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## **Editorial**

### **Smoothing out the Peaks and Valleys of High Altitude Sleep Apnea**

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*Abbreviation List*

AHI	Apnea hypopnea index
ODI	Oxygen desaturation index
OSA	Obstructive sleep apnea
SDB	Sleep disordered breathing

Sleep disordered breathing (SDB) is common in individuals living at high altitude (highlanders), with sleep apnea symptoms reported in up to 30%<sup>1</sup>, and increased prevalence and severity sleep apnea<sup>2</sup>, potentially exacerbating and/or accelerating the progression of the long-term sequelae of SDB. Highlanders with sleep apnea have a unique pattern of hypoxemia, with more marked intermittent hypoxemia from sleep apnea against a background of sustained hypoxemia from altitude.<sup>3</sup>

The impact of supplemental oxygen therapy on obstructive sleep apnea (OSA) has been extensively investigated in those living close to sea-level (lowlanders), but not in highlanders. In lowlanders, supplemental oxygen improves hypoxemia<sup>4-7</sup>, but does not meaningfully reduce the apnea hypopnea index overall (AHI).<sup>5-7</sup> The reported effects of supplemental oxygen on blood pressure in OSA are varied.<sup>4,6,7</sup> However, in highlanders with OSA, the effects of supplemental oxygen may be different due to the severity and unique pattern of hypoxemia that these patients experience.

Tan and colleagues<sup>8</sup>, conducted a randomised crossover trial, examining the effects of one night of supplemental oxygen in highlanders with OSA. They enrolled Tibetan men, born and living at 3200m for > 10 years, with suspected OSA and screening oximetry showing an oxygen desaturation index (ODI) of >30 /h. Participants underwent polysomnography on two occasions. On one night oxygen was supplemented at a flow rate of 2 L/min. On the alternate night, sham oxygen (air) was provided at the same flow rate.

Participants had severe sleep apnea on average, with a median AHI of 42.4 /h (31.8, 66.4) on sham oxygen. Perhaps unexpectedly, sleep apnea was almost entirely obstructive, with obstructive and central AHIs of 40.5 /h (28.2, 65.0) and 0.8 /h (0.1, 1.3) respectively on sham oxygen. In contrast, others have shown that central events are as common as obstructive events in highlanders.<sup>2</sup> By selection, the patients included by Tan and colleagues are probably not representative of most highlanders with sleep disordered breathing.

The authors found that supplemental oxygen therapy significantly improved sleep apnea severity, with reductions in the AHI of 18.9 /h (95%CI 9.4 to 28.0). This is in contrast to studies in lowlanders where, on average, oxygen has only a small or no effect on the AHI.<sup>5-7</sup> Supplemental oxygen also markedly reduced hypoxemia. The median oxygen desaturation index reduced from 50.1 /h (35.5, 67.8) to 16.4 /h (6.3, 22.0). The median percentage time with oxyhemoglobin saturation <90% decreased from 78.5% (64.1, 88.2) to 4.8% (0.4, 10.2), representing a substantially greater reduction in hypoxemia severity compared to oxygen studies in lowlanders who had relatively modest hypoxemia at baseline.<sup>4-7</sup> Although this study was not powered for secondary outcomes, the investigators found that the morning heart rate was reduced, and morning systolic blood pressure showed a trend towards reduction with supplemental oxygen.

However, there are important limitations of this study. First, supplemental oxygen and sham oxygen were each only given for one night and the longer-term effects of supplemental oxygen remain unknown. Second, the study enrolled participants with obstructive sleep apnea and it remains unclear whether treating high-altitude central sleep apnea provides clinical benefit. In addition, sleep disordered breathing events were mainly obstructive hypopneas which can be difficult to distinguish from central hypopneas. Third, the primary outcome reported hypopneas with a desaturation criterion, therefore supplemental oxygen may have improved the AHI simply by reducing desaturations without reducing obstructive events. However, the authors still report a reduction in the AHI when hypopneas were scored without a desaturation criterion (Chicago criteria), albeit less marked from 46.9 to 27.1 /h. Fourth, the authors enrolled men, exclusively. Women are less likely to develop periodic breathing with sojourns to high altitude.<sup>9</sup> Highland woman may therefore respond differentially to supplemental oxygen. Finally, the study was not designed to identify the mechanisms by which supplemental oxygen improved sleep apnea.

Potentially, supplemental oxygen may improve OSA severity in highlanders by dampening overly brisk ventilatory responses to airway obstruction – termed high loop gain – which may lead to hypocapnia and propagate further apneic activity. In lowlanders with OSA, exposure to hypoxia increases loop gain whereas supplemental oxygen

decreases loop gain.<sup>10</sup> Furthermore, lowlanders with OSA and high loop gain have greater AHI reductions with supplemental oxygen<sup>7</sup>, supporting alterations in loop gain as the mechanism by which supplemental oxygen may be reduce OSA severity in highlanders.

Tan and colleagues have shown that one night of supplemental oxygen improves the severity of OSA in highlanders. Further work is needed to see if this effect lasts in the longer-term and to see if this treatment improves other outcomes of sleepiness, cognition and cardiovascular endpoints. Whilst this study suggests some promise for supplemental oxygen, many high altitude population centers occur in low middle income countries, where limited access to electricity may preclude the use of oxygen concentrators as well as CPAP, and low-cost alternative strategies to improve overnight hypoxemia are likely to be needed. Future studies should aim to assess the mechanism of improvements in OSA severity in highlanders as this may also help to identify an endotype of lowlanders with OSA likely to respond to supplemental oxygen.

Significant questions remain unanswered in relation to hypoxemia in highlanders. While it has been well documented that sustained daytime hypoxemia is a risk factor for chronic mountain sickness<sup>11</sup>, the relative importance of specific nocturnal hypoxemia patterns remains unknown. The hypoxic conditions at high altitude exert selective pressure for genetic alterations that confer protection against sustained hypoxemia and the development of chronic mountain sickness in some high altitude populations<sup>12</sup>. The role of these genetic alterations in the predisposition to sleep apnea, intermittent hypoxia, and their cardiometabolic sequelae has not been studied. Since highlanders experience a broad range of hypoxemia severity and patterns that are often confounded by chronic cardiopulmonary disease at sea-level, studies at high altitude offer a unique window into the pathogenesis of and protective mechanisms against hypoxemia-related sequelae in a variety of chronic conditions, regardless of altitude.

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