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 chemoreceptors (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**

of inflammatory markers in a large sample of obstructive sleep apnea patients without comorbidities. Mediators Inflamm 2017;2017:4573756.


