Review Article

Intermittent hypoxia, cardiovascular disease and obstructive sleep apnoea

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Abstract: Obstructive sleep apnoea (OSA) is a common disorder and is associated with cardiovascular disease. Continuous positive airway pressure (CPAP), whilst reducing blood pressure, has not been shown to reduce cardiovascular events when used as a treatment solely for this purpose in patients with previous cardiovascular disease. Developing a better understanding of the mechanisms underlying cardiovascular disease in OSA is important to develop new treatments. Potential causative mechanisms for cardiovascular disease in OSA include arousal induced sympathetic activation, large intrathoracic pressure swings leading to shear stress on the heart and great vessels, and intermittent hypoxia (IH). This review discusses the role of IH, as a major physiological consequence of OSA, in the development of cardiovascular disease.

Keywords: Sleep apnea; obstructive; cardiovascular diseases; hypertension; hypoxia

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Introduction

Obstructive sleep apnoea (OSA) is a common condition (1,2), characterised by episodic upper airway narrowing during sleep. The episodic upper airway narrowing during sleep leads to intermittent hypoxia (IH) and arousals from sleep. There is a clear association between OSA and cardiovascular disease (3). OSA is associated with hypertension (4,5), increased sympathetic activation (6), endothelial dysfunction (7), oxidative stress (8), and possibly systemic inflammation (9). IH, recurrent arousals, recurrent intrathoracic pressure swings, and sleep fragmentation are thought to be key pathological processes in the development of cardiovascular disease in OSA (10). This review will focus on the role of IH in the development of cardiovascular disease.

Hypertension and sympathetic activation

Hypertension is one of the main risk factors for cardiovascular disease and the leading cause of mortality from stroke and ischaemic heart disease (11). OSA is associated with increased blood pressure (12), and with increased diagnoses of hypertension (4,5). Continuous positive airway pressure (CPAP) treatment for OSA has been shown to reduce both systolic and diastolic blood pressure by approximately 2 to 3 mmHg (13,14). The additional benefit of CPAP may be more marked in those with resistant hypertension on multiple medications (15), whilst benefits from the addition of CPAP to hypertension, responding to single agent therapies, are less marked (16).

Animal models of IH have shown its potential importance in the development of hypertension in OSA. Fletcher's group elegantly showed in some species of rodents that IH leads to a significant increase in blood pressure that are independent of hypercapnia (17). This was dependent on carotid chemoceptors (18), the sympathetic nervous system (19), the renal arteries (20), and the renin-angiotensin-aldosterone axis (21). Although there were large increases in blood pressure due to sympathetic activation, increases in heart rate were not seen with experimental IH. Sustained rises in blood pressure have been shown to be secondary to

upper airway occlusion and its consequences including IH, and not recurrent arousals, in a canine model of OSA (22).

Exposure to hypoxia is known to lead to elevations in blood pressure in healthy individuals, both in those exposed to sustained hypoxia at altitude (23), and those exposed to IH (24). Whilst increased sympathetic activity and increased blood pressure are seen with both sustained and IH, increases in heart rate are only seen with sustained hypoxia (24,25). The reasons for IH only leading to increased daytime blood pressure and not heart rate are unclear. A possible explanation may be sustained alterations in the renin-angiotensin-aldosterone axis following acute alterations in sympathetic activity with IH (21), with changes in sympathetic-vagal balance only leading acute elevations in heart rate during exposure to IH (26).

Acute blood pressure rises overnight are likely to be related to arousal. Blood pressure rises accompany arousal in healthy individuals with simulated apnoeas (27), and following spontaneous apnoeas in OSA patients (28). Blood pressure rises are similar when arousals are induced by apnoeas with or without supplemental oxygen in OSA patients (29), with arousals from an auditory stimulus in OSA patients (28), or with arousals from a combined auditory and vibratory stimulus in healthy volunteers (30). Hypoxia without arousal does not lead to acute blood pressure rises (28). IH in OSA may have a modulatory effect on sympathetic activation (31), and sustained hypoxia increases sympathetic activation for days following descent to sea level (25). The combination of OSA and hypoxia induced by travel to altitude in lowlanders causes elevations in blood pressure compared to levels prior to ascent, and this increase is somewhat mitigated by acetazolamide (32). Acetazolamide improves both mean oxygen saturations as well as the AHI at altitude so it is not clear if the effect on blood pressure is due to improvements in hypoxia or other mechanisms such as reduced arousal mediated sympathetic activity.

All of this evidence supports the importance of IH in leading to increased blood pressure in OSA via sustained increases in sympathetic activation. Supplemental oxygen in OSA, by attenuating IH, may lead to similar reductions in blood pressure as CPAP (14). To date there have been two randomised controlled trials looking at the longer-term effect of supplemental oxygen on blood pressure in OSA (33,34). Although supplemental oxygen was shown to reduce catecholamine, suggesting a reduction in sympathetic activation (34), supplemental oxygen had no effect on daytime blood pressure (33,34). Both of these studies have limitations; low flow rates of oxygen were used (2 or 3 L/min), patients with severe OSA or severe hypoxaemia were excluded (33), and CPAP had only a small treatment effect on blood pressure (1.9 mmHg). Therefore, these have not definitively established the role of overnight IH in the observed elevated diurnal blood pressures seen in patients with OSA.

Oxidative stress

Oxidative stress results from an imbalance between the production of reactive oxygen species (ROS) and antioxidant mechanisms. IH is thought to lead to oxidative stress by decreasing antioxidant mechanisms in periods of hypoxia and increasing ROS production during periods of reoxygenation; termed an ischaemia-reperfusion injury (35). Oxidative stress is thought to be a central mechanism in the development of cardiovascular disease (36). Oxidative stress may lead to hypertension via increased brain nuclei sympathetic activation and increased angiotensin II (37), and endothelial dysfunction which is thought to be a precursor of atheroma formation (38), and will be discussed later in this review. Whilst obesity and diabetes are more established risk factors for oxidative stress (39), the role of IH in OSA is less certain.

Animal experiments have shown tissue specific increases in oxidative stress following IH, for example; in the heart (40), in the brain (41), and in the mesenteric arteries (42). In human experiments, where healthy individuals were exposed to IH during the daytime, some blood biomarkers of oxidative stress have been found to increase (43).

OSA patients exhibit increased levels of ROS production from monocytes and granulocytes when compared to control subjects (44). In addition endothelial cells harvested from forearm veins of OSA patients show signs of increased inflammation and oxidative stress which is correlated to impaired endothelial function (38). A novel breath analysis technique has highlighted a family of compounds associated with OSA, which are linked to oxidative stress (45). However, elevated oxidative stress is not a universal finding in OSA, with others reporting no increases in systemic markers of oxidative stress in OSA (46-48).

Oxidative stress and its relationship to cardiovascular disease is tissue specific (49). Whilst blood is readily accessible, changes in traditional blood biomarkers of oxidative stress may not accurately reflect levels of oxidative stress in the coronary arteries or elsewhere in the cardiovascular system. Novel approaches are required to establish the role that tissue specific oxidative stress plays in

the development of cardiovascular disease in OSA.

Endothelial dysfunction

An important role of the endothelium is in sensing changes in blood flow and releasing substances that regulate arterial calibre in response to these flow changes, described as endothelial function. It has been recognized that impairment of endothelial function occurs in both hypertension (50), and in patients with coronary artery atherosclerosis (51), therefore it is commonly thought to be an early stage in the development of cardiovascular disease. Endothelial function is commonly assessed by measuring flow mediated dilatation at the brachial artery (52), and this non-invasive measurement is used as a surrogate marker of endothelial function elsewhere, such is in the coronary arteries.

Animal models suggest that IH only leads to endothelial dysfunction in the early stages of atherosclerosis. Only early preatherosclerotic mice, and not mice fed a high fat diet leading to advanced preatherosclerotic, had impaired endothelial function following IH compared to control (53). Endothelial dysfunction under conditions of IH may be dependent on inflammation and oxidative stress as the anti-inflammatory drug infliximab, and the antioxidant drug L-glutathione, both blocked this impairment (54). Others have found that whilst markers of oxidative stress were increased by IH, IH only leads to endothelial dysfunction in mice when combined with a high fat diet (55).

In vitro studies using endothelial cells exposed to donated microvesicles from the blood of individuals exposed to IH showed adverse effects on these endothelial cells' function (56). Experimental exposure to IH in healthy human volunteers, whilst leading to rises in blood pressure, may not cause the same effect on endothelial function as observed in animal and *in vitro* studies (57).

There is clear evidence of endothelial dysfunction in patients with OSA (58), and this is improved by treatment with CPAP (59,60). There is contrasting evidence from animal experiments, *in vitro* studies, and experimentally induced IH in healthy individuals as to the role of IH in OSA in causing endothelial dysfunction.

What determines cardiovascular risk in OSA?

There is an association between OSA and cardiovascular disease. In uncontrolled longitudinal observational studies, severe untreated OSA has been shown to be a risk factor for cardiovascular disease (3,61). Whilst adjustments are made for known confounders such as obesity in these longitudinal studies, they cannot account for unknown confounders such as compliance with anti-hypertensives and statins. Randomised control trials are needed to provide further insight into whether OSA has a causal role in the development of cardiovascular disease.

The SAVE trial is the first large RCT to look at the long-term effect of CPAP cardiovascular events (62). This did not show a reduction in cardiovascular events with CPAP compared to standard care. This study was powered to detect a difference in cardiovascular events despite only a moderate compliance with CPAP of, on average, 3.3 hours/night. The conclusions that can be drawn from this study are limited to secondary prevention of cardiovascular disease, and it may be that younger patients without prior cardiovascular disease would derive a benefit from CPAP, unlike the studied population (63). In addition the SAVE study did not include those most sleepy (patients with an Epworth sleepiness score or ESS >15 were excluded), nor those with severe hypoxaemia (patients with >10% of their sleep study time with oxygen saturations <80% were also excluded).

The severity of hypoxaemia may be of relevance in determining risk cardiovascular risk. The risk of cardiovascular disease with OSA in middle-aged community-based adults as part of the Sleep Heart Health Study was found to be related to the severity of oxygen desaturations (64). The relationship between OSA and cardiovascular disease was lost when considering hypopnoeas or oxygen desaturations <4%. This suggests that only more significant desaturations greater than this 4% threshold are those of relevance to the development of cardiovascular disease.

The results of the SAVE study suggest there is no additional benefit in reduction of cardiovascular risk in secondary prevention for OSA in patients without severe sleepiness or hypoxia (62). CPAP may reduce cardiovascular risk for those more sleepy or more severe OSA patients who will currently be treated for symptoms anyway (65). Future work is required to explore whether other therapies may be beneficial in reducing cardiovascular risk in OSA.

CPAP withdrawal

CPAP withdrawal is an experimental way of modelling the short-term consequences of OSA. CPAP withdrawal can be used to assess the physiological effects of OSA without

the confounding effects seen in cohort studies or the issues of low CPAP usage in conventional RCTs. Patients with known OSA who have been established on CPAP with good average usage, typically for over one year, are randomised to two weeks of sham CPAP (with return of significant OSA) or continued therapeutic CPAP (control group). The return of OSA during CPAP withdrawal is associated with a 9 mmHg rise in systolic, and 7.8 mmHg rise in diastolic, home early morning blood pressure (66), increased sympathetic activity with increased urinary normetanephrine and impaired endothelial function (58). Whilst blood and urine biomarkers of oxidative stress are not increased by CPAP withdrawal (47,48), sophisticated analysis of exhaled breath shows an increase in compounds associated with oxidative stress with CPAP withdrawal (45).

CPAP withdrawal is therefore a powerful experimental design to further explore the physiological changes in OSA. Currently we are running a trial assessing the effect of overnight supplemental oxygen during CPAP withdrawal on its ability to attenuate, or not, the expected blood pressure rise (ISRCTN: 17987510). This trial is using supplemental oxygen at a flow rate of 5 L/min, which is higher than previous trials (33,34), on morning blood pressure during CPAP withdrawal. Preliminary results are encouraging in showing a marked attenuation of IH with minimal effect on AHI and autonomic arousals (67).

Conclusions

IH is a key feature of OSA. There is clear evidence from animal models, *in vitro* studies and human experimental models of IH of its potential deleterious effects. There is evidence that IH leads to hypertension and sympathetic activation in humans, oxidative stress, and endothelial dysfunction. However, in OSA in addition to IH, there are other potential mechanisms that may lead to cardiovascular disease including arousal induced sympathetic activation, sleep fragmentation, and intra-thoracic pressure swings. A greater understanding of the relevant contributions of each of these mechanisms to the development of cardiovascular disease in OSA is of great importance. The SAVE trial showed no additional benefit of CPAP above standard care in preventing further cardiovascular events in patients with prior cardiovascular disease, with the notable exception that it did not include the most sleepy or hypoxemic patients. Supplemental oxygen therapy has the potential to both attenuate the IH and the increased morning blood pressure seen in OSA, but current randomised trials assessing this have had methodological limitations. A greater understanding of the role of IH in the development of cardiovascular in OSA is needed to determine if supplemental oxygen could be a therapy when CPAP is not tolerated, for example in non-sleepy individuals with OSA and resistant hypertension.

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Footnote

Conflicts of Interest: CD Turnbull has done some consulting work for Bayer outside of the scope of this manuscript.

References

1. Young T, Palta M, Dempsey J, et al. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med 1993;328:1230-5.
2. Heinzer R, Vat S, Marques-Vidal P, et al. Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study. Lancet Respir Med 2015;3:310-8.
3. 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. Lancet 2005;365:1046-53.
4. Peppard PE, Young T, Palta M, et al. Prospective study of the association between sleep-disordered breathing and hypertension. N Engl J Med 2000;342:1378-84.
5. Nieto FJ, Young TB, Lind BK, et al. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. Sleep Heart Health Study. JAMA 2000;283:1829-36.
6. Carlson JT, Hedner J, Elam M, et al. Augmented resting sympathetic activity in awake patients with obstructive sleep apnea. Chest 1993;103:1763-8.
7. Kato M, Roberts-Thomson P, Phillips BG, et al. Impairment of endothelium-dependent vasodilation of resistance vessels in patients with obstructive sleep apnea. Circulation 2000;102:2607-10.
8. Eisele HJ, Markart P, Schulz R. Obstructive sleep apnea, oxidative stress, and cardiovascular disease: evidence from human studies. Oxid Med Cell Longev 2015;2015:608438
9. Bouloukaki I, Mermigkis C, Tzanakis N, et al. Evaluation

of inflammatory markers in a large sample of obstructive sleep apnea patients without comorbidities. Mediators Inflamm 2017;2017:4573756.
10. Kohler M, Stradling JR. Mechanisms of vascular damage in obstructive sleep apnea. Nat Rev Cardiol 2010;7:677-85.
11. Lawes CM, Vander Hoorn S, Rodgers A, et al. Global burden of blood-pressure-related disease, 2001.Lancet 2008;371:1513-8.
12. Davies CW, Crosby JH, Mullins RL, et al. Case-control study of 24 hour ambulatory blood pressure in patients with obstructive sleep apnoea and normal matched control subjects. Thorax 2000;55:736-40.
13. Pepperell JC, Ramdassingh-Dow S, Crosthwaite N, et al. Ambulatory blood pressure after therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: a randomised parallel trial. Lancet 2002;359:204-10.
14. Hu X, Fan J, Chen S, et al. The role of continuous positive airway pressure in blood pressure control for patients with obstructive sleep apnea and hypertension: a meta-analysis of randomized controlled trials. J Clin Hypertens (Greenwich) 2015;17:215-22.
15. de Oliveira AC, Martinez D, Massierer D, et al. The antihypertensive effect of positive airway pressure on resistant hypertension of patients with obstructive sleep apnea: a randomized, double-blind, clinical trial. Am J Respir Crit Care Med 2014;190:345-7.
16. Thunström E, Manhem K, Rosengren A, et al. Blood pressure response to losartan and continuous positive airway pressure in hypertension and obstructive sleep apnea. Am J Respir Crit Care Med. 2016;193:310-20.
17. Fletcher EC, Lesske J, Qian W, et al. Repetitive, episodic hypoxia causes diurnal elevation of blood pressure in rats. Hypertension 1992;19:555-61.
18. Fletcher EC, Lesske J, Behm R, et al. Carotid chemoreceptors, systemic blood pressure, and chronic episodic hypoxia mimicking sleep apnea. J Appl Physiol (1985) 1992;72:1978-84.
19. Lesske J, Fletcher EC, Bao G, et al. Hypertension caused by chronic intermittent hypoxia--influence of chemoreceptors and sympathetic nervous system. J Hypertens 1997;15:1593-603.
20. Fletcher EC, Bao G, Li R. Renin activity and blood pressure in response to chronic episodic hypoxia. Hypertension 1999;34:309-14.
21. Fletcher EC, Orolinova N, Bader M. Blood pressure response to chronic episodic hypoxia: the renin-angiotensin system. J Appl Physiol (1985) 2002;92:627-33.
22. Brooks D, Horner RL, Kozar LF, et al. Obstructive sleep apnea as a cause of systemic hypertension. Evidence from a canine model. J Clin Invest 1997;99:106-9.
23. Parati G, Revera M, Giuliano A, et al. Effects of acetazolamide on central blood pressure, peripheral blood pressure, and arterial distensibility at acute high altitude exposure. Eur Heart J 2013;34:759-66.
24. Tamisier R, Pépin JL, Rémy J, et al. 14 nights of intermittent hypoxia elevate daytime blood pressure and sympathetic activity in healthy humans. Eur Respir J 2011;37:119-28.
25. Hansen J, Sander M. Sympathetic neural overactivity in healthy humans after prolonged exposure to hypobaric hypoxia. J Physiol 2003;546:921-9.
26. Almeida GPL, Trombetta IC, Cepeda FX, et al. The role of acute intermittent hypoxia in neutrophil-generated superoxide, sympathovagal balance, and vascular function in healthy subjects. Front Physiol.2017;8:4.
27. Ringler J, Garpestad E, Basner RC, et al. Systemic blood pressure elevation after airway occlusion during NREM sleep. Am J Respir Crit Care Med 1994;150:1062-6.
28. Ringler J, Basner RC, Shannon R, et al. Hypoxemia alone does not explain blood pressure elevations after obstructive apneas. J Appl Physiol (1985) 1990;69:2143-8.
29. Ali NJ, Davies RJ, Fleetham JA, et al. The acute effects of continuous positive airway pressure and oxygen administration on blood pressure during obstructive sleep apnea. Chest 1992;101:1526-32.
30. Davies RJ, Belt PJ, Roberts SJ, et al. Arterial blood pressure responses to graded transient arousal from sleep in normal humans. J Appl Physiol (1985) 1993;74:1123-30.
31. Smith ML, Niedermaier ON, Hardy SM, et al. Role of hypoxemia in sleep apnea-induced sympathoexcitation. J Auton Nerv Syst 1996;56:184-90.
32. Nussbaumer-Ochsner Y, Latshang TD, Ulrich S, et al. Patients with obstructive sleep apnea syndrome benefit from acetazolamide during an altitude sojourn: a randomized, placebo-controlled, double-blind trial. Chest 2012;141:131-8.
33. Gottlieb DJ, Punjabi NM, Mehra R, et al. CPAP versus oxygen in obstructive sleep apnea. N Engl J Med 2014;370:2276-85.
34. Mills PJ, Kennedy BP, Loredo JS, et al. Effects of nasal continuous positive airway pressure and oxygen supplementation on norepinephrine kinetics and cardiovascular responses in obstructive sleep apnea. J Appl Physiol (1985) 2006;100:343-8.

35. Neri M, Riezzo I, Pascale N, et al. Ischemia/reperfusion injury following acute myocardial infarction: a critical issue for clinicians and forensic pathologists. Mediators Inflamm 2017;2017:7018393.
36. Münzel T, Camici GG, Maack C, et al. Impact of oxidative stress on the heart and vasculature: part 2 of a 3-part series. J Am Coll Cardiol 2017;70:212-29.
37. Datla SR, Griendling KK. Reactive oxygen species, NADPH oxidases, and hypertension. Hypertension 2010;56:325-30.
38. Jelic S, Padeletti M, Kawut SM, et al. Inflammation, oxidative stress, and repair capacity of the vascular endothelium in obstructive sleep apnea. Circulation 2008;117:2270-8.
39. Niemann B, Rohrbach S, Miller MR, et al. Oxidative stress and cardiovascular risk: obesity, diabetes, smoking, and pollution: part 3 of a 3-part series. J Am Coll Cardiol 2017;70:230-51.
40. Chen L, Einbinder E, Zhang Q, et al. Oxidative stress and left ventricular function with chronic intermittent hypoxia in rats. Am J Respir Crit Care Med 2005;172:915-20.
41. Row BW, Liu R, Xu W, et al. Intermittent hypoxia is associated with oxidative stress and spatial learning deficits in the rat. Am J Respir Crit Care Med 2003;167:1548-53.
42. Troncoso Brindeiro CM, da Silva AQ, Allahdadi KJ, et al. Reactive oxygen species contribute to sleep apnea-induced hypertension in rats. Am J Physiol Heart Circ Physiol 2007;293:H2971-2976.
43. Pialoux V, Hanly PJ, Foster GE, et al. Effects of exposure to intermittent hypoxia on oxidative stress and acute hypoxic ventilatory response in humans. Am J Respir Crit Care Med 2009;180:1002-9.
44. Dyugovskaya L, Lavie P, Lavie L. Increased adhesion molecules expression and production of reactive oxygen species in leukocytes of sleep apnea patients. Am J Respir Crit Care Med 2002;165:934-9.
45. Schwarz EI, Martinez-Lozano Sinues P, Bregy L, et al. Effects of CPAP therapy withdrawal on exhaled breath pattern in obstructive sleep apnoea. Thorax 2016;71:110-7.
46. Paz Y Mar HL, Hazen SL, Tracy RP, et al. Effect of continuous positive airway pressure on cardiovascular biomarkers: the sleep apnea stress randomized controlled trial. Chest 2016;150:80-90.
47. Stradling JR, Schwarz EI, Schlatzer C, et al. Biomarkers of oxidative stress following continuous positive airway pressure withdrawal: data from two randomised trials. Eur Respir J 2015;46:1065-71.
48. Turnbull CD, Akoumianakis I, Antoniades C, et al. Overnight urinary isoprostanes as a marker of oxidative stress in obstructive sleep apnoea. Eur Respir J 2017;49. pii: 1601787.
49. Margaritis M, Sanna F, Lazaros G, et al. Predictive value of telomere length on outcome following acute myocardial infarction: evidence for contrasting effects of vascular vs. blood oxidative stress. Eur Heart J 2017;38:3094-104.
50. Antony I, Lerebours G, Nitenberg A. Loss of flow-dependent coronary artery dilatation in patients with hypertension. Circulation 1995;91:1624-8.
51. Cox DA, Vita JA, Treasure CB, et al. Atherosclerosis impairs flow-mediated dilation of coronary arteries in humans. Circulation 1989;80:458-65.
52. Celermajer DS, Sorensen KE, Gooch VM, et al. Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. Lancet 1992;340:1111-5.
53. Tuleta I, França CN, Wenzel D, et al. Intermittent hypoxia impairs endothelial function in early preatherosclerosis. Adv Exp Med Biol 2015;858:1-7.
54. Tuleta I, França CN, Wenzel D, et al. Hypoxia-induced endothelial dysfunction in apolipoprotein E-deficient mice; effects of infliximab and L-glutathione. Atherosclerosis 2014;236:400-10.
55. Badran M, Golbidi S, Devlin A, et al. Chronic intermittent hypoxia causes endothelial dysfunction in a mouse model of diet-induced obesity. Sleep Med 2014;15:596-602.
56. Khalyfa A, Zhang C, Khalyfa AA, et al. Effect on intermittent hypoxia on plasma exosomal micro RNA signature and endothelial function in healthy adults. Sleep 2016;39:2077-90.
57. Tremblay JC, Boulet LM, Tymko MM, et al. Intermittent hypoxia and arterial blood pressure control in humans: role of the peripheral vasculature and carotid baroreflex. Am J Physiol Heart Circ Physiol 2016;311:H699-706.
58. Kohler M, Stoewhas AC, Ayers L, et al. Effects of continuous positive airway pressure therapy withdrawal in patients with obstructive sleep apnea: a randomized controlled trial. Am J Respir Crit Care Med 2011;184:1192-9.
59. Kohler M, Craig S, Pepperell JCT, et al. CPAP improves endothelial function in patients with minimally symptomatic OSA: results from a subset study of the MOSAIC trial. Chest 2013;144:896-902.
60. Schwarz EI, Puhan MA, Schlatzer C, et al. Effect of CPAP therapy on endothelial function in obstructive sleep apnoea: A systematic review and meta-analysis. Respirology 2015;20:889-95.

61. 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;122:352-60.
62. McEvoy RD, Antic NA, Heeley E, et al. CPAP for prevention of cardiovascular events in obstructive sleep apnea. N Engl J Med 2016;375:919-31.
63. Lavie P, Herer P, Lavie L. Mortality risk factors in sleep apnoea: a matched case-control study. J Sleep Res 2007;16:128-34.
64. Punjabi NM, Newman AB, Young TB, et al. Sleep-disordered breathing and cardiovascular disease: an outcome-based definition of hypopneas. Am J Respir Crit Care Med 2008;177:1150-5.
65. National Institute for Health and Clinical Excellence. Continuous positive airway pressure for the treatment of obstructive sleep apnoea/hypopnoea syndrome. Technology appraisal guidance [TA139] Published date: 26 March 2008.
66. Schwarz EI, Schlatzer C, Rossi VA, et al. Effect of CPAP withdrawal on BP in OSA: data from three randomized controlled trials. Chest 2016;150:1202-1210.
67. Turnbull C, Johar A, Petousi N, et al. The effects of supplemental oxygen on obstructive sleep apnea during cpap withdrawal: preliminary dat from a randomised control trial. Am J Respir Crit Care Med 2017;195:A2579.

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