· 综述 ·

慢性心力衰竭合并肌肉衰减综合征的研究进展

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【摘 要】 肌肉衰减综合征是一种与年龄增长相关,以进行性全身骨骼肌质量减少、肌肉强度下降和肌肉功能减退为主要特征的临床综合征。慢性心力衰竭是心血管疾病中影响患者生存率的重要疾病之一。越来越多的研究发现慢性心力衰竭可能造成或加重肌肉衰减综合征的进展,其机制涉及营养不良、运动量下降、炎症反应、氧化应激及激素变化等。目前的治疗策略主要包括运动干预、营养支持和药物治疗。本文就近年慢性心力衰竭合并肌肉衰减综合征的发病机制及治疗方案等方面的研究进展进行综述。

【关键词】 老年人;慢性心力衰竭;肌肉衰减综合征;机制

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Progress of chronic heart failure complicated with sarcopenia

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【Abstract】 Sarcopenia is an age-dependent progressive and generalised skeletal muscle disorder, mainly characterized by loss of skeletal muscle mass, reduced muscle strength, and impaired functional capacity. Chronic heart failure is one of the important diseases that affect the survival rate of patients in cardiovascular diseases. More and more evidence shows that chronic heart failure may cause or exacerbate sarcopenia, and the mechanism involved are malnutrition, decreased physical activity, inflammatory response, oxidative stress and hormonal changes. Current treatment strategies mainly include exercise intervention, nutritional support and drug therapy. This paper reviews the progress in the pathogenesis, mechanism and treatment regimens for chronic heart failure patients complicated with sarcopenia in recent years.

【Key words】 aged; chronic heart failure; sarcopenia; mechanism

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肌肉衰减综合征(肌少症)是指年龄相关的骨骼肌质量下降及功能丧失,在 60~70 岁老年人群中肌少症患病率为 5%~13%,在≥80 岁老年人群中则高达 11%~50%[1],肌少症可引起多种不良预后。据报道约有 20%慢性心力衰竭(chronic heart failure, CHF)患者合并肌少症,与不伴有肌少症的心力衰竭患者相比,该部分患者心肺功能下降、力量和平衡能力减低,预后更差[2]。目前对于 CHF 合并肌少症患者的治疗方案十分有限,本文对 CHF 合并肌少症的研究现状进行综述。

1 肌少症研究现状及筛查和诊断标准

国际上各老年肌少症工作组都推出了适用于不同人群的肌少症诊断标准(表 1)。2010 年欧洲老年肌少症工作组(European Working Group on Sarcopenia in Older People, EWGSOP)推荐了肌少症综合性定义,即肌肉质量及肌肉功能下将,特别强调了肌少症诊断应包含身体活动能力的评估,即步行速度≤0.8 m/s[3]。2018 年 EWGSOP 提出了新的肌少症诊断流程,即发现-评估-确诊-严重程度分级[4],首先

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表1 肌少症筛查和诊断标准

Table 1 Recommended criteria for sarcopenia

Item	Recommended criteria for sarcopenia
EWGSOP2010	Pre-sarcopenia: low ASMI Sarcopenia: low ASMI+low muscle strength or low physical performance Severe sarcopenia: low ASMI+low muscle strength and low physical performance Low ASMI: DXA, M<7.2 kg/m^2, F<5.6 kg/m^2; BIA, M<10.7 kg/m^2, F<6.7 kg/m^2 Low muscle strength: handgrip strength, M<30 kg, F<20 kg Low physical performance: gait speed≤0.8 m/s
EWGSOP2018	Case finding: SARC-F or clinical suspicion Probable sarcopenia:low muscle strength Sarcopenia: low muscle strength+low ASMI Severe sarcopenia: low muscle strength+low ASMI+low physical performance Low muscle strength: handgrip strength, M<27 kg, F<16 kg; 5-time chair stand test, >15 s for 5 rises Low physical performance: gait speed≤0.8 m/s Low ASMI: DXA, M<7.0 kg/m^2, F<6.0 kg/m^2
AWGS2014	Sarcopenia: low ASMI+low muscle strength and/or low physical performance Low muscle strength: handgrip strength, M<26 kg, F<18 kg Low physical performance: gait speed≤0.8 m/s Low ASMI: DXA, M<7.0 kg/m^2, F<5.4 kg/m^2; BIA, M<7.0 kg/m^2, F<5.7 kg/m^2
AWGS2019	Case finding: CC (M<34 cm, F<33 cm) or SARC-F≥4 or SARC-CalF≥11 Probable sarcopenia:low muscle strength or low physical performance Sarcopenia:low ASMI+low physical performance or low physical performance Severe sarcopenia: low ASMI+low physical performance and low physical performance Low muscle strength: handgrip strength, M<28 kg, F<18 kg Low physical performance: 5-time chair stand test≥12 s Low ASMI: DXA, M<7.0 kg/m^2, F<5.4 kg/m^2; BIA, M<7.0 kg/m^2, F<5.7 kg/m^2

EWGSOP: European Working Group on Sarcopenia in Older People; AWGS: Asian Working Group for Sarcopenia; ASMI: appendicular skeletal muscle index; DXA: dual-energy X-ray absorptiometry; M: male; F: female; BIA: bioelectrical impedance analysis; SARC-F: strength, assistance walking, rising from a chair, climbing stairs, and falls; CC: calf circumference; SARC-CalF: strength, assistance with walking, rise from a chair, climb stairs, falls and calf.

通过简易五项评分量表(strength, assistance walking, rising from a chair, climbing stairs, and falls, SARC-F)发现疑似患者,然后用握力或5次起坐时间评估肌力,最后由骨骼肌质量测定做出肌少症诊断。此外,EWGSOP2018对于握力及四肢骨骼肌指数(appendicular skeletal muscle index, ASMI)诊断界值做了调整。由于亚洲人相对于西方人在人群种族、生活方式和体力活动方面存在差异,2014年亚洲肌少症工作组(Asian Working Group for Sarcopenia, AWGS)发布了适用于亚洲人群的肌少症诊断标准,相比于EWGSOP2010,握力和ASMI的诊断界值均做了下调[5]。2019年AWGS推出最新共识,相比EWGSOP2018强调肌肉力量是首要指标,AWGS2019认为肌肉力量和躯体功能下降均是肌肉质量下降的结果,因此只要肌力或功能下降,合并肌肉质量下降即可诊断肌少症,若肌力和功能同时下降,则为严重肌少症;AWGS2019建议使用SARC-F或小腿围(calf circumference, CC)筛查肌少症[6]。

2 慢性心力衰竭合并肌少症的临床研究

CHF对于患者肌肉功能及身体成分有显著影响,这与患者的住院率及死亡率升高相关[7]。Forman等[8]对2 815例CHF患者进行了连续6年的随访,发现CHF患者骨骼肌损耗速度远高于对照组。Bekfani等[9]招募了117例射血分数保留的有临床症状的CHF患者,发现19.7%患者四肢骨骼肌质量与躯体功能明显降低。Konishi等[10]发现超过一半的CHF患者伴有肌肉质量下降,较低的骨骼肌质量与CHF患者死亡风险增加独立相关,CHF患者低骨骼肌质量会降低患者有氧运动能力[11]。Beyer等[12]研究发现在有肌少症风险的人群中,握力与左室每搏量呈正相关,提示肌肉力量与心脏肥大、心脏重塑造成的心血管不良预后有关。因此,肌少症与CHF相互影响,二者可共同导致老年患者生活质量下降,增加其致残甚至死亡风险。

3 慢性心力衰竭合并肌少症的防治

3.1 运动训练

抗阻运动可改善骨骼肌的氧化能力和心血管系统的功能,为期8周的抗阻运动干预可使骨骼肌纤维毛细血管增加约19%,肌纤维横截面积增加18%[13]。有氧运动可促使肌卫星细胞募集与活化,

对 CHF 患者进行 12 周的有氧运动干预后,发现肌纤维直径显著增加,患者运动耐量、摄氧量峰值及左室射血分数显著增加[14]。联合运动即抗阻运动、有氧运动、平衡功能运动等相结合的运动方式,对于改善肌肉力量和躯体功能的效果优于单纯抗阻运动或单纯有氧运动[15]。

3.2 营养支持

有研究发现对老年肌少症患者予以富含亮氨酸的蛋白质补充剂干预 8 周,其肌肉质量、力量和躯体机能较对照组均得到明显改善[16];β-羟基-β-甲基丁酸是亮氨酸的代谢产物,可刺激蛋白质合成,抑制蛋白质分解,减轻运动引起的肌肉损伤,增加肌肉质量和力量,增强骨骼肌有氧运动和抗疲劳能力[17]。Omega-3 多不饱和脂肪酸具有抗炎特性,对老年人握力、下肢肌肉质量和力量提高均有显著效果[18]。

3.3 药物治疗

3.3.1 CHF 标准药物治疗 血管紧张素转化酶抑制剂(angiotensin converting enzyme inhibitors, ACEI)、利尿剂、醛固酮拮抗剂及 β 受体阻滞剂的合理运用可改善 CHF 患者症状,降低死亡率和住院率。ACEI 能改善内皮功能并减轻炎症反应,改善线粒体功能,提高胰岛素样生长因子 1(insulin-like growth factors 1, IGF-1)水平,促进骨骼肌摄取葡萄糖[19]。一项研究发现氯沙坦和依那普利可改善心力衰竭患者的运动耐量和躯体功能[20];而另一老年社区研究提示 ACEI 雷米普利、依那普利、赖诺普利、喹那普利、卡托普利的使用与肌肉质量和力量、躯体功能没有明显相关[21]。有报道称卡维地洛可延缓 CHF 患者恶病质进展,可能与其延长交感神经激活、促进体质量增加有关[22];长期服用美托洛尔长效制剂和卡维地洛可能通过降低体内儿茶酚胺类激素水平、改善血流动力学来增加体质量、部分逆转肌肉质量下降[23]。醛固酮拮抗剂可抑制骨骼肌细胞凋亡,改善血管内皮功能,增强肌肉收缩力[24]。尽管目前基础和临床研究发现 CHF 一线治疗药物对于骨骼肌质量、力量及躯体功能可能有益,但是不同的临床研究结果不一致,仍然需要进一步的研究比较各自抗心力衰竭标准治疗的获益,寻找最优的治疗策略。

3.3.2 激素治疗 (1)睾酮。男性 CHF 患者体内低睾酮水平可能与心肌损伤、运动能力下降和较高的死亡率相关。二氢睾酮可增强氨基酸转运蛋白的表达能力并增加骨骼肌纤维内蛋白质合成[25],但是在 CHF 患者生理范围内补充睾酮与改善运动能力、左室射血分数、生活质量等无显著相关。在接受睾酮补充治疗的男性 CHF 患者中,只有终点平均总睾酮 ≥ 25 nmol/L 的患者在治疗后表现出补充睾酮与运动能力提高相关[26]。(2)生长激素(growth hormone, GH)。生长激素/胰岛素样生长因子 1 轴(growth hormone/insulin-like growth factor 1 axis, GH/IGF-1 axis)是体内合成蛋白质的重要通路之一,虽然 GH 可以增加四肢骨骼肌质量,但是 CHF 患者予以 GH 或 IGF-1 干预并不能明显改善临床症状[27]。最近一项对 5 例伴有生长激素、睾酮缺乏并且射血分数降低的心力衰竭患者的研究发现,在 1 年的生长激素皮下注射治疗后,患者左室射血分数显著改善,N 末端 B 型钠尿肽前体水平显著下降;接受生长激素和睾酮联合替代治疗的患者最大摄氧量峰值和肌肉力量显著上升[28]。(3)肌肉生长抑制素。又称生长分化因子 8(growth differentiation factor-8, GDF-8),在女性 CHF 患者体内 GDF-8 信号传导通路增强,可能与肌少症的骨骼肌质量下降有关[29]。比马鲁人单抗与 GDF-8 竞争性结合受体,且亲和力更强,在老年肌少症患者中,通过静脉注射比马鲁人单抗能增加老年患者的肌肉质量和肌肉强度,并改善患者的活动能力[30]。

4 问题与展望

目前,对于慢性心力衰竭合并肌少症患者的筛查、诊断及治疗尚未得到足够的重视,其发生发展机制尚未完全阐明。尽管有研究显示运动训练联合营养支持有助于改善骨骼肌质量与功能,但截至目前仍缺乏公认有效的治疗方案,缺乏有效的临床证据,因此迫切需要进一步的深入研究。

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