Sleep apnoea

Jonathan C. Jun, Swati Chopra and Alan R. Schwartz

Affiliation: Dept of Medicine, Division of Pulmonary and Critical Care Medicine, Johns Hopkins University, School of Medicine, Baltimore, MD, USA.

Correspondence: Jonathan C. Jun, Johns Hopkins University School of Medicine, 5501 Hopkins Bayview Circle, Rm 4A.30A, Baltimore, MD 21224, USA. E-mail: jjun2@jhmi.edu

ABSTRACT   Sleep apnoea is a disorder characterised by repetitive pauses in breathing during sleep caused by airway occlusion (obstructive sleep apnoea) or altered control of breathing (central sleep apnoea). In this Clinical Year in Review, we summarise high-impact research from the past year pertaining to management, diagnosis and cardio-metabolic consequences of sleep apnoea.

@ERSpublications
In this year in review, we summarise the latest high-impact clinical research on obstructive and central sleep apnoea http://ow.ly/Xv0Kl

Introduction

Sleep apnoea is increasingly recognised for its health impacts, leading to growing interest about the management and consequences of this common disorder. To summarise the last 1–2 years of literature about sleep apnoea is no simple task, with over 4700 articles containing "sleep apnoea" (PubMed) published since the beginning of 2014. Therefore, in this review, we highlight those studies that are projected to have a tangible impact on clinical practice, or that provide novel insights into the consequences of sleep apnoea.

Management of sleep apnoea

Central sleep apnoea

A major development in the management of central sleep apnoea emerged this year, with the publication of the SERVE-HF (Adaptive Servo-Ventilation for Central Sleep Apnea in Systolic Heart Failure) study. 10 years ago, the CANPAP (Central Sleep Apnea and Heart Failure) study demonstrated that mitigating central sleep apnoea (reduction of apnoea–hypopnoea index (AHI) from ~40 to 20) in patients with systolic heart failure led to modest improvements in left ventricular ejection fraction (LVEF) and functional status, but did not improve 60-month transplant-free survival. With the development of adaptive servo-ventilation (ASV), which controls central apnoea/Cheyne–Stokes respiration in heart failure more effectively than continuous positive airway pressure (CPAP) [1] it was hoped that a more robust benefit of ASV could be detected. SERVE-HF enrolled 1325 European patients with symptomatic heart failure and LVEF <45% to control (n=659) or ASV (n=666) with a primary composite outcome of death from any cause/lifesaving cardiovascular intervention/unplanned heart failure hospitalisation; and secondary outcomes including time to death, death from cardiovascular disease, and metrics of functional status. Surprisingly, COWIE et al. [2] found that ASV increased the risk of death from any cause (34.8% versus 29.3%; p=0.01) or cardiovascular causes (29.9% versus 24.0%; p=0.006) with a trend towards worse outcome in the composite primary outcome. Mortality was increased despite a marked reduction in the AHI from ~31 to 6 events·h^{-1}. Subgroup analysis showed that those with lower LVEF and a higher proportion of Cheyne–Stokes breathing were particularly affected. Responding to these disappointing results, ResMed released an urgent Field Safety Notice on May 13, 2015 stating that ASV therapy should be considered contraindicated in symptomatic systolic heart failure patients (www.aasmnet.org/articles.aspx?id=5562). It remains unclear what led to deaths in the ASV group, but it has been proposed that ASV-mediated reductions in cardiac preload could play a role.

Moreover, Cheyne–Stokes breathing may confer beneficial effects in advanced heart failure, as summarised in a prescient editorial by Naughton [3] in 2012.

Abraham *et al.* [4] at Ohio State University (Columbus, OH, USA) treated central sleep apnoea with a different approach. A unilateral transvenous phrenic nerve stimulator (Remedē System; Respicardia Inc., Minnetonka, MN, USA) was programmed to deliver diaphragmatic impulses during sensed central apnoeas or hypopnoeas. The device was implanted into 57 patients with central sleep apnoea (AHI >20 events·h^{-1} and >50% central events) who were followed for 6 months to assess resolution of sleep disordered breathing. Significant improvements in AHI (∼50 to 27 events·h^{-1}) were observed, as well as improvements in sleep architecture, sleep efficiency and daytime sleepiness. Long-term cardiovascular outcomes have yet to be studied using this device.

Obstructive sleep apnoea

Electrical stimulation has also been applied to the hypoglossal nerve to ameliorate upper airway obstruction, as recently demonstrated by the STAR (Stimulator Therapy for Apnoea Reduction) trial. Strollo *et al.* [5] recruited a highly select group of OSA patients (AHI 20–50 events·h^{-1}, body mass index (BMI) <32 kg·m^{-2}, non-concentric airway collapse during drug-induced sleep endoscopy) who were unable to adhere to CPAP treatment, and implanted an upper airway simulation system (Inspire Medical Systems, Maple Grove, MN, USA). In total, 126 patients were recruited and all underwent implantation. At 12 months, the median AHI decreased from 29.3 to 9 events·h^{-1}. 66% of the participants exhibited a positive response (reduction of AHI of at least 50% and to <20 events·hr^{-1}); the remainder either exhibited no response or in some cases increased AHI. There were also associated improvements in sleep quality, hypoxaemia, and Epworth score. A subset of responding patients (n=46) were randomised to continue therapy (n=23) or have their device deactivated for 1 week (n=23). During this phase of the study, the continuation of therapy was effective, while withdrawal led to re-emergence of OSA [5]. There were two serious device-related adverse events requiring repositioning of the device, and some patients described uncomfortable tongue sensation. The device has been approved by the FDA and may become a viable option for selected CPAP-intolerant patients. Woodson *et al.* demonstrated the ongoing efficacy of upper airway stimulator therapy and subjective benefit in responding patients at 18 months [6].

While positional (usually lateral) sleep is commonly employed to treat certain patients with OSA, few studies have systematically examined the effect of prone sleep position. Bidarian-Moniri *et al.* [7] developed a customised mattress and pillow that effectively maintained subjects (n=27) in a prone sleep position for the majority of the night. The median AHI decreased from 23 to 7 events·h^{-1}; in subjects with non-positional OSA the median AHI decreased from 45 to 22 events·h^{-1}. The long-term efficacy and adherence to therapy with this technique remains to be seen.

In paediatric sleep apnoea, there has been uncertainty regarding what form of analgesia can be given safely after tonsillectomy. Kelly *et al.* [8] conducted a randomised controlled trial of children with OSA (n=91, aged 1–10) to receive acetaminophen and morphine (0.2–0.5 mg·kg^{-1} every 4 h, n=49), or acetaminophen and ibuprofen (10 mg·kg^{-1} every 6 h, n=42) post tonsillectomy with or without adenoidectomy. Home pulse oximetry was used to assess respiratory events. Both regimens were similarly effective for pain control. However, the post-operative oxygen desaturation index was unchanged in the ibuprofen group (4.5 to 3.0 events·h^{-1}) and increased in the morphine group (3.6 to 11.1 events·h^{-1}). These results suggest that opiates should be used with caution and that acetaminophen/ibuprofen can be effective for analgesia in this population.

Sleep apnoea and pulmonary disorders

Some recent studies have addressed management of sleep apnoea in the setting of specific pulmonary disorders. Sleep apnoea is a common comorbidity in patients with interstitial lung disease as recognised by recent idiopathic pulmonary fibrosis (IPF) guidelines [9]. In a non-randomised study of consecutive newly diagnosed patients with IPF, 55 out of 92 were found to have an AHI ⩾15 events·h^{-1} by polysomnography (PSG). Mermigkis *et al.* [10] studied the effect of CPAP on quality of life in these patients after 1 year. Good adherence to CPAP significantly improved measures of sleep and life quality. After 2 years, good adherence to CPAP was also associated with improved mortality *versus* poor adherence, although the number of observations was small. This study was cited in a recent review of IPF and sleep, building on the theme that sleep apnoea is a common and treatable impediment to functional status in IPF [11]. Pulmonary hypertension is also a common comorbidity with various forms of sleep disordered breathing. Hypoxaemia from sleep apnoea may aggravate pre-capillary pulmonary hypertension (idiopathic and chronic thromboembolic pulmonary hypertension (CTEPH)). Ulrich *et al.* [12] examined the impact of treating sleep apnoea with nocturnal oxygen, acetazolamide or placebo for 1 week in patients with pre-capillary pulmonary hypertension (n=23). Outcomes of the randomised cross-over study included 6 min walk distance, quality of life, New York Heart Association (NYHA) functional class and sleepiness.

With oxygen, there was correction of nocturnal hypoxaemia and lowering of AHI, associated with a modest improvement of 6 min walk distance, right ventricular fractional area change and NYHA status. By comparison, acetazolamide improved nocturnal oxygen level and lowered AHI but did not improve other outcomes. As this was a relatively short 1-week trial, it would be interesting to see if chronic nocturnal oxygen therapy in these patients confers persistent or cumulative benefits.

Management of OSA is undoubtedly affected by methods and metrics used to diagnose and classify the disorder. PSG, the current gold standard, is frequently being replaced by portable monitoring systems. Much of this practice shift is driven by costs, as recently quantified in an economic analysis by KIM et al. [13]. Patients with a high pre-test probability of OSA (n=373) were randomised to an in-laboratory pathway (PSG followed by CPAP titration) or a home-based pathway (portable monitoring followed by auto-titrating CPAP). From a payer perspective, costs of the in-laboratory pathway were about 17% higher than the home-based pathway. For providers, the costs of both pathways were comparable, resulting in a net negative operating margin for the home-based pathway. Authors raise concerns that patient care may suffer if economics become the principle driver of OSA diagnostic algorithms. In terms of the diagnostic comparability of testing modalities, data are becoming more widely available. A large scale, multi-centre European cohort included over 11 000 subjects, of whom, approximately half underwent PSG and other half polygraphy ($\geqslant$4 channels of data, no electroencephalography). AHI was lower by 30% in those who underwent polygraphy. These findings are explained, at least in part, by an overestimate of sleep time when EEG data are not available [14]. An additional source of variability stems from rules used to define hypopnoeas, as summarised by PENZEL et al. [15]. The 2012 American Academy of Sleep Medicine (AASM) guidelines defined hypopnoeas as a $\geqslant$30% decrease in nasal flow with $\geqslant$3% desaturation of arterial oxygen measured by pulse oximetry or EEG arousal. DUCE et al. [16] showed the impact of applying this definition in a retrospective set of 112 PSGs compared with more stringent AASM 2007 criteria. Not surprisingly, the more liberal AASM 2012 criteria resulted in a markedly higher prevalence of OSA. As mechanisms by which OSA affect health consequences are still poorly understood [17], the most meaningful definition is still unclear. In fact, recent editorials debate the premise of the AHI itself [18, 19], which does not distinguish between the derangements of OSA (e.g. hypoxia and sleep fragmentation) which may have distinctive consequences [18, 20].

OSA and cardiovascular disease
OSA and hypertension
Associations between OSA, CPAP and systemic hypertension have been extensively investigated over the last two decades and remain a subject of ongoing interest. 15 years ago, PEPPARD et al. [21] reported that the adjusted risks of developing hypertension over 4 years were increased by approximately three-fold by moderate–severe OSA in the Wisconsin Sleep Cohort Study. Last year, MOKHLESI et al. [22] re-examined this cohort to assess risks of hypertension, specifically related to rapid-eye-movement (REM) OSA. They demonstrated a graded relationship between increasing REM AHI and the prevalence and incidence of hypertension, regardless of whether the entire sample (n=1451), or subjects with REM-only OSA (n=742), was examined. Since REM constitutes a relatively small proportion of sleep time, it is not surprising that odds ratios for hypertension (~1.5 in those with REM AHI >15 events·h^{-1}) were smaller than for overall AHI in the study by PEPPARD et al. [21].

In the Heart Biomarker Evaluation in Apnoea Treatment (HeartBEAT) study, GOTTLIEB et al. [23] tested the hypothesis that supplemental oxygen, might also mitigate hypertension in OSA. Patients with moderate–severe OSA (AHI 15–50 events·h^{-1}, n=318) were randomised to CPAP, supplemental oxygen or control (healthy lifestyle and sleep education) for 12 weeks, followed by assessment of 24-h mean arterial blood pressure and cardiovascular biomarkers. Interestingly, CPAP lowered mean blood pressure ~2 mmHg and C-reactive protein, while there was no effect of benefit from oxygen or control. The reduction in blood pressure with CPAP occurred despite better adherence to oxygen (mean duration 4.8 h·night^{-1}) than CPAP (mean duration 3.5 h·night^{-1}). These findings support the concept that sympathetic activation rather than intermittent hypoxia per se, may be a final common pathway linking OSA to cardio-metabolic dysfunction [17, 24]. From a clinical standpoint, supplemental oxygen cannot be considered "salvage" therapy for OSA-related hypertension.

In line with HeartBEAT, recent meta-analyses of several trials conclude that CPAP leads to an overall 2–3 mmHg reduction in systolic and diastolic blood pressure [25, 26]. What remains a subject of ambiguity is what subset of hypertensive patients are most likely to respond to CPAP. For example, it has been hypothesised that those with resistant hypertension might particularly benefit [27]. In a randomised controlled trial, MUXFELT et al. [28] examined the impact of 6 months of CPAP (n=57) versus routine care (n=60) on blood pressure in patients with resistant hypertension and OSA (AHI >15 events·h^{-1}). By intention-to-treat analysis, they found no effect of CPAP, although a per-protocol analysis yielded a systolic nocturnal blood pressure reduction of 4.7 mmHg. By contrast, a recent Spanish study of CPAP for

resistant hypertension showed a ∼3 mmHg reduction in mean and diastolic blood pressure [29]. Taken together with other studies showing modest effects of CPAP in resistant hypertension [30], CPAP apparently decreases blood pressure to a similar or lesser degree in resistant hypertension as compared to non-resistant hypertension patients. Sanchez-de-la-Torre et al. [31] hypothesised that variable blood pressure responses to CPAP might be predicted by novel circulating biomarkers. Specifically, they examined plasma microRNA profiles in resistant hypertension patients with OSA before and after 3 months of CPAP. Three plasma microRNA molecules were highly predictive of a robust blood pressure lowering effect of CPAP. A lowering of aldosterone to renin ratio was also associated with positive CPAP response. It remains to be seen whether these "precision medicine" techniques will improve healthcare delivery and outcomes in the clinical setting.

A more detailed examination of the renin–angiotensin system (RAS) in OSA was recently undertaken by a pair of studies from Calgary, Canada. Nicholl et al. [32] demonstrated that CPAP reduces renin–angiotensin activity, with associated decreases in glomerular filtration rate and increases in renal plasma flow (in effect, a reduction in filtration fraction). CPAP also reduced plasma aldosterone and proteinuria. Zalucky et al. [33] further demonstrated that upregulation of the RAS was commensurate with the degree of nocturnal hypoxaemia. The authors suggest that the association between OSA and chronic renal disease may arise from hypoxia-induced hyperfiltration. A novel feature of these studies was the use of a standardised sodium-replete diet to suppress baseline RAS, and the assessment renovascular responses to angiotensin II infusion.

OSA and atherosclerosis

OSA is a risk factor for atherosclerotic cardiovascular disease [34], but there is also equipoise on this issue [35] and even data to suggest a possible "ischaemic preconditioning" effect of OSA mitigating the severity of acute myocardial infarction [36]. Kendzerska et al. [37] utilised health administrative data from St. Michael's hospital in Toronto, Canada to examine associations between OSA and cardiovascular disease. Adults with suspected OSA, who were referred for PSG between 1994 and 2010 (n ∼13 000) were followed until 2011 using health administrative data to assess the occurrence of a composite cardiovascular outcome (myocardial infarction, stroke, congestive heart failure, revascularization, death from any cause). Interestingly, the fully adjusted analysis did not identify AHI, but other variables such as T<90%, awakenings, leg movements, heart rate, and sleepiness as predictors of adverse outcomes. These observations add fuel to a debate about whether AHI should be considered the "holy grail" for assessing OSA severity [18, 38].

Roca et al. [39] recently examined the sex-specific association between OSA and subclinical myocardial injury (using high-sensitivity troponin T (hsTnT)), ventricular hypertrophy and heart failure. They accessed the combined Atherosclerosis Risk in Communities (ARIC) and Sleep Heart Health Study cohorts, containing large numbers of middle-aged subjects (916 men and 974 women). They found a positive correlation between OSA severity and hsTnT that withstood adjustment for age and BMI in women (odds ratio 1.34, 95% confidence interval 1.11–1.63); while in men, this correlation was not significant after adjustment. Similarly, moderate–severe OSA was associated with incident heart failure over ∼13 year follow-up only in women (hazard ratio 1.26, 95% CI 1.05–1.50) but not in men (HR 1.12, 95% CI 0.98–1.29). In addition, increased left ventricular mass and increased composite outcome of heart failure, death or left ventricular hypertrophy was associated only with OSA in women. The authors contrasted their findings with increased mortality and incident heart failure only in males with OSA in the Sleep Heart Health Study [35, 40]. They contend that differences might be ascribed to older participants and more severe OSA in the ARIC cohort. It has previously been shown that women manifest heightened autonomic arousal responses to OSA [41] which is one of the potential mechanisms cited in the study.

Buchner et al. [42] recently assessed myocardial infarct and salvage size in patients presenting with acute myocardial infarction. Consecutive patients presenting with acute myocardial infarction underwent percutaneous coronary intervention followed by polysomnography and cardiac MRI, and a repeat MRI 3 months later. They determined that sleep disordered breathing was associated with a larger infarct size, decreased recovery of viable myocardium at 3 months, and decreased LVEF (45% *versus* 54%). A similar protocol by these investigators focused on right heart mechanics showed a greater increase in right ventricle end-diastolic volume 3 months after an acute myocardial infarction in patients with sleep apnoea [42]. Caveats to interpreting these studies are limited sample size, a mixture of central and obstructive sleep events, and greater obesity in the sleep apnoea group. In addition, myocardial infarction can acutely aggravate sleep disordered breathing [43] which limits inferences about the direction of causality.

OSA and arrhythmia

Holmqvist et al. [44] published results from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF). This registry consists of 10 132 patients with atrial fibrillation followed for

2 years, of which 1841 reported a history of OSA. The presence of OSA was associated with more atrial fibrillation symptoms (22% *versus* 16%) anti-arrhythmic use (35% *versus* 31%) and higher risks of hospitalisation (HR 1.12) (all effects p<0.01). However, there were no differences in risks of death, major bleeding, atrial fibrillation progression or composite cardiovascular events. Among the 58% of OSA subjects reportedly on CPAP, there was a reduction in progression of atrial fibrillation. Of note, OSA diagnoses were based on physician report in this study.

OSA and metabolic health
OSA and glucose metabolism
OSA is a risk factor for incident diabetes [45] and recent studies explore this link with greater attention to patient-specific factors. BAKKER *et al.* [46] examined whether associations between OSA and fasting hyperglycaemia are influenced by ethnicity. They utilised the Multi-Ethnic Study of Atherosclerosis (MESA), comprised of 6813 patients from six sites in the USA, with 2166 who underwent polysomnography. As has been shown in other studies, they detected an independent effect of AHI on morning hyperglycaemia for the whole cohort. However, the association was observed specifically in African–American subjects (OR 2.14, 95% CI 1.12–4.08) and Caucasian subjects (OR 2.85, 95% CI 1.20–6.75) but not Chinese or Hispanic subjects. In the aforementioned historical Canadian cohort followed by KENDZERSKA *et al.* [47], the authors also observed a dose-effect of AHI on the incidence of diabetes, but no effect of CPAP. BAKKER *et al.* [48] provided insightful commentary, suggesting that the apparent failure of CPAP may be related to limited data from administrative databases, or irreversibility of established diabetes, and suggested that patients with prediabetes might be the optimal population for future CPAP trials.

In fact, a recent study by PAMIDI *et al.* [49] studied the effects of CPAP on glucose metabolism in pre-diabetics. Subjects were randomised to CPAP (n=26) or a placebo pill (n=13) and stayed in a sleep laboratory to ensure adherence to a full 8 h of CPAP per night for 2 weeks. Oral and intravenous glucose tolerance tests were performed before and after the intervention. Following CPAP therapy, insulin sensitivity improved, in association with reductions in blood pressure and norepinephrine levels. These results differ from prior studies in which CPAP adherence averaged ~4 h·night^{-1} [50–52]. Hence, recent studies suggest that certain individuals, by virtue of their ethnicity or underlying propensity for diabetes, are more susceptible to the diabetogenic effects of OSA; and that rigorous adherence to CPAP may mitigate the impact of OSA.

CPAP and weight relationships
Treatment with CPAP may have other, perhaps less desirable metabolic effects. QUAN *et al.* [53] recently examined the effect of 6 months of therapeutic *versus* sham CPAP on weight, in a subset of patients (n=812) from the Apnoea Positive Pressure Long-term Efficacy Study (APPLES) [54]. They found that subjects treated with therapeutic CPAP gained 0.35 kg while those treated with sham lost 0.70 kg, and greater adherence to therapy correlated with more weight gain. This year, DRAGER *et al.* [55] published a meta-analysis of 25 CPAP studies confirming modest weight gain with therapy. Putative mechanisms include reductions in energy expenditure during sleep, removal of hypoxia-induced anorexia, and attenuation of lipolysis [56, 57].

Interactions of CPAP and weight were also examined by CHIRINOS *et al.* [52] with attention to the comparative cardio-metabolic effects of treating OSA, obesity, or both. Obese subjects (BMI ⩾30 kg·m^{-2}) with moderate–severe OSA (AHI ⩾15 events·h^{-1}) and elevated C-reactive protein (>1 mg·L^{-1}) were randomly assigned to a weight-loss intervention (n=61), CPAP therapy (n=58) or combined weight-loss and CPAP (n=62) for 24 weeks. Insulin sensitivity, lipid profile, C-reactive protein and blood pressure were assessed at week 8 and 24. In the two groups incorporating weight loss, ~7 kg were lost by week 24 while weight was stable in the CPAP-only group. This weight reduction was associated with lower C-reactive protein, blood pressure and triglycerides, and improved insulin sensitivity. On the other hand, was no change in these parameters with CPAP monotherapy. Blood pressure was reduced to a similar extent in all groups by intention-to-treat analysis, with a possible synergistic effect of combined weight loss and CPAP among more adherent patients. This study provides important perspective on the relative merits of weight loss and CPAP in the clinical setting for those with morbid obesity.

Conclusions
In 2015, a theme is developing that susceptibility to certain consequences of sleep apnoea is influenced by demographic and anthropometric factors. The rise of home-based diagnostics and variability of hypopnoea rules present challenges to standardising the approach to sleep apnoea. Simultaneously, novel treatments are emerging for obstructive and central apnoea, and clinicians need to be aware of the risks and benefits of these therapies. Weight reduction should be a cornerstone of therapy for the cardiovascular health of obese OSA patients.

References

1   Teschler H, Dohring J, Wang YM, *et al.* Adaptive pressure support servo-ventilation: a novel treatment for Cheyne-Stokes respiration in heart failure. *Am J Respir Crit Care Med* 2001; 164: 614–619.

2   Cowie MR, Woehrle H, Wegscheider K, *et al.* Adaptive servo-ventilation for central sleep apnea in systolic heart failure. *N Engl J Med* 2015; 373: 1095–1105.

3   Naughton MT. Cheyne-Stokes respiration: friend or foe? *Thorax* 2012; 67: 357–360.

4   Abraham WT, Jagielski D, Oldenburg O, *et al.* Phrenic nerve stimulation for the treatment of central sleep apnea. *JACC Heart Fail* 2015; 3: 360–369.

5   Strollo PJ Jr, Soose RJ, Maurer JT, *et al.* Upper-airway stimulation for obstructive sleep apnea. *N Engl J Med* 2014; 370: 139–149.

6   Strollo PJ Jr, Gillespie MB, Soose RJ, *et al.* Upper airway stimulation for obstructive sleep apnea: durability of the treatment effect at 18 months. *Sleep* 2015; 38: 1593–1598.

7   Bidarian-Moniri A, Nilsson M, Rasmusson L, *et al.* The effect of the prone sleeping position on obstructive sleep apnoea. *Acta Otolaryngol* 2015; 135: 79–84.

8   Kelly LE, Sommer DD, Ramakrishna J, *et al.* Morphine or ibuprofen for post-tonsillectomy analgesia: a randomized trial. *Pediatrics* 2015; 135: 307–313.

9   Raghu G, Rochwerg B, Zhang Y, *et al.* An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline: treatment of idiopathic pulmonary fibrosis. An Update of the 2011 Clinical Practice Guideline. *Am J Respir Crit Care Med* 2015; 192: e3–19.

10   Mermigkis C, Bouloukaki I, Antoniou K, *et al.* Obstructive sleep apnea should be treated in patients with idiopathic pulmonary fibrosis. *Sleep Breath* 2015; 19: 385–391.

11   Schiza S, Mermigkis C, Margaritopoulos GA, *et al.* Idiopathic pulmonary fibrosis and sleep disorders: no longer strangers in the night. *Eur Respir Rev* 2015; 24: 327–339.

12   Ulrich S, Keusch S, Hildenbrand FF, *et al.* Effect of nocturnal oxygen and acetazolamide on exercise performance in patients with pre-capillary pulmonary hypertension and sleep-disturbed breathing: randomized, double-blind, cross-over trial. *Eur Heart J* 2015; 36: 615–623.

13   Kim RD, Kapur VK, Redline-Bruch J, *et al.* An economic evaluation of home *versus* laboratory-based diagnosis of obstructive sleep apnea. *Sleep* 2015; 38: 1027–1037.

14   Escourrou P, Grote L, Penzel T, *et al.* The diagnostic method has a strong influence on classification of obstructive sleep apnea. *J Sleep Res* 2015; 24: 730–738.

15   Penzel T, Schobel C, Fietze I. Revise respiratory event criteria or revise severity thresholds for sleep apnea definition? *J Clin Sleep Med* 2015; 11: 1357–1359.

16   Duce B, Milosavljevic J, Hukins C. The 2012 AASM respiratory event criteria increase the incidence of hypopneas in an adult sleep center population. *J Clin Sleep Med* 2015; 11: 1425–1431.

17   Mesarwi OA, Sharma EV, Jun JC, *et al.* Metabolic dysfunction in obstructive sleep apnea: a critical examination of underlying mechanisms. *Sleep Biol Rhythms* 2014; 12: 74–84.

18   Punjabi NM. Counterpoint: Is the AHI the best way to quantify the severity of sleep disordered breathing? No. *Chest* 2015 [In press; DOI: 10.1378/chest.14-2261].

19   Rapoport DM. Point: Is the AHI the best way to quantify the severity of sleep disordered breathing? YES. *Chest* 2015 [In press; DOI: 10.1378/chest.15-1319].

20   Thomas RJ, Guilleminault C, Ayappa I, *et al.* Scoring respiratory events in sleep medicine: who is the driver-biology or medical insurance? *J Clin Sleep Med* 2014; 10: 1245–1247.

21   Peppard PE, Young T, Palta M, *et al.* Prospective study of the association between sleep-disordered breathing and hypertension. *N Engl J Med* 2000; 342: 1378–1384.

22   Mokhlesi B, Finn LA, Hagen EW, *et al.* Obstructive sleep apnea during REM sleep and hypertension. results of the Wisconsin Sleep Cohort. *Am J Respir Crit Care Med* 2014; 190: 1158–1167.

23   Gottlieb DJ, Punjabi NM, Mehra R, *et al.* CPAP *versus* oxygen in obstructive sleep apnea. *N Engl J Med* 2014; 370: 2276–2285.

24   Brotman DJ, Girod JP. The metabolic syndrome: a tug-of-war with no winner. *Cleve Clin J Med* 2002; 69: 990–994.

25   Schein AS, Kerkhoff AC, Coronel CC, *et al.* Continuous positive airway pressure reduces blood pressure in patients with obstructive sleep apnea; a systematic review and meta-analysis with 1000 patients. *J Hypertens* 2014; 32: 1762–1773.

26   Fava C, Dorigoni S, Dalle Vedove F, *et al.* Effect of CPAP on blood pressure in patients with OSA/hypopnea a systematic review and meta-analysis. *Chest* 2014; 145: 762–771.

27   Parati G, Lombardi C, Hedner J, *et al.* Position paper on the management of patients with obstructive sleep apnea and hypertension: joint recommendations by the European Society of Hypertension, by the European Respiratory Society and by the members of European COST (COoperation in Scientific and Technological research) ACTION B26 on obstructive sleep apnea. *J Hypertens* 2012; 30: 633–646.

28   Muxfeldt ES, Margallo V, Costa LM, *et al.* Effects of continuous positive airway pressure treatment on clinic and ambulatory blood pressures in patients with obstructive sleep apnea and resistant hypertension: a randomized controlled trial. *Hypertension* 2015; 65: 736–742.

29   Martinez-Garcia MA, Capote F, Campos-Rodriguez F, *et al.* Effect of CPAP on blood pressure in patients with obstructive sleep apnea and resistant hypertension: the HIPARCO randomized clinical trial. *JAMA* 2013; 310: 2407–2415.

30   Varounis C, Katsi V, Kallikazaros IE, *et al.* Effect of CPAP on blood pressure in patients with obstructive sleep apnea and resistant hypertension: a systematic review and meta-analysis. *Int J Cardiol* 2014; 175: 195–198.

31   Sanchez-de-la-Torre M, Khalyfa A, Sanchez-de-la-Torre A, *et al.* 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.

32   Nicholl DD, Hanly PJ, Poulin MJ, *et al.* Evaluation of continuous positive airway pressure therapy on renin-angiotensin system activity in obstructive sleep apnea. *Am J Respir Crit Care Med* 2014; 190: 572–580.

33   Zalucky AA, Nicholl DD, Hanly PJ, *et al.* Nocturnal hypoxemia severity and renin-angiotensin system activity in obstructive sleep apnea. *Am J Respir Crit Care Med* 2015; 192: 873–880.

34   Martinez D, Klein C, Rahmeier L, *et al.* Sleep apnea is a stronger predictor for coronary heart disease than traditional risk factors. *Sleep Breath* 2012; 16: 695–701.

35   Gottlieb DJ, Yenokyan G, Newman AB, *et al.* Prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: the sleep heart health study. *Circulation* 2010; 122: 352–360.

36   Shah N, Redline S, Yaggi HK, *et al.* Obstructive sleep apnea and acute myocardial infarction severity: ischemic preconditioning? *Sleep Breath* 2013; 17: 819–826.

37   Kendzerska T, Gershon AS, Hawker G, *et al.* Obstructive sleep apnea and risk of cardiovascular events and all-cause mortality: a decade-long historical cohort study. *PLoS Med* 2014; 11: e1001599.

38   Rapoport DM. Rebuttal From Dr. Rapoport. *Chest* 2015 [In press; DOI: 10.1378/chest.15-1320].

39   Roca GQ, Redline S, Claggett B, *et al.* Sex-specific association of sleep apnea severity with subclinical myocardial injury, ventricular hypertrophy, and heart failure risk in a community-dwelling cohort: The Atherosclerosis Risk in Communities-Sleep Heart Health Study. *Circulation* 2015; 132: 1329–1337.

40   Punjabi NM, Caffo BS, Goodwin JL, *et al.* Sleep-disordered breathing and mortality: a prospective cohort study. *PLoS Med* 2009; 6: e1000132.

41   Jordan AS, McEvoy RD, Edwards JK, *et al.* The influence of gender and upper airway resistance on the ventilatory response to arousal in obstructive sleep apnoea in humans. *J Physiol* 2004; 558: 993–1004.

42   Buchner S, Eglseer M, Debl K, *et al.* Sleep disordered breathing and enlargement of the right heart after myocardial infarction. *Eur Respir J* 2015; 45: 680–690.

43   Tsukamoto K, Ohara A. Temporal worsening of sleep-disordered breathing in the acute phase of myocardial infarction. *Circ J* 2006; 70: 1553–1556.

44   Holmqvist F, Guan N, Zhu Z, *et al.* Impact of obstructive sleep apnea and continuous positive airway pressure therapy on outcomes in patients with atrial fibrillation-Results from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF). *Am Heart J* 2015; 169: 647–654.

45   Wang X, Bi Y, Zhang Q, *et al.* Obstructive sleep apnoea and the risk of type 2 diabetes: a meta-analysis of prospective cohort studies. *Respirology* 2013; 18: 140–146.

46   Bakker JP, Weng J, Wang R, *et al.* Associations between obstructive sleep apnea, sleep duration, and abnormal fasting glucose. The multi-ethnic study of atherosclerosis. *Am J Respir Crit Care Med* 2015; 192: 745–753.

47   Kendzerska T, Gershon AS, Hawker G, *et al.* Obstructive sleep apnea and incident diabetes. A historical cohort study. *Am J Respir Crit Care Med* 2014; 190: 218–225.

48   Bakker JP, Patel SR. Sleep apnea and diabetes: good friends or something more? *Am J Respir Crit Care Med* 2014; 190: 133–134.

49   Pamidi S, Wroblewski K, Stepien M, *et al.* Eight hours of nightly continuous positive airway pressure treatment of obstructive sleep apnea improves glucose metabolism in patients with prediabetes. A randomized controlled trial. *Am J Respir Crit Care Med* 2015; 192: 96–105.

50   Weinstock TG, Wang X, Rueschman M, *et al.* A controlled trial of CPAP therapy on metabolic control in individuals with impaired glucose tolerance and sleep apnea. *Sleep* 2012; 35: 617–625B.

51   Hoyos CM, Killick R, Yee BJ, *et al.* Cardiometabolic changes after continuous positive airway pressure for obstructive sleep apnoea: a randomised sham-controlled study. *Thorax* 2012; 67: 1081–1089.

52   Chirinos JA, Gurubhagavatula I, Teff K, *et al.* CPAP, weight loss, or both for obstructive sleep apnea. *N Engl J Med* 2014; 370: 2265–2275.

53   Quan SF, Budhiraja R, Clarke DP, *et al.* Impact of treatment with continuous positive airway pressure (CPAP) on weight in obstructive sleep apnea. *J Clin Sleep Med* 2013; 9: 989–993.

54   Kushida CA, Nichols DA, Holmes TH, *et al.* Effects of continuous positive airway pressure on neurocognitive function in obstructive sleep apnea patients: The Apnea Positive Pressure Long-term Efficacy Study (APPLES). *Sleep* 2012; 35: 1593–1602.

55   Drager LF, Brunoni AR, Jenner R, *et al.* Effects of CPAP on body weight in patients with obstructive sleep apnoea: a meta-analysis of randomised trials. *Thorax* 2015; 70: 258–264.

56   Patel SR. The complex relationship between weight and sleep apnoea. *Thorax* 2015; 70: 205–206.

57   Jun JC, Drager LF, Najjar SS, *et al.* Effects of sleep apnea on nocturnal free fatty acids in subjects with heart failure. *Sleep* 2011; 34: 1207–1213.