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REVIEW

A Review of Current Tools Used for Evaluating the Severity of Obstructive Sleep Apnea

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Abstract: Obstructive sleep apnea (OSA) is a common and heterogeneous disease characterized by episodic collapse within the upper airways, which leads to reduced ventilation and adverse consequences, including hypoxia, hypercapnia, sleep fragmentation, and long-term effects such as cardiovascular comorbidities. The clinical diagnosis of OSA and its severity classification are often determined based on the apnea–hypopnea index (AHI), defining the number of apneic and hypopnea events per hour of sleep. However, the limitations of the AHI to assess disease severity have necessitated the exploration of other metrics for additional information to reflect the complexity of OSA. Novel parameters such as the hypoxic burden have the potential to better capture the main features of OSA by maximizing the information available from the polysomnogram. These emerging measures have described multidimensional qualities of sleep-disordered breathing events and breathing irregularity and will ultimately result in better management of OSA.

Keywords: obstructive sleep apnea, apnea–hypopnea index, disease severity, hypoxic burden, polysomnogram

Introduction

Obstructive sleep apnea (OSA) is a highly prevalent and heterogeneous disorder characterized by repeated pharyngeal collapse, resulting in episodic reduced ventilation that causes blood gas exchanges to be disrupted and subsequent hypoxia, hypercapnia, and sleep fragmentation.[1–3] Global prevalence data show almost 1 billion patients with OSA,[4] predominantly in China, followed by North and South American countries, such as the United States and Brazil. The total cost of OSA in the United States in 2015 was 12.4 billion dollars, whereas data from resource-poor countries have not yet been collated. Among the many health concerns inherent to OSA, comorbidities such as cardiometabolic disorders and neurocognitive complications are the long-term consequences of the lack of precise management strategies for OSA.[5] The high prevalence and socioeconomic impact of this disorder necessitate that all nations—both resource-rich and developing countries—make substantial efforts to address this issue.[6,7] The current goal for healthcare systems internationally is to concentrate on providing universal diagnostic tools and effective treatment for OSA to achieve a positive impact on global health.[8]

As the understanding of physiological characteristics of sleep disturbance has advanced, the apnea–hypopnea index (AHI) is the tool used most commonly to diagnose and categorize the disease severity of OSA, and use of the AHI is a common practice in most studies.[9–12] However, the AHI has several important limitations: poor correlation of the AHI with clinical manifestations of OSA such as excessive daytime sleepiness, which may be measured both subjectively and objectively;[13,14] consequences resulting from the

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cardiovascular disease (CVD) risks that cannot be predicted precisely by the AHI;[15] and the increased risk of hypertension in patients with OSA with a higher AHI score, but no further positive relationship for an AHI score >15.[16] All of these weaknesses lead to questioning the extensive use of this metric as a major strategy to evaluate OSA.[17,18]

The poor performance of the AHI may result from it lacking the capacity to reflect the respiratory event duration and extent, the arousal threshold, sleep fragmentation, and other pathophysiological elements. For example, a respiratory event with a 2-minute duration has a totally different physiological impact on patients with OSA than events lasting only 20 seconds. Thus, limited information provided by the AHI may be the reason that a large clinical trial (the Sleep Apnea cardiovascular Endpoints trial) showed no CVD benefit from treatment with continuous positive airway pressure (CPAP) among individuals selected based on the AHI score,[19,20] although the ASAP-HF Pilot Trial compared standard of care therapy for acute decompensated heart failure versus addition of PAP therapy in patients with concomitant OSA, and found pulmonary hypertension was reduced with addition of PAP therapy.[21]

Undoubtedly, OSA has a strong relationship with diverse poor health outcomes, including cardiometabolic events, systemic hypertension, neurocognitive impairment, and all-cause mortality.[22–24] Intense disagreements have arisen within the science community on whether the diagnosis and treatment of this complex disease should be based solely on one parameter that displays only apnea and hypopnea polysomnogram (PSG) frequencies to the exclusion of more revealing data, such as the duration, magnitude, and distributions of oxygen desaturation in different sleep stages. Nevertheless, these other sleep traits have not been fully used in various versions of clinical practice guidelines or for expert consensus.[25]

This review aims to summarize the existing and emerging methods that quantify the severity of OSA beyond the data provided by the AHI score, based on a comprehensive exploration of the literature (Table 1), and to establish a broader vision to understand the pathophysiological diversity of OSA and its various susceptibilities.

Conventional Methods for PSG Data Analysis

Lowest Oxygen Saturation, Time Spent with Oxygen Saturation <90%, and Oxygen Desaturation Index

Obtaining just AHI from a PSG containing rich physiological data is as unacceptable as getting just the details of forced expiratory volume in one second (FEV1) from a complicated lung function test report, thus concern is growing regarding the loss of capturing other data. This

Table 1 Polysomnographic Metrics of Measuring Severity of OSA

Classification	Metrics	Pathophysiological Backgrounds	Complications Associated with OSA
Conventional and widely used	AHI	intermittent hypoxia	EDS,[13,14] CVD and all-cause mortality,[15] hypertension[16]
	ODI, T90, LSpO2		subclinical atherosclerosis,[25] all-cause mortality in HF,[26] postoperative complications[27–29]
	SIT		hypoxemia in sleep disorders[34]
Novel and promising	Hypoxic burden	intermittent hypoxia	CVD mortality,[15] BP,[35] and risk of incident HF[36]
	Obstruction severity		CVD and all-cause mortality[42]
	hypoxia load		CVD risk,[44] BP[45]
Emerging and potential	ApEn of oxygen saturation	indirect metric, mainly quantification of data regularity	Hypoxemia,[48,49] Associated with AHI[60]
	flow:drive ratio	pharyngeal obstruction	
	CPC, HRV, ORP	sympathetic activation, arousability	effect of CPAP titration,[54,58] CVD risk[52,57]
	Expiratory time constant	product of airway resistance and lung compliance	severe sleep apnea[61]

Abbreviations: OSA, obstructive sleep apnea; AHI, apnea–hypopnea index; ODI, oxygen desaturation index; T90, time spent with oxygen saturation <90%; LSpO2, lowest oxygen saturation; SIT, saturation impairment time; ApEn, approximate entropy; CPC, Cardiopulmonary coupling; HRV, heart rate variability; ORP, odds ratio product; EDS, excessive daytime sleepiness; CVD, cardiovascular disease; HF, heart failure; BP, blood pressure; CPAP, continuous positive airway pressure.

information includes an evaluation of nocturnal hypoxemia related to apnea and hypopnea, such as the time spent with oxygen saturation <90% (T90) or 80% (T80), the lowest oxygen saturation ($LSpO_2$), and the oxygen desaturation index (ODI), which is calculated as the frequency of desaturation events that is determined by a ≥3% or 4% decrease in peripheral oxygen saturation (SpO_2) from the baseline.

Several observational studies[26–33] have demonstrated these oxygen measures to be effective or even superior to the AHI in predicting adverse CVD outcomes and all-cause mortality. For example, more serious hypoxemia (defined as T90 ≥0.64%) was associated with subclinical atherosclerosis when crudely regarding T90 as a dichotomized variable.[26] Another study indicated that T90 was independently associated with increased all-cause mortality in patients with heart failure as a chronic stable condition.[27] A study claimed that hypoxemic burden measured by T90 was demonstrated to be more predictive for mortality than AHI and should be considered a key metric for therapies used to treat central sleep apnea.[28] Previous studies revealed that oximetry parameters, including T90, ODI, and $LSpO_2$, may play a role in predicting the postoperative complications after upper airway operations, bariatric surgery, and cardiac surgery in patients with OSA[29–31] and may provide information for risk stratification. A study exploring the relationship between OSA and diabetes-related complications showed that ODI was associated significantly with a decline in estimated glomerular filtration,[32] whereas another study of patients with OSA and diabetes mellitus found a relationship between $LSpO_2$ and hyperglycemia.[33]

An important caution is that these metrics derived from desaturation signals related to corresponding respiratory events are not specific to OSA causing intermittent hypoxemia—they also characterize chronic airway diseases, such as chronic obstructive pulmonary disease, leading to persistent hypoxemia. In addition, whether the specific cut-off point of oxygen desaturation should be 3% or 4% remains controversial to some extent, because a different definition results in a significant variation in findings.[34]

Another weakness of these metrics in terms of application is that the diagnostic and classification thresholds seem arbitrary, such as ODI3% and ODI4%, T90 ≥0.64%, and T90 ≥10%.[20,26,34] In addition, an inherent limitation of these derived variables is that they focus only on some of the major pathophysiological traits of OSA—oxygen duration, extent, and frequency—and inevitably ignore other elements, thus falling short of capturing the overall features of OSA and eventually failing to serve as a perfect marker in clinical practice.

Saturation Impairment Time

An early established parameter, the saturation impairment time (SIT) index, was calculated as an area under the desaturation curve by integrating the time and degree of desaturation below certain levels.[35] A study comparing the validity of the SIT index and time spent with oxygen saturation lower than various levels such as 90% (T90) or 80% (T80) for the quantitative evaluation of hypoxemia in sleep disorders, showed that the SIT score correlated well with T90 and T80. These results suggest that the SIT index may provide additional quantitative information to determine the severity of hypoxemia beyond the AHI.[36] Nevertheless, the use of the SIT index was assumed to have approximately the same inherent defects as T90 or ODI, and thus, to date, only limited literature is available for the SIT index, resulting in insufficient advances in this field.

Novel and Promising Parameters in Reinventing the Use of PSG

Hypoxic Burden

A recent study exhibited a novel parameter termed the hypoxic burden, which is determined as the average area under the desaturation curve associated with each respiratory event.[15] The area under the pre-event baseline was calculated within a specific search window obtained from overlying oximetry signals with respect to the end of each oxygen desaturation event. These data can be visualized as a triangle, with the desaturation duration and depth assumed to be the base and height, respectively. The hypoxic burden can then be approximately equal to the multiplication of the AHI score and the area above the desaturation curve, thus achieving an integration of the duration, depth, and frequency of respiratory-related events. The hypoxic burden was demonstrated to be associated with an increased CVD mortality among adults aged >40 years in two cohort studies (the Outcomes of Sleep Disorders in Older Men [MrOS] and the Sleep Heart Health Study [SHHS]) adjusted for multiple covariates, including the AHI.[15] In addition, a higher blood pressure[37] and the risk of incident heart failure in men[38] were demonstrated to be associated with this hypoxic burden after adjusting for confounding factors such as comorbidities.

Compared with a single-trait measure such as the AHI score, this emerging algorithm to quantify the hypoxemia

burden has provided a novel solution to measure the ventilatory disturbance and has made great progress in solving the mystery of the pathophysiology and multisystem outcomes of sleep-disordered breathing.[39] In addition, the hypoxic burden may serve to identify patients who may benefit from CPAP and bariatric surgery.[15] A limitation of the hypoxic burden identified was that while apnea and hypopnea events have been identified on sleep measures, no distinction was ever made between the obstructive and central sleep disturbances regardless of associated oxygen desaturation, and obstructive apnea and hypopnea were incorporated with equal weights. In addition, the algorithm of the hypoxic burden does not reflect the duration of respiratory events, which is a weakness of this sleep measure because it is unclear whether these impressive findings would remain significant after considering the event duration. This point is an important consideration because a study has already indicated that respiratory events of short duration may be more effective in predicting all-cause mortality than longer-duration events.[40]

Obstruction Severity

Similar to the hypoxic burden, a novel parameter termed obstruction *severity* is determined as a sum of the product of each respiratory event-associated area above the desaturation curve and the duration of the corresponding apneic or hypopnea event, then normalized with the total sleep time.[41] Where this metric differs from the hypoxic burden is that it considers the obstruction duration; thus, it captures a wider range of pathophysiological traits, including both the duration and the frequency of obstruction and desaturation events, plus the depth of desaturation, making it a virtually better measure with preferable prospects for application.[42] Based on the results of assessment for obstruction severity, Muraja-Murro et al found that the values for this derived variable were higher in the deceased and in patients with severe OSA with an AHI score ≥30 versus the control group of alive patients with matched AHI scores. Using multiple logistic regression analysis, these findings demonstrated that obstruction severity—not the AHI—was the only index related to all-cause mortality in patients with severe OSA.[43] In addition, the decrease in obstruction severity was as not remarkable as the decrease in the AHI score when treating patients with OSA with weight loss, which suggests that weight loss may not be an intervention that is as significant as the AHI indicates to reduce the severity of OSA.[44] Thus, the dependence on a single sleep metric such as the AHI to judge the efficacy of weight loss to manage OSA may present the risk of overestimation. For better clinical practice, the obstruction severity was further converted to an adjusted AHI score to advance its use for diagnosis and as a severity measure of OSA with the same classification threshold as the conventional AHI.[45] With this approach, the adjusted AHI led to a significant redistribution of OSA severity, causing a higher risk of CVD and all-cause mortality in patients with OSA with moderate and severe disease versus patients with the same severity categories based on the conventional AHI. Therefore, the method-adjusted AHI serves as a better metric to provide additional and more accurate information than the conventional AHI score alone in recognizing the risk of OSA-related complications such as CVD and all-cause mortality.[45]

To further clarify the definition of obstruction severity, the end of respiratory event-associated desaturation was determined as the area up to the last moment before the recovery of oxygen saturation. The ventilatory disturbance is better characterized if both the desaturation and recovery periods were incorporated in the obstruction severity calculation. In addition, the hypopnea events calculated in obstruction severity were scored following the rule that only ≥4% desaturation from the baseline met the criteria, leaving a smaller degree of desaturation excluded.[43,46] However, the risk of self-reported CVD has been suggested to be related more to hypopnea with ≥4% desaturation than <4% desaturation.[5] Thus, the obstruction severity may result in a modest underestimation of disease severity in OSA.

Hypoxia Load

A third novel parameter termed *hypoxia load* was designed to measure the nocturnal hypoxemic burden to better classify the severity of OSA. This sleep measure was used in a prospective observational study[47] showing a crude correlation between the hypoxia load—but not the AHI as an event-based metric—and the epicardial fat volume determined as a marker of CVD risk, although a causal effect has not yet been established. The hypoxia load was defined as a sum of the integrated area of all desaturation events using a trapezoidal rule, which differs slightly from the algorithm for the hypoxic burden as described previously. The hypoxia load was also demonstrated to be a promising marker of and a potential treatment target for blood pressure,[48] which suggests that further studies are

expected to illustrate the effect of the hypoxia load as a severity measure in predicting OSA outcomes.

In general, these new parameters, with a different perspective on PSG data, may provide more comprehensive information related to sleep-disordered breathing so that the intrinsic property of the physiological stress in OSA may be better assessed. However, their current use is limited by some details awaiting more evidence before reaching a consensus.

Emerging Potential Markers without Specific Quantification

Approximate Entropy

A new method called approximate entropy (ApEn), which is based on chaos theory, was evaluated in several clinical studies on CVD complications. The ApEn approach represents a quantification of biological regularity in time series data.[49] A smaller ApEn value corresponds to regularity and predictability, whereas a larger value indicates complexity and variability. In a recent study,[50] Nakayama et al suggested that an ApEn value of chest respiratory movements was associated with a supine AHI score in patients with OSA with multiple system atrophy. In another study, the ApEn of oxygen saturation was demonstrated to be related to the AHI, ODI, and T90.[51] In addition, a study on the correlation between the ApEn of oxygen saturation and the AHI based on analysis of oximetric data concluded that ApEn may be a useful approach in diagnosing OSA.[52] Moreover, studies on ventilatory instability in OSA[53,54] revealed that breathing irregularity may be an outcome of sleep-disordered breathing, because breathing instability improved after treating patients with OSA with CPAP. These findings suggest that ApEn may be a promising method for clinical assessment and as a target for management, especially with CPAP. Despite the substantial strength of this method, ApEn has the limitation that none of the physiological features of OSA, such as duration, frequency, and extent of desaturation, were considered when this new index was calculated. Before use in clinical practice, issues regarding the accuracy, practicality, and other aspects of ApEn remain to be resolved.

Cardiopulmonary Coupling, Heart Rate Variability, and Odds Ratio Product

An electrocardiogram (ECG)-based method has raised extensive attention after use in many studies to characterize the coupling of heart rate variability (HRV) and ECG-derived respiratory fluctuations and quantify the relative sleep quality as stable (high-frequency coupling, HFC) or unstable (low-frequency coupling, LFC), thus termed cardiopulmonary coupling (CPC).[55] This measure was proven to be correlated with objective sleep quality.[56] In addition, in one study, an increased HFC and decreased LFC were seen in a CPAP group, but not in the matched control group,[57] suggesting that CPC plays a potential role in reflecting and monitoring therapeutic effects for patients with OSA. Also, CPC may be a promising marker of measuring severity and a target for treatment response.

The HRV, defined as the fluctuation of RR intervals on an ECG, reflects the autonomic variation in the nervous system.[58] The time domain and frequency domain of HRV can be used to analyze autonomic nervous system activity. Abnormal HRV occurs when the autonomic nervous system function is impaired during OSA.[59] Analysis of HRV showed that abnormal HRV predisposes the patient to CVDs,[60] such as acute myocardial infarction. A recent study found that, compared with patients without OSA, the time domain of HRV decreases and the frequency domain increases in patients with OSA, and CPAP treatment reversed these changes in HRV. Therefore, the study concluded that HRV may help diagnose OSA and evaluate the effectiveness of CPAP treatment.[61]

Finally, the odds ratio product (ORP), determined as a continuous index of measuring the sleep depth extrapolated from the spectrum of an electroencephalogram (EEG), has correlations with arousability.[62] In another study, compared with participants with moderate-to-severe or no OSA, higher rapid eye movement (REM) ORP was more strongly (and negatively) associated with systolic blood pressure.[37] Thus, ORP may serve as a potential marker for CVD risk in patients with OSA.[55]

However, the CPC, HRV, and ORP, as well as some other newly developing techniques, still need to be strengthened because of their lack of specific criteria for diagnosis, severity evaluation, and indications for managing OSA.

Flow:Drive Ratio

One study quantified the severity of pharyngeal obstruction by using a continuous variable termed the flow:drive ratio, based on the features of flow shape in an individual breath during PSG.[63] This feature varied widely among patients with OSA independent of the AHI score, although an association was observed between flow:drive and the AHI. Considering that this emerging metric concentrates

mostly on the morphology of OSA without considering its major pathophysiological mechanisms, the role of the flow:drive ratio in the sequelae of OSA remains to be explored.

Expiratory Time Constant

The expiratory time constant (ETC), which reflects the tempo of pulmonary emptying in the lung mechanics, was captured based on the nasal pressure signal in PSG for patients with OSA with the overlap syndrome.[64] The AHI score was greater for patients with an ETC >0.5 seconds than patients who had an ETC ≤0.5 seconds. A larger ETC value was associated with an approximately 11-fold increase in the risk of severe sleep apnea (odds ratio 10.6, 95% confidence interval 3.9–51.1, $p = 0.005$), suggesting a role for this metric to be used in the classification and management of OSA. Further research is warranted to explore more specific applications in evaluating the overall severity and predicting the sequelae of OSA.

Integrated Grading System for OSA Severity

As heavy reliance on a single trait in OSA to evaluate the disease severity may result in underestimation or misjudgment, a new multidimensional model to assess OSA disease severity has been elaborated.[65] The frequency of respiratory events and the related acute systemic effects, such as T90, arousals, and, of equal importance, the long-term organ impact of OSA (e.g. hypertension, CVD, insulin resistance), were included in a three-dimensional model. The three-dimensional volume represents a synthetic analysis of severity to better adapt to the uses for clinical management.

A refined ABCD evaluation tool was also proposed based on the multi-element grading system that considers both organ damage and signs and symptoms, such as the Epworth Sleepiness Scale score, dozing episodes, self-assessed hypersomnia, and vigilance test results (Figure 1),[65,66] similar to the approach in the global strategy for chronic obstructive pulmonary disease.[67] The development and validation of biomarkers for these observable characteristics in OSA may be one of the priorities for future research.

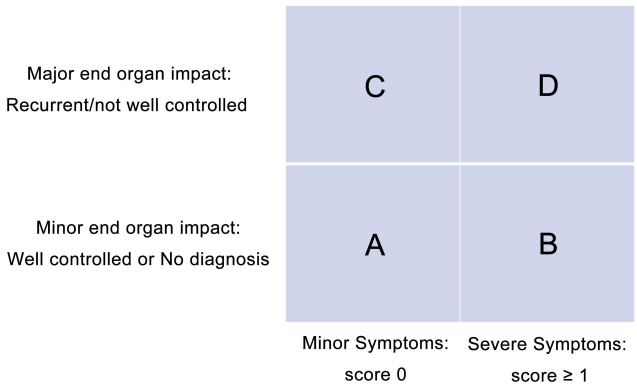

Figure 1 A refined ABCD evaluation tool based on the multielement grading system for OSA severity.

Note: A patient is considered to presented with minor symptoms (score 0) if all results are negative (Epworth Sleepiness Scale < 9, no dozing episodes or hypersomnia, negative vigilance test), or severe symptoms (score ≥ 1) if any of these tests are positive. The minor end organ impact means that the following diseases, including arterial hypertension, atrial fibrillation, heart-failure, diabetes, stroke, are well controlled or never diagnosed. A patient is considered to suffer from major end organ impact if any of these diseases are recurrent or not well controlled. Thus, Patients presenting with minor symptoms (score 0) are classified as group A or C, and patients suffering from minor end organ impact are classified as group A or B. Reproduced with permission from © ERS 2020: European Respiratory Journal 2018;52:3. doi:10.1183/13993003.02616-2017.[65]

Deep Learning/Machine Learning

Deep learning (DL) is a subset of machine learning and consists of various analysis methods including convolutional neural networks (CNNs) and long short-term memory (LSTM). The DL approach has been applied to medical settings and language processing and can extract the rich data contained in PSG and automatically finish sleep staging.[68] A study using three DL methods (CNN, LSTM, CNN + LSTM) to estimate the AHI[69] demonstrated the correlation r value between the gold standard AHI with an estimated value of 0.84, which showed that this system may serve as a convenient tool for a home-based sleep apnea test (HSAT). The HSAT is expected to be more efficacious and cost effective and to eventually play a crucial part in quantifying OSA in the future. Other studies have also used the DL model to predict sleep disorders in an asthma cohort[70] and to predict nocturnal blood pressure in patients with OSA.[71] With the rapid development of DL, it will not be long before DL methods are used widely in clinical practice.

Conclusion

It is unacceptable to acquire nothing but the AHI data from the massive amount of information stored in the PSG. Although conventional measures such as the AHI share serious limitations in various respects, novel parameters, such as the hypoxic burden and obstruction severity, are incorporating significantly more information on multidimensional traits of hypoxemia and desaturation during ventilatory disturbance. Thus, these methods are better in capturing the physiological stress and morphology in OSA and in predicting the outcomes of various conditions related to OSA. However, deficiencies

still exist for these methods because neither the difference between the physiological impact of hypopnea versus apnea nor the arousal intensity were elucidated, and the classification of desaturation events (central or obstructive) was not considered. In addition, other new methods, such as the decreases in pulse wave amplitude derived from noninvasive photoplethysmography, are also catching the attention of researchers.[72]

To date, there is a scarcity of literature to clarify the widely accepted or perfect diagnostic criteria and to guide strategies on effective or precise treatment of the major neurocognitive and CVD sequelae related to OSA. To better illustrate the disease severity of OSA in the future, a more comprehensive indicator—one that considers hypoxemia, desaturation, arousal threshold, loop gain, and sleep staging, especially during the REM period—will improve the ability to determine the severity and management of OSA. With this foundation, the science in sleep and respiratory medicine will undoubtedly advance.

Disclosure

The authors report no conflicts of interest in this work.

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