

睡眠呼吸暂停患者脑电梭形波与疾病严重程度的关系

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[摘要] **目的** 分析阻塞性睡眠呼吸暂停(obstructive sleep apnea, OSA)患者梭形波的变化, 探讨其与疾病严重程度的关系。**方法** 研究纳入了2019年7月至2021年4月就诊于广东省人民医院睡眠中心并采用Phillips Alice 6 LDXS设备进行多导睡眠监测的患者。患者年龄18~65岁, 未合并除OSA外的其他睡眠障碍或精神类疾病。将符合标准的患者根据呼吸暂停低通气指数(apnea-hypopnea index, AHI)分为正常对照组(AHI<5)、轻度(5≤AHI<15)、中度(15≤AHI<30)和重度(AHI≥30)OSA组。**结果** 共计入组252例患者, 平均年龄为44.8±11.7岁, 平均体质量指数(body mass index, BMI)为25.5±3.8 kg/m², 平均AHI为28.6±23.2次/时。正常对照组33例, 轻度OSA患者58例, 中度60例, 重度101例。对照组、轻度、中度及重度各组的梭形波数量依次为411.0(151.5, 1569.5)、315.5(150.0, 667.8)、251.0(96.0, 680.8)、224.0(75.0, 567.5), $P=0.002$; 各组梭形波密度分别为2.6(0.7, 7.4)、1.6(0.7, 2.9)、1.2(0.4, 3.7)、0.9(0.3, 2.5), $P<0.001$ 。N2期梭形波密度随着AHI和BMI的升高而下降(P 值分别为0.028及0.012)。**结论** 重度OSA患者的N2期梭形波数量和密度显著下降, 且N2期梭形波密度存在随着AHI和BMI的升高而降低的趋势。

[关键词] 阻塞性睡眠呼吸暂停; 梭形波; 多导睡眠图

[中图分类号] R56 **[文献标识码]** A **DOI:** 10.12019/j.issn.1671-5144.2021.03.010

The Relationship Between Obstructive Sleep Apnea and Sleep Spindles

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Abstract: Objective To access the changes of sleep spindles in patients with obstructive sleep apnea (OSA). **Methods** This is an observational, cross-sectional study consecutively recruited out patients at the sleep center of Guangdong Provincial People's Hospital, China between July 2019 and April 2021. Patients were aged 18~65 years and underwent overnight polysomnography (PSG) by Phillips Alice 6 LDXS. Exclusion criteria were any sleep disorder or mental health issues other than OSA including current treatment for sleep apnea, insomnia and depression. Subjects who reported taking sleep aids were also exclude. The participants were divided into four groups according to their apnea-hypopnea index (AHI): normal (AHI<5), mild (5≤AHI<15), moderate (15≤AHI<30), and severe (AHI≥30). One-way ANOVA or nonparametric test was used for comparison between groups. Associations between sleep spindles and other parameters were analyzed with a general linear model. **Results** 252 adults were included (33 in normal group, 58 had mild OSA, 60 had moderate OSA and 101 had severe OSA) with the mean age 44.8±11.7 years, mean body mass

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index (BMI) $25.5 \pm 3.8 \text{ kg/m}^2$ and mean AHI $28.6 \pm 23.2/\text{h}$. The numbers of sleep spindles in N2 was 411.0 (151.5, 1 569.5) in the normal, 315.5 (150.0, 667.8) in the mild, 251.0 (96.0, 680.8) in the moderate, 224.0 (75.0, 567.5) in the severe, with significance between group difference ($P=0.002$). The destiny of sleep spindles in N2 was 2.6 (0.7, 7.4) in the normal, 1.6 (0.7, 2.9) in the mild, 1.2 (0.4, 3.7) in the moderate and 0.9 (0.3, 2.5) in the severe, with significance between group difference ($P<0.001$). There was a trend that the destiny of sleep spindles in N2 decreased with the increase of AHI ($P=0.028$) and BMI ($P=0.012$). **Conclusions** The number and destiny of sleep spindles in N2 had a significant decrease in severe OSA patients and the destiny of sleep spindles in N2 decreased with the increase of AHI and BMI.

Key words: obstructive sleep apnea; spindles; polysomnography

阻塞性睡眠呼吸暂停(obstructive sleep apnea, OSA)可以通过间歇性缺氧和睡眠微觉醒^[1-2]导致患者的神经元损伤^[3],进而影响其记忆编码、处理和检索等功能^[4],加重或导致OSA患者的认知功能障碍。有研究表明,OSA患者发生认知功能障碍的风险是非OSA患者的2.27倍^[5]。睡眠梭形波是2期睡眠的特征性标志,具有容易鉴别和获取的特征,其数量与密度和蒙特利尔认知评估量表(Montreal Cognitive Assessment, MoCA)评分存在正相关关系^[6]。梭形波的减弱或消失,提示患者可能存在一定的神经功能损害^[7]和认知功能减退^[8]。本研究分析不同严重程度的OSA患者间睡眠梭形波数量及密度的变化。

1 对象与方法

1.1 研究对象

选取2019年7月至2021年4月就诊于广东省人民医院睡眠中心并接受多导睡眠监测(polysomnography, PSG)的患者。入选标准为:①年龄18~65岁,性别不限;②既往未进行持续气道正压通气(continuous positive airway pressure, CPAP)治疗;③采用Phillips Alice 6 LDXS设备进行睡眠监测。排除标准为:①怀疑中枢性睡眠呼吸暂停或陈-施式呼吸,或合并除OSA外的其他睡眠障碍;②焦虑、抑郁等精神病史;③既往服用促眠、安眠药物者;④PSG监测质量差;⑤总睡眠时间小于240分钟的患者。

1.2 OSA诊断及梭形波判读方法

入组的患者均进行整夜PSG检查,关灯时间在晚上9点至12点之间。记录数据包括眼动电

图、脑电图、下颌肌肌电图、心电图、口鼻气流、鼾声、胸腹运动、体位、脉搏血氧饱和度等。所有的操作均由经过规范化培训的睡眠中心医师进行,所采集的数据均根据美国睡眠医学学会(American Academy of Sleep Medicine, AASM)睡眠及相关事件判读手册(2.3版)标准进行人工评判。睡眠分为清醒期(wakefulness, W期)、非快动眼期(non-rapid eye movement sleep, NREM期)和快动眼期(rapid eye movement sleep, REM期),其中NREM期又可进一步分为N1期、N2期和N3期。呼吸暂停是指睡眠过程中口鼻气流较基线水平下降90%及以上,持续时间 ≥ 10 秒。低通气是指呼吸气流信号下降30%及以上,持续时间 ≥ 10 秒,同时伴有血氧饱和度下降3%及以上或微觉醒。将呼吸暂停和低通气的总次数除去总睡眠时间即获得呼吸暂停低通气指数(apnea-hypopnea index, AHI)^[9]。

睡眠梭形波是一种波幅逐渐增高,随后逐渐降低的形似纺锤状的节律性脑电波,频率在11~16 Hz之间,持续时间通常超过0.5s,是N2期睡眠的标志性波形(见图1)^[10]。研究中涉及的数据均由Phillips Alice 6 LDXS设备采集,使用C3通道分析进行梭形波分析。N2期梭形波数量是指在患者在整夜N2期睡眠中出现的梭形波的总个数,N2期梭形波密度定义为N2期梭形波数量/N2期睡眠时间。N3期梭形波数量和密度定义方法同N2期梭形波数量和密度。

1.3 统计学分析

正态分布的连续性计量资料采用(均值 \pm 标准差)表示,偏态分布的连续型计量资料采用中位数及四分位间距表示,计数资料采用率表示。正态

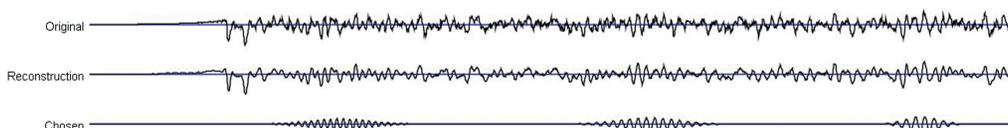


图1 梭形波示意图

Fig.1 Schematic diagram of sleep spindles

分布的数据采用方差分析进行组间比较,组间两两比较进一步采用以下方法:符合方差齐性的采用LSD方法检查各组间差异;方差不齐的采用盖姆斯-豪厄尔(Games-Howell)方法检查各组间差异。偏态分布的数据采用非参数检验进行组间比较。采用一般线性模型,进一步分析梭形波与患者年龄、性别、身体质量指数(body mass index, BMI)和OSA严重程度之间的关系。所有统计分析均采用SPSS 25.0完成。

2 结果

2.1 患者基本信息

共计入组 252 例患者,平均年龄为 44.8 ± 11.7 岁,平均 BMI 为 $25.5 \pm 3.8 \text{ kg/m}^2$,平均 AHI 为 28.6 ± 23.2 次/时。将受试对象按照 AHI 进行分组,其中 $\text{AHI} < 5$ 次/时为正常对照组, $5 \text{ 次/时} \leq \text{AHI} < 15$ 次/时为轻度 OSA 组, $15 \text{ 次/时} \leq \text{AHI} < 30$ 次/时为中度 OSA 组, $\text{AHI} \geq 30$ 次/时为重度 OSA 组。正常对照组 33 例,轻度 58 例,中度 60 例,重度 101 例。患者各组间的基本信息详见表 1。

2.2 不同严重程度 OSA 患者的睡眠结构差异

各组患者在 N1 期睡眠时长和睡眠效率上无明显差异。相比于正常与轻中度 OSA 者,重度 OSA 者的 N2 睡眠时间显著延长, N3 期睡眠时间显著减少,觉醒指数明显升高, REM 期睡眠时间相对减少。总体而言,重度 OSA 患者睡眠质量相对较差,详见表 2。

2.3 不同严重程度的 OSA 患者梭形波变化

相比于正常对照组, N2 期梭形波数量与密度在轻中度 OSA 者中未见明显变化,但在重度 OSA 者出现了显著的下降; N3 期的梭形波数量与密度在各组间无明显差异,见表 3。

2.4 梭形波变化的影响因素

进一步分析其他指标与 N2 期梭形波密度的关系,发现随着 AHI 和 BMI 的升高, N2 期梭形波密度存在下降的趋势。AHI 每增加 1 次/时, N2 期梭形波密度的自然对数值下降 0.010。BMI 每增加 1 kg/m^2 , N2 期梭形波密度的自然对数值下降 0.064。性别和年龄与 N2 期梭形波密度没有明显相关性,见表 4。

表 1 252 名患者基本信息

Tab.1 Baseline characteristics of 252 patients

Indicators	Normal (n=33)	Mild OSA (n=58)	Moderate OSA (n=60)	Severe OSA (n=101)
Male sex (%)	13 (39.4%) ^{cd}	39 (67.2%) ^d	47 (78.3%) ^a	94 (93.1%) ^{ab}
Age (yr)	37.9 ± 13.8 ^{bcd}	45.7 ± 11.8 ^a	46.1 ± 12.8 ^a	45.8 ± 9.6 ^a
BMI (kg/m^2)	21.9 ± 3.6 ^{bcd}	24.1 ± 2.5 ^{acd}	26.0 ± 3.7 ^{ab}	27.0 ± 3.5 ^{ab}
AHI (events/h)	2.1 ± 1.6 ^{bcd}	9.3 ± 2.7 ^{acd}	21.7 ± 4.2 ^{abd}	52.5 ± 16.7 ^{abc}
Time < 90% SpO ₂ (min)	0.0 (0.0, 0.0) ^{bcd}	0.6 (0.1, 2.8) ^{acd}	6.8 (1.7, 18.2) ^{abd}	44.2 (18.2, 135.0) ^{abc}

注: a. 为与正常组相比, $P < 0.05$; b. 为与轻度组相比, $P < 0.05$; c. 为与中度组相比, $P < 0.05$; d. 为与重度组相比, $P < 0.05$

Note: a. Significant difference as compared with the Normal group; b. Significant difference as compared with the Mild OSA group; c. Significant difference as compared with the Moderate OSA group; d. Significant difference as compared with the Severe OSA group

表 2 不同严重程度 OSA 患者的睡眠结构

Tab.2 Sleep macrostructural parameters in four groups

Indicators	Normal (n=33)	Mild OSA (n=58)	Moderate OSA (n=60)	Severe OSA (n=101)
N1 (min)	57.0 ± 33.4	52.5 ± 40.2	60.4 ± 39.1	63.8 ± 49.9
N2 (min)	226.7 ± 63.4	214.8 ± 60.4 ^d	218.6 ± 61.2 ^d	243.9 ± 81.3 ^{bc}
N3 (min)	68.4 ± 33.0 ^d	63.2 ± 39.0 ^d	61.1 ± 45.3	48.8 ± 44.8 ^{ab}
NREM (min)	352.0 ± 63.0	330.4 ± 64.9 ^d	340.1 ± 53.7	356.5 ± 69.0 ^b
REM (min)	59.4 ± 30.6	53.0 ± 34.4 ^c	65.5 ± 37.3 ^{bd}	53.4 ± 29.5 ^c
Sleep efficiency (%)	83.5 ± 13.5	80.5 ± 14.9	82.5 ± 11.8	84.6 ± 14.0
Arousal index (events/h)	8.3 (5.4, 12.9) ^{cd}	11.2 (6.9, 17.1) ^d	13.7 (8.6, 19.0) ^a	18.1 (11.9, 27.8) ^{ab}

注: a. 为与正常组相比, $P < 0.05$; b. 为与轻度组相比, $P < 0.05$; c. 为与中度组相比, $P < 0.05$; d. 为与重度组相比, $P < 0.05$

Note: a. Significant difference as compared with the Normal group; b. Significant difference as compared with the Mild OSA group; c. Significant difference as compared with the Moderate OSA group; d. Significant difference as compared with the Severe OSA group

表3 不同严重程度的OSA患者梭形波变化

Tab.3 Spindle analysis in four groups

Indicators	Normal (n=33)	Mild OSA (n=58)	Moderate OSA (n=60)	Severe OSA (n=101)
Sleep spindle N2 (number)	411.0(151.5, 1569.5) ^d	315.5(150.0, 667.8)	251.0(96.0, 680.8)	224.0(75.0, 567.5) ^a
Sleep spindle index N2 (min)	2.6(0.7, 7.4) ^d	1.6(0.7, 2.9)	1.2(0.4, 3.7)	0.9(0.3, 2.5) ^a
Sleep spindle N3 (number)	38.0(8.0, 136.0)	18.5(5.8, 46.0)	16.0(5.0, 53.0)	8.0(1.0, 44.0)
Sleep spindle index N3 (min)	0.8(0.1, 2.1)	0.3(0.1, 0.8)	0.4(0.1, 1.1)	0.5(0.1, 1.0)

注: a. 为与正常组相比, $P<0.05$; b. 为与轻度组相比, $P<0.05$; c. 为与中度组相比, $P<0.05$; d. 为与重度组相比, $P<0.05$

Note: a. Significant difference as compared with the Normal group; b. Significant difference as compared with the Mild OSA group; c. Significant difference as compared with the Moderate OSA group; d. Significant difference as compared with the Severe OSA group

表4 N2期梭形波密度(取自然对数)的影响因素

Tab.4 General linear model for natural logarithm of sleep spindle index N2

Variable	Estimate	SD	P values
Male	0.294	0.221	0.185
Age	-0.012	0.007	0.100
BMI	-0.064	0.025	0.012 [*]
AHI	-0.010	0.004	0.028 [*]

注: * $P<0.05$

Note: * $P<0.05$

3 讨论

OSA与全身多个系统疾病有关,是高血压、冠心病、糖尿病、痴呆、抑郁等一系列疾病的危险因素^[11]。研究表明,OSA患者的注意力、工作记忆、情景记忆和执行能力等功能均出现下降,认知功能出现不可逆的损害^[12]。临床上主要通过MoCA量表^[13]、简明精神状态量表(Mini-Mental State Examination, MMSE)^[14]等方法评估患者认知情况,耗时长、操作困难且易受其教育程度的干扰。多导睡眠监测作为OSA患者的常规诊断方法,通过监测患者夜间睡眠及呼吸情况明确疾病严重程度。目前多关注OSA患者的AHI、夜间缺氧程度及睡眠结构,较少关注脑电特征波的变化。梭形波起源于丘脑网状核团,由丘脑、丘脑-皮质回路的复杂运动产生^[15],可以阻止外部噪音干扰大脑,防止唤醒信号到达皮层,维持睡眠稳定^[16]。梭形波与患者认知状态密切相关,甚至可以在帕金森病中预测痴呆的发生发展^[17]。

目前关于梭形波的研究多见于儿童。Brockmann等发现轻度OSA患儿的N2期梭形波密度远低于正常儿童(分别为 70.71 ± 41.36 个/时, 110.88 ± 35.84 个/时, $P=0.008$)^[8]。Maski等也发现OSA患儿和单纯鼾症患儿的N2期梭形波密度低于

正常儿童(分别为 1.19 ± 0.6 个/分, 2.17 ± 1.1 个/分, $P=0.01$)^[18]。Brockmann等发现单纯鼾症患儿的N2、N3期梭形波密度均低于正常对照组^[19]。儿童时期是神经元髓鞘和大脑皮层的成熟阶段,对OSA缺氧带来的损害比较敏感,这可能是单纯鼾症患儿及轻度OSA患儿出现梭形波密度的变化,而我们研究中成年轻度OSA患者的N2期梭形波密度与正常对照组无明显组间差异的可能原因之一。

Mohammadi等对成人OSA患者开展了相关研究,共分析了23例正常对照组、8例轻度OSA患者、8例中度OSA患者及15例重度OSA患者的梭形波特征,发现各组间N2期梭形波密度没有明显差异,但重度OSA组的N3期梭形波密度普遍出现了下降^[20]。而本研究发现差异的主要指标为N2期梭形波密度而非N3期,这可能与患者种族不同、BMI不同、年龄不同以及样本量大小有关。

研究还发现了BMI与N2期梭形波密度呈负相关关系,这与之前报道的梭形波特征一文中的结果是一致的^[21]。同时,不少研究报道了肥胖,特别是腹型肥胖与早期认知功能损害密切相关^[22]。但在研究中未发现年龄与梭形波存在相关性,这与其他研究存在差异^[23],可能研究人群不同有关。在正常人群中,梭形波在儿童和青少年时期随着年龄的增长而增加^[24],而在成年人中则随着年龄的增长而下降^[25],这可能与丘脑皮层调节机制的发育、成熟和衰老过程有关^[26]。睡眠呼吸暂停作为慢性疾病,长期的夜间间歇性缺氧和打鼾可能造成丘脑皮层调节机制的受损,同时疾病造成的梭形波变化可能远超于其自然发展带来的变化,从而导致研究中未发现梭形波与年龄的相关关系。

本研究也存在一些不足之处。首先,研究中的正常对照组患者也为睡眠中心门诊患者,因此包含部分单纯鼾症患者。其次,研究未能进一步分析不同脑部区域、不同梭形波频率及不同睡眠

周期的梭形波差异。最后,本研究缺乏认知功能评估,无法将梭形波的变化与患者的认知情况结合起来进行进一步分析。

4 结 论

重度 OSA 患者存在 N2 期梭形波数量和密度显著下降,可能存在潜在的认知功能障碍发生风险,临床上需要重点关注,且 N2 期梭形波密度存在随着 AHI 和 BMI 的升高而降低的趋势。

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