

冠心病合并糖尿病PCI术后不同心脏运动康复机制的研究进展

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摘 要

冠心病和糖尿病常常相互伴随, 且两者共存时, 患者的心血管事件风险显著增加。经皮冠状动脉介入术(PCI)是冠心病的主要治疗手段之一, 但术后患者存在因合并糖尿病心脏功能恢复以及生活质量改善不及预期。心脏康复, 尤其是运动康复可显著改善冠心病合并糖尿病PCI术后患者的预后。本文综述了冠心病合并糖尿病患者在PCI术后不同心脏运动康复的机制研究进展, 以期为临床康复治疗提供参考依据。

关键词

冠心病, 糖尿病, 经皮冠状动脉介入术, 运动康复, 机制研究

Research Progress on Different Cardiac Exercises' Rehabilitation Mechanisms in Patients with Coronary Heart Disease and Diabetes Mellitus after PCI

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Abstract

Coronary Heart Disease (CHD) and Diabetes Mellitus (DM) are often associated with each other, and their coexistence significantly increases the risk of cardiovascular events. Percutaneous Coronary Intervention (PCI) is one of the main treatment methods for coronary heart disease, but the recovery of cardiac function and the improvement of quality of life in patients with diabetes mellitus after PCI are not as expected. Cardiac rehabilitation, especially exercise rehabilitation, can significantly improve the prognosis of patients with coronary heart disease and diabetes after PCI. In this paper, we reviewed the research progress on the mechanism of cardiac exercise rehabilitation in patients with coronary heart disease and diabetes mellitus after PCI, in order to provide reference for clinical rehabilitation treatment.

Keywords

Coronary Heart Disease, Diabetes Mellitus, Percutaneous Coronary Intervention, Exercise Rehabilitation, Mechanism Study

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1. 引言

冠心病是由于冠状动脉粥样硬化导致血管阻塞以及冠状动脉的功能改变, 最终引起心肌缺血、缺氧[1]。冠心病是如今对人类健康造成严重威胁的疾病之一, 近年来其发病率和死亡率仍在不断上升[2]。糖尿病是一种慢性内分泌和代谢性疾病, 主要表现为胰岛素缺乏和(或)胰岛素抵抗, 糖尿病已经成为一个全球范围内的重大公共健康问题[3]。约 90%的糖尿病患者为 2 型糖尿病(T2DM), 多发于成人, 患病率高[4]。目前糖尿病对于中国的医疗卫生体系和社会来说仍是一个沉重的负担[5]。冠心病和糖尿病二者之间存在复杂的病理生理联系, 具有共同的危险因素, 例如肥胖、炎症、氧化应激、胰岛素抵抗等因素[6]。当这两种疾病共存时, 将进一步加速组织和器官的损伤, 导致死亡率和残疾率增加[7]。PCI 术已被广泛应用于冠心病患者的血运重建, 但术后患者常因合并糖尿病而增加支架再狭窄及死亡的风险[8]。心脏运动康复是心脏康复的核心组成部分, 能够有效改善 PCI 术后患者的心肺功能、减少心血管事件发生率[9]。不同的运动康复策略及其生理机制在冠心病合并糖尿病患者中的应用日益受到关注。

2. 糖尿病合并冠心病的发病机制

长期以来, 糖尿病一直被认为是心血管疾病(CVD)的危险因素, 导致 CVD 发病和死亡风险升高[10]。

糖尿病合并冠心病的患者血液中高糖环境和游离脂肪酸可导致血管炎症[11], 进一步损伤内皮细胞, 进而加重共病患者动脉粥样硬化。Yang [12]等采用代谢组学方法通过血脂代谢物诊断 2 型糖尿病, 表明了机体脂代谢与 2 型糖尿病的相关性。脂质代谢紊乱可致胰岛素抵抗, 与糖尿病和冠状动脉疾病(CAD)密切相关[13][14]。目前, 主要有脂质超载和炎症两种观点, 胰岛素抵抗进而会引起胰岛素分泌增加, 最终导致脂质沉积在血管壁加重动脉粥样硬化。2004 年, Ceriello 教授在欧洲糖尿病研究学会(EASD)年会上提出共同土壤学说, 即氧化应激是胰岛素抵抗、糖尿病和 CVD 的共同发病基础。同时多项研究表明, 氧化应激是糖尿病及冠心病发生和发展的关键因素[15]-[18], 也是心血管事件的独立预后因子[19]。此外,

众多研究表明基因多态性在糖尿病合并冠心病患者疾病发生发展进程中均起到了特定的作用。有团队通过对脂联素受体 1(由 ADIPOR1 编码)的多态性研究发现, 糖尿病、冠心病及糖尿病合并冠心病患者风险等位基因的累积, 其可能导致疾病易感性增加[20]。Aghasizadeh [21]等研究发现血管生成素样 3(ANGPTL3)基因的单倍型与 CVD 风险、糖尿病、和血脂异常有关, 有助于识别对这些疾病具有遗传易感性的个体。

3. 冠心病合并糖尿病患者心脏运动康复的特殊性

冠心病合并糖尿病患者由于其代谢紊乱和炎症反应的特点, 对运动康复的反应可能与单纯冠心病患者有所不同:

(1) 血糖波动的影响: 糖尿病患者在运动过程中血糖波动, 容易发生低血糖反应[22]。有研究表明发生低血糖是 2 型糖尿病患者预后不良的标志[23]。Pieber [24]等的研究显示严重低血糖与全因死亡率之间存在显著关联, 并且发生过严重低血糖的患者在低血糖发作后发生主要大血管事件及短期死亡的风险更大。低血糖会激活交感肾上腺系统使交感神经兴奋, 导致心率、收缩压、心输出量和射血分数迅速增加, 中心收缩压因大血管弹性增加而下降[25], 这可能对心脏康复的安全性产生影响。个体化的心脏运动康复并不会增加运动过程中低血糖反应发生的风险, 还能减少夜间低血糖的发生[26]。

(2) 心血管自主神经病变的影响: 无论是冠心病与 2 型糖尿病共病的患者, 还是单纯罹患冠心病或者 2 型糖尿病的患者个体, 其心率变异性(HRV)各项指标的水平相较于健康对照组而言, 均呈现出明显降低的态势。其中, 冠心病合并 2 型糖尿病患者的 HRV 降低更为显著, 这一现象表明冠心病合并 2 型糖尿病患者的自主神经功能受损程度最为严重[27], 可能会影响心脏运动康复的耐受性和效果。

4. 心脏运动康复的基本机制

4.1. 心脏运动康复改善心功能

(1) 改善血管内皮功能: 在运动训练干预中, 一氧化氮生物利用率的提高、内皮祖细胞(EPCs)的增加和氧化应激的减少是预防冠心病内皮功能障碍以及降低心血管事件风险的主要因素。此外, 内皮依赖性超极化因子的保护和炎症抑制也发挥了作用[9]。Lee [28]等人的研究显示 2 型糖尿病的患者即使进行较低强度的运动也对内皮功能有生理学意义的影响。Ma [29]等的研究表明运动训练可以降低 2 型糖尿病患者 10 年动脉粥样硬化心血管疾病风险。14 项前瞻性研究的荟萃分析表明运动康复可改善血管内皮功能, 从而降低心血管事件发病率, 对心血管健康有显著影响[30]。维持 3 个月运动对减少心血管事件的有益效果将会持续至少 24 个月[31]。最新研究表明剪切应力 OSS 可以通过激活 STING 通路在体内和体外促进内皮功能障碍和动脉粥样硬化生成[32]。而运动改善内皮功能的生理机制就是由于反复灌注导致血管壁产生更高的剪切应力[33]。

(2) 调节代谢状态: 运动可提高胰岛素敏感性, 降低血糖水平, 同时改善脂质代谢, 这对于合并糖尿病的患者尤为重要。力量训练可以增加 GLUT4、胰岛素受体、蛋白激酶 B- α/β 、糖原合成酶 GS 的蛋白质含量和糖原合酶的总活性[34]。Zhao [35]等认为定期运动训练对患有糖尿病的成年人的胰岛素敏感性有显著益处。Way [36]等的研究表明, 运动改善胰岛素敏感性的效果可以在最后一次运动后持续 72 小时以上。Chorell [37]等人的研究显示运动时骨骼肌脂质利用率的提高可能会防止干扰胰岛素信号传导部位的特定脂质堆积。

(3) 抗炎和抗氧化作用: 动脉粥样硬化被认为是一种炎症性疾病, 因为低度炎症参与了从内皮功能障碍直至成熟斑块的形成、破裂以及最终发生急性血栓并发症的所有过程[38] [39]。Halvorsen [40]等的研究表明与健康对照相比, CAD 患者外周血单核细胞(PBMC)中的 NAMPT 水平升高, NAMPT 表达与 CAD

患者 PBMC 中的炎症标志物和氧化还原调节相关, 表明炎症在动脉硬化的发病机制中可能起重要作用。炎性细胞因子刺激血管平滑肌细胞局部产生 C 反应蛋白(CRP)。CRP 在促进血管炎症和降低内皮功能方面具有积极作用[41]-[43]。最近的研究表明, 高敏(hs)CRP 与动脉硬化之间也有着紧密联系[44]-[46]。而氧化应激作用于动脉硬化的发病机制, 可能导致血管炎症和平滑肌细胞增殖, 从而导致动脉弹性受损并加重心脏的炎症状态[38]。Cicek [47]等通过对 45 名超重和肥胖女性的随机对照试验发现运动训练会升高血浆抗炎蛋白五聚蛋白 3 (PTX3)浓度, 而 PTX3 与 hsCRP 之间存在显著的负相关。Tang [48]等发现与体重较轻的糖尿病小鼠相比, 接受有氧运动训练的糖尿病小鼠肾线粒体的线粒体超氧化物生产明显减少。运动康复可通过降低炎症标志物和氧化应激水平, 减缓动脉粥样硬化的进展。研究表明, 有氧运动通过激活 FGF21/FGFR1/PI3K/AKT 通路或抑制心磷脂酰基转移酶 1(ALCAT1)的高表达, 从而显著促进小鼠心脏内成纤维细胞生长因子(FGF21)的表达水平提升, 进而有效缓解氧化应激损伤, 改善心肌梗死后小鼠的心室重构[49]。

(4) 改善自主神经功能: 冠状动脉病变的进展与心肌缺血缺氧状况的恶化, 会导致交感神经与副交感神经的调控失衡, 干扰神经系统的正常运作, 使得 HRV 出现下降。冠状动脉病变会触发一系列炎性因子与神经因子的释放, 进而增强交感神经张力, 对 HRV 产生负面作用[50]。在心血管疾病的病情评估及不良预后预测中, 心率变异性占据着关键地位[51]。运动能够增强副交感神经张力, 降低交感神经活动, 从而改善心率变异性, 有助于心脏功能的恢复[52]。运动后心率恢复的速度是心脏迷走神经活性的可靠指标, 它与人类的运动能力、心血管疾病发病率和全因死亡率密切相关[53]。

4.2. 心脏运动康复减少 PCI 术后冠状动脉再狭窄

使用药物洗脱支架(DES)的 PCI 术是冠心病患者血运重建的成熟治疗选择[8], 然而 PCI 术后存在支架内再狭窄的风险, 在 2 年随访过程中, 3.9%~5.8%的患者会出现这种情况。Lee [54]等通过运动干预 74 名接受 DES 的急性心肌梗死患者, 并在 9 个月后进行血管造影随访, 最终发现定期运动训练可显著减少急性心肌梗死患者冠状动脉段支架的晚期管腔损失。Taraldsen [55]等研究发现接受 DES 的患者通过 3 个月的有氧运动后, 远端支架边缘的斑块负荷和坏死核心含量均有所减少, 其中有氧间歇训练组的减少幅度更大, 可以显著减少 PCI 术后冠状动脉再狭窄的风险。内皮功能和炎症反应的改善可能是运动减少冠状动脉再狭窄的原因之一[56]。

4.3. 心脏运动康复改善 PCI 术后患者焦虑抑郁情绪及生活质量

Van Dijk [57]等通过 10 年随访发现, 抑郁和焦虑使 PCI 术后患者 10 年死亡风险分别升高 77%和 50%, 并认为抑郁症是 PCI 术后全因死亡率的独立预测因素。Anderson [58]等的荟萃分析表明基于运动的 心脏康复治疗可以改善健康相关的生活质量(HRQoL)。HRQoL 是 PCI 术的关键结果指标, 而影响 HRQoL 的显著社会心理特征包括焦虑和抑郁。Zheng [59]等发现心脏运动康复训练不仅能改善 PCI 术后冠心病患者的心脏功能, 还能其减少焦虑和抑郁的程度。Aditi [60]等研究发现瑜伽可通过提高重度抑郁症患者血清中的脑源性神经营养因子(BDNF)进而改善其低落情绪。不过, 心脏运动康复改善 PCI 术后患者的焦虑抑郁情绪的具体机制仍不详, 亟待进一步研究。

5. 不同运动康复模式的改善心功能的机制和应用效果

目前针对冠心病合并糖尿病患者的运动康复主要包括有氧运动、抗阻运动和高强度间歇训练(High-Intensity Interval Training, HIIT)等不同模式:

(1) 有氧运动: 如步行、慢跑、八段锦、太极拳等, 能够促进心肺系统的血液循环, 加强心肺功能, 并从多方面改善机体糖代谢。此外, 有氧运动时肌肉对氧气的利用增加可促进葡萄糖的氧化分解, 并且

可以改善胰岛素敏感性, 增加肌肉对葡萄糖的吸收和利用, 进一步降低机体血糖水平[37]。中等强度的有氧运动能够降低 PCI 术后心血管事件的发生率, 其通过改变心血管疾病危险因素进而降低心血管不良事件的发生风险[61] [62]。有氧运动可能通过 NGF-TrkA-NET 信号转导途径改善心脏交感神经活性, 从而逆转心脏重塑并提升有氧能力和峰值摄氧量, 改善心功能[63]。

(2) 抗阻运动: 抗阻运动是使用肌肉力量抵抗阻力负荷的一种无氧运动, 通过激活 PI3K/Akt 通路促进 GLUT4 的表达和转位, 提高骨骼肌细胞支链氨基酸的转运及分解代谢, 增强胰岛素敏感性, 增加胰岛素对葡萄糖的转运能力, 进而改善血糖代谢[64]-[66]。对糖尿病患者, 抗阻运动与有氧运动结合的综合训练效果较为显著。为期 9 周的阻力运动训练可使收缩压和舒张压改善 4~8 mmHg, 同时血管内皮功能和总外周阻力得到改善, 而不会影响中枢动脉僵硬或心血管功能[67]。一项荟萃分析表明抗阻运动可以改善 PCI 术后患者的体力活动、心脏功能和生活质量[68]。在超过 12 周的运动方案中, 抗阻运动似乎在促进最大耗氧量的增加方面比有氧运动更有效[69]。抗阻运动同时也能够有效改善脂质代谢。有研究表明其可减少肝脏中脂质堆积, 肝脏中与脂质产生和炎症基因相关的 mRNA 表达降低, 脂肪酸氧化基因的 mRNA 增加[70]。抗阻运动可以使原本在骨骼肌中低表达的 FGF21 表达增加, FGF21 能诱导 Akt 磷酸化, 激活 PI3K/Akt 通路, 抑制肝脏葡萄糖产生, 降低血糖水平并提高胰岛素敏感性, FGF21 还能增强脂肪酸氧化, 促进骨骼肌对脂肪酸的利用[66]。抗阻运动刺激骨骼肌卵泡抑素样蛋白 1 (FSTL1) 的分泌, 促进心肌梗死大鼠心肌血管生成, 抑制病理重塑, 保护心功能[71]。还有研究表明抗阻运动提高了 Fndc5 mRNA 水平, 抑制了 TGF β 1-TGF β R2-Smad2/3 通路的激活, 激活了 AMPK-Sirt1 通路, 降低了梗死心脏的氧化应激、细胞凋亡和心肌纤维化水平, 促进了心脏功能[72]。

(3) 高强度间歇训练(HIIT): 近年来, HIIT 在心脏康复中的应用逐渐增多。Jiang [73]等通过对 60 名 PCI 术后患者的研究, 发现高强度间歇有氧运动能显著改善 PCI 术后患者的 6 分钟步行试验结果和运动耐量。Wormgoor [74]等的研究表明 HIIT 对于男性 2 型糖尿病患者的血糖控制、心脏代谢风险和微血管并发症标志物均有积极效果。Poon [75]等研究发现 HIIT 可以降低肥胖中年男性的心血管疾病发病风险。Ryan [76]等在 12 周的 HIIT 后, 发现其能在运动后第二天快速提高胰岛素敏感性。HIIT 可降低心血管患者血压, 改善胰岛素敏感性, 改善脂质代谢, 改善内皮功能, 逆转心室重构等[77]。患者在无监督的情况下往往很难长期坚持锻炼[56], 而 HIIT 持续 12 周就有显著成效[78], 使患者用更少的精力获益更多, 且更有可能继续坚持锻炼。更重要的是, HIIT 在运动训练强度的增加, 心肺耐力的改善幅度增加的同时, HIIT 还能够降低全因死亡率[79]。此外, Zhang [80]等的荟萃分析发现定期进行 HIIT 可大幅度减少支架冠状动脉段晚期管腔损失, 可大大减少支架再狭窄的风险, 这与患者心肺及内皮功能的改善和炎症的减轻有关。

6. 未来研究方向与挑战

目前的文献表明, 冠状动脉介入治疗后导致的动脉功能障碍在术后 4~12 周恢复[81] [82]。因此, 我们建议 CAD 患者在 PCI 术后 2~4 周内开始运动训练计划并且运动开始的时间应考虑患者的个体特征(年龄、疾病严重程度、合并症)以及运动处方的强度、频率和持续时间[83]。虽然心脏康复有益于冠心病合并糖尿病的 PCI 术后患者, 但目前心脏康复依从性仍较低[84]。Zhu [85]等将是否完成运动处方的一半的心血管疾病患者分组, 发现运动处方的实施率与心血管事件的发生有显著影响, 运动处方的高实施率组与较低的心血管事件相关。因此患者对于心脏运动康复方案的依从性也决定了其预后, 我们可以通过健康教育、家人监督和电子监测设备努力提高患者完成运动处方的比例。此外, 患者术后的焦虑抑郁情绪也会导致心脏康复的依从性低, 导致预后不佳, 临床医生除了关注疾病本身也要专注患者的心理健康。

7. 结论

冠心病合并糖尿病 PCI 术后患者的运动康复具有显著的临床价值。不同运动模式, 如有氧运动、阻力训练和 HIIT, 均能在改善心肺功能、控制血糖及降低心血管事件风险方面发挥作用。未来研究应致力于个体化康复方案的制定和不同运动模式作用机制的进一步阐明, 以提高患者的长期预后和生活质量。

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