综　　述

阻塞性睡眠呼吸暂停低通气综合征与心血管疾病关系的研究进展

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[摘要] 阻塞性睡眠呼吸暂停低通气综合征是一种高流行、低知晓的疾病，不仅与高血压相关，也与心脏结构和功能改变有关。而高血压和心脏重构已被证明是心房颤动的危险因素。睡眠呼吸暂停可能是导致高血压和心房颤动的重要且可治疗疾病之一，目前缺乏有效预防心房颤动的手段，通过治疗睡眠呼吸暂停或许可延迟或预防心房颤动发作。文章主要就高血压，心脏重构，心房颤动和睡眠呼吸暂停间的关系以及潜在的病理生理机制、可能的治疗手段等进行综述。

[关键词] 睡眠呼吸暂停低通气综合征；高血压；心脏重构；心房颤动

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Research progress on the relationship between obstructive sleep apnea hypopnea syndrome and cardiovascular disease

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[Abstract] Obstructive sleep apnea hypopnea syndrome is a high prevalence and low awareness disease, not only related to hypertension, but also related to changes in heart structure and function. Hypertension and cardiac remodeling have been shown to be risk factors for atrial fibrillation. Obstructive sleep apnea hypopnea syndrome may be one of the important and treatable diseases that cause hypertension and atrial fibrillation. Presently, there is no effective meansto prevent atrial fibrillation. By treating sleep apnea, it may be possible to delay or prevent the onset of atrial fibrillation. The article mainly reviews the relationship between hypertension, cardiac remodeling, atrial fibrillation and sleep apnea, as well as the underlying pathophysiological mechanisms and possible treatments.

[Key words] sleep apnea hypopnea syndrome; hypertension; cardiac remodeling; atrial fibrillation

0　引　　言

阻塞性睡眠呼吸暂停低通气综合征(obstructive sleep apnea hypopnea syndrome, OSAHS)是一种高度流行的疾病，据估计，成年男性和女性重度睡眠呼吸障碍的患病率分别为 17%和 9%[1]，更年期后女性的 OSAHS 患病率显著增加[2]。OSAHS 是一种由于睡眠期间上呼吸道的肌肉张力下降，导致上呼吸道反复塌陷和呼吸暂时停止，以胸腔压力波动、间歇性缺氧、自主神经功能紊乱、睡眠微觉醒和白天嗜睡为特点的疾病，因早期缺乏特异的临床表现，具有较低的知晓率，临床上诊断多依赖于多导睡眠图，并根据呼吸暂停低通气指数(apnea hypopnea index, AHI)判断其严重程度：轻度，AHI≥5；中度，AHI≥15；重度，AHI≥30[3]。OSAHS 带来的交感神经兴奋性、血儿茶酚胺上调、全身炎症和氧化应激等血液动力学和神经炎症变化显著增加 OSAHS 患者的心血管风险及死亡率[4]。持续气道

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正压通气(continuous positive airway pressure, CPAP)是治疗 OSAHS 的有效方法,患者的依从性显著限制了 CPAP 治疗的有效性,然而,OSAHS 相关心血管疾病的病理生理机制仍不完全清楚。本文就 OSAHS 与高血压、心脏重构和心房颤动间的关系,并对目前存在的治疗方案作一综述。

1 OSAHS 与心脏重构

1.1 血流动力学改变 OSAHS 时胸腔负压增加,会影响胸腔内器官功能,如肺扩张致气道远端感受器兴奋,激活迷走神经,以抵消上呼吸塌陷,同时胸腔内大血管及薄壁心房易受胸腔内压力波动的影响,如回心血量增加,右心容量超负荷[5]。心房钠尿肽(atrial natriuretic peptide, ANP)为心脏重构的保护因子,具有舒张血管,抑制心肌细胞损伤的作用,与对照组相比,OSAHS 患者的 ANP 浓度显著增高,可能是由于反复出现夜间上气道阻塞导致胸腔负压增大,回心血量增加,心房过度舒张,刺激 ANP 释放[6]。从侧面反映 OSAHS 可通过改变血流动力学,参与心脏重构及心肌损伤。

OSAHS 相关的间歇性的夜间缺氧和高碳酸血症将导致肺血管内皮损伤,诱发血管收缩,结构重塑,肺动脉压升高,表现为肺动脉硬度增加,及右肺动脉缩短分数下降等[7]。进一步加重右心室压力负荷,出现心肌肥厚到功能障碍的病理改变。最近有研究指出 OSASH 患者在发生肺动脉高压前,已观察到右心室发生结构及功能的改变[8]。表明肺动脉高压非唯一原因。左心室功能不全,也是导致右心室功能障碍的原因之一,因为 2 个心室之间存在紧密的解剖联系[9]。

1.2 氧化应激 心脏重构的病理特征是过多的细胞外基质沉积,破坏正常的心肌结构,导致心肌纤维化,OSAHS 引起的间歇性缺氧(intermittent hypoxia, IH)是心脏重构的最有力诱因之一,反复缺氧-复氧可通过诱导氧化应激反应,恶化心室肌细胞的内质网钙离子失稳[10],导致间质胶原蛋白增多、心肌细胞肥大及内皮间质转分化[11],增加左心室心肌细胞外基质的被动硬度[12]及心肌纤维化。

夜间低通气致 IH 和二氧化碳滞留通过刺激中枢和外周化学感受器,增加交感神经活动,明显增加 OSAHS 患者血液甚至尿液中的儿茶酚胺水平[13],过度激活肾素-血管紧张素-醛固酮系统(renin-angiotensin-aldosterone system, RAAS),其中血管紧张素及醛固酮是心室重构的促进因子,尤其是醛固酮[14],参与心肌细胞肥大,心室结构重塑的发生。

1.3 炎症反应 IH 还可介导 NF-kB 信号通路,调节基质金属蛋白酶转录,上调 IL-6、TNF-α 等炎性因子及 TGF-β 的表达[15],诱导心肌细胞凋亡,有效心肌细胞数量下降,血浆内皮素(endothelin, ET)浓度增高。ET 是一种强大的促纤维化和缩血管物质,能诱导心肌细胞肥大,进而导致心室纤维化和收缩力减弱。动物实验发现通过阻滞 ET 受体,可显著改善心室纤维化及功能障碍[16]。

OSAHS 相关的心脏重构的早期表现以左心室舒张功能不全为主[17],即左心室射血分数(left ventricular ejection fraction, LVEF)等心室收缩功能参数正常而左心室舒张功能参数,如二尖瓣血流速度(E/A 比)下降。一项针对 31 名严重 OSASH 患者的临床研究发现,与对照组相比,严重 OSASH 患者的左心室舒张功能明显降低,以心尖和中段纵向应变显著降低为主,而 LVEF 无明显下降[18]。另一项多中心随机对照研究显示,合并射血分数保留的心力衰竭的 OSAHS 患者左心室重构明显,且不论通过自适应伺服通风或联用最佳药物治疗,均有逆转左心室重构作用[19]。最近有研究提出心电图的心室除极波碎片化是 OSAHS 患者合并亚临床左心室功能障碍的独立预测因子,是更易量化的早期和亚临床左心室功能障碍的标记方式[20],且与心血管事件的不良预后密切相关。一项包括 17 个临床研究 747 例 OSAHS 患者的荟萃分析认为,OSAHS 患者的左心结构及功能均不同程度受损,与 OSAHS 严重程度相关[21]。另一项包括了 1503 名 OSASH 患者和 796 名健康对照的荟萃分析表明,OSASH 患者的右心室结构改变主要表现为室壁增厚、心室扩张,右心室功能明显受损,进一步加重 OSASH[22]。

2 OSAHS 与高血压

OSAHS 被认为是顽固性高血压(hypertention, HTN)最常见的继发性原因[23]。建议所有血压控制不佳的患者均应进行 OSAHS 筛查,HTN 患者中 30%患有中重度 OSAHS,而顽固性 HTN 患者中男性 OSAHS 的患病率高达 90%[24]。HTN 控制水平和 OSAHS 严重程度间存在线性相关,且与夜间颈动脉体化学感受敏感性升高、慢波睡眠减少有关[25],主要表现为非杓型 HTN,以夜间血压及 24 h 舒张压升高为主,OSAHS 相关的 HTN 患者,药物降压效果

不佳[26]。OSAHS相关HTN的病理生理机制主要为对低氧血症的化学反射反应[27],激活交感神经,通过作用于RAAS系统发挥升压作用[28]。另外,缺氧也刺激ANP释放增加,从而减弱对RAAS系统的抑制作用,可能是部分OSAHS患者发生HTN的重要因素[29]。间歇性缺氧可诱导肾交感神经兴奋,介导血管收缩甚至引起血管结构改变,最终导致HTN[30]。进一步损害血管舒张功能,形成恶性循环。IH也可损伤自主神经功能,主要表现为压力反射受损反应及心率变异性受损[31],破坏血压自身稳定,不仅与非杓型HTN有关,还与白天过度嗜睡、认知功能下降有关[32]。大量RCT临床研究证实了OSAHS和难治性HTN相关,CPAP、肾去交感神经等治疗有利于动态及夜间血压控制[33]。也有两者研究认为之间不仅限于因果关系而是复杂双向的关系,醛固酮[34]、内皮素[35]可能参与其中。

3 OSAHS与心房颤动

OSAHS与心律失常之间存在非常强的关联[36],IH还直接影响与心律失常相关的心力衰竭和呼吸衰竭。心房颤动(atrial fibrillation, AF)是最常见的心律不齐,2025年美国患有AF的人数预计从230万增加到1000万[37]。人口老龄化和传统的危险因素无法完全解释心房颤动发病率和患病率的增加,OSAHS可能部分解释AF的发生[38]。OSAHS和AF共同危险因素,如肥胖、年龄、人种,且具有极强的关联性[39]。在一项回顾性队列研究中发现男性是OSAHS患者发生AF的预测指标[40]。胸腔内压、血二氧化碳水平及氧化应激水平增加被认为是OSAHS患者心脏结构和电生理重构的重要病理机制,表现为心房扩大,心房电传导速度改变等。最近的一项临床研究显示,全心房传导时间是心房颤动独立且有力的预测指标,在严重OSAHS患者中,该指标显著延长,且与心房、心室容量超载有关的指标B型钠尿肽(B-type natriuretic peptide, BNP)亦显著升高,通过CPAP治疗后全心房传导时间及BNP均较基线值回落,表明OSAHS可诱发心房电生理及结构重塑,且这种重塑作用可通过CPAP治疗后逆转[41]。

4 治　疗

4.1 一般治疗 对颈围过大(特别是≥38 cm)的肥胖OSAHS患者进行健康教育,建议通过节食、运动,甚至减重手术,达到减重目的。一项临床随机对照试验证明强化减肥计划可显著减轻OSAHS患者的严重程度,还可改善脂质分布,控制血糖和C-反应蛋白等炎症指标[42]。最新一项荟萃分析,包含6个临床研究共241名肥胖OSAHS患者,表明全面的减肥计划,包括动机咨询,运动,饮食控制可减轻6%~7%的体重,手术的减重效果更强,约减轻15%~64.6%体重,可显著减轻OSAHS严重程度(AHI降低18%~44%)甚至消除OSAHS,改善气体交换以及白天嗜睡和肺动脉高压,降低心血管事件发生率[43]。

4.2 CPAP CPAP是目前治疗OSAHS最主要的手段之一,已经证实不仅可改善OSAHS症状,还可显著降低血压变异性[44]。反转高血压抵抗的人群中的夜间非杓型高血压[45]。对于患有顽固性高血压的OSAHS患者,CPAP治疗似乎有更大的降压幅度,收缩压可降低5~7 mmHg、舒张压可降低3~6 mmHg[46],长期坚持CPAP治疗可逆转病理性交感神经激活[47],改善心律不齐[48]。许多研究表明,CPAP降低了血压、炎症标志物,明显改善患者症状,然而对心血管事件无显著影响,可能与患者对CPAP治疗的依从性不高有关[49]。

4.3 药物治疗 交感神经、RAAS系统尤其是醛固酮在OSAHS相关心血管疾病中的作用逐渐被认识,目前发现应用盐皮质激素拮抗剂在顽固性高血压中具有降压及降低睡眠障碍性疾病的作用[50]。β1受体阻滞剂阻断可降低异常激活的交感神经,降低动脉僵硬度和24 h舒张压[51]。有研究证明利尿剂可使液体重分布[52],即腿部液体转移至颈部,加重OSAHS的阻塞症状。

4.4 手术干预 用于对CPAP依从性差的患者,可考虑手术干预[53]。手术选择包括上气道手术,如鼻腔重建、下颌推进、悬雍垂腭咽成形术、舌下神经刺激[54]、肾脏去神经治疗、温控射频组织消融等。最近RCT研究了肾脏去神经治疗不仅可降低顽固性高血压患者的血压水平,还可减轻OSAHS的严重程度[30]。

5 结　语

高血压可导致并加重心脏重构的发生,而心肌纤维化和电重构又是心房颤动的病理改变。可合理假设OSAHS带来的机械压力、神经-体液变化和氧化应激参与上述心血管疾病的发生发展,即

OSAHS 导致高血压尤其是顽固性高血压的发生，进一步加重 OSAHS 诱导的心脏重构及心房颤动，本文阐述了上述四者的关系以及目前存在的治疗策略，主要是 CPAP 在改善 OSAHS 的同时可降低高血压患者的血压水平以及心房颤动等心血管疾病的发生，近年来通过手术干预治疗 OSAHS 的成效显著，但能否逆转心肌纤维化、心脏重构，预防心房颤动等心血管疾病的发生，改善心房颤动患者预后，仍有待进一步研究。

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