The Right Heart Diaries in Sleep Disordered Breathing

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ABSTRACT

Epidemiologic studies show that sleep apnea increases risks for cardiovascular disease independently of individuals’ demographic characteristics or risk markers i.e., smoking, alcohol, obesity, diabetes, dyslipidemia, atrial fibrillation, and hypertension. Individuals with severe sleep apnea are at increased risk for pulmonary arterial hypertension. The underlying mechanisms explaining associations between obstructive sleep apnea and pulmonary arterial hypertension are not entirely delineated. Several intermediary mechanisms might be involved including sustained sympathetic activation, intrathoracic pressure changes, and oxidative stress. Other abnormalities such as disorders in coagulation factors, endothelial damage, platelet activation, and increased inflammatory mediators might also play a role in the pathogenesis of pulmonary hypertension and cardiovascular disease. Linkage between obstructive sleep apnea and pulmonary arterial hypertension is corroborated by evidence that treatment of sleep apnea with continuous positive airway pressure reduces systolic blood pressure, improves left ventricular systolic function, and diminishes platelet activation. Several systematic studies are necessary to explicate complex associations between sleep apnea and pulmonary hypertension.

Key words: Sleep apnea, pulmonary arterial hypertension, right heart
Short Term Pulmonary Vascular Changes Due To SDB

When compared to controls(15), nocturnal systemic circulation in SDB shows a decline in cardiac output (22%) and cardiac index (24 %) while a rise in systemic vascular resistance (18%) due to increased parasympathetic tone and decreased sympathetic tone when compared to daytime values (10,13). However Rapid eye movement (REM) sleep is characterized by a decrease in parasympathetic and an increase in sympathetic tone due to augmented baroreflex activity, resulting in an elevation of blood pressure and heart rate to levels similar to those registered during wakefulness although less than wakefulness (14). Blood pressure falls to its lowest level during the first few hours of sleep, followed by a marked surge in the morning hours coinciding with the transition from sleep to wakefulness. The average difference between waking and sleeping systolic and diastolic pressure is 10% to 20% (11). In the post wake up, there is a rise in cardiac output and stroke volume leading to high blood pressure. The absence of physical activity during the night is instrumental in the genesis of cardio-vascular (CV) circadian rhythm. When subjects rest during the daytime instead of being ambulant, the circadian variation in blood pressure and heart rate to levels similar to those registered during wakefulness although less than wakefulness (14). Blood pressure falls to its lowest level during the first few hours of sleep, followed by a marked surge in the morning hours coinciding with the transition from sleep to wakefulness.
contributing to acute changes in pulmonary artery pressure (PAP) (16). In NREM-SDB: systolic and diastolic PAP decline at the beginning of the respiratory event and begin to rise again at the resumption of airflow (17). In REM-SDB: PAP is higher during REM than NREM SDB, and the difference can be related to the more profound falls in SaO2 observed during REM sleep (18).

**Long Term Pulmonary Vascular Changes Due To SDB**

Repetitive cycles of hypoxia and reoxygenation due to SDB promotes alterations in endothelial function (19) which in turn causes diminished nitric oxide release (20). This contributes to increased vascular smooth muscle tone and vascular remodeling which is proportional to the severity and duration of nocturnal desaturations. In a necropsy study on 20 obese subjects, half of whom had presented with SDB, Ahmed et al. found muscularisation of arterioles with a diameter of <100 μm and moderate hypertrophy of muscle cells of the pulmonary arterial media (21). The finding of mild hypoxemia in PH patients with SDB without any apparent lung disease is intriguing (22). One possibility is that it may be because of subtle changes in small airway function associated with obesity and chest wall mass loading; however, a recent study of nocturnal desaturation and daytime hypoxemia in patients with SDB suggests that the direction of association may be from nocturnal desaturation to awake hypoxemia and not the reverse (22). One possible explanation raised by the authors of the latter study is that repeated nocturnal desaturation may lead to recurrent PH and pulmonary vascular injury that in turn may lead to mild hypoxemia. Severity of SDB and nocturnal desaturation have also been linked with an increased hematocrit levels (23), although not into the polycythemia range. When compared to controls, SDB patients demonstrate increased blood viscosity with the greatest differences on first rising in the morning (24). These observations are supported by findings that PH appears to worsen across the course of the night (25).

**Obstructive Sleep Apnea And Pulmonary Hypertension**

Currently, PH due to SDB is placed in group 3 of World Health Organization (WHO) classification (Table 1) (9). PH is common in patients with OSA, with reported estimates ranging between 16% and 42% (26,27). Discrepancies in prevalence estimates result from differences in study methodology. For example, most studies include only a small number of patients often unselected for comorbidities, and use varying definitions of pulmonary hyperten-

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### Obstructive Sleep Apnea And Right And Left Heart

Moderated-severe OSA (AHI ≥ 15) has been shown to have a deleterious effect over right (32,33) and left ventricular contractility (34) independently of other risk factors such as obesity, and pulmonary and arterial systolic pressure respectively (35). Of importance is that global and diastolic myocardial function of the left ventricle is impaired in OSA, even when systolic function is not. Concomitant atrial enlargement has also been reported in this population (36). The increase in atrial volume index could explain the predisposition of these patients to develop atrial fibrillation (37) with concomitant complications and/or perpetuation of heart failure. OSA is associated with increased right ventricular wall thickening but, contrary to left ventricular hypertrophy, right ventricular hypertrophy has not been confirmed as an independent predictor of adverse cardiovascular outcomes (38,39).

### Pathophysiology of OSA in Pulmonary Arterial Hypertension

**A. Effects of hypoxia:** A significant inverse correlation between PAP and SaO2 has been documented in most SDB patients, suggesting an integral role of hypoxia in the pathogenesis of nocturnal PH. Patients with PH tend to be more hypoxemic during daytime wakefulness than patients without PH, a finding that could either contribute to or result from PH (41). However administration of O2 to maintain SaO2 ≥90% has only prolonged the SDB without affecting the mean PAP or the amplitude of PAP swings (42). These findings can be explained by the counteractive vasoconstrictive effects of hypercapnia caused by prolonged SDB (43). PAP during O2 administration has been shown to decrease in younger patients with minor rises in transcutaneous carbon dioxide tension suggesting...
that structural vascular remodeling influences the pulmonary haemodynamic response to SDB (42). An additional possibility is that pulmonary hypoxic vasconstriction may develop slowly, requiring repetitive and profound desaturations to significantly increase PAP (41). SDB during NREM sleep recurs with relatively constant characteristics in each patient, making the analysis of a slow effect of hypoxia difficult. In animal model of SDB by means of repetitive airway obstructions of different duration, CV changes were analyzed over a wide range of SaO2 values (42). At the release of airway occlusion, PAP progressively increased as SaO2 decreased, but oxygen administration prevented the occurrence of the pulmonary hypertensive peaks (42).

**B. Mechanical Effects:** SDB-induced mechanical changes may also affect the pulmonary circulation (44). The lower intrathoracic pressure during NREM-SDB episode is found out to be associated with increased pulmonary vascular resistance (PVR) but lower pulmonary flow (RVSV) (45). This increase in PVR could not be ascribed to lung volume changes, absent during apneas, but may reflect the effects of negative intrathoracic pressure on the left heart. Limitation of left ventricle filling (LVF) filling and emptying (46) could at least contribute to increase PVR during SDB by increasing pulmonary venous pressure and blood volume (47). This hypothesis is further supported by the high pulmonary arterial wedge pressure documented during SDB (47) and by the possible, albeit infrequent, clinical presentation of obstructive sleep apnea (OSA) as nocturnal pulmonary edema (48). Thus, mechanical changes affect PVR during the apneic phase, while the pulmonary hypertensive peaks seem to be related mostly to hypoxemia, since they occur when intrathoracic pressure returns towards normal values and are blunted by oxygen administration (49).

**C. Autonomic Effects:** However, hypoxia may not be the only pathogenic factor responsible for the post-apneic increase in PAP. At the resolution of SDB, the similar behaviour of the pulmonary and systemic circulations (decrease in right ventricular stroke volumes (RVSV) and left ventricular stroke volumes (LVSV) and increase in pulmonary and systemic vascular resistance) may lead to the hypothesis that a generalized CV reflex may also play some role (50). The data available would not confirm the hypothesis of major, reflex-induced pulmonary circulatory changes, since PAP increased similarly during SDB in patients with or without the Shy-Drager syndrome. However, studying reflex mechanisms is difficult, especially for the pulmonary circulation which can only be approached invasively. Preliminary results obtained during repetitive airway obstruction in dogs suggested that an α-adrenergic pathway through the carotid body played only a minor role in the pathogenesis of pulmonary hypertension (49,51). On the other hand, in anaesthetized dogs, stimulation of peripheral chemoreceptors may inhibit hypoxic pulmonary vasoconstriction, whereas sympathetic activation would reduce pulmonary vascular tone during both hypoxia and hyperoxia (52).

**D. Oxidative stress and systemic inflammation:** The intermittent hypoxia (IH) due to SDB is implicated in vasoconstriction (53,54) and oxidative stress. Increased sympathetic surges associated with IH as compared to the continuous hypoxia (55) may reflect the oxidative stress produced by rebound hyperemia. Oxidative insult promotes the release of proinflammatory mediators, such as cyclo-oxygenase-2, tumor necrosis factor-alpha, and interleukins (56-58) leading to systemic inflammation, endothelial dysfunction and culminating in vascular non compliance (59). The dysfunctional endothelium has been observed in SDB patients without any overt vascular disease and is a precursor to atherogenesis, thrombogenesis, and reduced vascular lumen (54,55,60). Following the initial vasoconstrictive response, the restorative reperfusion generates shear stresses inhibiting complete recovery and eventually leads to persistent vasoconstriction (61). This combined with the reduced production of Nitric Oxide (NO) a potent vasodilator and increasing vascular sensitivity to endothelin-1 in SDB may result in the hemodynamic changes preceding the development of PH (54,62,63). In fact the vascular and endothelial dysfunction markers (endothelin-1, Thrombomodulin and ICAM) have recently been described to have a linear relationship with the severity of SDB (64).

**Management**

There is no doubt that effective treatment of SDB eliminates nocturnal PH. Positive pressure therapy is considered the most effective and widely used therapy for SDB. CPAP treatment has recently been shown to result in improvement of cardiac output by 10%, cardiac index by 9%, and a reduction in the systemic vascular resistance by 18% (65). Peripheral arterial blood flow, estimated by tonometry has also been shown to improve with CPAP therapy suggesting reversal of endothelial dysfunction in SDB patients (66). There is limited evidence for the effectiveness of CPAP treatment for SDB on PAP. In a study
of 29 SDB patients (with no cardiopulmonary disease), Alchanatis and colleagues compared doppler echocardiographic determined PAP measurements with 12 healthy controls before and after 6-month of CPAP treatment. A total of 20% of the SDB patients had PH that was clinically mild (mean PAP= 25.6 mm Hg). Greater age and increased BMI distinguished these from the patients with OSA without PH; 6 months of CPAP treatment was associated with reductions in mean PAP in both SDB patients with PH (25.6 ± 4.0 to 19.5 ± 1.5 mm Hg) and those without PH (14.9± 2.2 to 11.5 ± 2.0 mm Hg) (67). Sajkov and colleagues treated 20 patients with SDB and free of any cardiopulmonary disease with 4 months of CPAP therapy (68). Only 5 patients met criteria for PH, with a mean PAP for the whole group of 16.8 mmHg. To assess the reversibility of PH in these patients, PAP was measured by echocardiography at three levels of inspired oxygen (50%, 21% and 11%). After 4 months of CPAP therapy, PAP (for all patients) decreased to a mean of 13.9 mm Hg.

CPAP may also affect vasoreactivity, as the pulmonary artery pressure response to hypoxia was attenuated. Finally, in the first placebo-controlled trial of treatment of OSA in PH, Arias and colleagues recently reported the results of a randomized cross-over trial of CPAP and sham CPAP over 12 weeks in 23 patients with OSA (69). A total of 10 patients with PH (defined as pulmonary artery systolic pressure (PASP)≥ 30 mm Hg by Doppler echocardiography) were more obese, had more ventilatory limitation (reduced FVC), and more severe sleep apnea (by AHI and mean oxygen saturation) than the 13 patients without PH. CPAP therapy reduced PASP in all patients with OSA, though more so in those with PH at baseline (mean reductions, 8.5 vs. 2.6 mm Hg).

Conclusion

The increasing prevalence of SDB in the population suggests that the population attributable risk percent (the percentage of the total risk of cardiovascular disease due to sleep apnea) is high, making this an important public health issue; this is particularly true given that sleep apnea is a potentially modifiable risk factor. Short-term randomized controlled trials of CPAP in cardiovascular end points and long term observational cohort studies with follow-up of cardiovascular outcomes suggest a clinically significant cardiovascular risk reduction associated with the use of CPAP As a result; treatment of OSA may represent a novel target to reduce cardiovascular health outcomes.

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