

肠源性氧化三甲胺介导心脏骤停后综合征多器官损伤的机制

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[摘要] 心脏骤停后综合征(post-cardiac arrest syndrome, PCAS)以全身缺血再灌注损伤为核心病理基础, 导致严重的多器官功能障碍。近年来, 肠道菌群失衡及其代谢产物失调在急危重症中的作用受到广泛关注, 其中, 肠源性氧化三甲胺(trimethylamine-N-oxide, TMAO)是参与PCAS病理生理进展的关键代谢物。TMAO通过加剧心肌缺血再灌注损伤与心室重构, 加重神经功能损伤, 诱导肾小管损伤与纤维化, 以及增强血小板反应性并促进血栓形成等多途径在多器官层面介导PCAS进展。现有研究表明, TMAO通过激活炎症反应、触发氧化应激、诱导线粒体功能障碍及调控纤维化信号通路等机制介导PCAS后的多器官损伤。深入阐明肠源性TMAO的作用机制, 不仅有助于评估其作为PCAS预后标志物的临床价值, 也为探索靶向调控肠道代谢、改善PCAS预后提供了新的干预策略。

[关键词] 心脏骤停后综合征; 氧化三甲胺; 肠道微生物; 多器官功能损伤; 缺血再灌注损伤

Mechanisms of gut-derived trimethylamine-N-oxide in mediating multiple organ injury in post-cardiac arrest syndrome

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ABSTRACT

Post-cardiac arrest syndrome (PCAS) is characterized by systemic ischemia-reperfusion injury as its central pathological basis and is associated with severe multiple organ dysfunction. In recent years, increasing attention has been directed toward the role of gut microbiota dysbiosis and its metabolites in critically ill conditions. Among these metabolites, gut-derived trimethylamine-N-oxide (TMAO) has emerged as a key mediator involved in the pathophysiological progression of PCAS. TMAO contributes to the development of PCAS at the multi-organ level through multiple mechanisms, including aggravation of myocardial ischemia-reperfusion injury and ventricular remodeling,

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exacerbation of neurological dysfunction, induction of renal tubular injury and fibrosis, enhancement of platelet reactivity, and promotion of thrombosis. Accumulating evidence suggests that TMAO mediates multiple organ injury following PCAS through activation of inflammatory responses, induction of oxidative stress, promotion of mitochondrial dysfunction, and regulation of fibrosis-related signaling pathways. A comprehensive understanding of the mechanisms underlying gut-derived TMAO in PCAS may not only facilitate evaluation of its clinical value as a prognostic biomarker but also provide novel therapeutic strategies targeting gut microbial metabolism to improve outcomes in patients with PCAS.

KEY WORDS post-cardiac arrest syndrome; trimethylamine-N-oxide; gut microbiota; multiple organ injury; ischemia-reperfusion injury

心脏骤停后综合征(post-cardiac arrest syndrome, PCAS)是指患者发生心脏骤停(cardiac arrest, CA)后,经历全身性缺血损伤,并随着自主循环恢复(return of spontaneous circulation, ROSC)发生再灌注损伤,从而导致机体出现多器官功能障碍(multiple organ dysfunction syndrome, MODS)^[1]。PCAS患者发生MODS的病理生理过程复杂多样,包括心脏骤停后脑损伤(post-cardiac arrest brain injury, PCABI)、心肌梗死、全身缺血再灌注(ischemia-reperfusion, I/R)损伤和原发病持续存在等^[2-5]。目前针对PCAS的临床干预治疗手段有限,如亚低温治疗、高压氧治疗和血管活性药物治疗等,且疗效不佳。因此,寻找新的监测指标与治疗靶点有助于提高PCAS患者的存活率。

肠道菌群及其代谢产物的失衡参与了心肺复苏后I/R损伤的病理生理过程。其中,肠源性氧化三甲胺(trimethylamine-N-oxide, TMAO)在动脉粥样硬化、心力衰竭、神经系统损伤和心肾综合征(cardiorenal syndrome, CRS)等疾病中发挥了重要作用^[6]。而心脏、肾和神经系统是PCAS中较为常见的损伤靶器官。Hochstrasser等^[7]发现血浆TMAO与院外心脏骤停(out-of-hospital cardiac arrest, OHCA)患者院内死亡及其他不良事件的发生密切相关。但TMAO在PCAS中的致病机制及其对预后的影响仍不明确。因此,笔者将从心脏、神经系统、肾、凝血功能等方面入手,探讨TMAO在PCAS发生和发展中的重要作用,重点剖析TMAO在PCAS中心脏、脑、肾及凝血系统损伤中的分子机制,以期对PCAS的机制研究和靶向干预提供理论基础。

1 TMAO的来源、产生与代谢

1.1 TMAO的来源与膳食调控机制

TMAO是由肠道微生物菌群(gut microbiota, GM)通过膳食摄入并代谢生成的重要小分子代谢物。TMAO及其前体主要来源于以下3类典型膳食物质:第1类是磷脂酰胆碱,主要存在于蛋黄和红肉中;第2类是左旋肉碱,主要来源于红肉及乳制品等;第3类是甜菜碱,主要来源于海鲜和菠菜等食物。膳食结构的改变可显著影响循环TMAO水平,如摄入鱼类可显著增加血浆TMAO水平,其峰值可达其他食物摄入后的约50倍^[8]。由此可见,饮食模式的精准干预是调控体内TMAO水平的核心手段之一。

饮食干预TMAO生成主要通过限制前体物质摄入、改变前体的化学形态以及重塑菌群活性来实现。首先,限制富含胆碱和左旋肉碱的食物摄入,如红肉、蛋黄等,可短期内降低循环TMAO水平^[9]。前体物质的生物利用度与其化学形态密切相关,如补充胆碱酒石酸盐等游离型胆碱可显著升高TMAO的水平^[10]。其次,增加膳食纤维与多酚类物质的摄入,可重塑GM,从而抑制三甲胺(trimethylamine, TMA)合成。有研究^[11-12]显示,补充低聚半乳糖可下调产TMA关键酶胆碱三甲胺裂解酶(choline TMA-lyase, *Cut*)基因丰度,降低摄入红肉后血清TMAO的水平。最后,石榴多酚提取物和竞争性酶抑制剂3,3-二甲基-1-丁醇(3,3-dimethyl-1-butanol, DMB)也可以抑制前体物质向TMA的转化,最终调控TMAO的生成^[13]。

1.2 肠道代谢产生TMAO的微生物途径

膳食摄入后,GM可将胆碱、磷脂酰胆碱、左旋肉碱及甜菜碱等底物代谢为TMA。其中,厚壁菌门

和拟杆菌门在TMA生成过程中占主导地位^[14]。

胆碱可与辅助蛋白S-腺苷-1-蛋氨酸激活蛋白结合形成复合物, 其在催化酶CutC/D作用下被裂解, 最终转化为TMA^[15]。而左旋肉碱则可依赖于双组分加氧酶还原酶系统(carnitine monooxygenase/reductase system, CntA/B)代谢为TMA^[16]。此外, 磷脂酰胆碱、左旋肉碱、甜菜碱等在甜菜碱还原酶作用下生成TMA^[16]。由此可见, 膳食中的前体物质可通过3类关键酶(即CutC/D、CntA/B和甜菜碱还原酶)代谢为TMA。

合成的TMA在肝被黄素单加氧酶(flavin-containing monooxygenase, FMO)氧化为TMAO。TMA在小肠被吸收后经过门静脉循环被送入肝。人体肝中存在5种FMOs, 而TMA主要被FMO3进一步氧化为TMAO^[17]。随后, TMAO再次进入体循环, 分布至肝、脑、骨骼肌、肾及肠道等组织中。值得注意的是, TMAO除了作为代谢终产物在循环中积累外, 还能够诱导巨噬细胞清道夫受体表达上调, 促进胆固醇沉积, 加速泡沫细胞形成, 从而加速动脉粥样硬化发生与进展^[18]。

1.3 TMAO的排泄

循环中TMAO主要依赖于有机阳离子转运体(organic cation transporter, OCT)通过尿液以原型排出。其中, OCT2转运蛋白主要在肾中表达, 是TMAO排泄的主要转运体^[19-21]。除此以外, 亦有小部分TMAO可通过汗液、粪便和呼吸等其他代谢途径排出, 从而共同维持体内TMAO稳态(图1)。因此, 当肾功能受损, 出现少尿或无尿时, 循环中TMAO浓度可能会升高。

1.4 PCAS病理状态下TMAO代谢的动态变化

在PCAS病理状态下, TMAO的动态平衡被显著破坏。首先, PCAS引发全身性缺血再灌注损伤导致肠道屏障功能受损, 产生TMA的相关菌群, 如厚壁菌门、拟杆菌门等丰度或活性改变, 从而介导TMA和TMAO水平升高^[7, 22]。其次, PCAS并发的急性肾损伤(acute kidney injury, AKI)导致经尿液排泄的TMAO显著减少^[23]。综上, 在PCAS状态下, TMAO生成增加与排泄减少, 二者的协同作用导致其在循环中急剧升高, 加剧多脏器功能衰竭。

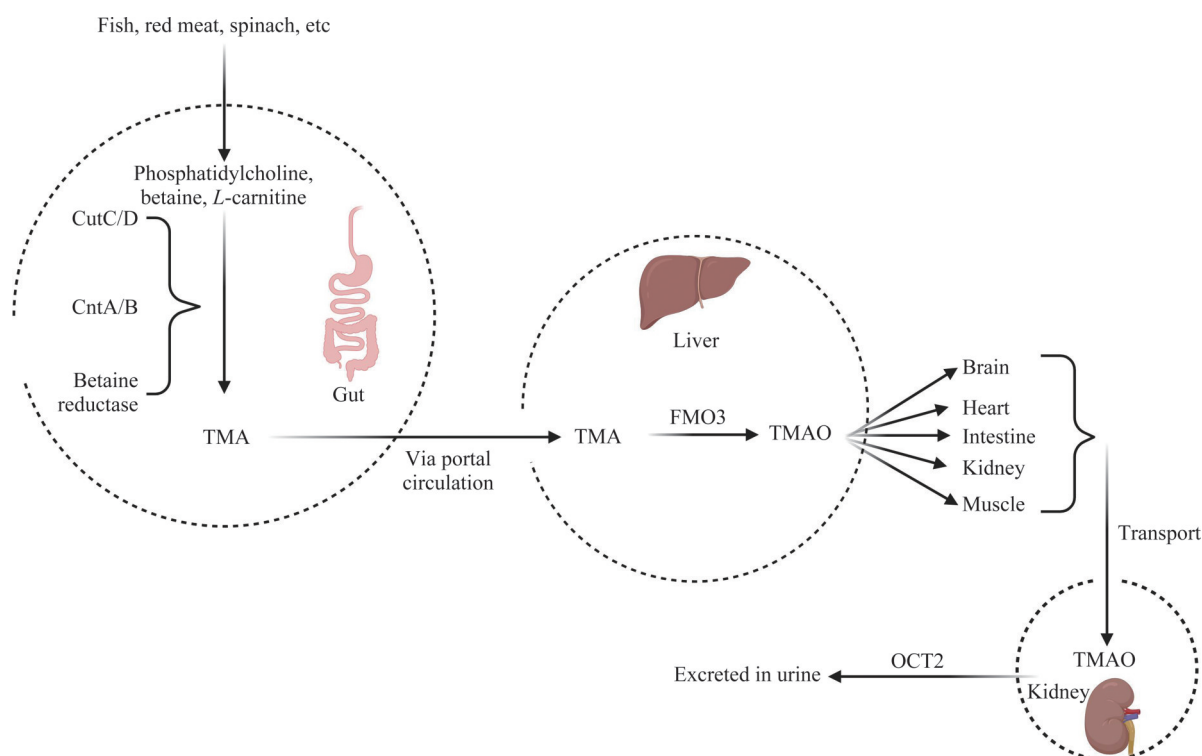


图1 TMAO的产生与代谢通路

Figure 1 Generation and metabolic pathway of TMAO

Cut: Choline TMA-lyase; CntA/B: Carnitine monooxygenase/reductase system; TMAO: Trimethylamine-N-oxide; TMA: Trimethylamine; FMO3: Flavin-containing monooxygenase 3; OCT2: Organic cation transporter 2.

2 TMAO与PCAS后的多器官损伤

2.1 心肌损伤

心肺复苏后,常发生心肌I/R损伤(myocardial ischemia-reperfusion injury, MIRI),其病理过程涉及氧化应激、钙离子超载、能量代谢障碍、细胞凋亡、内质网应激、铁死亡及心肌坏死等多重机制,主要表现为心肌顿抑、微血管阻塞、再灌注诱发的心律失常和致死性心肌再灌注损伤^[2]。

TMAO前体TMA可诱导线粒体内氧自由基(mitochondrion reactive oxygen species, mtROS)堆积,这些多余的mtROS不仅可直接破坏线粒体的膜与蛋白质,还通过打开线粒体通透性转化孔(mitochondrial permeability transition pore, MPTP)与其他凋亡途径一同引起心肌受损与心肌细胞死亡^[24-25]。一项关于心力衰竭与棕色脂肪组织的研究^[26]指出,给予小鼠高水平TMAO可显著降低其线粒体复合酶IV活性,从而显著降低其心肌组织中磷酸肌酸与腺苷三磷酸(adenosine triphosphate, ATP)水平,而MPTP的开放是导致ATP耗竭、线粒体肿胀与细胞色素c(cytochrome c, Cyt c)释放的关键事件,加速了细胞凋亡的进程。研究^[27-28]发现,TMAO可加重内质网(endoplasmic reticulum, ER)应激反应,未折叠蛋白进一步加重心肌损伤,并产生更多ER应激损伤,同时TMAO与蛋白激酶R样内质网激酶(protein kinase R-like endoplasmic reticulum kinase, PERK)结合,通过炎症参与细胞凋亡与细胞损伤进程。因此,TMAO可能通过增加mtROS生成、促进MPTP开放、加重ER应激等机制,加重MIRI。

除氧化应激外,复苏后全身性急性炎症反应也是MIRI的重要致病机制之一。有研究发现,OHCA患者血清中促炎性细胞因子如肿瘤坏死因子- α (tumor necrosis factor- α , TNF- α)和白细胞介素(interleukin, IL)-6的水平显著升高^[29],而抑制TMAO生成的药物DMB可降低这些因子的水平^[3],提示TMAO可能通过促进炎症反应参与心肌再灌注损伤。值得注意的是,DMB可显著降低炎症因子的水平并改善预后,提示TMAO可通过炎症相关通路介导心肌再灌注损伤,并促进CA后心力衰竭与心室重构^[3]。

ROSC后肾功能损伤是引起心力衰竭的重要危险因素之一,TMAO可能加速了CRS的进展。CRS的病理生理机制是心输出量骤减导致肾灌注量不足。研究^[3]显示,CRS模型大鼠使用DMB,可显著降低大鼠心力衰竭指标心房钠尿肽、脑钠肽与促纤维化标志物转化生长因子- β (transforming growth factor-beta, TGF- β)、胶原蛋白I、胶原蛋白III与金属蛋白酶抑制

因子2的水平,同时下调炎症因子TNF- α 、IL-6、IL-8在心脏中的表达,改善左室射血分数下降与心室重构。另有研究^[30]发现,TMA可升高收缩压,但其机制难以仅用肾素-血管紧张素系统(renin-angiotensin system, RAS)解释,可能与TMA/TMAO相关的电解质紊乱有关。在尿量减少时,经肾代谢的TMAO减少,TMAO水平升高,加剧CA后心肌损伤,形成PCAS中心肌损伤与肾损伤的恶性循环。

除了急性损伤外,TMAO升高亦对ROSC后心脏功能减退、心腔扩大和心肌肥厚的代偿过程产生深远影响。CA导致TMAO升高,可促进心肌细胞、细胞外基质、胶原纤维网等结构与功能发生改变,从而促进心室重构进展。研究发现,TMAO可能是通过抑制线粒体正常功能表达而加剧心肌细胞凋亡^[24]。TMAO可通过Toll样受体4(Toll-like receptor 4, TLR4)增加核因子 κ B(nuclear factor kappa-B, NF- κ B)表达,诱导主动脉内皮细胞和血管平滑肌细胞炎症因子表达,从而促进心肌纤维化和心肌细胞肥大^[28,31]。TMAO还可通过上调TGF- β 1及其细胞内信号转导分子Sma和Mad相关蛋白(Sma- and Mad-related protein, Smad3),共同构成TGF- β 1/Smad3信号通路,刺激胶原蛋白I与胶原蛋白III合成,进一步加速心肌纤维化形成^[32]。TMAO可通过沉默信息调节因子2同源蛋白(sirtuin, SIRT)3、超氧化物歧化酶2(superoxide dismutase 2, SOD2)和mtROS构成的SIRT3/SOD2/mtROS信号通路激活核苷酸结合结构域富含亮氨酸重复序列和含热蛋白结构域受体3(NLR family pyrin domain containing protein 3, NLRP3),诱导胱天蛋白酶(caspase)-1活化及IL-1 β 合成和释放,从而加剧血管炎症和心室重构^[24]。此外,TMAO可通过抑制腺苷活化蛋白激酶(AMP-activated protein kinase, AMPK)和SIRT1组成的AMPK/SIRT1信号轴而显著升高细胞内ROS水平,从而诱导NF- κ B、TNF- α 、IL-1 β 合成释放,促进动脉粥样硬化^[33],从而加重心肌缺血损伤。这些研究共同提示,TMAO可能通过激活炎症反应、加重线粒体功能障碍与促进心肌纤维化,在复苏后心肌损伤与心力衰竭的发生和发展中发挥重要作用。

2.2 脑损伤

肠脑轴已成为神经系统疾病研究的重点。目前认为,在CA后,脑组织可能经历了能量代谢障碍、兴奋性毒性、细胞内钙超载、氧化/硝化应激和炎症反应等病理改变。而TMAO在PCABI中同样起重要作用^[4]。

第一,TMA通过增加mtROS水平而增加MPTP

开放,加重神经细胞凋亡。线粒体内膜中的Cyt c在神经元I/R损伤和凋亡中发挥重要作用^[34]。同时,在神经元凋亡进程中,MPTP与凋亡蛋白Bax可促进Cyt c释放,这一过程作为凋亡的起点,形成了由凋亡蛋白酶激活因子-1(apoptotic protease-activating factor-1, Apaf-1)、caspase-9和Cyt c共同组装形成的Apaf-1/caspase-9/Cyt c凋亡复合物,进一步加快神经元凋亡进程^[35-38]。故升高的TMA可通过mtROS的堆积而增加MPTP开放。

第二,TMAO可增强氧化应激与再灌注损伤。TMAO水平升高与缺血性脑卒中严重程度密切相关^[39],提示其可能通过加重氧化应激和炎症参与脑I/R损伤。CA发生后,ROSC后神经系统同样存在I/R损伤,这与缺血性脑卒中的过程类似。TMAO可激活NLRP3炎症小体,增加脑内ROS水平,导致线粒体功能障碍^[33]。TMAO可通过抑制甲硫氨酸亚砷还原酶A,降低氧化损伤的修复能力,加重海马区神经元凋亡^[40]。

第三,TMAO可能参与对PCABI中神经免疫细胞的调控。神经系统的免疫细胞,如小胶质细胞、星形胶质细胞,可在炎症因子诱导下分化为不同亚型,参与PCAS后脑损伤^[41-42]。小胶质细胞可分化为M1、M2型,其中M1型可分泌TNF- α 、IL-1 β 等促炎性细胞因子进一步损伤血脑屏障的紧密连接蛋白,从而加重脑水肿^[43-45]。同时,由于ROS中间体、补体系统、NF- κ B通路、TLR等^[46]的诱导作用,小胶质细胞可产生趋化因子,加重已缺血组织的白细胞浸润,进一步加重炎症损伤。一方面TMAO可通过SIRT3/SOD2/mtROS诱导NLRP3等炎性小体产生,通过TLR4诱导促炎细胞因子NF- κ B表达;另一方面TMAO可通过抑制AMPK/SIRT1信号轴提高细胞内ROS水平,从而诱导NF- κ B、TNF- α 、IL-1 β 等炎症因子释放,通过调控炎症的方式参与对神经免疫细胞的调控^[3, 24, 28, 33]。

第四,TMAO可通过慢性炎症增加脑血管粥样硬化风险,促进血小板聚集而提高脑血栓形成可能性,加重脑缺血性损伤。TMAO激活TLR4、髓样分化初级反应蛋白88(myeloid differentiation primary response 88, MyD88)与NF- κ B通过TLR4/MyD88/NF- κ B通路引发神经系统慢性炎症^[47]。

不难看出,TMAO可通过加重线粒体功能障碍、促进氧化应激反应、调控神经免疫细胞、增强炎症反应介导PCAS后脑损伤,但具体分子机制仍需要进一步研究。

2.3 肾损伤

循证医学证据表明,升高的TMAO与多种肾病有所关联,其中包括AKI、慢性肾脏病(chronic kidney disease, CKD)和终末期肾病等。PCAS后,TMAO可加重氧化应激、免疫紊乱与炎症反应、组织纤维化,为肾损伤提供了触发条件。

首先,TMAO可加剧CA后肾I/R损伤。尿囊素作为尿酸代谢产物,是肾I/R氧化应激的一种标志,其在I/R发生24 h后显著上升^[5]。Serkova等^[5]发现TMAO与尿囊素水平高度相关。这提示TMAO可能在PCAS后肾I/R损伤中发挥重要作用。在机制上,TMAO可通过抑制一氧化氮(nitric oxide, NO)产生、促进平滑肌细胞增殖、增加活性氧(reactive oxygen species, ROS)水平,诱导内皮细胞功能障碍,并通过调控NADPH氧化酶4(NADPH oxidase 4, NOX4)与SOD增强氧化应激,从而导致肾血流量下降及AKI发生^[48]。此外,TMAO还可诱导肾小管上皮细胞凋亡,加速AKI进展^[49-50]。一项敲减小鼠含黄素单氧化酶3(flavin-containing monooxygenase 3, FMO3)基因的实验^[51]则提示降低TMAO可以显著改善I/R损伤后肾功能及肾小管损伤评分,同时可降低ER应激表达的活化转录因子4(activating transcription factor 4, ATF4)、CCAAT/增强子结合蛋白同源蛋白(CCAAT/enhancer-binding protein homologous protein, CHOP)水平,减轻急性肾功能损伤。值得一提的是,在PCAS后,肠道屏障受损导致TMAO进入循环。肾损伤分子-1(kidney injury molecule-1, KIM-1)是一种由T细胞免疫球蛋白域和黏蛋白域蛋白1基因编码的跨膜糖蛋白,往往在肾缺血等病理状态下高表达,提示肾小管间质纤维化、炎症浸润及肾小球硬化^[30]。研究^[30]显示,摄入高剂量TMAO,可使大鼠血清KIM-1升高,并合并尿糖和尿蛋白升高,表明短期TMAO升高可损伤肾实质和肾小管。上述研究均说明,PCAS后肾I/R损伤,可引起血清TMAO升高,诱导肾细胞氧化应激、上调KIM-1,损伤肾小管及实质,加速AKI的发生。

其次,PCAS后I/R损伤常伴随炎症因子风暴。TMAO可激活炎症通路,促进IL-6、TNF- α 等因子释放,这些炎症因子在肾基底膜及实质沉积,增强局部免疫损伤,加重肾炎症及功能障碍。

除了AKI外,TMAO还可加重慢性肾损伤与纤维化。PCAS等因素可导致肠道屏障受损,使得TMAO、吲哚酚硫酸盐、对甲酚硫酸盐在内的肠源性尿毒症毒素入血,加速肠道屏障破坏,进入体循环

中加速CKD与肾纤维化进展^[52]。另有研究^[53-54]发现, TMAO可激活TGF- β 1/Smad3通路, 并参与由p38和丝裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)组成的p38/MAPK通路、细胞外信号调节激酶1/2(extracellular signal-regulated kinase 1/2, ERK1/2)通路, 促使肾成纤维细胞分化为肌成纤维细胞, 并维持炎症因子表达稳定。*FMO3*基因敲除实验则可延缓肾纤维化进展^[51]。

2.4 凝血功能异常

CA患者中急性冠脉综合征占比可达50%~70%^[55], 而血管内皮损伤通常是血栓形成的起始环节。已有研究^[36]表明, TMAO可加重血管内皮损伤、加速血栓形成。在PCAS病理生理过程中, 血管内皮损伤与血栓形成是临床重点关注的环节, 而长期卧床、机体高凝状态也使抗凝与溶栓策略不可忽视。

在PCAS后, TMAO水平升高, 促进血管内皮损伤与炎症反应。有研究^[36]报道, TMAO可上调炎症因子, 如IL-6、TNF- α 的释放, 加重血管内皮损伤; 同时通过上调血管细胞黏附分子-1表达并激活蛋白激酶C(protein kinase C, PKC)与NF- κ B, 通过PKC/NF- κ B信号通路, 增强血小板黏附能力, 进一步加速动脉粥样硬化进程。

此外, TMAO参与了PCAS后高凝状态的形成。TMAO可促进血小板膜磷脂分解, 通过磷脂酶C途径促进三磷酸肌醇生成, 进而触发细胞内钙库释放Ca²⁺, 导致血小板活化^[36]。另有研究^[36, 56]发现, TMAO促进凝血酶的产生和组织因子活性, 增加Ca²⁺释放, 加速血小板微管环状带和骨架蛋白收缩, 加速血凝块回缩, 促进血栓形成。

2.5 其他

2.5.1 肠道损伤

肠道保护屏障由顶端跨膜蛋白组成, 包括密封蛋白(claudin)、闭合蛋白(occludin)、上皮钙黏素(E-cadherin)和细胞质连接蛋白等, 可阻止肠内容物、有害物质进入血液, 而TMAO可破坏屏障保护功能。PCAS发生后, 缺氧缺血促使上皮紧密连接蛋白表达下降, 破坏肠道屏障完整性。肠源性尿毒症毒素及细菌DNA可通过破损的肠道进入循环, 并进一步加重肠道屏障损伤。同时, PCAS可显著升高循环中TMAO含量, 形成正反馈循环, 加重肠道损伤。多发伤患者早期亦出现肠道菌群失调及血浆TMAO水平升高, 后者与MODS密切相关; 而创伤性脑病亦可见到类似现象, 并在短时间内引起胃肠道功能障碍、炎症及屏障破坏^[57-58]。此外, 已有学者^[57, 59]提出

“微生物-肠-脑轴”理论, 认为脑损伤可破坏该轴路, 导致肠道屏障功能下降、神经内分泌及免疫调节紊乱, 并在胃酸侵袭下加重缺血性损伤, 从而影响多器官功能及预后。

2.5.2 肝损伤

一项关于药物性肝损伤的研究^[60]发现, *FMO3*在药物性肝损伤的人与小鼠的肝细胞中表达上调, 可能是通过结合抑制转录因子环磷酸腺苷反应元件结合蛋白(cyclic adenosine monophosphate response element binding protein, CREB)3, 从而导致ER应激, 并最终导致肝细胞凋亡; 类似的现象出现在接受野百合碱诱导的肝窦阻塞综合征患者中, 在接受对乙酰氨基酚或野百合碱后, 患者也会出现*FMO3*表达升高及TMAO血清浓度升高。

目前尚缺乏直接证据表明TMAO在PCAS后肠道或肝损伤中的作用。未来需要进一步探索TMAO在这些脏器损伤及MODS中的具体机制。

3 预后

尽管TMAO在PCAS预后评估方面展现出潜在价值, 但目前临床研究仍处于初步探索阶段。TMAO及其相关代谢物在不同心血管急症场景中均表现出一定的预测效能, 但其在CA人群中的应用仍需进一步验证。

在ST段抬高型心肌梗死患者中, TMAO联合甘油三酯葡萄糖指数可显著提升主要不良心血管事件的风险识别能力^[61]。针对CA人群的研究则揭示了更具特异性的关联。一项纳入OHCA患者的队列研究^[7]发现, 入院时血浆TMAO水平与患者院内死亡及远期神经系统预后不良显著相关, 且这一关联独立于传统危险因素及肾功能指标, 提示TMAO在OHCA整体人群中具有早期风险分层的潜力。另一项研究^[62]聚焦于因二级预防指征而植入埋藏式心脏复律除颤器的患者, 发现血浆TMA水平升高是远期不良心血管事件的独立危险因素; 研究者基于左心室射血分数、TMA及其他多种代谢物构建的“VT-C3”评分系统, 为该类具有高复发风险的患者提供了更为精准的风险分层工具。上述研究均提示, 从TMAO到其前体TMA, 不同代谢物对不同病因、不同阶段的CA人群均具备较好的预后预测价值, 但具体关联趋势与核心作用代谢物存在差异。

值得注意的是, 上述研究并未对导致CA的根本病因进行分层报告, 限制了其结论向不同病因亚组的外推性。因此, 目前基于TMAO与PCAS预后的证据仍存争议, 且现有模型多基于小规模单中心队列,

缺乏大规模外部验证。TMAO作为PCAS预后标志物的可靠性还有待进一步论证。未来仍需要通过多中心、大样本的前瞻性研究,并结合多组学技术深入挖掘,以构建更加精准、稳定的预测模型。

4 展 望

肠源性TMAO介导了PCAS的多器官损伤,主要累及了心脏、中枢神经系统、肾、凝血系统、肠道屏障及肝等,控制TMAO摄入可能有助于缓解PCAS后的多器官损伤。虽然近年来围绕TMAO的研究不断深入,但仍面临诸多挑战,未来需重点关注以下问题:第一,深入阐明TMAO在PCAS多器官损伤中的具体分子机制;第二,尽管已有基于初步临床研究的预后模型,但这些发现多源于小样本、单中心研究,其预测效能与临床适用性尚需大规模、多中心前瞻性研究进一步验证;第三,探索靶向TMAO途径的临床干预策略对PCAS多器官保护的疗效,并验证其安全性及有效性。通过深入揭示TMAO的作用机制,有望为PCAS患者的多器官保护与干预提供新的理论依据与治疗方向。

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