慢性阻塞性肺疾病合并肌少症研究进展

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摘 要: 慢性阻塞性肺疾病(COPD)是一种复杂的、具有高度异质性的全身性疾病。肌少症作为 COPD 多种合并症中之一,能够加速疾病进程,增加致残率和全因死亡率。近年来研究发现, COPD 合并肌少症的危险因素为活动受限、营养不良、脂肪沉积等。结合肺功能相关指标与肌肉测量技术能够较精确的预测住院患者生存率和死亡率,在此基础上进行个性化干预,对疾病转归和预后改善具有重大的临床意义。本文对 COPD 与肌少症的危险因素、诊断、干预治疗等方面进行综述。

关键词: 慢性阻塞性肺疾病; 肌少症; 危险因素

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Progress of chronic obstructive pulmonary disease complicated with sarcopenia

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Abstract: Chronic obstructive pulmonary disease (COPD) is a complex and highly heterogeneous systemic disease. As one of the multiple complications of COPD, sarcopenia can accelerate the disease process, increase the disability rate and all-cause mortality. In recent years, studies have founded that the risk factors of COPD with sarcopenia were limited activity, malnutrition, fat deposition and so on. Combined with pulmonary function related indicators and muscle measurement techniques, the survival and mortality rates of hospitalized patients can be predicted more accurately. On this basis, individualized intervention is of great clinical significance to improve the outcome and prognosis of the disease. This article reviewed the risk factors, diagnosis, intervention and treatment of COPD and sarcopenia.

Key words: chronic obstructive pulmonary disease; sarcopenia; risk factor

慢性阻塞性肺疾病(COPD)是临床常见呼吸系统疾病,不仅累及呼吸系统,更是一种复杂的、影响多个系统、多病共存(共病)的临床综合征,65 岁以上老年人发病率为 14%。共病是 COPD 的重要表现,往往加速 COPD 的死亡进程[1-2],其合并症之一的肌少症可显著增加跌倒发生风险,导致骨折、失能甚至死亡[3-4]。80 岁以上的老人肌少症患病率高达 50%, COPD 患者的肌肉减少使其独立性和活动能力进丧失,疾病晚期合并严重肌少[5-6]。

1 概述

在 COPD 发生发展过程中,营养消耗、慢性炎症、氧化应激是导致肺外合并症的主要原因。COPD 患者 50 岁之后每年肌力下降 1.5%~3.0%, 肌肉减少 1%~2%。研究[6-8]表明 15%~40% 的 COPD 患者合并有肌少症,尤以股四头肌萎缩最常见。股四头肌肌纤维类型和肌氧化表型转换,导致骨骼肌能量利用率和运动耐力下降,同时气道受阻, COPD 患者最终"被迫制动",以致成为患者死亡独立相关因素[9-11]。此外,胸大肌和背阔肌作为辅助吸气肌,面积和肌力在 COPD 患者中更低,出现功能障碍后加重气道阻塞。肌肉减少导致 COPD 患者住院时间延长,严重增加了社会和家庭负担,并增加了患者残疾、死亡风险[12-13]。

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2　COPD 与肌少症的危险因素

2.1　活动受限

COPD 患者通气受阻,并逐渐出现运动耐量降低,分析原因可能为: ① 生理衰老与肌纤维转换,呼吸肌收缩效率降低,呼吸做功和静息能量消耗(REE)更多[14]; ② 呼吸肌运动不良,最大吸气压和最大呼气压降低[15],活动耐力减退,机械刺激减少,肌肉逐渐萎缩; ③ 高风险患者使用激素等药物加速蛋白质分解并抑制合成,造成肌肉不断消耗。研究[16-17]发现,亚洲 COPD 患者肌少症发病率较欧美人群高约 25%。肺功能分级(GOLD)和改良呼吸困难问卷(mMRC)分级越高,患者功能受限越严重,合并肌少症者肺功能指标更差。肺康复训练可以改善 COPD 患者合并肌少症和衰弱患者的握力、步速和骨骼肌指数,这间接表明肺功能与肌少症密切相关,肺功能的改善有利于逆转肌少症的进展。

2.2　营养不良

COPD 患者呼吸做功显著增加,能量供给不足,导致骨骼肌分解以补充蛋白质和糖原。营养不良与 COPD 互为因果,相互影响。营养不良的 COPD 患者肺部过度充气,弥散功能降低,蛋白质合成代谢失衡[18], 常表现为较低的第 1 秒用力呼气量(FEV_1%)、握力和脱脂指数(FFMI),甚至发展成为恶病质,严重影响预后。欧洲呼吸学会为改善 COPD 患者的活动耐力和预后水平,提出了代谢表型和营养风险分层评估,指出对 COPD 患者进行日常营养评估及早期干预有利于提高患者的呼吸功能和延长生存时间[19]。

2.3　脂肪沉积

肌肉功能受限和肌肉质量之间呈 U 型关系,体质量增加与肌力不对等可能与脂肪沉积有关。脂质沉积是炎症因子增多的原因,并介导蛋白质分解和阻碍机体稳态重建。ROLLAND Y 等[20-21]发现肌少性肥胖与脱脂体质量(FFM)减少相关, AUYEUNG T W[22]研究证明下肢肌肉质量和 FFM 的比值、体质量与 FFM 的比值低于或超过 0.75 时,均会出现身体功能的恶化。一项关于肌少症和腹型肥胖与 COPD 关系的研究[23-24]中, 86.5%、80.6%、78% 的 COPD 患者分别表现为肌少、腹型肥胖和肌少性肥胖; 其中 COPD 正常体质量组中男性肌少合并腹型肥胖者超过 80%(女性超过 70%), 腹型肥胖患者的肺功能、炎性指标和身体表现能力均较正常组差。“肥胖悖论”即肥胖对于老年人来说虽然一定程度上抵消了肌少造成的跌倒风险,但心血管疾病风险增高。肥胖对于老年慢性病患者利弊与否,未来还需大规模的研究证实。

2.4　炎症和氧化应激

炎症浸润是 COPD 气道、血管、肺组织病理改变的原因之一。炎症介质造成肺上皮细胞的破坏和气道渗出增加,气流阻力增大; 氧化应激能溶解肺泡上皮细胞,减弱肺重建,造成炎症扩散和氧化/抗氧化的失衡,进一步加重患者的呼吸做功和静息能量消耗(REE)消耗,引起肌肉分解。研究[25-26]发现, 60% 的 COPD 患者存在高代谢状态,加重营养失衡。另一研究[27-28]发现股四头肌的耐力随血氧的降低而下降,证实了缺氧诱导骨骼肌炎症和氧化应激,组织氧化应激造成肌肉受到持续损伤,而抗氧化治疗后肌肉耐力显著提高。急性加重期入院的 COPD 患者肌肉恶化加速,表明了全身炎症是肌少症和恶病质等并发症发生的共同原因。

2.5　微生物菌群

近年来,研究[29]发现肠道微生物菌群与肺部微生物菌群具有一定同源性及分化一致性,肠与肺通过微生物、免疫功能相互影响,相互调节,称为肠-肺轴。稳定期及加重期的 COPD 患者气道中均存在高浓度细菌,健康小鼠肺泡灌洗液能够缓解肠道菌群紊乱的肺炎小鼠感染症状,暴露于烟草等毒素的小鼠在口服益生菌制剂后肺部炎症变化明显改善,同时流行病学[30-31]发现 COPD 与胃肠病互为危险因素。肠道菌群与骨骼肌构成肠-肌轴,老年人肠道屏障功能减弱,菌群丰富度下降和致病菌增加使得菌群易位、炎症扩散,造成肌肉代谢降低和分解加快[32]。

3　肌少症诊断技术的发展

肌少症筛查中 SARC-F 问卷、6 min 步行实验(6MWD)、递增穿梭步行测试(ISWT)是 COPD 患者常用的评估工具,可以评估心肺适应能力(CRF)和下肢肌肉功能,并预测死亡[33-34]。双能 X 线测量法(DXA)、生物电阻抗法(BIA)是衡量肌肉减少程度的常用方法,但 BIA 对于肌肉脂肪分布的显影不如 DXA, 对脱脂指数(FFMI)的描述精确性不足。FFMI 不仅与肺功能相关,还与 COPD 死亡率独立相关,低 FFMI 预示发病率和死

亡率的增加[35-36]。目前 B 超、CT、MRI 因为方便简易,能够较精确的测量肌肉面积和脂肪组织,在临床逐渐广泛使用。2018 年欧洲老年人肌肉减少症工作组发布的共识中指出测量第三腰椎(L3)肌肉横截面积可以作为 DXA 等诊断肌少症的替代工具。利用 CT 测量 L3 骨骼肌面积显示出超过 56% 的呼吸衰竭患者合并有肌肉减少[37]。此外,中国研究[38]使用 CT 对重症 COPD 患者测量胸 12 椎体水平背侧肌群密度(T12DMA),证实了 T12DMA 也是预测住院死亡率及长期生存率的独立危险因子。

4 COPD 合并肌少症的干预和治疗

4.1 药物治疗

针对肌少症的药物治疗方案也同样适用于 COPD 患者,如维生素 D、炎症因子拮抗剂、肌肉生长抑素抑制剂,激素类药物等被广泛推荐联合抗阻力运动改善肌肉质量和身体功能。研究[39]发现,支气管扩张药 β 受体激动剂沙丁胺醇能够增加骨骼肌肌原纤维蛋白质合成速率,福莫特罗能够调节亮氨酸代谢,从而促进人体蛋白质合成[40-41];同时茶碱在改善机械通气相关的呼吸肌疲劳的过程中作用显著,N-乙酰半胱氨酸能减缓肝病小鼠腓肠肌肌力的下降[42]。此外,血管紧张素转化酶抑制剂(ACEI)、血管紧张素Ⅱ受体拮抗剂(ARB)、二甲双胍类药物通过抗炎抗氧化、抑制纤维化作用,正在成为逆转肌肉萎缩的潜力药物[43]。尽管目前对于 COPD 合并肌少症的认识已有了重要进展,但尚未有明确的用药共识或指南,未来的研究重点将放于临床试验上,探索出适用药、通用药来改善年龄相关的、慢病相关的肌肉萎缩。

4.2 非药物干预

4.2.1 肺康复:抗阻力运动通过机械刺激促进骨骼肌肥大,减少脂肪蓄积,延缓肌肉衰减。尽管 COPD 有着相应级别的药物治疗方案,但日益进展的肺脏负担仍会导致运动耐量下降。美国胸科学会和欧洲呼吸学会推荐肺康复综合干预措施,旨在改善 COPD 患者生理和心理状况,逆转肺外表现及合并症[44]。为期至少 8 周的运动和呼吸肌训练对 COPD 患者既能提高肌肉力量,也能改善气流受限症状,并能部分逆转肌少症和衰弱,降低了再住院风险和死亡率[45]。英国、美国、澳大利亚等发达国家在采用接受过专业肺康复培训的医疗人员实施患者干预后,显著降低了医疗费用和节约了紧急医疗资源。

4.2.2 营养干预:营养支持能减轻 COPD 患者的全身炎症反应,提高肌肉合成和呼吸肌做功效能,改善肺气肿。欧洲肠外营养学会推荐慢性消耗性疾病的患者蛋白质日摄入量为 1.5 g/kg, 重症患者可达到 2.0 g/kg。老年人因为食欲、进食、消化等原因,很难通过饮食达到足够的蛋白质摄入。口服营养制剂富含碳水化合物、氨基酸、维生素、微量元素等,是调整患者营养状态的重要方法。经营养补充剂治疗的 COPD 患者在体质量、FFM、CRF、肌力等方面均有改善,全身炎症反应也得到了缓解[46-47]。

4.2.3 微生物干预:目前,肠道微生物菌群调节已被视为一种非传统的个性化干预措施。动物实验[48]证实了微生物菌群调节对于小鼠的重要性,表明微生物能够干预合成代谢以及机体内环境。COPD 急性加重通常由细菌感染引起,因此加重期患者要首先控制感染。小鼠实验[49-50]中,干预肠道菌群后肌肉萎缩标志物表达下降,活动耐力和炎症水平得到缓解。研究[51-52]发现,益生菌能够提高老年人免疫功能和活动水平,虽然目前还处于萌芽阶段,但未来可期。

5 总 结

COPD 患者更容易出现肌肉质量和力量的降低,而肌少症也会加剧肺功能的恶化。两者之间相互作用使得这一共病组合成为影响生活质量、活动能力、疾病预后的重要因素。尽管近些年对 COPD 合并肌少症已有了一定了解,但如何采取有效的治疗方法预防疾病进展,逆转功能恶化,改善预后仍是临床面临的新挑战。

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