Pulmonary, Sleep, and Critical Care Updates

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In 2012, the *Journal* published several influential studies that have enhanced our knowledge of the pathophysiology, management, and consequences of sleep-disordered breathing (SDB). The aim of this update is to highlight these discoveries.

PATHOPHYSIOLOGY OF SLEEP-DISORDERED BREATHING

In obstructive sleep apnea (OSA), the upper airway recurrently collapses during sleep due to an imbalance in forces that usually maintain pharyngeal patency. Given the importance of upper airway motor control, Saboisky and colleagues sought to confirm the presence of neurogenic changes and quantify the extent of neural remodeling in hypoglossal nerve branches (1). In this study of 31 patients, 17 of whom had OSA, genioglossus EMG signals and motor unit potential trains were extracted and analyzed quantitatively. This study revealed that the genioglossus motor unit potential trains were longer in duration and larger in size index in patients with OSA versus control subjects, strong indicators of neurogenic change. These changes were attributed to motor unit remodeling from denervation, collateral sprouting, and reinnervation and were associated with the severity of hypoxemia during sleep.

In an accompanying editorial, Levy and colleagues suggested that the cross-sectional study design did not allow separation of cause and effect (2). Although pharyngeal neuropathy might be a consequence of SDB, it may also perpetuate OSA. The authors acknowledged that more studies are required regarding these neurogenic changes.

Given the evidence for hypoglossal neurogenic dysfunction in OSA, specific treatment modalities such as hypoglossal nerve stimulation (HGNS) may have a therapeutic role. HGNS is potentially efficacious in patients with OSA intolerant of continuous positive airway pressure (CPAP) (3). Schwartz and colleagues sought to determine if the efficacy of HGNS was due to its ability to improve airflow and to relieve airway obstruction (4). This study of 30 patients with OSA found that HGNS produced marked dose-related increases in airflow without arousal from sleep. Although all patients achieved near-normal flow with HGNS, patients with persistent inspiratory airflow limitation required higher stimulus intensity to achieve peak flow, suggesting this subset of patients needed recruitment of other pharyngeal dilator muscles. Overall,

the authors believed their findings supported the need for further research into HGNS, including awaiting the results of multiple ongoing multinational randomized trials, although early unpublished reports have been disappointing.

CONSEQUENCES OF SDB

Evidence for Increased Oncologic Mortality

Despite considerable evidence implicating SDB as a risk factor for cardiovascular disease and diabetes, there have been no major studies examining the relationship between SDB and cancer until recently. Using a murine melanoma model, Almendros and colleagues subjected mice to intermittent hypoxemia to mimic OSA for 6 hours daily for 14 days (5). The group subjected to intermittent hypoxemia had a twofold increase in the growth of melanoma tumors compared with control mice. The authors concluded that this study provided evidence that intermittent hypoxemia, mimicking OSA, enhanced tumor progression.

In complement, Nieto and colleagues performed a 22-year follow-up of more than 1,500 people in Wisconsin, assessing the association of SDB and cancer (6). Fifty out of 112 total deaths in this cohort were from cancer, most frequently lung cancer ($n = 8$). Both total ($P = 0.001$) and cancer mortality ($P = 0.005$) were observed to increase significantly with increasing SDB severity after adjusting for age, sex, body mass index (BMI), and smoking. Additional adjustments for physical activity, alcohol use, education, and sleep duration did not change these results. The hypoxemia index (% sleep time $< 90\%$ saturation) was strongly associated with cancer mortality in a dose-response fashion, with a hazard ratio (HR) of 8.6 for increased cancer mortality in the most hypoxemic group ($> 11.2\%$ of time). Interestingly, results appeared to be strongest in nonobese and nonsleepy participants with moderate to severe OSA.

Based on available data, the authors hypothesized that the intermittent hypoxemia associated with SDB may augment angiogenesis and therefore tumor progression, although further studies are required to clarify underlying mechanisms. Overall, an association between SDB and cancer mortality is apparent, requiring further investigation.

Evidence for Diabetic Complications

OSA is a common coexistent disorder in type 2 diabetes (T2DM). Given that OSA and diabetes share common pathophysiology, Tahrani and colleagues sought to study potential relationships between OSA and diabetic peripheral neuropathy (DPN) (7). This observational cross-sectional study recruited 266 patients with diabetes without known OSA. DPN was assessed using the Michigan Neuropathy Screening Instrument and a monofilament test, and OSA was assessed by home sleep testing. Nitrosative and oxidative stress, both implicated in DPN pathology, were measured in addition to microvascular function to elucidate underlying disease mechanisms.

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One hundred fifty-one (65%) of the patients with diabetes were found to have OSA, and 17% of these patients had severe OSA. At baseline, the patients with diabetes with OSA were older, had longer diabetes duration, higher systolic blood pressure, and higher obesity measures in addition to more sleepiness compared with those without OSA. They also had worse foot insensitivity, higher Michigan Neuropathy Screening Instrument scores, and a higher overall DPN prevalence (60 vs. 27%, $P < 0.001$). Despite these differences, OSA remained independently associated with DPN and foot insensitivity after adjustment for covariates (odds ratio [OR], 2.82 for having DPN in OSA-positive patients; $P = 0.003$); DPN prevalence remained higher in the OSA-positive group in a subsequent matched-group analysis (53% in OSA-positive vs. 24% in OSA-negative, $P = 0.0001$). Although there were no significant differences in DPN prevalence between patients with different OSA severities, DPN severity correlated significantly with OSA severity ($P = 0.02$) and closely with nocturnal hypoxemia severity ($P = 0.08$) independent of major confounders. Serum nitrotyrosine and plasma lipid peroxidase were higher in patients with diabetes with DPN and in those with OSA. In concert with this finding, patients with diabetes with OSA were also found to have impaired microvascular blood flow regulation.

Many important conclusions can be drawn from this study. First, there is a significantly higher prevalence of DPN in patients with diabetes with OSA than those without OSA, and DPN worsens with OSA severity. Second, the strong association of OSA and DPN in patients with T2DM suggests that clinicians should be vigilant about diagnosing OSA in this population and that future prospective studies are needed to assess DPN reversibility with CPAP treatment. Finally, the discovery of potential mechanistic links between OSA and DPN in T2DM, such as nitrosative/oxidative stress and abnormal microvascular blood flow regulation, also suggest new investigative/therapeutic targets for DPN.

TREATMENT OF SDB

Effects of Bilevel Ventilation in Patients with Mild Obesity Hypoventilation Syndrome

Although studies have suggested that patients with obesity hypoventilation syndrome (OHS) benefit from noninvasive ventilation (NIV) therapy, minimal data exist to evaluate the usefulness of this therapy in OHS. Borel and colleagues randomized 35 patients with newly diagnosed OHS to bilevel therapy or 1 hour of lifestyle counseling with a specialized nurse (control group) (8). Inflammatory, metabolic, cardiovascular, and ventilatory markers in addition to sleepiness assessments were performed before randomization and after 1 month of treatment.

The NIV treatment significantly improved all nocturnal oxygen indices and reduced daytime PaCO_2 (-3.5 ± 1.35 mm Hg) and apnea-hypopnea index (AHI) ($-40.3 \pm 11.05/\text{h}$). However, in this intervention group, patients' subjective daytime sleepiness did not improve beyond that of the control group nor were there significant improvements in any measured inflammatory, metabolic, or cardiovascular parameters despite significant improvement in sleep hypoxemia. The authors concluded that NIV (for the duration provided) may not be sufficient to reverse many of the chronic consequences of OHS, such as persistent systemic and vascular inflammation. In addition to improving the ventilatory parameters with NIV in these patients, additional treatment modalities may be necessary to lower their cardiovascular and metabolic risk profiles.

Effects of CPAP Treatment in Sleepy Patients with Mild to Moderate OSA

Given conflicting prior results evaluating CPAP efficacy in mild to moderate OSA, the CPAP Apnea Trial North American

Program (CATNAP) sought to determine the usefulness of CPAP to improve functional status in sleepy patients with mild to moderate OSA (9). This double-blind, randomized, placebo-controlled parallel group study enrolled 239 participants with excessive daytime sleepiness (Epworth Sleepiness Scale [ESS] $> 10/24$) with newly diagnosed mild to moderate OSA (AHI, 5–30/h with $> 3\%$ desaturation) who were naive to CPAP. After completing diagnostic polysomnograms followed by CPAP titration studies, participants were randomized to 8 weeks of active or sham CPAP (rather than placebo tablet intervention). After 8 weeks, those assigned to sham CPAP were crossed over to the active CPAP treatment protocol for an additional 8 weeks. Patients completed a variety of assessments, including sleep-related daytime function evaluation as measured by the Functional Outcomes Sleep Questionnaire (FOSQ, completed weekly at home), generic health-related quality-of-life questionnaire (Short Form-36 Health Survey [SF-36]), self-reported (ESS) and objective sleepiness tests, mood assessments, and ambulatory blood pressure at baseline and after 8 weeks of intervention.

The adjusted mean change in total FOSQ score, the primary outcome measure, from baseline to after 8 weeks with intervention was 0.89 for the active group and -0.06 for the placebo group (difference in mean changes, 0.95; $P = 0.006$) corresponding to an effect size of 0.41 (95% CI, 0.14–0.67). In the active CPAP group, there was also a significant association between mean daily hours of CPAP use and change in FOSQ total score ($r = 0.25$, $P = 0.008$), which did not exist in the sham CPAP group. In participants originally randomized to sham CPAP, the mean improvement in total FOSQ score from the beginning to the end of the crossover phase was 1.73 ± 2.5 ($P < 0.00001$), with an effect size of 0.69. In terms of secondary outcomes, the active CPAP group showed significant improvements in many FOSQ subscale scores (except social outcome and intimacy and sexual relationships), physical components of the SF-36, ESS score, and total mood disturbance.

Study participants had a low mean duration of daily CPAP use (4.0 ± 2.0 h in active CPAP and 3.1 ± 2.1 h in sham CPAP), and 71% of the active treatment arm participants still had ESS scores greater than 10 at the end of the intervention; however, given a similar 4-hour average in the clinical setting, Weaver and colleagues (9) concluded that their study was reflective of typical clinical outcomes for milder OSA. Overall, this study supports CPAP use in sleepy patients with mild to moderate OSA given improvements in functional status, quality of life, and symptoms with such therapy. As Peker editorialized, the results of this study add to level I evidence supporting CPAP treatment to improve quality of life from “option” to “guideline” in sleepy patients with OSA, regardless of severity (10).

Effects of CPAP Treatment in Nonsleepy Patients with OSA

Similar to sleepy patients with mild OSA, the indication for CPAP in nonsleepy patients with OSA is also debated. On one hand, prior short-term randomized control trials have shown no effect of CPAP on hypertension and clinical variables in this patient subset (11, 12); on the other hand, given the association of OSA and cardiovascular morbidity, clinicians often still recommend the long-term use of CPAP treatment. Therefore, as part of the Spanish Sleep and Breathing Network, Barbe and colleagues undertook a multicenter randomized controlled trial to evaluate the effect of CPAP treatment on hypertension and cardiovascular events in nonsleepy patients with OSA (13). Seven hundred twenty-five patients with OSA (AHI $> 20/\text{h}$) but without daytime hypersomnolence (ESS $< 10/24$) were allocated to receive CPAP or no treatment for roughly 4 years. Fifty percent of the sample was hypertensive at inclusion. In the CPAP group, 68 patients developed new hypertension and

28 cardiovascular events, resulting in an incidence density of 11.02 per 100 person-years. In the control group, 79 patients developed new hypertension and 31 cardiovascular events, resulting in an incidence density of 9.20 per 100 person-years. The incidence density ratio was 0.83 ($P = 0.20$). Secondary outcomes analyzing the effect of CPAP on the incidence of hypertension or cardiovascular events across subgroups of AHI also showed no significant difference from the control group ($P = 0.48$). A *post hoc* analysis suggested that CPAP treatment may reduce incident hypertension and cardiovascular events in CPAP-adherent patients, although such findings are clearly exploratory.

Overall, the authors concluded that treatment with CPAP did not lead to a statistically significant reduction in the incidence of hypertension or cardiovascular events, although statistical power was not robust. In the future, a larger and longer study will likely be necessary to define CPAP benefits fully.

Effects of CPAP Treatment in Normotensive Patients with OSA

Prior studies have shown an independent association between OSA and cardiovascular morbidity; however, the association with new-onset hypertension in normotensive patients with low cardiovascular risk has not been well studied. Marin and colleagues performed a prospective cohort study of 1,889 patients to determine if OSA was an independent risk factor for incident hypertension and if CPAP therapy reduced this risk (14). Incident hypertension was documented at annual follow-up visits in 705 patients (37.3%). Compared with control subjects, the adjusted HRs for incident hypertension were greater among patients with OSA ineligible for CPAP (1.33; 95% CI, 1.01–1.75), among those who declined CPAP (1.96; 95% CI, 1.44–2.66), and among those nonadherent with CPAP (1.78; 95% CI, 1.23–2.58). The HR for incident hypertension was low in patients with OSA who were treated with CPAP (0.71; 95% CI, 0.53–0.94).

When stratified by OSA severity, the unadjusted incidence of hypertension was similar within each OSA severity category among patients who did not get treatment for OSA. The incidence of new-onset hypertension was significantly lower in patients with severe OSA treated with CPAP compared with patients with untreated severe OSA (crude incidence rate, 6.83 vs. 3.21 per 100 person-years; $P < 0.001$). The increased risk observed between untreated OSA and new-onset hypertension, as well as the reduction in this risk with long-term CPAP therapy in moderate to severe OSA, provides further evidence of the pathogenesis of cardiovascular disease related to SDB.

Effects of CPAP in Elderly Patients with OSA

Martinez-Garcia and colleagues studied the impact of OSA and CPAP treatment on cardiovascular mortality in the elderly (15). This prospective observational study of 943 patients (aged > 65 yr) with suspected OSA divided patients into four groups after polysomnography or respiratory polygraphy: control group, mild to moderate OSA without CPAP, severe OSA without CPAP, and OSA with CPAP.

Their analysis found that patients with severe untreated OSA or poor CPAP adherence had a greater risk of cardiovascular death (including stroke, heart failure, and myocardial infarction) compared with control subjects (HR, 2.25; $P = 0.001$). Interestingly, this group had increased risk of all-cause mortality (HR, 1.99; $P = 0.001$) and specifically increased mortality from stroke (HR, 4.63; $P = 0.046$) and from heart failure (HR, 3.93; $P = 0.031$), but there was no association with an increased risk of death from ischemic heart disease (HR, 1.09; $P = 0.23$). Of note, no significant differences in cardiovascular mortality were noted

between elderly patients with OSA treated with CPAP, those with mild to moderate OSA without treatment, and those without OSA. Overall, CPAP treatment was associated with a reduced risk of all-cause and cardiovascular mortality to levels similar to older patients without OSA. This important study underlined the importance of randomized trials to assess the impact of treating severe OSA in the elderly.

Effects of Weight Loss Treatment in Obese Patients with OSA

In addition to CPAP and oral appliances, providers also recommend weight loss to patients in whom obesity is likely contributing to OSA. To explore weight loss further, Dixon and colleagues organized a randomized controlled trial of 60 obese patients to determine whether surgical weight loss was more effective than conventional weight loss for OSA (16). Obese patients (BMI, 35–55 kg/m²) with recently diagnosed OSA on CPAP therapy were randomized to a conventional weight loss program or a laparoscopic adjustable gastric banding.

Patients lost a mean of 5.1 kg in the conventional weight loss program compared with 27.8 kg in the bariatric surgery group. The AHI decreased by 14/h (to 43.2/h) in the conventional weight loss group and by 25.5/h in the bariatric surgery group (to 39.5/h), for a between-group difference of 11.5/h, which was not statistically significant ($P = 0.18$). The surgery group had a greater improvement in the SF-36 physical component score. Both groups experienced a reduction in daytime sleepiness and depression and an improvement in the 6-minute walk test, although there were no significant between-group differences. The authors concluded that greater weight loss in the surgical group did not translate into a significant difference in AHI or better therapeutic effect for OSA. The individual effects of weight loss were variable and likely related to modest weight loss beyond which there was less benefit. Based on these findings, providers should be cautious before stopping CPAP in patients with OSA losing weight.

PEDIATRIC SLEEP MEDICINE

Genetics of Pediatric OSA

Mechanisms of end-organ damage in children with OSA are poorly understood but may be due in part to oxidative stress and inflammation resulting in epigenetic changes. The study by Kim and colleagues is the first to assess DNA methylation in the phenotypic variance of OSA in children (17). The first phase of this study identified specific highly methylated inflammatory genes. Twelve children with OSA, matched for age, sex, ethnicity, AHI, and BMI, were separated into two groups based on high (> 1.5 mg/dl) versus low levels of high-sensitivity C-reactive protein (hsCRP). DNA methylation levels of 24 inflammatory-related genes were assessed. A subsequent case-control study of 47 children with OSA and 31 control subjects aimed to confirm the differences identified in the first phase.

The investigators made two important discoveries. First, hypermethylation of forkhead box P3 (Foxp3) occurred in the high- but not low-titer hsCRP group, a finding validated in the subsequent case-control study. Second, methylation of Foxp3 was linearly associated with severity of OSA even after adjusting for confounding factors, and it was correlated with other markers of inflammation (myeloid-related protein 8/14, hsCRP, apolipoprotein B). Although mechanisms were not specifically explored, the authors suggest epigenetically mediated down-regulation of specific T cell lymphocyte subpopulations is responsible for inflammatory phenotypes in OSA.

In her accompanying editorial, Yang credited Kim for the pioneering work (18) and identified several additional areas requiring further investigation, including the effects of epigenetics in

T-lymphocyte subpopulation imbalance, mechanisms of inflammatory phenotypes with DNA methylation, and the role of non-coding RNA and histone modifications in the development of disease phenotypes. Ultimately, epigenetics may not only provide further insight into the pathogenesis of SDB but also offer diagnostic and therapeutic insights in disease management. Given that epigenetic changes can be inherited, these discoveries may also have implications for health of the offspring.

Consequences of Pediatric OSA

Childhood obesity is a major factor in adverse health outcomes of hypertension, diabetes, and future adult cardiovascular disease. SDB has also been linked to neurobehavioral disruption, particularly deficits in attention, learning, memory, and brain plasticity. Therefore, Spruyt and colleagues sought to demonstrate and quantify the bidirectional mediator effects of body weight, SDB, and cognitive function (19).

This prospective study recruited 351 healthy children, 6 to 10 years old, without previously identified developmental delays or learning difficulties. Overnight polysomnography and neurocognitive testing were performed. They found (1) SDB amplified the adverse cognitive and weight outcomes by 55 and 46%, respectively; (2) weight amplified SDB and cognitive outcomes 39 to 40%, respectively; and (3) poor cognitive ability increased adverse weight and SDB outcomes by 2.9- and 7.9-fold, respectively. Good cognitive performance appeared to be protective against the development of SDB and high BMI. Based on these findings in healthy children, the authors emphasized the multidirectional relationships of BMI, SDB, and cognitive function and the potential impact of public health efforts targeting childhood obesity.

Treatment of Pediatric OSA

Although the primary treatment of childhood OSA is adenotonsillectomy, there is an increasing role of positive airway pressure (PAP) therapy in obese children and in those with craniofacial abnormalities. However, the effects of PAP therapy on neurocognitive function have been insufficiently evaluated.

Marcus and colleagues reported findings from a prospective clinical trial comparing CPAP to bilevel pressure release therapy in 52 PAP-naïve children aged 2 to 16 years (20). Neurobehavioral assessments of sleepiness, symptoms of attention deficit/hyperactivity disorder, behavior, and quality of life were performed before and 3 months after PAP use. PAP titration studies demonstrated improvements in AHI, arousal index, and oxygen saturation. Despite suboptimal PAP use (3 h/night), significant improvements were seen across all neurobehavioral tests, even in very young children and in those with developmental delays.

An accompanying editorial by Horne emphasized the importance of PAP use in children (21). The findings of Marcus provide evidence of improved clinical outcomes and are important in helping clinicians counsel parents on the benefits of PAP adherence. Further work should be done to elucidate the hours of PAP therapy needed across ages in which total sleep requirements may differ and to determine best strategies for early CPAP compliance in children.

HIGH-ALTITUDE PHYSIOLOGY

Ventilatory responses to hypoxia and the effects of hypoxemia are important in acute mountain sickness. Richalet and colleagues sought to explore the association between an individual's physiologic parameters and risk of high-altitude illness and further assess these parameters' discrimination ability in a risk prediction model (22). Over 17 years, 1,326 participants were included in

this study based on their plan for an upcoming journey of at least 3 days above 4,000 m of altitude with overnight sleeping above 3,500 m. Subjects underwent routine hypoxic exercise testing before their journey and then sent back questionnaires after their journey detailing neurologic and respiratory symptoms.

Among these respondents, severe acute mountain sickness occurred in 314 (23.7%), high-altitude pulmonary edema in 22 (1.7%), and high-altitude cerebral edema in 13 (0.98%). Among participants who did not use acetazolamide ($n = 917$), a previous history of severe high altitude illness (SHAI) (OR, 12.82), ascent greater than 400 m/d (OR, 5.89), history of migraine (OR, 2.28), ventilatory response to hypoxia at exercise less than 0.78 L/min/kg (OR, 6.68; $P = 0.001$), and desaturation at exercise greater than or equal to 22% (OR, 2.50; $P = 0.001$) were each independently associated with SHAI. The last two parameters significantly improved the discrimination ability of the risk prediction model (C-statistic rose from 0.81 to 0.88; $P = 0.001$). Overall, this study suggests an important association between physiologic parameters, such as marked desaturation and low ventilatory response to hypoxia with exercise, and a higher risk of developing SHAI. Clinicians may be able to determine patients' risk of SHAI before high-altitude journeys.

CONCLUSIONS

In a field where diagnostic testing and treatment have preceded a thorough understanding of the harm of disease and benefits of therapy, the contributions to the literature this past year are notably important. Sleep research is also helping to define important and underappreciated systemic interactions, such as how maternal experiences may relate to disease in the offspring through epigenetics (17), how respiratory abnormalities may yield diabetic neuropathy (7), and how sleep deprivation may contribute to community-acquired pneumonia (23). A greater understanding of disease mechanisms will improve our ability to identify those at highest risk of adverse health outcomes and potentially offer additional therapeutic targets.

Author disclosures are available with the text of this article at www.atsjournals.org.

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