REGULAR ARTICLE

Sleep Disordered Breathing and Exercise in Pulmonary Hypertension

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Exercise intolerance is a common feature of many cardiopulmonary diseases including pulmonary hypertension (PH) and sleep disordered breathing (SDB), which includes obstructive sleep apnea and obesity hypoventilation syndrome. Physiologic abnormalities in both PH and SDB can drive exercise intolerance, and biological mechanisms overlap among the conditions including systemic inflammation, oxidative stress, metabolic dysfunction, and endothelial dysfunction. Despite this understanding, evidence establishing clear causal relationships among PH, SDB, and exercise intolerance is lacking. Data show that treatment of SDB may improve exercise capacity, and exercise training likely improves SDB, although these relationships specifically in PH remain understudied. In this manuscript, we summarize existing data of mechanisms and clinical observations in PH, SDB and exercise and identify gaps and opportunities for future investigation.

INTRODUCTION

Exercise intolerance is the hallmark of most cardiopulmonary diseases, including pulmonary hypertension (PH). In PH, subjective and objective assessments of exercise capacity are paramount in diagnosis, risk stratification, and therapeutic decision making. Sleep disordered breathing (SDB), including obstructive sleep apnea (OSA) and obesity hypoventilation syndrome (OHS), is associated with PH in a relationship that is likely bidirectional yet not completely understood. PH related to SDB is classified as Group 3 PH according to the most recent international consensus guidelines,[1] although the intersection among PH, SDB, and exercise likely involves Group 2 PH or PH due to left-heart disease and/or heart failure with preserved ejection fraction. Delineating PH subgroups is beyond the scope of this review but outlined in the most recent consensus guidelines.[1] There is a growing understanding that OSA and OHS are linked to physiologic abnormalities and limitations in exercise, even in those without apparent cardiopulmonary comorbidities.

Nocturnal hypoventilation and hypoxemia are the pathophysiologic basis for both OSA and OHS. PH is typically mild in isolated OSA,[2] although prolonged nocturnal hypoxemia is associated with worse hemodynamics in OSA when PH is suspected.[3] OSA severity is quantified by the Apnea-Hypopnea Index (AHI). The relationship between hypopneas, nocturnal hypoxia, and their systemic effects are reviewed separately.[4] Accordingly, in OHS, the risk for pulmonary vascular disease is much higher.[5,6] The prevalence of PH secondary to SDB remains unclear; however, OHS is common in the general population (0.4% of the general US population[7] and 17%–30% in high-risk individuals such as those with obesity and OSA[8]). When PH occurs as a complication of OHS, it is frequently quite severe and is associated with both right ventricular (RV) failure and poor long-term outcomes.[9] Given the growing obesity epidemic in the Western world, PH related to SDB is likely to become a more prevalent problem deserving of dedicated study.

Many overlapping mechanisms exist among SDB, PH, and exercise intolerance, including systemic inflammation, endothelial dysfunction, metabolic dysfunction, and cardiac impairment (Box). Despite this overlap, insights into causality among these conditions and the directionality of the relationships remains unclear. Much more work is needed to understand these relationships from epidemiologic associations to molecular mechanisms. In this review, we aim to discuss the current literature describing the relationships between SDB, PH, and exercise and identify gaps that are deserving of further study.

We will primarily discuss observations in adults. Although guidelines recommend screening echocardiograms for children with severe SDB[10] and treatment of concomitant SDB and PH has been demonstrated to improve exercise intolerance,[11] the prevalence of PH in the pediatric population is likely lower than commonly thought,[12] and more comprehensive study is needed. Mechanisms connecting these conditions in the pediatric population overlap with what is known in the adult population and are reviewed extensively elsewhere.[13]

MECHANISMS OF SDB AND EXERCISE INTOLERANCE IN PH

The primary pathophysiology of OSA is repetitive occlusion of the upper airway during sleep, which results in nocturnal

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Box. Shared themes of exercise intolerance in SDB and PH

Systemic inflammation
• Perivascular inflammation in PH
• Activation of HIFs
• Increased activity of NADPH oxidase and oxidative stress
• Thromboembolism in OSA due to oxidative stress
Endothelial dysfunction
• In part, instigated by chronic intermittent hypoxia
• Circulating endothelial progenitor cells may be part of the reparative vascular response to injury or a cancerlike tumorigenesis
• May correlate with leg fatigue during exercise
Skeletal muscle dysfunction
• Cellular metabolic dysfunction
• Diaphragmatic muscle proteolysis
• Respiratory muscle atrophy leads to ventilatory insufficiency
Mutual beneficial effects of exercise training and PAP therapy
• Exercise improves AHI and VO_2max
• PAP improves exercise performance with and without cardiopulmonary disease (including PH): VO_2max and heart rate recovery
• PAP improves pulmonary artery pressures

SDB = sleep disordered breathing; PH = pulmonary hypertension; HIF = hypoxia inducible factor; OSA = obstructive sleep apnea; PAP = positive airway pressure; AHI = apnea-hypopnea index.

hypoxemia and arousals.[14] OHS is characterized by obesity-related changes in the respiratory system, alterations in respiratory drive, and breathing abnormalities during sleep, all leading to chronic nocturnal hypoventilation.[15] Physiologic effects on pulmonary hemodynamics are consistently observed in patients with SDB. The increased intrapleural pressure seen during apneic episodes of SDB likely increases left atrial pressure and RV afterload.[16] Hypoxic episodes cause hypoxic vasoconstriction of the pulmonary vasculature, raising the pulmonary vascular resistance (PVR) and RV afterload, and activating hypoxia inducible factors (HIFs) that are responsible for downstream metabolic dysfunction, upregulation of VEGF, and activation of inflammatory and oxidative stress pathways (Figure 1). This culminates in endothelial dysfunction, a hallmark of all pulmonary vascular diseases that is clearly potentiated by SDB.[17]

Systemic inflammation and oxidative stress are shared mechanistic hallmarks of SDB and PH and likely contribute to exercise intolerance in both disorders.[18,19] In humans, chronic perivascular inflammation is linked to the loss of pulmonary vascular compliance and extracellular matrix remodeling and fibrosis in PH.[20,21] In preclinical PH models, HIFs and TNF-α mediate inflammation and potentiate oxidative stress via increased production of reactive oxygen species (ROS). Both mediators are hypothesized to regulate NADPH oxidases that are important sources of ROS, but human studies establishing the link among these processes are inconsistent, reinforcing the need for further mechanistic studies.[22–24]

Mice exposed to chronic intermittent hypoxia (simulating the nocturnal desaturations observed in SDB) developed PH associated with increased NADPH oxidase and increased activity of platelet-derived growth factor β and downstream protein kinase B.[25] Mice with inactive NADPH oxidase had a decrease in the development of PH and these molecular derangements, suggesting that NADPH oxidase may be a common mechanistic link between SDB and PH.[25] Several vasoactive mediators have been implicated in the overlapping pathogenesis of SDB and PH including serotonin, angiopoetin-1, endothelin-1, and nitric oxide. Stimulated by hypoxia, these mediators have a common effect in both SDB and PH by promoting pulmonary vascular remodeling and biventricular dysfunction.[26] Data suggesting that the oxidative stress generated by nocturnal hypoxia in OSA can predispose patients to venous thromboembolism but can be ameliorated by continuous positive airway pressure (CPAP) are encouraging[27]; however, these observations are confounded by concomitant obesity and advanced age, which are known risk factors for these processes. Unfortunately, human studies at manipulating these pathways in both SDB and PH have been disappointing and further work is needed.

Endothelial dysfunction is a critical common hallmark of both SDB and PH and likely inextricably tied to systemic inflammation and oxidative stress. Central to the pathobiology of both pulmonary vascular remodeling and risk of cardiovascular disease, endothelial dysfunction in both diseases is, in part, instigated by chronic intermittent hypoxia.[28,29] Circulating endothelial progenitor cells (EPCs) have long been hypothesized to play a role in both OSA and PH, either as part of the reparative vascular response to injury or instigating a cancerlike tumorigenesis. Studies in OSA have yielded conflicting results,[30,31] and although more encouraging data establish a role for EPCs in the pathobiology of PAH,[32,33] translation from preclinical studies to humans remains limited. Few studies link endothelial dysfunction in OSA with exercise and PH. Using a noninvasive device to approximate endothelial dysfunction, Jen et al.[34] were unable to detect a correlation between arterial stiffness after exercise and severity of OSA but did correlate vessel stiffness with leg fatigue and oxygen pulse (a marker of cardiac output). Studies using direct assessments of endothelial function related to exercise in OSA and PH remain lacking.

Significant gaps linking exercise intolerance to the many mechanisms that connect SDB and PH remain. Increasing our understanding of skeletal muscle dysfunction in these disorders will likely help to address this knowledge gap. Metabolic dysfunction is observed in the skeletal muscle of both patients with OSA and pulmonary arterial hypertension (PAH).[35,36] Although data recapitulating this dysfunction during exercise are limited, diaphragmatic dysfunction is a

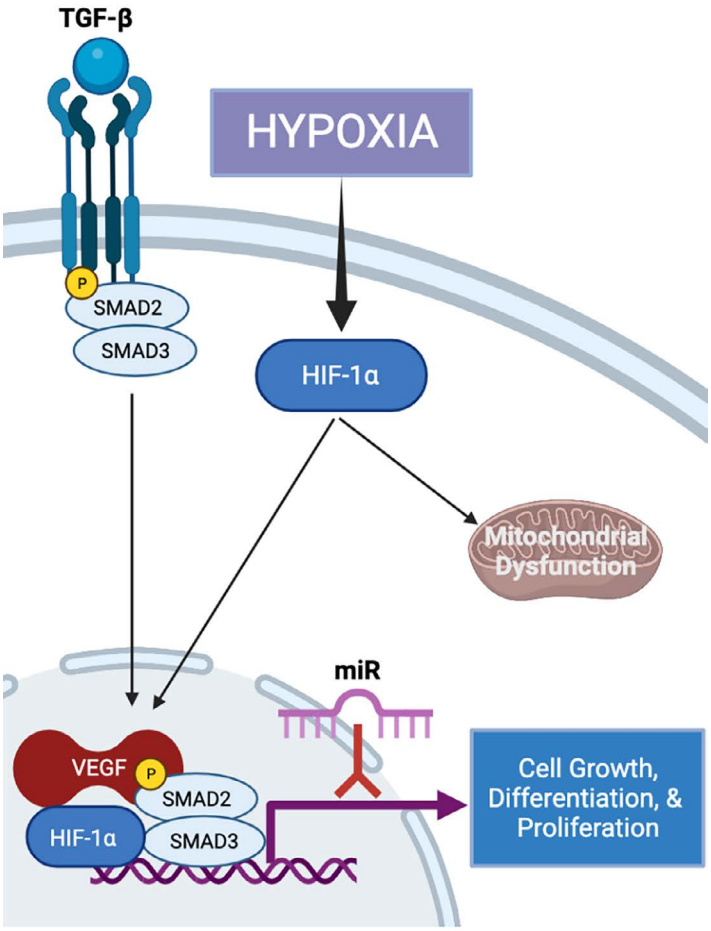

Figure 1: Shared molecular mechanisms of Group 3 pulmonary hypertension (PH) and sleep disordered breathing (SDB). TGF-β signaling and hypoxia inducible factor-1 alpha (HIF-1α) both activate VEGF expression which can lead to increased cell growth, differentiation, and proliferation. MicroRNAs (miRs) can regulate gene expression and prevent these downstream effects in pre-clinical models. HIF-1α is also theorized to play a significant role in mitochondrial dysfunction in both SDB and PH, though the exact mechanisms have yet to be clearly elucidated. Figure adapted from Singh et al. Circ. Res. 2021.[70]

likely contributor to exercise intolerance in both OSA and PAH. In PAH, reduced diaphragmatic muscle fiber cross-sectional area in experimental PH has been associated with increased proteolytic activity. These findings were recapitulated in human disease, suggesting that respiratory muscle atrophy is specifically implicated in the ventilatory inefficiency observed in PAH patients.[37] Abnormal cardiovascular responses to exercise in OSA are consistently observed in the forms of abnormal diastolic blood pressure response,[38] chronotropic incompetence,[39] heart rate recovery after exercise,[40,41] and left-ventricular dysfunction.[42–45] Systolic dysfunction of the RV is an inevitable consequence of persistent increases in afterload and may be the most pronounced in PAH patients with severe nocturnal hypoxemia and OSA.[46] As with Group 1 PAH, a sex-based differential response of the RV to afterload in all Group 3 PH with worsening RV function likely exists in males despite females having a significantly higher PVR.[47]

Though numerous physiologic and molecular mechanisms overlap between SDB and PH, their links to exercise intolerance remain unclear. Much more dedicated clinical and mechanistic study is needed.

EXERCISE IMPAIRMENT IN SDB AND PH

A growing body of evidence links SDB, particularly OSA, to exercise impairment. A recent meta-analysis demonstrated that, compared with healthy controls, subjects with OSA had decreased mean peak oxygen consumption (VO_2max),[48] a parameter considered an overall measure of health and one that is widely associated with mortality in health and disease. Although reduced VO_2max is not observed across all studies examining cardiopulmonary exercise testing in OSA,[49] other physiologic changes with exercise, including decreased peak heart rate and increased diastolic blood pressure, are consistently observed in patients with OSA.[48,50,51] Some of the physiologic abnormalities characteristic of pulmonary vascular disease, such as decreased ventilatory efficiency (VE/VCO_2) and reduced oxygen pulse,[52] have not been demonstrated in OSA.[48,50] Although the cardiopulmonary mechanisms of exercise impairment are different between PH and OSA, it is easy to postulate that these might combine to worsen exercise impairment where PH and OSA coexist. However, data examining the impact of OSA on exercise specifically in PH are more limited. In a heterogeneous PH population, those with OSA were older and had worse resting oxygenation that those without OSA, but no differences in any exercise parameters were found, including six-minute walk distance (6MWD), VO_2max, and VE/VCO_2.[53] Most other studies characterizing OSA in PH have less robust exercise data and have not consistently demonstrated that OSA reduces 6MWD in PH.[54–56]

With all these data, it is challenging to know if the association between OSA and exercise impairment is causal or if body mass index (BMI), comorbidities, and baseline levels of physical activity confound the relationship. In a large sleep cohort, increased reported amount of exercise was associated with a reduced degree of SDB, even after adjustment for age, sex, and body habitus.[57] In a recent study of 450 precapillary PH patients, those with OSA had a reduced 6MWD but were older, had more comorbidities (such as obesity, hypertension, diabetes, and coronary artery disease), were more likely to have left heart abnormalities on echocardiogram, and substantially more likely to have a diagnosis of atypical PAH.[55] However, the association between OSA and atypical PAH remained

even after adjustment for age, sex, and BMI. Further examination of the interplay between OSA, comorbidities, and exercise is needed, particularly given the increasing recognition of comorbidities and the atypical phenotype in PAH.

THERAPEUTIC INTERVENTIONS

Some, albeit limited, data examine the impact of exercise on SDB or the effects of treatment for SDB on exercise performance. Individual studies have demonstrated aerobic exercise can reduce the severity of OSA.[58,59] Pooled estimates from meta-analyses demonstrated regimented exercise improves AHI, VO_2max, and measures of daytime sleepiness and sleep quality with little[60] or no[61] change in BMI. The exercise regimens in these studies are typically aerobic exercise targeting anaerobic threshold, although one analysis found a combination of resistive and aerobic exercise resulted in greater improvement in the OSA severity.[61] Notably, these studies routinely exclude patients with significant cardiopulmonary disease, including PH.

Emerging data show that treatment for SDB, particularly positive airway pressure, can improve exercise performance in patients both with and without cardiopulmonary disease and PH. Several small studies have shown that short-term CPAP improves exercise capacity in OSA without significant cardiopulmonary comorbidities.[62–64] Maeder et al.[65] found that effective longer-term CPAP use in otherwise healthy patients with newly diagnosed OSA improved VO_2max and heart rate reserve. Interestingly, the improvement in VO_2max was seen primarily in those with mild-moderate OSA, which may have been explained by increased effort during the cardiopulmonary exercise testing (CPET) compared with those with severe OSA. More recent work examined the effects of CPAP on exercise capacity in patients with cardiopulmonary comorbidities and PH. In moderate-severe OSA patients with some cardiovascular comorbidities (hypertension and ischemic heart disease), 8 weeks of CPAP improved VO_2max, minute ventilation, and peak oxygen pulse.[66] Sykes et al.[67] examined the effects of OSA and PH on exercise capacity in patients undergoing cardiac rehabilitation, indicated for significant cardiac disease, mostly heart failure with reduced ejection fraction and sequelae of coronary artery disease. Patients with OSA were more likely to have PH (defined by echocardiography), and while improvements in exercise capacity were not different between those with and without PH, patients with PH and OSA treated with CPAP had greater improvements in exercise capacity. Limited data also suggest that positive pressure therapy in patients with CPAP and PH can lower pulmonary artery pressures (as measured by echocardiography)[68,69]; however, more robust studies, including those using invasive hemodynamics, are required.

Although the current research is limited, effects of exercise on SDB are likely beneficial, and conversely, SDB treatment may improve exercise performance. The magnitude and longer-term clinical significance of these effects and in which patient populations they are the most impactful remain to be determined.

PRACTICAL CONSIDERATIONS FOR EXERCISE AND SDB IN PH

Screening for SDB is standard when evaluating a patient for PH and exercise intolerance[1]; based on epidemiologic evidence suggesting increased risk of severe disease, special attention should be given to patients with risk factors for OHS such as obesity, hypertension, and diabetes. In patients whom SDB is suspected, standard diagnostics including polysomnography are sufficient to detect the disease. Assessments of exercise capacity are typically performed by 6MWT in most PH centers. Although CPET is not uniformly used for the diagnosis and management of PH, it may be particularly helpful to assess cardiovascular and pulmonary responses to exercise when OSA and PH are clinically suspected. Some differences in CPET may be useful in differentiating between circulatory (Group 1 PAH) and ventilatory (Group 3 PH) limitations to exercise (Table 1). Guideline recommendations[1] and common clinical practice are to treat SDB in PH and refer PH patients for supervised rehabilitation programs. While these may be viewed as occurring in parallel, the mechanistic and clinical links between SDB and exercise would seem to suggest that these treatments might be synergistic in PH.

CONCLUSIONS

Exercise intolerance exists in both SDB and PH; however, the causality of these relationships, the mechanisms that underpin them, and the directions in which they occur remain understudied. Despite this, many of the pathophysiological mechanisms that drive SDB and PH clearly overlap, including systemic inflammation, oxidative stress, metabolic dysfunction, and endothelial dysfunction. Exercise intolerance occurs commonly in patients with SDB with or without PH, and both treatment of SDB and exercise training can improve clinical outcomes. The precise benefits, long-term therapeutic effects, and populations which find the most benefit have yet to be elucidated. Future work should focus on deep characterization of biological mechanisms that contribute to exercise intolerance

Table 1. Cardiopulmonary Exercise Test (CPET) Criteria That May Differentiate Group 1 PAH From Group 3 PH[a]

Criteria favoring Group 1 PAH	Criteria favoring Group 3 PH
Features of circulatory limitation to exercise: • Preserved breathing reserve • Reduced O_2 pulse • Low CO/VO_2 slope • Mixed venous oxygen saturation at lower limit • No change or decrease in $PaCO_2$ during exercise	Features of ventilatory limitation to exercise: • Reduced breathing reserve • Normal O_2 pulse • Normal CO/VO_2 slope • Mixed venous oxygen saturation above lower limit • Increase in $PaCO_2$ during exercise

Abbreviations: CPET = cardiopulmonary exercise test; PAH = pulmonary arterial hypertension; PH = pulmonary hypertension.

[a]Adapted from Nathan et al. *Eur Respir J*. 2019;53(1):1801914.[2]

in SDB and PH and careful study of longitudinal relevant clinical outcomes in well-defined populations so treatment recommendations regarding exercise in these conditions can be made clear.

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