DOI:
10.1080/08037051.2018.1443391

Document Version
Peer reviewed version

Citation for published version (APA):
Ratneswaran, C., Pengo, M. F., Xiao, S., Luo, Y.-M., Rossi, G. P., Polkey, M. I., Moxham, J., & Steier, J. S. (2018). The acute effect of continuous positive airway pressure titration on blood pressure in awake overweight/obese patients with obstructive sleep apnoea. *Blood Pressure*, 1-9. Article BP-2017-0206.R1. Advance online publication. https://doi.org/10.1080/08037051.2018.1443391

THE ACUTE EFFECT OF CONTINUOUS POSITIVE AIRWAY PRESSURE TITRATION ON BLOOD PRESSURE IN AWAKE OVERWEIGHT/OBESE PATIENTS WITH OBSTRUCTIVE SLEEP APNOEA

Short title: ACUTE EFFECT OF CPAP ON BLOOD PRESSURE

Culadeeban RATNESWARAN [1,2], Martino F PENGO [2,3], Sichang XIAO [2,4], Yuanming LUO [4], Gian Paolo ROSSI [3], Michael I POLKEY[5], John MOXHAM[1], Joerg STEIER [1,2]

1 Faculty of Life Sciences and Medicine, King's College London, UK

2 Lane Fox Unit/ Sleep Disorders Centre, Guy's & St Thomas' NHS Foundation Trust, London, UK

3 Clinica dell'Ipertensione Arteriosa - Department of Medicine (DIMED), University of Padua, Italy

4 State Key Laboratory of Respiratory Disease, The First Affiliated Hospital of Guangzhou Medical School, Guangzhou, China

5 Royal Brompton & Harefield NHS Foundation Trust, London, UK

Correspondence to:

Dr Culadeeban Ratneswaran

Lane Fox Unit / Sleep Disorders Centre, Guy's & St Thomas' NHS Foundation Trust, Westminster Bridge Road, London SE1 7EH, UK; tel +44 (0) 2071883434 Culadeeban.ratneswaran@gstt.nhs.uk

Word count: 2572

Number of tables: 2

Number of figures: 3

Sources of support

The authors gratefully acknowledge the support from the clinical team at the Sleep Disorders Centre at Nuffield House, Guy's & St Thomas' NHS Foundation Trust. Dr Pengo's salary was partially funded by the Italian Hypertension Society. Professor Polkey's contribution to this work was supported by the NIHR Respiratory Biomedical Research Unit at the Royal Brompton and Harefield NHS Foundation Trust and Imperial College who part funded his salary. Prof Moxham's and Dr Steier's contributions were partially supported by the National Institute for Health Research (NIHR) Biomedical Research Centre based at Guy's and St Thomas' NHS Foundation Trust and King's College London, UK. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

Conflicts of interests

The authors have no conflicts of interest to declare.

ABSTRACT

Objectives Continuous positive airway pressure (CPAP) improves upper airway obstruction in patients with obstructive sleep apnoea (OSA), who often are overweight-obese. Although it is thought that CPAP improves long-term blood pressure control (BP), the impact of acute and short-term CPAP use on the cardiovascular system in obese patients has not been described in detail.

Methods Obese patients (body mass index, BMI>25kg/m^2) with OSA were studied awake, supine during incremental CPAP titration (4-20cmH_2O, +2cmH_2O/3mins). BP was measured continuously with a beat-to-beat BP monitor (Ohmeda 2300, Finapres Medical Systems, Amsterdam/NL), BP variability (BPV) was calculated as the standard deviation of BP at each CPAP level, the 95% confidence interval (95%CI) was calculated and changes in BP and BPV were reported.

Results 15 patients (12male, 48 ± 10) years, BMI 38.9 ± 5.8 kg/m^2) were studied; the baseline BP was 131.0 ± 10.2 / 85.1 ± 9.1 mmHg. BP and BPV increased linearly with CPAP titration (systolic BP r=0.960, p<0.001; diastolic BP r=0.961, p<0.001; systolic BPV r=0.662, p=0.026; diastolic BPV r=0.886, p<0.001). The systolic BP increased by +17% (+23.15 (7.9, 38.4) mmHg; p=0.011) and the diastolic BP by +23% (+18.27 (2.33, 34.21) mmHg; p=0.009), when titrating CPAP to 20cmH_2O. Systolic BPV increased by +96% (+5.10 (0.67, 9.53) mmHg; p<0.001) and was maximal at 14cmH_2O, and diastolic BPV by +97% (+3.02 (0.26, 5.78) mmHg; p<0.001) at 16cmH_2O.

Conclusion Short-term incremental CPAP leads to significant increases in BP and BPV in obese patients with OSA while awake. Careful titration of pressures is required to minimise the risk of nocturnal awakenings while improving BP control.

Key words: hypertension, variability, sympathetic, cardiovascular, obesity

Introduction

Obstructive sleep apnoea (OSA) is characterised by intermittent episodes of complete or partial upper airway obstruction that lead to recurrent apnoeas or hypopnoeas during sleep [1]. These respiratory events cause sleep fragmentation and diminished quality of sleep, thus leading to excessive daytime sleepiness [2], cognitive dysfunction [3], as well as to increased risk of road traffic accidents [4]. OSA is associated with significant comorbidities [5], such as cardiovascular disease [6, 7] and hypertension [8], stroke [9], coronary heart disease [10], diabetes [11, 12] and the metabolic syndrome [13]. Obesity is an important risk factor for the development of OSA and the two conditions share a complex interaction, with poor sleep and sleepiness also facilitating weight gain independent of OSA [14, 15]. Obesity [16] and OSA [17] are independently related to increased sympathetic tone, hypertension and associated comorbidities.

Continuous positive airway pressure (CPAP) is the most effective treatment for OSA [18]. It maintains upper airway patency during sleep [19], inflates the chest and offloads the respiratory system [20, 21]. When effectively titrated, CPAP reduces OSA symptoms, such as sleepiness [22, 23], but also associated breathlessness [24, 25]. Importantly, CPAP improves blood pressure (BP) control in sleepy patients with OSA [26] and decreases blood pressure variability (BPV) [27]. Thus, it might reduce cardiovascular related mortality and morbidity [28].

Indeed, the use of CPAP in OSA was thought to reduce the risk of fatal cardiovascular events in both men [29] and women [30], and also in the elderly [31]. However, recent results of the SAVE trial have failed to show any long-term cardiovascular benefit in patients with underlying cardiovascular disease and OSA, who were established on CPAP [28]. Currently,

it remains unclear as to why CPAP has failed to improve long-term cardiovascular risks, but patient adherence is likely to contribute to variable long-term outcomes [28, 32].

When initiating CPAP therapy pressure titration is crucial for the respiratory control of apnoeas and hypopnoeas. Pressure levels impact on patient's adherence to treatment, in that CPAP needs to be tolerable and comfortable [25]. In this context, it is important to recognize that short-term CPAP adherence has been shown to predict long-term usage [33] and this underlines the importance of utilising acceptable pressure levels for patients early on.

We hypothesised that acute increase in CPAP pressure during titration in obese patients with OSA might impact on BP and BPV due to increased intra-thoracic pressures, and that these effects need to be taken into account when delivering CPAP in such patients. Hence, we sought to systematically assess prospective the beat-to-beat BP while titrating CPAP in the awake obese patients with OSA.

Methods

Patients were recruited from the Sleep Disorders Centre at Guy's & St Thomas' NHS Foundation Trust, London, UK. The local Research Ethics Committee approved the study; informed written consent was obtained from each participant (06/Q0703/224). Inclusion criteria were age older >18 years, a body-mass index (BMI) above >25kg/m^2 and confirmed OSA, as defined by an apnoea-hypopnea index (AHI) >15/h, AHI >5/h if they were symptomatic (Epworth Sleepiness Scale >10 points). Specific exclusion criteria were inability to tolerate incremental CPAP titration, or psychological disorders that confounded the observation. One patient had an anxiety disorder (claustrophobia) and was excluded from

the study. Another patient requested to stop at 14cmH_2O, despite tolerating CPAP titration; these data were included in the analysis. All patients had equal and palpable radial arteries, they did not have any muscular tension, vascular fistulae, or aortic arch abnormalities that might impact upon the accuracy of peripheral blood pressure measurements. Anthropometric data were collected including age, gender, height, weight, BMI, neck, waist and hip circumference, Mallampati score, and smoking history.

Protocol

Patient age, gender, height and weight were recorded. An electronic hand-held spirometer (Carefusion Micro I, Micromedical, Basingstoke, UK) was used to record the forced expiratory volume in one second (FEV_1) and the forced vital capacity (FVC) in the seated posture with a nose clip. Prior to further measurements patients were asked to rest quietly on a bed in a standardised supine posture (legs straight and uncrossed, hands by their side with their palms facing down, and head/shoulders supported using a pillow so that they felt no efforts to maintain head and neck posture) for five minutes. Patients were studied awake, supine at rest (CPAP=0cmH_2O) and with a full-face mask (ResMed Mirage Quattro full face mask, ResMed Ltd, Oxfordshire, UK), and during incremental CPAP (CPAP S8, Resmed Ltd, Oxfordshire, UK) titration (4-20 cmH_2O; increments of + 2cmH_2O each 3minutes). The protocol finished either when patients had reached a CPAP of 20 cmH_2O for 3minutes or when they felt that the pressures were unpleasant or caused breathlessness. BP was measured with a beat-to-beat BP monitor (Ohmeda 2300, Finapres Medical Systems, Amsterdam/NL) applied to the middle phalanx of the index finger of each participant, in order to continuously measure the finger blood pressure (radial artery of index finger) [34]; this technique has been shown to accurately reflect systemic arterial pressure [35]. The device was auto-calibrated at the beginning, after 15 minutes and at the end of the CPAP titration, as described elsewhere [36]. BPV was calculated as the standard deviation of BP at each CPAP level. Results were

analysed with the first minute on a new pressure level disregarded in order to account for equilibration of ventilation and increased variability when ramping up the pressures, and the last two minutes on each level being analysed and averaged.

Sleep study

A sleep study was undertaken the night prior to the morning physiological study to determine the AHI [37], and the 95th percentile of CPAP that was required to avoid upper airway occlusion [38]. The results were analysed and confirmed by expert sleep technicians.

Statistical analysis

Data were analysed using SPSS V23.0 (SPSS, Chicago, IL/USA). Data were tested for normal distribution using the Shapiro-Wilk test. Pearson product-moment correlation coefficient was used for bivariate analyses for normally distributed data, Spearman's rank correlation was used for cases with non-normally distributed data. BPV at each CPAP level was calculated as the mean of the standard deviation of all patients blood pressure during the last 2 minutes on each CPAP pressure. The change in blood pressure from baseline (delta, Δ) was calculated for all individuals as the mean BP of the last two minutes at the CPAP level which had the highest average reading, minus the mean BP of the last two minutes with no CPAP (0cmH_2O; mask off). These results were tested using the paired samples t-test. Systolic and diastolic blood pressure were expressed as mean ± standard error, the 95% confidence interval (95%CI) was reported for BP changes on CPAP. Statistical level of significance was defined with a p-value <0.05.

RESULTS

Patient characteristics

15 patients (12males, 48 ± 10 years, BMI 38.9 ± 5.8 kg/m^2) with a confirmed diagnosis of OSA were studied (Table 1). The patients were middle-aged, predominantly male (80%), and obese, with one patient being in the overweight category (number 4). Two patients had mild OSA (number 3 and 15) and all others had moderate-severe OSA. Patients had relatively normal spirometry. All but one patient completed the study protocol, reaching a CPAP level of 20 cmH_2O; subject number 2 stopped at 14 cmH_2O due to breathing discomfort. A total of 5 patients had a known history hypertension (number 3, 5, 6, 11, 13), four of whom were established on treatment, and one had not been taking treatment. Of the patients not known to have hypertension, 4 were hypertensive at baseline based on a diastolic blood pressure $\geq$ 90 [39].

BP and BPV

On CPAP the systolic BP increased by +17% (95%CI: 6-28%; p=0.011) and the diastolic BP by +26% (95%CI: 3-49%; p=0.009) (Figure 1). The mean systolic BP variability increased maximally from baseline by +96% (95%CI: 13-180%; p<0.001; 0-14 cmH_2O), the diastolic BPV increased maximally by +97% (95%CI: 8-185%; p<0.001; 0-16 cmH_2O; Table 2). There were no significant differences between the patients with known hypertension and those without (BP, systolic p=0.827; BP, diastolic p=0.274; systolic BPV p=0.868; diastolic BPV p=0.556).

CPAP and BP / BPV

The average change in BP at each incremental CPAP level is displayed in figure 1. The average systolic BPV at each CPAP level is displayed in figure 2, and the average diastolic BPV at each CPAP level is displayed in figure 3. Incremental CPAP titration was associated

with higher systolic (r=0.960, p<0.001) and diastolic BP (r=0.961, p<0.001), as well as with higher systolic (r=0.662, p=0.026) and diastolic BPV (r=0.886, p<0.001).

DISCUSSION

This study showed that the acute application of CPAP in obese patients with OSA while awake leads to significant increases in blood pressure and blood pressure variability during pressure titration. The diastolic BP rises by up to +23%, and the systolic BP by up to +17%. BPV, a marker of sympathetic activity, almost doubles (+96 to 97%) during acute and incremental CPAP titration in these patients. There is a strong linear correlation between applied level of CPAP and the observed changes.

Clinical Significance of Findings

Obstructive Sleep apnoea (OSA) is an independent risk factor for cardiovascular morbidity and mortality, which is thought to be secondary to increased sympathetic activity, and hypertension [40, 41]. This is likely to be mediated by a number of pathways contributing to intermittent hypoxia and hypercapnia [42], increased oxidative stress, systemic inflammation [43], and amplified sympathetic activity [44]. Patients with OSA exhibit increased sympathetic activation while awake and asleep [45]. Amplified sympathetic drive has also been described to develop in obese patients, independent of hypertension [46], although the degree to which this is related to the underlying OSA is not entirely understood [47]. These pathophysiological mechanisms are thought to chronically elevate blood pressure, subsequently impacting on endothelial integrity, causing atherosclerosis and hence increased cardiovascular morbidity [48]. The impact of intermittent arterial hypoxia on the sympathetic nervous system is a central focus of the cardiovascular effects induced by OSA. Chronic intermittent periods of hypoxia and hypercapnia result in increased oxidative stress, which in

turn lead to chemoreflex stimulation, upregulation of central and peripheral chemoreceptors and increased sympathetic nerve activity [49, 50]. Acute changes in sympathetic drive and blood pressure have been less well described [45, 51].

Bonsignore et al [52] found in a similar cohort of 18 obese patients (BMI 35.5 ± 6.1) with severe OSA (AHI 58 - 134 events/hr) that CPAP application, by means of preventing apnoeas while asleep, decreased systolic and diastolic BPV by improving baroreflex control (no difference to absolute BP). They used the Finapres system to record beat-to-beat BP during full-night polysomnography; however, their "acute" application of CPAP was overnight with a predetermined pressure (average 11.2 ± 3.0 cmH_2O) from baseline studies (18 ± 9 days earlier) aimed specifically to prevent obstructive events and normalise SaO_2 during sleep.

Likewise, an earlier paper using a Finapres device in a similar cohort of 8 patients (7 male) with severe OSA (>4% SaO_2 dips/hr: 50.5) who were predominantly obese (BMI 36.9 km/m^2), middle-aged (52 yrs) tried to investigate the cause of post-apnoea blood pressure rises. Six of the patients had been studied during the first night of CPAP use, with two patients previously being established on CPAP between 2 and 4 years (treatment discontinued 3 nights earlier). BP was investigated in different stages: firstly, during 30 minutes of wakefulness, then during 30 minutes of OSA, followed by 30 minutes of OSA plus supplementation of oxygen to maintain saturation >96%, followed by 30 minutes of nasal CPAP therapy to avoid apnoeas, hypopnoeas and snoring. Despite the fact that the AHI was elevated during the OSA phase compared to CPAP phase, the application of CPAP did not reduce systolic or diastolic BP. However, it did cause a reduction in BPV, compared to the OSA phase and wakefulness [53].

Despite similar demographic cohorts and investigational techniques, both of these studies have significant methodological differences to our observational investigation of the *immediate* physiological effect of incremental CPAP titration on BP and BPV. Both papers

describe the impact on asleep patients, and currently there is limited data demonstrating the acute effects of CPAP on BP whilst awake [54].

Indeed, CPAP as a treatment for OSA is thought to positively impact on cardiovascular outcomes [29], as it maintains upper airway patency and avoids recurrent periods of hypoxia, arousal and high intra-thoracic pressure changes. However, the results of the recent SAVE trial have shown that CPAP may not confer significant benefits with regards to long-term cardiovascular outcomes in OSA [28]. By investigating moderate to severe OSA patients (n=2,717, mean follow-up 3.7 years) with comorbid cardiovascular disease, the investigators reported no benefit in the group that was established on CPAP when compared to usual care (hazard ratio 1.10; 95%CI 0.91 to 1.32; p=0.34). The findings were reinforced by an earlier study in minimal symptomatic OSA patients [55]. In addition, the SAVE trial may have selected less affected OSA patients by excluding those with an Epworth Sleepiness Scale >15, and those with severe oxygen desaturations (<80% for >10% of the recording time). Furthermore, it did not exclude smokers (15.9% in the CPAP-arm) and compliance in the CPAP group was limited to about 3.3-hours (mean operating time per night). Despite this, the impact of CPAP on cardiovascular outcomes remains contentious.

These results become important when putting the results of the current study in context: CPAP is the most effective treatment to offset upper airway obstruction and, thus, improving intermittent hypoxia, arousal and pressure changes that are associated with uncontrolled OSA. However, the application of a constant high intrathoracic pressure using CPAP can in itself cause relevant increases in systolic and diastolic blood pressure, as well as in BPV, which could in itself partially offset the benefits of a good respiratory control. While the primary goal of CPAP is to eliminate the OSA syndrome including excessive day time sleepiness, the value of avoiding higher CPAP pressures than required to achieve an

acceptable respiratory control may need to be discussed further. Assessing neural respiratory drive during CPAP titration via diaphragmatic EMG might be one way of achieving this [56]. Further, slightly reduced CPAP levels to offset most respiratory events could be enough to facilitate long-term respiratory control while reducing problems with compliance [25].

Previously, the SERVE HF trial had observed an increased risk of cardiovascular death when adaptive servo-ventilation (ASV) was utilised to treat central sleep apnoea in patients who had heart failure and who were established on maximal medical management. The study compared patients with ASV *vs* patients on maximal medical management only. An increased risk of cardiovascular death was observed in patients who had never had a prior hospital admission (hazard ratio 2.59, 95% CI 1.54–4.37, $p<0.001$) and in the group who had previously had resuscitation (hazard ratio 1.57, 1.01–2.44, $p=0.045$) [57]. Long-term outcomes were worse in patients with a left ventricular ejection fraction below 45%. Although our patient cohort included patients with OSA and not with heart failure the immediate impact of acute CPAP on BP in other patient groups should be investigated further to understand the impact on cardiovascular pathophysiology.

Limitations

Our patient cohort (15) is quite small and so the results cannot be widely generalised, though the conclusions and hypotheses warrant further and urgent evaluation. Importantly, this was an observational study of the acute effects of CPAP. The study does not take into account the PAP required to achieve upper airway patency in each patient, and, hence, cannot determine the levels of PAP that patients would be exposed to in the long-term.

Beat-by-beat blood pressure was recorded in the sleep laboratory overlooked by a trained physician. Hence, a “white coat” effect may have been a confounding factor, although upon

completion of CPAP titration patients were observed until their blood pressure had normalised again. The studied cohort entailed obese individuals, five patients had a history of hypertension and four further patients were slightly hypertensive at baseline measurement. Obesity is known to independently increase sympathetic activity [58, 59], as is hypertension [60]. These confounders may have exacerbated the observed effect of CPAP on blood pressure, and our data should not be generalised to non-obese non-hypertensive patients. Obstructive sleep apnoea and hypertension frequently coexist, with hypertension commonly discovered in patients with sleep apnoea. Nevertheless, our sub-analysis revealed no significant differences between patients with a history of hypertension against those without in any of the outcomes. Heart failure is an important comorbidity in this cohort of patients and an acute physiological effect of CPAP needs to be considered when pressurising the chest.

Recording changes in the blood pressure using a finger-cuff device is considered to be reliable [61], however, it is not validated for baseline systolic and diastolic measurements. The baseline measurements in this study were recorded using brachial artery blood pressure readings in the traditional way. Our finger-cuff device (Finapres) was used only for tracking beat-to-beat changes in blood pressure to allow us to calculate both the standard deviation (as a measure of blood pressure variability) and the change in blood pressure during CPAP titration. Continuous beat-to-beat blood pressure recordings better reflect any haemodynamic changes as opposed to intermittent blood pressure readings [62].

It is noteworthy that the studied patients were awake. CPAP in the sleep laboratory is generally used to treat the asleep patient, although it is first applied when still awake. However, it is more commonly used in awake patients in other settings, in particular in the critically ill patient [63] with acute pulmonary oedema [64]. The short-term impact of acute

CPAP on the cardiovascular system might not only alter sympathetic tone but could also impact on cardiac function in patients with chronic heart failure, although this is beyond the remit of the current investigation. It will be important to establish how BP and BPV respond over longer periods that include sleep. In addition, there is a lack of a CPAP control where only mask was applied with no added pressure. Although BP in this context would be fairly predictable other factors related to a white coat hypertension over time might become relevant.

Conclusion

Acute incremental CPAP leads to an increase in blood pressure and blood pressure variability in awake and obese patients with OSA. To systematically address any effects of CPAP on BP and BPV it is important to better understand the pathophysiological changes and long-term effects of this treatment in OSA patients. Studies in patients with coexisting OSA and heart failure are of particular interest. Advanced physiological monitoring of patients with OSA while undergoing CPAP titration with a focus on both the intrathoracic and cardiovascular components could improve our mechanistic understanding of the value of this treatment.

Contributors

All listed authors confirm that they have fulfilled the following criteria, as required by the International Committee of Medical Journal Editors (www.icmje.org): substantial contributions to the conception or design of the work; or the acquisition, analysis or interpretation of data for the work and drafting the work or revising it critically for important intellectual content and final approval of the version to be published and agreeing to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declaration of Helsinki

This study complies with the Declaration of Helsinki. Locally appointed ethics committee has approved the research protocol and that informed consent has been obtained from the subjects (or their legally authorized representative).

REFERENCES

1. Malhotra A, White DP. Obstructive sleep apnoea. The lancet. 2002;360(9328):237-245.
2. Slater G, Steier J. Excessive daytime sleepiness in sleep disorders. J Thorac Dis. 2012;4(6):608-616.
3. Beebe DW, Gozal D. Obstructive sleep apnea and the prefrontal cortex: towards a comprehensive model linking nocturnal upper airway obstruction to daytime cognitive and behavioral deficits. J Sleep Res. 2002;11(1):1-16.
4. Howard ME, Desai AV, Grunstein RR, et al. Sleepiness, sleep-disordered breathing, and accident risk factors in commercial vehicle drivers. Am J Respir Crit Care Med. 2004;170(9):1014-1021.
5. Mokhlesi B, Ham SA, Gozal D. The effect of sex and age on the comorbidity burden of OSA: an observational analysis from a large nationwide US health claims database. Eur Respir J. 2016;47(4):1162-1169.
6. Bradley TD, Floras JS. Obstructive sleep apnoea and its cardiovascular consequences. The Lancet. 2009;373(9657):82-93.
7. Shahar E, Whitney CW, Redline S, et al. Sleep-disordered breathing and cardiovascular disease: cross-sectional results of the Sleep Heart Health Study. Am J Respir Crit Care Med. 2001;163(1):19-25.
8. Narkiewicz K, Somers VK. Obstructive sleep apnea as a cause of neurogenic hypertension. Curr Hypertens Rep. 1999;1(3):268-273.
9. Palomäki H, Partinen M, Juvela S, et al. Snoring as a risk factor for sleep-related brain infarction. Stroke. 1989;20(10):1311-1315.
10. 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(3):695-701.
11. Punjabi NM, Sorkin JD, Katzel LI, et al. Sleep-disordered breathing and insulin resistance in middle-aged and overweight men. Am J Respir Crit Care Med. 2002;165(5):677-682.

12. Steier J, Martin A, Harris J, et al. Predicted relative prevalence estimates for obstructive sleep apnoea and the associated healthcare provision across the UK. Thorax. 2014 Apr;69(4):390-2. doi: 10.1136/thoraxjnl-2013-203887. PubMed PMID: 24062427; eng.
13. Levy P, Bonsignore MR, Eckel J. Sleep, sleep-disordered breathing and metabolic consequences. Eur Respir J. 2009;34(1):243-260.
14. Palm A, Janson C, Lindberg E. The impact of obesity and weight gain on development of sleep problems in a population-based sample. Sleep Med. 2015;16(5):593-597.
15. Slater G, Pengo MF, Kosky C, et al. Obesity as an independent predictor of subjective excessive daytime sleepiness. Respir Med. 2013;107(2):305-309.
16. Rahmouni K, Correia MLG, Haynes WG, et al. Obesity-associated hypertension new insights into mechanisms. Hypertension. 2005;45(1):9-14.
17. McNicholas WT, Bonsignore MR, Management Committee of EUCAB. Sleep apnoea as an independent risk factor for cardiovascular disease: current evidence, basic mechanisms and research priorities. Eur Respir J. 2007;29(1):156-178.
18. Sharples LD, Clutterbuck-James AL, Glover MJ, et al. Meta-analysis of randomised controlled trials of oral mandibular advancement devices and continuous positive airway pressure for obstructive sleep apnoea-hypopnoea. Sleep Med Rev. 2016;27:108-124.
19. Sullivan C, Berthon-Jones M, Issa F, et al. Reversal of obstructive sleep apnoea by continuous positive airway pressure applied through the nares. The Lancet. 1981;317(8225):862-865.
20. Steier J, Jolley CJ, Seymour J, et al. Increased load on the respiratory muscles in obstructive sleep apnea. Respir Physiol Neurobiol. 2010;171(1):54-60.
21. Steier J, Jolley CJ, Seymour J, et al. Neural respiratory drive in obesity. Thorax. 2009;64(8):719-725.
22. Tomfohr LM, Ancoli-Israel S, Loredo JS, et al. Effects of continuous positive airway pressure on fatigue and sleepiness in patients with obstructive sleep apnea: data from a randomized controlled trial. Sleep. 2011;34(1):121-126.

23. Marshall NS, Barnes M, Travier N, et al. Continuous positive airway pressure reduces daytime sleepiness in mild to moderate obstructive sleep apnoea: a meta-analysis. Thorax. 2006;61(5):430-434.

24. Parish JM, Lyng PJ. Quality of life in bed partners of patients with obstructive sleep apnea or hypopnea after treatment with continuous positive airway pressure. CHEST Journal. 2003;124(3):942-947.

25. Xiao S, Bastianpillai J, Ratneswaran C, et al. Continuous Positive Airway Pressure and Breathlessness in Obese Patients with Obstructive Sleep Apnea: A Pilot Study. Sleep. 2016;39(6):1201.

26. Bazzano LA, Khan Z, Reynolds K, et al. Effect of nocturnal nasal continuous positive airway pressure on blood pressure in obstructive sleep apnea. Hypertension. 2007;50(2):417-423.

27. Pengo MF, Ratneswaran C, Berry M, et al. Effect of Continuous Positive Airway Pressure on Blood Pressure Variability in Patients With Obstructive Sleep Apnea. J Clin Hypertens. 2016;18(11):1180-1184.

28. McEvoy RD, Antic NA, Heeley E, et al. CPAP for prevention of cardiovascular events in obstructive sleep apnea. N Engl J Med. 2016;375(10):919-931.

29. Marin JM, Carrizo SJ, Vicente E, et al. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. The Lancet. 2005;365(9464):1046-1053.

30. Campos-Rodriguez F, Martinez-Garcia MA, de la Cruz-Moron I, et al. Cardiovascular mortality in women with obstructive sleep apnea with or without continuous positive airway pressure treatment: a cohort study. Ann Intern Med. 2012;156(2):115-122.

31. Martínez-García M-A, Campos-Rodríguez F, Catalán-Serra P, et al. Cardiovascular mortality in obstructive sleep apnea in the elderly: role of long-term continuous positive airway pressure treatment: a prospective observational study. Am J Respir Crit Care Med. 2012;186(9):909-916.

32. Weaver TE, Grunstein RR. Adherence to continuous positive airway pressure therapy: the challenge to effective treatment. Proc Am Thorac Soc. 2008;5(2):173-178.

33. Budhiraja R, Parthasarathy S, Drake CL, et al. Early CPAP use identifies subsequent adherence to CPAP therapy. Sleep. 2007;30(3):320.

34. Wesseling KH, Settels JJ, de Wit Bd. The measurement of continuous finger arterial pressure noninvasively in stationary subjects. Biological and psychological factors in cardiovascular disease: Springer; 1986. p. 355-375.

35. Kurki T, Smith NT, Head N, et al. Noninvasive continuous blood pressure measurement from the finger: optimal measurement conditions and factors affecting reliability. J Clin Monit. 1987;3(1):6-13.

36. Omboni S, Parati G, Frattola A, et al. Spectral and sequence analysis of finger blood pressure variability. Comparison with analysis of intra-arterial recordings. Hypertension. 1993;22(1):26-33.

37. Epstein LJ, Kristo D, Strollo Jr PJ, et al. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. J Clin Sleep Med. 2009;5(3):263-276.

38. Gozal D, Iber C, Parthasarathy S, et al. Clinical guidelines for the manual titration of positive airway pressure in patients with obstructive sleep apnea. J Clin Sleep Med. 2008;4(2):157.

39. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J. 2016;37(29):2315-2381.

40. Somers VK, White DP, Amin R, et al. Sleep apnea and cardiovascular disease: An American heart association/American college of cardiology foundation scientific statement from the American heart association council for high blood pressure research professional education committee, council on clinical cardiology, stroke council, and council on cardiovascular nursing in collaboration with the national heart, lung, and blood institute national center on sleep disorders research (national institutes of health). J Am Coll Cardiol. 2008;52(8):686-717.

41. Floras JS. Sleep apnea and cardiovascular risk. J Cardiol. 2014;63(1):3-8.
42. Prabhakar NR, Kumar GK. Mechanisms of sympathetic activation and blood pressure elevation by intermittent hypoxia. Respir Physiol Neurobiol. 2010;174(1):156-161.
43. Del Rio R, Moya EA, Parga MJ, et al. Carotid body inflammation and cardiorespiratory alterations in intermittent hypoxia. Eur Respir J. 2012;39(6):1492-1500.
44. Fletcher EC. Effect of episodic hypoxia on sympathetic activity and blood pressure. Respir Physiol. 2000;119(2):189-197.
45. Somers VK, Dyken ME, Clary MP, et al. Sympathetic neural mechanisms in obstructive sleep apnea. J Clin Invest. 1995;96(4):1897.
46. Grassi G, Seravalle G, Cattaneo BM, et al. Sympathetic activation in obese normotensive subjects. Hypertension. 1995;25(4):560-563.
47. Narkiewicz K, Van De Borne PJH, Cooley RL, et al. Sympathetic activity in obese subjects with and without obstructive sleep apnea. Circulation. 1998;98(8):772-776.
48. Bruno RM, Rossi L, Fabbrini M, et al. Renal vasodilating capacity and endothelial function are impaired in patients with obstructive sleep apnea syndrome and no traditional cardiovascular risk factors. J Hypertens. 2013;31(7):1456-1464.
49. Somers VK, Dyken ME, Mark AL, et al. Sympathetic-nerve activity during sleep in normal subjects. N Engl J Med. 1993;328(5):303-307.
50. Somers VK, Mark AL, Zavala DC, et al. Contrasting effects of hypoxia and hypercapnia on ventilation and sympathetic activity in humans. J Appl Physiol. 1989;67(5):2101-2106.
51. Hedner J, Ejnell H, Sellgren J, et al. Is high and fluctuating muscle nerve sympathetic activity in the sleep apnoea syndrome of pathogenetic importance for the development of hypertension? J Hypertens. 1988;6(4):S529-S531.
52. Bonsignore MR, Parati G, Insalaco G, et al. Baroreflex control of heart rate during sleep in severe obstructive sleep apnoea: effects of acute CPAP. Eur Respir J. 2006;27(1):128-135.
53. Ali NJ, Davies RJO, Fleetham JA, et al. The acute effects of continuous positive airway pressure and oxygen administration on blood pressure during obstructive sleep apnea. Chest. 1992;101(6):1526-1532.

54. Pengo MF, Bonafini S, Fava C, et al. Cardiorespiratory interaction with continuous positive airway pressure. J Thorac Dis. 2018;10(1):S57-S70.
55. Craig SE, Kohler M, Nicoll D, et al. Continuous positive airway pressure improves sleepiness but not calculated vascular risk in patients with minimally symptomatic obstructive sleep apnoea: the MOSAIC randomised controlled trial. Thorax. 2012;67(12):1090-1096. doi: thoraxjnl-2012-202178.
56. Luo YM, Moxham J, Polkey MI. Diaphragm electromyography using an oesophageal catheter: current concepts. Clin Sci. 2008;115(8):233-244.
57. Eulenburg C, Wegscheider K, Woehrle H, et al. Mechanisms underlying increased mortality risk in patients with heart failure and reduced ejection fraction randomly assigned to adaptive servoventilation in the SERVE-HF study: results of a secondary multistate modelling analysis. Lancet Respir Med. 2016;4(11):873-881.
58. Hall JE, Hildebrandt DA, Kuo J. Obesity hypertension: role of leptin and sympathetic nervous system. Am J Hypertens. 2001;14(S3):103S-115S.
59. Tuck ML. Obesity, the sympathetic nervous system, and essential hypertension. Hypertension. 1992;19(1 Suppl):I67.
60. Rahmouni K, Correia MLG, Haynes WG, et al. Obesity-associated hypertension. Hypertension. 2005;45(1):9-14.
61. Imholz BPM, Wieling W, van Montfrans GA, et al. Fifteen years experience with finger arterial pressure monitoring: assessment of the technology. Cardiovasc Res. 1998;38(3):605-616.
62. Nowak RM, Sen A, Garcia AJ, et al. Noninvasive continuous or intermittent blood pressure and heart rate patient monitoring in the ED. The American journal of emergency medicine. 2011;29(7):782-789.
63. Demoule A, Chevret S, Carlucci A, et al. Changing use of noninvasive ventilation in critically ill patients: trends over 15 years in francophone countries. Intensive Care Med. 2016;42(1):82-92.
64. Peter JV, Moran JL, Phillips-Hughes J, et al. Effect of non-invasive positive pressure ventilation (NIPPV) on mortality in patients with acute cardiogenic pulmonary oedema: a meta-analysis. The Lancet. 2006;367(9517):1155-1163.

Individual tables and captions

Subject (n)	Age (yrs)	Gender	BMI (kg/m^2)	AHI (hrs^{-1})	FEV_1 (L/%pred)	FVC (L/%pred)	FEV_1/FVC (%)	SBP	DBP	HTN	Drug
1	34	M	32.6	28.0	3.49 / 81	4.66 / 89	75	132	92	No	-
2	38	M	37.2	23.0	4.13 / 102	5.09 / 103	81	131	76	No	-
3	54	F	49.7	10.4	1.43 / 70	1.59 / 65	90	132	77	Yes	R, A
4	57	M	27.9	51.2	3.64 / 106	4.13 / 96	88	125	98	No	-
5	54	M	40.4	77.4	3.09 / 86	3.80 / 84	81	149	98	Yes	none
6	54	M	42.6	18.7	3.00 / 83	3.85 / 85	78	127	97	Yes	A
7	49	M	36.7	22.6	2.77 / 76	3.53 / 79	79	128	78	No	-
8	48	M	38.7	20.0	2.35 / 62	3.79 / 80	62	125	88	No	-
9	37	F	37.3	52.0	1.88 / 83	2.68 / 101	70	127	81	No	-
10	53	M	30.8	40.0	3.16 / 99	3.60 / 91	88	113	78	No	-
11	62	M	41.5	16.3	2.45 / 75	3.62 / 86	68	151	84	Yes	B, D
12	46	F	36.4	20.0	1.53 / 63	2.25 / 80	68	134	90	No	-
13	60	M	44.7	24.7	3.13 / 93	4.01 / 93	78	144	83	Yes	A, I/H
14	31	M	44.9	69.4	4.28 / 90	5.49 / 95	78	131	90	No	-
15	37	M	42.1	9.0	3.57 / 92	4.50 / 95	79	132	87	No	-
Mean	**47.6**	**3F:12M**	**38.9**	**32.2**	**2.9 / 84.1**	**3.8 / 83.5**	**77.5**	**132**	**86**	**n=5**	
SD	**9.9**		**5.8**	**21.1**	**0.9 / 13.3**	**1.0 / 19.8**	**8.0**	**10**	**8**		

Table 1: Participant demographics and baseline variables, mean and standard deviation (SD). FEV_1 = forced expiratory volume in one second. FVC = forced vital capacity. SBP = baseline systolic blood pressure. DBP = baseline diastolic blood pressure. HTN = hypertension. A = Amlodipine, B = Bendroflumethiazide, D = Doxazosin, I/H = Irbesartan/Hydrochlorthiazide, R = Ramipril. %pred = precent predicted.

	BP, baseline (mean ± sd)	BP, maximal (mean ± sd)	Δ BP (95%CI)	p-value
BP systolic (mmHg)	137.3 ± 18.9	160.5 ± 23.5	23.2 (7.9, 38.4)	0.011
BP diastolic (mmHg)	70.0 ± 13.6	88.2 ± 18.5	18.3 (2.3, 34.2)	0.009
BPV systolic (mmHg)	5.3 ± 2.6	10.4 ± 5.5	5.1 (0.7, 9.5)	< 0.001
BPV diastolic (mmHg)	3.1 ± 1.6	6.2 ± 2.2	3.0 (0.3, 5.8)	< 0.001

Table 2: Baseline (0 cmH_2O) and maximum blood pressure (BP), blood pressure variability (BPV) and change in BP (delta BP: maximum – baseline), analysed using the paired t-test. SD = standard deviation.

Figure Legends:

Figure 1: CPAP titration and blood pressure changes (mean ± standard error) from baseline (n=15). Systolic blood pressure (grey line), diastolic blood pressure (black line).

Figure 2: Systolic blood pressure variability (mean ± standard error) presented at each level of CPAP (0-20cmH_2O).

Figure 3: Diastolic blood pressure variability (mean ± standard error) presented at each level of CPAP (0-20cmH_2O).