



眠期间反复发生呼吸暂停的一种慢性呼吸系统疾病,其在  $\geq 65$  岁人群中的发病率高达 50%<sup>[2]</sup>。OSAHS 的病理生理学机制十分复杂,目前尚未完全阐明。总体来说,OSAHS 是上呼吸道解剖结构异常和睡眠期呼吸道改变相互作用所导致的结果<sup>[4]</sup>,其主要病理生理学特征为慢性间歇性低氧 (chronic intermittent hypoxia, CIH) 和睡眠碎片化 (睡眠障碍)。

上呼吸道阻塞可直接导致胸腔内压下降,通常低至  $-60$  mm Hg ( $1$  mm Hg =  $0.133$  kPa),这种血流动力学变化可导致心室内压和大血管管壁侧压增加,增加心脏前后负荷<sup>[8]</sup>。机体长期处于 CIH 环境中,可产生氧化应激反应,导致周期性缺氧、复氧和活性氧 (reactive oxygen species, ROS) 的形成<sup>[9]</sup>,启动炎症反应,引起血管舒张功能下降以及血管重塑,导致肺动脉压力增高,进而增加右心室后负荷,发生右心室肥厚,引起心肌缺血,最终发生心力衰竭<sup>[10]</sup>。有研究表明,ROS 可与核酸、蛋白质、脂质发生反应,导致 DNA 损伤、蛋白质氧化和脂质过氧化,促进细胞坏死或凋亡<sup>[11]</sup>。ROS 还可通过增加白细胞特异性和内皮特异性黏附分子的表达,诱导内皮细胞功能障碍,进而导致微血管损伤<sup>[12]</sup>。此外,CIH 可激活交感神经系统 (sympathetic nervous system, SNS) 和肾素-血管紧张素-醛固酮系统 (renin-angiotensin-aldosterone system, RAAS),引起心肌损伤,促进心肌重塑,最终导致心力衰竭。另外,CIH 可引起气体交换障碍,导致间断性出现动脉血氧分压降低和二氧化碳分压升高,进而反复激活中枢神经系统,引起觉醒,导致睡眠碎片化。有研究表明,睡眠碎片化与心血管不良预后有关,其中 OSAHS 是最常见的睡眠障碍性疾病<sup>[13]</sup>。此外,OSAHS 因 CIH 引起机体过氧化应激反应,导致 DNA 损伤和抑制小胶质细胞 (BV2 细胞) 增殖,损伤海马神经元,导致认知功能障碍,加速机体衰老<sup>[14]</sup>。

综上所述,OSAHS 可引起机体氧化应激、炎症反应和内皮功能障碍、神经激素激活以及加速衰老。

## 2 OSAHS 在 HFpEF 中的作用

HFpEF 占心力衰竭的 50% 以上,具有高发病率、高病死率和高再住院率的特点。据统计,HFpEF 目前影响全球约 2% 的人口,预计到 2035 年,HFpEF 的发病率在老龄化人口中将增加 50%;由于高龄与共病之间的复杂相互作用,HFpEF 的治疗成为目前心血管医学中的难题<sup>[15]</sup>。虽然目前已对 HFpEF 的多种发病机制进行了研究,但其确切机制尚不清楚。研究表明,OSAHS 通过对氧化应激、炎症反应和内皮功能障碍、神经激素激活、衰老等的影响在 HFpEF 发病机制中发挥着重要的作用<sup>[16-18]</sup>。

**2.1 氧化应激** 氧化应激是指机体在受到有害刺激时,体内氧化与抗氧化失衡的一种状态。CIH 是 OSAHS 的一个病理生理学特征,其产生的直接后果是氧化失衡,产生 ROS,进一步诱导氧化应激;反过来,机体过度氧化应激将导致心肌细胞产生更多的 ROS,二者之间形成恶性循环。DHARUMAN 等<sup>[19]</sup>研究发现,OSAHS 患者血液中氧化应激标志物高级氧化蛋白产物 (advanced oxidation protein products, AOPP) 水平升高,且其升高水平与 OSAHS 严重程度有关而 CPAP 可降低 OSAHS 患者血液中 AOPP 水平,提示氧化应激在 OSAHS 的发病中起着重要作用。氧化应激在心肌重塑和 HFpEF 的病理生理过程亦发挥着关键作用。有研究表明,抗氧化物质姜辣素可通过调节磷脂酰肌醇 3-激酶/蛋白激酶 B/哺乳动物雷帕霉素靶蛋白信号通路抑制 ROS 生成,减少心肌细胞的凋亡<sup>[20]</sup>。另有研究表明,CIH 可激活基质金属蛋白酶 (matrix metalloproteinase, MMP),导致细胞外基质 (extracellular matrix, ECM) 的组成发生改变<sup>[21]</sup>。FRANCZAK 等<sup>[22]</sup>通过临床研究发现,OSAHS 患者血清 MMP-2 活性显著升高,且其升高水平与 OSAHS 严重程度相关,提示 OSAHS 可通过改变 ECM、启动心室重塑参与 HFpEF 的发生、发展。HFpEF 的特点是射血分数正常,早期心室结构的改变通常表现出舒张功能障碍。研究表明,OSAHS 患者早期出现舒张功能障碍<sup>[23]</sup>。综上所述,OSAHS 通过氧化应激在 HFpEF 的病理生理学机制中起着至关重要的作用。

**2.2 炎症反应和内皮功能障碍** CIH 是 OSAHS 的病理生理学特征,被认为是引起 OSAHS 患者全身炎症反应和内皮功能紊乱的重要病理生理学机制之一,而炎症反应和内皮功能障碍是 HFpEF 的主要病理生理学特征,因此,OSAHS 可能通过炎症反应和内皮功能障碍参与 HFpEF 的发生、发展。研究表明,OSAHS 患者血清中核因子- $\kappa$ B (nuclear factor- $\kappa$ B, NF- $\kappa$ B) 表达上调,导致下游促炎细胞因子 C 反应蛋白 (C-reactive protein, CRP)、肿瘤坏死因子- $\alpha$  (tumor necrosis factor- $\alpha$ , TNF- $\alpha$ )、白细胞介素 (interleukin, IL)-6 和 IL-1 $\beta$  的表达增加,从而引起全身炎症反应<sup>[24]</sup>。WANG 等<sup>[25]</sup>研究发现,选择性 Rho 相关卷曲螺旋形成蛋白激酶抑制剂可通过下调 Ras 同源基因家族成员 A 蛋白水平,有效抑制慢性间歇性低氧大鼠 Ras 同源基因家族成员 A/Rho 相关卷曲螺旋形成蛋白激酶信号通路的激活,且可通过抑制 NF- $\kappa$ B 的活性减少下游炎症因子的表达,从而减轻 CIH 大鼠的心肌重塑。内皮功能障碍是一种全身性病理状态,其特征是由于内皮源性血管活性介质的释放而导致血管收缩和舒张不平衡。PENG 等<sup>[26]</sup>

研究表明,OSAHS患者体内内皮素-1(endothelins-1, ET-1)水平偏高,提示存在内皮功能障碍。一项纳入50例中重度OSAHS患者的荟萃分析研究表明,严重的OSAHS可导致内皮损伤,表现为可溶性细胞间黏附分子-1和ET-1水平升高<sup>[27]</sup>。在OSAHS患者体内,因CIH触发了机体氧化应激、全身炎症反应和交感神经激活,导致血管内皮活性物质合成过程中的关键酶内皮性一氧化氮合成酶等活性下降,致血管收缩和舒张平衡被打破,最终导致内皮功能障碍。由此可见,OSAHS可能通过全身炎症和内皮功能障碍参与HFpEF发病机制,而减轻机体的炎症反应和血管内皮功能障碍可能会延缓HFpEF的进展。

**2.3 神经激素激活** SNS和RAAS激活在HFpEF的病理生理机制中发挥着重要作用。OSAHS引发SNS过度激活,并进一步激活RAAS,导致外周血管压力增加,心脏负荷加重,最终发生心力衰竭。有研究显示,OSAHS患者血浆中儿茶酚胺水平显著增高,提示OSAHS患者体内存在SNS过度激活<sup>[28]</sup>。CETIN-ATALAY等<sup>[29]</sup>研究发现,CIH小鼠体内儿茶酚胺水平升高;同时,对CIH小鼠行药理学抑制、肾上腺切除术或颈动脉体切除术后发现,CIH小鼠体内儿茶酚胺水平下降,进一步证实OSAHS可激活SNS。此外,一项研究表明,CPAP可通过抑制交感神经活性治疗OSAHS<sup>[30]</sup>。目前,关于OSAHS患者体内RAAS被激活的证据有限,有研究表明,OSAHS患者体内血浆醛固酮水平升高,且其升高程度与OSAHS严重程度呈正相关,提示OSAHS激活了RAAS<sup>[31]</sup>。此外,一项研究表明,醛固酮拮抗剂螺内酯改善了OSAHS患者病情<sup>[32]</sup>,间接证实OSAHS参与了RAAS的激活。OSAHS引起SNS和RAAS激活后,将会增加钠水潴留,引起心脏负荷加重,最终导致心力衰竭。而心力衰竭引起的钠水潴留也可能在OSAHS的发病机制中发挥重要作用,二者互为影响、相互作用。综上所述,OSAHS患者体内神经激素过度激活在HFpEF中发挥着重要作用,抑制神经激素活性可延缓HFpEF的发生、发展。

**2.4 衰老** 衰老影响HFpEF的病理生理过程,与衰老相关的结构和功能变化通常被认为是HFpEF的重要风险因素。OSAHS被认为是多种与衰老相关疾病的独立危险因素,已有研究证实,未经治疗的OSAHS与衰老相关疾病的进展有关<sup>[33-34]</sup>。因此,OSAHS可能不仅是一种与衰老相关的疾病,而且还加速了机体的衰老。多项研究表明,OSAHS患者的DNA损伤程度高于健康人,提示OSAHS可导致细胞损伤,可能是由于OSAHS患者易触发机体氧化应激,导致线粒体功能障碍<sup>[35-36]</sup>。此外,有研究表明,CPAP治疗可降低OSAHS患者的线粒体DNA/核

DNA比值,减少线粒体损伤<sup>[37]</sup>。端粒是存在于真核细胞线状染色体末端的一小段DNA-蛋白质复合体,其长度反映细胞复制史和复制潜能,随着细胞分裂次数的增加,端粒的长度逐次变短,当达到临界值后细胞周期停止,细胞发生衰老或凋亡,因此,端粒长度代表细胞的寿命。研究表明,与健康人相比,OSAHS患者的端粒长度较短,提示OSAHS可能通过缩短端粒长度加速细胞衰老过程<sup>[38-39]</sup>。此外,OSAHS病理生理学特征之一的睡眠碎片化可引起DNA损伤和小胶质细胞的增殖抑制,导致海马神经元受损,OSAHS患者出现认知功能减退,进而加速机体衰老。因此,早期诊断和治疗OSAHS,可从细胞和分子水平上延缓机体衰老或与衰老相关的HFpEF进展。

### 3 CPAP在OSAHS合并HFpEF治疗中的作用

CPAP是治疗OSAHS的首选方法,其可使患者在睡眠期间保持呼吸道畅通,减少夜间间歇性缺氧、复氧和觉醒的次数。炎症反应被认为是HFpEF的病理生理学机制之一,已有研究证实,CPAP具有抗炎和降低氧化应激的特性<sup>[40-41]</sup>。目前,关于CPAP在HFpEF患者治疗中的作用研究较少。有研究表明,与常规治疗相比,对HFpEF合并OSAHS的患者给予CPAP治疗后,患者的脑利钠肽水平及左心房的容积指数显著降低,提示CPAP治疗可改善此类患者的临床症状和心脏舒张功能<sup>[42-43]</sup>。众所周知,心脏重构的级联反应过程中,右心室力学的变化发生在功能性和结构性心脏损伤之前,右心室功能的评估可能是检测心脏细微变化的基石。有研究证实,OSAHS患者的右心室舒张功能障碍发生在临床心功能不全和肺动脉高压开始之前,且CPAP治疗可改善OSAHS患者的右心室舒张功能<sup>[44]</sup>。因此,CPAP治疗可能会延缓HFpEF的发生和发展,但尚需对OSAHS合并HFpEF行CPAP治疗的患者进行大规模的随访研究以进一步证实。

### 4 结语

OSAHS作为HFpEF的独立危险因素,通过氧化应激、炎症反应、神经激素激活、衰老等在HFpEF的发生、发展过程中起着重要作用,但OSAHS的诊断常被忽视,若能早发现、早诊断并进行有效干预,可能延缓HFpEF的发生、发展。因目前关于HFpEF的治疗方法非常有限,所以,合并症的早期诊断和治疗显得至关重要。已证实CPAP治疗OSAHS合并HFpEF患者在早期可能是有效的,但目前相关研究较少,尚需进行大规模的研究。

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