

· 综述与专论 ·

肠道菌群与心力衰竭合并抑郁的研究进展

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【摘要】 心力衰竭患者容易罹患抑郁, 二者相互影响, 导致患者生活质量降低与预后不良。肠道菌群作为人体最大的微生态系统, 其组成、结构及功能变化与宿主的生理和病理状态密切相关。目前, “肠-心/脑轴”已用于解释肠道微生物、血管疾病及情绪状态之间的联系, 是心力衰竭与抑郁的重要共病基础。本文综述了肠道微生物、代谢产物、迷走神经等在心力衰竭与抑郁发生、发展中的作用机制, 提出地中海饮食、益生菌、菌群移植等具有改善微生物-肠-心/脑轴的潜力, 为心力衰竭共病抑郁患者的治疗提供了新的切入点。

【关键词】 心力衰竭; 抑郁; 肠道菌群; 代谢产物; 综述

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Advances in Gut Microbiota in Heart Failure Combined with Depression

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【Abstract】 Heart failure patients are prone to depression, and interact with each other, leading to lower quality of life and poor prognosis of patients. As the largest microecosystem in the human body, changes in the composition, structure and function of the gut microbiota are closely related to the physiological and pathological states of the host. Currently, the “gut-heart/brain axis” has been used to explain the link between gut microbiota, cardiovascular diseases, and mood states, which is an important comorbid basis for heart failure and depression. In this paper, we reviewed the mechanisms of gut microbiota, metabolites, and vagus nerve in the development of heart failure and depression, and propose that mediterranean diet, probiotics, and microbiota transplantation have the potential to improve the “microbiota-gut-heart/brain axis”, providing a new perspective for the treatment of heart failure patients comorbid with depression.

【Key words】 Heart failure; Depression; Gut microbiota; Metabolite; Review

近年来,随着人口老龄化和心血管危险因素持续流行,心力衰竭(以下简称心衰)在我国发病率始终居高不下,给患者及社会医疗带来巨大负担^[1]。尽管心衰的规范化诊疗取得了一定的进展,但鉴于各种合并症的伴发,当前指南在精神心理支持、自我管理、运动康复等方面对医生及患者提出了更高的要求^[2-3]。

抑郁是一种常见的精神障碍,心境低落、自杀观念或行为等是其常见的临床特征^[4]。一项前瞻性研究表明,与正常人群相比,抑郁患者更容易发生心血管事件甚至进展为心衰($HR=1.41$, $95\%CI=1.07\sim1.87$)^[5]。此外,心衰患者同样容易罹患抑郁,且抑郁严重程度与心衰患者心血管事件及不良预后相关($HR=1.40$,

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95%CI=1.22~1.60)^[6]。心衰与抑郁的发病机制涉及诸多危险因素,包括性别、血小板活化反应、炎症、神经内分泌失调等,目前尚无普遍适用且有效的诊疗手段识别或治疗心衰共病抑郁患者^[7-8]。因此,迫切需要探究心衰与抑郁的具体共病机制,以提供新的诊疗策略。近年来,多项研究表明肠道微生物及其代谢产物通过肠-心或肠-脑轴参与心血管疾病或精神疾病的发生发展^[9-10]。因此,本文就心衰与抑郁患者中肠道菌群及其代谢产物改变及作用机制做一综述,以期“肠-心/脑轴”的理论提供有力补充,为临床上识别和减轻心衰患者抑郁症状提供新的见解。

1 文献检索策略

以“Heart failure” and “Depression” “Heart failure” and “Gut microbiota” “Depression” and “Gut microbiota” “Heart failure” and “Metabolite” “Depression” and “Metabolite”为英文检索词,检索PubMed、Web of Science 数据库;以“心力衰竭”“抑郁”“肠道菌群”“代谢产物”为中文检索词,检索中国知网、万方数据知识服务平台。检索时间为2008年1月—2023年3月。纳入标准:(1)以肠道微生物及其代谢产物与心力衰竭或抑郁相关的文献;(2)论点、论据真实可靠,与主题关联度高的文献。排除标准:逻辑严谨性低且可信度差的文献。最终纳入相关文献76篇。

2 肠道菌群

人类肠道是一个动态的、复杂的微生态系统,包含数百种细菌,数量约为 1×10^{14} 个^[11]。正常的肠道菌群主要由6门类细菌组成,即拟杆菌门、厚壁菌门、变形菌门、放线菌门、梭杆菌门和疣微菌门^[12]。在不同个体中,这些菌群的结构和比例并不相同,而这种多样性主要受宿主因素(遗传差异、年龄与性别)与环境因素(生活方式、饮食与抗生素的使用)影响^[13-14]。

肠道菌群参与体内食物的消化吸收,主要通过糖分解和蛋白水解2种代谢途径来实现^[15]。在糖分解途径中,菌群通过酵解机体难以消化吸收的膳食纤维,产生人体大部分的短链脂肪酸(short-chain fatty acids, SCFAs)和少量支链脂肪酸(branch chain fatty acids, BCFAs)^[16]。在蛋白水解途径中,除了生成SCFAs和BCFAs,还会产生氨、胺、硫醇、酚、吲哚等多种生物活性化合物^[17]。除帮助宿主消化食物外,肠道菌群还能通过多种途径与宿主相互影响,如调节肠道黏膜屏障功能,协助免疫组织激活,影响肠内容物抗原耐受能力,阻止病原微生物繁殖等^[18-19]。此外,肠道菌群借助各种信号分子与肠道黏膜表面的模式识别受体结合,触发

多种下游信号传导通路,刺激机体产生炎症或抗炎免疫应答^[20]。因此,菌群失调是多种疾病发生发展的推动力量。

3 肠道微生态失调与心衰、抑郁的联系

心衰患者体内血液再分配可导致结合珠蛋白2前体表达上调、紧密连接蛋白1表达下调,造成肠道通透性增加及肠上皮屏障功能受损,导致肠道菌群丰度改变,代谢产物及内毒素等释放入血^[21-22]。易位的菌群及代谢产物激发炎症反应,影响循环及中枢神经系统功能,形成恶性循环^[23]。

3.1 菌群多样性改变

目前,随着16S rRNA、宏基因组等测序技术的发展,对于心衰、抑郁患者中肠道微生态的变化也有了更全面的认识。早期研究发现,与健康人群相比,心衰患者肠道菌群多样性降低,主要微生物发生移位,其中科里杆菌科、丹毒丝菌科和瘤胃球菌科丰度显著减少^[24]。随后的组学研究进一步证实心衰患者中有益菌丰度显著降低(产丁酸盐菌及乳酸杆菌等),而致病菌丰度显著增加(柯林斯菌属、弯曲杆菌属及志贺菌属等)^[25-26]。另一方面,抑郁症与肠道紊乱同样存在关联。YANG等^[27]通过宏基因组发现重度抑郁患者肠道内多种噬菌体及菌种发生改变,其中布劳特菌属和优杆菌属的丰度减少与抑郁症状显著相关。此外,一项荟萃分析显示拟杆菌属、副杆菌属、Barnesiella属等在抑郁患者中富集,而厚壁菌门、颤螺旋菌科(UCG 003、UCG 002)与普通拟杆菌属则显著耗竭^[28]。更重要的是,KELLY等^[29]发现将“抑郁性菌群”移植到无菌小鼠体内可诱导抑郁样行为及特征,包括快感缺乏以及绝望状态等。综上所述,特定微生物改变与心衰或抑郁的疾病易感性存在关联。

3.2 SCFAs

SCFAs主要由肠道有益菌代谢膳食纤维产生,在肠内及肠外(心血管、大脑等)参与诸多生物过程。研究显示,SCFAs可结合G蛋白偶联受体通过内皮依赖的方式介导血压改变^[30]。另一项研究表明,心衰患者心肌线粒体肉碱棕榈酰转移酶1活性降低常导致长链脂肪酸氧化受损,而SCFAs相关能量代谢独立于该途径,可作为氧化ATP生成的替代碳源^[31]。一项临床研究显示,与非抑郁人群相比,抑郁患者肠道乙酸盐与丙酸盐浓度显著降低,且在倾向性匹配后,丙酸盐浓度与抑郁评分呈负相关^[32]。SONG等^[33]发现肠道丙酸盐或丁酸盐可穿过血脑屏障降低无菌小鼠小胶质细胞活化、促进大脑中Ac-H3K9表达,改善神经炎症及抑郁症状。此外,SCFAs还可以作为信号分子影响白色脂肪组织、胰岛细胞及炎症反应细胞等,从而参与心衰与抑郁疾病的发生发展^[34]。

3.3 氧化三甲胺 (trimethylamine N-oxide, TMAO)

TMAO 是常见的肠源性代谢产物之一, 主要由胆碱经肠道菌群裂解及肝脏黄素单加氧酶氧化生成。2014 年研究人员首次在心衰患者中观察到血浆 TMAO 水平升高, 且高水平 TMAO 与患者全因死亡风险增高独立相关 ($HR=2.2$, $95\%CI=1.42\sim3.43$, $P<0.001$)^[35]。随后的临床前实验表明, TMAO 可通过诱导心肌纤维化、内皮细胞炎症以及心肌线粒体功能障碍直接影响心脏, 从而加重心衰的进展^[36-37]。近期研究发现, 心肌梗死后精神障碍严重患者血浆 TMAO 显著升高^[38]。此外, TMAO 可降低血脑屏障上紧密连接蛋白的表达^[39], 通过刺激小胶质细胞激活和神经炎症增加, 进一步加剧认知功能障碍^[40]。

3.4 色氨酸

色氨酸是人体必需氨基酸, 受肠道微生物直接或间接调节, 其代谢产物具有免疫、代谢、神经调节等功能。研究表明, 超过 90% 的 5-羟色胺由色氨酸经肠色素细胞生产, 其通过肠道迷走神经突触受体与脑干神经元通信继而发挥改善抑郁症状作用^[41]。此外, LUKIĆ 等^[42]观察到无菌小鼠海马体和前额叶皮层中色氨酸和血清素水平大幅降低, 抑郁行为显著增加。另一方面, 肠道菌群可促进吲哚胺 2, 3-双加氧酶 1 的表达影响色氨酸-犬尿氨酸代谢途径, 导致循环中犬尿氨酸水平增高诱导抑郁样行为^[43]。值得注意的是, 循环犬尿氨酸及其代谢物可影响内皮依赖性血管舒张、诱导氧化应激, 参与心血管疾病的发生、发展^[44]。一项临床研究观察到慢性心衰患者中血清犬尿氨酸水平与高敏 C 反应蛋白及白细胞呈正相关, 单因素回归分析提示血清犬尿氨酸可预测心衰患者出院后不良心血管事件 ($HR=1.43$, $P=0.033$)^[45]。

3.5 脂多糖

脂多糖是革兰阴性细菌细胞壁特有的成分, 主要由肠道微生物死亡裂解后释放到肠道微环境并进入血液循环系统。与心衰-肠道假说一致的是, 失代偿性心衰患者血液中脂多糖的水平明显升高, 这种与心衰相关的内毒素血症可能参与心衰患者的全身性炎症^[46]。另一方面, 脂多糖可通过刺激线粒体功能障碍与巨噬细胞极化诱导心脏内炎症因子表达^[47]。QIN 等^[48]研究发现, 脂多糖可激活小胶质细胞并增加其谷氨酰胺酶的合成, 后者导致抑郁状态下丘脑-垂体-肾上腺轴的过度激活。此外, 近期一项动物研究表明, 脂多糖可以通过 Toll 样受体 4 加重心衰后大鼠的神经炎症^[49], 其可能是心衰共病抑郁的潜在机制之一。

3.6 γ -氨基丁酸 (γ -aminobutyric acid, GABA)

GABA 是一种来源于肠道的重要神经递质, 主要由食物中谷氨酸代谢合成。CHEN 等^[50]发现外源性补

充 GABA 可抑制心脏 Bax/Bak 的凋亡通路, 减轻自发性高血压大鼠的心肌细胞凋亡。研究表明, 左心肥厚大鼠中枢 GABA 能神经元受到抑制, 后者进一步介导自主神经功能紊乱, 增加心肌工作负荷, 加速心衰进展^[51]。另一方面, GABA 同样参与了抑郁症的发生发展。STRANDWITZ 等^[52]通过 16S rRNA 发现产 GABA 菌群水平降低与抑郁症密切相关。值得注意的是, 增强 GABA 能神经元活性、提升 GABA 神经递质水平在治疗抑郁症在动物模型中已取得了令人鼓舞的效果^[53]。综上所述, 肠道 GABA 代谢与心衰共病抑郁密切相关。

4 迷走神经通路

迷走神经是“肠-脑轴”中重要的信息调节通路, 该通路的中断或紊乱, 可能导致精神障碍, 如认知、行为、情感等^[54]。NEUFELD 等^[55]发现, 与肠道微生态健全的小鼠相比, 无菌小鼠在应激后下丘脑-垂体-肾上腺轴呈高反应性, 且循环皮质醇水平增高。此外, 心衰患者抑郁症状的严重程度与外周血单个核细胞的免疫迁移相关, 后者增加 β -肾上腺素受体的敏感性^[56]。增高的皮质醇水平及 β -肾上腺素受体敏感性降低了迷走神经张力, 进一步加重外周及中枢炎症^[57-58]。考虑 SCFAs 受体、神经递质受体、肠肽等在迷走神经传入中大量表达, 迷走神经通路可能参与肠道代谢分子对心脏、大脑的远程调节^[59-60]。值得注意的是, 长双歧杆菌等益生菌对小鼠情绪行为和中枢神经受体的改善作用同样依赖迷走神经的传入^[61-62]。此外, HAN 等^[63]通过神经元投射与标记证实肠迷走神经传入调节的臂旁黑质背外侧通路在奖赏行为和多巴胺活动中起着关键作用。

5 调节肠道微生态

肠道微生态失衡与心衰、抑郁的发生发展密切相关。恢复菌群结构, 改善微生物-肠-心/脑轴, 为心衰共病抑郁患者提供了新的治疗切入点。本文主要从地中海饮食、益生菌、益生元、菌群移植等方面, 探讨通过调节肠道菌群治疗心衰共病抑郁患者的可行性。

5.1 地中海饮食

地中海饮食是现代营养学推荐的一种饮食模式, 其强调膳食纤维、不饱和脂肪酸及优质蛋白质的摄入。2019 年美国心力衰竭协会发表的共识声明强调地中海饮食模式对有心衰风险或已确诊心衰的患者是合适、有益的选择^[64]。一项多中心干预研究发现坚持地中海饮食模式的心衰患者心肺功能及活动意愿较高^[65]。此外, WALKER 等^[66]评估 Framingham 心脏研究数据发现坚持地中海饮食有助于维持神经认知健康、减轻心脏重塑。类似地, 一项病例对照研究发现, 对于焦虑或抑郁患者地中海饮食的高依从性与急性心肌梗死等心血管事件呈

负相关,提示地中海饮食可能是心血管疾病与抑郁共病患者的一个显著保护因素^[67]。

5.2 益生菌

益生菌主要指适量食用时对宿主健康有益的活微生物,包括乳酸杆菌、丁酸杆菌、鼠李糖乳杆菌等。一项荟萃分析显示,服用益生菌可显著降低受试者的抑郁评分($95\%CI=-0.51\sim-0.09, P=0.005$)^[68]。另一项实验发现,喂养鼠李糖乳杆菌6周后,实验鼠脑部GABA受体基因表达显著提升,有助于促进脑内GABA分泌,继而缓解了动物焦虑、抑郁相关行为^[62]。同样地,补充鼠李糖乳杆菌可减弱缺血性心衰大鼠左心室肥厚,改善左心室收缩和舒张功能,并且在停止喂养后其相关益处仍可长期持续^[69]。需要强调的是,尽管益生菌在辅助治疗方面取得了一定的进展,然而益生菌剂量、服用时间及与药物相互作用等额外因素还没有彻底地阐明,需要进行进一步的科学研究。

5.3 益生元

益生元指一类可选择性刺激肠道菌群活性及生长而对宿主产生有益的影响的膳食补充剂。一项动物实验显示,以发酵麦麸为基础的益生元复合物可刺激心衰大鼠肠道乳酸杆菌生长,改善肠道生态失调、减轻内毒素血症^[70]。此外,半乳聚糖可通过抑制凋亡级联来减轻心肌梗死大鼠心肌损伤,改善心室重构^[71]。另一项随机对照研究表明,补充菊粉可协助鼠李糖乳杆菌降低冠心病患者循环炎症因子水平及抑郁评分^[72]。类似地,秋葵多糖可通过缓解肠道菌群失调,降低结肠、血清及海马炎症水平,改善慢性应激诱导的抑郁样行为^[73]。

5.4 菌群移植

菌群移植主要通过植入健康粪便中功能菌群,重塑菌群结构,协助疾病的治疗。动物研究表明,菌群移植通过恢复5-羟色胺水平、抑制脑胶质细胞活化,从而缓解抑郁样行为^[74]。临床试验显示,与安慰剂组患者相比,菌群移植组患者肠道多样性得到改善,抑郁评分显著降低^[75]。在心血管疾病方面,ZHANG等^[76]发现心房颤动易感老年大鼠的肠道微生态和心房炎症小体活性可通过移植年轻大鼠的健康菌群得到恢复,从而预防心房颤动的发生发展。此外,ZHONG等^[77]证实水洗菌群移植治疗对高血压患者有较好的降压作用,且降压持续时间长于常规口服药物。遗憾的是,目前尚无心衰共病抑郁动物及临床相关的菌群移植试验,未来仍需要进一步研究以推动肠道菌群治疗在心衰共病抑郁患者中的应用。

6 总结

随着研究深入,肠道菌群参与心衰与抑郁共病的机制逐步阐明,以“肠-心/脑轴”为核心调节为治疗提

供了新切入点。心衰时肠道血流灌注减少、肠道屏障被破坏,导致菌群失调,诸多肠道功能产物代谢紊乱,如SCFAs、色氨酸、GABA含量降低,LPS、TMAO反向升高。上述代谢产物直接或间接(迷走神经通路)引起外周及神经炎症、心肌细胞氧化应激、胶质细胞活化,进而引起心功能恶化、诱导抑郁行为或情绪的产生。另一方面,抑郁进一步加重了菌群紊乱,最终形成恶性循环。需要强调的是,尽管地中海饮食、益生菌、益生元、菌群移植等治疗方式在心衰或抑郁患者中展现出不俗的治疗效果,但其具体治疗机制、潜在不良反应尚不明确。基于此,未来需要更多的研究以明确和建立“微生物-肠-心/脑轴”的关系网络,实现通过菌群调控协助改善心衰共病抑郁患者的临床症状及预后。

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