·综 述·

氧化三甲胺是潜在的心力衰竭治疗靶点和预后标志物

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[摘 要] 研究表明,肠道菌群及其代谢产物参与了各类心血管疾病的发生发展过程,且与疾病的预后进展有着密不可分的关系。在心力衰竭患者中,内脏低灌注会导致肠道缺血,肠道通透性发生改变,进而使细菌及其毒素易位入血,引发局部或全身炎症反应。肠道菌群代谢产物氧化三甲胺(trimethylamine N-oxide,TMAO)参与了心力衰竭的病理过程,如加剧心肌肥厚和纤维化、诱发炎症反应、通过影响肾功能恶化心衰。文章就氧化三甲胺为靶点的心力衰竭治疗及其作为心力衰竭预后标志物进行综述。

[关键词] 肠道菌群;氧化三甲胺;心力衰竭;治疗;预后标志物

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Trimethylamine N-oxide: potential therapeutic targets and prognostic biomarkers of heart failure

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[**Abstract**] Studies reveal that the gut microbiota and its metabolites play an important role in the pathogenesis and progression of various cardiovascular diseases, and are inseparably related to the prognosis of the disease.In patients with heart failure, splanchnic hypoperfusion leads to intestinal ischemia and alters intestinal permeability, and then translocates bacteria and their toxins into the blood circulation, triggering local orsystemic inflammatory responses. Trimethylamine N-oxide (TMAO), as a metabolite of gut microbiota, is involved in the pathological process of heart failure, such as exacerbating cardiac hypertrophy and fibrosis, inducing inflammatory responses, and worsening heart failure by affecting renal function. This article reviews trimethylamine N-oxideas as the therapeutic target of heart failure and as a prognostic marker of heart failure.

[**Key words**] gut microbiota; trimethylamine N-oxide; heart failure; treatment; prognostic biomarker

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研究表明,在心力衰竭的病理生理机制以及疾病的发生发展过程中,肠道菌群及其代谢产物起着不可忽视的作用[1-2]。部分学者提出了心力衰竭发病机制的“肠道假说”。该假说表明,由于心输出量的减少以及体循环淤血,心力衰竭患者会发生肠道缺血,导致肠道上皮细胞水肿和肠壁纤维化。长期的上述改变会导致肠上皮功能障碍,包括肠道屏障受损、营养吸收减少以及肠黏膜通透性增加,进而促进细菌及内毒素易位,进一步促使炎症因子释放,最终导致心力衰竭慢性炎症的发生,加剧心肌纤维化[3]。肠道菌群是肠道微生态中最重要的活性成分之一,其直接参与了宿主的生长发育、营养代谢、免疫调节和肠道稳态的维持。健康人群体内厚壁菌门、拟杆菌门占比最大,各种原因导致肠道菌群失调时,肠道菌群组分占比发生变化,其中以厚壁菌门与拟杆菌门的变化最为显著[4]。日常饮食中的胆碱和磷脂酰胆碱等被肠道菌群代谢为三甲胺

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(trimethylamin,TMA),后者再由肠道吸收后经门静脉进入肝脏并被黄素单加氧酶家族(flavin-containing mono-oxygenase,FMO),尤其是黄素单加氧酶3(flavin-containing mono-oxygenase 3,FMO3)氧化为氧化三甲胺(trimethylamine N-oxide,TMAO)[5],最后主要到达肾脏由尿液排出[6]。TMAO与动脉粥样硬化、高血压、心肌梗死、心力衰竭等多种心血管疾病密切相关[7],并能预示缺血性心力衰竭的住院时长及不良预后事件[8]。本文就TMAO为靶点的心力衰竭治疗及其作为心力衰竭预后标志物进行综述。

1 TMAO在心力衰竭发生发展中的作用

1.1 TMAO加剧心肌肥厚和纤维化

Li等[9]研究表明,TMAO能直接诱导心脏肥大和纤维化,并且这种诱导通过激活Smad3信号通路来实现,此外Smad3特异性抑制剂SIS3能减弱这种刺激。Yang等[10]发现,在心肌梗死小鼠中,喂食高胆碱饮食或补充TMAO可导致心功能恶化和心肌纤维化,可能是由于加速了成纤维细胞向肌成纤维细胞转化所致。此外,实验表明TMAO处理后的成纤维细胞体积增加,且α-平滑肌肌动蛋白(α-SMA)、Ⅰ型胶原蛋白、转化生长因子β受体Ⅰ(TGF-βR1)和磷酸化Smad2表达增加。在另一项研究中也得到了类似的结果,给动脉结扎术诱导心力衰竭的小鼠喂食TMA合成的抑制剂3,3-二甲基-1-丁醇(3,3-dimethyl-1-butanol,DMB)能延缓心衰时心室重构的过程,且通过调节TGF-β1/Smad3信号通路和p65 NF-κB信号通路延缓心室重塑和电重构[11]。

1.2 TMAO诱发炎症反应

炎症反应是心力衰竭发生发展的重要因素,也是心血管疾病不良预后的主要因素之一。慢性心力衰竭的疾病进展过程中,局部和全身炎症反应与心力衰竭的相互作用也是其显著特征之一[12]。Chen等[13]进一步研究表明,TMAO可通过抑制Sirtuin-3(SIRT3)以及超氧化物歧化酶2(superoxide dismutase 2,SOD2)活性来促进线粒体活性氧(mtROS)积累,进一步诱导NOD样受体热蛋白结构域相关蛋白3(NOD-like receptor thermal protein domain associated protein 3,NLRP3)炎症小体激活,NLRP3炎症小体分泌Caspase-1、IL-1β和IL-18,进而诱导血管炎症的发生。在颈动脉结扎小鼠上,研究员们发现TMAO可通过激活NF-κB、NLRP3炎症小体以及内质网应激通路诱导血管炎症,促进血管重塑[14]。在慢性肾脏病的小鼠身上,研究员们也发现了类似结果,TMAO通过激活NLRP3炎症小体以及NF-κB信号通路促进血管钙化[15]。此外,Liu等[16]实验表明,TMAO可刺激肝细胞释放外泌体(exosomes,Exos),Exos被人主动脉内皮细胞吸收,部分通过NF-κB信号转导,从而促进炎症标志物的表达和内皮功能障碍。

1.3 TMAO通过影响肾功能恶化心力衰竭

除了心脏损伤外,肾功能的变化在心力衰竭进展中的作用同样至关重要。由于肾脏在TMAO排泄中起着关键作用,因此肾功能的损害与血浆TMAO水平升高密切相关。多项研究发现,TMAO水平与肾功能呈负相关[17-18]。Hu等[19]研究发现,TMAO水平降低可减缓肾间质纤维化以及肾功能障碍的进展。肾纤维化以及肾功能障碍会进一步导致水钠潴留,进而加重心衰[20]。此外,动物实验表明降低TMAO水平能减轻CRS2小鼠(联合冠状动脉结扎诱导的心肌梗死和次全肾脏切除手术小鼠)的心脏和肾脏损害,并通过抑制炎症来防止疾病进展[21]。

2 TMAO是心力衰竭治疗的潜在靶点

2.1 饮食干预

血浆TMAO水平与饮食密切相关,膳食调整如何影响心血管疾病一直是引人关注的问题。既往研究表明,富含饱和脂肪、动物蛋白和糖类的西方饮食会促进肠道微生物群失调,上调血浆TMAO水平,并增加心血管疾病的风险[22]。Wang等[23]研究表明,与白肉或非肉类蛋白质来源(保持总热量不变)相比,主要蛋白质来源为红肉的饮食会显著增加血浆TMAO的水平,并且减少肾脏的TMAO排泄。从TMAO来源来看,研究表明戒断饮食中的TMAO可以降低循环中的TMAO水平[24]。此外,Videja等[25]研究发现模拟禁食饮食(fasting mimicking diet,FMD)可以通过限制热量摄入和动物源性蛋白质消耗来降低血浆TMAO水平。地中海式饮食的特点是水果、蔬菜、坚果、豆类、全谷物和海鲜的摄入量相对较高,饮酒量适中,红肉/加工肉和饱和脂肪酸的摄入量较低[26]。一项来自巴西的横断面研究显示,在考虑群体的经济因素和饮食习惯之后,地中海饮食可降低心力衰竭的发病率与不良预后结局[27]。控制高血压的饮食方式(dietary approaches to stop hypertension,DASH)主要限制了糖分、红肉以及脂肪的摄入,研究表明采用DASH饮食模式的心力衰竭患者的体重减轻,且血压、脑钠肽(brain natriuretic peptide,BNP)等心功能指标也得到了改善[28]。

2.2 益生菌干预

益生菌是有益的非病原微生物,通过诱导免疫调节、减少生理应激、抑制病原体、调节肠道微生物和改善肠道的屏障功能等来改善人体健康[29]。在载脂蛋白E基因敲除(ApoE-/-)小鼠中,研究员发现鼠李糖乳杆菌可通过减少氧化应激和炎症来减少小鼠的动脉粥样硬化病变大小[30]。在心肌梗死大鼠模型中,给予鼠李糖乳杆菌干预可以减轻左心室重构,心超功能指标也显示大鼠左心室功能得到改善[31]。最近研究也表明,益生菌能降低血浆TMAO水平,可推测益生菌对心脏的保护作用可能部分是通过减少TMAO水平来实现的[32-33]。在一项随机对照试验中,慢性心力衰竭患者运用布拉氏酵母菌短期治疗可改善左心室射血分数(left ventricular ejection fractions,LVEF)(+6.6%,P=0.005;对比安慰剂:+4.2 %,P=0.173)和左心房直径(-0.29 cm,P=0.044 ;对比安慰剂:+0.20 cm,P=0.079),并降低患者血清肌酐、尿酸和超敏C反应蛋白水平[34]。然而另一项前瞻性多中心随机临床研究Gut-Heart的结果显示,在接受标准治疗基础上使用利福昔明以及布拉氏酵母菌治疗3个月,对于心力衰竭人群的LVEF、微生物群多样性或测量的生物标志物如TMAO等没有显著影响[35]。同时,益生菌的安全性仍然存在争议,存在长期使用益生菌导致菌血症和肝脓肿的病例报道,免疫功能低下的患者应当谨慎使用[36]。

2.3 TMA裂解酶抑制剂

TMA裂解酶将膳食胆碱转化为TMA的细菌酶,DMB是一种天然的TMA裂解酶抑制剂。高胆碱饮食小鼠给予DMB可降低小鼠血浆TMAO水平并且减少泡沫细胞以及动脉粥样硬化斑块的形成,并且没有明显的毒性反应[28]。Roberts等[37]发现,碘甲基胆碱(iodomethylcholine,IMC)和氟甲基胆碱(fluoromethylcholine,FMC)作为CutC/D的抑制剂,显著降低了高胆碱喂食小鼠的TMAO水平,逆转了TMAO诱导的血小板活性升高和血栓形成。Organ等[24]研究表明,IMC可减轻膳食胆碱对压力超负荷心力衰竭小鼠的影响,改善心力衰竭小鼠的左心室重构、心脏功能障碍和心脏纤维化。

2.4 粪菌移植(fecal microbiota transplantation,FMT)

FMT已被证实在治疗复发性、抗生素耐药性艰难梭菌感染方面有显著效果[38]。在自身免疫性心肌炎小鼠模型中,FMT治疗平衡了肠道菌群,提高了F/B比,并减轻了心肌炎[39]。此外,研究员发现从老年小鼠向年轻小鼠的粪便移植可引起心肌纤维化,这种改变与NLRP3炎症小体的增加有关,并且从年轻小鼠到老龄小鼠的粪便移植降低了NLRP3水平[40]。但是FMT仍有等许多局限性需要解决,如感染和排异等[36]。目前还未有FMT的相关心力衰竭治疗的临床报道。

3 TMAO作为心力衰竭的预后标志物

在HIV感染患者中,TMAO水平与弥漫性心肌纤维化相关,并被确定为预测早期结构性心脏病的潜在标志物[41]。一项对720例稳定性慢性心力衰竭患者的研究发现,TMAO水平升高与心力衰竭队列中的死亡风险增加3.4倍,且在调整传统风险因素和BNP之后,TMAO水平升高仍能预测患者5年死亡风险[42]。一项对189例缺血性心力衰竭(ischaemic-heart failure,IHF)患者的研究发现,在进行了校正之后,高TMAO+高NT-proBNP组的患者全因死亡风险最高(HR=3.11,95%CI:1.53~6.31,P<0.001),且两种生物标志物升高的IHF患者住院时间更长。此外,研究员还发现TMAO联合NT-proBNP对于IHF患者全因死亡具有良好的预测价值(AUC=0.727,95% CI :0.640~0.813,敏感度为55.0%,特异度为83.1%)[8]。Li等[43]发现在超敏C反应蛋白(hypersensitive-C-reactive-protein,hsCRP)水平较高(6.68 mg/L)的患者中,TMAO 每增加1个单位,急性心肌梗死(acute myocardial infarction,AMI)并发心力衰竭的患者出现主要不良心脏事件的风险增加20%,表明高血浆TMAO水平与AMI合并心力衰竭患者的预后不良独立相关。Kinugasa等[44]研究表明,TMAO水平升高与射血分数保留型心力衰竭患者的再入院率和病死率增加独立相关,且高TMAO组与低TMAO组的死亡风险比为2.06。一项剂量-反应数据的荟萃分析显示,患者TMAO水平每增加10 μmol/L,全因病死率会增加7.6%[45]。可以看出,TMAO作为心血管不良事件风险指标有很大前景,有成为心力衰竭患者不良预后独立预测工具的巨大潜力。

4 总结与展望

多项体外实验和临床研究表明,肠道菌群代谢产物TMAO与心力衰竭之间存在着密不可分的关系。目前证据表明,TMAO直接或间接参与了心力衰竭的起病和进展,而TMAO水平的升高又与心力衰竭严重程度部分相关,但TMAO与心力衰竭之间

的因果关系尚未十分明确。尽管目前认为TMAO升高是心力衰竭的危险因素，但一些研究认为TMAO可能对心血管系统有益[46-48]。一项研究显示，在右心室衰竭的小鼠模型中，长期的TMAO水平升高可保护线粒体能量代谢和心脏功能，并表明TMAO在心脏代谢疾病中可能存在保护作用[46]。另一项对高血压大鼠的实验发现，血浆TMAO的适度增加并不会对心血管系统造成负面影响，并且增加膳食TMAO摄入能减少压力超负荷引起的舒张功能障碍[48]。但是目前对于TMAO与心力衰竭机制的研究仍只是冰山一角，还需要进一步补充和完善病理生理机制，探究更明确的疾病发生发展机制，从而找到更有效的治疗靶点或诊断和预测工具。

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