·综述·

阻塞性睡眠呼吸暂停与心力衰竭相关性研究进展

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【摘 要】 随着老龄化的进程加快,阻塞性睡眠呼吸暂停(OSA)与心力衰竭(HF)的患病率呈明显升高趋势。研究表明,OSA与HF互为因果,相互影响。OSA是HF的独立危险因素,HF又会引起OSA,这会使HF的症状进展、住院和死亡等不良后果的风险增加。OSA与HF之间的相互作用与上气道阻塞和慢性间歇性低氧密不可分。对于OSA相关性HF,目前没有明晰的诊疗方案。针对两者的发病机制及症状,HF治疗药物通常推荐与OSA的一线治疗方法持续气道正压通气合并使用。本文对OSA与HF相关性研究的最新进展予以综述,旨在为后续更有效的针对性治疗提供必要的参考。

【关键词】 阻塞性睡眠呼吸暂停;心力衰竭;低氧血症;持续气道正压通气

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Progress in research on obstructive sleep apnea and heart failure

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【Abstract】 With the acceleration of ageing process, the prevalence of obstructive sleep apnea (OSA) and heart failure (HF) has been significantly increasing. Studies show that OSA and HF are causal and mutually influential. OSA is an independent risk factor for HF, which in turn causes OSA, increasing the risk of adverse outcomes such as symptom progression, hospitalization, and death in HF. The interaction between OSA and HF is inextricably linked to upper airway obstruction and chronic intermittent hypoxia. Currently, there is no definitive diagnosis and treatment protocol for OSA-associated heart failure. Considering the pathogenesis and symptoms of both, HF treatment drugs are usually recommended to be combined with continuous positive airway pressure, the first-line treatment for OSA. In this article, we reviewed the research on OSA and HF to provide necessary references for subsequent more effective targeted treatment.

【Key words】 obstructive sleep apnea; heart failure; hypoxia; continuous positive airway pressure

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心力衰竭(heart failure,HF)指心脏结构和(或)功能改变导致静息和(或)运动时心内压升高和(或)心输出量不足,并伴有钠尿肽水平升高和(或)肺部或全身充血客观表现的临床综合征,基于左心室射血分数(left ventricular ejection fraction,LVEF)分为射血分数降低的心力衰竭(heart failure with reduced ejection fraction,HFrEF; EF<40%),射血分数轻度降低的心力衰竭(heart failure with mildly reduced ejection fraction,HFmrEF; EF 40%~49%),射血分数保留的心力衰竭(heart failure with preserved ejection fraction,HFpEF; EF≥50%)[1]。阻塞性睡眠呼吸暂停(obstructive sleep apnea,OSA)是由睡眠期间咽部气道反复塌陷引起的慢性疾病[2]。反复睡眠中断导致夜间间歇性低氧、胸内负压升高、交感神

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经活动增加等一系列病理生理学改变出现。这些改变可能会影响心脏功能,导致长期心脏重塑,最终可能引起 HF 出现[3]。并且 HF 也可能会引起 OSA 发生[4]。

1 OSA 与 HF 相关流行病学

大量研究表明 HF 患者中 OSA 患病率约为 40%[2]。随着呼吸暂停低通气指数(apnea hypopnea index,AHI)增加,HF 患病率逐渐增加,在 AHI≥30 事件的患者中,睡眠呼吸暂停患者 HF 患病率增加了 2.38 倍[1]。

OSA 可能导致高血压,引起心室肥厚,逐渐进展为 HFpEF[5]。一项针对 HFpEF 患者的研究报告称,睡眠呼吸障碍患病率在 50%~70%,其中大多数患有 OSA[3]。冠状动脉事件发生风险与 HFrEF 和 HFmrEF 关系较强,HFmrEF 与 HFrEF 与心肌梗死风险相关性高于 HFpEF[6]。Arzt 等[7]纳入 3 289 例 HF 患者发现,与 HFrEF 相比,HFpEF 组睡眠呼吸障碍患者 OSA 的比例更高,而 HFrEF 患者中枢性睡眠呼吸暂停的患病率最高。

2 OSA 相关 HF 的机制

2.1 OSA 引起 HF 的机制

2.1.1 慢性间歇性低氧 OSA 患者因气道阻塞导致的低通气和(或)呼吸暂停及血氧波动会引起间歇性低氧血症,这会促进活性氧(reactive oxygen species,ROS)的产生[3],诱导氧化应激、系统性炎症、交感神经兴奋、肾素血管紧张素醛固酮系统(renin-angiotensin-aldosterone-system,RAAS)激活。

ROS 与含氮碱基和脱氧核糖核酸(deoxyribonucleic acid,DNA)发生氧化反应引起线粒体基因组的突变或缺失并累积,这会改变 ROS 与超氧化物歧化酶、谷胱甘肽过氧化物酶等酶之间的平衡,减少抗氧化防御[8]。心肌细胞线粒体 DNA 含量和基因表达的降低会导致其功能受损,引起心肌病发生[9]。此外,ROS 会激活心脏 Na^+/Ca^{2+} 交换器,通过 Ca^{2+} 依赖性途径引发心脏肥大,并促进 Ca^{2+}/钙调素依赖性蛋白激酶Ⅱ的激活,导致心肌细胞死亡增加[10]。

间歇性低氧通过上调心肌中转录因子缺氧诱导因子-1α、核因子 κB(nuclear factor kappa-B,NF-κB)和起保护作用的红系衍生的核转录相关因子 2[nuclear factor(erythroid-derived 2)-like 2 protein,Nrf2],导致诱导型一氧化氮合酶、肿瘤坏死因子-α、白细胞介素-6、E-选择素、细胞间黏附分子和血管细胞黏附分子的表达,这些会引起内皮激活,导致一氧化氮生物利用度降低、内膜中层增厚和动脉粥样硬化,影响心肌活力和收缩力[11,12]。

间歇性低氧驱动颈动脉体内缺氧诱导因子表达异常,造成血红素加氧酶 2 氧化并减少,引起一氧化碳含量降低导致硫化氢生成增加,从而触发血管球细胞去极化,增加交感神经的活动[13],这又会刺激 RAAS 系统,包括过度刺激血管紧张素Ⅱ和醛固酮,引起内皮功能障碍、动脉弹性减低和水钠潴留[14]。

2.1.2 胸内负压波动 间歇性低氧发作期间,上气道阻塞使胸内负压增加,引起左心室后负荷增加[15]。当呼吸恢复后,静脉回流增加,右心室前负荷增加。而 OSA 诱导的低氧血症又会导致肺动脉血管收缩和肺动脉高压[16]。这些都导致右心室扩张和舒张期室间隔向左移位,从而损害左心室充盈并减少其前负荷。左心室后负荷的增加和前负荷的减少降低了 OSA 患者的心输出量。长期循环,导致心脏结构变化、心肌缺血坏死。

2.2 HF 引起 OSA 的机制

由于重力作用,白天直立时液体在腿部积聚,随着睡眠时体位变化转变为仰卧时转入颈部。这种液体移位可能导致颈部静脉扩张和(或)咽喉周围软组织水肿,从而增加咽喉周围组织压力,致使上气道周径缩小,引起气道塌陷和咽部阻塞[4]。使用生物电阻抗测量睡眠前后腿部液体容量,发现 HF 患者腿部液体容量的夜间减少与 OSA 严重程度之间存在密切关系[17]。

3 OSA 合并心力衰竭的治疗

3.1 气道正压通气治疗

持续气道正压通气(continuous positive airway pressure,CPAP)是 OSA 的主要治疗方法。研究表明 CPAP 治疗可以改善中重度 OSA 患者心室和心房功能。Zota 等[18]对 OSA 患者超声心动图评估表明,2 个月 CPAP 治疗会改善 OSA 和心脏代谢合并症患者的左心室整体纵向应变和三尖瓣环收缩期位移。并且,Kim 等[19]对 OSA 患者超声心动图进行研究也发现,CPAP 治疗 3 个月后,左心室整体纵向应变显著改善,但左心室尺寸和左心室射血分数均没有差异,右心室面积变化分数显著改善,但并未改善右心室整体纵向应变。Kondratavičevienė等[20]研究发现,CPAP 治疗 3 个月后,肥胖 OSA 患者左心房和右心房整体纵向应变均有所改善。至此,以上研究皆发现 CPAP 治疗能改善心功能,但是对于各心脏参数指标的变化,由于各试验研究的 OSA 患者严重程度不同,样本量和 CPAP 治疗时间不等,会存在差异。

另一方面,氨基末端脑钠尿肽(N-terminal pro-brain natriuretic peptide,NT-pro-BNP)和肌钙蛋白浓度已被确定为HF诊断和预后预测的关键生物标志物,新的生物标志物如半乳糖凝集素-3和ST-2在评估HF预后方面的价值也得到认可[21]。Chang等[22]研究证实,中重度OSA患者CPAP治疗2个月后可降低NT-pro-BNP,但没有发现对高敏心肌肌钙蛋白有显著影响;而最近一项荟萃分析则表明CPAP治疗不会改变OSA患者的NT-pro-BNP水平[23]。Khalaji等[24]进行荟萃分析发现,重度OSA与更高水平的半乳糖凝集素-3有关,CPAP治疗降低OSA患者的半乳糖凝集素-3外周水平。

上述研究说明CPAP可以改善OSA合并HF患者病情。但是患者对这种治疗的依从性不高,可能与患者的个人因素、OSA严重程度有关[25]。

3.2 药物治疗

HF恶化可能会增加OSA风险,药物治疗是临床治疗HF的常用方法。Revol等[26]发现利尿剂能改善肥胖高血压患者的OSA严重程度,通过防止液体潴留来降低OSA严重程度。沙库巴曲-缬沙坦(sacubitril valsartan,SV)是血管紧张素受体脑啡肽酶抑制剂,Wang等[27]发现SV与HFrEF患者OSA患者LVEF升高有关,进而促进左心室和左心房逆向重塑以及AHI的改善。

一些动物实验初步表明药物治疗对间歇性低氧引起的心血管损害有积极作用,但还需临床试验反复证明。有研究表明,阿托伐他汀抑制氧化应激,降低间歇性低氧大鼠心脏组织丙二醛水平、超氧化物歧化酶活性和相关因子水平[28];还能通过抑制TLR4、MYD88及下游炎症因子mRNA表达和蛋白质水平、减少氧自由基产生来改善心肌损伤[29]。褪黑激素具有抗氧化和抗炎特性[30],Yeung等[31]发现褪黑激素可减轻间歇性低氧诱导大鼠心肌炎症和纤维化和缺血/再灌注损伤。此外,中药黄芪甲苷Ⅳ(astragaloside Ⅳ,AS-Ⅳ)具有抵抗炎症、氧化应激、纤维化作用[32]。Zhang等[33]荟萃分析发现,AS-Ⅳ通过降低心脏前后负荷及抑制心肌肥大来保护心脏。Jiang等[34]发现AS-Ⅳ可以减弱心肌凋亡和钙破坏。

3.3 其他

由于HF是所有心脏疾病的晚期表现,会同时出现多系统功能障碍。因此,对于CPAP治疗配合度低、不耐受的患者,可考虑悬雍垂腭咽成形术、舌下神经刺激、上下颌前移手术;对于病情危及生命的患者可取气管切开术来缓解病情;也可对不同程度的OSA合并HF患者实施减肥、运动、戒酒、体位疗法、口咽锻炼等个体化的治疗方案[35]。

4 小 结

综上,OSA可以通过慢性间歇性低氧及胸腔内压力波动等机制导致HF的发生,HF患者体液潴留和再分布也会引起OSA症状出现。对OSA合并HF患者,CPAP治疗能够改善心功能严重程度。而目前药物治疗还处于发展阶段,需要继续探索更多更好的药物,从而确立OSA合并HF防治的新策略。

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