Update in Sleep Medicine 2013

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The clinical, epidemiological, and basic science addressing sleep apnea management, risk factors, and health outcomes has made continued advances. In this review, articles relevant to sleep apnea published in 2013 in the *Journal* and selected articles published elsewhere that highlight key advances are summarized.

Sleep Apnea and Cancer

Despite increasing evidence suggesting obstructive sleep apnea (OSA) as a risk factor for cardiovascular disease (CVD), less is known regarding the relationship between OSA and cancer. It has been shown in a mouse model of melanoma that intermittent hypoxia mimicking OSA enhances tumor growth and increases lung metastasis (1). In addition, the Wisconsin cohort researchers have reported increased cancer mortality in patients with severe OSA (2). However, data regarding cancer incidence in association with OSA have been lacking. In a retrospective analysis of data from 4,910 consecutive patients investigated for suspected OSA between 2003 and 2007, Campos-Rodriguez and coworkers evaluated cancer incidence during a median follow-up of 4.5 years (3). The researchers used the apnea hypopnea index (AHI) and percent time with oxygen saturation less than 90% as markers of OSA severity. By the end of the study period, 261 patients (5.3%) had received a diagnosis of cancer. Statistical analyses revealed increasing hazard ratios (HRs) for cancer incidence with increasing oxygen saturation less than 90% categories after adjusting for multiple confounders. However, AHI was not associated with cancer incidence in the adjusted analyses, except for patients younger than 65 years. The authors concluded that increased overnight hypoxia is associated with increased cancer incidence. Despite the retrospective study design and varying sleep assessments, the study provides important data implicating OSA as a risk factor for incident cancer. Prospective studies are needed to confirm this association and to investigate whether a specific cancer location or cancer subtype is more likely related to OSA.

Sleep Apnea Pathophysiology

Sleep apnea represents a heterogeneous group of disorders with a multifactorial etiology. Across individuals there are variable contributions attributable to anatomic and physiological risk factors and variable degrees of positional and state (rapid eye movement [REM] vs. other) dependencies. In clinical practice, however, few tools are available to distinguish among different sleep apnea phenotypes. Given the emergence of new mechanical, behavioral, and pharmacological interventions, there is a need to improve the "personalization" of sleep apnea therapy through more precise characterization of each patient's pathophysiology.

The Multifactorial Basis of OSA

Eckert and colleagues have proposed a conceptual framework for characterizing anatomic and physiological risk factors that uses a three-point scale (termed "PALM") that incorporates information on four pathophysiological traits: (P) passive critical closing pressure of the upper airway, a measure of anatomic vulnerability; (A) arousal threshold; (L) loop gain; and (M) muscle responsiveness (4). These attributes were measured in a study of 75 individuals (58 with OSA treated with continuous positive airway pressure [CPAP]) who underwent several nights of monitoring with measurement of breathing, muscle, and arousal responses to variations in upper airway collapse induced by dropping CPAP support. The results demonstrated a large variation in these risk factors across subjects, indicating pathophysiological heterogeneity. A high closing pressure was strongly associated with more severe OSA. However, at lower closing pressures, there was a wide variation in AHI. Among the patients with OSA, approximately 20% had a noncollapsible airway by closing pressure, 36% had poor genioglossus responsiveness, and 37% had a low arousal threshold. The study estimated that 28% of patients with OSA have multiple nonanatomic risk factors and that these factors contribute to the pathogenesis of OSA in 56% of patients. The authors suggested the potential to use the PALM framework for future evaluations of targeted therapies that address specific risk factors, such as use of sedatives for treatment of high arousal responses or oxygen or carbon dioxide for treatment of individuals with high loop gain. The challenge will be to develop well-tolerated and noninvasive tests that can be

(Received in original form March 17, 2014; accepted in final form April 30, 2014)

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Am J Respir Crit Care Med Vol 189, Iss 11, pp 1345–1350, Jun 1, 2014

DOI: 10.1164/rccm.201403-0497UP
Internet address: www.atsjournals.org

applied in clinical settings and to further test the short- and long-term predictive information of individual and interactive risk factors. Furthermore, as Parthasarathy discussed in an editorial, there is a need to further identify the causal determinants of the physiological components that comprise the PALM framework, which likely will benefit from further research that incorporates imaging technologies, genetic and epigenetic studies, and computational biology approaches (5).

The Mechanisms for Sleep Apnea in REM Sleep

REM-predominant sleep apnea has distinct clinical correlates. In REM sleep, a state of generalized skeletal hypotonia and high sympathetic nervous system tone, apneas and hypopneas are often increased in frequency and severity. Grace and colleagues challenged an existing hypothesis that genioglossal inhibition occurs in REM sleep due to motor inhibition by the neurotransmitters glycine and γ-aminobutyric acid (6). In experimental studies in rats across sleep–wake states, these authors examined the mechanisms that account for profound motor inhibition typical of REM sleep. Their study identified an inhibitory signaling pathway that involves muscarinic acetylcholine receptors and G-coupled inwardly rectifying potassium channels that suppresses genioglossus activity specifically in REM sleep. Furthermore, they showed that genioglossal activity can be increased in REM by blocking this inhibitory pathway. In an accompanying editorial, Veasey and White discussed the implications of this discovery on pharmacotherapy for OSA (7). While acknowledging the importance of identifying these new targets for treating REM-related hypotonia and sleep apnea in REM, Veasey and White highlighted the need to use animal models of OSA to further test whether inactivation of muscarinic receptors in the hypoglossal nerve will be sufficient to prevent REM-related airway collapse occurring from state- and position-dependent influences. They also noted the need to consider pharmacological therapies that address upper airway patency in REM and non-REM sleep, which likely will involve manipulation of multiple neuroreceptors.

Abnormal Central Respiratory Processing in Pediatric Sleep Apnea

To characterize respiratory afferent cortical processing in children with sleep apnea, Huang and colleagues investigated respiratory and auditory afferent processing in children with OSA before and after treatment (8). Respiratory-related evoked potentials (RREP) were studied to assess central nervous system processing of upper airway stimuli, and auditory-evoked potentials were assessed to investigate cortical responses to nonrespiratory stimuli. Measurements were made in stage N3 sleep in 24 children with a wide range of OSA severity and in 24 age-matched, nonsnoring control subjects. RREP amplitudes were lower in the children with OSA compared with the control group, indicating a blunting of responses to upper airway pressor receptor stimulation. In contrast, auditory-evoked potentials responses were not different between the groups. In a subgroup of children with OSA studied 4 months after surgery, no improvement in RREP was observed despite AHI improvement. The authors suggested that a mechanism for childhood OSA includes deficits in central nervous system processing of afferent upper airway stimuli. Similar deficits have been described in adult patients with OSA and thus point to common underlying etiologies for pediatric and adult OSA.

Respiratory Neuroplasticity and Potential Protective Effects

Animal models suggest that individual vulnerability to sleep apnea may be influenced by respiratory neuroplasticity, such as modeled by long-term facilitation (LTF) to acute intermittent hypoxemia (AIH) and chronic intermittent hypoxemia (CIH). LTF is the progressive increase in respiratory motor output observed after exposure to intermittent hypoxemia. The potential use of AIH to restore respiratory motor function has been reported in patients with cervical spine injuries (9). Because LTF may stabilize breathing, a further understanding of the mechanisms for LTF may identify novel therapeutics. The potential to modulate LTF in a rat model of amyotrophic lateral sclerosis was reported by Nichols and colleagues (10). This study demonstrated that two strategies can be used to improve respiratory neural output: (*1*) exposure to AIH to induce phrenic motor plasticity, and (*2*) neural fetal progenitor cell transplants to improve phrenic motor neuron survival and function. These experiments, although most directly applicable to amyotrophic lateral sclerosis, have implications for understanding how acute or chronic exposure to intermittent hypoxemia, and respiratory plasticity in general, may modulate the clinical expression of disease severity in patients with sleep apnea.

Sleep Apnea and CVD

A burgeoning interest in sleep apnea derives from the increasing appreciation of its role in the pathogenesis of atherosclerosis and hypertension and contribution to CVD. New translational, clinical, and epidemiological data are summarized below.

Pathogenic Mechanisms of Atherosclerosis Induced by Chronic Intermittent Hypoxia

Despite accumulating research evidence linking OSA to atherosclerotic disease, the mechanisms by which CIH induces atherosclerosis are not fully understood. Mice that have been exposed to CIH exhibit impaired lipoprotein clearance and decreased activity of lipoprotein lipase (LPL) in adipose tissue; LPL inhibition has been associated with increased adipose levels of a potent LPL inhibitor, angiopoietin-like 4 (Angptl4) (11). To determine whether CIH induces dyslipidemia and atherosclerosis by increasing adipose Angptl4 via hypoxia-inducible factor-1, Drager and colleagues performed experiments in $ApoE^{-/-}$ mice (*1*) exposed to CIH, treated with Angptl4-neutralizing antibody; (*2*) exposed to CIH, treated with saline; (*3*) exposed to intermittent air, treated with Angptl4-neutralizing antibody; and (*4*) exposed to intermittent air, treated with vehicle (12). They also measured Angptl4 mRNA levels in adipose tissue from patients with OSA. Novel findings were that (*1*) depletion of adipose Angptl4 abolishes CIH-induced dyslipidemia and atherosclerosis in mice, (*2*) adipose Angptl4 is regulated by hypoxia-inducible factor-1, and (*3*) Angptl4 mRNA levels in subcutaneous adipose tissue correlate with the severity of nocturnal hypoxemia in patients with OSA. The researchers suggested that up-regulation of adipose Angptl4 may play a role in the progression of atherosclerosis in OSA.

Impact of CPAP on Endothelial Function in Minimally Symptomatic OSA

Given conflicting data regarding CPAP efficacy in nonsleepy patients, Kohler and

colleagues sought to determine whether CPAP improves vascular function in minimally symptomatic OSA (13). Arterial stiffness and endothelial function (flow-mediated dilation [FMD]) were studied in 208 and 64 participants, respectively, in a randomized controlled trial (RCT) of CPAP versus standard care in patients with minimally symptomatic OSA. After 6 months, there was no evidence of an impact of CPAP on arterial stiffness, whereas FMD was significantly improved (+2.1%; 95% confidence interval [CI], 1.0–3.2) in the CPAP group. A larger improvement in FMD was observed in association with longer CPAP use. Given the improvement in endothelial function on CPAP, the researchers concluded that OSA, regardless of daytime hypersomnolence, may contribute to CVD.

Impact of CPAP on Resistant Hypertension

Although more than 70% of patients with resistant hypertension have OSA, there has been little evidence about the effect of CPAP on blood pressure (BP) in this setting. Martinez-Garcia and collaborators randomized 194 patients with resistant hypertension and OSA to 12 weeks of CPAP or no CPAP (14). The primary blinded end point was the change in 24-hour mean BP after 12 weeks. The intention-to-treat analysis showed a greater decrease in 24-hour mean BP in the CPAP group (3.1 mm Hg; 95% CI, 0.6–5.6) and a greater decline in 24-hour diastolic BP but not in 24-hour systolic BP. Moreover, the percentage of patients displaying a nocturnal BP dipper pattern at the 12-week follow-up was greater in the CPAP group than in the control group (35.9 vs. 21.6%). There was a positive correlation between hours of CPAP use and the decrease in several BP measurements. The investigators concluded that 12 weeks of CPAP treatment improved 24-hour mean and diastolic BP and improved the nocturnal BP pattern, although further research is necessary to assess longer-term outcomes.

OSA in Coronary Artery Disease and Impact of CPAP

Baseline data of an RCT among 662 revascularized patients with coronary artery disease (CAD) revealed that 63.7% had an AHI $\geq$ 15, but the majority did not report daytime hypersomnolence (15). Another study followed 192 patients with acute myocardial infarction (MI) and 96 matched control subjects without CAD (16) for 6 years. Patients with OSA (n = 126) were offered CPAP treatment. After adjustment for confounders, treated patients with OSA (n = 71) had a lower risk of recurrent MI (adjusted HR, 0.16; 95% CI, 0.03–0.76) and revascularization (adjusted HR, 0.15; 95% CI, 0.03–0.79) than untreated patients with OSA, and similar to patients without OSA.

OSA and Subclinical Myocardial Injury

Despite the increasing knowledge regarding independent associations between OSA and CAD, the underlying mechanisms are not well understood. Querejeta Roca and colleagues addressed the relationship between OSA severity, cardiac biomarkers, and prospective cardiovascular outcomes in 1,655 individuals without CVD at baseline (17). Cardiac biomarkers were high sensitivity troponin T (hs-TnT), a circulating biomarker reflecting myocardial injury, and N-terminal pro B type natriuretic peptide (NT-proBNP), reflecting ventricular wall stress. After adjusting for potential confounders, increasing AHI was associated with higher hs-TNT levels but not with NT-proBNP levels. Over a median of 12.4-year follow-up, hs-TnT was related to risk of death or incident heart failure in all OSA categories. The authors concluded that OSA severity was associated with higher levels of hs-TnT in middle-aged to older individuals, suggesting that subclinical myocardial injury caused by OSA may play a role in the subsequent risk of cardiac disease. In contrast, a study of 136 patients presenting with an acute nonfatal MI demonstrated that lower hs-TNT levels occurred in patients with more severe OSA, suggesting that these findings may be related to a cardioprotective role of ischemic preconditioning due to OSA (18). As highlighted in an editorial by Olafiranye and colleagues, it is unclear at what point OSA leads to myocardial damage and at what point the risks associated with OSA outweigh the benefits of a possible ischemic preconditioning (19).

Endothelial Progenitor Cells in Acute Myocardial Infarction and Sleep-disordered Breathing

Circulating endothelial progenitor cells (EPCs) provide an endogenous repair mechanism to counteract endothelial cell injury and enhance tissue repair after ischemic vascular injury (20). EPCs are mobilized endogenously in response to tissue ischemia and hypoxia, and have been suggested to play a protective role in acute myocardial infarction (AMI) (21). It has been unclear whether concomitant sleep-disordered breathing (SDB) can modulate EPC mobilization and function in the setting of AMI. Given the hypothesis that chronic intermittent hypoxia (IH) may induce compensatory responses in the context of AMI, Berger and colleagues compared EPC numbers and functions in patients with AMI with SDB (AMI-SDB) and without SDB (AMI-only) (22). These researchers found that circulating EPCs, angiogenic T cells, and vascular endothelial growth factor in monocytes were significantly higher in patients with AMI-SDB, whereas plasma stromal cell–derived factor-1a levels were significantly lower. Also, endothelial cell–colony forming unit numbers and their paracrine effects on endothelial tube formation were significantly higher in AMI-SDB compared with AMI-only patients. Similarly, in cell cultures from healthy subjects, endothelial cell–colony forming unit numbers and their paracrine effects on endothelial tube formation were increased after exposure to IH *in vitro* compared with normoxia. The authors concluded that recurrent episodes of hypoxia/reoxygenation in patients with AMI with mild to moderate SDB can activate adaptive mechanisms associated with increased recruitment, proliferation, and angiogenic EPC properties, which may improve endothelial function and provide cardioprotection in the context of AMI. As commented in the accompanying editorial by Kheirandish-Gozal and Farré, additional information on the time course and vasculogenic properties of EPCs in SDB may further clarify the role of EPCs in modulating angiogenesis and influencing endothelial repair processes (23).

Effects of Sleep Apnea Subtypes on Stroke Volume in Patients with Heart Failure

Both OSA and central sleep apnea (CSA) with Cheyne-Stokes respiration (CSR) in patients with heart failure have been linked to increased mortality (24). Given that obstructive events generate negative intrathoracic pressure that reduces left ventricular preload and increases afterload whereas central events do not, Yumino and collaborators hypothesized that OSA

should lead to greater hemodynamic compromise than CSA (25). To determine the effects of sleep apnea subtypes on stroke volume in patients with systolic heart failure, the researchers estimated stroke volume from before to the end of obstructive and central events using digital photoplethysmography during polysomnography. Stroke volume decreased by 6.8% during obstructive events but increased by 2.6% during central events. For obstructive events, reduction in stroke volume was associated with left ventricular ejection fraction, duration of respiratory events, and degree of oxygen desaturation. The authors concluded that obstructive and central events have opposite hemodynamic effects in heart failure patients. An accompanying editorial by Cao and colleagues (26) noted several limitations of the study, namely the small sample, the predominance of obstructive events, and the fact that central apneas were not defined clearly. Because the study group had both OSA and CSA, changes in stroke volume with CSA-CSR might be compensatory. Future measurement of stroke volume in heart failure patients with pure CSA-CSR may provide further insight.

Sudden Death

In 2005, Gami and coworkers reported that sudden cardiac death (SCD) is 2.6-fold more likely to occur during sleep in individuals with OSA, which is the time when SCD is least likely in individuals without OSA and in the general population (27). The same research group recently addressed if OSA independently increases the risk of SCD in a longitudinal study of 10,701 consecutive adults (28). During an average follow-up of 5.3 years, 142 patients had resuscitated or fatal SCD (annual rate, 0.27%). In multivariate analysis, SCD was associated with AHI $>$ 20 (HR, 1.60), mean nocturnal oxygen saturation $<$ 93% (HR, 2.93), and oxygen nadir saturation $<$ 78% (HR, 2.60; all $P < 0.001$). The authors concluded that OSA predicted incident SCD. These findings should encourage further research of the mechanisms of SCD in individuals with OSA as well as clinical trials of OSA therapy in populations at risk for SCD.

Treatment Advances

First-line therapies for adult and pediatric OSA are CPAP and adenotonsillectomy, respectively. However, the evidence needed to tailor each treatment for groups most likely to benefit has been limited, as are data identifying the role of alternative treatments. In 2013, there were several important publications that began to narrow these research gaps.

The Role of Adenotonsillectomy for Treatment of Childhood OSA

Although adenotonsillectomy is the first-line therapy for childhood OSA, there has never been a randomized controlled study addressing its role in OSA management. In 2013, the results of the multicenter Childhood Adenotonsillectomy Trial were reported (29). This trial randomized 464 children, ages 5 to 9 years with OSA without severe oxygen desaturation or morbid obesity, to a 6-month period of watchful waiting and supportive care (WWSC) or to early adenotonsillectomy (eAT). The study's primary outcome was an objective measure of attention and executive functioning. Numerous secondary outcomes were evaluated, including parent- and teacher-reported measures of behavior and polysomnography change. Compared with WWSC, surgery was not associated with significant improvement in attention/executive function. In contrast, moderate to large improvements were observed with eAT compared with WWSC for behavioral outcomes, sleepiness, sleep-related breathing symptoms, and quality of life measures. Normalization of the polysomnogram occurred in both groups but more so in the eAT group (79 vs. 46%). Polysomnographic indices also improved more in the eAT compared with WWSC. Subgroup analyses showed less improvement in some outcomes among obese children and African Americans. The authors concluded that early adenotonsillectomy is associated with beneficial improvements in clinically relevant outcomes. However, the lack of cognitive decline in the conservatively managed children as well as the normalization of the polysomnogram in a large proportion suggested that medical management and reassessment may be a valid option for children with minimal symptoms. The authors noted the need for additional research to further understand subgroup differences in responses and for evaluating the role of surgery in younger children who may be susceptible to untreated OSA. This trial established the feasibility of conducting a controlled trial of a surgical intervention in children.

Oral Appliances for OSA Treatment

Mandibular advancement devices (MAD) have been shown to decrease the AHI but often to a lower extent than achieved with CPAP. The literature has largely supported the use of MADs in patients with mild disease or in those who cannot tolerate CPAP. To address the role of MADs in moderate to severe OSA, Philips and colleagues conducted a crossover RCT comparing CPAP and a custom-fit MAD on a wide variety of health outcomes measured after 1 month of therapy (30). From an initial sample of 126 randomized patients with a mean AHI of 29.5 and BMI of 29.5, 108 completed each 1-month period of CPAP and MAD interventions. Polysomnographic resolution was twice as frequent with CPAP compared with MAD. However, patient-reported adherence was higher with MAD, and a higher proportion of patients preferred MAD (51%) than CPAP (21%). Improvements in blood pressure were not observed in either group. Sleepiness, driver simulation performance, and quality of life measures improved in both groups, with equivalent or greater improvements with MAD compared with CPAP. The authors suggested that their findings challenged the existing practice of reserving MAD use for patients with mild to moderate OSA, although they acknowledged the need for longer-term intervention studies. In an accompanying editorial, White (31) further discussed the challenges in translating the study findings to clinical care and raised the possibility that patients, regardless of disease severity, be offered a choice of one therapy or another and then be closely followed for response and need for alternative interventions. One challenge of this paradigm is the costs associated with custom fabrication of oral devices, some of which will be shown to be ineffective or not well tolerated.

Another RCT comparing a MAD with CPAP by Doff and colleagues (32) included patients across the entire OSA severity spectrum but followed outcomes for up to 2 years, allowing patients to "crossover" to alternative treatment if initial therapy was unsuccessful. Over time, more patients dropped out under the oral appliance arm than under CPAP (47 vs. 33%). Similar to

the shorter-term study by Philips, although polysomnographic improvement was higher in the CPAP arm, both groups experienced comparable improvements in sleepiness and quality of life. This study supported the use of MAD as a long-term alternative to CPAP. However, the discrepancies between polysomnographic and subjective improvements to each treatment and the suggestion of longer-term greater attrition in the MAD group raise the need for larger, long-term intervention studies.

Optimizing CPAP Adherence with Behavioral Interventions

Although CPAP therapy is highly efficacious in a majority of patients with OSA, its use is limited by variable adherence, with as many as 25% of patients stopping CPAP use after 1 year. Aloia and colleagues reported the results of an RCT that compared 1-year CPAP adherence in 277 patients with moderate or more severe OSA randomized to a motivational enhancement intervention, an education intervention, or standard medical care (33). Over 1 year, average nightly CPAP use decreased in all groups to 3.86, 4.34, and 3.73 hours for the motivational enhancement, education, and standard care groups, respectively, with no statistically significant difference among groups. First-week adherence patterns influenced long-term adherence and intervention responses. Early good CPAP users benefited most from the education intervention, moderate users benefited from the motivational intervention, and low users did not benefit from any intervention tested. The authors suggested that initial adherence patterns may guide the use of education and behavioral interventions to those patients most likely to benefit.

Conclusions

There have been lags between the clinical recognition of sleep apnea and the clinical, epidemiological, basic, and translational research needed to improve the care of the millions of patients suffering from this disorder. In the last year, there have been advances in developing a more comprehensive understanding of the pathophysiology of OSA in adults and children, including identification of an interaction among anatomic and nonanatomic risk factors. Identification of candidate molecular pathways provides direction for future pharmacotherapy research. New cellular mechanisms that link OSA to atherogenesis and cardiovascular disease also have been identified, with provocative data indicating the importance of adaptive responses to hypoxemia in modulating the physiological behavior of the airway and angiogenesis in multiple tissues. Clinical and epidemiological studies provide further evidence indicating that OSA significantly contributes to cardiovascular-related morbidity and possibly to cancer incidence, and controlled trials indicate that OSA treatment with CPAP or oral appliances mitigates CVD risk factors. Differences in treatment responses have been commonly described, underscoring the need for larger studies and consideration of individual risk factor profiling in refining treatment strategies in sleep apnea phenotypes. ■

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

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