Update in Sleep-disordered Breathing 2016

Najib T. Ayas^{1,2}, Luciano F. Drager^{3,4}, Mary J. Morrell^{5,6}, and Vsevolod Y. Polotsky⁷

¹Sleep Disorders Program and ²Department of Medicine, University of British Columbia, Vancouver, British Columbia, Canada; ³Hypertension Unit, Heart Institute (InCor) and ⁴Hypertension Unit, Renal Division, University of Sao Paulo Medical School, Sao Paulo, Brazil; ⁵Sleep and Ventilation Unit, National Heart and Lung Institute, Imperial College London, London, United Kingdom; ⁶National Institute for Health Research Respiratory Disease Biomedical Research Unit at the Royal Brompton and Harefield National Health Service Foundation Trust and Imperial College London, London, United Kingdom; and ⁷Division of Pulmonary and Critical Care Medicine, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland

In this review, we summarize the key articles relevant to sleep-disordered breathing that have been published in the *Journal* and selected articles published elsewhere over the last year. Because of space constraints, we have not included studies related to obesity hypoventilation.

Control of Breathing

The hypoxic ventilatory response (HVR) is a fundamental physiological response to hypoxia involving an acute increase in minute ventilation. This is mediated by peripheral chemoreceptors in the carotid bodies, followed by short-term potentiation mediated by integrated input from the carotid body and catecholaminergic respiratory central pattern generator neurons of the pons and ventral medulla, and finally short-term depression (a roll-off phenomenon) (1). Both abnormally depressed and augmented HVR result in sleep-disordered breathing.

Using a mouse model, Mahmoud and colleagues (2) described a novel mechanism of genetic control of the HVR via 5' adenosine monophosphate-activated protein kinase (AMPK), a critical regulator of energy supply in the body (3). On activation, AMPK turns off anabolic pathways and turns on catabolic pathways compensating for deficits in ATP supply. Mahmoud and colleagues have shown that conditional knockout of *AMPK- α 1* and

AMPK- α 1 subunits in catecholamine-producing cells suppresses all components of the HVR, resulting in hypoventilation in hypoxic conditions and central apneas (2). The severity of hypoventilation was proportional to the severity of hypoxic exposure. In contrast, the hypercapnic ventilatory response was not affected. The AMPK double knockout did not affect responses to hypoxia in the isolated carotid body preparation, whereas hypoxic activation of dorsal and ventral regions of brainstem was significantly attenuated according to functional magnetic resonance imaging. These data suggest that AMPK deficiency may predispose to sleep-disordered breathing, whereas AMPK up-regulation may be protective in the hypoxic environment (e.g., high altitude). Furthermore, the work of Mahmoud and colleagues (2) disavows a previous paradigm that AMPK may act on carotid body glomus cells to regulate the HVR (1), indicating that the effect occurs in central pattern-generating neurons.

Notably, AMPK has recently been shown to mediate another adaptive mechanism to high altitude. Hypoxia induces adenosine accumulation, activating erythrocyte A2B adenosine receptor up-regulating erythrocyte AMPK, which, in turn, phosphorylates and activates bisphosphoglycerate mutase, thus inducing 2,3-bisphosphoglycerate production and O₂ release from red blood cells (4).

In summary, AMPK appears to be a critical enzyme involved in adaptation to high altitude and may be implicated in the pathogenesis of sleep-disordered breathing. Human genetic studies assessing a potential role of AMPK in obstructive sleep apnea (OSA) would be of great interest.

Genetics of OSA

OSA is a heterogeneous disorder, which incorporates several distinct phenotypes (5). Phenotypic complexity and significant modifying effects of obesity, age, ethnicity, and comorbid cardiopulmonary disease argue strongly for the polygenic nature of OSA (6).

Deciphering the genotype associated with a particular phenotype may identify novel therapeutic targets. Cade and colleagues presented the largest genome-wide association study in OSA to date, in which they examined genetics of OSA in Hispanic Americans according to several different phenotypic traits, including the apnea-hypopnea index (AHI), mean SaO₂, and mean event duration (7). The AHI was significantly associated with polymorphism in the G-protein receptor *GPR83*, a protein expressed in multiple brain regions of relevance for OSA, including the hypoglossal nucleus, dorsal motor nucleus of vagus, and the nucleus of solitary tract. Average apnea and hypopnea duration,

(Received in original form January 8, 2017; accepted in final form March 20, 2017)

Author Contributions: All authors contributed to writing the manuscript and read and approved the article for submission.

Correspondence and requests for reprints should be addressed to Najib T. Ayas, M.D., M.P.H., University of British Columbia Hospital Sleep Clinic, 2211 Westbrook Mall, Vancouver, BC V6T 2B5, Canada. E-mail: nayas@providencehealth.bc.ca

Am J Respir Crit Care Med Vol 195, Iss 12, pp 1561–1566, Jun 15, 2017

Copyright © 2017 by the American Thoracic Society

Originally Published in Press as DOI: 10.1164/rccm.201701-0048UP on May 21, 2017

Internet address: www.atsjournals.org

which may reflect both hypoxic sensitivity and arousal threshold, was associated with β -arrestin 1 (*ARRB1*), which physically interacts and regulates hypoxia inducible factor 1 alpha (*HIF-1 α*) and impacts the expression of *HIF-1 α* target genes, including vascular endothelial growth factor A. *HIF-1 α* mediates hypoxic sensitivity in the carotid bodies and, therefore, the *ARRB1* polymorphism may be implicated in OSA causality. Event duration was also associated with polymorphism in several loci associated with a key transcription factor of lipid biosynthesis, sterol regulatory element binding protein (*SREBP*), including the insulin signaling gene insulin-induced gene 2, which blocks *SREBP-1*, and a positive *SREBP-1* regulator, phospholipase C, β 1 (7). *SREBP-1* is inducible by intermittent hypoxia and was found to be implicated in intermittent hypoxia-induced dyslipidemia and fatty liver (8).

The same group of authors used linkage analysis in the Cleveland Family Study to identify a strong association between polymorphism in the angiopoietin-2 gene (*ANGPT2*), an endothelial factor modulating vascular and inflammatory responses, and mean nocturnal SaO_2 (9). Future large genetic studies are needed to replicate these findings (6). In addition, translational experiments in animal models based on genome-wide association study results will be important to understand disease pathogenesis.

Impact of Mild OSA

Mild OSA is a highly prevalent disease, affecting more than 20% of the population (10). The Official Research Statement of the American Thoracic Society targeted a formidable task to summarize the evidence regarding adverse neurocognitive and cardiovascular clinical outcomes of mild OSA (11). Mild OSA was defined according to the Chicago criteria (12) as AHI or respiratory disturbance index or oxygen desaturation index ranging from 5/h to less than 15/h, regardless of the definition of a hypopnea.

Mild OSA is associated with a 0.5-point increase in mean Epworth Scale of Sleepiness score, whereas other data on cognitive impairment, risk of motor vehicle accident, and quality of life was inconsistent. Continuous positive airway pressure (CPAP) treatment modestly improved

subjective sleepiness and quality of life, but there was no effect on objective sleepiness. Population-based longitudinal studies showed that mild OSA is not associated with increased cardiovascular or all-cause mortality. Currently, there is no clear evidence that treatment of mild OSA reduces mortality rate (11).

CPAP may thus be indicated in sleepy patients with mild OSA, but asymptomatic patients with mild disease may not be at risk of long-term complications and thus may not benefit from CPAP or another specific therapy. Studies of more precise OSA thresholds that do not require therapy in the absence of symptoms are needed.

OSA in Women

In women, sleep apnea is associated with fatigue, depression, anxiety, and a poorer perception of their health status. There are surprisingly few studies focusing on the impact of treatment of OSA in women. Thus, the recent study by Campos-Rodriguez and colleagues is a welcome addition (13). These investigators completed a randomized controlled trial of 307 women with moderate to severe OSA. Three months of CPAP improved quality of life, including anxiety and depressive symptoms, mood, and daytime sleepiness, highlighting the importance of detecting and treating women with OSA.

Pamidi and colleagues assessed the potential impact of sleep apnea in pregnant women (14). Specifically, in their study of 234 pregnant women, sleep apnea in the third trimester (AHI threshold of 10/h) was significantly associated with a small-for-gestational-age infant (odds ratio, 2.65). The potential long-term impacts on these children and whether therapy of sleep apnea improves fetal outcomes are areas that require further study.

Sleep-disordered Breathing in Heart Failure

Recent data from May and colleagues suggest that the cardiovascular risk of sleep-disordered breathing is greater in older people (15). Using data from a multicentre, community-based cohort of 2,911 older (≥ 65 yr) men monitored with polysomnography, they found that central sleep apnea (CSA) and CSA with Cheyne-

Stokes respiration were associated with an increased risk of atrial fibrillation (AF) in 843 men followed up over a mean duration of 6 years. The incidence of AF over the follow-up period was 12% (99 cases). Surprisingly, OSA and hypoxia did not predict incident AF.

In the same cohort of elderly men, the presence of CSA and Cheyne-Stokes respiration were also associated with incident heart failure (16). OSA, however, was not. Whether CSA is causative of heart failure or represents an early symptom of heart failure is open to speculation (17).

In terms of treatment of CSA in heart failure, the SERVE-HF (Adaptive Servo Ventilation [ASV] in Patients with Heart Failure) landmark trial was published late in 2015 (18). This was a multicenter study that enrolled 1,325 patients with a left ventricular ejection fraction of less than or equal to 45% and New York Heart Association class III or IV heart failure or New York Heart Association class II heart failure with at least one heart failure-related hospitalization within 24 months before randomization. Patients were randomized to usual care plus ASV or usual care alone. The primary end point was the composite of death from any cause, lifesaving cardiovascular intervention, or unplanned hospitalization for worsening heart failure. The intention-to-treat analysis showed no difference in the composite end point; however, there was an unexpected but significant increase in all-cause and cardiovascular death in the ASV group at a mean follow-up of 31 months.

Before decreasing "rest in peace" to ASV (19), it is important to consider the following points. In the SERVE-HF trial, substantial nonadherence to the study protocol was seen: 29% of patients either discontinued or never used ASV, whereas 16% of patients randomly assigned to control crossed over to positive airway pressure (PAP). ASV compliance was low, averaging only 3.4 hours per night. A potential reason for low compliance was that the majority of treated subjects used a full face mask. The available ASV machines have distinct algorithms depending on the manufacturer, which may have different hemodynamic impacts and effects on ventilation. Therefore, new studies (such as the ADVENT [Adaptive Servo Ventilation on Survival and Frequency of Hospital Admissions in Patients with Heart Failure and Sleep Apnea] trial) are needed before

making definitive recommendations. Nevertheless, at this point, ASV should be avoided in patients with predominately CSA and systolic dysfunction with symptomatic heart failure.

Another novel treatment of CSA is transvenous phrenic nerve stimulation. In a recent randomized study of 151 patients with CSA (20), transvenous stimulation resulted in a significant reduction in AHI. We await future studies to determine if more robust clinical outcomes are improved with this technology.

OSA and Hypertension

Oxygen and reactive oxygen species sensing in the carotid bodies mediates the development of hypertension in OSA (21), but individual susceptibility to hypertension, antihypertensive drugs, and CPAP vary among patients (22). Therefore, identification of therapeutic targets for hypertension in the carotid bodies is an important area of research. The purinergic receptor P2X3 was found to be up-regulated in carotid bodies of hypertensive rats and humans; P2X3 antagonism reduced arterial pressure and basal sympathetic activity and normalized blood pressure in hypertensive rats (23). Further studies in animal models of sleep-disordered breathing and genetic studies in human OSA will show relevance of this discovery for OSA-induced hypertension.

New evidence has evaluated the effectiveness of CPAP in patients with OSA in whom an antihypertensive agent alone was insufficient to control blood pressure (24). Patients with new onset of hypertension (with and without OSA) were initially placed on 50 mg losartan for 6 weeks, with 24-hour blood pressure being assessed before and after therapy. Interestingly, losartan reduced blood pressure in patients with and without OSA, but the reductions were less in the OSA group. In the next 6 weeks, patients with OSA continued to receive losartan and were randomized to CPAP ($n = 24$) or no CPAP ($n = 23$). Additional CPAP therapy resulted in no significant changes in 24-hour BP measures but did reduce nighttime systolic blood pressure by 4.7 mm Hg. However, in a per-protocol analysis, all 24-hour blood pressure values were reduced significantly in the 13 patients with OSA who used CPAP at least 4 hours per night. There are a

few lessons we can learn from this study (25). First, traditional treatment for hypertension in patients with OSA may be more difficult than in patients without OSA. It is reasonable to speculate that the mechanisms of OSA inducing high blood pressure are not limited to the renin angiotensin system activation. The observed additive effects of CPAP when effectively used reinforce this concept. Second, consistent with the observed results in several studies, the cardiovascular benefit of OSA treatment is dependent on CPAP adherence.

CPAP and Diabetes Control

In patients with diabetes, three studies evaluated the impact of CPAP on glycemic control in patients with OSA. Martínez-Cerón and colleagues (26) performed a 6-month parallel study evaluating the effects of CPAP ($n = 26$) or no CPAP ($n = 24$) on glycated hemoglobin (HbA1c) levels in overweight/obese patients with type 2 diabetes (two successive HbA1c values greater than 6.5%) and OSA. At 6 months of follow-up, the CPAP group achieved a greater decrease in HbA1c values than control subjects (-0.4% ; 95% confidence interval [CI], $20.7\text{--}20.04\%$; $P = 0.029$). Secondary outcomes (including insulin resistance and sensitivity, and serum levels of IL-1b, IL-6, and adiponectin) also improved with CPAP.

These results are consistent with a rigorous physiologic study by Mokhlesi and colleagues (27). In this study, 22 patients with diabetes were randomized to sham or active CPAP in the laboratory for 1 week; CPAP adherence was achieved by continuous supervision (7.92 h/night). CPAP resulted in a significant reduction in 24-hour mean plasma glucose and a trend to lower insulin levels.

In the same issue of the *Journal*, Shaw and colleagues (28) reported a multicenter randomized trial evaluating the effects of CPAP versus usual care for 6 months in patients with type 2 diabetes (HbA1c between 6.5 and 8.5%) and moderate to severe OSA. Contrary to the findings of Martínez-Cerón and colleagues (26), of the 298 participants who met entry criteria, no differences between the study groups were seen in HbA1c.

How can we explain this apparent inconsistency? As noted in the

accompanying editorial (29), the baseline demographics were fairly similar between the two clinical trials. Moreover, despite distinct OSA severity inclusion criteria, mean baseline AHI was comparable. However, in the study by Martínez-Cerón and colleagues (26), almost all patients were treated with oral agents, and $\sim 42\%$ were receiving insulin. In contrast, in the Shaw and colleagues study, about half of patients were not taking any diabetes medications, and those receiving insulin were excluded (28). The mean baseline HbA1c from the study by Shaw and colleagues was lower, consistent with better glycemic control and milder baseline disease (28). In addition, in the Martínez-Cerón study (26), fixed CPAP pressure was applied during the treatment period, whereas Shaw and colleagues used PAP in auto-adjusting mode (28). Auto-PAP may not be as effective as fixed CPAP in improving cardiometabolic outcomes, but this finding requires additional investigation (30). The adherence with PAP was slightly greater in the study by Martínez-Cerón (5.2 vs. 4.9 h/night) which may also be a partial explanation of the difference in results (26). Finally, there was a modest reduction in body mass index in the control versus the CPAP group in the study by Shaw and colleagues (28), which was not appreciated in the study by Martínez-Cerón and colleagues (26).

Further studies are needed to identify metabolic phenotypes that predict CPAP response and to investigate the optimal amount and mode of CPAP that is required to improve glycemic control.

Pertinent to this discussion is the issue of modest weight gain after CPAP therapy, which is noted to be fairly common (31). In an interesting study by Tachikawa and colleagues, 63 patients had a comprehensive metabolic assessment after 3 months of CPAP (32). Basal metabolic rate dropped significantly after CPAP therapy and thus likely contributed to weight gain. However, weight gain was also associated with poor eating behavior, highlighting the importance of attention to this aspect of lifestyle modification after CPAP.

CPAP and Cardiovascular Disease Prevention

In RICCADSA (Randomized Intervention with CPAP in Coronary Artery Disease and OSA) (33), 244 nonsleepy patients with

established coronary artery disease and moderate to severe OSA were randomized to CPAP or usual care for a median follow-up of 57 months. The primary end point was the first event of repeat revascularization, myocardial infarction, stroke, or cardiovascular mortality. The authors found no differences in the incidence of the primary end point (CPAP: 18.1% vs. usual care: 22.1%; hazard ratio, 0.80; 95% CI, 0.46–1.41) in the intention-to-treat analysis.

More recently, results from the Sleep Apnea Cardiovascular Endpoints (SAVE) trial (34) have been published. SAVE was a multicenter trial comprising 2,717 patients (1,700 from China) with a history of coronary artery disease or cerebrovascular disease and untreated moderate to severe OSA. These patients were neither severely sleepy nor hypoxemic during sleep. They were randomly assigned to receive CPAP plus usual care or usual care alone. The primary outcome was a composite death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for unstable angina, heart failure, or transient ischemic attack. In a mean follow-up of 3.7 years, CPAP did not result in a lower rate of the primary end point (hazard ratio with CPAP, 1.10; 95% CI, 0.91 to 1.32). CPAP was able to significantly improve quality of life, mood, daytime sleepiness, and work productivity. In a propensity analysis of patients adherent to CPAP (average of ≥ 4 h/night), CPAP resulted in a lower risk of stroke and composite end point of cerebral events than those in the usual care group.

There are important messages to be understood from these two studies (35, 36). First, the findings may not be extrapolated to symptomatic patients. Growing evidence suggest that these patients represent a different OSA phenotype. However, ethical reasons may prevent us from clarifying this important topic in sleepy people with OSA. Second, it is conceivable that in the secondary prevention scenario, with coexisting multiple comorbidities and medications, untreated OSA may not be a strong additional risk factor. However, this argument did not find support in a recent multicenter observational cohort evaluating patients with coronary artery disease (37). Third, these trials were limited by the overall low CPAP adherence (e.g., < 4 h/night in the SAVE study); this is a crucial issue and may at least partially explain the neutral results. To illustrate, in

the SAVE study, a propensity analysis of patients adherent to CPAP (average of ≥ 4 h/night) showed that CPAP-adherent patients had a significantly lower risk of stroke and composite end point of cerebral events than those in the usual care group. Similarly, in the RICCADSA study, there was a significant cardiovascular risk reduction in those who used CPAP for greater than or equal to 4 h/night (hazard ratio, 0.29; 95% CI, 0.10–0.86).

OSA and Lung Function

Both chronic obstructive pulmonary disease and OSA are common and are associated with increased risk of all-cause mortality. Previous studies have suggested that the concomitant presence of both disorders (overlap syndrome) worsens outcomes (38). Putcha and colleagues used the community-based Sleep Heart Health Cohort to assess the potential interaction of these two disorders. (39) Specifically, the investigators studied 6,173 participants for the occurrence of all-cause mortality. Somewhat surprisingly, the impact of lung function was less in patients with sleep-disordered breathing than in patients without sleep-disordered breathing; in other words, for every reduction in FEV₁ of 200 ml, all-cause mortality increased by 11% in patients without sleep apnea but only by 6% in patients with sleep apnea. As discussed in the accompanying editorial (38), potential explanations of this effect include a survivor effect in this fairly elderly cohort, residual confounding, and a potential plateau in risk above a sleep apnea threshold. Nevertheless, future studies are needed to better understand the relationships between sleep apnea and reduced lung function.

Personalized Treatment of OSA with Non-CPAP Alternatives

CPAP is the treatment of choice for OSA. However, not all patients tolerate CPAP, and adherence to treatment is often low. Thus, there is a need to improve adherence and to develop alternative therapies. One approach is to personalize treatment depending on the precise anatomical and physiologic characteristics of the patients (40).

Oral appliances have been used effectively to treat OSA. Despite overall benefit, it is difficult to predict which patients will respond to treatment. By investigating different physiological traits, Edwards and colleagues (41) have shown that passive upper-airway collapsibility and loop gain can predict the resolution of OSA (measured using AHI) in patients treated with oral appliances ($r^2 = 0.07$; $P = 0.001$). Overall, the appliances made the upper airway less collapsible, without influencing muscle function, loop gain, or arousal threshold. Patients with OSA in whom the pharyngeal airway was less collapsible and with lower loop gain were most responsive to treatment. This finding offers a potential target for clinical management, allowing personalized treatment and potentially improving adherence (5).

OSA is caused by a state-dependent reduction in pharyngeal dilator muscle activity, which in susceptible individuals leads to upper airway closure. The administration of 200 mg of desipramine, a tricyclic antidepressant that is believed to stimulate pharyngeal muscles, in 10 healthy subjects prevented the sleep-related reduction in tonic (but not phasic) genioglossus EMG activity (42). It was also associated with a reduction in the passive critical closing pressure and maintenance of upper airway patency during the application of negative pressure. Tricyclic antidepressants such as desipramine offer the potential for pharmacological treatment of OSA; however, potential side effects (43), such as a reduced REM sleep and symptoms of dry mouth and constipation, may limit their use, and further studies in patients with OSA are needed.

Pediatric Sleep Apnea

In a large study by Hunter and colleagues (44), 1,010 children (5–7 yr old) from the community were recruited from public schools and studied with polysomnography. As AHI increased, cognitive performance decreased significantly. This correlation was found across a broad domain of cognitive function, stressing the potential importance of sleep apnea in affecting future academic goals. However, as mentioned in the accompanying editorial

(45), it may be premature to recommend widespread screening and treatment, given potential risks and unclear efficacy of therapies such as adenotonsillectomy.

Another emerging frontier is the use of biomarkers in pediatric OSA. A novel study by Khalyfa and colleagues (46) studied one potential mechanism of vascular dysfunction. One hundred twenty-eight children (5–10 yr of age) were stratified by obesity and presence of OSA. Exosomal microRNA-630 expression was reduced in children with OSA and endothelial dysfunction (defined as delayed time to

peak post-occlusal reperfusion) and normalized after treatment of OSA with adenotonsillectomy. Future studies are needed to determine whether this biomarker is a useful screening tool for vascular risk in children with sleep apnea and whether it may represent a useful target for future therapies (47).

Conclusions

Over the last year, the field of sleep-disordered breathing has continued to

advance, and much has been learned about the pathophysiology, epidemiology, and treatment of sleep apnea. Major studies have been recently published concerning the impact of CPAP therapy on cardiovascular outcomes, therapy of CSA, and the impact of OSA on health outcomes. However, more work needs to be done in this exciting field, and we look forward to the studies to be published in the upcoming years. ■

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

References

1. Gozal D. The energy crisis revisited: AMP-activated protein kinase and the mammalian hypoxic ventilatory response. *Am J Respir Crit Care Med* 2016;193:945–946.
2. Mahmoud AD, Lewis S, Juričić L, Udoh UA, Hartmann S, Jansen MA, Ogunbayo OA, Puggioni P, Holmes AP, Kumar P, et al. AMP-activated protein kinase deficiency blocks the hypoxic ventilatory response and thus precipitates hypoventilation and apnea. *Am J Respir Crit Care Med* 2016;193:1032–1043.
3. Hardie DG. AMPK—sensing energy while talking to other signaling pathways. *Cell Metab* 2014;20:939–952.
4. Liu H, Zhang Y, Wu H, D'Alessandro A, Yegutkin GG, Song A, Sun K, Li J, Cheng NY, Huang A, et al. Beneficial role of erythrocyte adenosine A2B receptor-mediated AMP-activated protein kinase activation in high-altitude hypoxia. *Circulation* 2016;134:405–421.
5. Cistulli PA, Sutherland K. Deep phenotyping in obstructive sleep apnea: a step closer to personalized therapy. *Am J Respir Crit Care Med* 2016;194:1317–1318.
6. Pham LV, Polotsky VY. Genome-wide association studies in obstructive sleep apnea: will we catch a black cat in a dark room? *Am J Respir Crit Care Med* 2016;194:789–791.
7. Cade BE, Chen H, Stilp AM, Gleason KJ, Sofer T, Ancoli-Israel S, Arens R, Bell GI, Below JE, Bjorntes AC, et al. Genetic associations with obstructive sleep apnea traits in Hispanic/Latino Americans. *Am J Respir Crit Care Med* 2016;194:886–897.
8. Li J, Nanayakkara A, Jun J, Savransky V, Polotsky VY. Effect of deficiency in SREBP cleavage-activating protein on lipid metabolism during intermittent hypoxia. *Physiol Genomics* 2007;31:273–280.
9. Wang H, Cade BE, Chen H, Gleason KJ, Saxena R, Feng T, Larkin EK, Vasan RS, Lin H, Patel SR, et al. Variants in angiopoietin-2 (ANGPT2) contribute to variation in nocturnal oxyhemoglobin saturation level. *Hum Mol Genet* [online ahead of print] 18 Oct 2016; DOI: 10.1093/hmg/ddw324.
10. Peppard PE, Young T, Barnett JH, Palta M, Hagen EW, Hla KM. Increased prevalence of sleep-disordered breathing in adults. *Am J Epidemiol* 2013;177:1006–1014.
11. Chowdhuri S, Quan SF, Almeida F, Ayappa I, Batool-Anwar S, Budhiraja R, Cruse PE, Drager LF, Griss B, Marshall N, et al.; ATS Ad Hoc Committee on Mild Obstructive Sleep Apnea. An official American Thoracic Society research statement: impact of mild obstructive sleep apnea in adults. *Am J Respir Crit Care Med* 2016;193:e37–e54.
12. American Academy of Sleep Medicine Task Force. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The report of an American Academy of Sleep Medicine Task Force. *Sleep* 1999;22:667–689.
13. Campos-Rodríguez F, Queipo-Corona C, Carmona-Bernal C, Jurado-Gamez B, Cordero-Guevara J, Reyes-Núñez N, Troncoso-Acevedo F, Abad-Fernández A, Terán-Santos J, Caballero-Rodríguez J, et al.; Spanish Sleep Network. Continuous positive airway pressure improves quality of life in women with obstructive sleep apnea: a randomized controlled trial. *Am J Respir Crit Care Med* 2016;194:1286–1294.
14. Pamidi S, Marc I, Simoneau G, Lavigne L, Olha A, Benedetti A, Sériès F, Fraser W, Audibert F, Bujold E, et al. Maternal sleep-disordered breathing and the risk of delivering small for gestational age infants: a prospective cohort study. *Thorax* 2016;71:719–725.
15. May AM, Blackwell T, Stone PH, Stone KL, Cawthon PM, Sauer WH, Varosy PD, Redline S, Mehra R; MrOS Sleep (Outcomes of Sleep Disorders in Older Men) Study Group. Central sleep-disordered breathing predicts incident atrial fibrillation in older men. *Am J Respir Crit Care Med* 2016;193:783–791.
16. Javaheri S, Blackwell T, Ancoli-Israel S, Ensrud KE, Stone KL, Redline S; Osteoporotic Fractures in Men Study Research Group. Sleep-disordered breathing and incident heart failure in older men. *Am J Respir Crit Care Med* 2016;193:561–568.
17. Naughton MT. Heart failure and sleep-disordered breathing: the chicken or the egg? *Am J Respir Crit Care Med* 2016;193:482–483.
18. Cowie MR, Woehle H, Wegscheider K, Angermann C, d'Ortho MP, Erdmann E, Levy P, Simonds AK, Somers VK, Zannad F, et al. Adaptive servo-ventilation for central sleep apnea in systolic heart failure. *N Engl J Med* 2015;373:1095–1105.
19. Bradley TD, Floras JS. Adaptive servo-ventilation and the treatment of central sleep apnea in heart failure: let's not throw the baby out with the bathwater. *Am J Respir Crit Care Med* 2016;193:357–359.
20. Costanzo MR, Ponikowski P, Javaheri S, Augostini R, Goldberg L, Holcomb R, Kao A, Khayat RN, Oldenburg O, Stellbrink C, et al.; REMEDÉ System Pivotal Trial Study Group. Transvenous neurostimulation for central sleep apnoea: a randomised controlled trial. *Lancet* 2016;388:974–982.
21. Peng YJ, Nanduri J, Khan SA, Yuan G, Wang N, Kinsman B, Vaddi DR, Kumar GK, Garcia JA, Semenza GL, et al. Hypoxia-inducible factor 2α (HIF-2α) heterozygous-null mice exhibit exaggerated carotid body sensitivity to hypoxia, breathing instability, and hypertension. *Proc Natl Acad Sci USA* 2011;108:3065–3070.
22. Sánchez-de-la-Torre M, Khalyfa A, Sánchez-de-la-Torre A, Martínez-Alonso M, Martínez-García MÁ, Barceló A, Lloberes P, Campos-Rodríguez F, Capote F, Díaz-de-Aza MJ, et al.; Spanish Sleep Network. Precision medicine in patients with resistant hypertension and obstructive sleep apnea: blood pressure response to continuous positive airway pressure treatment. *J Am Coll Cardiol* 2015;66:1023–1032.
23. Pijacka W, Moraes DJ, Ratcliffe LE, Nightingale AK, Hart EC, da Silva MP, Machado BH, McBryde FD, Abdala AP, Ford AP, et al. Purinergic receptors in the carotid body as a new drug target for controlling hypertension. *Nat Med* 2016;22:1151–1159.

24. Thunström E, Manhem K, Rosengren A, Peker Y. Blood pressure response to losartan and continuous positive airway pressure in hypertension and obstructive sleep apnea. *Am J Respir Crit Care Med* 2016;193:310–320.
25. White DP. Is continuous positive airway pressure an effective and practical antihypertensive agent? *Am J Respir Crit Care Med* 2016;193:238–239.
26. Martínez-Cerón E, Barquiel B, Bezos AM, Casitas R, Galera R, García-Benito C, Hernanz A, Alonso-Fernández A, García-Río F. Effect of continuous positive airway pressure on glycemic control in patients with obstructive sleep apnea and type 2 diabetes: a randomized clinical trial. *Am J Respir Crit Care Med* 2016;194:476–485.
27. Mokhlesi B, Grimaldi D, Beccuti G, Abraham V, Whitmore H, Delebecque F, Van Cauter E. Effect of one week of 8-hour nightly continuous positive airway pressure treatment of obstructive sleep apnea on glycemic control in type 2 diabetes: a proof-of-concept study. *Am J Respir Crit Care Med* 2016;194:516–519.
28. Shaw JE, Punjabi NM, Naughton MT, Willes L, Bergenstal RM, Cistulli PA, Fulcher GR, Richards GN, Zimmet PZ. The effect of treatment of obstructive sleep apnea on glycemic control in type 2 diabetes. *Am J Respir Crit Care Med* 2016;194:486–492.
29. Pamidi S, Tasali E. continuous positive airway pressure for improving glycemic control in type 2 diabetes: where do we stand? *Am J Respir Crit Care Med* 2016;194:397–400.
30. Pépin JL, Tamisier R, Baguet JP, Lepaulle B, Arbib F, Arnol N, Timsit JF, Lévy P. Fixed-pressure CPAP versus auto-adjusting CPAP: comparison of efficacy on blood pressure in obstructive sleep apnoea, a randomised clinical trial. *Thorax* 2016;71:726–733.
31. Drager LF, Brunoni AR, Jenner R, Lorenzi-Filho G, Benseñor IM, Lotufo PA. Effects of CPAP on body weight in patients with obstructive sleep apnoea: a meta-analysis of randomised trials. *Thorax* 2015;70:258–264.
32. Tachikawa R, Ikeda K, Minami T, Matsumoto T, Hamada S, Murase K, Tanizawa K, Inouchi M, Oga T, Akamizu T, et al. Changes in energy metabolism after continuous positive airway pressure for obstructive sleep apnea. *Am J Respir Crit Care Med* 2016;194:729–738.
33. Peker Y, Glantz H, Eulenburg C, Wegscheider K, Herlitz J, Thunström E. Effect of positive airway pressure on cardiovascular outcomes in coronary artery disease patients with nonsleepy obstructive sleep apnea: the RICCADSA randomized controlled trial. *Am J Respir Crit Care Med* 2016;194:613–620.
34. McEvoy RD, Antic NA, Heeley E, Luo Y, Ou Q, Zhang X, Mediano O, Chen R, Drager LF, Liu Z, et al.; SAVE Investigators and Coordinators. CPAP for prevention of cardiovascular events in obstructive sleep apnea. *N Engl J Med* 2016;375:919–931.
35. Parthasarathy S. The positive and negative about positive airway pressure therapy. *Am J Respir Crit Care Med* 2016;194:535–537.
36. Mokhlesi B, Ayas NT. Cardiovascular events in obstructive sleep apnea: can CPAP therapy SAVE lives? *N Engl J Med* 2016;375:994–996.
37. Lee CH, Sethi R, Li R, Ho HH, Hein T, Jim MH, Loo G, Koo CY, Gao XF, Chandra S, et al. Obstructive sleep apnea and cardiovascular events after percutaneous coronary intervention. *Circulation* 2016;133:2008–2017.
38. Sankari A, Rowley JA. The role of lung function in adverse health outcomes related to sleep-disordered breathing: new insights into the overlap syndrome. *Am J Respir Crit Care Med* 2016;194:930–931.
39. Putcha N, Crainiceanu C, Norato G, Samet J, Quan SF, Gottlieb DJ, Redline S, Punjabi NM. Influence of lung function and sleep-disordered breathing on all-cause mortality: a community-based study. *Am J Respir Crit Care Med* 2016;194:1007–1014.
40. Deacon NL, Jen R, Li Y, Malhotra A. Treatment of obstructive sleep apnea: prospects for personalized combined modality therapy. *Ann Am Thorac Soc* 2016;13:101–108.
41. Edwards BA, Andara C, Landry S, Sands SA, Joosten SA, Owens RL, White DP, Hamilton GS, Wellman A. Upper-airway collapsibility and loop gain predict the response to oral appliance therapy in patients with obstructive sleep apnea. *Am J Respir Crit Care Med* 2016;194:1413–1422.
42. Taranto-Montemurro L, Edwards BA, Sands SA, Marques M, Eckert DJ, White DP, Wellman A. Desipramine increases genioglossus activity and reduces upper airway collapsibility during non-REM sleep in healthy subjects. *Am J Respir Crit Care Med* 2016;194:878–885.
43. Brownell LG, West P, Sweatman P, Acres JC, Kryger MH. Protriptyline in obstructive sleep apnea: a double-blind trial. *N Engl J Med* 1982;307:1037–1042.
44. Hunter SJ, Gozal D, Smith DL, Philby MF, Kaylegian J, Kheirandish-Gozal L. Effect of sleep-disordered breathing severity on cognitive performance measures in a large community cohort of young school-aged children. *Am J Respir Crit Care Med* 2016;194:739–747.
45. Kirk VG, Yunker WK. Treating pediatric obstructive sleep apnea: do we have the data? *Am J Respir Crit Care Med* 2016;194:656–658.
46. Khalyfa A, Kheirandish-Gozal L, Khalyfa AA, Philby MF, Alonso-Álvarez ML, Mohammadi M, Bhattacharjee R, Terán-Santos J, Huang L, Andrade J, et al. Circulating plasma extracellular microvesicle microRNA cargo and endothelial dysfunction in children with obstructive sleep apnea. *Am J Respir Crit Care Med* 2016;194:1116–1126.
47. Katz SL, Pillar G. Obstructive sleep apnea, obesity, and endothelial dysfunction in children. *Am J Respir Crit Care Med* 2016;194:1046–1047.