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·综述·

运动训练促进缺血下肢血管新生、改善行走功能的研究进展 *

葛红卫 1

随着社会人口老龄化和饮食结构调整,下肢动脉硬化性闭塞症(arteriosclerosis obliterans, ASO)和血栓闭塞性脉管炎(thromboangiitis obliterans, TAO) 等慢性缺血性疾病总体发病率逐年上升[1],间歇性跛行(intermittent claudication,IC)是此类疾病的主要症状,发展到后期有静息痛和肢体末端感染破溃。虽然动脉重建和腔内血管成形的发展使众多患者免于截肢,但对于动脉远端缺乏理想流出道及并有严重的心肺疾病、糖尿病等患者的治疗却相当棘手[2]。如何有效提高患者的行走距离,改善下肢血供是目前研究的热点之一。

最近研究发现,运动训练(exercise training, ET)可以改善患者缺血下肢血供, 增加无痛行走距离 (pain-free walking distance, PWD) 和最大行走距离 (maximal walking distance, MWD),改善生存质量。目前已成为治疗 IC 患者的热点,尤其对于膝关节平面以下的动脉闭塞性 IC 患者,ET 的疗效优于手术治疗, 被认为是当前保守治疗的金标准 [3—4]。1988 年, Housleg [5] 提出 “戒烟和坚持步行” 的治疗原则。1999 年, Remijnse-Tamefius 等[6] 指出,凡无绝对手术适应证的 IC 患者,都可通过步行锻炼,达到改善或消除缺血症状的临床表现,增加步行距离的目的。短期的 ET 就能提高 IC 患者的运动能力,已经得到康复中心的广泛应用[7]。

1 ET 改善患者下肢缺血的实例

Ambrosetti 等[7]对 26 例中等强度跛行的老年患者进行了短期 (4 周) 的运动训练来评价其提高患者运动能力的可行性。研究结果显示,1 名患者跛行现象消失(步行 1000m 以上无下肢疼痛), 另外 25 名患者的平均 PWD 增加 2 倍以上(75—174m),平均 MWD 显著增加(204—381m)。期间患者无心血管等方面的并发症发生, 老年患者对 ET 的耐受性较理想。

洪彪等[8]对 16 例 IC 患者进行了步行锻炼的疗效观察和分析,结果表明,除 1 例无效外,2 例好转,13 例均有显著效果;15 例患足不再发凉,PWD 及患者的踝肱指数(ABI)均较治疗前显著提高。

2 ET 促进缺血肢体血管新生、提高跛行患者行走能力的可能机制

2.1 血管新生的概念

目前对血管新生的认识主要是: 血管发生(vasculogenesis)和血管生成(angiogenesis)。血管发生是胚胎发育过程中,胚外中胚层一些间充质细胞聚集成血岛,其外层为内皮祖细胞 (endothelial progenitor cells ,EPCs), 内层为造血干细胞(hematopoietic stem cell ,HSC)。多个血岛腔隙相互连接成管样结构,形成原始血管床;在此基础上,血管内皮细胞(endothelial cell, EC) 通过出芽的方式形成新的血管分支并相互连接成血管网,称为血管生成[9,13]。

1997 年 Asahara 等[10]证实并命名了循环外周血中存在的 EPCs。EPCs 主要定居于骨髓,在一定条件下可以释放。血管发生和血管生成也同样见于成熟个体组织损伤修复和某些病理生理过程[11]。

治疗性血管新生是指将外源性血管新生诱导因子转入缺血组织中促进其血管新生和侧支血管形成,包括血管生成和血管发生[12]。

2.2 ET 促进缺血肢体血管新生

缺血肢体本身有天然的代偿作用,表现为缺血局部形成侧支循环、促血管新生因子及其受体表达上升,促进新生血管和侧支循环的形成[13—14]。骨骼肌的血管系统能发生自身重塑以提高活动肌肉的供氧,重塑发生于现存的血管系统不能满足组织的新陈代谢、组织活动和外周动脉阻塞时的需要时,表现为侧支血管的扩展(arteriogenesis)和毛细血管的发展(angiogenesis)[15—16]。运动通过剪切应力提高、VEGF-R 的信号表达,诱导内皮细胞的增殖和分化,促进侧支动脉形成和毛细血管的新生发展[16]。运动诱导血管适应性改变,骨骼肌局部血流量的提高,毛细血管密度的增加;血流对血管壁剪切应力的增强,刺激内皮细胞释放各种生长因子等一系列复杂的反应[16]。

2.3 ET 与促血管生成因子、细胞因子的表达

2.3.1 ET 促进血管内皮生长因子 (vascular endothelial growth factor, VEGF)的高表达:VEGF 是一种高度特异的血管内皮细胞有丝分裂原,能促进内皮细胞分裂、增殖、迁移、趋化;能通过促进单核巨噬细胞迁移,进而分泌多种血管生长因子, 间接促进血管新生;VEGF 介导的信号促进了组织基质金属蛋白酶(matrix metalloproteinase, MMPs)的活化,MMPs 是促进毛细血管周围基底膜降解的最主要产物,细胞外基质的降解是血管新生的必要过程[16]。VEGF 通过作用于 EPCs 表面的 2 种受体即 VEGFR1 和 VEGFR2, 动员骨髓 EPCs 入外周血、诱导 EPCs 的增殖,并定位到缺血组织,在原位分化形成成熟的内皮细胞,从而形成新的血管[17]。另外,VEGF 能刺激内皮细胞合成一氧化氮(NO)并上调一氧化氮合酶(NOS)的表达,进而升高血管通透性,使炎性细胞渗透到组织中,这可能进一步促进血管新生[21]。

运动能有效地提高外周血 VEGF 水平[18—19,21]。规律性的运动训练,在一定时间内增加了肢体的血氧需求,缺氧情况下发生一系列的应急反应:缺氧诱导因子-1(HRG-1)的释放,诱导骨髓基质细胞(BMSCs)高表达 VEGF[20]。Iemitsu 等[21]

* 审校:何延政,刘勇(四川省泸州医学院)

1 四川省泸州医学院 175 信箱 (血管外科 04 级研究生),646000
作者简介:葛红卫,男,硕士,住院医师

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用实验观察了年迈大鼠在运动后和非运动组心肌血管新生的情况,运动组做 8 周游泳锻炼后检测得心肌中 VEGF 及其相关蛋白表达比非运动组明显增高,心肌微血管密度也增高显著。

2.3.2 ET 和粒细胞集落刺激因子(granulocyte colonystimulating factor, G-CSF):G-CSF 能有效动员骨髓 EPCs 的释放[22—23,25]。G-CSF 能使中性粒细胞释放弹性蛋白酶和组织蛋白酶 G,这些蛋白酶能诱导骨髓基质细胞黏附带的分裂,干扰了 EPCs 等干细胞和骨髓间质细胞之间的相互作用,促进了 EPCs 游离出骨髓进入血流[23]。

人体运动 1h 后外周血中嗜中性粒细胞记数明显增加并保持到 2h 后;血浆 G-CSF 水平在运动后 2h 显著提高[24]。有人依据了运动后白细胞介素(IL-6)、G-CSF、flt-3 配子计数增加,用流式细胞仪检测了 20 名青壮年划船手在休息时和运动后的外周血,发现在超负荷运动后外周血中的 EPCs 比休息时成倍地增长[25]。G-CSF 也通过使中性粒细胞释放 VEGF 促进血管新生[26]。

2.3.3 ET 和一氧化氮(NO):当前已经证实动脉生成是由 NO、成血管因子和血管切应力共同调节。有效地刺激了血管紧张度引起新的侧支动脉管腔形成。NO 介导的血管传导性的增加能帮助更大的侧支血流灌注到肢体的远端和闭塞端。NO 产物对于外源性血管生长因子递呈的或运动训练促进的治疗性血管新生的功效都是至关重要的[27]。ET 能增强血流对动脉壁的切应力,刺激内皮细胞释放一氧化氮(NO),运动训练比动脉闭塞本身更能促进 NO 的释放[27]。

在人和动物模型上,ET 均已被证明能增强血管的内皮功能以及 NO 依赖的血管舒张功能。血管内皮功能对于维护血管床的健康、血管腔和阻力血管的舒张功能都是很重要的。同时坚持锻炼能纠正缺血肢体氧自由基生成失调对组织的损伤[28]。

2.3.4 ET 和其他因子:运动训练能提高血浆白细胞介素-1(interleukin-1, IL-1)、肿瘤坏死因子(tumor necrosis factor, TNF)等水平[29],两者被证实能动员骨髓 EPCs 入血,促进血管新生[30—31]。

2.4 ET 动员骨髓 EPCs 促进缺血肢体血管发生:ET 是动员 EPCs 的有效手段[32—33]。EPCs 可能是成年血管再生的关键细胞。Rehman J 等[34]对 22 名志愿者进行了临床论证,从事运动训练,并检测了运动前后的 EPCs 和外周血成血管细胞和成血管生长因子等指标,发现运动后人体的外周血 EPCs 比运动前提高了 4 倍,分离出的成血管细胞也提高了 2.5 倍。运动可达到治疗性血管新生的效果。然而这种 EPCs 在成年外周循环中含量极少,提示骨髓内含有更多的 EPCs 可用于治疗性血管新生[33—35]。同时 EPCs 又能分泌 VEGF、HGF、G-CSF、GM-CSF 等促血管生长因子[34]。

3 ET 对患有其他器质性疾病的间歇性跛行患者的可行性

James 等[36]在对 134 例病情稳定的心肌缺血患者进行了常规运动和急性运动试验,结果显示两项运动比单独常规医药护理更能减轻患者的精神压力、降低了心血管危险的发生。糖尿病存在长期的血管损伤,有氧运动训练能有效提高血管内皮功能[37]。运动诱导患肢肌肉中毛细血管数量增多,血氧供给及循环改善,组织有氧代谢增加,减轻了患肢缺血引起的炎症性病变对血管内皮和组织的损伤。不仅提高了行走距离,同时减少了下肢缺血期间组织再灌注损伤[38]。

4 小结

运动训练对于间歇性跛行患者具有有效、安全、简便、可靠等优点,适用于中到重度跛行特别是伴有器质性疾病的老年患者。

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