, and fit. Mask leaks were monitored and corrections made accordingly. CPAP (Respironics Inc., Murrysville, PA) titration was performed using a uniform and standard approach. Titration usually began at CPAP of 5 cm of water and titrated to eliminate obstructive sleep disordered breathing events. If central apneas developed, the pressure was increased to monitor for improvement; if not, the pressure was brought back down to the pressure that eliminated the obstructive events. The development and persistence of central sleep apnea on CPAP as defined above led to ASV titration. ASV titration was performed using a ResMed VPAP Adapt SV (ResMed Ltd., NSW, Australia). The EEP was started at 5 cm of water or at the CPAP that eliminated OSA during the CPAP.
titration. Titration of EEP was performed by the technician to eliminate OSA, while the pressure support was on default settings (minimum inspiratory pressure support of 3 cm of water, maximum inspiratory pressure support of 10 cm of water above EEP that was controlled by the internal algorithm of the machine to target minute ventilation). The back-up rate was in the auto mode. The EEP could be adjusted to a maximum of 15 cm of water pressure.

**Comparison and Outcomes**

We assessed the effectiveness of ASV to treat CSA and CompSAS between the CHF group and chronic opioid group. For the primary analysis, we considered treatment successful if the ASV settings resulted in an AHI < 10/h. As a secondary analysis, we also looked at our data using an AHI threshold for control of < 5/h at the optimally prescribed EEP (that EEP that eliminated obstructive events while minimizing central events and sleep disruption, based on sleep specialist’s review of PSG). Finally, we assessed and compared sleep architecture, arousal index, periodic leg movements, and predictors for ASV success between the 2 groups.

**Statistical Analyses**

All analyses were done in Statistical Analysis System (SAS; version 9.2; SAS Institute, Cary, NC). The primary outcome was ASV success defined as AHI < 10. The secondary outcome was defined as AHI < 5 at the optimum EEP measured during ASV titration. Logistic regression was used to determine which variables predicted ASV success in the overall group as well as separately within the CHF and opioid groups. All p-values were 2-tailed, and statistical significance was defined with p < 0.05. Univariate analyses were first conducted on factors including BMI, age, and AHI during the diagnostic study, AHI on CPAP titration (CPAP AHI), bicarbonate levels (since most patients did not have arterial blood gas analysis to identify PaCO2 levels) and presence or absence of atrial fibrillation, gender, and EF from echocardiogram to identify factors that were independently associated with ASV success. Models were built with 3 different ASV success criteria, one defined as overall titration period AHI < 10/h, and the others with AHI < 5/h or 10/h at the optimum EEP. Based on the Wald test from logistic regression, predictors with p-value < 0.25 were included as candidates for multivariate analysis. This cutoff was selected rather than the traditional p-value cutpoint of 0.05 so as to include important co-variates in the model. Stepwise selection was performed in which the most nonsignificant (p-value > 0.05) and non-con founding co-variates (change in parameter estimate > 20%) were removed iteratively from the model. Hosmer-Lemeshow Goodness of fit test was used to assess model fit. All models were assessed at p < 0.05.

**RESULTS**

**Demographics**

Of 108 patients meeting our selection criteria, 61 (56.48%) had CSA during the diagnostic portion of the night and belonged to the CHF group. Of the 61 patients with CSA, 19 (31.1%) had CSR. Chronic opioid users comprised the remaining 47 of our 108 subjects; among them, 28 had CompSAS (59.6%), while the remaining 19 had CSA. The sample included 77 males (71.3%) and 31 females (28.7%) who ranged in age from 26 to 89 years. Among the males, 23 (29.9%) were CHF and 54 (70.1%) were in the CHF group. Similarly, no significant differences were noted in ASV success (as defined by an AHI < 10/h) between overall CSA patients (irrespective of whether they belonged to the CHF or chronic opioid group) and CompSAS patients (64.2% vs 65.7%, p = 0.8826). The average EEP was 8

**Table 1—Demographic characteristics**

<table>
<thead>
<tr>
<th></th>
<th>CHF N= 61</th>
<th>Opioid N = 47</th>
<th>All N = 108</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Median (IQR)</td>
<td>Mean ± SD</td>
<td>Median (IQR)</td>
</tr>
<tr>
<td></td>
<td>73.0 (64.0, 77.0)</td>
<td>70.9 ± 9.4</td>
<td>61.0 (49.0, 68.0)</td>
</tr>
<tr>
<td>Body mass index (BMI)</td>
<td>32.8 (26.9, 35.8)</td>
<td>30.8 ± 5.8</td>
<td>31.6 (27.9, 39.7)</td>
</tr>
<tr>
<td>Ejection fraction from echocardiogram (%)</td>
<td>40.0 (27.0, 51.0)</td>
<td>40.6 ± 15.5</td>
<td>62.0 (58.0, 66.0)</td>
</tr>
<tr>
<td>Atrial fibrillation N (%)</td>
<td>27.0 (87.1)</td>
<td>4.0 (12.9)</td>
<td>31.0 (28.7)</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>54/7</td>
<td>23/24</td>
<td>77/31</td>
</tr>
</tbody>
</table>

**Efficacy**

There was no significant difference between the groups in overall ASV success defined as AHI < 10/h (p = 0.236). Of those in the opioid group, 28 (59.6%) found success with ASV, compared to 43 (70.5%) of those in the CHF group. When success was defined as AHI < 5/h at the optimum EEP, there was again no significant difference between the groups having ASV success (χ^2 p-value = 0.812). Of those in the opioid group, 29 (61.7%) found success with ASV, compared to 39 (63.9%) of those in the CHF group. Similarly, no significant differences were noted in ASV success (as defined by an AHI < 10/h) between overall CSA patients (irrespective of whether they belonged to the CHF or chronic opioid group) and CompSAS patients (64.2% vs 65.7%, p = 0.8826). The average EEP was 8
There was also a significant difference in mean EF between the groups (60.3 vs. 40.6, p < 0.001) and in the presence of atrial fibrillation (4% vs. 27%, p < 0.001) in the opioid vs. the CHF group, respectively.

Table 3—Polysomnographic sleep characteristics

<table>
<thead>
<tr>
<th></th>
<th>All Subjects</th>
<th>CHF n = 61</th>
<th>Opioid n = 47</th>
<th>p value (opioid vs. CHF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dx N1%</td>
<td>24.5 ± 17.4</td>
<td>19.3 ± 17.2</td>
<td>27.9 ± 16.9</td>
<td>0.018</td>
</tr>
<tr>
<td>Dx N2%</td>
<td>49.2 ± 16.3</td>
<td>51.7 ± 16.8</td>
<td>47.5 ± 15.9</td>
<td>0.225</td>
</tr>
<tr>
<td>Dx N3%</td>
<td>17.3 ± 18.1</td>
<td>22.7 ± 21.6</td>
<td>13.8 ± 14.5</td>
<td>0.029</td>
</tr>
<tr>
<td>Dx REM%</td>
<td>9.0 ± 9.7</td>
<td>6.3 ± 9.2</td>
<td>10.8 ± 9.7</td>
<td>0.026</td>
</tr>
<tr>
<td>Dx ARLI</td>
<td>50.3 ± 27.3</td>
<td>46.6 ± 35.7</td>
<td>53.0 ± 20.1</td>
<td>0.333</td>
</tr>
<tr>
<td>Dx PMLI</td>
<td>36.8 ± 52.2</td>
<td>22.5 ± 54.0</td>
<td>46.5 ± 48.9</td>
<td>0.024</td>
</tr>
</tbody>
</table>

Values expressed as mean ± standard deviation. Dx N1%, N2%, N3%, REM% = Percentage of N1, N2, N3, and REM sleep during the diagnostic portion of the sleep study. Dx ARLI = Arousal index during the diagnostic portion of the sleep study. Dx PMLI = Periodic leg movement index during the diagnostic portion of the sleep study.

Summary distributions of sleep architecture, arousal index, and periodic leg movements in our subjects are found in Table 3. Overall, there was a decrease in stage N1, increase in stages N2 and N3, and decrease in stage R in the opioid group compared to the CHF group. The periodic leg movement index (PLMI) and arousal index was lower in the opioid group than in the CHF group.

Predictors of ASV Success

Logistic regression showed that BMI and CPAP AHI were inversely predictive of overall ASV success using the AHI < 10/h criterion (OR 0.920; CI 0.861, 0.983 and OR 0.984: CI 0.970, 0.998, respectively; Table 4). When ASV success was defined by AHI < 5/h at the optimum EEP, BMI, CSR, bicarbonate levels were all significant predictors of ASV success (OR 0.851: CI 0.775, 0.934; OR 0.213: CI 0.062, 0.727; OR 1.218: CI 1.008, 1.471, respectively). Unit increases in BMI, unit increases in HCO3, and presence of CSR were each associated with decreased likelihood of ASV success (Figure 1). Of note, in the last model, CSR and HCO3 were not significant in univariate analysis; however, they were forced in to the multivariate model due to biologic relevance and came out as significant predictors of ASV success. Overall, higher measures of BMI, especially in the overweight class, correlated with lower probability of ASV success with AHI < 10/h (p = 0.0005) and AHI < 5/h at optimum EEP (p = 0.0048). Interestingly, the highest proportion of those who had failures at AHI < 10/h (37%) had a BMI in the range of 30-36 (Figure 1).

DISCUSSION

The findings of this study indicate that ASV is as effective in the treatment of central and complex sleep apnea in chronic opioid users as it is in patients with CHF. Overall success rates using more liberal criteria (AHI < 10 on ASV titration) or more stringent criteria (AHI < 5/h at best EEP), were statistically not different. The predictors for success with ASV in both groups were lower BMI, higher bicarbonate values, and absence of CSR. This is not the result we expected. We had hypothesized that ASV would be more likely to succeed in patients with CHF, especially if they had CSR. Although not specifically part of our initial hypothesis, we had considered it likely that since patients...
Table 4—Univariate and multivariate correlates of ASV success

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model 1 (AHI &lt; 10)</th>
<th></th>
<th>Model 2 (AHI &lt; 5 at Optimum EEP)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariate OR (95%CI)</td>
<td>p</td>
<td>Multivariate OR (95%CI)</td>
<td>p</td>
</tr>
<tr>
<td></td>
<td>Multivariate OR (95%CI)</td>
<td>p</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>0.92 (0.87, 0.98)</td>
<td>0.011</td>
<td>0.92 (0.86, 0.98)</td>
<td>0.014</td>
</tr>
<tr>
<td>Age</td>
<td>1.01 (0.98, 1.04)</td>
<td>0.634</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnostic test AHI</td>
<td>0.99 (0.98, 1.01)</td>
<td>0.211</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPAP AHI</td>
<td>0.99 (0.97, 1.00)</td>
<td>0.03</td>
<td>0.98 (0.97, 1.0)</td>
<td>0.023</td>
</tr>
<tr>
<td>Atrial fibrillation*</td>
<td>1.13 (0.47, 2.75)</td>
<td>0.781</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender**</td>
<td>0.88 (0.36, 2.14)</td>
<td>0.781</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EF</td>
<td>0.99 (0.97, 1.0)</td>
<td>0.655</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CSR*</td>
<td>0.98 (0.39, 2.48)</td>
<td>0.965</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CSA*</td>
<td>1.01 (0.44, 2.29)</td>
<td>0.985</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCO₃⁻</td>
<td>0.97 (0.83, 1.14)</td>
<td>0.704</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opioid***</td>
<td>0.62 (0.28, 1.38)</td>
<td>0.237</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Covariates modeled as: *Yes vs No; **Males vs Females; ***Opioid group vs CHF group.

Table 5—Oxygen saturation during the diagnostic study vs. ASV titration

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Patients (Mean ± SD)</th>
<th>CHF (Mean ± SD)</th>
<th>Opioid (Mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean baseline oxygen saturation</td>
<td>Diagnostic study 92.5 ± 2.5%</td>
<td>92.6 ± 2.1</td>
<td>92.3 ± 3.0</td>
</tr>
<tr>
<td></td>
<td>ASV titration 93.6 ± 2.1</td>
<td></td>
<td>93.5 ± 2.3</td>
</tr>
<tr>
<td>Percentage of time spent above 90% oxygen saturation</td>
<td>Diagnostic study 81.7 ± 21.6</td>
<td>83.9 ± 16.9</td>
<td>76.3 ± 27.4</td>
</tr>
<tr>
<td></td>
<td>ASV titration 91.7 ± 15.6</td>
<td></td>
<td>92.6 ± 15.4</td>
</tr>
</tbody>
</table>

All values were statistically significantly better, with p < 0.001 in the ASV titration compared to the diagnostic study.

Figure 1—Overall percent success and failure by BMI

Proportions of overall success and failure by body mass index (BMI). Unit increases in BMI were associated with decreased likelihood of ASV success. The greatest difference in proportion of successes compared to failures at AHI < 10/h (19%) occurred among those with a BMI in the range of 24 to < 32. The difference between proportion of success compared to failures in this BMI range was even more pronounced (25%) when success was defined as AHI < 5/h at optimum EEP.
with CHF and CSR often have lower PaCO₂ and bicarbonate levels, that bicarbonate levels would inversely correlate with likelihood of success. Again, this proved to not be the case.

Of the 108 patients, ASV was successful in reaching an AHI < 5 in 63% and AHI < 10 in 73.2%. These rates are consistent with findings of most other studies. Success rates for ASV (using an AHI < 10) in patients with CompSAS have been reported in as low as 18%14 and as high as 100%15 associated with chronic opioid use, and in more mixed populations as 70% to 100%.8,16-20 Published success rates for patients with CSR have ranged from 73% to 100%.8,21-25 Although our overall success rates were not dissimilar to prior reports, the reason why ASV succeeds in controlling some, but not all types of central sleep apnea remains elusive. Possible mechanisms for ASV failure might include inadequate stabilization of the upper airway, high interface leak, ineffective pressure support, patient-ventilator dyssynchrony due to poorly timed pressure support, or unstable sleep leading to oscillation between ventilatory control patterns.

Role of Upper Airway Stabilization, Interface Leak, and Ineffective Pressure Support

CPAP provides a pneumatic splint for the upper airway throughout the breathing cycle and successfully treats obstructive sleep apnea (OSA). The inspiratory pressure on ASV is titrated to eliminate OSA, while the variable inspiratory pressure support along with the back-up rate tries to eliminate the central sleep disordered breathing events. CPAP has some success in studies to treat CSA in the setting of heart failure,26-28 though overall effectiveness is inferior to ASV.3,4,7,26 In contrast, CPAP alone is most often ineffective in controlling sleep disordered breathing in patients with chronic opioid use.12,14 In our own study, though it helped to control OSA, CPAP overall was unsuccessful in controlling central sleep disordered breathing in opioid users, and in fact worsened the CSA, similar to findings in other studies. When using ASV, it appears that we achieved adequate EEP, since on ASV the OMAI was only 3.4 ± 6.7/h. Therefore, we do not think the ASV failures were due to inadequate stabilization of the upper airway. It also seems likely that leak was not a major contributor, since titration was performed manually under direct sleep technologist observation; the technologists promptly adjust interfaces when leaking is detected. However, we did not measure leak, and this could be an opportunity for improvement in our practice and outcomes. The fact that higher BMI was associated with lower likelihood of ASV success may speculatively reflect an expected decreased effectiveness of pressure support in enhancing tidal volumes when the respiratory compliance is reduced by obesity. We did not measure tidal volumes in a calibrated fashion, and thus were not able to compare volumes between ASV success and failures.

Patient-Ventilator Dyssynchrony

Failure via ventilatory-patient dyssynchrony might be expected when ventilatory patterns being generated by the ASV do not match or compensate adequately for the patient’s pattern. We had postulated that since different underlying mechanisms result in central sleep apnea patterns in patients with chronic opioid use vs. CHF that the interaction of the central respiratory controller with ASV algorithms would be characteristically different. The central sleep apnea patterns noted with CSR (in association mostly with CHF) are most pronounced during NREM sleep and clearly represent the manifestation of a respiratory system with high loop gain and delayed feedback. The pattern is typically reduced during REM sleep because ventilation is less reliant on feedback mechanisms. The resultant ventilatory pattern is predictable and we thought would result in better synchrony with the ASV algorithm. In contrast, most opioid induced sleep disordered breathing patterns are less periodic, poorly attenuated in REM, and the pathophysiology is complex and less well worked out. Opioids appear to exert differential effects on central and peripheral chemoreceptors.30 In addition, opioids inhibit the inspiratory rhythm generating neurons located in the pre-Bötzinger complex neurons, but do not appear to affect the expiratory motor neurons located in the retrotrospinal nucleus/parafacial respiratory group.31 Thus opioids interfere with normal ventilatory rhythmosgenesis and regulation, resulting in less predictable patterns of ventilation than in CSR. Some of the breathing patterns in chronic opioid users are similar to those in heart failure patients, such as the presence of OSA and the cluster breathing pattern, though the cycle lengths in the periodic breathing pattern are considerably shorter in the cluster breathing than in the CSR pattern seen in heart failure patients. In contrast, ataxic/Biot breathing pattern is a non-periodic irregular breathing pattern seen in chronic opioid users but not in CHF.

There were differences in the proportion of sleep stages between the CHF and opioid group during the diagnostic study (Table 3), with a higher percentage of stage N3 and lower REM in the chronic opioid group than the CHF group. Decrease in REM has been reported in chronic opioid users22; however, results are conflicting for NREM sleep. Most studies show a decrease in stage N1 and an increase in stage N2 compared to controls not on opioids, but the results are conflicting with stage N3.12,22 We found a higher percentage of stage N3 in chronic opioid group than the CHF group. Our reported percentage of stage N3 is higher than the previous reported literature in chronic opioid users.12,22 Whether this has any effect on the efficacy of the PAP therapy is unclear, though we believe it not to be the case.

We postulated that the ASV algorithm would synchronize ventilation more poorly with opioid-related SDB than with CHF-associated patterns. We did not demonstrate this. In fact, when we analyzed the influence of CSR pattern on ASV success by forcing CSR into the regression model, its presence correlated negatively. This may be reflective of imprecise characterization of the breathing patterns. Patients might have experienced CSR for only relatively short percentages of the study (for example, 3-5 min out of an entire night) and yet would be characterized as having demonstrated CSR. Our hypothesis regarding a positive correlation between a regular cyclic breathing pattern and ASV success might be better studied by using a more global measure of periodicity across the entire study, such as percent of time spent in a periodic pattern; we did not design our study to accommodate such measures. CSR associated with CHF is most often accompanied by hypopnoea, which we thought might be reflected in serum bicarbonate levels, thus hypothesizing that lower serum bicarbonate levels would be associated with a greater likelihood of ASV success. Again,
our hypothesis was proven incorrect. This may be influenced by the fact that not all of our subjects had bicarbonate levels immediately prior to ASV titration. Some of the levels were obtained shortly afterward as a result of other clinical needs. It is possible the bicarbonate levels do not represent in any way the PaCO2 levels at the time of ASV titration. Therefore, the contribution of this mechanism for ASV failure cannot be reliably inferred from our data.

Although our study identified BMI, CSR, and HCO3 levels as significant predictors of ASV success, there may be other factors that might determine success with ASV in chronic opioid users that we did not discern. The type and duration of opioids, the predominant breathing pattern, i.e., cluster vs. ataxic/ Biot breathing pattern, comorbid conditions, and co-ingestion of other medications such as benzodiazepines may be other factors that should be assessed and possibly controlled for, in future studies.

The main limitation of our study is the retrospective nature of our assessment, with no prospective randomization or blinding performed. Referral bias is also likely, and this may have affected the overall effectiveness of ASV, as patients referred to our center were the ones who likely failed therapies elsewhere. While our sample size was small and could have resulted in a type II error, post hoc power calculation of 77% suggests that a type II error is not unlikely with this sample size. Another limitation of our study was the use of bicarbonate levels to indirectly assess pCO2, as most patients did not have arterial blood gas analysis around the time of their PSG. Though our assumption was that bicarbonate values would inversely correlate with pCO2, it is possible that bicarbonate levels may have been affected by various conditions such as the use of diuretics. Not reporting the exact dose of opioids consumed around the time of the PSG, or whether the patients were concomitantly taking benzodiazepines, is another limitation of our study. Due to the retrospective nature of our study, however, we knew that the patients were on opioids based on the medication list; it was difficult to assess the exact dose at the time of the PSG or the type of chronic pain syndrome, as this information was not available on the consult or progress note. We compared two patient cohorts with different underlying diseases. However, both CHF and chronic opioid use are associated with central sleep apnea, and ASV is currently being used to treat varied types of central sleep apnea.

The main intent of this study was to assess whether ASV would be an effective treatment for central sleep apnea, inclusive of CSR and CompSAS, and irrespective of the underlying cause or disorder that triggers it. CompSAS that occurs in the setting of chronic opioids may be different in pathophysiology (probably a “dulling” of the loop gain mechanism) than that due to CSA/CSR (where the loop gain is high with increased chemosensitivity). Therefore, we hypothesized that ASV as a treatment option would not work well in patients on chronic opioids. Although previous data suggest that both CSA and CompSAS improve over time in some patients undergoing treatment with CPAP,13 the retrospective nature of our study design did not allow us to address this, as all patients in our sample with persistent CSA on CPAP immediately underwent ASV titration. A future prospective and randomized study could be designed to specifically address this question. The main purpose of this study was to assess which patients are most likely to acutely succeed with ASV, rather than determining whether ASV would succeed better than CPAP of chronic use. Also, most studies in our center are performed based on the split-night protocol.34 Though there might have been differences in the proportion of obstructive and central sleep disordered breathing between the first and second half of the night, it would be difficult to speculate whether it would have made a difference, as all our patients in this study were selected based on the split night protocol. Additionally, we used only the VPAP Adapt SV, which is a ResMed device and not the Respironics BiPAP AutoSV device during our ASV titration. There are differences between these two machines in how they address the underlying central sleep disordered breathing events. The AutoSV uses a different target (peak flow) in its servomechanism, while the VPAP Adapt SV targets the minute ventilation. Consequently, our findings may not apply to patients using the Respironics BiPAP autoSV. Despite these limitations, our data are the most comprehensive regarding the use and comparing the effectiveness of ASV between CHF and chronic opioid groups. Also, our sample size is the largest on opioid users using ASV to treat their sleep disordered breathing.

CONCLUSION

In conclusion, we did not find a statistically significant difference in the effectiveness of ASV between the CHF patients and chronic opioid users, with the overall success rate approaching around 70%, as defined by an AHI of less than 10/h. With the increasing use of chronic opioids and increasing prevalence of congestive heart failure and their associated breathing disorders, further studies are needed to assess predictors for success in this group of patients.

REFERENCES


ACKNOWLEDGMENTS

Dr. Ramar acknowledges funding via an internal faculty development grant from the Mayo Clinic Department of Internal Medicine to prepare and submit this manuscript. Work for this study was performed at Mayo Clinic, Rochester, MN, USA.

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Submitted for publication February, 2012
Submitted in final revised form April, 2012
Accepted for publication April, 2012
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DISCLOSURE STATEMENT

This was not an industry supported study. Dr. Morgenthaler is the principal investigator in a multicenter trial for which his institution as received funding from ResMed. The other authors have indicated no financial conflicts of interest.
In 1997 the American Academy of Pain Medicine and the American Pain Society stated that “it is now accepted…that respiratory depression induced by opioids tends to be a short lived phenomenon, generally occurs only in opioid-naïve patients and is antagonized by pain. Therefore, withholding the appropriate use of opioids from a patient who is experiencing pain on the basis of respiratory concerns is unwarranted.” In addition, Papaleontiou et al. published a meta-analysis in 2010 on the efficacy and safety of opioid intake in chronic non-cancer pain.\(^2\) Constipation, nausea, and dizziness represented the top three side effects, with a prevalence between 22% and 30%. However, obstructive or central apnea/hypopnea, hypoventilation during sleep, and impairment of respiratory drive remained unmentioned.\(^3\)

Can general practitioners, pain therapists and oncologists reassure their patients regarding respiratory side effects in long-term treatment with opioids? It is without doubt, that for far too long sufficient palliation has been withheld from pain patients, in fear of side effects, addiction, and misuse of opioids. However, improved knowledge combined with changing attitudes has helped to normalize the use of the most important relievers of pain, leading to a large increase in opioid prescription.\(^4\)\(^,\)\(^5\) Moreover, opioids are prescribed not only to relieve pain, but also, for example to alleviate dyspnea in patients with chronic pulmonary disorders.\(^6\)\(^,\)\(^7\) Finally, opiate addiction remains a growing and largely unsolved problem, leading to the incorporation of an increasing number of patients world-wide in methadone maintenance programs.\(^8\) Bearing in mind this widened use of opioids, observations of sleep related breathing disorders (SRBD) are alarming. Kelly et al. described fatal or life-threatening events in children who underwent adenotonsillectomy for obstructive sleep apnea. These children possessed genetic alterations that led to an increased morphine production from codeine.\(^9\) Many such reports of perioperative complications in sleep apnea patients have been published.

In 2007 the broad spectrum of SRBD under opioids were described retrospectively by Walker et al.\(^1\) Besides obstructive disturbances, they found central apneas, ataxic or irregular respiration, and periods of sustained hypoventilation.

However, we have to admit frankly that our knowledge of the pathophysiology of opioid-induced sleep apnea is still very limited. Pattinson reviewed the control of respiration under opioid intake.\(^10\) The author pointed out that respiration becomes shallow and irregular leading to hypercapnia and hypoxia. The respiratory disturbances differed according to the mode of administration. Whereas rapid intravenous boli induced apneas, long-term infusions led to a gradual increase of hypercapnia, thereby contributing to the maintenance of respiration. The effect of opioids on the respiratory rhythm has not been conclusively explored. Peripheral and central chemosensitivity play a major role, leading to a reduction of the hypoxic and hypercapnic ventilatory response. However, the extent of the interference and the precise location of the interception of the reflexes are unclear. This retards the pharmaceutical development of opioids with sufficient analgesic properties but minimized respiratory side effects.

Having said all this, physicians will mostly be interested in data relating to the clinical presentation, optimal diagnosis, and treatment of opioid-induced sleep apnea. Are there specific signs and symptoms of opioid induced sleep apnea? They are certainly associated with dizziness, impaired concentration, and daytime sleepiness. But is it possible to differentiate between central nervous system effects and breathing disturbances? Generally speaking, sleepiness and deficits in neurocognitive parameters cease during long-term application, so that even driving may be permitted. However, this trend is not to be expected in SRBD. Another clinically relevant but unsolved problem is the question of whether the outcome of opioid users with or without SRBD differs.

In this current issue, Ramar et al.\(^1\) present an important study focusing on the question of the best available therapy of respiratory disturbances during sleep. They investigated patients with central breathing disturbances due to chronic heart failure or chronic opioid use, who had failed to respond to treatment with constant CPAP. Adaptive servoventilation (ASV) enabled sufficient therapy in the majority of heart failure and opioid patients. The study provides preliminary data, as it was retrospective and the largest sample to date from everyday practice, and in that sense, it is representative of the real-life situation.

In 2008 two studies with contradictory results were published in this journal.\(^2\) While Farney failed to show a differ-
ence between CPAP and ASV, Javaheri found an effective treatment with ASV in a small group of opioid induced sleep apnea patients. The latter results, now being proven by Ramar’s data, could be expected due to the algorithm of adaptive servoventilation. CPAP may interfere with SRBD in several ways: it stabilizes the upper airways and counterbalances upper airway obstruction; the positive thoracic pressure reduces left ventricular cardiac afterload and therefore improves the ejection fraction; and finally, CPAP can enlarge lung volumes and reduce ventilation-perfusion mismatch. However, CPAP does not influence, or only marginally influences breathing rhythm and chemosensitivity. In contrast, ASV combines the effects of CPAP (positive expiratory pressure) with variable pressure support and the application of mandatory breaths. Therefore, disturbances of respiratory drive and periods of hypoventilation can be counterbalanced. Interestingly, a higher bicarbonate level was a predictor of ASV success. This surprising finding could have, as discussed by the authors, technical reasons. However, it could also indicate extensive periods of hypoventilation as a part of the SRBD. Based on Ramar’s data, the question remains why 30% to 40% of patients with heart failure or opioid induced sleep apnea, respectively, could not be treated optimally. The choice or setting of the device, the mode of reaction of the algorithm, and interface problems may contribute to this phenomenon. However, the results suggest an advantage to the early use of adaptive servoventilation after optimal medical therapy.

Sleep specialists should try to avoid repeating history. The epochal invention of CPAP by Sullivan led to a rather generalized perception of obstructive sleep apnea, but importantly at the same time, to the implementation of the optimal treatment. This coincidence—although of huge value for the patient—handicapped detailed exploration of the pathophysiological background. Opioid-induced sleep apnea is, as pointed out above, even more unclear. Increasing evidence in this field suggests a treatment advantage with adaptive servoventilation. However, all efforts should be undertaken to better understand the clinical presentation, pathophysiology, and prognosis. Opioid-induced sleep apnea is a real problem as the rapidly increasing prevalence indicates. We are however a long way from truly understanding its relevance.

Future studies should try to characterize the different phenotypes of breathing disturbances as precisely as possible. This also has implications for coming guidelines.

REFERENCES


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Submitted for publication September, 2012
Accepted for publication September, 2012
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DISCLOSURE STATEMENT

Dr. Randerath has received speaking fees and research support from Weinmann, Respironics, Resmed, Heinen und Löwenstein. Sandhya George has indicated no financial conflicts of interest.

CITATION

Central sleep apnea (CSA) is associated with a number of clinical conditions, including congestive heart failure, brain stem lesions, as well as with opioid use in the absence of other risk factors. A significant association with opioid use was first described by Teichtahl et al. in 2001,1 then further demonstrated in individuals on long-term methadone maintenance by Wang and Teichtahl.2 Recently, Alattar and Scharf described a case series of CSA in patients using opioids for chronic pain.3 Treatment has focused on positive airway pressure (PAP) therapy and ventilatory-assist devices, with varying degrees of success.4

REPORT OF CASE

A 35-year-old male presented with complaints of excessive daytime sleepiness. His medical history included major depression, necessitating electroconvulsive therapy and psychiatric hospitalization, hypertension, and severe headaches since childhood. He had failed numerous headache prophylactic medications and ultimately was prescribed opioids. At initial presentation to the sleep clinic, his medications included fentanyl lollipops, fentanyl transdermal patch, hydrocodone, triamterene, fluoxetine, and venlafaxine. He was also using dextroamphetamine/amphetamine and methylphenidate for sleepiness and ramelteon and temazepam to aid sleep initiation. His sleep schedule was suboptimal: bedtime was 02:00; perceived sleep latency was 30 min, with awakenings up to 4 times during the sleep period for various reasons; rise-time was 07:00; and sleep was described as non-refreshing.

The patient complained of excessive sleepiness (Epworth score of 16), mild snoring, and witnessed apneas. Physical exam showed pulse 84, blood pressure 119/79, oxygen saturation 97%, body mass index (BMI) 31.5, and a Mallampati class 2 airway.

Polysomnography was performed (Table 1). Respiratory events and sleep architecture were scored according to the 2007 AASM scoring manual.5 The study was consistent with CSA.

After several PAP titrations, the patient was prescribed bilevel PAP at 12 IPAP/8 EPAP with a back-up rate of 12 and 3 liters per minute of oxygen through the machine. The patient said that this allowed him to sleep more continuously but did not improve his daytime sleepiness. Despite these modest improvements in his symptoms, repeated titration studies showed persistent central apneas. It was repeatedly recommended that he discontinue or reduce use of opiates and temazepam as well as the stimulants since these were certainly affecting his sleep pattern. However, the patient stopped using bilevel treatment and was lost to follow-up in the sleep clinic.

The patient continued seeing a neurologist for his headaches and he ultimately agreed to 30-day inpatient narcotic detoxification. This succeeded in eliminating opiates from his regimen, which was confirmed by urine toxicology testing. Approximately 5 years after the initial evaluation, the patient was further evaluated by his neurologist for ongoing headaches. He still complained of some daytime fatigue and depression. Medications included venlafaxine, duloxetine, olanzapine, verapamil, and simvastatin. Epworth score was 10 and BMI was 36.7. Polysomnography was ordered by his neurologist. As seen in Table 1, the frequency of disordered breathing events was normal.

DISCUSSION

This patient experienced reversal of severe CSA after discontinuation of opiates. Once withdrawn from opiates, he continued to complain of mild daytime fatigue, though this was modestly improved as indicated by his Epworth score. Clearly, however, this patient had multiple factors influencing his excessive sleepiness, including depression and sedating effects of his medications. Interestingly, this patient’s weight actually increased during the period of follow-up—thereby removing a potential confounding factor in the reversal of his disease.

To our knowledge, there has been only one other published case report demonstrating reversal of CSA after withdrawal of...
opioids. In that case, however, no confirmatory polysomnography was performed. Our case demonstrates the importance of recognizing the role of opioids in the development of sleep disordered breathing, specifically CSA. Previous studies have demonstrated a dose dependent relationship between opioid use and severity of CSA. Possibly, in our patient, the use of high-dose multiple opioid preparations was associated with the observed severe degree of CSA. In this individual, and other selected patients, withdrawal of opioid therapy may be a successful mode of therapy.

Table 1—Polysomnography results

<table>
<thead>
<tr>
<th></th>
<th>Initial PSG</th>
<th>Subsequent PSG following detoxification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total sleep time (min)</td>
<td>367.5</td>
<td>231.5</td>
</tr>
<tr>
<td>Sleep efficiency (%)</td>
<td>90.3</td>
<td>55</td>
</tr>
<tr>
<td>Slow wave sleep (% total)</td>
<td>1.4</td>
<td>6.4</td>
</tr>
<tr>
<td>REM sleep (% total)</td>
<td>1.1</td>
<td>16.6</td>
</tr>
<tr>
<td>Obstructive apnea/hypopneas (#)</td>
<td>37</td>
<td>5</td>
</tr>
<tr>
<td>Central apneas (#)</td>
<td>260</td>
<td>3</td>
</tr>
<tr>
<td>RDI</td>
<td>50.3</td>
<td>2.9</td>
</tr>
<tr>
<td>Minimum oxygen saturation (%)</td>
<td>43</td>
<td>88</td>
</tr>
<tr>
<td>T &lt; 90% (min)</td>
<td>15.0</td>
<td>1.4</td>
</tr>
<tr>
<td>Arousal index</td>
<td>28.1</td>
<td>5.2</td>
</tr>
</tbody>
</table>

Data from initial and subsequent polysomnograms. PSG, polysomnography; RDI, respiratory disturbance index (apneas plus hypopneas plus respiratory event related arousals per hour of sleep).

REFERENCES


SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication March, 2012
Submitted in final revised form May, 2012
Accepted for publication May, 2012
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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 common condition with high rates of morbidity and mortality. The prevalence of this disease has increased substantially, along with the cost of diagnosing and treatment of this condition. Despite its association with cardiovascular diseases, sleep apnea remains underdiagnosed in patients with heart disease. Meanwhile, there has been increased development and promotion of new, advanced, and more expensive devices by industry to treat sleep apnea despite the lack of any evidence that these devices have superior clinical outcomes. Following is a case which highlights both these issues.

REPORT OF CASE

TC, a 44-year-old obese African American male with a BMI of 41, longstanding history of hypertension, non-smoker, with no history of alcohol use, and a 2-3 year history of progressively increasing shortness of breath and cough, was diagnosed with New York Heart Association (NYHA) class III heart failure (HF) in July 2008. Electrocardiogram (ECG) findings were notable for bialtrial abnormality and borderline left ventricular (LV) hypertrophy, with no evidence of heart block. Echocardiogram showed severe dilatation and global hypokinesis of LV with a LV ejection fraction (LVEF) of 10% and moderately reduced right ventricular (RV) function. Left heart catheterization did not show any occlusive coronary artery disease. Right heart catheterization showed elevated right atrial (RA) pressure at 17 mm Hg, pulmonary capillary wedge pressure (PCWP) of 30 mm Hg, pulmonary artery (PA) pressure of 74/30 mm Hg, and severely reduced right ventricular (RV) function. Cardiopulmonary exercise test showed maximum oxygen consumption ($\text{VO}_2$) of 12 cc/kg/minute. His clinical presentation was consistent with idiopathic dilated cardiomyopathy of unknown etiology. An endomyocardial biopsy was not performed to rule out any treatable causes of heart failure, in keeping with current recommendations by the American Heart Association/American college of Cardiology (AHA/ACC). He was treated with aspirin and maximal tolerated doses of ACE receptor inhibitor, β-blocker, and a diuretic. An ICD (implantable cardioverter-defibrillator) was placed, and he was evaluated and placed on the cardiac transplant list.

Due to his longstanding history of snoring, witnessed apneas, and excessive daytime sleepiness (Epworth Sleepiness Scale [ESS] score of 17), he was evaluated for OSA in December 2008. Polysomnography, performed with a split-night protocol revealed an apnea-hypopnea index (AHI) of 68 with a $\text{SaO}_2$ nadir of 58%. Respiratory events were all obstructive in nature with no central apneas. Continuous positive airway pressure (CPAP) titration to a maximum pressure of 20 cm H$_2$O was unsuccessful in controlling the obstructive respiratory events. He was also noted to develop central apneas, not present on diagnostic polysomnography, along with a high leak with increasing pressures. He was prescribed a bilevel device, set at a maximum pressure of 25/21 cm water pressure, after a retitration study in the sleep laboratory, during which a pressure of 28/23 cm water was insufficient to control obstructive apneas and hypopneas. This was again associated with central apneas on increasing the pressures (so called CPAP-emergent central apnea). Significantly, he had evidence of high leak on both titration studies.

On subsequent follow-up appointments, he demonstrated fairly good compliance of > 80% with his bilevel device, despite complaints of dry mouth. He continued to have a high leak, along with an elevated AHI of 15-17 on download of smart card data. The patient had difficulty tolerating the high pressures, and at one point tracheostomy was considered for control of apneas but rejected by the transplant team due to fear of infection following transplant, as the patient would be on immunosuppressants.

He underwent an adaptive servoventilation (ASV) titration study in October 2009. Expiratory positive airway pressure (EPAP) was titrated to 18 cm water pressure with elimination of all obstructive apneas and hypopneas. During this study he had minimal leak and no evidence of central apneas as EPAP
pressures were being increased. He was prescribed an ASV machine, set with a minimum EPAP of 18 cm, maximum inspiratory positive airway pressure (IPAP) of 25 cm, minimum pressure support (PS) of 0, maximum PS of 7, and a backup respiratory rate of 10.

Despite all the problems with PAP therapy during this year, his symptoms of OSA and heart failure improved. NYHA functional class improved from Class III to Class I over the next year. VO2 increased from 12 cc/kg/min at initial evaluation to 20 cc/kg/min two years later. Repeat echocardiograms at periodic intervals showed gradually improving cardiac function. Echocardiogram with Doppler done in June 2011 showed mild global LV dysfunction, with a LVEF at 45% to 50%. There was mild LA and LV enlargement. RA and RV were normal with significant reduction of estimated PA systolic pressure to 30 mm Hg. Daytime sleepiness was no longer present, with improvement of ESS to 5. He no longer required a cardiac transplant.

Download of smart card data on subsequent appointments showed no leak, with complete control of apneas at an EPAP average device pressure of 18 cm for ≤ 90% of time and average PS of 2. All breaths were patient triggered. In other words, this device was functioning as a CPAP machine set at a fixed pressure of 18 cm (minimum EPAP was set at 18), with no leak and complete control of apneas.

**DISCUSSION**

This case is interesting because it highlights a number of important points. First is the association of obstructive sleep apnea with heart failure. Sleep disordered breathing (OSA and central sleep apnea) is common in patients with heart failure, but the diagnosis is frequently missed, as the typical symptoms of OSA may not be present.7 The prevalence can be as high as 50% in patients with reduced ejection fraction.8 In the Sleep Heart Health Study, a large prospective, multicenter observational cohort study over 9 years, obstructive sleep apnea was associated with an increased risk of incident heart failure in both middle-aged and elderly males and reduced survival in younger males.9 There was also a dose-response relationship, with a higher AHI being associated with a greater risk of developing heart failure as well as increased mortality. In one observational study of 296 patients with severely reduced cardiac function (median LVEF of 33%), patients with severe sleep disordered breathing had a 2-fold increased risk for death, which improved in the patients who were treated with CPAP.10

OSA may worsen cardiac function by increasing afterload due to the negative intrathoracic pressure generated during respiratory efforts against an occluded upper airway.11 Sleep apnea has also been shown to cause progression of heart failure possibly due to intermittent hypoxia.12,13 It is well known that cardiac function improves with PAP therapy.14,15 This is not only as a consequence of positive intrathoracic pressure reducing transmural pressure, which reduces afterload, but preload is also reduced. Both lead to improvement in ejection fraction.16,17 In a retrospective study of over 30,719 Medicare beneficiaries with heart failure, those who were tested, diagnosed, and treated for OSA had a better 2-year survival rate than subjects with heart failure who were not tested for OSA. Similarly, among subjects who were tested and diagnosed with OSA, those who were treated had a better 2-year survival rate than those who were not treated.18

It is now recommended that physicians caring for patients with heart failure need to be aware of the presence of OSA and its effect on causing progression of heart failure, along with the role of treatment of sleep apnea and other therapies for heart failure.19,20 An expert consensus statement from the AHA/ACC recommends that with the current epidemic of obesity, hypertension, and heart failure, the prevalence and consequences of OSA are likely to increase. There needs to be an increased interaction between sleep specialists and cardiologists in diagnosing and treating this condition.21

Second, this case also highlights a possible etiology of CPAP-emergent central apnea. Several hypotheses have been proposed to explain CPAP-emergent central apnea; most of these hypotheses suggest that CPAP-emergent central apnea resolves over time.22 It has been shown in one study of patients with both OSA and CHF to be related to a high respiratory controller gain prior to application of CPAP.23 A high leak leading to CO2 washout could also be responsible. It may be due to the changes in CO2 excretion that occur with relief of the upper airway, leading to a fall in pCO2 below the apneic threshold.24 Sleep fragmentation with frequent sleep-wake transitions occurring with initiation of CPAP can lead to central apneas.25 Adaptive servoventilation (ASV) has been shown to be superior to CPAP in treating central sleep apnea, but there have been no long-term studies showing superior clinical outcomes.26,27 There are currently two ongoing multicenter, randomized controlled trials, ADVENT-HF and SERVE-HF,31 to evaluate the cost effectiveness and efficacy of ASV in treating patients with heart failure and central sleep apnea.

It is my view that this patient developed a dilated non-ischemic cardiomyopathy, most likely due to severe untreated OSA, with hypertension and hypoxemia, present for many years. It is possible that other etiologies of heart failure such as viral myocarditis, sarcoidosis, and rare conditions like amyloidosis and hemochromatosis may have been present, and an endomyocardial biopsy would have better elucidated the cause of heart failure.4 However, the clinical scenario presented strongly suggests that the cause of heart failure in this patient was obstructive sleep apnea. Treatment of OSA with PAP therapy, along with the associated improvement in hypoxemia, in conjunction with medical therapy for hypertension and heart failure contributed significantly to improved cardiac function to the extent that he did not require a cardiac transplant.

With PAP therapy, he developed central apneas, possibly due to a high leak. Over time, central apneas were no longer present as evidenced by smart card data with no use of PS (PS of 2 being insignificant) and all breaths being patient triggered. PAP requirements to keep the upper airway open were reduced to a much lower level along with minimal leak. This may have been due to increased compliance and volume of the upper airway, partly due to improved ejection fraction, with reduced congestion of the upper airway. Reduced CPAP pressures requirements may also be due to reduced collapsibility of the upper airway with increasing lung volume from continued CPAP use,29 loss of weight, and decreased heart size. It is possible that reduced inflammation of the upper airway over time with CPAP use may have played a role.28,30 It is important to note that this patient

*Journal of Clinical Sleep Medicine, Vol. 8, No. 5, 2012*
was treated with an ASV device, which eventually functioned as a CPAP machine.

In conclusion, this case should heighten the awareness of the association of heart failure and OSA. It also illustrates the improvement in cardiac function with positive pressure therapy. CPAP-emergent central apnea has multiple etiologies, and in most patients resolves over time, and does not need to be treated. Finally, pressure requirements to treat severe OSA may decrease over time.

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ACKNOWLEDGMENTS

Work for this study was performed at Thomas Jefferson University Hospital, Philadelphia, PA.

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Submitted for publication September, 2011
Submitted in final revised form January, 2012
Accepted for publication January, 2012
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DISCLOSURE STATEMENT

This was not an industry supported study. The author has indicated no financial conflicts of interest.
Restless legs syndrome (RLS), also known as Willis-Ekbom disorder, is 2-3 times more prevalent during pregnancy than in the general population, with peak prevalence in the third trimester and resolution of symptoms for many by one month after delivery. Independent predictors of RLS during pregnancy are a past history of RLS when not pregnant, a family history of RLS, a history of RLS during prior pregnancy, and hemoglobin ≤ 11 g/dL. Preexisting RLS also predicts greater severity during pregnancy than before pregnancy. More than half of women affected during pregnancy report severe or very severe RLS symptoms.

**REPORT OF CASE**

A 23-year-old female presented for management of chronic, moderate-to-severe RLS prior to becoming pregnant. Diagnosis was at age 19, but she recalled RLS symptoms since early childhood. Family history was positive for moderate-to-severe RLS with periodic limb movements in sleep (PLMS) affecting her biological mother and younger sister. For one year prior to the visit she reported consistently bothersome RLS symptoms that occurred most nights, associated with sleep disturbance, daytime fatigue, and PLMS observed by her husband. She took citalopram 20 mg/day because of depression with anxiety and panic attacks since age 16 years, with good control of those symptoms. The patient was also on levonorgestrel/ethinyl estradiol and ferrous sulfate (65 mg elemental iron). Oral iron had been started 3 months prior to the visit when her serum ferritin was low at 15 mcg/L. At the initial visit ferrous sulfate was replaced with extended-release iron due to gastrointestinal discomfort (daily dose 100 mg elemental). In addition, citalopram was replaced with fluoxetine 20 mg/day, because more is known about its use during pregnancy.

One month later ferritin had increased to 23 mcg/L, but 1.5 months after that was only 28 mcg/L with a high total iron binding capacity of 527 mcg/dL (normal 250-400) and borderline low saturation of 15% (normal 15-50), indicating ongoing iron deficiency; hemoglobin was 14.8 g/dL (normal 11.0-16.0). However, RLS symptoms were notably improved with these changes and concurrent discontinuation of the oral contraceptive pill (OCP) for planned pregnancy (Figure 1). Nonetheless, because of concern about potential worsening of RLS during pregnancy and limited progress in improving her iron status with oral iron, intravenous iron sucrose 1,125 mg was given in 5 treatments over 7 days. She became pregnant the week following the last treatment. Ferritin rose to 347 mcg/L, and RLS symptoms remitted completely within 1 month of intravenous iron.

The patient remained on fluoxetine and took a daily prenatal vitamin during the pregnancy, delivering a healthy, full-term girl by caesarean section. At a sleep clinic visit 7 weeks postpartum, she reported continued full remission of RLS symptoms and full control of depression and anxiety; ferritin was 51 mcg/L. She resumed daily oral iron (100 mg elemental). However, 5 months postpartum with ferritin at 62 mcg/L, RLS symptoms relapsed coincident with restarting of the OCP. Nonetheless, RLS symptoms were mild and manageable over the following 2 years with ferritin in the 60-100 mcg/L range (Figure 1). She remained on fluoxetine (20 mg/day), iron, and the OCP, with good control of depression and anxiety as well.

**DISCUSSION**

The etiology of RLS during pregnancy has not been adequately defined. Although there is convincing evidence for a major role of iron deficiency in the pathophysiology of RLS for non-pregnant individuals, and demands on iron stores during...
Figure 1—Serum ferritin levels before, during, and after first pregnancy of a young woman with preexisting moderate-to-severe RLS

RLS, restless legs syndrome; IV, intravenous; OCP, oral contraceptive pill.

pregnancy are significant,6 serum ferritin levels have not been found to be lower in pregnant women with RLS compared to controls.7,9 Also, the rapid improvement in RLS postpartum is difficult to account for by total iron stores, which typically remain low postpartum.6,8 However, iron availability may be as important as total iron stores. Postpartum, maternal red blood cell (RBC) mass contracts and approximately 450 mg of iron rapidly becomes available for other uses.6 During pregnancy, the developing fetus and placenta, as well as expanding maternal RBC mass, draw down iron stores and compete with other tissues for iron, potentially decreasing availability to the brain of the remaining stored iron.6 Lower ferritin levels prepartum suggest that women who develop RLS start out at a disadvantage.9 In addition, lower hemoglobin during pregnancy2-7 suggests that women with RLS during pregnancy may be at a disadvantage in the competition for iron. Treatment with iron before pregnancy can boost brain iron before there is intensified competition for available iron.

Estrogen has been postulated as a factor for RLS during pregnancy but evidence is conflicting.7,8 Recently, a prospective study found estrogen use to be an independent risk factor predicting incident RLS in women.10 This case illustrates some interesting issues regarding the possible etiology and treatment of RLS related to pregnancy. While intravenous iron administration and a rise in serum ferritin to 347 mcg/L were associated with full remission of RLS, RLS symptoms had improved significantly prior to that coincident with a modest rise in ferritin from 15 to 28 mcg/L, coupled with discontinuation of an OCP and switching from citalopram to fluoxetine.11 Surprisingly, there were no RLS symptoms during the second or third trimester. However, mild relapse occurred five months postpartum coincident with resumption of the OCP, despite a ferritin level of 62 mcg/L and no other changes in medication. Overall, these findings suggest benefit from intravenous iron prior to pregnancy but that more than one factor may mediate the expression of RLS.

Iron treatment for non-pregnancy, “idiopathic” RLS is typically recommended when serum ferritin is below 50 mcg/L, based on the results of placebo-controlled oral and IV iron trials.12 This is in contrast to the “normal” range of 11-307 mcg/L when considering treatment for iron deficiency anemia. However, there are no specific guidelines for iron treatment of RLS during pregnancy. In this case of known, moderate-to-severe RLS we chose to boost iron stores prior to pregnancy with IV iron, when oral iron was not successful in raising serum ferritin to above 50 mcg/L.

REFERENCES

The Effect of Continuous Positive Airway Pressure Treatment on Blood Pressure: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Study Objectives: We sought to provide an updated systematic review and meta-analysis of studies investigating the effect of positive airway pressure (PAP) treatment for obstructive sleep apnea (OSA) on systolic and diastolic blood pressure (SBP, DBP).

Methods: Two independent investigators undertook a systematic search of the PubMed database (1980-2012) to identify randomized controlled trials comparing therapeutic PAP to sham-PAP, pill placebo, or standard care over at least one week in adult OSA patients without major comorbidities. The mean, variance, and sample size for diurnal and nocturnal SBP and DBP data were also extracted independently from each study. Random effects meta-analyses were conducted, followed by pre-specified subgroup and meta-regression analyses.

Results: 32 studies were identified, with data available from 28 studies representing n = 1,948 patients. The weighted mean difference in diurnal SBP (−2.58 mm Hg, 95% CI −3.57 to −1.59 mm Hg) and DBP (−2.01 mm Hg, 95% CI −2.84 to −1.18 mm Hg) both significantly favored PAP treatment over control arms, with similar results seen in nocturnal readings. Statistically significant reductions in BP were seen in studies whose patients were younger, sleepier, had more severe OSA, and exhibited greater PAP adherence. Meta-regression indicated that the reductions in DBP with PAP were predicted by mean baseline BP (β = −0.22, p = 0.02) and Epworth Sleepiness Scale scores (β = −0.27, p = 0.04).

Conclusions: PAP treatment for OSA is associated with modest but significant reductions in diurnal and nocturnal SBP and DBP. Future research should be directed towards identifying subgroups likely to reap greater treatment benefits as well as other therapeutic benefits provided by PAP therapy.

Keywords: Systematic review, meta-analysis, obstructive sleep apnea, positive airway pressure, hypertension, blood pressure, lung.

Citation: Montesi SB; Edwards BA; Malhotra A; Bakker JP. The effect of continuous positive airway pressure treatment on blood pressure: a systematic review and meta-analysis of randomized controlled trials. J Clin Sleep Med 2012;8(5):587-596.
can result from PAP treatment, but it is unclear which patient subgroups may benefit most from treatment.

Many additional large randomized controlled trials have been published since 2007. We therefore aimed to perform an updated systematic review and meta-analysis of randomized controlled trials comparing therapeutic PAP to sham-PAP, pill placebo, or standard care over at least one week in adult OSA patients without major comorbidity. A secondary aim was to investigate the influence of treatment duration, age, daytime sleepiness, OSA severity, baseline BP, and adherence to treatment, using both subgroup analyses and meta-regression techniques.

METHODS

Being a review of published literature, this investigation did not require ethical review.

Literature Search

The PubMed database was searched for randomized controlled trials of PAP among OSA patients using the following search string in PubMed format: ((((“Sleep Apnea Syndromes”[Mesh]) OR (apn*)) OR (hypopn*)) OR (sleep apn*)) OR (obstructive sleep apn*)) OR (OSA)) OR (OSAS)) OR (OSAHS)) OR (SAHS)) AND (((((“Continuous Positive Airway Pressure”[Mesh])) OR (Continuous positive airway pressure)) OR (positive airway pressure)) OR (CPAP)) OR (PAP)) AND (((“Randomized Controlled Trial”[Publication Type]) OR (Clinical Trial)[Publication Type])) OR (random*)) OR (clinical trial)). The search was limited to the dates 1 January 1980 to 1 January 2012.

The reference lists of previous meta-analyses on this topic identified during the PubMed search were scanned for additional suitable studies. Any papers or peer-reviewed abstracts that were referenced in any of the identified studies (see literature exclusion criteria below) were also eligible for potential inclusion. Finally, our list of identified studies was forwarded to the first, last and/or corresponding author/s of these studies, who were asked to suggest further suitable publications if known to them.

Literature Exclusion Criteria

Authors SBM and JPB independently identified and excluded all qualitative reviews, commentaries, letters, and meta-analyses from the pooled literature set. The same authors then independently applied the following exclusion criteria to the abstracts of all identified publications in the order of “PICOS” (patient/intervention/comparator/outcome/study design):

(a) patients did not have a diagnosis of OSA made either during full polysomnography, cardiorespiratory monitoring, or oximetry; (b) patients had significant comorbidity; (c) patients were aged < 18 years; (d) the study investigated an intervention other than auto-PAP, flexible PAP, or standard continuous PAP applied at therapeutic pressure; (e) the study included a comparator other than sham-PAP, pill placebo, or standard care; (f) the study did not include office BP and/or ABPM measured at ≥ 2 time points; (g) the study was not randomized; (h) the treatment arms were < 1 week long. We anticipated that many publications would report BP as a secondary outcome measure, and therefore all studies reaching point (f) were inspected in full rather than relying on the information contained in the abstract. If any studies reported duplicate data, only the latest publication was retained. Publication in a language other than English was not grounds for exclusion. Any disagreements as to study eligibility were discussed until consensus was reached.

Data Extraction

Data extraction was also conducted independently by authors BAE and JPB. BP data were extracted as systolic and diastolic values, measured diurnally (primary analyses) and nocturnally. When studies reported both 24-h ABPM and office BP, the ABPM data were extracted. If studies measuring 24-h ABPM did not split the data into diurnal/nocturnal, the data were classified as diurnal. Studies that measured office BP did not contribute to the nocturnal data; if office BP was measured throughout the day, morning (preferable) or midday data were extracted. If BP was measured at more than one follow-up time point, data from the final end point were extracted.

The mean difference in BP between PAP and control arms in crossover trials was calculated as [end-trial BP in PAP arm minus end-trial BP in control arm]. The mean difference in BP between PAP and control arms in parallel trials was calculated as [(end-trial BP in PAP arm minus baseline BP in PAP arm) minus (end-trial BP in control arm minus baseline BP in control arm)]. If a measure of variance (either standard deviation, standard error of the mean, or confidence interval) for the within-arm change in BP was not reported, it was calculated using standard methods for paired data assuming a correlation of r = 0.5. If any descriptive or BP data were missing or unclear, we attempted to email the first, last, and/or corresponding author and allowed up to 8 weeks response time.

Statistical Analysis

Statistical analyses were conducted by author JPB using Stata Version 12 (StataCorp; TX, USA). Forest plots were produced using Review Manager (RevMan) Version 5.1 (Nordic Cochrane Center, Copenhagen, Denmark). The following Stata commands were used: metan (Version 3.04; September 2010), meta (Version 2.2; September 2010), metabias, metafunnel, metatab, and metareg.

It was decided a priori that due to the diverse patient characteristics and experimental protocols anticipated in the final literature set, random effects models using DerSimonian and Laird methodology would be applied during all meta-analyses. A random effects model assumes that the true effect size varies between studies due to clinical and methodological diversity; the alternative fixed effect model assumes that the true effect size is the same for all studies and any between-studies variance is due solely to sampling error. If there is zero heterogeneity between studies, both models will yield the same result; when heterogeneity is present the confidence interval of the summary effect will be wider with the more conservative random effects model.

The pooled effect and 95% confidence interval (CI) for each meta-analysis was calculated using the weighted effects of contributing individual studies and summarized graphically in a forest plot. Sensitivity analysis (the process by which one study at a time is excluded from the pooled analysis to determine if any studies exert undue influence on the model) was then conducted. The Q-statistic for each analysis—a statistical test of heterogeneity—was considered significant at p ≤ 0.10 by convention. The I² statistic—the percentage of observed
RESULTS

Identification and Description of Included Studies

A total of 1,041 suitable studies were identified through the PubMed search. Of these publications, the authors screened the abstracts of 927 and the full text of 114. The reasons for excluding 1,006 of these studies are shown in Figure 1. Of the remaining 35 studies (all published as complete papers), 4 reported duplicate BP data, and the most recently-published of these was produced for each meta-analysis in order to assess visually publication bias, which was also assessed statistically using Egger’s and Begg’s tests.

For the primary outcomes only (diurnal SBP and DBP), pre-specified subgroup analyses of trial structure (parallel versus crossover), comparator type (sham-PAP versus all other types), treatment duration (≥ 4 weeks versus < 4 weeks), age (≥ 50 years versus < 40 years), Epworth Sleepiness Scale (ESS) score (≥ 11/24 versus < 11/24), apnea-hypopnea index (AHI ≥ 30 events/h vs < 30 events/h), baseline hypertension (SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg versus SBP < 140 mm Hg or DBP < 90 mm Hg), and PAP adherence (≥ 4 h/night vs < 4 h/night) were performed. Each p-value obtained in sub-group analyses was corrected using a Bonferroni approach. Separate pre-specified random effects meta-regression analyses were performed using treatment duration, mean age at baseline, mean ESS at baseline, mean AHI at baseline, PAP adherence, and mean BP at baseline (SBP or DBP as appropriate) as continuous predictors. Subgroup and meta-regression analyses were performed using the diurnal BP data only, in order to avoid inflating the type I error rate.

Additional Data Obtained

We are grateful to Drs. Dimsdale, Drager, Lloberes, Lozano, Oliveira, Poyares, Sharma and Tomfohr for supplying additional data and/or information on study design.6-13

Meta-Analyses

Diurnal BP

For our primary analyses (diurnal SBP and DBP), we were able to extract analyzable data for 1,948 patients from 28 studies (87.5% of the 32 studies identified). As shown in Figure 2, only 4 studies showed significant differences in SBP and DBP between PAP and control arms, with a further 2 studies showing significant differences in DBP only. In the pooled analyses, diurnal SBP and DBP were both significantly reduced by PAP treatment compared with control (pooled SBP change −2.58 mm Hg, 95% CI −3.57 mm Hg to −1.59 mm Hg, p ≤ 0.001; pooled DBP change −2.01 mm Hg, 95% CI −2.84 to −1.18, p ≤ 0.001). The Q-tests for SBP (Q(27) = 20.51, p = 0.81) and DBP (Q(27) = 34.90, p = 0.14) were both nonsignificant, and the I² values for SBP and DBP did not indicate substantial heterogeneity (0% for SBP and 22.6% for DBP).

The results of the planned subgroup analyses are shown in Table 3. Diurnal SBP was significantly reduced by PAP in both parallel and crossover studies, whereas diurnal DBP was only significantly reduced by PAP in parallel studies. Both diurnal SBP and DBP were significantly reduced only in studies utilizing a sham-PAP control, studies with treatment duration ≥ 4 weeks, studies with mean age at baseline < 50 years, studies with mean ESS at baseline ≥ 11/24, studies with mean AHI at baseline ≥ 30 events/h, studies with mean BP adherence ≥ 4 h/night, and studies with patients who were not hypertensive at baseline on average (all p ≤ 0.05 using a Bonferroni correction).

Meta-regression indicated no significant effect of AHI, age, treatment duration, or adherence to PAP, on diurnal SBP or DBP (all p > 0.05). Baseline diurnal SBP was not a significant predictor of the weighted mean difference in diurnal SBP between PAP and control, however as shown in Figure 3A, baseline diurnal DBP was a significant predictor of the weighted mean difference in diurnal DBP (β = −0.22, standard error of the mean 0.09, p = 0.02). Baseline ESS was a significant predictor of the weighted mean difference in diurnal DBP (β = −0.27, standard error of the mean 0.12, p = 0.04; see Figure 3B), and this association approached significance for diurnal SBP (β = −0.37, standard error of the mean 0.19, p = 0.06).

Finally, sensitivity analyses found that no study, when removed individually, changed the statistical significance of the pooled result.

Nocturnal BP

Nocturnal SBP and DBP data were available for 661 patients from 10 studies. Both were both significantly reduced by PAP treatment compared with control (pooled nocturnal SBP change −4.09 mm Hg, 95% CI −6.24 mm Hg to −1.94 mm Hg, p ≤ 0.001; pooled nocturnal DBP change −1.85 mm Hg, 95% CI −3.57 mm Hg to −0.17 mm Hg, p = 0.03). The Q-tests for SBP (Q(9) = 9.55, p = 0.39) and DBP (Q(9) = 12.21, p = 0.20) were both nonsignificant, and the I² values for SBP and DBP (3.7% and 26.3%, respectively) did not indicate substantial heterogeneity. No subgroup or meta-regression analyses were planned for the nocturnal BP data. During sensitivity analysis, no study changed the statistical significance of the pooled result when removed from each meta-analysis individually.

Assessment of Publication Bias

We found no evidence of publication bias when Funnel Plots were inspected for each meta-analysis (not shown), although there is a possibility that further unpublished studies exist which we were unable to identify. The results of the Egger’s...
DISCUSSION

Our meta-analyses show that PAP treatment significantly reduces diurnal and nocturnal SBP and DBP compared with non-therapeutic comparators (sham-PAP, pill placebo, or standard care), despite only a few trials reporting statistically significant results individually. The weighted mean reductions in diurnal SBP (−2.58 mm Hg) and DBP (−2.01 mm Hg), and nocturnal SBP (−4.09 mm Hg) and DBP (−1.85 mm Hg), were reasonably small and would be unlikely to be considered clinically significant for an individual without additional treatment benefits occurring alongside. These results are in agreement with existing meta-analyses, despite the fact that more than double the number of studies were available to us in our updated literature search. Along with our quantitative results indicating minimal heterogeneity between studies, this provides evidence of a consistent effect across studies despite diverse locations and methodological approaches.

In terms of study design, planned subgroup analyses indicated that the reductions in diurnal SBP and DBP were larger in parallel studies, studies with at least four weeks treatment dura-
Hypertension and OSA in those aged over 60 years. The study, which did not detect a significant association between age and OSA, is in agreement with data from the Sleep Heart Health Study.

Significant reductions in diurnal SBP and DBP were evident in both subgroup analyses and meta-regression. As anticipated, this analysis did not reach values with statistical significance. Few trials targeted hypertensive patients during recruitment, suggesting that this analysis was underpowered particularly after Bonferroni adjustment for multiple comparisons.

Meta-regression analyses indicated that with every 10 mm Hg increase of diurnal DBP at baseline, a drop in diurnal DBP of 2.22 mm Hg with PAP compared with control could be expected (p = 0.02). Similarly, with every 5-point increase in ESS score at baseline, a drop in diurnal DBP of 2.22 mm Hg with PAP compared with control could be expected (p = 0.02). Similarly, with every 5-point increase in ESS score at baseline, a drop in diurnal DBP of 2.22 mm Hg with PAP compared with control could be expected (p = 0.02).

### Table 1—Design characteristics of identified studies

<table>
<thead>
<tr>
<th>First Author, Year</th>
<th>City &amp; Country</th>
<th>Centers</th>
<th>Trial type</th>
<th>Intervention / Comparator</th>
<th>Duration of trial (weeks) / Duration of washout (days)</th>
<th>Level of blinding as stated in paper</th>
<th>OSA criteria (events per hour)</th>
<th>BP criteria (mm Hg)</th>
<th>Method of BP measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Engelman, 1996$^{14}$</td>
<td>Edinburgh, UK</td>
<td>1</td>
<td>Crossover</td>
<td>CPAP / Sham-PAP</td>
<td>3 / None</td>
<td>Single</td>
<td>AH1 ≥ 5</td>
<td>None</td>
<td>ABPM</td>
</tr>
<tr>
<td>Dementide, 2005$^{15}$</td>
<td>San Diego, USA</td>
<td>1</td>
<td>Parallel</td>
<td>CPAP / Sham-PAP</td>
<td>1 / N/A</td>
<td>Double</td>
<td>RDI &gt; 15</td>
<td>None</td>
<td>ABPM</td>
</tr>
<tr>
<td>Barri, 2001$^{16}$</td>
<td>Throughout Spain</td>
<td>6</td>
<td>Parallel</td>
<td>CPAP / Sham-PAP</td>
<td>6 / N/A</td>
<td>Single</td>
<td>AH1 ≥ 30</td>
<td>None</td>
<td>ABPM</td>
</tr>
<tr>
<td>Faccenda, 2003$^{17}$</td>
<td>Edinburgh, UK</td>
<td>1</td>
<td>Crossover</td>
<td>CPAP / PAP</td>
<td>4 / N/A</td>
<td>Single</td>
<td>AH1 ≥ 15</td>
<td>Excluded patients on BP altering medications</td>
<td>ABPM</td>
</tr>
<tr>
<td>Monastero, 2001$^{18}$</td>
<td>Throughout Spain</td>
<td>6</td>
<td>Parallel</td>
<td>CPAP / No treatment</td>
<td>24 / N/A</td>
<td>Single</td>
<td>AH1 10-30</td>
<td>None</td>
<td>Office</td>
</tr>
<tr>
<td>Pepperell, 2002$^{19}$</td>
<td>Oxford, UK</td>
<td>1</td>
<td>Parallel</td>
<td>CPAP / Sham-PAP</td>
<td>4 / N/A</td>
<td>Double</td>
<td>OD1 (4%) &gt; 10</td>
<td>None</td>
<td>ABPM</td>
</tr>
<tr>
<td>Barnes, 2002$^{20}$</td>
<td>Melbourne and Adelaide, Australia</td>
<td>2</td>
<td>Crossover</td>
<td>CPAP / PAP</td>
<td>8 / N/A</td>
<td>Single</td>
<td>AH1 5-30</td>
<td>None</td>
<td>ABPM</td>
</tr>
<tr>
<td>Becker, 2003$^{21}$</td>
<td>Marburg, Germany</td>
<td>1</td>
<td>Parallel</td>
<td>CPAP / Sham-PAP</td>
<td>9 / N/A</td>
<td>Single</td>
<td>AH1 ≥ 5</td>
<td>None</td>
<td>ABPM</td>
</tr>
<tr>
<td>Barnes, 2004$^{22}$</td>
<td>Melbourne and Adelaide, Australia</td>
<td>2</td>
<td>Crossover</td>
<td>CPAP / PAP</td>
<td>12 / 14</td>
<td>Single</td>
<td>AH1 5-30</td>
<td>None</td>
<td>ABPM</td>
</tr>
<tr>
<td>Ip, 2004$^{23}$</td>
<td>Hong Kong, China</td>
<td>1</td>
<td>Parallel</td>
<td>CPAP / No treatment</td>
<td>4 / N/A</td>
<td>Single</td>
<td>AH1 ≥ 15</td>
<td>Excluded patients with a history of hypertension</td>
<td>Office</td>
</tr>
<tr>
<td>Alonzo-Fernandez, 2006$^{24}$</td>
<td>Madrid, Spain</td>
<td>1</td>
<td>Crossover</td>
<td>CPAP / Sham-PAP</td>
<td>12 / N/A</td>
<td>Double</td>
<td>AH1 ≥ 10</td>
<td>Excluded BP &gt; 135/85</td>
<td>ABPM</td>
</tr>
<tr>
<td>Campos-Rodriguez, 2006$^{25}$</td>
<td>Seville, Spain</td>
<td>1</td>
<td>Parallel</td>
<td>CPAP / Sham-PAP</td>
<td>4 / N/A</td>
<td>Double</td>
<td>AH1 ≥ 10</td>
<td>Excluded BP &lt; 140/90 &amp; not on antihypertensives</td>
<td>ABPM</td>
</tr>
<tr>
<td>Hui, 2006$^{26}$</td>
<td>Hong Kong, China</td>
<td>1</td>
<td>Parallel</td>
<td>CPAP / Sham-PAP</td>
<td>12 / N/A</td>
<td>Double</td>
<td>AH1 ≥ 5</td>
<td>None</td>
<td>ABPM</td>
</tr>
<tr>
<td>Mills, 2006$^{27}$</td>
<td>San Diego, USA</td>
<td>1</td>
<td>Parallel</td>
<td>CPAP / Sham-PAP</td>
<td>2 / N/A</td>
<td>Single</td>
<td>AH1 &gt; 15</td>
<td>Excluded patients on antihypertensives</td>
<td>Office</td>
</tr>
<tr>
<td>Norman, 2006$^{28}$</td>
<td>San Diego, USA</td>
<td>1</td>
<td>Parallel</td>
<td>CPAP / Sham-PAP</td>
<td>2 / N/A</td>
<td>Single</td>
<td>AH1 ≥ 15</td>
<td>Excluded BP &gt; 170/105</td>
<td>ABPM</td>
</tr>
<tr>
<td>Robinson, 2006$^{29}$</td>
<td>Oxford, UK</td>
<td>1</td>
<td>Crossover</td>
<td>CPAP / Sham-PAP</td>
<td>4 / 14</td>
<td>Double</td>
<td>OD1 (4%) &gt; 10</td>
<td>Excluded BP &lt; 140/90 &amp; not on antihypertensives</td>
<td>ABPM</td>
</tr>
<tr>
<td>Coughlin, 2007$^{30}$</td>
<td>Liverpool, UK</td>
<td>1</td>
<td>Crossover</td>
<td>CPAP / Sham-PAP</td>
<td>6 / 6</td>
<td>Double</td>
<td>AH1 ≥ 15</td>
<td>Excluded BP &gt; 180/110</td>
<td>Office</td>
</tr>
<tr>
<td>Drager, 2007$^{31}$</td>
<td>Sao Paulo, Brazil</td>
<td>1</td>
<td>Parallel</td>
<td>CPAP / No treatment</td>
<td>16 / N/A</td>
<td>Single</td>
<td>AH1 &gt; 30</td>
<td>Excluded BP &gt; 140/90</td>
<td>ABPM</td>
</tr>
<tr>
<td>Lam, 2007$^{32}$</td>
<td>Hong Kong, China</td>
<td>2</td>
<td>Parallel</td>
<td>CPAP / No treatment</td>
<td>10 / N/A</td>
<td>Unblinded</td>
<td>AH1 ≥ 5-40</td>
<td>None</td>
<td>Office</td>
</tr>
<tr>
<td>Cross, 2008$^{33}$</td>
<td>Edinburgh, UK</td>
<td>1</td>
<td>Crossover</td>
<td>CPAP / Sham-PAP</td>
<td>6 / 7</td>
<td>Double</td>
<td>AH1 ≥ 15</td>
<td>None</td>
<td>Office</td>
</tr>
<tr>
<td>Kohler, 2008$^{34}$</td>
<td>Oxford, UK</td>
<td>1</td>
<td>Parallel</td>
<td>CPAP / Sham-PAP</td>
<td>4 / N/A</td>
<td>Double</td>
<td>OD1 (4%) &gt; 10</td>
<td>None</td>
<td>Both</td>
</tr>
<tr>
<td>Alonzo-Fernandez, 2009$^{35}$</td>
<td>Palma de Mallorca, Spain</td>
<td>1</td>
<td>Crossover</td>
<td>CPAP / Sham-PAP</td>
<td>12 / None</td>
<td>Double</td>
<td>AH1 ≥ 10</td>
<td>Excluded BP &gt; 135/85</td>
<td>ABPM</td>
</tr>
<tr>
<td>Comendere, 2009$^{36}$</td>
<td>Vancouver, Canada</td>
<td>1</td>
<td>Crossover</td>
<td>CPAP / No treatment</td>
<td>4 / 28</td>
<td>Unblinded</td>
<td>AH1 ≥ 15</td>
<td>None</td>
<td>ABPM</td>
</tr>
<tr>
<td>Oliveira, 2009$^{37}$</td>
<td>Sao Paulo, Brazil</td>
<td>1</td>
<td>Parallel</td>
<td>CPAP / Sham-PAP</td>
<td>24 / N/A</td>
<td>Double</td>
<td>AH1 ≥ 20</td>
<td>None</td>
<td>Office</td>
</tr>
<tr>
<td>Barbi, 2010$^{38}$</td>
<td>Throughout Spain</td>
<td>14</td>
<td>Parallel</td>
<td>CPAP / No treatment</td>
<td>52 / N/A</td>
<td>Unblinded</td>
<td>AH1 ≥ 19</td>
<td>Excluded BP &lt; 140/90 or not on antihypertensives</td>
<td>ABPM</td>
</tr>
<tr>
<td>Duran-Cantolla, 2010$^{39}$</td>
<td>Throughout Spain</td>
<td>11</td>
<td>Parallel</td>
<td>CPAP / Sham-PAP</td>
<td>12 / N/A</td>
<td>Double</td>
<td>AH1 ≥ 15</td>
<td>Excluded BP &gt; 140/90 or not on antihypertensives</td>
<td>ABPM</td>
</tr>
<tr>
<td>Lam, 2010$^{40}$</td>
<td>Hong Kong, China</td>
<td>1</td>
<td>Parallel</td>
<td>CPAP / No treatment</td>
<td>12 / N/A</td>
<td>Unblinded</td>
<td>AH1 ≥ 15</td>
<td>Excluded BP &lt; 140/90</td>
<td>ABPM</td>
</tr>
<tr>
<td>Lizano, 2010$^{41}$</td>
<td>Barcelona, Spain</td>
<td>1</td>
<td>Parallel</td>
<td>CPAP / Sham-PAP</td>
<td>1 / N/A</td>
<td>Double</td>
<td>AH1 ≥ 15</td>
<td>None</td>
<td>Office</td>
</tr>
<tr>
<td>Nguyen, 2010$^{42}$</td>
<td>Stanford, USA</td>
<td>1</td>
<td>Parallel</td>
<td>CPAP / Sham-PAP</td>
<td>12 / N/A</td>
<td>Double</td>
<td>RDI ≥ 15</td>
<td>None</td>
<td>Office</td>
</tr>
<tr>
<td>Drager, 2011$^{43}$</td>
<td>Sao Paulo, Brazil</td>
<td>1</td>
<td>Parallel</td>
<td>CPAP / No treatment</td>
<td>12 / N/A</td>
<td>Single</td>
<td>AH1 &gt; 30</td>
<td>Excluded BP &gt; 140/90</td>
<td>Both</td>
</tr>
<tr>
<td>Kohler, 2011$^{44}$</td>
<td>Zurich, Switzerland</td>
<td>1</td>
<td>Parallel</td>
<td>CPAP / Sham-PAP</td>
<td>2 / N/A</td>
<td>Double</td>
<td>OD1 (4%) ≥ 10</td>
<td>None</td>
<td>Office</td>
</tr>
<tr>
<td>Sharma, 2011$^{45}$</td>
<td>New Delhi, India</td>
<td>1</td>
<td>Crossover</td>
<td>CPAP / Sham-PAP</td>
<td>12 / 28</td>
<td>Double</td>
<td>AH1 ≥ 15</td>
<td>Excluded patients on antihypertensives</td>
<td>Office</td>
</tr>
</tbody>
</table>

**ABPM:** ambulatory blood pressure monitoring; **AH1:** apnea-hypopnea index; **BP:** blood pressure; **CPAP:** continuous positive airway pressure; **N/A:** not applicable; **OD1:** oxygen desaturation index; **OSA:** obstructive sleep apnea; **RDI:** respiratory disturbance index; **UK:** United Kingdom; **USA:** United States of America.
relate to daytime sleepiness remain unclear but may relate to cortical or subcortical arousals occurring at the termination of respiratory events coinciding with repeated surges in BP. There is some evidence that this cardiovascular response to arousal is attenuated in the elderly, which may partly explain our finding that age was not predictive of the BP reduction with PAP.15

The results of all other meta-regression analyses were non-significant—most likely due to the fact that significant heterogeneity between studies was not found—which highlights a deficiency in the literature. Despite the fact that studies recruited a heterogeneous sample of OSA patients (see Table 1) such that the within-study variances of baseline age, AHI, and adherence were wide, the means of these covariates were similar such that the within-study variances of baseline age, AHI, and adherence were wide, the means of these covariates were similar to that of a large pooled sample would also allow for the inclusion of a number of other important co-variates that were not investigated here, such as the arousal index and the influence of antihypertensive medications, the latter of which would be particularly useful in interpreting our meta-regression results suggesting greater reductions in BP when patients were hypertensive at baseline.

This meta-analysis builds on previous analyses by including data from an additional 1,170 patients from 13 studies—more intensive at baseline. The meta-regression analyses were non-significant due to the high degree of variability in the data. The results of all other meta-regression analyses were non-significant—most likely due to the fact that significant heterogeneity between studies was not found—which highlights a deficiency in the literature. Despite the fact that studies recruited a heterogeneous sample of OSA patients (see Table 1) such that the within-study variances of baseline age, AHI, and adherence were wide, the means of these covariates were similar such that the within-study variances of baseline age, AHI, and adherence were wide, the means of these covariates were similar.
Figure 2—Forest plots comparing the effects of PAP and control on (A) diurnal SBP, and (B) diurnal DBP

For each study, the square represents the mean difference in blood pressure between PAP and control arms and the width of the line represents the 95% confidence interval; a line crossing the 0 mm Hg vertical line indicates no significant difference at α = 0.05. The diamond summarizes the pooled effect; the apex represents the overall mean difference in diurnal SBP between PAP and control arms, and the width represents the 95% confidence interval. In both plots, the diamond does not cross the 0 mm Hg vertical line, hence there is a significant difference between PAP and control in terms of the change in diurnal SBP (−2.58 mm Hg, p ≤ 0.001) and diurnal DBP (−2.01 mm Hg, p ≤ 0.001). DBP, diastolic blood pressure; PAP, positive airway pressure; SBP, systolic blood pressure.
our search terms were sensitive enough to capture all available literature; hence it is unlikely that our results have been heavily influenced by publication bias. Furthermore, by performing sensitivity analyses, we are confident that no single trial exerted undue influence on any of the meta-analyses presented here.

Some may consider the overall observed effect of PAP on BP to be minor and may question the benefits of treating OSA. We would offer several lines of logic in response. Firstly, although a 2-3 mm Hg change in BP could be considered trivial for an individual, at a population level the impact of OSA treatment on BP could have substantial benefits (for example, decreasing the risk of stroke). Secondly, we would agree that if the sole purpose of PAP were to lower BP, we would favor antihypertensive medications. However, the other benefits of PAP on daytime symptoms, driving risk, and possible cardiovascular benefits are noteworthy. Third, profound surges in BP are well known to occur in the physiological response to apnea, although such surges are typically not assessed using noninvasive technology with intermittent readings in clinical trials. Given that these BP surges may be a substrate for plaque rupture, we would encourage focus on hard cardiovascular outcomes, rather than surrogate outcome measures such as daytime BP. Finally, Gueney et al. have regarded hypertension as a central disorder of autonomic control given that counter-regulatory mechanisms tend to maintain BP within a relatively narrow range based on changes in vasoconstriction or vasodilation. As such, one might predict that the effect of PAP on BP could have substantial benefits (for example, differing equipment, timing and number of devices used).

Our meta-analysis has a number of limitations that need to be considered. Despite attempts to gather unpublished data from study authors, our data set was not complete. However, we were able to analyze diurnal BP data from almost 90% of identified trials and as such believe that our synthesized results are an accurate summary of the literature. Secondly, we analyzed BP data across trials with substantial methodological diversity (for example, differing equipment, timing and number of devices used). Further, despite attempts to gather unpublished data from study authors, our data set was not complete. However, we were able to analyze diurnal BP data from almost 90% of identified trials and as such believe that our synthesized results are an accurate summary of the literature. Finally, we performed meta-regression analyses to explore the impact of various factors on the effect of PAP on BP. In meta-regression analyses, SBP and DBP were considered continuous predictors. Bold indicates statistical significance at p ≤ 0.05 after Bonferroni adjustment for multiple comparisons. #p = 0.06; ##p ≤ 0.05. β meta-regression co-efficient is the predicted change in BP for every one-unit increase in the predictor variable. AHI, apnea-hypopnea index; DBP, diastolic blood pressure; ESS, Epworth Sleepiness Scale; ODI, oxygen desaturation index; PAP, positive airway pressure; RDI, respiratory disturbance index; SBP, systolic blood pressure.

Table 3—Results of subgroup and meta-regression analyses

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>Diurnal SBP</th>
<th>Diurnal DBP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Weighted mean difference (mm Hg)</td>
<td>95% Confidence Interval</td>
</tr>
<tr>
<td>Trial structure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parallel</td>
<td>-2.6</td>
<td>-4.0 to -1.3</td>
</tr>
<tr>
<td>Crossover</td>
<td>-2.5</td>
<td>-4.0 to -1.1</td>
</tr>
<tr>
<td>Comparator type</td>
<td></td>
<td></td>
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<tr>
<td>Sham-PAP</td>
<td>-3.0</td>
<td>-4.2 to -1.7</td>
</tr>
<tr>
<td>Pill placebo or standard care</td>
<td>-2.0</td>
<td>-3.6 to -0.5</td>
</tr>
<tr>
<td>Treatment duration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 4 weeks</td>
<td>-2.5</td>
<td>-3.6 to -1.5</td>
</tr>
<tr>
<td>&lt; 4 weeks</td>
<td>3.7</td>
<td>-8.1 to 0.6</td>
</tr>
<tr>
<td>Mean age at baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 50 years</td>
<td>-2.1</td>
<td>-3.5 to -0.6</td>
</tr>
<tr>
<td>&lt; 50 years</td>
<td>-3.3</td>
<td>-4.7 to -1.9</td>
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<tr>
<td>Mean ESS at baseline</td>
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<td></td>
</tr>
<tr>
<td>≥ 11/24</td>
<td>-4.3</td>
<td>-5.8 to -2.8</td>
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<tr>
<td>&lt; 11/24</td>
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<td>Mean AHI/RDI/ODI at baseline</td>
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<td></td>
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<tr>
<td>≥ 30 events/hour</td>
<td>-2.9</td>
<td>-4.0 to -1.8</td>
</tr>
<tr>
<td>&lt; 30 events/hour</td>
<td>-1.7</td>
<td>-4.2 to 0.8</td>
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<tr>
<td>Mean PAP adherence</td>
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<td></td>
</tr>
<tr>
<td>≥ 4 hours/night</td>
<td>-2.9</td>
<td>-4.1 to -1.8</td>
</tr>
<tr>
<td>&lt; 4 hours/night</td>
<td>-1.8</td>
<td>-4.0 to 0.3</td>
</tr>
<tr>
<td>Hypertension at baseline*</td>
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<td></td>
</tr>
<tr>
<td>SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg</td>
<td>-3.1</td>
<td>-5.9 to -0.3</td>
</tr>
<tr>
<td>SBP &lt; 140 mm Hg or DBP &lt; 90 mm Hg</td>
<td>-2.5</td>
<td>-3.6 to -1.4</td>
</tr>
</tbody>
</table>

*In meta-regression analyses, SBP and DBP were considered continuous predictors. Bold indicates statistical significance of subgroup analyses at p ≤ 0.05 after Bonferroni adjustment for multiple comparisons. *p = 0.06; **p ≤ 0.05. β meta-regression co-efficient is the predicted change in BP for every one-unit increase in the predictor variable. AHI, apnea-hypopnea index; DBP, diastolic blood pressure; ESS, Epworth Sleepiness Scale; ODI, oxygen desaturation index; PAP, positive airway pressure; RDI, respiratory disturbance index; SBP, systolic blood pressure.
of BP measurements), which is an unfortunate but unavoidable limitation of meta-analyses of this kind. We were also forced to calculate estimated differences in paired BP data based on the assumption of an $r = 0.5$ correlation when these data were not reported. This requirement undoubtedly introduced a minor degree of error into our data set.

In conclusion, the use of PAP in the treatment of OSA results in a modest yet significant reduction in BP, with the greatest effect seen with nocturnal SBP values. As more is learned of the cardiovascular effects of OSA, further testing will be needed to assess the role of PAP in mitigating such effects. Patient level meta-analysis may prove beneficial, especially in terms of defining the patient subgroups which would sustain the largest benefit from PAP.

**ABBREVIATIONS**

- ABPM, ambulatory blood pressure monitoring
- AHI, apnea-hypopnea index
- BMI, body mass index
- BP, blood pressure
- CI, confidence interval
- DBP, diastolic blood pressure
- ESS, Epworth Sleepiness Scale
- ODI, oxygen desaturation index
- OSA, obstructive sleep apnea
- PAP, positive airway pressure
- PICOS, patient/intervention/comparator/outcome/study design

**REFERENCES**


**Figure 3**—Scatterplots of the weighted mean difference between PAP and control for each study against (A) mean diurnal DBP at baseline, and (B) mean ESS score at baseline.


ACKNOWLEDGMENTS

The authors thank Drs. Dimsdale, Drager, Lloberes, Lozano, Oliveira, Poyares, Sharma, and Tomfohr for their help in providing missing data for these analyses. Dr. Edwards is supported by the National Health and Medical Research Council of Australia’s CJ Martin Overseas Biomedical Fellowship (1035115). Dr. Malhotra is supported by NIH (R01HL085188-04, R01HL090897-03, 5K24HL093218-03, 1P01HL095491-01A1) and AHA (0840159N) grants. No financial support was obtained for this investigation. All work performed at Sleep Disorders Research Program, Brigham & Women’s Hospital & Harvard Medical School, Boston MA.

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication March, 2012
Submitted in final revised form April, 2012
Accepted for publication April, 2012
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DISCLOSURE STATEMENT

This was not an industry supported study. Dr. Malhotra is a consultant for Philips Respironics, SHC, SGS, Apnicure, Apexon, and Pfizer. Dr. Bakker has received funding from Philips Respironics. The other authors have indicated no financial conflicts of interest.
The American Academy of Sleep Medicine (AASM) Sleep Apnea Definitions Task Force reviewed the current rules for scoring respiratory events in the 2007 AASM Manual for the Scoring of Sleep and Associated Events to determine if revision was indicated. The goals of the task force were (1) to clarify and simplify the current scoring rules, (2) to review evidence for new monitoring technologies relevant to the scoring rules, and (3) to strive for greater concordance between adult and pediatric rules. The task force reviewed the evidence cited by the AASM systematic review of the reliability and validity of scoring respiratory events published in 2007 and relevant studies that have appeared in the literature since that publication. Given the limitations of the published evidence, a consensus process was used to formulate the majority of the task force recommendations concerning revisions.

The task force made recommendations concerning recommended and alternative sensors for the detection of apnea and hypopnea to be used during diagnostic and positive airway pressure (PAP) titration polysomnography. An alternative sensor is used if the recommended sensor fails or the signal is inaccurate. The PAP device flow signal is the recommended sensor for the detection of apnea, hypopnea, and respiratory effort related arousals (RERAs) during PAP titration studies. Appropriate filter settings for recording (display) of the nasal pressure signal to facilitate visualization of inspiratory flattening are also specified. The respiratory inductance plethysmography (RIP) signals to be used as alternative sensors for apnea and hypopnea detection are specified. The task force reached consensus on use of the same sensors for adult and pediatric patients except for the following: (1) the end-tidal PCO2 signal can be used as an alternative sensor for apnea detection in children only, and (2) polyvinylidene fluoride (PVDF) belts can be used to monitor respiratory effort (thoracoabdominal belts) and as an alternative sensor for detection of apnea and hypopnea (PVDFsum) only in adults.

The task force recommends the following changes to the 2007 respiratory scoring rules. Apnea in adults is scored when there is a drop in the peak signal excursion by ≥ 90% of pre-event baseline using an oronasal thermal sensor (diagnostic study), PAP device flow (titration study), or an alternative sensor, and the event meets duration and respiratory effort criteria for an obstructive, mixed, or central apnea. A central apnea is scored in children when the event meets criteria for an apnea, there is an absence of inspiratory effort throughout the event, and at least one of the following is met: (1) the event is ≥ 20 seconds in duration, (2) the event is associated with an arousal or ≥ 3% oxygen desaturation, (3) (infants under 1 year of age only) the event is associated with a decrease in heart rate to less than 50 beats per minute for at least 5 seconds or less than 60 beats per minute for 15 seconds. A hypopnea is scored in children when the peak signal excursions drop is ≥ 30% of pre-event baseline using nasal pressure (diagnostic study), PAP device flow (titration study), or an alternative sensor, for ≥ the duration of 2 breaths in association with either ≥ 3% oxygen desaturation or an arousal.

In children and adults, surrogates of the arterial PCO2 are the end-tidal PCO2 or transcutaneous PCO2 (diagnostic study) or transcutaneous PCO2 (titration study). For adults, sleep hypventilation is scored when the arterial PCO2 (or surrogate) is > 55 mm Hg for ≥ 10 minutes or there is an increase in the arterial PCO2 (or surrogate) ≥ 10 mm Hg (in comparison to an awake supine value) to a value exceeding 50 mm Hg for ≥ 10 minutes. For pediatric patients hypventilation is scored when the arterial PCO2 (or surrogate) is > 50 mm Hg for > 25% of total sleep time. In adults Cheyne-Stokes breathing is scoring when both of the following are met: (1) there are episodes of ≥ 3 consecutive central apneas and/or central hypopneas separated by a crescendo and decrescendo change in breathing amplitude with a cycle length of at least 40 seconds (typically 45 to 90 seconds), and (2) there are five or more central apneas and/or central hypopneas per hour associated with the crescendo/decrescendo breathing pattern recorded over a minimum of 2 hours of monitoring.

**Keywords:** AASM Manual for the Scoring of Sleep and Associated Events, scoring respiratory events in sleep, sleep apnea definitions, apnea and hypopnea, respiratory effort related arousals, hypventilation, Cheyne-Stokes breathing

**Commentary:** A commentary on this article appears in this issue on page 621.

**Citation:** Berry RB; Budhiraja R; Gottlieb DJ; Gozal D; Iber C; Kapur VK; Marcus CL; Mehra R; Parthasarathy S; Quan SF; Redline S; Strohl KP; Ward SLD; Tangredi MM. Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. J Clin Sleep Med 2012;8(5):597-619.
Table 1—Levels of recommendation and sensor classification

<table>
<thead>
<tr>
<th>Levels of Recommendation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>[Recommended]</strong></td>
<td>Recommended rules for the routine scoring of respiratory events that should be followed.</td>
</tr>
<tr>
<td><strong>[Acceptable]</strong></td>
<td>Rules that may be used as alternatives to the Recommended rules at the discretion of the clinician or investigator. (Either the Recommended or Acceptable should be followed).</td>
</tr>
<tr>
<td><strong>[Optional]</strong></td>
<td>Rules that do not need to be followed, but may be at the discretion of the clinician or investigator</td>
</tr>
</tbody>
</table>

**Respiratory Sensor Classification**

<table>
<thead>
<tr>
<th>Level</th>
<th>Sensor Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommended</strong></td>
<td>The sensor that should be used for scoring a respiratory event</td>
</tr>
<tr>
<td><strong>Alternative</strong></td>
<td>Sensors that can be used for scoring a respiratory event if the recommended sensor is not functioning or the signal is not reliable</td>
</tr>
</tbody>
</table>

1.0 INTRODUCTION

In 2007 the American Academy of Sleep Medicine (AASM) published rules for scoring respiratory events in the *AASM Manual for the Scoring of Sleep and Associated Events, 1st ed.* (hereafter referred to as the 2007 scoring manual). Widespread use of the rules has resulted in questions about rule interpretation and application. The 2007 scoring manual steering committee has addressed a number of questions concerning the respiratory rules on the scoring manual frequently asked questions (FAQs) page of the AASM website. Since 2007 several publications have addressed the impact of the respiratory scoring rules on the diagnosis of obstructive sleep apnea in children and adults. Additional publications concerning the technology of respiratory monitoring have also appeared. Given these developments, the Board of Directors of the AASM considered the need for reappraisal of the scoring rules almost five years after publication. The Board of Directions subsequently appointed the Sleep Apnea Definitions Task Force (hereafter referred to as the task force) to consider possible revisions to the scoring rules and to make recommendations concerning changes.

2.0 METHODS

The task force consisted of nine of the original thirteen individuals who authored the review of the evidence used to develop the 2007 respiratory scoring rules and four additional individuals with clinical experience in the application of the respiratory scoring rules. The task force met by conference call on several occasions and once face to face. The goals of the task force were: (1) to clarify and simplify the respiratory scoring rules, (2) to review evidence for new monitoring technologies relevant to the scoring rules, and (3) to strive for greater concordance between adult and pediatric rules. It is hoped that the discussion in this publication will prove useful in the clinical realm and stimulate further research concerning the existing knowledge gaps for which more evidence is needed.

The task force reviewed the 1999 sleep related breathing disorders in adults consensus publication, the comprehensive scoring of respiratory events review that provided evidence for the 2007 scoring manual, and the *International Classification of Sleep Disorders, 2nd edition.* A PubMed search for relevant articles published since 2005 was performed. The following terms were paired with numerous terms for respiratory events and relevant technology: scoring, interpretation, definition, validity, reliability, precision, measurement. Additional articles were pearled from relevant evidence papers.

The strength of evidence for the task force recommendations includes (standard), (guideline), (consensus), or (adjudication). Standard recommendations are based on level 1 evidence or overwhelming level 2 evidence. Guideline recommendations are based on level 2 evidence or consensus of level 3 evidence. Consensus recommendations are based on consensus of the task force. Adjudication reflects consensus of the AASM Board of Directors when the task force was unable to make a recommendation. When there was an absence of high-level evidence, recommendations were based on consensus. A modified RAND consensus process was followed. The task force drafted respiratory definitions ballot items with a wide spectrum of possible definitions including the 2007 definitions. After initial voting on definitions, there was discussion and editing of items that failed to reach consensus. Voting and editing of definitions continued until a consensus was reached. All task force members disclosed potential conflicts of interest. Individual members abstained from voting on ballot questions concerning technology when there was a question of a potential conflict of interest based on prior research funding. The Board of Directors of the AASM reviewed the recommendations of the task force and requested clarification or suggested reappraisal of certain respiratory rules based on recent publications. Following further voting and editing, the Board of Directors approved a set of revised respiratory rules.

Although proposed revisions to the rules are shown here at the conclusion of each section to make the discussion more understandable, the final and complete set of rules can be found in the online AASM Manual for the Scoring of Sleep and Associated Events, Version 2.0, which is a web-based document, amenable to updates as new literature emerges. This manuscript reviews the issues confronted by the task force during their review as well as the rationale behind the revisions. In the 2007 scoring manual, the levels of recommendation were: Recommended, Alternative, Optional. In this document the level “Alternative” is changed to “Acceptable” to correspond with terminology in the new scoring manual (Version 2.0) (Table 1). In the 2007 scoring manual, sensors were specified (recommended) for detection of apnea, hypopnea, and respiratory effort. Alternative sensors were specified for use if the recommended sensor failed or was not accurate. This terminology will be continued in this document (Table 1).

3.0 RECOMMENDATIONS FOR ADULT AND PEDIATRIC PATIENTS

3.1 Technical Considerations for Adult and Pediatric Patients

In considering the definitions of respiratory events, the task force recognized that most of the 2007 scoring manual defini-
tions include a recommendation for the sensors to be used for event detection. While the major focus of the task force was to update the definitions of respiratory events, it was also necessary to consider sensor technology as it relates to event definitions. It must be recognized that the information obtained from any sensor depends critically on the proper placement of the sensor and appropriate adjustment of gain and filters for viewing the signal. To be accurate, some sensors may require calibration procedures. Filter settings were recommended for most sensors, and the flow waveform provides evidence of airflow limitation and decreased upper airway resistance. Based on consensus and clinical evidence, the task force recommends that the PAP device flow signal should be used to score apneas and hypopneas during PAP titration. Of note, the magnitude of oral airflow, if present, during a PAP titration with a nasal mask is not estimated by the PAP flow signal.

While the 2007 scoring manual lists the use of respiratory inductance (inductive) plethysmography (RIP) sensors as mates by the PAP flow signal.

### Table 2—Recommended sensors for routine respiratory monitoring

<table>
<thead>
<tr>
<th>Respiratory Parameter</th>
<th>Sensor</th>
</tr>
</thead>
</table>
| Airflow (use both oronasal thermal flow sensor and nasal pressure transducer during diagnostic study) | • Oronasal thermal airflow sensor* (to score apnea in diagnostic study)  
• Nasal pressure transducer** (to score hypopnea in diagnostic study)  
• PAP device flow signal (to score apneas and hypopneas in PAP titration study) |
| Respiratory Effort (select one) | • Esophageal manometry  
• Dual thoracoabdominal RIP belts***  
• Dual thoracoabdominal PVDF belts [Acceptable] in adults |
| Oxygen Saturation | Pulse oximetry |

Level of recommendation = [Recommended] in adults and children unless otherwise noted. *Including PVDF airflow sensor; **with or without square root transformation; ***calibrated or uncalibrated; RIP, respiratory inductance plethysmography; PVDF, polyvinylidene fluoride.

### Table 3—Alternative sensors for scoring respiratory events during diagnostic study

<table>
<thead>
<tr>
<th>Respiratory Event</th>
<th>Sensor</th>
</tr>
</thead>
</table>
| Apnea (select one) | • Nasal pressure transducer*  
• RIPsum**  
• RIPflow**  
• PVDFsum [Acceptable] in adults  
• End-tidal PCO2 [Acceptable] in children |
| Hypopnea (select one) | • Oronasal thermal airflow sensor***  
• RIPsum**  
• RIPflow**  
• Dual thoracoabdominal RIP belts**  
• PVDFsum [Acceptable] in adults |

Alternative sensors are used for scoring events if the recommended sensor fails or the signal is not reliable. Level of recommendation = [Recommended] in adults and children unless otherwise noted. *With or without square root transformation; **calibrated or uncalibrated; ***including PVDF airflow sensors; RIP, respiratory inductance plethysmography; PVDF, polyvinylidene fluoride.

### Table 4—Other sensors for respiratory monitoring

<table>
<thead>
<tr>
<th>Respiratory Event</th>
<th>Sensor</th>
</tr>
</thead>
</table>
| Snoring (select one) | • Acoustic sensor (e.g., microphone)  
• Piezoelectric sensor  
• Nasal pressure transducer |
| Hypoventilation (select one) | • Arterial PCO2 (diagnostic or titration study)  
• Transcutaneous PCO2* (diagnostic or titration study)  
• End-tidal PCO2* (diagnostic study only) |

Level of recommendation for all sensors = [Recommended] in adults and children. *See discussion for caveats of use, and if scoring the respiratory event is recommended or optional.
RIP signal is usually not performed in routine clinical PSG unless the technology for calibration during natural breathing is available. During apnea, the RIPsum and RIPflow signals show absent or minimal excursions, and during hypopnea, the excursions are diminished compared to baseline breathing. Of note, airflow limitation can be inferred from subtle qualitative changes in the inspiratory portion of the thorax RIP, abdominal RIP, and RIPsum signals, or from flattening of the inspiratory portion of the RIPflow waveform. The recommended RIP signals for scoring apnea and hypopnea events are specified in Tables 2 and 3.

The 2007 scoring manual recommends use of the nasal pressure signal for scoring hypopnea in both adults and children. While the detection of hypopnea depends on the reduction in the amplitude of the signal, the inspiratory portion of the nasal pressure waveform provides additional useful information. Flattening of the shape of the inspiratory nasal pressure waveform is a surrogate for airflow limitation and is included in the respiratory effort related arousal (RERA) rules in the 2007 scoring manual. Visualization of flattening of the signal requires that the nasal pressure signal be recorded either as a DC signal or an AC signal with a low-frequency filter setting (cutoff frequency) that is sufficiently low (frequency cutoff 0.03 Hz or lower) (Figure 1). Snoring can also be detected as an oscillation superimposed on the unfiltered nasal pressure signal if an appropriate high-frequency filter setting is used (100 Hz). The task force recommends that appropriate high and low filters settings be specified for nasal pressure recording in future revisions of the scoring manual.

### 3.1.2 Sensors for Apnea Detection

In the 2007 scoring manual the *recommended* sensor for detecting apnea in both adults and children is an oronasal thermal sensor (Table 1 for definition of *recommended*). Oronasal thermal sensors have the advantage of being able to detect both nasal and oral airflow. Thermal sensors detect a change in temperature between inhaled and exhaled gas. Here thermal airflow sensors include thermistors, thermocouples, or polyvinylidene fluoride (PVDF) sensors. The task force found no evidence to change this recommendation for diagnostic sleep studies, although it broadened the definition of thermal sensors to include PVDF sensors.

The 2007 scoring manual recommends somewhat different *alternative* sensors for apnea detection in adults (nasal pressure transducer or RIP) and children (nasal pressure transducer, end-tidal PCO₂, and summed RIP) (Table 1 for definition of *alternative*). The nasal pressure signal is not the *recommended* sensor for apnea detection as the signal may show decrease excursions (decreased amplitude) during mouth breathing. Due to the non-linear characteristics of the nasal pressure signal (proportional to the flow squared), the signal underestimates low flow rates and could result in a hypopnea appearing to be an apnea. A square root transformation of the nasal pressure signal more closely approximates flow and minimizes this problem.

As noted above, the excursions of the RIPsum and RIPflow signals usually have minimal amplitude during apnea. However, during obstructive apnea continued excursions in the RIPsum or RIPflow signals may be seen if the thorax and abdominal belt signals do not precisely sum to zero. This problem is minimized by calibration of the RIP signals; however, even the calibrated RIPsum may not remain accurate due to belt movement or changes in patient position.

Studies have evaluated the accuracy of RIPsum or RIPflow as a surrogate of tidal volume/airflow to detect apneas and hypopneas in adults and children. These studies usually analyzed the combination of apneas and hypopneas. That is, a separate analysis for apneas and hypopneas was not performed. In one study of calibrated RIP, the use of the RIPsum and RIPflow signals to determine the apnea hypopnea index (AHI) showed good agreement with a pneumotachograph (accurate flowmeter). Another study using uncalibrated RIP to determine the AHI found the intermeasurement agreement between use of the RIPsum and pneumotachograph to be considerably lower than between nasal pressure and pneumotachograph. A separate analysis for apnea and hypopnea detection was not performed. Respiratory belts utilizing a PVDF sensor can also provide a sum signal as well as thoracoabdominal signals. One study in adult patients being evaluated for suspected obstructive sleep apnea (OSA) suggests that the PVDFsum signal may have utility as a method for apnea/hypopnea detection independent of direct airflow monitoring (nasal pressure or thermistry). The PVDFsum signal identified apnea based on a reduction in signal amplitude to 10% of baseline and hypopnea by a 50% reduction in signal. There was good agreement between classification of patients with an AHI ≥ 5/hour using PVDFsum compared to detection of airflow by thermistry and nasal pressure. In a separate part of the study, ten normal subjects simulated central and obstructive apneas while monitored with a pneumotachograph, RIP belts, and PVDF belts. Respiratory events defined as > 50% drop in signal amplitude were identified and compared. The PVDF sensor performed as well as the RIP when compared against the pneumotachograph in terms of the total number of respiratory events that were detected. Further evidence for the utility of the PVDF signals (thoracoabdominal belts or sum) to detect apnea/hypopnea is needed.

In summary, there is evidence that RIPflow or RIPsum (in adults and children) or PVDFsum (in adults only) may be used as an alternative sensor for apnea detection with the under-
standing that most studies analyzed the combination of apneas and hypopneas. Calibration of RIP may improve the accuracy of RIPflow and RIPsum, but a head-to-head comparison of AHI results using the same sensor, with and without calibration, has not been performed. Further comparisons between PVDFsum, RIPsum, or RIPflow, and an oronasal thermal sensor for detection of apneas (both central and obstructive) are needed.

The end-tidal PCO\textsubscript{2} signal is listed as an alternative sensor for apnea detection in pediatric patients in the 2007 scoring manual. A more accurate description of the signal is exhaled PCO\textsubscript{2}, but the phrase end-tidal PCO\textsubscript{2} monitoring is widely used. Monitoring of exhaled PCO\textsubscript{2} is routinely performed during pediatric PSG, and the absence of signal deflections (no CO\textsubscript{2} exhaled) has been used to score apneas (Figure 2).\textsuperscript{3,39} The side stream method is most commonly used and consists of gas suctioned via a nasal cannula to an external sensor at bedside. Mouth breathing and occlusion of the nasal cannula can impair the ability of end-tidal PCO\textsubscript{2} monitoring to detect apnea. One must remember that the magnitude of signal excursion depends entirely on the highest value of PCO\textsubscript{2} in the exhaled breath rather than the magnitude of tidal volume or flow. Signal excursions can persist during inspiratory apnea if small expiratory puffs with a high PCO\textsubscript{2} are present.\textsuperscript{40} A large study in infants compared the ability of the RIPsum, end-tidal PCO\textsubscript{2}, and oronasal thermistor monitoring to detect apnea.\textsuperscript{39} End-tidal PCO\textsubscript{2} detected 182 of 196 apneas detected by either a thermistor or RIPsum.

After review of the existing evidence, the task force decided upon recommended (Table 2) and alternative (Table 3) sensors for apnea detection. The task force concluded that the recommended sensor for apnea detection during diagnostic study should continue to be an oronasal thermal sensor in adults and children [Consensus] (Consensus). The task force also reached consensus on specification of the nasal pressure signal or the RIPsum or RIPflow signals from calibrated or uncalibrated RIP as the alternative (sensor) signals for apnea detection during diagnostic study in adults and children [Recommended] (Consensus). In adults the PVDFsum signal may also be used as an alternative sensor for apnea detection, although the ability to differentiate obstructive apneas versus hypopneas has not been defined [Acceptable] (Adjudication). The end-tidal PCO\textsubscript{2} is another alternative apnea sensor in children if other sensors are not functioning or not available [Acceptable] (Consensus). As noted in the previous section, the PAP device flow signal is the recommended signal for apnea detection during PAP titration. Alternative sensors for apnea detection during PAP titration studies are not specified.

### 3.1.3 Sensors for Hypopnea Detection

Hypopnea detection requires a sensor to reliably detect a reduction in airflow or tidal volume. The gold standard for airflow detection is a pneumotachograph, usually placed in the outlet of a mask over the nose and mouth, which measures the pressure drop across a linear resistance.\textsuperscript{9,10,23,24,40} However, this technology is not practical for clinical studies. The 2007 scoring manual recommends a nasal pressure transducer with or without square root transformation as the recommended sensor for detection of airflow for identification of hypopnea in adults.\textsuperscript{1} In children the untransformed nasal pressure signal is recommended. The 2007 scoring manual also recommends somewhat different alternative hypopnea sensors for adults (calibrated or uncalibrated RIP, oronasal thermal sensor) and children (oronasal thermal sensor).

As noted above, nasal pressure monitoring (nasal cannula connected to a pressure transducer) provides a signal proportional to the square of the flow.\textsuperscript{36} A square root transformation of the signal provides a more accurate estimate of flow, but the accuracy of the transformed nasal pressure signal typically deteriorates over a night of monitoring due to factors such as changes in catheter position.\textsuperscript{23} The effect of using a transformed rather than untransformed nasal pressure signal on the apnea hypopnea index is usually small; the AHI based on the transformed signal is slightly lower.\textsuperscript{1,22} The utility of nasal pressure monitoring has been documented in a significant number of publications\textsuperscript{19,23-25,29-32} and is sensitive to even subtle changes in airflow. The inspiratory portion of the nasal pressure waveform can display flattening, a surrogate of airflow limitation when using appropriate filter settings. As noted above, the major disadvantage of nasal pressure monitoring is the inability to detect or estimate the magnitude of oral airflow.\textsuperscript{32}

Oronasal thermistors and thermocouples detect the presence of airflow due to a change in sensor temperature, as exhaled gas is warmed to body temperature. The signal from these thermal devices is not proportional to flow\textsuperscript{33,61} and often overestimates flow as flow rates decrease.\textsuperscript{33} Excursions in the signal typically show some decrement during hypopnea, although not as prominent as those in the nasal pressure signal.\textsuperscript{39} Thermal sensors using polyvinylidene fluoride (PVDF) film produce a signal that is roughly proportional to the temperature difference between the two sides of the film and have a faster response time than thermistors or thermocouples.\textsuperscript{34,35} One study comparing the ability of an oronasal PVDF airflow sensor to a pneumotachograph in ten patients with OSA found that the output of a PVDF airflow sensor tracked the magnitude of changes in flow with reasonable accuracy.\textsuperscript{34} Although this study did not directly compare the PVDF sensor to traditional thermal sensors, it does
suggest that PVDF sensors more accurately estimate the magnitude of airflow. While the inspiratory PVDF waveform may not routinely exhibit flattening during airflow limitation, PVDF sensors have the advantage over nasal pressure sensors of being able to detect oral airflow. One can also argue that hypopnea definitions are based on changes in amplitude rather than signal contour. A limitation of the evidence for using PVDF airflow sensors for hypopnea detection is the small number of patients that have been studied. A study of PVDF airflow sensors in children has yet to be published.

As noted above, the calibrated or uncalibrated RIP signals (RIPsum, RIPflow, thorax and abdominal belt excursions) also decrease during hypopnea. Studies of uncalibrated and calibrated RIP have shown reasonable accuracy in detection of hypopnea. However, in some very obese patients inspiration is associated with small thoracoabdominal excursions making use of RIP for detection of hypopnea more difficult. Heitman et al. found the event by event device agreement between a pneumotachograph and the RIP-sum (uncalibrated RIP). Clark and coworkers found the nasal pressure signal to be more sensitive for detection of airflow limitation than RIPflow (calibrated RIP). Thurnheer et al. found the bias in AHI between nasal pressure (transformed or untransformed) and a pneumotachograph to be similar to that between RIPflow (calibrated RIP) and the pneumotachograph. One might expect calibration of RIP to improve the accuracy of hypopnea detection, but this is rarely performed in clinical PSG. Another issue is that not all commercially available PSG systems provide a RIPsum and/or a RIPflow signal. As noted in the discussion of apnea sensors, the PVDFsum signal (from PVDF effort belts) appears to have utility for detection of apneas and hypopneas based on a single study in adults. As with other hypopnea sensors, the PVDFsum does not appear to be as sensitive for detecting events (based entirely on flow) as nasal pressure. The ability of PVDFsum to detect hypopnea when combined with arterial oxygen desaturation remains to be determined.

Given the above considerations, the task force was able to reach consensus on the recommended (Table 2) and alternative (Table 3) sensors for hypopnea detection in adults and children during diagnostic polysomnography. The task force recommends that the recommended sensor for detection of airflow for identification of hypopnea in adults and children continue to be a nasal pressure transducer (with or without square root transformation) [Recommended] (Consensus). The simplicity and sensitivity of nasal pressure and the ability for scorers to easily recognize changes in flow based on changes in shape as well as amplitude are distinct advantages. Alternative sensors for identification of hypopnea in adults and children include oronasal thermal sensors (including PVDF airflow sensors) or calibrated or uncalibrated RIP (RIPsum, RIPflow, dual thoracoabdominal RIP belts) [Recommended] (Consensus). The PVDFsum is an alternative hypopnea sensor to be used in adults only [Acceptable] (Adjudication). As noted earlier, the PAP device flow signal is the recommended signal for hypopnea detection during PAP titration. Alternative sensors for hypopnea detection during PAP titration studies are not specified.

3.1.4 Sensors for Detection of Respiratory Effort

The 2007 scoring manual recommends esophageal manometry or calibrated or uncalibrated respiratory inductance plethysmography for detection of respiratory effort in adults and children. Esophageal manometry is the gold standard for detection of respiratory effort, and the signal excursions provide an estimate of the magnitude of effort. However, esophageal manometry is rarely used in clinical practice due to its invasiveness and patient discomfort. Instead, the monitoring of thoracoabdominal excursions is used to detect the presence of respiratory effort. The magnitude of these excursions may or may not be proportional to esophageal pressure excursions, yet for routine clinical sleep monitoring, the detection of respiratory effort to differentiate central and obstructive apnea is the major concern. Failure to detect respiratory effort when present may result in the incorrect classification of an obstructive apnea as central. In one study of 22 patients with OSA using strain gauge sensors positioned on the chest and abdomen, 422 events were classified as central apneas; however, 156 of the events were reclassified as obstructive based on esophageal pressure tracings.

The 2007 scoring manual did not specify the use of dual effort belts (thoracoabdominal belts) for detection of respiratory effort. Nevertheless, this is standard clinical practice for a number of reasons. Some patients have larger excursions in either the thorax or abdominal belts during the night, and this can vary with body position. If one effort belt fails, the other still provides information about respiratory effort. During bio-calibration the polarity of belt signals is adjusted so that belt distension results in signal excursion in the same direction for both belts. Use of dual belts has the additional advantage of the ability to demonstrate paradoxical motion of the thorax and abdomen and adds the ability to identify events as obstructive (Figure 2).

The technology available for respiratory effort belts includes strain gauges, impedance plethysmography, inductance plethysmography (RIP), and belts with piezoelectric or PVDF sensors. An advantage of the RIP technology is that inductance of the band and ultimately the signal output depends on the entire surface area enclosed by the band. Effort belts with piezoelectric or PVDF sensors typically utilize a single sensor between belt material surrounding the thorax and abdomen. The signal depends on variations in the tension on the sensor which may or may not reflect the magnitude of thoracoabdominal excursions. Studies have shown that RIP belts are able to detect subtle changes in respiratory effort and out of phase (paradoxical) motion of the thorax and abdomen excursions is often noted during obstructive apnea or hypopnea. Calibration of RIP signals should improve the accuracy of this sensor technology for detection of respiratory effort. However, even calibrated RIP may not detect feeble respiratory effort in some patients with misclassification of obstructive apneas as central. Of note, many of the studies documenting the accuracy of RIP used belts from one or two manufacturers, yet RIP belts are currently supplied by many different manufacturers, and information on the specific technology used for a given belt is not available to the clinician. Validation studies for each type of RIP belt would increase confidence that their performance is similar to the belts used in previous investigations.
Prior to publication of the 2007 scoring manual, many sleep centers used piezoelectric effort belts. Today use of RIP belts has replaced piezoelectric belts in most sleep centers. The task force found scant evidence directly comparing RIP and piezoelectric effort belts with respect to the AHI or detection of central apnea.\textsuperscript{45,46} Montserrat et al. did find that subtle changes in piezoelectric belt signals were useful in detecting subtle increases in respiratory effort.\textsuperscript{16} A recent study directly compared RIP belts and effort belts using a PVDF sensor.\textsuperscript{8} Monitoring was performed with both types of belts in place in 50 adult patients referred for evaluation of possible obstructive sleep apnea (OSA). Respiratory events were scored using montages with either RIP or PVDF belt signals visible to detect respiratory effort. Although there were differences in the AHI values between the sensor types in some patients, overall the results obtained by both technologies were very similar. The average number of central apneas, obstructive apneas, hypopneas, and the overall AHI as determined using RIP versus PVDF belts for respiratory effort detection were almost identical and showed a high level of agreement as assessed by the $\kappa$ statistic. Thus, PVDF sensor effort belts appear to adequately detect respiratory effort in adults.\textsuperscript{8} Unlike RIP signals, there have been no studies of PVDF belts in children. More validation studies directly comparing effort belts with different technology (RIP versus piezoelectric, RIP versus PVDF) are needed.

The 2007 scoring manual includes surface diaphragmatic/intercostal electromyography (EMG) as an \textit{alternative} sensor for detection of respiratory effort. Bursts of the diaphragmatic/intercostal EMG signal are noted with each inspiration. Similar monitoring methods as those used for recording of anterior tibial muscle EMG can be used. However, unlike leg EMG, the diaphragmatic/intercostal EMG signal is often contaminated with prominent electrocardiographic activity. There continues to be scant literature on the use of surface EMG to detect respiratory effort.\textsuperscript{47,48} Although diaphragmatic/intercostal EMG monitoring is potentially useful as an adjunct to other methods of detecting respiratory effort, the task force felt that more research in this area is needed.

Given the above considerations, the task force decided to uphold the 2007 manual recommendation that esophageal manometry or calibrated or uncalibrated dual thoracoabdominal RIP belts be used for detection of respiratory effort in adults and children (Table 2) [Recommended] (Consensus). It was concluded that dual thoracoabdominal PVDF belts may be used to detect respiratory effort in adult patients but with a lower level of recommendation due to limited published evidence (Table 2) [Acceptable] (Adjudication).

### 3.1.5 Detection of Blood Oxygen

The task force did not find evidence to change the 2007 recommended sensor for estimation of arterial oxygen saturation which is pulse oximetry (Sp$_O_2$) with an appropriate averaging time (Table 2) [Recommended] (Consensus). It was noted that the presence of carboxyhemoglobin (e.g., in heavy smokers) may result in the Sp$_O_2$ being higher than the true fraction of total hemoglobin bound to oxygen.\textsuperscript{49} Accurate measurement of the amount of carboxyhemoglobin requires use of a co-oximeter that uses the absorption of four or more wavelengths of light (compared to two wavelengths in routine oximetry). The presence of carboxyhemoglobin also shifts the oxygen hemoglobin saturation curve to the left causing a given Sp$_O_2$ to be associated with a lower than expected partial pressure of oxygen.

Because of the sigmoid shape of the oxyhemoglobin dissociation curve, a much greater drop in arterial partial pressure of oxygen (Pa$_O_2$) occurs in the setting of a drop of 4% from a baseline saturation of 96% to 92% (Pa$_O_2$ change ~18 mm Hg) compared to the same drop of 4% from a baseline saturation of 92% to 88% (Pa$_O_2$ change ~ 9 mm Hg). Therefore, linking respiratory event definitions to a specific change in saturation for event detection requires a greater fall in the Pa$_O_2$ for patients with a high baseline saturation (e.g., 98%) than those with lower baseline saturations. The desaturation associated with a respiratory event is defined as a drop from a baseline Sp$_O_2$ preceding the event to the nadir in the Sp$_O_2$ following the event. While identification of the nadir in the Sp$_O_2$ following a respiratory event is usually straightforward, selecting a “baseline” Sp$_O_2$ in a patient with back-to-back respiratory events is more difficult. The highest Sp$_O_2$ following a respiratory event can exceed values present during stable breathing. Defining a “baseline Sp$_O_2$” during sleep may be difficult in such patients. While the above ambiguities in Sp$_O_2$ measurement were recognized, the task force did not recommend changes in terminology or measurement.

### 3.1.6 Detection of Snoring

The 2007 AASM scoring manual did not recommend a sensor for snoring. There is a paucity of published data on snoring sensors. Optimal visualization of snoring requires a high frequency filter setting that permits recording/display of rapid oscillations (100 Hz recommended in the 2007 scoring manual).\textsuperscript{1} Snoring may be visualized in the nasal pressure signal as high-frequency oscillations\textsuperscript{12} superimposed on the slower varying flow signal but is not seen in the PAP device flow signal which is either filtered or too under-sampled to show the high-frequency vibrations. Snore sensors are typically piezoelectric sensors that detect vibration of the neck or microphones that record the sound of snoring. The AASM guidelines for continuous positive airway pressure (CPAP) and for NPPV titration\textsuperscript{14,15} both listed a snore signal as an option for recording. Based on limited information, the task force recommends several sensors as options for snore detection: the unfiltered nasal pressure signal, piezoelectric sensors to detect vibration, or acoustic sensors (e.g., microphone) to record sound (Table 4) [Recommended] (Consensus). The ability of the sensor to detect simulated snoring should be demonstrated before sleep recording. The task force concurs with the 2007 manual that whether or not to monitor snoring is at the discretion of the clinician or investigator [Optional] (Consensus).

### 3.1.7 Detection of Hypoventilation

The gold standard method for documenting hypoventilation is the processing of an arterial sample for determination of the arterial partial pressure of carbon dioxide (Pa$_CO_2$). Given the difficulty of drawing an arterial sample during sleep, the 2007 scoring manual states that finding an elevated Pa$_CO_2$ obtained immediately after waking would provide evidence of hypoventilation during sleep. Regardless of whether this value underestimates the sleeping Pa$_CO_2$, the ability to draw or process an arterial blood gas sample is rarely available in sleep centers. In
Conclusion and Future Directions

The task force considered the literature on the accuracy of end-tidal CO₂ and transcutaneous PCO₂ as surrogates for determination of arterial PCO₂. Sanders et al. found that both Pₜₑ₆.CO₂ and Pₜₑ₆.CO₂ monitoring did not provide an accurate estimation of PaCO₂ during sleep; however, this study was limited by the technology used, i.e., Pₜₑ₆.CO₂ was measured using a loose-fitting mask, which would be unlikely to result in an adequate waveform. A study of Pₜₑ₆.CO₂ during the awake postoperative state in both non-obese and obese patients found the average Pₜₑ₆.CO₂ values to differ from the PaCO₂ by around 8 mm Hg (nasal cannula) or 6 mm Hg (nasal cannula + oral guide). Another study evaluated the utility of Pₜₑ₆.CO₂ for determining daytime hypoventilation in a group of patients with neuromuscular disease. Although fairly accurate in some patients, in others there was a large difference between the Pₜₑ₆.CO₂ and PaCO₂.

A number of studies have evaluated the accuracy of Pₜₑ₆.CO₂ compared to PaCO₂ or capillary PCO₂. Maniscalco et al. found the average PaCO₂ – Pₜₑ₆.CO₂ difference to be -1.4 mm Hg (95% confidence interval -1.7 to 7.5 mm Hg) in a group of obese adult patients with various disease processes. In a recent study, Storre et al. compared capillary blood gas PCO₂ and Pₜₑ₆.CO₂ from 3 different devices in a group of patients being started on nocturnal noninvasive ventilation. The bias (PaCO₂ – Pₜₑ₆.CO₂ drift uncorrected) for one device was as low as 0.8 mm Hg, with the limits of agreement extending from -4.9 to 6.5 mm Hg. Paiva and coworkers used Pₜₑ₆.CO₂ monitoring during sleep in 50 children receiving chronic NPPV. Twenty-one patients had nocturnal hypoventilation (without desaturation on oximetry). Of these 21 patients, 18 did not have daytime hypoventilation (capillary blood gas). The authors concluded that Pₜₑ₆.CO₂ monitoring was useful for detection of unsuspected nocturnal hypoventilation. Senn and coworkers compared transcutaneous and arterial PCO₂ measurement in a group of patients undergoing mechanical ventilation. The mean difference ± 2 SDs between Pₜₑ₆.CO₂ and PaCO₂ during stable ventilation was 3 ± 7 mm Hg.

A number of investigations compared values obtained from simultaneous measurements of Pₜₑ₆.CO₂ and Pₜₑ₆.CO₂. Kirk et al. analyzed the findings of PSG with simultaneous monitoring of Pₜₑ₆.CO₂ and Pₜₑ₆.CO₂ in 609 children. In 437 patients, the difference between the mean nocturnal Pₜₑ₆.CO₂ and Pₜₑ₆.CO₂ was between -4 and +4 mm Hg. Of note, interpretable results were found in 61% of PSGs for Pₜₑ₆.CO₂ and 71.5% for Pₜₑ₆.CO₂. Thus, obtaining interpretable data using either Pₜₑ₆.CO₂ or Pₜₑ₆.CO₂ is often challenging. Hirabayashi and coworkers studied awake, spontaneously breathing adults and found the bias ± 2 SD of end-tidal and transcutaneous PCO₂ measurements compared to PaCO₂ to be 0.48 ± 8.2 for Pₜₑ₆.CO₂ and -6.3 ± 9.8 mm Hg for Pₜₑ₆.CO₂. The authors concluded that transcutaneous monitoring was more accurate. Casati and colleagues compared Pₜₑ₆.CO₂ and Pₜₑ₆.CO₂ to PaCO₂ in a group of anesthetized mechanically ventilated patients. The exhaled CO₂ was sampled between the endotracheal tube and the ventilator circuit. The Pₜₑ₆.CO₂ was within 3 mm Hg of the PaCO₂ in 21 of 45 pairs sampled, and the Pₜₑ₆.CO₂ was within 3 mm Hg of the PaCO₂ in 7 of 45 pairs sampled. The authors concluded that Pₜₑ₆.CO₂ was more accurate than Pₜₑ₆.CO₂.

In summary, it appears that both Pₜₑ₆.CO₂ and Pₜₑ₆.CO₂ have clinical utility as surrogates of PaCO₂ during diagnostic studies. At least in some settings, these surrogates may be more
useful for following trends in the PaCO₂ than providing a highly accurate estimate of the exact PaCO₂ value. Use of both methodologies requires careful review of tracings to determine if artifacts are present. Ptc CO₂ is the preferred methodology in patients with lung disease, significant mouth breathing, or those who are using supplemental oxygen or mask ventilation. The clinician should recognize that Ptc CO₂ values can occasionally be quite spurious and clinical judgment is needed. When readings do not match the clinical setting, a change in sensor site or recalibration may be needed. Ptc CO₂ is preferred where breath-to-breath changes in PaCO₂ need to be detected. In this setting, the ability to detect an increase in PCO₂ associated with a respiratory event is clinically useful.

The task force concurred with the 2007 manual that whether or not to monitor hypoventilation in adults during diagnostic study or PAP titration is at the discretion of the clinician or investigator [Optional] (Consensus). Monitoring hypoventilation in children during diagnostic study is [Recommended] (Consensus) and during PAP titration is [Optional] (Consensus). The task force recommends that arterial PCO₂, transcutaneous PCO₂, or end-tidal PCO₂ be used for detecting hypoventilation during diagnostic study in both adults and children (Table 4) [Recommended] (Consensus). During PAP titration in both adults and children, either arterial PCO₂ or transcutaneous PCO₂ is the recommended method to detect hypoventilation (Table 4) [Recommended] (Consensus). There are a number of caveats that accompany these recommendations: (1) Sensors should be properly calibrated according to manufacturer specifications. (2) Clinical judgment is essential when assessing the accuracy of end-tidal PCO₂ and transcutaneous PCO₂ readings. The values should NOT be assumed to be accurate surrogates of the arterial PCO₂ when the values do not fit the clinical picture. (3) Transcutaneous PCO₂ should be calibrated with a reference gas according to the manufacturer’s recommendations and when the accuracy of the reading is doubtful. (4) End-tidal PCO₂, to be accurate, a plateau in the PCO₂ versus time wave form should be present. Validation of the surrogate PCO₂ with a simultaneous PaCO₂ or capillary gas is ideal but not required.

### 3.1.8 Summary of Sensor Recommendations

As a reminder, sensors noted here as recommended have corresponding alternative sensors that may only be used if the recommended fails or is inaccurate. At this time alternative sensors are only named for identifying apneas and hypopneas in diagnostic studies. For monitoring of airflow during diagnostic studies, both an oronasal thermal sensor and a nasal pressure transducer should be used [Recommended] (Table 2). For apnea detection, the oronasal sensor is the recommended sensor and the nasal pressure can serve as an alternative sensor [Recommended]. Other alternative apnea sensors include use of RIPsum, RIPflow [both Recommended] and PVDFsum (adults only) or end-tidal PCO₂ (children only) [both Acceptable] (Table 3). During PAP titration studies, the PAP device flow is the signal that should be used for apnea detection [Recommended]. For hypopnea monitoring during diagnostic studies, nasal pressure is the recommended sensor [Recommended]. Alternative hypopnea sensors include an oronasal thermal sensor, RIPsum, RIPflow, dual thoracoabdominal RIP belts [all Recommended], or PVDFsum (adults only) [Acceptable]. During PAP titration studies, the PAP device flow is the sensor to be used for hypopnea detection [Recommended]. For respiratory effort monitoring (Table 2), use esophageal manometry or thoracoabdominal RIP belts (adults and children) [both Recommended] or thoracoabdominal PVDF effort belts (adults only) [Acceptable]. Pulse oximetry is the sensor to be used for oxygen saturation [Recommended]. Detecting snoring is [Optional], and a nasal pressure transducer, piezoelectric sensor, or acoustic sensor (e.g., microphone) should be used [Recommended] (Table 4). Detection of hyperventilation is [Optional] in adults, [Recommended] in children during diagnostic study only, and the following may be used for diagnostic studies: arterial PCO₂, transcutaneous PCO₂, or end-tidal PCO₂ [Recommended] (Table 4). For PAP titration studies, arterial PCO₂ or transcutaneous PCO₂ may be used [Recommended].

### 3.2 Event Duration Rules for Adult and Pediatric Patients

The 2007 scoring manual states that the event duration for scoring either apnea or hypopnea is measured from the nadir preceding the first breath that is clearly reduced to the beginning of the first breath that approximates baseline breathing amplitude. The only recommended revision to the 2007 scoring manual is to explicitly mention the recommended signal to be used for measurement. For apnea duration, the oronasal thermal sensor signal (diagnostic study) or PAP device flow signal (PAP titration study) should be used to determine the event duration [Recommended] (Consensus). For hypopnea event duration, the nasal pressure signal (diagnostic study) or PAP device flow signal (PAP titration study) should be utilized [Recommended] (Consensus). If the recommended sensor fails or the signal is inaccurate an alternative sensor signal can be used. The ability to determine baseline breathing is a problem in patients that have nearly continuous events. The AASM “Chicago consensus paper” states, “Baseline is defined as the mean amplitude of stable breathing and oxygenation in the 2 minutes preceding onset of the event (in individuals who have a stable breathing pattern during sleep) or the mean amplitude of the 3 largest breaths in the 2 minutes preceding onset of the event (in individuals without a stable breathing pattern).” The 2007 scoring manual states, “When baseline breathing amplitude cannot be easily determined (and when underlying breathing variability is large), events can be terminated when either there is a clear and sustained increased in breathing amplitude, or in the case where an oxygen desaturation has occurred, there is event-associated oxygen re-saturation of at least 2%.” The task force recommends that the 2007 manual guideline for determining baseline breathing be upheld [Recommended] (Consensus).

### 3.3 Definition of RDI and ODI for Adult and Pediatric Patients

Both the 1999 Chicago consensus paper and the ICSD-2 recommended that the sum of apnea, hypopneas, and RERAs per hour of sleep be used to diagnose OSA (along with symptoms). Neither of these documents, the practice parameters for PSG™ or the 2007 scoring manual, defines the metric “RDI” (respiratory disturbance index). Others have defined RDI as the sum of the AH1 (apneas plus hypopneas per hour of sleep) and RERA index (RERAs per hour of sleep). The literature is
very confusing, with many articles defining RDI as the number of apneas and hypopneas per hour of sleep. The Centers for Medicare and Medicaid defines the term RDI as the number of apneas and hypopneas per hour of monitoring. The task force reached consensus on the definition of RDI as the sum of the AHI and RERA index. However, reporting of the RDI metric should be considered [Optional] (Consensus) as scoring RERAs is also considered [Optional]. Some task force members also felt that if a hypopnea definition is used that includes arousal, that an oxygen desaturation index (ODI) defined as the number of ≥ 3% arterial oxygen desaturations per hour of sleep should be reported. This metric reflects the respiratory events per hour associated with desaturation. The task force did reach consensus on whether this should be required and thus recommended that reporting ODI remains [Optional] (Consensus).

**Definitions of RDI and ODI [Recommended] (Consensus)**

\[
\text{RDI} = \text{AHI} + \text{RERA index} \\
\text{ODI} = \geq 3\% \text{ arterial oxygen desaturations/hour}
\]

### 4.0 ADULT SCORING RULES

#### 4.1 Apnea Rule for Adults

The task force carefully examined the apnea rule in the 2007 scoring manual for possible revisions or clarifications. It reads, “Score an apnea when all the following criteria are met: (1) There is a drop in the peak thermal sensor excursion by ≥ 90% of baseline, (2) The duration of the event lasts at least 10 seconds, and (3) At least 90% of the event’s duration meets the amplitude reduction criteria for apnea.” Notably, the 2007 scoring manual rule for apnea does NOT require an associated arterial oxygen desaturation. The task force found no evidence to support a change in the 2007 scoring manual recommendation for a ≥ 90% drop in oronasal thermal flow lasting at least 10 seconds (adults). Of note, the basis for a 90% drop in the thermal sensor signal is entirely arbitrary, but is an attempt to operationalize the requirement of “absent or nearly absent airflow” that often appears in the literature for the definition of an apnea. As previously discussed, the task force did clarify that the PAP device flow sensor be used for scoring apnea during PAP titration and name alternative apnea sensors for diagnostic study (Tables 2 and 3).

The 2007 scoring manual apnea rule included a third requirement to address situations where the duration of the qualifying drop in airflow is significantly shorter than the event duration as defined by the event duration rule. This stipulation has resulted in numerous questions to the 2007 Scoring Manual Steering Committee for clarification. In one interpretation of the rule, only 9 contiguous seconds of the event duration must meet amplitude criteria. The requirement that 90% of event duration must meet amplitude criteria was not a part of the Chicago consensus paper definitions and does not appear in apnea definitions elsewhere in the literature prior to 2007. There are cases where there is a drop ≥ 90% of baseline in airflow that lasts for longer than 10 seconds but much less than 90% of the event duration (see Figure 3). Using the 2007 apnea rule, one cannot score such an event as an apnea. This event may not meet hypopnea criteria and therefore cannot be scored as either an apnea or hypopnea. In addition, the length of a respiratory event as defined by the event duration rule may be more difficult to define than the duration of the drop in airflow meeting amplitude criteria. For these reasons, the task force eliminated requirement 3 and added a note addressing the situation in which a shorter portion of a longer hypopnea event qualifies as an apnea.

**Apnea Rule for Adults [Recommended] (Consensus)**

Score a respiratory event in adults as an apnea if both of the following are met:

1. There is a drop in the peak signal excursion by ≥ 90% of pre-event baseline using an oronasal thermal sensor (diagnostic study), positive airway pressure device flow (titration study), or an alternative apnea sensor.
2. The duration of the ≥ 90% drop in sensor signal is ≥ 10 seconds.

Note: If a portion of a respiratory event that would otherwise meet criteria for a hypopnea meets criteria for an apnea, the entire event should be scored as an apnea. The duration of the event is from the nadir in flow preceding the first breath that is clearly reduced to the start of the first breath that approximates baseline breathing.

It should be noted that the task force also considered the possibility of combining both apneas and hypopneas into a single respiratory event. The numbers of both event types are ultimately combined to compute an apnea-hypopnea index. The Chicago consensus paper defined obstructive/hypopnea events and central apnea/hypopnea events. However, the task force felt that the definitions of an apnea and subtypes are relatively straightforward compared to hypopnea. In addition, there is a large literature and historical precedent of separating events into apnea and hypopnea. Use of a combined hypopnea event also provides some challenges. For example, how would one define a mixed apnea/hypopnea event? Given these considerations the task force did not recommend a change in the current practice of scoring apneas and hypopneas separately.

#### 4.1.1 Classification of Apnea

The classification of apnea as obstructive, mixed, or central in the 2007 scoring manual is based on respiratory effort. The definitions are consistent with those appearing in previous literature. The Chicago consensus paper did not specifically define mixed apnea because of the lack of reliability in scoring these events. The task force considered combining obstructive and mixed events as well as a revision of the definition of central and mixed apneas to address events where there are only 1 or 2 obstructive breaths (see Figure 4). If one changes the central apnea definitions to allow 1 or 2 obstructed breaths, then a change in the mixed apnea definition must follow. The choice of how many obstructive breaths to allow and still consider an event to be central seems entirely arbitrary. After discussion, the task force recommended that the definitions of obstructive, central, and mixed apnea in the 2007 scoring manual not be revised (Consensus).

#### 4.2 Hypopnea Rules for Adults

The definition of a hypopnea (a reduction rather than absence in airflow) continues to be an area of considerable controversy. The concept of hypopnea was originally introduced to address those situations in which a drop in arterial oxygen saturation was associated with a change in airflow rather than absence of airflow. Block et al. scored a hypopnea if “flows in the nose and...
mouth decreased and chest movement decreased and desaturation occurred. The technology used included airflow detection by thermistors attached to mouth and lip and chest movement detection by impedance plethysmography. Gould et al. defined hypopnea based on a reduction in uncalibrated RIP thoracoabdominal belt excursions (a surrogate estimate of tidal volume). The 1999 consensus conference defined an apnea-hypopnea as a 10-second or longer event characterized by either a clear decrease (> 50%) of a valid measure of breathing or a clear amplitude reduction (but < 50% decrease) of a validated measure of breathing associated with either an arousal or ≥ 3% oxygen desaturation occurring near the termination of the putative event.

The 2007 scoring manual provides two hypopnea definitions (recommended and alternative, also known as “4A” and “4B”). The need for two definitions was a product of controversy concerning the most appropriate hypopnea definition as well as the fact that the Centers of Medicare and Medicaid Services (CMS) currently accepts only the recommended definition. The recommended hypopnea definition requires a 30% or greater drop in flow for 10 seconds or longer associated with ≥ 4% oxygen desaturation. The alternative hypopnea definition requires a ≥ 50% in flow for 10 seconds or longer associated with a ≥ 3% oxygen desaturation OR an arousal. The hypopnea rule for children is similar to the adult rule except for the minimum duration.

The task force noted that different hypopnea definitions can result in considerably different AHI values. Ruehlend et al. retrospectively scored studies of 320 consecutive adult patients evaluated in the sleep center for suspected OSA. This is a population that should have an increased likelihood of having OSA. An AHI was determined using the Chicago consensus paper criteria and the two 2007 scoring manual hypopnea definitions (Table 5). Adding arousal to the hypopnea definition (as done in the alternative hypopnea definition of the 2007 scoring manual) added a fairly modest increase to the percentage diagnosed with OSA compared to use of the recommended hypopnea definition. Furthermore, even using the more liberal 2007 scoring
greater drop in nasal pressure excursions for 10 seconds or
3% Versus 4% Oxygen Desaturation
The recommended hypopnea definition requires a 30% or
greater drop in nasal pressure excursions for 10 seconds or

Table 5—Effect of hypopnea definitions on the AHI in a group
of patients undergoing polysomnography for suspected
obstructive sleep apnea

<table>
<thead>
<tr>
<th>Criteria</th>
<th>AHI cutoff ≥ 5/hour</th>
<th>AHI ≥ 15/hr</th>
</tr>
</thead>
</table>
| Chicago Criteria: (50% drop in accurate flow OR
discernible drop in flow + ≥ 3% desaturation or arousal) | 92%                 | 67%         |
| AASM scoring manual A (recommended)             | 59%                 | 38%         |
| AASM scoring manual B (alternative)             | 76%                 | 50%         |

Data from Ruehl et al. Apnea hypopnea indices (AHIs) were originally calculated using hypopnea scoring criteria requiring either > 50% airflow reduction or a lesser airflow reduction with associated ≥ 3% oxygen desaturation or arousal (Chicago criteria). AHIs using the recommended and the alternative hypopnea definitions of the 2007 AASM Manual for the Scoring of Sleep and Associated Events were then derived in separate passes of the previously scored data. In this process, hypopneas that did not satisfy the stricter hypopnea definition criteria were removed.

Table 6—Scoring reliability of different respiratory indices
(N = 20)

<table>
<thead>
<tr>
<th>Scoring of Sleep and Associated Events</th>
<th>AHI-flow (using flow only)</th>
<th>AHI-flow and ≥ 3% desaturation</th>
<th>AHI-flow and ≥ 4% desaturation</th>
<th>AHI-flow and ≥ 3% desaturation or arousal</th>
<th>AHI-flow and ≥ 4% desaturation or arousal</th>
<th>Arousal index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scoring manual</td>
<td>Scoring of Sleep and</td>
<td>Associated Events</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(recommended)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AASM scoring manual A (alternative)</td>
<td>915</td>
<td>0.97</td>
<td>0.99</td>
<td>0.77</td>
<td>0.95</td>
<td>0.54</td>
</tr>
<tr>
<td>AASM scoring manual B (alternative)</td>
<td>912, 914</td>
<td>0.74</td>
<td>0.99</td>
<td>0.77</td>
<td>0.95</td>
<td></td>
</tr>
</tbody>
</table>

The current scoring manual does not mandate that the obstructive portion have more than one obstructive breath.

manual alternative hypopnea definition, 24% of the patients being evaluated would not have been diagnosed with OSA using an AHI ≥ 5/hour.

Given the above considerations, the task force readdressed the hypopnea definition issue with respect to: (1) the required arterial oxygen desaturation, (2) the inclusion of arousal criteria, and (3) the qualifying drop in flow (30% versus 50%).

3% Versus 4% Oxygen Desaturation
The recommended hypopnea definition requires a 30% or greater drop in nasal pressure excursions for 10 seconds or longer associated with ≥ 4% oxygen desaturation. At the time that the 2007 scoring manual task force examined the literature (pre 2006) there was considerable evidence that respiratory events linked to arterial oxygen desaturation of either ≥ 3 or 4% identified individuals at increased risk of cardiovascular consequences. The current task force found further evidence to support this conclusion. For example, Punjabi et al. found respiratory events based on a desaturation of at least 4% were associated with an increased risk of cardiovascular consequences. Further analysis of Wisconsin cohort data and Sleep Heart Health study data suggests that the use of ≥ 3% desaturation criterion yields an AHI that is as predictive of adverse outcomes as an AHI based on ≥ 4% oxygen desaturation criterion. This is to be expected, given the very high correlation of > 0.95 between the AHIs determined using 3% versus 4% oxygen desaturation. Mehra et al. used a definition of hypopnea based on ≥ 3% desaturation and found significant associations between AHI and the risk of atrial fibrillation or complex ventricular ectopy in older men without self-reported heart failure. A study by Stamatakis et al. found that levels of desaturation of 2% or 3% were associated with fasting hyperglycemia. A recent study using a hypopnea definition requiring ≥ 3% oxygen desaturation found an association between incident stroke and obstructive sleep apnea. Recognizing the apparent equivalence of hypopnea definitions requiring ≥ 3% or ≥ 4% desaturation, the task force has recommended adoption of the 3% criterion. However, it should be noted that using ≥ 3% instead of ≥ 4% desaturation requirement for defining hypopnea does increase the AHI substantially (Table 6), with median AHI in a general community sample being almost twice as great using a 3% as a 4% criterion. Therefore, thresholds for identification of the presence and severity of OSA, and for inferring health-related consequences of OSA, must be calibrated to the hypopnea definition employed.
Inclusion of Arousal in Hypopnea Definition

The alternative definition of hypopnea for adults in the 2007 scoring manual requires a 50% or greater drop in nasal pressure excursions for 10 seconds or longer associated with either ≥ 3% desaturation or an arousal. Whether or not to include arousal as part of the hypopnea definition remains controversial. Opponents of inclusion of arousal in the hypopnea definition cite the fact that the majority of studies have not found an association between arousal frequency and adverse cardiovascular outcomes (independent of arterial oxygen desaturation). Another argument against inclusion of arousal in the hypopnea definition is that the scoring of arousals is said to be less reliable and would consequently reduce the reliability of scoring respiratory events. Opponents of inclusion of arousal criteria in the hypopnea definition also argue that the current Medicare/Medicaid hypopnea definition does not consider arousals and that a hypopnea definition based only on flow and oxygen saturation would be applicable to limited channel sleep testing (i.e., out-of-center sleep testing). One can also argue that milder sleep apnea patients would not be excluded if diagnosis of obstructive sleep apnea syndrome was based on the number of apnea, hypopneas, and respiratory effort related arousals (RERAs) per hour of sleep. The ICSD-2 diagnostic criteria for OSA are based on this metric (≥ 15/hour or ≥ 5/hour with symptoms).

Proponents of inclusion of arousal in the hypopnea definition cite evidence that sleep fragmentation without arterial oxygen desaturation can be associated with symptoms (e.g., daytime sleepiness) and that treatment with CPAP can improve symptoms and objective sleepiness. For symptomatic patients with milder OSA and a significant proportion of events associated with arousal but not ≥ 3% desaturation, the AHI may be ≥ 5/hour using the alternative hypopnea definition but not the recommended definition. While a metric based on the AHI + RERA index may be greater than 5/hour in such patients, RERAs are not scored in many sleep centers and not recognized by Medicare. Of interest, if one uses a hypopnea definition based on desaturation or arousal there are relatively few RERA events. There is a paucity of data concerning symptomatic patients with an AHI < 5/hour using the recommended hypopnea definition. Guilleminault et al. analyzed a cohort of 35 lean subjects diagnosed with OSA based on the Chicago consensus paper definition of hypopnea (50% drop in flow OR discernible drop in flow + ≥ 3% desaturation or arousal). The cohort was selected based on demonstrated improvement of OSA after treatment with CPAP or surgery (based on repeat sleep study) and improvement in subjective sleepiness. The original diagnostic studies were rescoring, and 40% of the patients had an AHI < 5/hour using a hypopnea definition based only on flow and ≥ 4% oxygen desaturation. Therefore, in the admittedly carefully selected cohort, a significant number of patients (40%) who benefited from treatment would NOT meet diagnostic criteria for OSA based on the recommended hypopnea definition and therefore not qualify for CPAP treatment. There is a paucity of data demonstrating a relationship between increased arousals and adverse cardiovascular outcomes. Supporters of the inclusion of arousal in the hypopnea definition cite biological plausibility of arousals leading to sympathetic nervous system activation and data showing sympathetic activation related to arousals with increased chin EMG activity (movement arousals). Cortical arousal stimuli sufficient to induce a K complex have been shown to elicit sympathetic activity. Of interest, an analysis of the Cleveland Family Study by Sulit et al. did find the arousal index correlated with the risk of hypertension whereas desaturation did not. This study did not evaluate if an AHI definition including arousal or desaturation had a higher association with the presence of hypertension than a hypopnea definition based solely on desaturation. Another study found an association between the arousal index and white matter disease in older adults. Using a hypopnea definition that included arousal criteria, a recent study found that the combination of an elevated AHI and daytime sleepiness was predictive of increased mortality in older adults. No analyses using a hypopnea definition based on oxygen desaturation alone were reported.

Regarding the issue of hypopnea definition and portable monitoring, proponents of the alternative hypopnea definition point out that this would simply underscore that PSG is more sensitive for detection of significant respiratory events than limited channel testing. PSG would permit scoring of hypopneas based on arousal as well as arterial oxygen saturation. Respiratory events that cause arousal but are associated with relatively minor drops in the arterial oxygen saturation could be identified as hypopneas. This would allow identification and treatment of a wider spectrum of symptomatic patients.

Concerning the scoring reliability of hypopneas, proponents of a hypopnea definition based on arousal as well as desaturation present several arguments. First, a 2007 AASM review concluded that the scoring of arousals when scorers were trained had moderate reliability. The review found evidence that visualization of information other than the EEG and EMG during scoring (e.g., respiratory channels) can improve the reliability of arousal scoring. The frequently quoted study of Whitney et al. provides information on the reliability of hypopneas associated with arousal. Twenty randomly chosen studies of good quality were scored by each of 3 scorers. The scorers first identified candidate apnea and hypopnea based only on flow (although oximetry tracings were visible) and then combined events with the presence or absence of arousals (based on a single EEG derivation) and various degrees of arterial oxygen desaturation (Table 6). Arousals were scored based on EEG without regard to respiration. The intraclass correlation (ICC) was highest when respiratory events were linked to oxygen desaturation. The ICC correlation was much lower for the scoring of arousals. However, respiratory events based on flow and the presence of arousal had a better ICC (0.77). Moreover, the reliability of events based on flow, oxygen desaturation, or arousal was even higher (Table 6). Of note, arousal scoring was based on a single EEG derivation from data acquired during an unattended study. In the discussion section of the paper, the authors stated that when the two most experienced scorers performed the analysis, the arousal scoring ICC correlation was much higher (0.72). Indeed, subsequent tracking of reliability showed that, over the course of the Sleep Heart Health Study, the ICC for arousal scoring varied between 0.72 and 0.78. A recent analysis of the data from the Osteoporotic Fractures in Men Sleep Study found the inter scorer reliability (intraclass correlations coefficients [ICC]) for the arousal index
based on central derivations to be 0.80. Of note, in current practice arousals are scored based on frontal, central, and occipital derivations with montages typically showing respiratory channels. The above considerations suggest that adding arousals to the hypopnea definition will not significantly reduce scoring reliability of hypopneas.

30% Versus 50% Drop in Flow

The task force considered the use of different flow criteria in hypopnea definitions. The 2007 scoring manual definitions of hypopnea for adults use either a 30% drop in flow (recommended definition) or 50% drop (alternative definition). The single pediatric definition requires a 50% drop in flow. Given the difficulty of accurately measuring flow or tidal volume in clinical settings, linking a change in flow or tidal volume to a physiological consequence would help identify an event as physiologically relevant. The degree of oxygen desaturation for a given reduction in airflow varies widely between individuals and depends on baseline arterial oxygen desaturation, oxygen stores (lung volumes), obesity, and the presence or absence of lung disease. Therefore a less than 50% drop in flow could result in significant oxygen desaturations in some individuals, while in others a desaturation may not occur.

Proponents of using the 30% drop argued that a 30% drop should identify a clear change in breathing from baseline. Furthermore, they argue that the associated consequences (desaturation or arousal) are more important for estimation of an event’s physiological significance than the magnitude of drop in flow (as a percentage of baseline). That is, a 30% drop in flow associated with 4% desaturation likely has physiological significance but would not be scored if one required a 50% drop in flow. Proponents of a 50% drop cite the current use of this value in the adult alternative definition and the pediatric hypopnea definition.

Hypopnea Summary

The above discussion outlines the difficulties in choosing a single definition for hypopnea. Although there were dissenters, the task force reached consensus on a definition of a hypopnea rule in adults using a 30% drop in the nasal pressure excursion for 10 seconds or greater associated with ≥ 3% desaturation OR an arousal. The majority of the task force felt that a hypopnea definition based only on desaturation would result in misdiagnosis of some patients in whom respiratory events fragment sleep but result in minor drops in the SpO2. While there seems little doubt that cardiovascular morbidity is associated with oxygen desaturation, the goals of OSA treatment address a much wider range of symptoms including daytime sleepiness, insomnia, and non-restorative sleep. The task force also recognizes that the proposed definition of hypopnea is not currently accepted by the Centers for Medicare and Medicaid Services (CMS) reimbursement. For Medicaid and Medicare patients the use of a hypopnea definition based on a 30% drop in flow and 4% or greater desaturation will need to be used to ensure reimbursement until reimbursement policies are changed to reflect the new hypopnea definition. Following the logic of the proposed revised apnea definition, the requirement that the qualifying drop in flow must occupy > 90% of the event duration was removed from the hypopnea definition.

Hypopnea Rule for Adults [Recommended] (Consensus)

Score a respiratory event as a hypopnea if all of the following are met:
1. The peak signal excursions drop by ≥ 30% of pre-event baseline using nasal pressure (titration study), PAP device flow (titration study), or an alternative hypopnea sensor.
2. The duration of the ≥ 30% drop in flow is ≥ 10 seconds.
3. There is ≥ 3% oxygen desaturation from pre-event baseline or the event is associated with an arousal.

Note: If necessary, the number of hypopneas using a definition requiring ≥ 30% drop in flow for ≥ 10 seconds that is associated with ≥ 4% desaturation may additionally be reported to qualify a patient for PAP reimbursement (e.g., Medicaid or Medicare patients).

4.2.1 Classification of Hypopnea

The task force discussed the clinical utility of scoring hypopneas as either obstructive or central events. In the 2007 scoring manual, the definition of Cheyne-Stokes breathing (CSB) does mention central hypopnea. The CMS criteria for reimbursement of a PAP device with a backup rate requires that 50% of events be central in nature. Some patients with CSB or complex sleep apnea have a large proportion of central hypopneas. Scoring central hypopneas would allow them to qualify for a device with a backup rate. In addition, as will be discussed below, many of the publications on CSB in heart failure include central hypopneas in computing an AHI. As the scoring of hypopneas as central or obstructive is clinically useful, the task force sought to define these two events, taking note of the definitions used in other publications. The Chicago consensus paper defined central apnea/hypopnea events as those events with a reduction in airflow and a clear reduction in esophageal pressure swings from baseline that parallels chronologically the reduction in airflow. The 2007 scoring manual only states that “classification of a hypopnea as obstructive, central, or mixed should not be performed without a quantitative assessment of ventilatory effort (esophageal manometry, calibrated RIP, or diaphragmatic/intercostal EMG).” This presents a problem as calibrated RIP excursions do not always reflect the magnitude of respiratory effort (as measured by esophageal pressure excursions) and esophageal manometry is rarely used.

In general, an obstructive hypopnea is one in which the reduction in airflow is mainly due to increased upper airway resistance, and a central hypopnea is one in which the reduction in flow is mainly due to a reduction in ventilatory effort. The fact that there can be some overlap should be noted as obstructive hypopneas may be characterized by an initial reduction in effort followed by a progressive increase until the event is terminated (Figure 5). Obstructive hypopneas are usually associated with flattening of the inspiratory portion of the nasal pressure (or PAP device flow) waveform, often associated with snoring, and sometimes associated with thoracoabdominal paradox (Figure 6). Central hypopneas are typically characterized by absence of flattening of the inspiratory portion of the nasal pressure or PAP flow waveform (or flattening is present but unchanged from baseline breathing) and absence of thoracoabdominal paradox in the thoracic and abdominal RIP band excursions (Figure 7).
The task force reviewed definitions of central and obstructive hypopnea in the literature with an emphasis on articles discussing CSB.89-93 One study defined a hypopnea as obstructive versus central if paradoxical thoracoabdominal excursions were noted or when the reduction in flow was out of proportion to the decrease in thoracoabdominal excursions (e.g., in central hypopnea the decrease in flow was proportional to the decrease in effort).90

Most articles have defined a central hypopnea on the basis of a lack of paradox in thoracoabdominal RIP belts and/or absence of flattening in the nasal pressure signal.89,91 Of note, in some studies hypopnea was defined based on a 50% drop in tidal volume (using RIP) without a requirement for associated desaturation or arousal.91 Lanfranchi et al. defined central hypopnea as ≥ 50% decrease in RIPsum lasting 10 seconds or longer followed by ≥ 2% desaturation.92 In this study, subjects with an obstructive AHI ≥ 5/hour were excluded. Ryan and coworkers defined central hypopnea as ≥ 50% decrease in RIPsum lasting 10 seconds or longer with in-phase thoracoabdominal motion and absence of flow limitation on the nasal pressure signal.93 In a study of CPAP and heart failure, Javaheri classified hypopnea as obstructive if paradoxical thoracoabdominal excursions occurred or if the airflow decreased out of proportion to the reduction in the thoracoabdominal excursions; otherwise hypopneas were classified as central.90

Some members of the task force felt that some mention of respiratory effort should be made in the definitions of central and obstructive hypopnea. Others noted that thoracoabdominal movements (RIP excursions) are not a direct measure of the amount of respiratory effort (e.g., esophageal pressure excursions). Task force members pointed out that a decrease in RIP excursions cannot differentiate obstructive and central hypopneas because the excursions may decrease in both types of hypopneas (see Figures 6 and 7). Although a disproportionate increase in effort when compared to flow can be indicative of obstruction, this is difficult to operationalize. The task force recommended the following definitions for scoring hypopneas as obstructive or central [Recommended] (Consensus) but also recommended that performing such scoring be [Optional] (Consensus). Such a separation of hypopneas into central or obstructive is not clinically indicated in the majority of patients.

**Classifying Hypopnea in Adults [Recommended] (Consensus)**

If electing to score obstructive hypopneas, score a hypopnea as obstructive if ANY of the following criteria are met:

1. Snoring during the event
2. Increased inspiratory flattening of the nasal pressure or PAP device flow signal compared to baseline breathing
3. Associated thoracoabdominal paradox occurs during the event but not during pre-event breathing

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**Figure 5**—Examples of a central (A) and an obstructive (B) hypopnea are shown

(A) A central hypopnea is characterized by lack of flattening in the airflow (nasal pressure) and a reduction in respiratory effort (esophageal pressure excursions). The reduction in flow is chronologically parallel to the reduction in effort. (B) An obstructive hypopnea is characterized by airflow limitation (flattening of the nasal pressure waveform) and increasing respiratory effort without an increase in airflow (nasal pressure). In this figure inspiration is upward.

**Figure 6**—An example of an obstructive hypopnea with snoring, flattening of the nasal pressure (NP) waveform, and paradoxical motion of the chest and abdominal (ABD) respiratory inductance plethysmography excursions

**Figure 7**—A central hypopnea in a patient with Cheyne-Stokes breathing is illustrated

NP is the nasal pressure signal. There is no evidence of snoring or thoracoabdominal paradox in the RIP bands (RIPthorax and RIPabdomen). There is no evidence of airflow limitation (flattening of the nasal pressure signal). The direction of inspiration is upward in this figure.
If electing to score central hypopneas, score a hypopnea as central if NONE of the following criteria are met:
1. Snoring during the event
2. Increased inspiratory flattening of the nasal pressure or PAP device flow signal compared to baseline breathing
3. Associated thoracoabdominal paradox occurs during the event but not during pre-event breathing

### 4.3 Respiratory Effort-Related Arousal Rule for Adults

The utility of scoring RERAs (an option in the 2007 scoring manual) is greatest when using a hypopnea definition not based on arousal. As noted above, if a definition of hypopnea is used which requires an associated desaturation OR arousal, then there are relatively few events scored as RERAs. The task force recommended only minor changes to the current RERA definition. One change includes the use of PAP device flow flattening rather than nasal pressure flattening during PAP titration. The task force acknowledges that “RERA” events are usually scored based on changes in nasal pressure (or PAP flow) rather than esophageal manometry. In this case, an increase in respiratory effort is inferred rather than being directly documented, leading some investigators to coin such an event as a “flow limitation arousal.” Nevertheless, the term RERA is widely used, and the task force members did not feel a change in terminology was needed. Task force members recommend that the scoring of RERA events remains [Optional] (Consensus).

**RERA Rule for Adults [Recommended] (Consensus)**

If electing to score respiratory effort-related arousals, score a respiratory event as a RERA if there is a sequence of breaths lasting at least 10 seconds characterized by increasing respiratory effort or by flattening of the inspiratory portion of the nasal pressure (diagnostic study) or PAP device flow (titration study) waveform leading to arousal from sleep when the sequence of breaths does not meet criteria for an apnea or hypopnea.

### 4.4 Hypoventilation Rule for Adults

A common definition of awake hypoventilation is an arterial PCO$_2$ (PaCO$_2$) $> 45$ mm Hg. In choosing a respiratory definition of hypoventilation for sleep studies there are two considerations. The first consideration is to identify a greater than normal increase in PaCO$_2$ from wake to sleep, that is, hypoventilation that is “sleep-related.” The second is to identify an abnormal PaCO$_2$ during sleep. In the 1999 Chicago consensus paper,$^9$ it was stated that the normal increase in PaCO$_2$ from wakefulness to sleep was from 2 to 7 mm Hg based on studies of arterial PaCO$_2$ during sleep in normal subjects.$^{96,97}$ “Sleep hypoventilation” was defined as a $\geq 10$ mm Hg increase in PaCO$_2$ from wake to sleep. The 2007 scoring manual also defined hypoventilation as $\geq 10$ mm Hg increase in PaCO$_2$ during sleep compared to an awake supine value. In neither definition was a minimum duration for the increased PaCO$_2$ specified. In Table 7, patient A has a 10 mm Hg increase in PaCO$_2$, and would meet the criteria for hypoventilation according to the 2007 AASM scoring manual. Patient B also has a 10 mm Hg increase, but many would not consider a PaCO$_2$ of 45 mm Hg during sleep to represent hypoventilation. Patient C presents with awake hypoventilation and only a small increase in PaCO$_2$ with sleep onset; yet, most would consider this patient to have hypoventilation during sleep. Of interest, local carrier determinations (LCDs) for the Center for Medicare and Medicaid services (CMS) has recently added a hypoventilation category for patient qualification for a respiratory assist device (e.g., bilevel PAP, bilevel PAP with a backup rate).$^{88}$ The criteria include a daytime PaCO$_2$ $\geq 45$ mm Hg, and either a PaCO$_2$ during sleep or immediately on awakening that is $\geq 7$ mm Hg greater than the awake PaCO$_2$ or a facility-based PSG demonstrates $SpO_2 \leq 88\%$ for at least 5 minutes of nocturnal recording time (minimum 2 hours of recording time) not caused by obstructive upper airway events.$^{88}$

As noted above, end-tidal PCO$_2$, and transcutaneous PCO$_2$ rather than PaCO$_2$ are usually measured in the sleep center. There are normative data for P$_{ET}$CO$_2$ in pediatric patients.$^{98-100}$ However, there is a paucity of normative data for adult P$_{ET}$CO$_2$, and for P$_{TC}$CO$_2$ in all age groups. Midgren et al.$^{101}$ studied normal adults and found an average awake P$_{ET}$CO$_2$ of 46 mm Hg with the highest value during sleep being 52 mm Hg. These data are from a 1987 article, and transcutaneous technology has advanced since this study. Morrell et al.$^{102}$ found that P$_{ET}$CO$_2$ increased from 38.7 mm Hg to 40.7 mm Hg during the wake-sleep transition in a group of normal subjects. Chin et al.$^{103}$ found that the P$_{TC}$CO$_2$ increased during sleep by about 11 mm Hg in hypercapnic and 6 mm Hg in normocapnic OSA patients.

Based on data that normal individuals rarely have a PaCO$_2$ > 55 mm Hg during sleep, the task force chose this threshold for sleep hypoventilation, with a minimum duration of 10 minutes, based on consensus. The task force considered the addition of a change in PaCO$_2$ (or surrogate PCO$_2$) from wakefulness to sleep with the proviso that the absolute sleeping PaCO$_2$ (or surrogate) value should reach a value that clearly represents hypoventilation. The duration of 10 minutes is admittedly arbitrary; however, normative data for the amount of total sleep time at different PaCO$_2$ values does not exist in sleeping adults. As noted in the earlier section on signals for detection of hypoventilation, scoring hypoventilation during sleep in adults is at the discretion of the clinician or investigator [Optional]. If reporting hypoventilation, the duration of hypoventilation as a percentage of total sleep time should be reported.

**Hypoventilation Rule for Adults [Recommended] (Consensus)**

If electing to score hypoventilation, score hypoventilation during sleep if either of the below occur:
1. There is an increase in the arterial PaCO$_2$ (or surrogate) to a value $> 55$ mm Hg for $\geq 10$ minutes

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**Table 7—Three patients with possible ‘sleep hypoventilation’**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Awake PaCO$_2$</th>
<th>Sleep PaCO$_2$</th>
<th>Change in PaCO$_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>40</td>
<td>50</td>
<td>10</td>
</tr>
<tr>
<td>B</td>
<td>35</td>
<td>45</td>
<td>10</td>
</tr>
<tr>
<td>C</td>
<td>50</td>
<td>55</td>
<td>5</td>
</tr>
</tbody>
</table>

Values are PaCO$_2$ in mm Hg.
2. There is ≥ 10 mm Hg increase in PaCO\(_2\) (or surrogate) during sleep (in comparison to an awake supine value) to a value exceeding 50 mm Hg for ≥ 10 minutes. Note: [Recommended] surrogates include end-tidal PCO\(_2\) or transcutaneous PCO\(_2\) for diagnostic study or transcutaneous PCO\(_2\) for PAP titration study.

### 4.5 Cheyne-Stokes Breathing Rule for Adults

Cheyne-Stokes breathing (CSB) is a specific form of periodic breathing (waxing and waning amplitude of flow or tidal volume) characterized by a crescendo-decrescendo pattern of respiration between central apneas or central hypopneas.\(^{1,9}\) The pattern of CSB is important to note as it may reflect unrecognized congestive heart failure and is a risk factor for early mortality or the need for heart transplant in patients with known heart failure.\(^{9,92,104}\) The 2007 scoring manual definition of CSB requires a minimum of 3 consecutive cycles for a run of central apneas or hypopneas to be considered CSB (Figure 8). An AH\(_I\) ≥ 5/hour (duration of monitoring not specified) due to CSB OR a minimum duration of 10 consecutive minutes of this pattern of breathing was also required. Interestingly, the ICSD-2 diagnostic criteria for CSB requires 10 central apneas per hour of sleep.\(^{10}\)

A longer cycle length as well as the crescendo-decrescendo breathing pattern differentiate CSB from other forms of cyclic central apnea, but the specifics of defining cycle length vary between publications concerning CSB. All authors define cycle length as the duration of the central apnea (or hypopnea) + the duration of a respiratory phase (Figure 8). More specifically, Hall et al.\(^{105}\) defined cycle length as the time from the start of the respiratory phase to the end of the subsequent apnea (start of next respiratory phase). Wedewardt and coworkers\(^{106}\) defined cycle length as the time from beginning of a central apnea to the end of the next crescendo-decrescendo respiratory phase (start of the next apnea). Given the requirement of at least 3 consecutive central apneas, the task force adopted the latter definition of cycle length (Figure 8). If central hypopneas occur, the cycle length may be more ambiguous but can be defined as the time from the zenith in the respiratory phase preceding the central hypopnea to the zenith of the next respiratory phase.

Patients with a number of disorders including primary central sleep apnea and narcotic induced central apnea can exhibit periodic breathing with a waxing and waning of respiration. A typical pattern is central apnea – respiratory phase (breathing) – central apnea. Unlike CSB, the respiratory phase (between central apneas) of patients with primary central apnea or narcotic induced central apnea does NOT usually have a crescendo-decrescendo pattern, and the duration of the respiratory phase is typically shorter than in CSB. However, a minority of these patients may exhibit a respiratory phase with a crescendo-decrescendo pattern (Figure 9).

What cycle length or length of breathing between consecutive apneas (respiratory phase) is required to score as CSB (Figure 10)?\(^{108}\) As few as three breaths could show a crescendo-decrescendo pattern. When CSB is associated with systolic heart failure the respiratory phase is long and the cycle length is approximately 60 seconds. Hall et al.\(^{105}\) compared the patterns of respiration in patients with idiopathic central sleep apnea (primary CSA) and CSB due to systolic heart failure. Patients with CSB had a longer cycle length due to a longer respiratory phase between central apneas (data shown in Table 8). The duration of central apnea was similar in the two groups of patients. A longer cycle length (and respiratory phase) was associated with more impaired cardiac function.

CSB has been described in patients after cerebrovascular accidents\(^{107}\) and in patients with diastolic heart failure (normal ejection fraction).\(^{108}\) In general, one might expect the cycle lengths to be shorter in these patients. While some might disagree with classifying the pattern of breathing exhibited by these groups of patients as CSB, there are no guidelines available regarding the minimum cycle length or respiratory phase duration to score CSB. A study of patients with CSB and various degrees of left ventricular dysfunction (Table 9) found considerable variation in the cycle length. Those individuals with a normal left ventricular ejection fraction exhibited a mean cycle length of 49.1 ± 17.4 seconds.\(^{108}\) Based on the above data, one might choose a minimum cycle length of 40 seconds to score CSB (or at least 5 to 6 breaths in the respiratory phase between apneas or hypopneas).

How many CSB events must be present to consider the patient as having CSB? Some patients have a transition from obstructive to central events during the same night (believed to be associated with increasing left ventricular filling pressure and ventilatory drive).\(^{109}\) Patients with both obstructive sleep apnea and heart failure may not exhibit CSB until late in the night or when in the supine position. CSB can also appear during a PAP titration after elimination of the obstructive component of breathing events. In the Outcomes of Sleep Disorders in Older Men (MrOS) Study, CSB was defined as the presence of at least 5 consecutive minutes of breathing with a CSB pattern.\(^{72}\) Using this definition for CSB, Mehra and colleagues found an association between the presence of CSB...
and complex ventricular ectopy independent of self-reported heart failure.72 Mared et al. defined the presence of CSB in patients when this breathing pattern occupied more that 10% of the recording time.110 As noted above, the CSB scoring rule in the 2007 scoring manual requires at least 3 consecutive central apneas and/or central hypopneas interspersed with a CSB pattern of breathing and either a central AHI of 5/hour or 10 consecutive minutes of CSB. The monitoring period for computation of the AHI was not specified. If one assumes a cycle time of 60 seconds, requiring 10 consecutive minutes equates to about 10 consecutive central events. Do the events have to be consecutive? Would two runs of five CSB events not be as convincing as a 10-event run?

There is also evidence that the presence or amount of CSB could have some prognostic significance in patients with heart failure. Lanfranchi and coworkers92 followed a group of patients with chronic heart failure documented as having CSB by PSG. A central AHI > 30/hour was a bad prognostic sign for survival. Non-survivors had a greater portion of the night in periodic breathing. Amir et al.111 studied a group of patients with advanced systolic heart failure and found that a longer duration of CSB was associated with higher mortality and a higher NT-proBNP, a marker of poor cardiac function. In this study the mean duration of CSB time was about one hour. Based on these studies, it may be useful to specify the amount

Figure 9—The tracings illustrate periodic breathing in a 35-year-old male with no evidence of cardiac disease who is not taking narcotic medication.

Figure 10—Various possibilities of periodic breathing with a crescendo-decrescendo pattern.

Are these all Cheyne-Stokes Breathing?

Table 8—Cycle length of periodic breathing in patients with and without (systolic) heart failure.

<table>
<thead>
<tr>
<th></th>
<th>Cycle Length</th>
<th>Number of Breaths in Ventilatory Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary central sleep apnea</td>
<td>37.3 ± 3.0 sec</td>
<td>4.5 ± 0.7</td>
</tr>
<tr>
<td>CSA-CSB (CHF)</td>
<td>59.0 ± 4.9 sec</td>
<td>11.7 ± 1.4</td>
</tr>
</tbody>
</table>

Data from Hall et al.106 CSA-CSB, central sleep apnea with Cheyne-Stokes Breathing; CHF, congestive heart failure.
of CSB. The task force recommends that a parameter reflecting the CSB duration (absolute or percentage of total sleep time) or the number of CSB events should be specified in the sleep study report if possible [Recommended] (Consensus).

Given the above considerations, the task force proposed a revised CSB definition. The minimum amount of CSB respiration that must be present is arbitrary but was chosen as an AHI of ≥ 5/hour (associated with CSB) with a minimum monitoring period of 2 hours. For most patients this is equivalent to requiring about 10 CSB respiratory events. The wording clearly specifies that central apneas OR central hypopneas can separate periods of crescendo-decrescendo respiration. It was felt that specifying a minimum AHI over a minimum monitoring time would replace the need to specify a minimum total duration of CSB.

Cheyne-Stokes Breathing Rule for Adults [Recommended] (Consensus)

Score a respiratory event as Cheyne-Stokes breathing if both of the following are met:
1. There are episodes of at least 3 consecutive central apneas and/or central hypopneas separated by a crescendo and decrescendo change in breathing amplitude with a cycle length of at least 40 seconds (typically 45 to 90 seconds).
2. There are 5 or more central apneas and/or central hypopneas per hour associated with the crescendo/decrescendo breathing pattern recorded over a minimum of 2 hours of monitoring.

Note: The duration of CSB (absolute or as a percentage of total sleep time) or the number of CSB events should be presented in the study report.

5.0 PEDIATRIC SCORING RULES

5.1 Ages for which Scoring Rules for Children Should Be Used

The 2007 AASM scoring manual specifies that the respiratory scoring rules for children can be used for infants and children < 18 years. There is the option of using adult respiratory scoring rules for children ≥ 13 years. The task force considered a change in the current rule to one recommending that pediatric rules be used for all children younger than 18 years. When the AASM pediatric scoring rules were developed, there were no data available specifically pertaining to adolescents; therefore, it was suggested that adolescents aged 13-18 years could be scored using either pediatric or adult criteria. Since then, two studies have shown significant differences in respiratory parameters when the PSGs of adolescents aged 13-18 years were scored using pediatric versus adult criteria. A study of normal adolescents showed that they had a significantly higher AHI when pediatric scoring rules were used. Another study of adolescents with suspected OSA also showed a significant difference in AHI using pediatric versus adult scoring rules, especially between the pediatric rule and the recommended adult rule for hypopneas. In addition, significantly more children would have been diagnosed with OSA using pediatric versus adult rules. Some members of the task force felt strongly that all patients younger than 18 years should be scored according to pediatric scoring rules. However, the task force was unable to reach a consensus to change the current AASM scoring rule concerning the age range for use of respiratory scoring rule for children. The current AASM scoring rule does allow the clinician the option of using pediatric scoring rules for patients ≥ 13 but < 18 years. The clinician could elect to use pediatric scoring rules for these older children based on the consideration of the recent studies just described. In addition, with a similar proposed definition for hypopnea in adults and children (see section on hypopnea below), this concern may be less of an issue.

Cheyne-Stokes Breathing Rule for Children (Recommended)

Score a respiratory event as Cheyne-Stokes breathing if both of the following are met:
1. There are episodes of at least 3 consecutive central apneas and/or central hypopneas separated by a crescendo and decrescendo change in breathing amplitude with a cycle length of at least 40 seconds (typically 45 to 90 seconds).
2. There are 5 or more central apneas and/or central hypopneas per hour associated with the crescendo/decrescendo breathing pattern recorded over a minimum of 2 hours of monitoring.

5.2 Apnea Rule for Pediatric Patients

The task force considered the same issues regarding defining apnea as for adults. Positive airway pressure device flow was added as a sensor to detect apnea during positive airway titration, and the requirement that the duration of the event meeting amplitude criteria must be ≥ 90% of the event’s duration was removed. The minimum duration of the drop in flow is two respiratory cycles as in the 2007 scoring manual. As not all events with absent airflow and effort are scored as central apneas, a general definition of apnea requires that events meet criteria for obstructive, central, or mixed apnea.

Apnea Rule for Pediatric Patients [Recommended] (Consensus)

Score a respiratory event as an apnea if it meets all of the following criteria:
1. There is a drop in the peak signal excursion by ≥ 90% of the pre-event baseline using an oronasal thermal sensor (diagnostic study), PAP device flow (titration study), or an alternative apnea sensor (diagnostic study).
2. The duration of the ≥ 90% drop lasts at least the minimum duration as specified by obstructive, central, or central apnea duration criteria.
per minute for more than 10 seconds. The proposed pediatric study of normal infants, none had a heart rate less than 55 beats per minute for more than 10 seconds.113 The proposed pediatric task force members who thought this was a com-

5.2.1 Classification of Pediatric Apnea

The proposed revised obstructive apnea definition is similar to the one recommended for adults. The central apnea definition differs from adults as normal infants and children may have a considerable number of short central pauses in respiration not associated with desaturation or arousal. Such events are felt to be within normal variation limits.51,113,114 The central apnea definition is similar to the 2007 scoring manual central apnea definition except that a provision for children less than 1 year of age has been added. In these individuals, a central apnea is believed to be significant if followed by significant bradycardia (a decrease in heart rate to < 50 beats per minute for at least 5 seconds or < 60 beats per minute for 15 seconds). In one study of normal infants, none had a heart rate less than 55 beats per minute for more than 10 seconds. In the proposed pediatric mixed apnea definition differs from the adult definition in that the central portion may be present before or after the obstructive portion of the event. This option was added at the request of pediatric task force members who thought this was a common clinical occurrence. An example of a mixed apnea with the central portion following the obstructive portion in a 3-year-old child is shown in Figure 11.

Classification of Pediatric Apnea [Recommended] (Consensus)

Score a respiratory event as an obstructive apnea if it meets apnea criteria for at least the duration of 2 breaths during baseline breathing and is associated with the presence of respiratory effort throughout the entire period of absent airflow.

Score a respiratory event as a central apnea if it meets apnea criteria, is associated with absent inspiratory effort throughout the entire duration of the event, and at least one of the following is met:

1. The event lasts 20 seconds or longer.
2. The event lasts at least the duration of two breaths during baseline breathing and is associated with absent inspiratory effort during one portion of the event and the presence of inspiratory effort in another portion, regardless of which portion comes first.

3. The event meets respiratory effort criteria for obstructive, central, or mixed apnea.

5.3 Hypopnea Rule for Pediatric Patients

The hypopnea definition for pediatrics in the 2007 scoring manual requires a 50% drop in flow with either ≥ 3% oxygen desaturation or arousal. This is very similar to the current recommendation of the task force for the hypopnea definition for adults except that the minimum duration is 2 breaths. The main issue was whether to use a 30% drop in flow as in the adult definition or retain the 50% drop in flow in the current pediatric hypopnea definition. Advantages of the 50% drop include the ability to compare results with some previously published papers. An advantage of using a 30% drop is that both pediatric and adult definitions would be similar. It was also felt that using a 50% drop would create a class of events with > 30% drop but less than a 50% drop in flow that if associated with an arousal or desaturation would not be scored (unless scored as a RERA). The task force consensus was to use 30% drop in flow; thus, the hypopnea rule is the same for children as for adults except for the minimum duration of 2 breaths (rather than 10 seconds).

Hypopnea Rule for Pediatric Patients [Recommended] (Consensus)

Score a respiratory event as a hypopnea if it meets all of the following criteria:

1. The peak signal excursions drop by ≥ 30% of pre-events baseline using nasal pressure (diagnostic study), PAP device flow (titration study) or an alternative hypopnea sensor (diagnostic study).
2. The duration of the ≥ 30% drop lasts for at least 2 breaths.
3. There is ≥ 3% desaturation from pre-event baseline or the event is associated with an arousal.

5.3.1 Classification of Pediatric Hypopnea

The recommended scoring rules for scoring pediatric hypopneas as either central or obstructive are the same as for adults [Recommended] (Consensus), and classifying hypopneas in pediatric patients should be considered as [Optional] (Consensus).

5.4 Respiratory Effort-Related Arousal Rule for Pediatric Patients

The task force revised the definition of RERA in pediatric patients to be similar to that recommended for adults except for a few differences. The minimum duration is 2 breaths, and snoring or an elevation in the end-tidal PCO₂ is included as supporting the diagnosis of RERA. The pediatric RERA rule in the 2007 scoring manual includes an increase in the transcutaneous PCO₂ included as a scoring criterion; however, the device response is too slow for RERA identification and the criterion was removed. As in adults, the task force felt that scoring RE-RAs should be [Optional] (Consensus).
RERA Rule for Pediatric Patients [Recommended] (Consensus)
If electing to score respiratory effort-related arousals, score a respiratory event as a RERA if there is a sequence of breaths lasting at least 2 breaths (or the duration of two breaths during baseline breathing) when the breathing sequence is characterized by increasing respiratory effort, flattening of the inspiratory portion of the nasal pressure or PAP device flow waveform, snoring, or an elevation in the end-tidal PCO₂ leading to arousal from sleep when the sequence of breaths does not meet criteria for an apnea or hypopnea.

5.5 Hypoventilation Rule for Pediatric Patients
There are more normative data for the use of end-tidal PCO₂ and transcutaneous PCO₂ during sleep in children compared to adults. The existing scoring rule was felt to be consistent with currently available data. The task force agreed that the 2007 scoring manual scoring rule for hypventilation in children should remain unchanged until further published data are available.

Hypoventilation Rule for Children [Recommended] (Consensus)
Score hypoventilation during sleep when > 25% of the total sleep time as measured by either the arterial PCO₂ or surrogate is spent with a PCO₂ > 50 mm Hg.

5.6 Periodic Breathing Rule for Pediatric Patients
The task force found no evidence suggesting that the current definition of periodic breathing be significantly changed. The task force recommends a periodic breathing respiratory definition that is similar to the 2007 scoring manual except that “greater than 3 episodes” is replaced by “greater than or equal to 3 episodes.” This was felt to be more inclusive.

Periodic Breathing Rule for Pediatric Patients [Recommended] (Consensus)
Score a respiratory event as periodic breathing if there are ≥ 3 episodes of central apnea lasting ≥ 3 seconds separated by no more than 20 seconds of normal breathing.

6.0 SUMMARY
The definitions of respiratory events and recommendations concerning monitoring technology will continue to evolve as more knowledge is gained about the effect of using different definitions or technology on outcomes. Improved ability to predict patients who will improve symptomatically with treatment (especially in patients with “milder” obstructive sleep apnea) is clearly needed. It is hoped that this document is simply a starting point of a new process to provide a flexible and evolving set of respiratory definitions. The recommendations in this document are based predominantly on consensus. The task force attempted to carefully weigh the current evidence as well as to respond to concerns raised by the sleep community about the recommendations in the 2007 scoring manual. Many areas of uncertainty remain. No set of definitions can completely cover the wide variety of respiratory events encountered by clinicians. There is no substitute for clinical correlation of PSG findings with the clinical symptoms of the patient being evaluated.

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ACKNOWLEDGMENTS

The task force thanks Christine Stepanski, MS, and Richard Rosenberg, PhD, for their valuable assistance during the consensus process and the Board of Directors of the AASM for their guidance and support. The task force also thanks Drs. Berry and Marcus for supplying the figures.

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication August, 2012
Accepted for publication August, 2012
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DISCLOSURE STATEMENT

This was not an industry supported study. Drs. Berry and Redline have received a research grant from Dymedix, Inc. The other authors have indicated no financial conflicts of interest.

619 Journal of Clinical Sleep Medicine, Vol. 8, No. 5, 2012
In this issue of the *Journal of Clinical Sleep Medicine*, the Sleep Apnea Definitions (SAD) task force of the American Academy of Sleep Medicine (AASM) redefines many of the respiratory rules found in the 2007 *AASM Manual for the Scoring of Sleep and Associated Events*. This task force labored over a two-year period, analyzing the recent literature pertaining to respiratory events and sensor technology, and striving to reach consensus on a new set of respiratory rules. The paper details some significant changes including a single definition of a hypopnea. In addition, there is now the option to score hypopneas as central or obstructive. There is also greater concordance between adult and pediatric scoring rules for various respiratory events. (Please refer to the forthcoming new version of the scoring manual for the final version of the rules for scoring respiratory events.) As the AASM Board of Directors worked through adopting these changes, significant consternation was raised about adopting a singular hypopnea definition using 3% oxygen desaturation with or without arousals since the Center for Medicare and Medicaid Services (CMS) still uses only a 4% desaturation definition. The AASM sent a letter to CMS in July asking them to consider changing their criteria based on this new document. As of the writing of this editorial, we have not received a response from CMS. We realize that for the time being, this will create some problems for labs that have not been using the 3% rule; however, we are hopeful that soon enough, there will be one agreed upon rule for both clinical, CMS, and research studies. Congratulations to the SAD task force for all their hard work on this project.

With the development of new respiratory rules by the SAD task force underway, the AASM Board of Directors began to grapple with how to update the scoring manual. Because of the need to be flexible for future changes, a decision was made to convert the printed scoring manual to an online product. An online version has several advantages: it can be easily updated in response to new evidence and member inquiries; it is accessible from a variety of locations using smartphones, tablets, and computers. The online version allows for more detailed and colorful graphics, and the timely inclusion of answers to frequently asked questions. The board approved a Scoring Manual Committee with members chosen for their expertise applicable to the different sections of the scoring manual. The 2012-2013 members include: Richard Berry, chair; Charlene Gamaldo (legs); Bradley Vaughn (EEG); Carole Marcus (pediatrics); Rita Brooks (AAST representative); and Susan Harding (breathing). In addition to moving the manual online, the mandate of the task force is to, on a regular basis, review and update the *AASM Manual for the Scoring of Sleep and Associated Events* to ensure it is current with AASM practice parameters, clinical guidelines, and policy, and addresses the evolution of clinical literature and technology.

In order to make timely and appropriate changes, the Scoring Manual Committee will, at minimum on a quarterly basis, review inquiries from *Manual* users including but not limited to: individuals, sleep centers, industry representatives, and government agencies. The new scoring manual e-mail (scoringmanual@aasmnet.org) will provide a conduit for stakeholders to submit their questions and comments. The Scoring Manual Committee will hold a face-to-face meeting at the annual meeting of the Associated Professional Sleep Societies, and when deemed appropriate by either the committee or the Board of Directors, a member forum will be held at the annual meeting. On an annual basis, the Scoring Manual Committee will be tasked with providing a critique of the rules by individual section. Such a review will include requests from users for revisions of the text. Some years, the Scoring Manual Committee may simply indicate that the rules remain valid and supported. Other years, the critique will include suggestions for clarification, minor modifications and/or major revisions of scoring rules.

In the case of major revisions, AASM staff will evaluate the proposed rules in need of change and institute a formal literature search for relevant materials. The results of the search will be analyzed by the Scoring Manual Committee and presented to the board as evidence along with a new set of rules. All additions, deletions, changes, corrections and explanations will require board approval prior to implementation. Acceptable evidence to make changes may include published research in peer-reviewed journals. Such research may have been financially supported by government, industry and/or public or private foundations. Anecdotal evidence such as testimonials from users of novel technology may be considered as well. The Scoring Manual Committee may request supportive information from users advocating major revisions. It is hoped that this process...
NA Collop, MM Tangredi, and RB Berry

will allow flexibility in updating rules as new technologies, studies, and information become available.

The AASM Board of Directors has decided to charge an annual subscription fee of $25.00 for electronic access to the scoring manual. The easiest way to subscribe will be with the membership dues renewal and could be either an individual subscription or a center subscription, meaning all who work in a center would be permitted access. Subscriptions will run on a calendar year and will be formatted for regular monitor as well as tablet/mobile-device viewing. Each time the journal is updated, it will receive a new version number which should be used for referencing. Older versions of the manual will continue to be accessible with the annual subscription.

We hope that you will find all these changes advancements in the AASM’s desire to remain relevant and on point with emerging technologies and research.

CITATION

SUBMISSION & CORRESPONDENCE INFORMATION
Submitted for publication August, 2012
Accepted for publication August, 2012
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DISCLOSURE STATEMENT
The authors have indicated no financial conflicts of interest.
An Unusual Cause of Insomnia

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A 23-year-old African American male was referred for sleep maintenance insomnia for the past several years. He complained of occasional morning headaches. He denied snoring, hypnagogic hallucinations, sleep paralysis, and cataplexy. His Epworth Sleepiness Scale score (ESS) was 12/24.

At age 16, he was diagnosed with a posterior fossa medulloblastoma (T3) and underwent surgical resection, radiation, and chemotherapy and has had no evidence of recurrence on recent brain magnetic resonance imaging. He has no history of taking any medications known to affect the central nervous system, including narcotics/opioids. His body mass index was 18 kg/m², and he had mild slurred speech. His oropharynx was normal. His oxygen saturation while breathing room air was 91%.

His room air arterial blood gas (ABG) that was performed because of the relatively low oxygen saturation showed a pH of 7.38, pCO₂ of 57 mm Hg, and pO₂ of 65 mm Hg. His chest x-ray was normal. He had no polycythemia, and echocardiography findings were normal.

QUESTION: What is the cause of this patient's insomnia?
PSG (scored using the American Academy of Sleep Medicine recommended criteria) revealed poor sleep efficiency of 45% with a total of 80 central apneas and 17 hypopneas, and an overall apnea-hypopnea index (AHI) of 33/h (NREM AHI: 16/h, REM AHI 99/h). The overall arousal index was 31.2/h. A fragment of his PSG is shown in Figure 1.

The patient’s ABG showed chronic hypercapnia without increased alveolar-arterial (A-a) oxygen gradient, which would be consistent with hypoventilation due to drive or weakness rather than lung disease. Pulmonary function testing revealed normal spirometry and lung volumes. Normal spirometry would be expected in hypercapnia due to ventilatory drive. Because he had difficulty following the instructions for the measurements of maximum inspiratory (MIP) and expiratory pressures (MEP) which registered low values, diaphragmatic electromyography was performed, which showed normal bilateral phrenic nerve responses and normal needle electrode examination of the right hemi-diaphragm. There was no evidence of excessive dead space ventilation as a contributing factor to chronic hypercapnia with a Vd/Vt of 0.36 that was determined at rest. Although a formal hypercapnic ventilatory response was not performed, his work up has virtually eliminated other potential causes of chronic hypercapnia and was presumed likely due to a blunted ventilatory drive. He was treated with nocturnal noninvasive ventilation using a bilevel machine in the spontaneous/timed mode with improvements in sleep efficiency and AHI.

It is important to remember that insomnia has a variety of causes, and CSA has to be considered should the history suggest the possibility. Previous studies have reported that brain-stem tumors are associated with CSA, before and even after surgical resection.\(^1\)\(^2\) Our case is unique in that a predominant presenting complaint of insomnia has not been reported in patients who have undergone surgical resection of brainstem tumors with consequent CSA.

**ANSWER:** Central sleep apnea (CSA), likely due to impaired central drive. This patient has hypercapnic CSA and a presumed blunted ventilatory drive as a result of his previous brain surgery and radiation for medulloblastoma.
PEARLS

1. CSA should be suspected as a cause of insomnia in a patient who has had resection of posterior fossa tumors.
2. In those with a blunted ventilatory drive, ABG values show chronic hypercapnia with a normal pO₂ (A-a) gradient. Other causes of hypercapnia should be looked for.
3. Brainstem tumors, even after successful resection, have been associated with CSA.
4. Treatment of hypercapnic CSA includes nocturnal noninvasive ventilation.

REFERENCES


CITATION


SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication September, 2011
Submitted in final revised form January, 2012
Accepted for publication February, 2012
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DISCLOSURE STATEMENT

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