# 抗阻训练对慢性心力衰竭合并肌少症的影响及相关机制研究进展

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【摘要】肌少症是一种与增龄相关的老年综合征,以进行性骨骼肌含量、肌力下降及功能障碍为主要特征。慢性心力衰竭是各类心血管疾病进展的晚期阶段,其症状与骨骼肌功能降低和骨骼肌细胞变化有关,与肌少症的发生发展密切相关。运动干预是治疗肌少症的重要手段。其中抗阻训练与降低慢性心力衰竭患者再住院率和改善其生活质量密切相关。现对慢性心力衰竭合并肌少症的发病机制以及抗阻训练对其影响及相关机制进行综述,以期为慢性心力衰竭合并肌少症患者的临床诊疗提供科学依据。

【关键词】肌少症;慢性心力衰竭;抗阻训练
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# Effect and Related Mechanisms of Resistance Training on Chronic Heart Failure Complicated with Sarcopenia

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【**Abstract**】Sarcopenia is a kind of senile syndrome related to aging, which is characterized by progressive decline in skeletal muscle volume and muscle strength and dysfunction. Chronic heart failure (CHF) is the terminal manifestation of various cardiovascular diseases. Its symptoms are related to the decline of skeletal muscle function and changes in skeletal muscle cell, and are closely related to the occurrence and development of sarcopenia. Exercise intervention is an important means of treating sarcopenia. Among them, resistance training is closely related to reducing the readmission rate and improving the life quality of CHF patients. This article reviews the pathogenesis of CHF complicated with sarcopenia, the effect of resistance training on it and related mechanisms, in order to provide scientific basis for clinical diagnosis and treatment of CHF patients with sarcopenia.

【**Key words**】Sarcopenia; Chronic heart failure; Resistance training

肌少症是一种与年龄相关的老年综合征,以进行性骨骼肌含量、肌力下降及功能障碍为特征,可严重影响老年人生活质量,给社会和家庭带来沉重负担。采用亚洲肌少症工作组诊断标准,肌少症在普通老年人群中的患病率约为 10%。慢性心力衰竭(chronic heart failure, CHF)是各类心血管疾病进展的晚期阶段,常表现为体力下降、乏力及呼吸困难等。这些症状不仅与心脏泵血功能受损、血流动力学异常和心肌细胞凋亡有关,还与骨骼肌功能降低和骨骼肌细胞变化有关,与肌少症的发生发展密切相关。一项关于心力衰竭合并症的研究(SICA-HF 研究)[1]结果显示,CHF 患者的肌少症患病率比健康老年人高出近 20%。CHF 可导致肌少症患者跌倒、骨质疏松及衰弱,最终可能发展为心脏恶病质,升高再住院率和死亡率。虽然尚无 CHF 合并肌少症的特效治疗方法,但近来多项研究表明,抗阻训练(resistance training, RT)可显著提高患者的肌力和肌肉量。现对 CHF 合并肌少症的发病机制以及 RT 对其影响及相关机制进行综述,以期为 CHF 合并肌少症患者的临床诊疗提供科学依据。

## 1 CHF 合并肌少症的发病机制

肌少症为 CHF 常见并发症之一,有研究[2]表明,CHF 可通过多种病理生理机制促进肌少症的发生发展,包括体力活动减少、营养不良、慢性炎症、泛素-蛋白酶体系统通路过度激活、雄激素水平低下、肾素-血管紧张素系统异常激活以及药物等。

### 1.1 营养不良

CHF 患者处于能量负平衡状态,导致蛋白质-能量营养不良症[3-4]。食欲减退是 CHF 患者的常见表现,与肌肉量和肌力下降独立相关[5]。CHF 患者胃肠道淤血,可引起食欲不振、腹胀、恶心、呕吐和便秘等消

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化道症状，最终造成厌食和营养吸收不良[6]。此外，一些治疗 CHF 的药物，如地高辛，也是厌食的潜在原因[7]。

### 1.2 缺乏体力活动

CHF 患者由于缺乏体力活动甚至长期卧床，影响哺乳动物雷帕霉素靶蛋白（mammalian target of rapamycin，mTOR）信号转导及氨基酸转运蛋白的表达，导致骨骼肌蛋白质合成减少[8-9]，进而引起骨骼肌萎缩及功能下降。长期卧床也会降低老年患者的胰岛素敏感性，进一步对骨骼肌代谢稳态产生不良影响[10]。

### 1.3 肌肉血流量低

CHF 患者心输出量减少可导致骨骼肌血流量下降，进而影响肌力与肌肉量。对于 CHF 患者，运动会加重组织缺血，促进乳酸堆积。CHF 患者容易出现内皮功能障碍，表现为前臂及下肢的基线和峰值反应性充血时血流量低下，这是肌少症的重要发病机制[11]。

### 1.4 炎症反应

CHF 患者常伴有慢性低水平全身炎症反应，炎症标志物如肿瘤坏死因子-α、C 反应蛋白和白细胞介素-6 水平的升高与肌肉量和肌力的下降相关，其释放到血液循环后将进一步激活全身炎症反应，对骨骼肌产生持续负面影响，导致肌肉萎缩[12]。此外，肌少症性肥胖可促进促炎细胞因子的释放，而促炎细胞因子也会对肌肉量和肌力产生负面影响[13]。

### 1.5 激素变化

在 CHF 患者体内合成分解代谢失衡，胰岛素样生长因子-1（insulin-like growth factor-1，IGF-1）和生长激素等促进合成代谢的激素水平下降将造成患者机体功能下降和肌少症[14-15]。CHF 患者血浆血管紧张素Ⅱ水平在神经内分泌激活的代偿机制下升高，其通过影响 IGF-1 信号转导，加速细胞凋亡，促进骨骼肌蛋白分解以及抑制食欲，最终导致肌肉流失。睾酮与雄激素受体结合，通过促分裂原活化的蛋白激酶途径促进蛋白质转录，促进肌肉蛋白质合成，而 CHF 患者睾酮水平低下，可引起肌肉量减少和功能障碍。肌肉生长抑制素（myostatin，MSTN）属于转化生长因子-β 家族，是骨骼肌生长发育的负调控因子。研究已证实，CHF 患者 MSTN 水平明显升高。此外，CHF 患者胃饥饿素水平下降，胃饥饿素是一种调节食欲、促进食物摄入和生长激素释放的肽类物质，其水平降低与老年 CHF 患者肌少症的发生相关。

### 1.6 泛素-蛋白酶体系统激活

CHF 患者骨骼肌萎缩可表现为肌原纤维蛋白水平失衡，即蛋白质降解的增加。泛素-蛋白酶体系统是蛋白质降解的重要途径，降解过程由一组 E3 泛素连接酶完成，包括 Atrogin-1 和肌肉环指蛋白-1，是骨骼肌蛋白降解过程中的重要调控因子，它们在 MSTN/转化生长因子-β 信号通路的作用下被诱导，在肌少症的发生发展中起关键作用[16]。

## 2 RT 对 CHF 合并肌少症的影响

CHF 合并肌少症尚无针对性治疗手段或药物，也缺乏规范的临床诊疗指南或共识。目前，运动结合营养干预是治疗肌少症最有效的方法[17]。针对 CHF 合并肌少症患者 RT 的临床试验较少，但既往研究已证实 RT 可增强 CHF 患者肌力和肌肉耐力，同时也可改善肌肉对氧气的吸收和利用能力，提高患者日常生活能力及生活质量。

### 2.1 肌力

Groennebaek 等[18]对 36 例 CHF 患者在 RT 干预前后进行了肌力测试和肌肉活检，评估肌肉纤维形态和线粒体呼吸功能变化。该研究结果显示，与对照组相比，RT 使最大等长肌力增加了 29.7 Nm（95% *CI* 10.8 ~ 48.6，$P$ = 0.003）、线粒体功能每毫克增加 19.1 pmol/s（95% *CI* 7.3 ~ 30.8，$P$ = 0.002），因此，RT 可提高 CHF 患者肌力，改善肌肉线粒体功能。Fisher 等[19]将 17 项 CHF 患者进行 RT 和有氧运动（aerobic exercise，AE）干预的研究进行了荟萃分析，与 AE 组相比，RT 增强了下肢［SMD 0.76（95% *CI* 0.26 ~ 1.25），$P$ = 0.003］和上肢肌力［SMD 0.85（95% *CI* 0.35 ~ 1.35），$P$ = 0.000 9］。因此，RT 为防治 CHF 患者肌力丢失的有效手段。

### 2.2 肌肉耐力

肌肉耐力是指肌肉在重复运动或阻力负荷下抵抗持久性的能力。Selig 等[20]对 39 例 CHF 患者进行了观察，对膝关节与肘关节间断 RT 后（每周 3 次，持续 12 周），伸肌和屈肌的肌肉耐力提高了 21% ±21%（$P$ <0.01）。针对 CHF 患者，6 分钟步行试验是一种简便、安全的运动耐量评估方案，Pu 等[21]对 16 例老年 CHF 女性患者与 80 例同龄健康女性人群进行比较，患有 CHF 的女性患者肌力明显较低（$P$ < 0.000 1）。该研究对受试者随机进行 10 周的 RT 或对照拉伸运动，RT 组患者肌肉耐力平均提高 299% ± 66%，对照组提高 1% ± 3%（$P$ = 0.001），6 分钟步行试验距离平均增加（49 ± 14）m（提高 13%），对照组为（-3 ± 19）m（降低 3%）（$P$ = 0.03）。

### 2.3 有氧代谢能力

峰值摄氧量可反映人体最大有氧代谢能力以及肌肉对氧气的吸收和利用能力。Munch 等[22]观察到 6 周RT 可提高 CHF 患者的峰值摄氧量（0.15 L/min）

和峰值功率(11 W),并且 RT 所需的时间和能量消耗比 AE 组更少,表明 RT 是一种具有时效性的运动模式,有利于提高纽约心功能分级Ⅰ~Ⅱ级的 CHF 患者对运动的依从性。

### 2.4 日常生活能力与生活质量

AE 通常不会改变肌力,因此不能纠正与肌少症相关的身体残疾。多项研究[23-24]已证实,RT 后 CHF 患者的日常生活能力有所提高,有助于减少身体残疾的发生;临床工作中常使用明尼苏达心力衰竭生活质量问卷(Minnesota Living with Heart Failure Questionnaire,MLHFQ)评估心力衰竭患者健康相关生活质量,MLHFQ 分值与生活质量呈负相关。Sadek 等[25]研究观察到,3 个月 RT 后,CHF 患者 MLHFQ 评分显著降低(降低 30%,$P<0.05$)。

### 2.5 心脏结构功能

RT 可改善 CHF 患者各项心脏结构功能参数,证实了 RT 的安全性。Palevo 等[26]对纽约心功能分级Ⅱ~Ⅲ级的 CHF 患者进行 24 次 RT 后(每周 3 次,8 周),患者左室射血分数(0.32~0.37)和每搏输出量(46~53 mL/次)较对照组改善更明显($P<0.05$)。此外,动物实验结果表明,RT 能改善 CHF 大鼠的室内压上升支最大变化速率($+dp/dt_{max}$)与室内压下降支最大变化速率($-dp/dt_{max}$)(分别为 33% 和 29%),且不会导致左心室收缩功能和结构的恶化[27-28],不会对血流动力学造成不利影响[29]。2014 年美国的一项研究[30]对 CHF 大鼠进行 8 周的 RT 后观察到,RT 能改善 CHF 大鼠的血流动力学和肺水肿,右心室代偿性肥大减轻 28%($r=0.41$,$P=0.01$)。

## 3 RT 改善 CHF 合并肌少症的机制

RT 改善 CHF 合并肌少症患者的机制尚未得出确切结论。Gielen 等[31]发现,RT 后 CHF 患者肌肉环指蛋白-1 水平降低,这表明它阻断了泛素-蛋白酶体系统的激活,减少骨骼肌蛋白降解。Lenk 等[32]观察到,与健康人群相比,CHF 患者骨骼肌中的肌肉生长抑制素信使 RNA 增加了 2 倍($P=0.05$),肌肉生长抑制素蛋白含量增加了 1.7 倍($P=0.01$)。在进行 12 周 RT 后,肌肉生长抑制素信使 RNA 减少 36%,肌肉生长抑制素蛋白减少 23%。其他可能的机制还包括:RT 可通过激活 mTOR/自噬激活激酶 1、PI3K/Akt/mTOR 以及 IGF-1/PI3K/Akt/mTOR 等信号通路,提高肌肉耗氧量、增加毛细血管数量、促进骨骼肌蛋白质合成、提高骨骼肌质量及功能[33-34],RT 可刺激过氧化物酶体增殖物激活受体 γ 辅激活因子 1α 的表达,过氧化物酶体增殖物激活受体 γ 辅激活因子 1α 参与调节控制线粒体生物发生和负责肌肉形态和生理功能的信号通路,保护肌肉免受炎症反应、氧化损伤、细胞自噬与凋亡、肌肉蛋白水解等破坏及降解机制的影响[35]。RT 还可通过调节自噬标记蛋白 LC3-Ⅱ/LC3-Ⅰ比值、Beclin1、自噬相关基因 5/7/12 及其蛋白,抑制骨骼肌细胞自噬,改善增龄所致的肌肉量减少与功能障碍[36-37]。RT 可通过线粒体基因 NDUFB6 或过氧化物酶体增殖物激活受体等信号通路,以及上调 p53 蛋白表达,提高骨骼肌线粒体含量及其氧化能力,进而改善胰岛素抵抗,促进 CHF 患者肌肉蛋白质的合成[38]。此外,RT 还可通过减少氧化应激、抑制炎症反应、升高 IGF-1/MSTN 比值等,改善 CHF 患者骨骼肌结构与功能[39]。

## 4 CHF 合并肌少症患者的 RT 治疗方案

RT 是外周骨骼肌在克服阻力时进行的主动运动。由亚洲肌少症工作组发布的《肌少症诊断及治疗共识》(2019 更新版)[40]提出:RT 能显著提高肌少症患者骨骼肌含量与功能,有助于维持身体机能,减轻肌少症对患者生活的影响,改善患者预后。《慢性心力衰竭心脏康复中国专家共识》(2020 年版)[41]指出,心脏康复是贯穿 CHF 患者全生命周期的综合性医疗措施,其 5 大处方包括:药物处方、运动处方、营养处方、戒烟处方和心理处方等,其中,运动处方是 CHF 患者心脏康复的核心要素,如无禁忌证,应根据肌力测试结果,个体化制定 RT 处方,包括强度、频率、持续时间、方式、进展以及注意事项。RT 种类多样,包括:自身抗重力、哑铃、RT 器械、沙袋、弹力带和弹力管等。因 CHF 合并肌少症患者的肌力、肌肉量下降,建议其早期选择弹力带、小哑铃或抬腿等克服自身体重的训练。每周对每个肌群进行 2~3 次 RT(2 次锻炼至少间隔 48 h),以提高患者各肌群的肌力与耐力。每次训练 8~10 个肌群,每组 10~15 次,目标为每个肌群训练 1~3 组,组间休息 2~3 min。

对于急性冠脉综合征早期、恶性心律失常、血压未控制、急性全身性疾病、空腹血糖 >16.7 mmol/L、血糖波动较大等情况下不建议进行 RT。CHF 合并肌少症患者多为中老年人,基础疾病多,身体情况较差。运动过程中,应由专业心脏康复团队人员全程陪护和指导,运动过程中严密监测患者的血压、心率和心电图动态变化,以保障 RT 的安全性及疗效。

## 5 总结与展望

受性别、年龄和种族的影响,肌少症尚无统一诊断标准。而 CHF 作为心血管领域最常见的一类临床综合征,其发病率长期处于上升趋势。CHF 合并肌少症的患者日益增多,目前虽无针对性治疗措施,但越来越多研究发现 RT 可通过各种分子机制促进骨骼肌

蛋白合成,提高肌肉质量及功能。在临床工作中,可通过心肺运动试验等方式评估患者具体病情,制定个体化的 RT 治疗方案,有效延缓 CHF 患者肌少症的进展,改善患者预后。

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