

Obesity and Pulmonary Hypertension. What's the Link?

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Severe pulmonary hypertension (PH) is a rare disorder characterized by multifactorial etiology and shared pathophysiology. The belief that primary pulmonary hypertension (PPH) is an idiopathic variety mostly affecting younger women may still be held by some. However, PH has often been reported in overweight and obese individuals and postmenopausal women.¹ Earlier studies have also suggested that combination of obesity and higher altitude favors the development of pulmonary arterial hypertension. Hypercapnic acidemia and increased total blood volume have been implicated in this group of patients. Pulmonary artery systolic pressures (PASP) greater than 40 mmHg is found in 6% of otherwise normal individuals age 50 years or older and in 5% of individuals with a BMI greater than 30kg/m².²

Overall, the widely held view has been that alveolar hypoxia is the main pathophysiologic cause of vasoconstriction in obese patients living at sea level or higher altitudes. In 1947, Motley et al demonstrated that breathing a gas mixture containing 10% oxygen induced a rise in pulmonary artery pressure (PAP).³ Papers dating back more than three decades have documented increases in PAP associated with hypoxemia related to sleep disordered breathing (SDB). It is well known that apneic episodes during sleep are associated with transient elevations in PAP, which return to baseline when breathing resumes after relief of obstruction. Earlier studies suggested that daytime hypoxemia attributable to abnormal lung function was the main cause of pulmonary hypertension in patients with sleep apnea. Whether transient hypoxemias and associated elevations in PAP with obstructive events during sleep are adequate to produce daytime resting "fixed" pulmonary vascular disease, or whether daytime hypoxemia is required remains unclear. It is also less certain whether daytime pulmonary arterial hypertension also occurs in OSA patients without underlying pulmonary or cardiac disease. Additionally, studies have shown that the severity of SDB as measured by apnea-hypopnea index (AHI) and the PAP elevations often fail to correlate.

Sajkov et al⁴ were amongst the first to demonstrate that hypoxemia in PH patients with obstructive sleep apnea syndrome (OSAS) could not be explained by impairment of lung or cardiac function, BMI and smoking history. However, most of the studies that have tackled this question (including

the one done by Sajkov) have used echocardiography based pulmonary artery pressures and the few that have used the gold standard Right heart catheterization (RHC) used a definition of mean pulmonary artery pressure (mPAP) >20 mmHg. At present, pulmonary arterial hypertension is defined as a mean PAP greater than 25mmHg at rest or 30 mmHg with exercise, as measured by RHC. The largest such study found PAH in 17% patients but it also included some patients with chronic obstructive pulmonary disease (COPD).⁵ Smaller series of patients with OSA but no clinical history of COPD have reported daytime PAH as measured by RHC in 20-42% patients.^{6,7}

Thus, despite acute nocturnal increases in PAP associated with obstructive apneas, proof that OSA causes PH has been limited by other co-morbidities related to obesity. The three biggest confounders making this issue difficult to be explored are associated COPD in OSAS patients (overlap syndrome), Obesity Hypoventilation Syndrome (OHS) and underlying concomitant left ventricular dysfunction in patients with OSA. OHS as defined at present is characterized by combination of obesity (BMI $\geq 30\text{kg/m}^2$) and chronic daytime hypercapnia (PaCO₂ >45 mmHg); and sleep disordered breathing in the absence of other known causes of hypercapnia.⁸ PH has been shown to be more frequent and mean PAP higher in patients with OHS or the overlap syndrome when compared to patients with pure OSAS only.⁹ Elevated mPAP associated with higher pulmonary capillary wedge pressure (PCWP) from underlying elevated left ventricular end-diastolic pressure and in some studies apnea associated have been other potential confounders.¹⁰ Other difficulties related to exploring this issue are technical concerns regarding non-invasive measurement of pulmonary artery pressure in obese OSA patients and difficulties in identifying suitable controls i.e, obese patients with PH and without OSA. Studies are also needed to investigate the role of humoral vasoactive factors like natriuretic peptides, nitric oxide or norepinephrine and individual genetic predisposition to account for different remodeling responses to hypoxia in the pulmonary circulation. In OSAS patients no neutrally mediated effect of apneas on PAP has been demonstrated.

PH seen in association with OSA is generally regarded as mild and can be attributed to elevated pulmonary vascular resistance (PVR) because cardiac output and PCWP are normal at least at rest. Although the association between left sided-heart disease and OSA is widely accepted, most studies of OSA patients with PH do not differentiate between pre-capillary (PAH) and post-capillary pulmonary hypertension (PVH). Additionally a good proportion of the studies do not even report PCWP.^{6, 9} while some explain higher PAP on the basis of PCWP alone. Elevations in both PCWP and PVR have been reported to contribute to PH in patients with OHS. A recent study of referred patients who met the WHO criteria for PAH from Duke University reported PCWP > 15 mmHg in 25% of the patients. These patients were predominantly obese (58%) and all had normal LVEF%.¹¹ In our retrospective analysis of 8254 patients who underwent RHC for suspected PH, mean Right atrial pressure, mean PA diastolic pressure, mean PCWP and mean cardiac output increased proportionately with increase in BMI regardless of the underlying contributory disease process.¹²

The debate about whether OSA alone can be a cause of sustained pulmonary arterial hypertension continues, but based on the above literature, the latest revision of the Clinical Classification of Pulmonary Hypertension identifies SDB as a part of the category of respiratory disorders associated with PH.¹³ The most direct evidence comes from observations that treatment of OSA with continuous pulmonary arterial pressure (CPAP) may lower daytime PAP. OSA patients with PH seem to have increased pulmonary vascular reactivity to hypoxia compared to patients without PH and CPAP has been reported to decrease pulmonary vascular reactivity to hypoxia.¹⁴ In studies from Stanford as early as 1978, 50% reduction in PAP was noted in six selected patients with OSA after tracheostomy. In a recent randomized placebo-controlled cross-over trial of effective versus sham CPAP in 23 patients with OSA, effective CPAP was associated with decreases in echocardiographic measurements of PASP especially in patients with PH or left ventricular diastolic dysfunction at baseline.¹⁵ This trial was limited by baseline differences in obesity and lung function between the two groups. Larger randomized studies are needed to identify more definitively any sustained effects of CPAP therapy on PH and right heart function and to better establish any role for CPAP as one of the rapidly evolving therapeutic options for PH.

COMPETING INTERESTS

None Declared

AUTHOR DETAILS

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