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阻塞性睡眠呼吸暂停影响急性缺血性卒中的研究进展

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摘　要

急性缺血性卒中是全球范围内致残率和致死率最高的疾病之一，该病因大脑血供突然中断导致脑细胞缺氧死亡，可造成永久性神经功能障碍甚至危及生命。阻塞性睡眠呼吸暂停是全球性公共卫生问题之一，据统计30到69岁人群中约有10亿人受累，其特点是睡眠期间上气道反复发生的部分或完全阻塞，临床表现为响亮且不规则的打鼾、夜间窒息感或憋醒，导致睡眠相关慢性间歇性低氧及睡眠碎片化，继而出现日间嗜睡、记忆力减退，重度患者可并发认知功能下降、行为异常及心脑血管系统损害。现有研究表明，阻塞性睡眠呼吸暂停既可能是急性缺血性卒中的危险因素，也可能是其并发症，两者关系错综复杂，相互影响，显著损害了患者的生活质量，增加心脑血管不良事件再发风险。因此，深入探究阻塞性睡眠呼吸暂停影响急性缺血性卒中的病理生理机制及预后，具有重要的临床与科研意义。

关键词

急性缺血性卒中，阻塞性睡眠呼吸暂停

Research Progress of Obstructive Sleep Apnea Affecting Acute Ischemic Stroke

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Abstract

Acute ischemic stroke is one of the diseases with the highest morbidity and mortality in the world. The sudden interruption of cerebral blood supply leads to hypoxic death of brain cells, which can cause permanent neurological dysfunction and even life-threatening. Obstructive sleep apnea (OSA) is a global public health problem, affecting an estimated 1 billion people aged 30 to 69 years. It is characterized by recurrent partial or complete obstruction of the upper airway during sleep. It is clinically manifested as a noisy and irregular snoring, a feeling of choking at night, or a suffocating awakening, leading to sleep-related chronic intermittent hypoxia and sleep fragmentation. Then, daytime sleepiness and memory loss occur, and severe patients may be complicated by cognitive decline, behavioral abnormalities, and cardiovascular and cerebrovascular system damage. Existing studies have shown that obstructive sleep apnea may be both a risk factor and a complication of acute ischemic stroke. The relationship between obstructive sleep apnea and acute ischemic stroke is complex and affects each other, significantly impairing the quality of life of patients and increasing the risk of recurrence of adverse cardiovascular and cerebrovascular events. Therefore, it is of great clinical and scientific significance to explore the pathophysiological mechanism and prognosis of obstructive sleep apnea in acute ischemic stroke.

Keywords

Acute Ischemic Stroke, Obstructive Sleep Apnea

1. 引言

一项针对卒中或短暂性脑缺血发作后睡眠呼吸障碍的患病率荟萃分析显示[1]，急性缺血性卒中(Acute Ischemic Stroke, AIS)后睡眠呼吸障碍(sleep disordered breathing, SDB)的患病率显著升高，约 70%的 AIS 患者有阻塞性睡眠呼吸暂停(obstructive sleep apnea, OSA)，其中 33%为重度。Dominguez [2]对西班牙、Lin [3]台湾地区 AIS 患者研究后均发现，中重度 OSA 的患病率约 69%，显著高于普通人群。Camilo [4]发现巴西地区 AIS 患者中，重度 OSA 患者长期功能预后相对不良。值得注意的是，Zhang [5]发现在 AIS 前，患有 OSA 似乎并不增加卒中的严重程度，提示 OSA 患者体内可能存在某种内源性神经保护机制。本文旨在深入探讨 OSA 影响 AIS 发生发展的病理生理机制及 OSA 对 AIS 患者预后的影响，通过对相关文献进行系统梳理与分析，总结现有研究成果，指出研究不足，从而为临床实践中 AIS 合并 OSA 患者的早期筛查、诊断和治疗提供理论依据，进一步制定个体化精准诊疗策略。

2. OSA 影响 AIS 发生发展的病理生理机制

2.1. 氧化应激

Sun [6]发现持续间歇性缺氧可促进程序性死亡配体 1 (PD-L1)过度表达，通过抑制 T 细胞增殖、促进调节性 T 细胞分化，可减少自身免疫损伤及维持外周耐受，这可能是 OSA 并不增加卒中严重程度的病理生理机制之一。王龙[7]研究发现在中重度 OSA 患者中，血清氧化型低密度脂蛋白水平显著升高，超氧化物歧化酶活性明显降低，提示氧化应激反应增强。Bassetti [8]和 Hale [9]报道，反复低氧复氧会导致交感

神经过度兴奋和脑血流动力学异常，直接增加心脑血管事件风险。Xu [10]发现，OSA 通过缺氧和影响 AIS 患者的睡眠结构加重神经功能损害，特点是总睡眠时间减少，睡眠效率降低，合并 OSA 时浅睡眠 1 期延长，深睡眠缩短，提示脑梗死患者深睡眠缩短与较差的预后相关。

2.2. 炎症反应

陈左然[11]发现在 AIS 患者中，中重度 OSA 患者的中性粒细胞/淋巴细胞比值、血小板/淋巴细胞比值显著升高。屈雪萍[12]和 Huang [13]进一步发现，AIS 合并 OSA 患者的血清 IL-6、血清内皮素-1 和血管细胞黏附分子-1 水平显著升高，且与呼吸暂停低通气指数(AHI)呈正相关。这可能会引发脑血管痉挛与血脑屏障破坏，使脑梗死体积扩大。Das [14]则发现 OSA 患者发生 AIS 前后，血浆血管生成素-2 和可溶性细胞间黏附分子-1 水平显著变化，提示 OSA 可能通过调控血管炎症微环境影响卒中的发生与发展。上述研究表明，OSA 严重程度与系统炎症水平密切相关。

2.3. 凝血功能异常

嵇朋[15]发现，AIS 伴 OSA 组的超敏 C 反应蛋白、D-二聚体及纤维蛋白原降解产物水平均显著高于单纯 AIS 组，这些生化标志物的异常可能反映了 OSA 患者体内存在慢性炎症状态和凝血功能异常。Huang [13]和黄真灿[16]研究发现 AIS 合并 OSA 患者的血清纤维蛋白原、E-选择素、组织型纤溶酶原激活物表达升高，且与 AHI 呈正相关，提示 OSA 可能通过促进血小板活化、凝血系统激活，增加血栓形成风险，从而影响卒中的发生发展。

2.4. 内皮细胞损伤

Chen [17]发现长链非编码 RNA NEAT1 可通过抑制 Apelin/Nrf2/HO-1 信号通路加剧微血管内皮细胞凋亡。Gabryelska [18]报道，OSA 患者血清脑源性神经营养因子(BDNF)水平显著降低，而促炎因子肿瘤坏死因子-α 升高。Javaheri[19]与徐玲[20]证实，OSA 通过诱发全身炎症反应，促进白细胞介素-6 (IL-6)、肿瘤坏死因子-α (TNF-α)等炎症因子释放，加速血管内皮损伤及动脉粥样硬化进程。值得注意的是，Filchenko [21]认为夜间心率变异性及内皮功能可作为预测缺血性卒中后心脑血管事件复发的生物标志物，为 AIS 合并 OSA 患者的生物标志物预测方面提供了新思路。

2.5. 动脉粥样硬化

Woo [22]提出 OSA 相关的间歇性低氧主要通过激活 HIF-1α/LOX-1 通路、促进 MMP-9 分泌、增强血小板活化共同加速颅内动脉粥样硬化易损斑块的进展。Ioannidou [23]和 Blueher [24]报道，吸烟和肥胖相关的代谢紊乱(如胰岛素抵抗)可加重 OSA 的夜间低氧血症，进而加速动脉粥样硬化进程，进而影响 AIS 的发生发展进程。

2.6. 神经调控

Biose [25]报道，OSA 患者中 HPA 轴超敏反应是介导脑血管病变的核心枢纽，包括皮质醇节律紊乱、高血压控制不佳甚至导致脑血管疾病的发生。嵇朋[26]通过建立 OSA 合并 AIS 大鼠模型的研究发现，OSA 通过激活 Rho/ROCK 信号通路可导致脑血管收缩与血脑屏障破坏，其临床研究[27]证实 AIS 合并 OSA 患者的脑血管反应性显著降低，其屏气指数较非 OSA 组下降。这种脑血流自动调节能力的受损，可能使脑组织对缺血缺氧更为敏感。Zhang [5]对超急性期醒后卒中患者的观察研究发现 AIS 合并 OSA 患者存在褪黑素昼夜节律紊乱、皮质醇分泌异常及时钟基因表达失调，这种生物钟的破坏可能通过损害脑血管弹性与血流调节功能增加卒中复发风险。Tsivgoulis [28]发现 OSA 所致的高碳酸血症可诱导缺血脑组

织的颅内血流减少。Uscamaita [29]报道，在 AIS 病理进程中，可能通过激活 NF-κB 通路诱导 MMP-9 过度表达导致血脑屏障破坏及继发性脑损伤，提示进一步探究 MMP-9 在卒中急性期的动态变化及靶向干预策略可能具有重要临床价值。

3. OSA 对 AIS 患者预后的影响

3.1. 神经功能

Sanders [30]发现合并 OSA 的 AIS 患者入院时 NIHSS 评分更高，且糖尿病、高血压等合并症更多，这些因素共同导致了更差的临床结局。张倩云[31]研究发现，AHI 每增加 1 个单位，转归不良的风险增加 4.4% (OR = 1.044, 95% CI: 1.002~1.089, P = 0.042)。Menon [32]采用多导睡眠监测(PSG)和神经功能评估工具的前瞻性研究，证实了 OSA 通过加重夜间低氧血症和睡眠结构紊乱，导致脑血流调节功能受损，进而影响神经功能恢复。值得注意的是，Edrissi [33]报道 AIS 合并 OSA 患者中女性比例显著更高，且其神经功能缺损程度更严重，这可能与女性绝经后雌激素下降导致对延髓呼吸中枢的保护作用减弱、抑郁及焦虑共病率高相关。Devenish [34]则发现，OSA 合并 AIS 的男性患者 90 天内出现不良功能结局的风险显著升高，可能与男性氧化应激易感性升高、更严重的夜间低氧血症以及全气道阻塞事件占比高有关。这提示需建立性别差异化干预策略。

3.2. 认知功能

Wu [35]报道 OSA 对 AIS 急性期认知功能障碍的影响可能通过血清 ADEs 中的补体蛋白介导。Liu [36]和 Meng [37]发现 OSA 合并短暂性脑缺血发作患者在 12 个月随访期间的认知功能下降更为明显，尤其是记忆和执行功能领域，提示 OSA 可能通过慢性脑缺氧加速认知衰退进程。钱洪春[38]认为 AHI 升高是认知功能损害的危险因素，夜间睡眠效率升高是保护因素。其中梗死病灶的位置与认知功能损害相关。黄勉[39]报道，AIS 合并 OSA 患者的定向力、计算力、延迟回忆等认知领域受损明显，MMSE 总分及画钟试验得分显著降低。王雯[40]发现 AIS 合并 OSA 患者的认知功能损害与事件相关电位 P300 潜伏期延长密切相关，其中前额叶和中央区功能受损，提示 OSA 可能通过影响大脑皮层电活动而损害认知功能。此外，OSA 患者的梗死病灶累及额叶、颞叶等认知相关脑区，糖尿病史和高同型半胱氨酸血症更易损害患者认知功能。但值得注意的是，现有研究多关注短期认知功能变化，缺乏长期随访数据，无法明确 OSA 对 AIS 患者认知功能的长期影响。

3.3. 情绪障碍

Gabryelska [18]发现脑源性神经营养因子信号通路可能通过调控 Ras/MAPK、PI3K/Akt 和 PKC/PLC 等信号通路的发育和功能，参与 OSA 患者抑郁、失眠的病理生理过程。一项全国流行病学调查[41]显示，失眠和/或嗜睡的 OSA 患者的主观睡眠质量受到损害，导致焦虑或抑郁的恶性循环。陈乐辉[42]发现 OSA 可能通过影响睡眠结构和脑功能，导致 AIS 患者出现情绪障碍。Ito [43]提出这可能与 OSA 患者体内抗氧化防御系统代偿性增强有关。Zhu [44]发现 OSA 与卒中后焦虑的发生显著相关，提示 OSA 可能通过影响情绪调节网络参与卒中后焦虑的病理过程。Patel [45]发现 OSA 合并焦虑患者的卒中预后更差，医疗资源利用率更高，凸显了多维度精神心理干预的重要性。

3.4. 心脑血管事件再发风险

Wu [46]指出 OSA 在心血管疾病患者中非常常见，且 OSA 会增加心血管疾病死亡的风险[47]。Mattaliano [48]报道 AIS 合并 OSA 患者左室体积增大，左房增大。庾建英[49]发现，AIS 合并 OSA 患者的脑

心综合征发生率随 OSA 严重程度的增加而升高，提示 OSA 可能通过加重心肌缺血和心电紊乱，增加心脏并发症的风险。

4. 干预 OSA 对改善 AIS 预后的作用

睡眠作为一种可改变的行为，可作为降低卒中复发和死亡风险的二级预防目标[9]。其中包括行为干预、持续正压通气治疗和药物治疗[25]。

4.1. 行为干预

Donald [50]报道使用关于 OSA 的健康宣传手册和视觉量表可提高患者对 OSA 筛查的接受度。张倩雲[31]发现，BMI 每增加 1 kg/m^2，OSA 严重程度升高 21.3%，体育锻炼可降低 OSA 患者的 AHI (OR = 0.236, P = 0.004)，改善患者预后。Camilo [51]根据卒中亚型，推荐不同的体位疗法。其中幕上梗死推荐 30˚侧卧位，脑干梗死推荐 45˚半卧位，小脑梗死推荐俯卧位。提示可以根据患者情况，个性化定制治疗方案。Losurdo [52]和 Qian [53]发现吞咽干预可同时改善卒中后 OSA 和吞咽障碍，其机制与增强口咽肌力量、改变上呼吸道结构有关。一项双盲交叉病例研究[54]证实呼吸肌训练对增强颈脊髓损伤患者的呼吸肌力量、改善肺功能、减轻 OSA 和嗜睡的严重程度是可行的。

4.2. 持续正压通气治疗

AIS 与 OSA 均强调以综合治疗为主，目前对 AIS 合并 OSA 患者主要使用持续正压通气治疗。Barlin [55]报道一例急性大脑中动脉闭塞患者在接受静脉溶栓期间，患者呼吸睡眠暂停发作，神经功能恶化，经过紧急无创双相气道正压通气矫正(BiPAP)，其中动脉完全再通。提示在 AIS 患者中，可考虑无创通气矫正作为一种辅助治疗选择。徐玲[20]报道，BIPAP 治疗 12 小时内应用 CPAP 治疗，可有效改善神经功能缺损症状，尤其是中重度 OSA 患者。Fu [56]发现 CPAP 治疗在 AIS 和 OSA 患者中是可行的，并可能改善这些患者的神经预后。王龙[7]、孙丙毅[57]、Dominguez-Mayoral [2]和魏从兵[58]报道了 CPAP 治疗对 AIS 合并 OSA 患者的好处，包括改善神经功能、降低氧化应激水平和提高生活质量。Zhu [59]认为大多数高危 OSA 合并 AIS 患者在 CPAP 后易发生侧支循环，其中年龄、AHI、NIHSS、NO、MoCA、MMSE 等因素是影响侧支循环发生的重要决定因素。Siarnik [60]和 Müller [61]报道，在 AIS 亚急性期早期启动 CPAP 治疗，患者 6 个月时的治疗依从性可达 62.3%，且依从性与神经功能恢复呈正相关。Bradicich [62]报道 OSA 患者主要不良心脑血管事件风险率取决于长期良好的 CPAP 依从性。在降低心血管风险方面，年轻、困倦、OSA 更严重、低氧血症负担更高、无明显心血管终末器官疾病的患者可能特别受益于 CPAP 治疗。值得注意的是，宋学萍[63]认为 CPAP 治疗对不同梗死类型的患者效果存在差异，对完全前循环梗死、部分前循环梗死和后循环梗死患者的神经功能恢复改善显著，对腔隙性梗死(LACI)患者效果不明显，提示可能需要根据卒中类型制定个体化的 CPAP 治疗方案。与此同时，AIS 患者使用 CPAP 的实际依从性仅为 38.7%，设备不适、认知障碍、设备便携性不足[64]等是主要障碍，CPAP 治疗依从性差(<4 小时/晚)的患者 AIS 复发风险增加 1.8 倍，提示提高治疗的依从性是改善预后的关键。因此，综合管理 OSA 合并症(如高血压、糖尿病)是改善 AIS 预后的重要策略。

4.3. 药物治疗

现有证据表明有些治疗失眠的药物可以用于治疗卒中相关失眠。包括苯二氮䓬类(阿普唑仑、艾司唑仑、地西泮等)、非苯二氮䓬类(唑吡坦、右旋佐匹克隆、扎来普隆等)、褪黑素及褪黑素受体激动剂(雷美替胺、阿戈美拉汀等)、食欲素受体拮抗剂(雷美替胺、苏沃雷生等) [65]。Chen [66]报道曲唑酮可改善 AIS 后 OSA 的严重程度，可能与调节睡眠结构和上气道肌肉张力有关。Miyake [67]报道 l-鸟氨酸补充剂有缓

解疲劳相关压力和改善睡眠质量的潜力。根据患者睡眠障碍类型，选择合适的药物，可能会改善患者的生活质量。

5. 筛查与评估工具的优化

Martins [68]报道STOP-BANG问卷在老年AIS患者中的筛查效能，发现其灵敏度和特异度分别为82%和75%。Pataka [69]则建议结合柏林问卷和Epworth嗜睡量表进行综合评估。曾婷婷[70]认为四变量评分和改良四变量评分的筛查效率较高，曲线下面积分别为0.806和0.807，这为临床快速识别高风险患者提供了可靠工具。Lin [71]通过XGBoost模型和Logistic回归分析确定与卒中患者中重度OSA相关的显著特征，发现年龄、性别、BMI、颈围、ESS评分与中重度OSA显著相关。Dominguez-Mayoral [72]研究证实，OSA筛查和治疗计划可显著改善AIS患者的生活质量，提示系统化管理的重要性。Sanchez [73]认为通过睡眠教育可提高筛查患者的依从性和准确性。Chernyshev发现[74]与多导睡眠图PSG相比，便携式住院心肺筛查OCST在AIS患者中可提供相似的诊断信息，认为OCST是早期诊断AIS患者OSA的可靠筛查工具。Leino [75]建立的神经网络分析可通过夜间血氧饱和度信号实现OSA的简便筛查，其准确率可达85.7%。Sindorf [76]开发的无线可穿戴传感器技术可在24小时内完成筛查，为急诊环境下OSA的早期识别提供新方法。刘伟[77]指出虽然便携式睡眠监测因其便捷性在临床中得到广泛应用，但多导睡眠图(PSG)目前仍是诊断OSA的金标准。

6. 总结与展望

随着对OSA影响AIS发生发展的病理生理机制及OSA对AIS患者预后的影响不断深入了解，其相关信号传导通路，病理生理机制及在AIS发生进展过程中对预后可能影响等不断被阐明，我们发现OSA与AIS密切相关，两者互相影响，影响患者的生活质量。基于现有研究的不足，未来研究可从以下方面展开：1) 延长随访时间，开展大样本、多中心随机对照试验，进一步验证OSA与AIS两者间的相互作用，深入探讨OSA影响AIS的病理生理机制及分子信号通路，为疗效评估和风险预测提供依据；2) 设计性别分层的亚组分析，揭示雌激素在OSA合并AIS中的保护机制；3) 开展社区人群的研究，评估OSA在AIS发病中的实际患病率和危险因素，为AIS的一级预防提供依据；4) 推动AI技术与便携式睡眠监测设备的结合，实现AIS患者OSA的床旁快速诊断；5) 探索个性化的治疗方案，提高临床医师对OSA的认识，根据患者的OSA严重程度、合并症等因素，整合多学科等领域的资源，制定全面的OSA合并AIS的管理方案，改善患者预后。

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