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# Obstructive Sleep Apnea and Pulmonary Hypertension in Children

David G. Ingram [a,*], Alvin V. Singh [a], Zarmina Ehsan [a], Brian F. Birnbaum [b]

[a] Division of Pulmonary and Sleep Medicine, Children's Mercy Hospital, 2401 Gillham Road, Kansas City, MO
[b] Division of Cardiology, Children's Mercy Hospital, 2401 Gillham Road, Kansas City, MO

**EDUCATIONAL AIMS**

The reader will come to appreciate:

1. The mechanisms of altered pulmonary hemodynamics in children with obstructive sleep apnea.
2. The current evidence for the co-occurrence and treatment of obstructive sleep apnea and pulmonary hypertension in children.
3. A set of relevant suggested actions in selected clinical scenarios when caring for children with OSA and/or pulmonary hypertension.

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SUMMARY

Obstructive sleep apnea (OSA) is a common pediatric breathing disorder, affecting 1-5% of all children. Pulmonary hypertension (PH), a severe complication of OSA, is associated with significant morbidity and mortality. Despite this important relationship between OSA and PH, there is sparse literature addressing this subject in children. This review will examine the putative relationship between OSA and PH, synthesize the available literature in children, and suggest a reasonable approach, despite limited data, for clinicians. We conclude that available evidence suggests many children with OSA have evidence of PH (estimates ranging from 0% to 85%) and vice versa (estimates ranging from 6% to 24%). Furthermore, previous studies demonstrate that treatment of the OSA, either with surgery or non-invasive ventilation, ameliorates pulmonary artery pressures to the extent of cure in a substantial number of cases. Future studies are required to better delineate the true co-occurrence of these diseases and help predict which patients are at greater risk for this serious complication. Clinicians who maintain a healthy vigilance for this important interaction of disease states will likely recognize opportunities to intervene and improve prognoses in these patients.



## INTRODUCTION

Obstructive sleep apnea (OSA) is a relatively common disorder, affecting 1-5% of all children, and is associated with deleterious health effects [1]. Furthermore, children with selected conditions with features that predispose to OSA, such as Down syndrome or Prader Willi syndrome, are at substantially increased risk of OSA with a prevalence up to 70-80% [2,3] and lower surgical cure rates [4–6]. While OSA has been associated with much morbidity, including learning/behavioral problems, growth problems, and cardiovascular complications [1], one of the most potentially serious complications is pulmonary hypertension (PH). Untreated pulmonary hypertension in children can lead to right heart failure with decreased cardiac output and may contribute to increased morbidity and mortality [7]. While the precise prevalence of PH in children is not well known, children with chronic cardiopulmonary conditions such as cystic fibrosis, sickle cell disease, bronchopulmonary dysplasia, and congenital heart disease are at higher risk [7]. In contrast to adults [8,9], there is a relative paucity of literature regarding OSA and PH in children and, to the best of our knowledge, no recent reviews. Therefore, in the current article we review the putative relationship between OSA and PH, synthesize the available literature in children, and suggest a reasonable approach for clinicians caring for these children in the face of limited data.

* Corresponding author. Division of Pulmonary and Sleep Medicine, Children's Mercy Hospital, 2401 Gillham Road, Kansas City, MO, 64108, Tel.: +816 983 6644, fax: 816 983 6626.
*E-mail address:* dgingram@cmh.edu (D.G. Ingram).

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## PUTATIVE RELATIONSHIP BETWEEN OSA AND PULMONARY HYPERTENSION

Pulmonary arterial hypertension is a chronic disorder of the pulmonary vasculature, characterized by a progressive increase in pulmonary vascular resistance that can lead to right heart failure and death [10]. The definition for children with pulmonary hypertension (PH) uses the same criteria as in adults; mean pulmonary artery pressures (mPAP) 25 mmHg as measured via cardiac catheterization at rest; furthermore, if the pulmonary artery capillary wedge pressure is $\leq$ 15 mmHg and pulmonary vascular resistance (PVR) >3 Wood units, this identifies that PH as pre-capillary in nature [11]. Patients with mPAP between 21 and 25 mmHg are at risk for developing frank PH. Etiologies of PH are classified according to the Nice classification system (Table 1) [12]. OSA is part of Group 3 PH, which primarily deals with disease of the respiratory system. The adult literature largely supports a significant association between OSA and PH [13].

Echocardiography is one method to monitor the severity of PH, most commonly by evaluating the tricuspid regurgitant jet velocity (TRJV) in order to estimate a pulmonary artery pressures in children. Cardiac catheterization can be used to obtain a mean pulmonary artery pressure (the gold standard). This requires sedation and often anesthesia, which greatly affects cardiac and pulmonary blood flow and pressure estimates when compared to a crying and agitated child who is undergoing echocardiography. Sometimes, TRJV can be under or over-estimated which may affect the estimation of PAP one makes [14].

Establishing the prevalence of PH in adults with OSA is difficult due to variability in diagnostic methods [9]. Increased prevalence of PH in adults with OSA has been described. In a group of 220 patients with OSA diagnosed by polysomnography (AHI > 20/hour), 17% had PH [as diagnosed by mPAP $\geq$ 20 mmHg via right heart catheterization (RHC)]. This study did not utilize the current threshold for PH diagnosis of mPAP 25 mmHg, but pressures of 21-24 mmHg may be considered borderline [11]. Adults with PH also had increased lung obstruction (decreased $FEV_1$/FVC), increased $PaCO_2$, decreased $PaO_2$, decrease mean arterial overnight oxygen saturation and increased BMI [15].

Conversely, the prevalence of sleep apnea in adults with PH has also been evaluated. One study examined 169 patients with PH, diagnosed by RHC (with NYHA classification II and III - stable disease), and evaluated them for sleep apnea with polysomnography. Approximately 27% of these patients had an AHI > 10/hour, with 16% having OSA and 11% having central sleep apnea. The mean AHI for this group was 20 episodes per hour [16]. Therefore, adults with PH have a high prevalence of OSA, and adults with OSA have an increased risk of acquiring PH [9].

Physiologically, upper airway obstruction causes alveolar hypoxia, increasing pulmonary vascular resistance and precapillary pulmonary artery pressures [8]. Pulmonary blood flow is further increased by the negative intrathoracic pressure generated against a closed upper airway. This increase in venous return (and subsequent right ventricular preload and stroke volume) shifts the interventricular septum to the left, thereby reducing left ventricular compliance. This contributes to an increase in pulmonary venous pressure [8]. In children who have smaller airways, even small decreases in the radius of their airways can greatly increase resistance which may have deleterious effects on their cardiopulmonary system.

On a molecular level, animal models have shown that intermittent episodes of hypoxia act on multiple factors. The factors responsible for structural and pressure modifications within the pulmonary vasculature include hypoxia-inducible factor-1 (HIF-1) and its secondary messengers, erythropoietin and vascular endothelial growth factor (VEGF), and endothelin-1 (ET-1) [17]. It has been reported that impaired function of these factors leads to endothelial dysfunction through the presence of altered nitric oxide (NO) dependent vasodilation responses in patients with OSA. OSA is also known to increase the formation of C reactive protein (CRP) in the liver, as well as the formation and release of cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6) and tumor necrosis alpha (TNF-$\alpha$) and promote the release of leptin and adipokines. Circulating monocytes are also activated which then express monocyte chemotactic protein (MCP-1) which causes increased adhesion on the endothelial cell surface and reduce the expression and activity of endothelial nitric oxide synthase (eNOS) and promote apoptosis [18]. These changes promote endothelial dysfunction and limit the capacity of NO-induced vasodilation within the pulmonary vasculature. These deleterious effects from OSA increase the systemic inflammatory pattern within the body which causes a more directed effect in the cardiovascular system and the pulmonary vasculature. Various biomarkers, particularly highly sensitive CRP (hsCRP) and IL-6 have been implicated as possible markers in adults and children with OSA, which further argues that OSA causes a systemic inflammatory state within the body [19]. In order to understand the basic mechanisms that are caused by intermittent hypoxia, studies at the cellular level with multiple cells from different systems within the body should be conducted [20].

**Table 1**
Nice Classification system.

| |
|---|
| 1. Pulmonary arterial hypertension |
| 1.1 Idiopathic PAH |
| 1.2 Heritable PAH |
| 1.2.1 BMPR2 |
| 1.2.2 ALK-1, ENG, SMAD9, CAV1, KCNK3 |
| 1.2.3 Unknown |
| 1.3 Drug and toxin induced |
| 1.4 Associated with connective tissues disease, HIV infection, portal hypertension, congenital heart diseases, schistosomiasis |
| 1' Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis |
| 1" Persistent pulmonary hypertension of the newborn |
| 2. Pulmonary hypertension due to left heart disease |
| 2.1 Left ventricular systolic dysfunction |
| 2.2 Left ventricular diastolic dysfunction |
| 2.3 Valvular disease |
| 2.4 Congenital/acquired left heart/inflow/outflow tract obstruction and congenital cardiomyopathies |
| 3. Pulmonary hypertension due to lung diseases and/or hypoxia |
| 3.1 Chronic obstructive pulmonary disease |
| 3.2 Interstitial lung disease |
| 3.3 Other pulmonary disease with mixed restrictive and obstructive pattern |
| 3.4 Sleep-disordered breathing |
| 3.5 Alveolar hypoventilation disorders |
| 3.6 Chronic exposure to high altitude |
| 3.7 Developmental lung diseases |
| 4. Chronic thromboembolic pulmonary hypertension |
| 5. Pulmonary hypertension with unclear multifactorial mechanisms |
| 5.1 Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy |
| 5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis |
| 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders |
| 5.4 Other: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH |

## REVIEW OF THE LITERATURE IN CHILDREN

### *Co-occurrence of OSA and PH in Children*

The co-occurrence of OSA and PH has been recognized for quite some time (see Tables 2 and 3 for the most informative studies).