·综 述·

夜间间歇性缺氧相关评估指标的研究进展

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[摘 要] 阻塞性睡眠呼吸暂停是一种常见的疾病,其患病率正在逐年上升,由其引发的夜间间歇性缺氧与多种不良健康结局有密切关系,因此,探索简单、可靠而全面的夜间间歇性缺氧评估指标,一直是近年来研究的热点。文章总结了目前夜间间歇性缺氧相关指标的不同评估方法,包括表征间歇性缺氧的频率(氧饱和度下降指数)、持续时间(氧饱和度低于90%时间、饱和度损伤时间)、低氧幅度(最低血氧饱和度、血氧饱和度下降幅度)等单项评估指标及低氧负荷、低氧负荷指数、低氧负担、睡眠呼吸障碍指数等综合性评估指标。

[关键词] 夜间间歇性缺氧;阻塞性睡眠呼吸暂停;评估指标

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Progress in the assessment of indicators related to nocturnal intermittent hypoxia

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[**Abstract**] Obstructive sleep apnea is a common disease, the prevalence of which is increasing year by year, and the nocturnal intermittent hypoxia triggered by it is closely related to a variety of adverse health outcomes, therefore, it is a hotspot to search for a simple, reliable and comprehensive index to assess intermittent night hypoxia in recent years. In this paper, we summarized the different evaluation methods of the indexes related to nocturnal intermittent anoxia, including the frequency (oxygen saturation decline index), duration (time when oxygen saturation is below 90% and saturation damage time), and hypoxia amplitude (lowest oxygen saturation, oxygen saturation decline amplitude), etc, and comprehensive assessment indicators such as hypoxic load, hypoxic load index, hypoxic load, and sleep-disordered breathing index, etc.

[**Key words**] nocturnal intermittent hypoxia; obstructive sleep apnoea; assessment indicators

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阻塞性睡眠呼吸暂停(obstructive sleep apnea, OSA)是一种常见的睡眠呼吸障碍疾病,其患病率正在不断上升,目前主要依靠多导睡眠监测仪(polysomnography, PSG)确定的呼吸暂停低通气指数(apnea-hypopnea index, AHI)来诊断和评估OSA的严重程度[1]。OSA的主要特点是在睡眠中反复发作上呼吸道塌陷和阻塞,由此会引起机体反复地缺氧-再氧合即间歇性缺氧(intermittent hypoxia, IH),这是OSA相关心血管疾病及代谢综合征的主要病理生理学机制之一[2]。目前临床对于IH严重程度的评估指标主要是夜间最低脉氧饱和度(minimum of pulse oxygen saturation values, $MinSpO_2$),并以此进行严重程度分级。但实际工作中发现,单纯依靠$MinSpO_2$难以客观真实反映夜间缺氧的严重程度[3]。近年来,较多学者针对夜间IH的评估及其临床意义进行了相关研究,文章分类梳理了夜间IH相关评估指标的定义及临床意义并进行综述。

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1 IH

缺氧的定义是组织氧合水平降低[4]，可用动脉血氧饱和度表示，动脉血氧饱和度是通过血气分析获取的，但其为有创操作，且无法动态实时获取，故临床工作中常用脉搏血氧仪测定的脉搏氧饱和度（pulse oxygen saturation，SpO_2）代替。由于OSA患者夜间上呼吸道塌陷是发作性及反复性的，因而引发的缺氧是间歇性的[2]。关于IH的定义，不同研究团队报道不尽相同，具体如下。2008年，Mogri等[5]定义睡眠IH为SpO_2<90%超过5 min，且$MinSpO_2$<85%，或者超过30%的总睡眠时间内SpO_2<90%。2015年，Zalucky等[6]将IH定义为 SaO_2<90%的时间占比≥记录时间的12%，并对OSA患者夜间缺氧的严重程度进行了分级：即夜间平均SpO_2≥90%为中度缺氧，平均SpO_2<90%为重度缺氧。2021年，Krieger等[7]将IH定义为SpO_2下降≥4%，持续时间至少6 s。

IH与OSA的不良结局及预后密切相关。Zalucky等[6]研究发现，OSA患者夜间IH的严重程度与肾素血管紧张素系统活性增加的程度相关。研究证明，IH是睡眠呼吸暂停导致心力衰竭的直接危险因素[8]。同时IH还与血小板活化增加相关，可能是血栓形成和心血管事件（cardiovascular disease，CVD）发生的关键因素[7]。Uysal等[9]将SpO_2<90 %的时间占记录时间的百分比（P90）、氧饱和度下降指数（oxygen desaturation index，ODI）、平均去饱和度百分比（average percent desaturation，AD）和$MinSpO_2$这4个标准低氧血症变量相结合，并证明其可预测日间过度嗜睡（excessive daytime sleepiness，EDS）。

2 夜间IH相关评估指标

2.1 ODI

ODI对应于每小时氧去饱和事件的平均数量[1]，一般从脉搏血氧仪中获得，具有方便、经济、广泛可用的特点，是目前临床中用于诊断OSA的重要指标。有研究认为ODI可替代AHI用于严重OSA患者的筛选[10]。但主流观点认为，ODI缺乏特异性和敏感性，不能作为多导睡眠监测的替代方法用于诊断睡眠相关的呼吸障碍[11]。ODI的临床应用也有相关报道：ODI是CVD的独立预测因子[12]；与亚临床动脉粥样硬化、心衰的全因死亡率及术后并发症相关[13]。同时，ODI有助于在糖尿病患者中筛查OSA[14]；此外，高水平ODI可能与警觉状态依赖性代谢的破坏有关[15]。

ODI仅描述IH的频率，忽略了其持续时间与深度，且不能区分中枢性呼吸暂停和阻塞性呼吸暂停。若存在氧去饱和程度较深，持续时间较长，患者的ODI反而较小，无法客观体现OSA的严重程度并予量化。SpO_2较基线下降3%还是4%界定为氧去饱和目前是有争议的，不同的SpO_2下降程度在不同个体和合并症之间可能存在很大差异[16]。此外，若存在影响SpO_2的其他因素时，ODI可能不准确。

2.2 $MinSpO_2$

$MinSpO_2$是目前评估睡眠呼吸暂停并发IH严重程度的重要指标，主要用于OSA严重程度的分级。据报道，$MinSpO_2$与EDS[10]、糖尿病[17]、认知能力[18]、CVD结局[19]及悬雍垂-腭-咽成形术（uvulopalatopharyngoplasty，UPPP）术后不良事件相关[20]。然而，$MinSpO_2$仅反映整夜瞬时的SpO_2，当存在其他影响SpO_2的因素时，如贫血、心功能不全、周围血管疾病、慢性阻塞性肺病等，$MinSpO_2$是否能真实反映由OSA引起的IH的严重程度则存在疑问。此外，目前SpO_2的测量主要是通过佩戴于指尖的脉氧仪获取，可能会因患者末梢指端血液循环不佳、甲癣、假指甲、不同品牌脉氧仪监测准确性及患者配合度等因素而影响结果的可靠性。因此，临床尝试采用粘贴式的生物贴片，以获得更准确的SpO_2值。

2.3 氧饱和度低于90%时间（time below 90% oxygen saturation，T90）

T90通常用于量化夜间长期暴露于IH所致的损伤，即夜间低氧负荷[1]。T90被认为与CVD风险独立相关，可以预测CVD的病死率，并在许多研究中被广泛使用[21-24]。有研究表示，T90可以描述OSA的高危表型，即在中重度OSA患者中，T90与2型糖尿病的共病风险及5年病死率增加有很强的相关性。肥胖和轻至中度慢性阻塞性肺疾病（chronic obstructive pulmonary disease，COPD）与T90增加有关[24]。

然而，T90仅测量SpO_2<90%的时间，无法完全反映呼吸暂停的深度和频率；也未区分由呼吸暂停或低通气引起的低氧事件。目前研究中，并没有明确的T90界值来划分OSA患者夜间IH的严重程度，常适用于慢性气道疾病，如可导致持续性低氧的COPD。

2.4 低氧负荷（hypoxic burden，HB）

HB或称睡眠呼吸暂停特异性低氧负荷（sleep apnea-specific hypoxic burden，SASHB），由Azarbarzin等[25]首次提出，定义为氧去饱和曲线下总面积除以总睡眠时间。以低氧事件发生前100 s内的最大血氧饱和度作为基线，基线与滞后于呼吸暂停或低通气事件相应的氧去饱和曲线围成的面积，再除以总睡

眠时间即为低氧负荷，氧去饱和曲线下面积近似为三角形，并采用公式HB=AHI×（氧去饱和深度×氧去饱和持续时间）/2计算，单位为（%·min）/h。该指标可以排除低氧事件间期的干扰，捕捉睡眠期间与呼吸事件相关的低氧总负荷，用以量化OSA的严重程度[26]。

研究发现HB与AHI、ODI、T90等传统参数显著相关，可全面评估OSA的严重程度[25]。其不仅可以预测CVD的病死率，还有助于识别心脏病风险[25]。在患高血压的OSA患者中，经过持续正压通气治疗后，HB的降低与收缩压的下降成正比[27]，这说明HB或许可以成为OSA患者治疗的监测指标之一；同时，有研究证明HB可为OSA患者的卒中危险分层提供依据[26]，也可以预测静脉血栓事件[28]，据此临床上可参考HB进行预防，减少事件的发生。HB能反映OSA更多细节特征，且相比AHI或ODI，与嗜睡程度的相关性更显著，因此可考虑将HB纳入OSA的诊断和严重程度的评估[29]。

由于不同持续时间呼吸暂停或低通气事件引发的血流动力学反应、生理后果和临床意义不同[30]。而HB未能涵盖引发缺氧的呼吸暂停或低通气事件的持续时间，且无法从PSG数据中直接获得，需要特定的算法和软件支持，增加了计算的复杂性。更需要注意的是，OSA患者夜间氧去饱和图形是动态变化的，HB将氧去饱和曲线下面积近似视为三角形计算[3]，相关氧去饱和面积可能被低估，不能确定以上方面是否对结果有影响，目前还需要大量研究进一步验证HB的有效性并予以量化。

2.5 低氧负荷指数（hypoxia burden index，HBI）

HBI是在HB概念提出后，评价其严重程度的量化指标，其定义为SpO_2<90%的总氧去饱和面积除以总睡眠时间。研究结果显示HBI与AHI、T90、MinSpO_2显著相关，同时，HBI是CVD的独立相关因素[31]。在计算HBI时，将基线饱和度定义为90%，认为当SpO_2>90%时，氧分压值>60 mmHg，轻微的血氧降低不会影响细胞的生理功能。但SpO_2等于90%时的累积损害是否影响预后，尚不明确。

2.6 低氧负担（hypoxia load，HL）

同样，HL也定义为氧去饱和曲线下的总面积除以总睡眠时间，总面积采用梯形面积公式计算，HL与心肌梗死患者心外膜脂肪量相关[2]。HL综合了任何原因的低于100%的氧去饱和事件，是空腹血糖的独立预测因子[2]；此外，轻度的SpO_2下降（<2%）与代谢功能障碍独立相关[32]，这意味着任何低于100%的氧去饱和程度都可能对葡萄糖代谢产生不利影响。因此，HL或许可以作为一种新的标志物，将OSA与其相关不良代谢状态联系起来。

2.7 梗阻严重程度（obstruction severity，ObsSev）

为了提高呼吸事件相关氧去饱和严重程度评估的准确性，Kulkas等[33]引入 $\mathrm{ObsSev}=\frac{\sum_{n=1}^{L}(\mathrm{HypDur_n}\times\mathrm{DesArea_n})}{\mathrm{TST}}+\frac{\sum_{n=1}^{L}(\mathrm{ApDur_n}\times\mathrm{DesArea_n})}{\mathrm{TST}}$，相比于HB，ObsSev考虑到单个事件的持续时间，因此它可以量化的病理生理特征更多。研究发现，ObsSev可以预测OSA相关的CVD结局[34]，且与警觉性受损相关[35]。

然而，ObsSev中将氧去饱和定义为SpO_2低于基线值的4%，而未考虑低于基线值3%的情况，这容易忽略轻度OSA。此外，由于ObsSev也可以捕捉其他非OSA疾病（心血管或呼吸合并症）诱发的缺氧，可能高估相关氧去饱和面积。

2.8 睡眠呼吸障碍指数（sleep breathing impairment index，SBII）

SBII由Cao等[36]建立，是综合呼吸事件及事件相关的低氧血症、氧减及复氧过程得出的参数，计算同ObsSev，但SBII选择从每个呼吸事件开始的100 s作为窗口期确定相应的呼吸暂停或低通气相关的氧去饱和，并将低于基线值3%的氧去饱和事件纳入计算，因此较ObsSev量化范围更广。研究表明，SBII与心血管发病率的增加独立相关，但二者之间可能存在非线性关系[36]。

Cao等[36]研究发现，OSA严重程度可能与CVD发病率之间无线性关联。需要注意的是，此研究中计算氧去饱和面积的方法等同于HB，也将其简化为三角形，同样忽略了IH夜间氧去饱和图形是动态变化的特性，导致计算的氧去饱和面积与实际氧去饱和面积存在差别。

2.9 麦吉尔血氧评分（McGill oximetry score，MOS）

由于卫生保健资源的有限，大多数患儿无法行PSG检查来诊断是否患OSA，因此用MOS来识别OSA患儿，并进行OSA严重程度的分级[37]。

一项研究显示[38]，连续两晚使用MOS检测OSA显示出良好的一致性，表明一晚的脉氧测定就可以筛查OSA；但在另一项研究中却发现[39]，只进行一晚脉氧测定可能不足以筛查OSA，而且持续时间≥4 h的MOS才可以有效检测OSA。但MOS可以帮助确定手术麻醉剂量、减少不良围手术期事件的发生[40]。

MOS的应用有限，合并其他疾病的儿童OSA假阳性率较高，例如有潜在肺部疾病的儿童在短暂的

呼吸暂停或低通气后更有可能出现SpO_2下降，因此，MOS评分异常合并其他疾病的儿童是否有OSA还有待确认[38]。

2.10 其他指标

除上述指标以外，还有一些IH评估指标也被报道，但临床相关研究及应用较少（表1）。

表1 其他IH相关评估指标

Table 1 Other IH-related assessment indicators

Clinical indicator	Clinical application and characteristic
SIT	Integrating the time and degree of desaturation below a certain level and calculating the area under the desaturation curve, which is the SIT[41]. The SIT correlates well with T90 and T80 and may indirectly reflect the severity of nocturnal hypoxia in patients[41]. However, to date, the literature on this indicator is limited, resulting in insufficient progress in related areas.
Decrease in SpO_2	The magnitude of SpO_2 decline, which is mainly used to assess the severity of OSA, discusses apnea and hypoventilation separately, suggesting that we may need to consider the weighting of the two when assessing the adverse consequences of OSA, and that we should not generalize[42].
SpO_2 ApEn	ApEn is an indicator of the variability of the data, and in the field of sleep, SpO_2 ApEn has been used to study the connection between respiratory changes and functional brain activity during different sleep stages[43]. In other studies, it is commonly used to analyze electroencephalogram (EEG) signals in normal people with epilepsy[44] and Alzheimer's patients[45]. Different stages of disease or different states of the body may reflect changes in EEG, and ApEn, if it can capture such changes, may be able to serve as a basis for the diagnosis and identification of disease.
ODR and ORR	ODR and ORR can describe the rate of change of oxygen saturation per second during hypoxia-reoxygenation[46]. Studies have shown that ODR and ORR correlate with blood pressure in patients with OSA[45] and that ODR is an EDS[47] predictor. However, since ODR values can only be calculated in a closed system, the coverage of this index is not comprehensive enough.
ΔIx	ΔIx, which represents the change between successive oxygen saturation (SaO_2) data measured at constant time intervals, has a high sensitivity for diagnosing OSA and can therefore be used to exclude the diagnosis of OSA, but has a poor specificity, and is therefore currently recommended only as an adjunct to screening in the clinical setting[48].
DesDur	DesDur is independently associated with CVD outcomes[33-34], and is the best independent predictor of mortality and indirectly to assess myocardial injury in patients with heart failure combined with OSA[49]. However, DesDur does not account for 3% oxygen desaturation and tends to overlook mild OSA.
DesSev	DesSev is associated with daytime somnolence[49], risk of impaired alertness[35], diabetes mellitus[50] and myocardial damage[49]. However, as with DesDur, DesSev tends to ignore mild OSA, and because DesSev can also capture hypoxia induced by other non-OSA conditions (cardiovascular or respiratory comorbidities), this leads to an overestimation of the associated desaturated area.
REDTA	REDTA[51] defined as the sum of the areas between the SpO_2 trace and the 100% oxygen desaturation baseline for all artificially scored respiratory events divided by 3 600, and primarily quantifies the duration and depth of oxygen desaturation associated with respiratory events and the number of respiratory events, and therefore can be used to measure nocturnal hypoxic injury. Chazal et al. [51] suggested that REDTA could predict CVD, but there have been fewer subsequent related studies.
AHDI	ADHI[33] is the sum of the percentage of apnea, hypoventilation, and oxygen desaturation time in total sleep time, and unlike the AHI, it takes the duration of oxygen desaturation into account, which distinguishes well between healthy individuals and patients with OSA. However, the degree of oxygen desaturation is not elaborated in the AHDI, and the literature on the AHDI is limited to date, with a lack of further research progress reported in this area.

SIT: saturation impairment time; SpO_2 ApEn: approximate entropy of oxygen saturation; ODR: oxygen desaturation rate; ORR: oxygen resaturation rate; ΔIx: oxygen saturation variability index; DesDur: desaturation duration; DesSev: desaturation severity; REDTA: the respiratory event desaturation transient area; AHDI: apnea-hypopnea desaturation index.

3 总结与展望

OSA所造成的夜间IH通常包括呼吸事件相关氧去饱和发生的频率、持续时间和低氧幅度3个方面。然而，无论从表征频率(如ODI)、持续时间(T90、SIT、DesDur)、低氧幅度($MinSpO_2$、ODR与ORR等)的单一指标还是综合性的夜间IH相关评估指标(如HB、HBI、HL、ObsSev、SBII等)都无法对夜间IH进行客观精确而全面地评估。各种IH相关指标用于评估夜间IH的程度都存在各自的优势和缺陷(表2)，且缺乏多中心的验证，限制了其临床应用及推广。因此，需要进一步寻找更准确、全面且易于应用的评估指标及方法。为了更加精确地计算IH负荷，或许可考虑借助先进的人工智能数据分析算法及机器学习，收集睡眠呼吸暂停持续时长、氧饱和度降低的严重程度、AHI、ODI、$MinSpO_2$、T90、觉醒指数等多导睡眠监测中获取的客观数据及Epworth嗜睡量表、STOP-Bang问卷等主观数据，采用数学建模的方式构建新的计算公式。另外，各种计算IH程度的方法尚处于萌芽阶段，需要利用目前公开的数据库进行大数据、多中心的临床验证。此外，为了使IH的评估指标能更好地反映OSA的病理生理特征以及疾病负担，也可考虑结合心肺功能检测、血清标志物等数据进行综合评估。综上所述，如何寻找更精确的评估指标用于评价夜间IH的严重程度，是当前睡眠医学领域的一个重要研究方向，对提高相关疾病的诊断和治疗水平具有重要指导意义。

表2 IH相关评估指标的临床应用及缺陷

Table 2 Clinical applications and deficiencies of IH-related assessment indicators

Categorization	Indicator	Complication associated with OSA	Deficiency
Desaturation frequency	ODI	CVD	Controversial definition of desaturation by describing only the frequency of the IH
Desaturation duration	T90	CVD, type 2 diabetes, and COPD	Only the duration of IH is described, ignoring the effect of the degree of oxygen drop
	SIT	Severity of nocturnal hypoxia in OSA	
	DesDur	Myocardial injury, and heart failure mortality	
Desaturation depth	$MinSpO_2$	EDS, diabetes mellitus, cognitive ability, CVD outcomes, and post-UPPP adverse events	Reflecting only the depth of IH and results are susceptible to device accuracy and patient movement
	ODR and ORR	Hypertension, and EDS	
Synthesis	HB	CVD mortality, venous thrombosis piece, and stroke risk stratification	All of them can only be obtained indirectly from PSG, and the calculation methods have not yet been unified, therefore, they are currently only used in scientific research, and multi-center and big data studies are still needed to explore their accuracy and clinical value
	HBI	CVD	
	HL	Myocardial infarction, and abnormal glucose metabolism	
	SBII	Incidence of CVD	
	ObsSev	CVD outcomes, impaired vigilance, and EDS	

SIT: saturation impairment time; DesDur: desaturation duration; ODR: oxygen desaturation rate; ORR: oxygen resaturation rate.

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