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Nocturnal Hypoxemia in Respiratory Medicine: Pathophysiology, Measurement and Association with Outcomes

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Abstract:
Nocturnal hypoxemia is a prevalent feature of various respiratory diseases, significantly impacting patient outcomes and therapeutic strategies. Oximetry, a non-invasive and widely accessible tool, enables the measurement of nocturnal hypoxemia through oxyhemoglobin saturation (SpO_2)-derived metrics such as the oxygen desaturation index, percentage of sleep time with SpO_2 below 90%, mean SpO_2, and measures of the area under the desaturation curve (e.g., sleep apnea specific hypoxic burden). While these metrics are well established in obstructive sleep apnea (OSA), their application in other respiratory conditions, including chronic obstructive pulmonary disease (COPD), pulmonary hypertension, obesity hypoventilation syndrome, heart failure, neuromuscular disorders, pregnancy, and high-altitude residents, remains an area of active investigation. This review explores the pathophysiology of hypoxemia in these conditions and evaluates the role of SpO_2-derived metrics in risk stratification beyond OSA. We also discuss the challenges of interpreting SpO_2 data, particularly the difficulty differentiating disease-related hypoxemia from comorbid OSA. Additionally, we examine the limitations of oximetry, including sensor inaccuracies, motion artifacts, and skin pigmentation. Finally, we emphasize the need for further research to standardize these metrics across diverse conditions and advocate for their integration into clinical practice to enhance patient management and outcomes.

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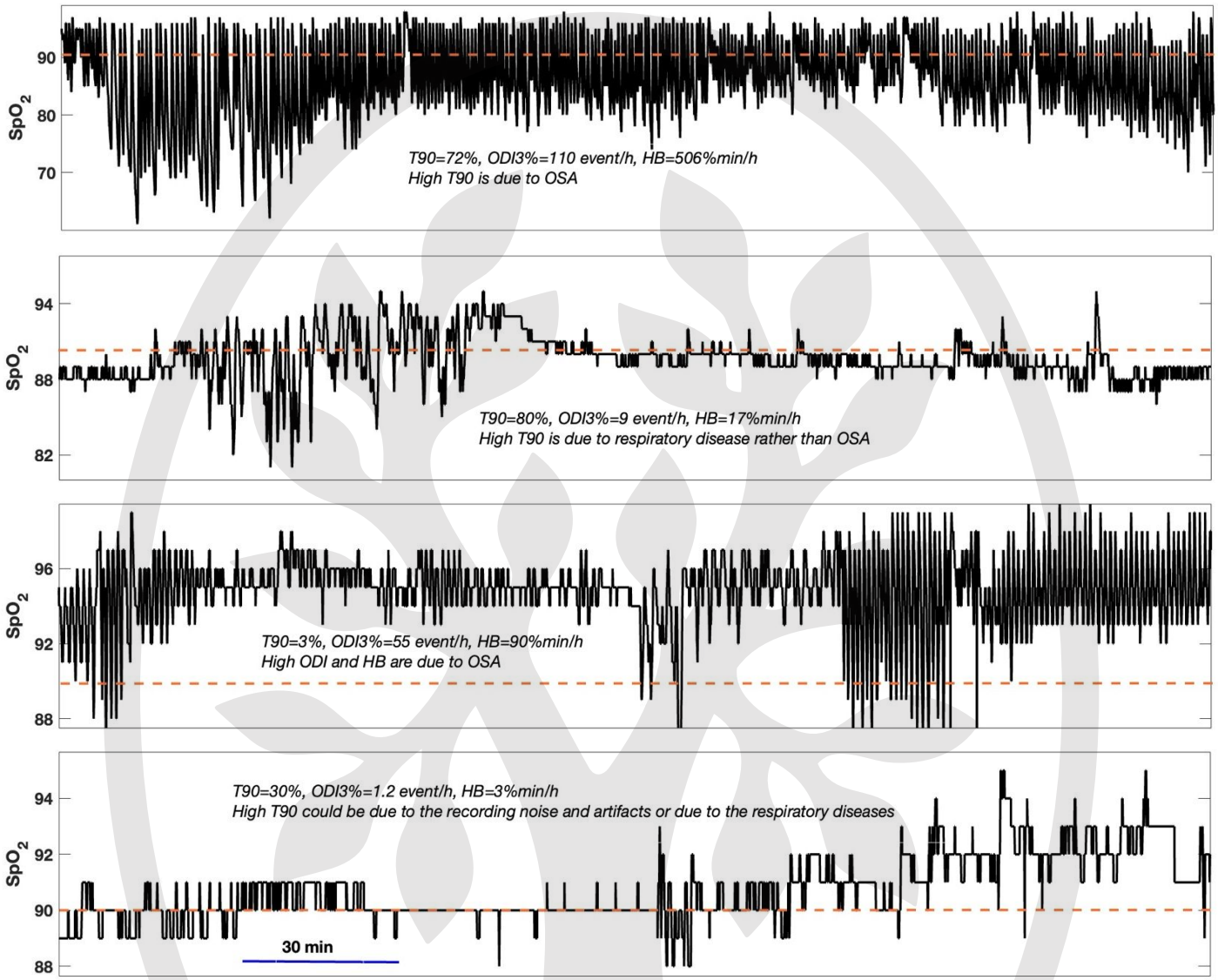

Figure 1: Nocturnal oximetry recordings (around 3 hours) of four individuals with different levels of T90, ODI and HB. The orange dashed line shows the 90% level of SpO_2. Abbreviations: ODI=Oxygen Desaturation Index; SpO_2 = Peripheral Oxygen Saturation; T90= Time below 90% SpO_2; HB: hypoxic burden.

Nocturnal Hypoxemia in Respiratory Medicine: Pathophysiology, Measurement and Association with Outcomes

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MH and AA contributed to data extraction and manuscript drafting. All authors contributed to interpreting the findings and critically revising the manuscript. All authors have approved the manuscript in its final form.

Abstract

Nocturnal hypoxemia is a prevalent feature of various respiratory diseases, significantly impacting patient outcomes and therapeutic strategies. Oximetry, a non-invasive and widely

accessible tool, enables the measurement of nocturnal hypoxemia through oxyhemoglobin saturation (SpO_2)-derived metrics such as the oxygen desaturation index, percentage of sleep time with SpO_2 below 90%, mean SpO_2, and measures of the area under the desaturation curve (e.g., sleep apnea specific hypoxic burden). While these metrics are well established in obstructive sleep apnea (OSA), their application in other respiratory conditions, including chronic obstructive pulmonary disease (COPD), pulmonary hypertension, obesity hypoventilation syndrome, heart failure, neuromuscular disorders, pregnancy, and high-altitude residents, remains an area of active investigation. This review explores the pathophysiology of hypoxemia in these conditions and evaluates the role of SpO_2-derived metrics in risk stratification beyond OSA. We also discuss the challenges of interpreting SpO_2 data, particularly the difficulty differentiating disease-related hypoxemia from comorbid OSA. Additionally, we examine the limitations of oximetry, including sensor inaccuracies, motion artifacts, and skin pigmentation. Finally, we emphasize the need for further research to standardize these metrics across diverse conditions and advocate for their integration into clinical practice to enhance patient management and outcomes.

Keywords: Nocturnal hypoxemia, Pulse Oximetry, Respiratory disease, Hypoxic burden, OSA

Introduction

The Respiratory System and Its Role in Hypoxemia

The respiratory system is crucial in maintaining oxygen homeostasis by facilitating gas exchange between the atmosphere and the bloodstream [1, 2]. It comprises the lungs, airways, diaphragm, and associated respiratory muscles, all of which work together to ensure the efficient uptake of oxygen (O_2) and the removal of carbon dioxide (CO_2), a metabolic byproduct. The lungs oxygenate blood by transferring O_2 from inhaled air into the pulmonary circulation while expelling CO_2 through exhalation [3].

Oxygen is essential for cellular metabolism, and a deficiency—termed hypoxia/ hypoxemia (hypoxia: inadequate oxygen supply to tissues and organs, hypoxemia: low oxygen levels in the blood)—can have significant physiological consequences [4]. Hypoxemia is defined as an abnormally low arterial oxygen level and can result from impairments in pulmonary ventilation, diffusion, or perfusion [5]. It is frequently observed in respiratory diseases that compromise lung function, reducing the efficiency of oxygen uptake. If left untreated, hypoxemia

can trigger systemic effects, including increased sympathetic nervous system activity, pulmonary vasoconstriction, and organ dysfunction, ultimately elevating the risk of morbidity and mortality [4-6].

Hypoxemia Types and Their Implications

Hypoxemia can be broadly classified into two types: intermittent hypoxemia (IH) and sustained hypoxemia (SH) [4]. Intermittent hypoxemia is characterized by episodic decreases in blood oxygen levels, which can occur in conditions such as obstructive sleep apnea (OSA), where oxygen saturation fluctuates throughout the night and is associated with a wide range of physiological responses such as changes in heart rate and cortical activity [7, 8]. In contrast, sustained hypoxemia is characterized by persistently low oxygen levels, which is commonly seen in diseases such as chronic obstructive pulmonary disease (COPD), pulmonary hypertension and high-altitude residents [1, 2]. Both types can contribute to disease progression and worsening outcomes, but their underlying mechanisms and effects may differ [9-12].

The measurement of hypoxemia is essential for diagnosing and managing respiratory diseases [13]. Traditionally, oxygen levels are assessed using arterial blood gas (ABG) analysis, which is invasive and not suitable for continuous monitoring. Non-invasive methods, such as pulse oximetry, are more commonly used in clinical settings. Pulse oximetry measures the oxygen saturation of hemoglobin (SpO_2) in the blood and provides a continuous, non-invasive way to assess oxygenation status. However, it has limitations, particularly in capturing the full extent of hypoxemia, especially during nocturnal periods when many respiratory conditions manifest [13-15].

Changes in SpO_2 levels and impact on nocturnal hypoxemia during sleep

Sleep has a profound effect on ventilation, gas exchange, and cellular metabolism. During sleep, ventilation decreases beyond what is expected from reduced metabolic demands[16, 17]. Two mechanisms contribute to hypoventilation: A) Increased resistance of the upper airway due to hypotonia of the pharyngeal dilator muscles and B) Alteration of the ventilatory response. These changes, which are not significant in a normal individual, are more intense in individuals with sleep respiratory disorders. In the awake individual, the central airway, which would tend to collapse due to the effect of negative inspiratory intraluminal pressure, is kept open by the stimulation of the

pharyngeal and laryngeal dilator muscles [18]. During sleep, the normal hypotonia of the central airway dilator muscles causes a slight increase in airflow resistance, often resulting in snoring and, in men over 40, in short and infrequent episodes of obstructive apnea. These episodes last less than 10 seconds and do not cause significant changes in arterial gases. If the hypotonia is excessive and especially if there are factors contributing to upper airway obstruction, more frequent and prolonged episodes of obstructive apnea occur with pathological consequences[19, 20].

Measurement of hypoxemia *in OSA*

In the context of OSA, frequent episodes of upper airway obstructions often lead to oxygen desaturation, and SpO_2 is monitored to identify "clinically significant" respiratory events [21]. SpO_2-derived metrics are crucial for assessing the severity of OSA-related nocturnal hypoxemia. In addition, based on standard guidelines, the inclusion of respiratory events in the apnea-hypopnea index (the primary measure of OSA severity) often requires a 3 or 4% oxygen desaturation[22]. Other metrics that are intended to quantify nocturnal hypoxemia include the oxygen desaturation index (ODI), which measures the frequency of oxygen saturation drops; T90, which quantifies the percentage of time spent below a specific oxygen saturation threshold (e.g., 90%); mean SpO_2, the average oxygen saturation throughout the night; minimum SpO_2 (min SpO_2), the lowest recorded oxygen saturation; and desaturation area, which quantifies the magnitude and duration of desaturation events [8, 23-26]. However, not all these metrics precisely quantify the extent of OSA-related hypoxemia and are impacted by other non-OSA-related conditions.

In recent years, several methods have been proposed to better capture the severity of OSA-related hypoxemia[8, 25]. These methods have been reviewed in depth elsewhere[21, 27]. Among these metrics, "hypoxic burden", a measure of frequency, depth and duration of OSA-related oxygen desaturation, has been shown to be associated with CVD-related and all-cause mortality[25], incident CVD[28], kidney disease[29], white matter hyperintensity[30], daytime sleepiness[31], and CPAP-related cardiovascular benefits[32]. Future prospective studies are needed to confirm and extend these findings.

Hypoxemia in Other Respiratory Diseases

While SpO_2-derived metrics are extensively utilized in assessing nocturnal hypoxemia in OSA, their application in other respiratory diseases remains less defined. Conditions such as

COPD, pulmonary hypertension, obesity hypoventilation syndrome (OHS), and heart failure also exhibit nocturnal hypoxemia, but the relationship between SpO_2-derived nocturnal hypoxemia metrics and disease severity in these disorders is not as well established [33]. A significant challenge in these conditions is distinguishing between hypoxemia resulting from sustained respiratory dysfunction and that induced by intermittent events like coexisting OSA (Figure 1). For instance, patients with COPD may experience both sustained hypoxemia due to chronic respiratory impairment and intermittent hypoxemia from concurrent OSA, complicating the interpretation of SpO_2 metrics [12, 34, 35] for effective clinical decision-making processes.

This review aims to explore the utilization of SpO_2-derived metrics in assessing nocturnal hypoxemia across various respiratory diseases beyond OSA. We will examine the pathophysiology of hypoxemia in each condition, review studies investigating the use of SpO_2 metrics for quantifying disease severity and assess how these metrics can aid in patient risk stratification and treatment selection (Table 1). Additionally, we will discuss the challenges in measurement and address the distinction between hypoxemia due to the primary disease versus the contribution of coexisting OSA. Lastly, we will briefly review the potential limitations of oximetry and the nocturnal hypoxemia metrics.

Chronic Obstructive Pulmonary Disease (COPD)

Pathophysiology

COPD refers to a group of lung diseases, primarily chronic bronchitis and emphysema, characterized by persistent airflow limitation [36, 37]. COPD remains a leading cause of morbidity and mortality globally, with smoking being the predominant risk factor, although environmental pollutants and genetic predispositions also contribute [38]. The pathophysiology of COPD is characterized by chronic inflammation and structural changes in the airways and lung parenchyma, resulting in airway obstruction, alveolar destruction, and impaired gas exchange [36, 39]. Hypoxemia in COPD arises from impaired ventilation-perfusion matching, wherein the alveolar ventilation is insufficient relative to pulmonary capillary perfusion [40]. This imbalance leads to reduced oxygen uptake and elevated carbon dioxide levels in the blood, manifesting as chronic respiratory symptoms, such as cough, sputum production, and dyspnea [2, 40]. As COPD progresses, the lungs' ability to respond to hypoxia diminishes, leading to sustained hypoxemia, which becomes more prominent during exercise and sleep [2].

Metrics for nocturnal hypoxemia assessment

Key parameters used to assess nocturnal desaturation include the frequency of the drops, mean nocturnal SpO_2 and the percentage of time spent below a specific saturation threshold, such as 90% or 80% [41-43]. In COPD, the severity of nocturnal hypoxemia is closely linked to the level of daytime hypoxemia[44]. For example, a of daytime and nighttime arterial oxygen saturation in 41 COPD patients found that patients with lower daytime saturations exhibited significantly greater mean and maximum falls in SpO_2 at night [45]. In addition, one study suggested that both total-sleep-time-related hypoxemia (measured by %sleep time below 90% SpO_2) and REM-specific nocturnal hypoxemia (measured by %sleep time below 85% SpO_2) predict mortality, however, REM-related desaturation appeared to predict improved survival with supplemental oxygen use [46]. A study assessing the relationship between lung function and sleep parameters in patients with OSA and COPD indicated that T90 was negatively correlated with different lung function indices (e.g., forced vital capacity (FVC)) [47]. Furthermore, in another study of COPD patients, T90 was strongly correlated with mean pulmonary artery pressure [48]. These studies emphasized the use of SpO_2-derived metrics to enhance risk stratification and assess treatment effects in COPD patients.

Overlap with OSA

OSA is prevalent in COPD patients, with an incidence of approximately 10–15% higher than in the general population [12, 34, 49]. The coexistence of COPD and OSA (overlap syndrome) complicates the interpretation of nocturnal hypoxemia. COPD patients with OSA tend to experience more severe hypoxemia during sleep because they begin each apnea episode in a hypoxemic state, whereas patients with isolated OSA typically saturate to normal levels between apneas. This makes COPD-OSA patients more susceptible to complications of chronic hypoxemia, such as cor pulmonale and polycythemia [34]. It is crucial for clinicians to distinguish between hypoxemia due to COPD and hypoxemia caused by OSA in order to guide appropriate treatment strategies[35, 49].

Pulmonary Hypertension (PH)

Pathophysiology

Pulmonary hypertension (PH) is a condition characterized by elevated pressure in the pulmonary arteries, leading to increased right ventricular afterload and potential right heart failure[50, 51]. The underlying pathophysiology includes pulmonary vasoconstriction, vascular remodeling, and increased pulmonary vascular resistance, all of which contribute to impaired oxygenation and hypoxemia. PH can occur as an isolated condition or as a secondary consequence of diseases such as COPD, left heart disease, or chronic thromboembolic disease [52-54]. Hypoxemia in PH often results from impaired gas exchange due to ventilation-perfusion (V/Q) mismatch, diffusion limitations, and reduced pulmonary capillary surface area[51]. As PH progresses, oxygen saturation levels decline, particularly during exertion or sleep, exacerbating right heart strain and worsening prognosis. In more advanced stages, pulmonary vascular remodeling leads to the thickening and stiffening of the arterial walls, further impairing oxygen exchange. The resultant right ventricular dysfunction contributes to carbon dioxide retention and further desaturation events, compounding hypoxemia severity [50, 55, 56].

Metrics for hypoxemia assessment

Studies have demonstrated the clinical significance of SpO_2-derived metrics in PH, particularly in assessing disease severity and prognosis. In PH, nocturnal desaturation is an essential but often overlooked marker of disease progression and worsening pulmonary hemodynamics [51, 57]. In a large retrospective study analyzing polysomnographic data from 493 PH patients, higher nocturnal hypoxemia, defined as T90, was significantly associated with increased mean pulmonary artery pressure, pulmonary vascular resistance, and right atrial pressure, underscoring its potential utility as a prognostic marker [58]. Similarly, an investigation into patients with idiopathic pulmonary fibrosis assessed the relationship between resting PaO_2 and T90 over a 24-hour period. The study found that lower resting PaO_2 was associated with prolonged periods of nocturnal hypoxemia. However, T90 did not correlate with systolic pulmonary artery pressure, suggesting that while T90 reflects nocturnal hypoxemia severity, it may not directly predict PH severity in this population [59]. Another study comparing sleep parameters in patients with interstitial lung disease (ILD) with and without PH found that those with PH exhibited significantly higher T90 compared to those without PH [60].

Overlap with OSA

OSA is frequently observed in PH patients and represents an important confounder in assessing nocturnal hypoxemia[33]. The coexistence of OSA and PH exacerbates nocturnal hypoxemia and may further accelerate right ventricular dysfunction [33]. Patients with PH across various aetiologies exhibit a high prevalence of OSA, and conversely, OSA increases the risk of PH[61]. In a study of 169 patients with pulmonary arterial hypertension, 26.6% had an apnea-hypopnea index >10 events/h, with 16% having OSA and 10.6% having central sleep apnea [62]. Overall, 27%–30% of OSA patients without left ventricular dysfunction or hypoxemic lung disease develop PH [63]. Notably, OSA patients with PH experience a lower quality of life and higher mortality compared to those without PH [64].

Obesity Hypoventilation Syndrome (OHS)

Pathophysiology

Obesity Hypoventilation Syndrome (OHS) is a disorder characterized by chronic hypoventilation in individuals with obesity, resulting in hypercapnia (elevated blood carbon dioxide levels) and, in some cases, hypoxemia [65]. The pathophysiology of OHS involves multiple factors, including mechanical airway obstruction, reduced chest wall compliance, and diminished central respiratory drive, particularly during sleep. Excess adipose tissue around the thorax and abdomen can impair diaphragmatic movement, further restricting ventilation and exacerbating gas exchange abnormalities [65-67]. Intermittent hypoxemia and hypercapnia are hallmarks of OHS, contributing to significant complications such as pulmonary hypertension, right heart failure, and chronic respiratory failure [65, 68]. If left untreated, OHS can lead to increased morbidity and mortality [69]. Diagnosis is typically based on clinical symptoms, obesity-related comorbidities, and arterial blood gas analysis, with non-invasive positive pressure ventilation often required for management[70].

Metrics for hypoxemia assessment

Various measures of nocturnal hypoxemia have been assessed in OHS, including T90, nadir SpO_2, and mean SpO_2. Additionally, some studies have explored the combined use of SpO_2 parameters with biochemical markers such as serum bicarbonate levels to improve diagnostic accuracy [71-73]. One study examined the utility of T90 as a diagnostic marker for OHS but found that it lacked sufficient sensitivity and specificity. The findings suggest that T90 alone is not a

reliable diagnostic tool and should be complemented by biochemical assessments, such as arterial blood gas analysis [74]. One study assessed the potential benefit of sleep apnea-specific hypoxic burden (%min/h) to identify obesity-related sleep hypoventilation in adults with no other respiratory or neurological diseases who underwent polysomnography or polygraphy. The results showed Hypoxic burden as a measure of intermittent hypoxemia has a low correlation with transcutaneous CO_2 pressure and a low ability to diagnose obesity-related sleep hypoventilation[75]. Additionally, prolonged nocturnal hypoxia reflected by lower mean SpO_2 and increased T90 was significantly associated with calculated HCO_3 and OHS presence and severity. These findings suggest that monitoring these indices may aid in early detection and risk stratification in obese individuals with suspected sleep-disordered breathing [68]. Given that OHS involves both sustained and intermittent hypoxemia, further analysis is needed to refine nocturnal hypoxemia measures for distinguishing OHS from OSA.

Heart Failure (HF)

Pathophysiology

Heart failure (HF) is a condition characterized by the heart's inability to pump blood effectively, leading to inadequate tissue perfusion and oxygenation [76]. The pathophysiology of hypoxemia in HF is multifactorial, involving both diminished cardiac output and pulmonary edema, which disrupts alveolar gas exchange [77]. One additional potential contributor to nocturnal hypoxemia is Cheyne-Stokes respiration (CSR), a common breathing pattern observed in HF, which is characterized by alternating periods of hyperventilation and hypoventilation. This cyclical breathing pattern leads to fluctuating oxygen saturation levels, further complicating the clinical presentation of HF-related hypoxemia [76, 77].

Metrics for hypoxemia assessment

Nocturnal hypoxemia has emerged as a significant predictor of adverse health outcomes in HF patients. In patients with Heart Failure with Reduced Ejection Fraction (HFrEF), nocturnal hypoxemia measures have been identified as an independent risk factor for all-cause mortality[78]. Specifically, a cohort study involving 280 patients with HFrEF assessed nocturnal hypoxemia using multiple pulse oximetry-derived indices, including T90, Area of the SpO_2 curve below 90%, and Event-related and non-specific T90 components. After adjusting for established risk factors,

T90, non-specific T90, the area under 90% SpO_2, and the non-specific area under 90% SpO_2 remained statistically significant predictors of mortality. In contrast, event-related indices did not demonstrate a significant association [78].

Overlap with OSA

The presence of OSA poses a challenge in the assessment of nocturnal hypoxemia in HF. Patients with coexisting chronic heart failure and OSA often experience hypoxemia driven by both pulmonary congestion and recurrent respiratory events. Moreover, central sleep apnea—characterized by diminished or absent respiratory effort due to instability in ventilatory control—is especially prevalent in patients with HF[79]. The interplay between these conditions can exacerbate cardiovascular dysfunction, with significant implications for endothelial health [80]. A study investigating arterial endothelial function in HF patients with and without sleep disordered breathing found that the severity of nocturnal hypoxemia, rather than the frequency of respiratory events, was the primary determinant of vascular impairment. However, neither the AHI nor the ODI showed a meaningful association, suggesting that cumulative hypoxemic exposure may be more relevant than discrete respiratory events in predicting cardiovascular risk [81]. Another prospective cohort study investigated the prognostic significance of hypoxemia in HF patients using several desaturation metrics, including T90, ODI, and mean SpO_2. Multivariate analysis revealed a significant associations with sustained hypoxemic metrics (e.g. T90 and mean SpO_2) but not the ODI [82].

Neuromuscular Disorders and Spinal Cord Injury (SCI)

Pathophysiology

Neuromuscular disorders (NMDs) encompass a diverse group of diseases that impair muscle and/or nerve function, resulting in weakness and dysfunction. In these conditions, respiratory muscles are frequently compromised, leading to ventilation impairment and subsequent nocturnal hypoxemia [83, 84]. Similarly, spinal cord injury (SCI) involves damage to the spinal cord, leading to partial or complete loss of motor, sensory, and autonomic functions. Individuals with high-level SCI, particularly at the cervical or upper thoracic levels, often experience significant respiratory impairment due to paralysis of respiratory muscles, predisposing them to nocturnal hypoxemia [85]. Both NMDs and SCI significantly impact the diaphragm and intercostal

muscles, increasing the likelihood of sleep-related hypoventilation [85, 86]. The severity of nocturnal hypoxemia in these conditions often correlates with disease progression, with advanced stages exhibiting more pronounced respiratory dysfunction [84]. Additionally, neuromuscular diseases can impair central respiratory control, further diminishing the ability to maintain stable ventilation, particularly during sleep [84].

Metrics for hypoxemia assessment

Overnight pulse oximetry serves as a cost-effective screening tool for detecting nocturnal respiratory disturbances in patients with neuromuscular diseases. A typical pattern observed in these patients includes a low baseline oxygen saturation with cyclical desaturation, particularly in early disease stages. There has been limited studies in these patients. For example, in a small study involving patients with ALS, measures of nocturnal hypoxemia were associated with poor memory retention, suggesting a potential link between nocturnal oxygen desaturation and cognitive impairment in ALS [87].

Overlap with OSA

Sleep-disordered breathing, including nocturnal hypoventilation, central apneas, and obstructive apneas, is prevalent in ALS patients[88, 89]. A study reported that ALS patients experience up to ten times more apnea/hypopnea events per night compared to healthy individuals, suggesting frequent episodes of intermittent nocturnal hypoxia. The precise etiology of this intermittent hypoxia remains unclear; however, polysomnographic studies indicate that central respiratory drive dysregulation or respiratory muscle fatigue, rather than OSA, may be the primary contributors [90]. Individuals with SCI, particularly those with cervical injuries, also have a heightened risk of OSA, with prevalence rates three to four times higher than in the general population. In patients with SCI, intermittent hypoxemia and sleep fragmentation have been associated with adverse cardiovascular consequences [85]. A study on cervical SCI patients highlighted an increased susceptibility to OSA, as indicated by an elevated ODI of 4% during sleep [91]. These findings underscore the necessity for targeted screening and management strategies to mitigate the adverse effects of nocturnal hypoxemia in neuromuscular disorders and SCI populations.

Pregnancy

Pathophysiology

Pregnancy induces significant physiological adaptations in the respiratory system, including increased tidal volume and altered ventilation-perfusion ratios to accommodate the growing metabolic demands of both the mother and fetus [92-94]. While most women adapt effectively to these changes, some may experience hypoxemia, particularly during sleep. In late pregnancy, the expanding uterus exerts pressure on the diaphragm, impairing ventilation and contributing to nocturnal oxygen desaturation. This effect is particularly pronounced during REM sleep when respiratory drive is naturally diminished [95, 96]. Pregnancy-related hypoxemia is further exacerbated in women with preexisting respiratory conditions, such as asthma or obesity. Additionally, pregnancy-induced hypertension and preeclampsia can negatively impact respiratory mechanics, leading to increased airway resistance, pulmonary edema, and subsequent hypoxemia [97, 98].

Metrics for hypoxemia assessment

Research on the utility of SpO_2-derived metrics in pregnancy has demonstrated their value in identifying nocturnal hypoxemia and predicting adverse maternal and fetal outcomes. For instance, a randomized controlled trial evaluating the effects of aerobic and breathing exercises in pregnant women found that such interventions significantly improved mean oxygen saturation levels [99]. A study of pregnant women reported that an ODI ≥10 was associated with an increased incidence of congenital abnormalities and neonatal respiratory distress syndrome [100]. Similarly, higher ODI levels during pregnancy have been linked to an increased likelihood of delivering small-for-gestational-age infants [101]. A large-scale study involving 3,006 women in early pregnancy and 2,326 in mid-pregnancy utilized home sleep apnea testing to assess nocturnal hypoxia. A hypoxic burden (averaged desaturation area, %min) exceeding 6.8% minutes in early pregnancy was associated with a higher risk of preeclampsia, independent of OSA severity. In mid-pregnancy, a hypoxic burden exceeding 11.8% minutes was linked to an increased risk of gestational diabetes and a low Apgar score (<7 at 1 min), even after adjusting for OSA severity [102]. In contrast, a comparative study assessing arterial oxygen saturation in 60 pregnant women across different trimesters and 60 non-pregnant controls found no statistically significant differences in SpO_2 levels between groups [103].

Physiological changes during pregnancy predispose women to a higher risk of developing OSA. Factors such as increased body weight, airway edema, and upper airway collapsibility due to hormonal fluctuations contribute to this heightened susceptibility [104-106]. A study examining the relationship between SDB and pregnancy outcomes found that among obese pregnant women, those with altered pulse oximetry readings had a higher incidence of congenital abnormalities, suggesting a possible link between maternal hypoxemia and fetal development [100]. Moreover, mid-pregnancy nocturnal hypoxemia measured as T90 and an increasing hypoxemic burden from early to mid-pregnancy has been associated with a higher risk of delivering large-for-gestational-age (LGA) infants [107].

High-Altitude Residents

Pathophysiology

Living at high altitudes leads to chronic exposure to reduced atmospheric oxygen, which triggers physiological adaptations such as increased ventilation and erythropoiesis to maintain adequate oxygen delivery to tissues [108]. However, despite these compensatory mechanisms, some individuals experience persistent hypoxemia, particularly during sleep [109, 110]. The pathophysiology of hypoxemia in high-altitude residents is multifactorial, involving both environmental factors (e.g., reduced barometric pressure and oxygen availability) and physiological responses that may be insufficient to fully compensate for the hypoxic stress [111, 112]. During sleep, nocturnal hypoxemia at high altitudes is exacerbated by hypoventilation, particularly during REM sleep, when the ventilatory drive is further diminished. This leads to recurrent desaturation events, which are commonly observed in individuals residing above 2,500 meters [108, 109].

Metrics for hypoxemia assessment

Numerous studies have evaluated SpO_2 metrics in high-altitude environments to establish reference values and assess acclimatization patterns. A large-scale study established reference SpO_2 values for individuals aged 1 to 80 years, covering elevations from sea level to the highest permanent human habitation. The results revealed a progressive decline in SpO_2 with increasing altitude, particularly beyond 2,500 meters [113]. A study using continuous SpO_2 monitoring from finger pulse oximeters showed that while SpO_2 levels initially decrease upon altitude exposure,

partial recovery is observed over time, reflecting physiological adaptation [114]. Additionally, lower SpO_2 values have been linked to an increased risk of acute mountain sickness [114]. The effects of nocturnal hypoxia on cognitive performance at high altitudes have also been examined. In one study, eleven healthy adults underwent progressive nocturnal hypoxia exposure over two weeks in an altitude tent [115]. Despite experiencing significant nocturnal hypoxemia, participants exhibited no impairments in objective vigilance or working memory, nor did they report increased subjective sleepiness [115].

Overlap with OSA

The interaction between OSA and high-altitude exposure has been the subject of increasing research interest. When OSA individuals ascend to altitudes above 1,600 meters, comparable to many popular tourist destinations, hypobaric hypoxia exacerbates sleep-disordered breathing [116]. At high altitudes, OSA patients experience a combination of obstructive and central apneas due to hypoxia-induced instability in ventilatory control [116, 117]. This results in both intermittent and sustained hypoxemia, leading to pronounced sympathetic activation, increased heart rate, cardiac arrhythmias, and systemic hypertension. These physiological changes raise concerns that individuals with OSA may face an elevated risk of cardiovascular and other adverse events during high-altitude exposure [116, 117].

Limitations of Oximetry and Nocturnal Hypoxemia Metrics

Several limitations impact the accuracy, reliability, and clinical utility of pulse oximetry. These limitations arise from inherent technical constraints, physiological variations, and external factors that influence SpO_2 readings. First, while pulse oximetry provides a convenient method for continuous monitoring, its accuracy is reduced in certain clinical settings. For example, a study comparing oxygen saturation levels measured by pulse oximetry and ABG analysis in 102 hypoxemic patients admitted to intensive care units found that when SpO_2 levels fall below 90%, pulse oximetry may not be reliable enough for accurate oxygenation assessment [118]. Other studies suggested that there may be bias and discrepancies between different pulse oximeters and ABG measurements in critically ill patients [119] and people with uncontrolled diabetes [120, 121]. Second, SpO_2 readings are influenced by peripheral circulation, which may be compromised in conditions such as SCI, neuromuscular disorders, obesity, and heart failure. In SCI patients with

lower limb paralysis or individuals with poor perfusion, weak signals from pulse oximeters can lead to inaccurate SpO_2 measurements [122-124]. Third, Pulse oximetry relies on calibration curves based on healthy individuals. Early calibration techniques used Beer-Lambert law calculations, but optical scattering and reflection effects resulted in overestimated SpO_2 values, especially at lower saturations. Calibration studies were limited by ethical constraints, preventing the induction of severe hypoxemia (≤75-80% SaO_2) in volunteers, which affects SpO_2 accuracy in critically ill patients [125]. Fourth, Pulse oximetry measures hemoglobin saturation but may not provide adequate information on respiratory function and ventilation, carbon dioxide levels, pH, or blood oxygen content. Conditions such as anemia may yield falsely reassuring SpO_2 values, as hemoglobin saturation can be normal despite reduced oxygen-carrying capacity [126, 127]. Fifth, optical interference, skin pigmentation, and nail polish could affect SpO_2 measurements. For example, research suggests that pulse oximetry is less accurate in individuals with darker skin due to increased melanin interfering with light absorption, prompting the U.S. Food and Drug Administration to issue a warning regarding the potential inaccuracy of pulse oximeters in patients with pigmented skin [14, 128-132]. Finally, factors, including smoothing, motion artifacts, and coexisting conditions could influence the SpO_2 measurements and their interpretations.

Conclusion and Future Directions

Common nocturnal hypoxemia metrics, such as ODI, T90, and mean SpO_2, do not capture the full spectrum of hypoxemic events. For intermittent hypoxemia, these indices often fail to incorporate the duration, frequency, and physiological impact of desaturations. The standard SpO_2 threshold for defining hypoxemia is typically set at 90%, yet this cutoff may not be appropriate for all populations. Patients with chronic respiratory diseases, such as COPD, may require a lower threshold (≤88%) for clinical relevance. Uniform SpO_2 thresholds can lead to misclassification, underestimating hypoxemia severity in some patients. To address these challenges, future research should focus on developing and validating SpO_2-derived metrics that integrate desaturation dynamics and severity; combining oximetry with other modalities, such as capnography and sleep staging, to provide a more comprehensive assessment of hypoxia-related pathology; implementing personalized SpO_2 thresholds based on patient characteristics (age, comorbidities, baseline oxygen levels) to improve hypoxemia classification. In addition, technical issues related to pulse oximetry itself also warrant attention. SpO_2 measurements are subject to inaccuracies due to calibration

differences among devices and signal quality degradation from motion artifacts, poor perfusion, or improper sensor placement. Notably, recent evidence has highlighted racial disparities in pulse oximetry accuracy—individuals with darker skin pigmentation may experience overestimated oxygen saturation levels, leading to under-recognition of clinically significant hypoxemia. These discrepancies can have serious implications for diagnosis, monitoring, and treatment decisions. Therefore, future research should also aim to refine the optical and algorithmic components of pulse oximeters to ensure equitable and reliable measurements across diverse populations and clinical contexts. By addressing these limitations and expanding the scope of nocturnal hypoxemia assessment, clinicians will be better equipped to evaluate the impact of hypoxia across various respiratory conditions. This, in turn, will facilitate more targeted interventions aimed at mitigating the long-term consequences of chronic hypoxemia.

Figure 1: Nocturnal oximetry recordings (around 3 hours) of four individuals with different levels of T90, ODI and HB. The orange dashed line shows the 90% level of SpO_2. Abbreviations: ODI=Oxygen Desaturation Index; SpO_2 = Peripheral Oxygen Saturation; T90= Time below 90% SpO_2; HB: hypoxic burden.

Table 1: Oximetry-derived nocturnal hypoxemia severity metrics in respiratory medicine.

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Table 1: Oximetry-derived nocturnal hypoxemia severity metrics in respiratory medicine.		
Metrics	*Definition and application in respiratory disease*	*Potential limitations*
ODI	Number of desaturation events (typically ≥3% or ≥4%) per hour of sleep. Commonly used to measure intermittent hypoxemia in COPD, OHS and OSA diagnosis and severity classification.	Does not account for duration or depth of desaturation; influenced by desaturation threshold; may miss longer, milder events; depends on sampling rate and artifact rejection.
Mean SpO2	Average oxygen saturation throughout the sleep period. Reflects overall oxygenation status and is associated with prognosis in diseases like COPD, heart failure, and pulmonary hypertension.	Does not reflect intermittent desaturations or variability; may mask underlying events; affected by sensor accuracy and signal dropout.
Min SpO2	Lowest oxygen saturation recorded during sleep. Used in assessing severity of desaturation, particularly in those lining in high altitude, COPD and sleep apnea.	Single-point measure; highly susceptible to artifacts or transient events; may not reflect clinical impact.
T90/T88/T85	Percentage of total sleep time spent with SpO_2 below 90%, 88% or 85%. Used to quantify severity of sustained nocturnal hypoxemia in COPD, OHS, and interstitial lung disease.	Threshold-based; may not capture intermittent and brief but physiologically important events; dependent on baseline SpO_2 and may misclassify individuals with low baseline values.
Desaturation pattern	Morphology and recurrence of desaturation events considering specific duration and frequency of hypoxemic events. May provide	Not standardized specifically in terms of defining intermittent and sustained hypoxemia; interpretation varies across

	insight into the type of hypoxemia in respiratory disorder such as OSA, OHS and COPD.	studies; requires advanced signal analysis and may be affected by sleep architecture variability and sensor reliability.
OSA-related hypoxic burden	Integrated area under the desaturation curve below a defined threshold or in response to obstructive events considering a specific search window for everyone. Represents the depth and duration of oxygen desaturation. Emerging metric in OSA, COPD, OHS, hypoxemia during pregnancy and heart failure prognosis.	Studies are needed to define clinical thresholds; not yet widely adopted in clinical practice specifically beyond OSA.
Abbreviations: ODI = Oxygen Desaturation Index; SpO_2 = Peripheral Oxygen Saturation; T90 = Time below 90% SpO_2; T88 = Time below 88% SpO_2; OSA = Obstructive Sleep Apnea; COPD = Chronic Obstructive Pulmonary Disease; OHS = Obesity Hypoventilation Syndrome.		