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·综　述·

冠状动脉微循环障碍：非阻塞性冠心病潜在发病机制

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［**摘要**］ 冠状动脉微循环障碍严重影响着人类健康，因心绞痛行冠状动脉造影检查的患者中非阻塞性冠心病较为常见。冠状动脉微循环障碍可能与非阻塞性冠心病患者心绞痛的发生密切相关，然而微血管性心绞痛与冠状动脉微循环障碍的关系尚不明确。本文就冠状动脉微循环障碍的主要危险因素（如糖尿病、炎症反应、衰老、性别等）、发病机制（内皮细胞功能紊乱、平滑肌细胞功能障碍等）和治疗手段的研究进展作一综述。

［**关键词**］ 冠状动脉微循环障碍；内皮细胞功能障碍；微血管性心绞痛；冠心病
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Coronary microvascular dysfunction: the potential mechanism of non-obstructive coronary artery disease

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［**Abstract**］ Coronary microvascular dysfunction (CMD) seriously affects human health. Non-obstructive coronary artery disease (NOCAD) is common in patients undergoing coronary angiography for angina. CMD may be closely related to the incidence of angina in NOCAD patients; however, the relationship between microvascular angina and CMD is still unclear. This review focuses on the main risk factors (diabetes mellitus, inflammation, aging, gender, etc.), pathogenesis (endothelial cell dysfunction, smooth muscle cell dysfunction, etc.) and treatment of CMD.

［**Key words**］ coronary microvascular dysfunction; endothelial cell dysfunction; microvascular angina; coronary disease
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冠状动脉微循环系统由前小动脉、小动脉、小静脉和毛细血管等构成。心肌缺血是由心脏代谢与血流之间的平衡受到破坏所致，许多心肌缺血患者因心绞痛症状而被怀疑为冠状动脉粥样硬化性心脏病（简称冠心病）而行冠状动脉造影检查，但是约40%行冠状动脉造影检查的心绞痛患者造影结果提示无明显的冠状动脉血管阻塞[1]。Lindahl等[2]开展的大型临床研究结果显示，约8%行冠状动脉造影检查的急性心肌梗死患者为冠状动脉非阻塞性急性心肌梗死。Cannon等[3-4]提出了微血管性心绞痛（microvascular angina，MVA）的概念，用以解释冠状动脉造影正常的心绞痛，认为冠状动脉微循环障碍（coronary microvascular dysfunction，CMD）可能是引发冠状动脉非阻塞性急性心肌梗死的原因。在过去的

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30 多年里，大量可用于评估冠状动脉功能状态的侵入性和非侵入性技术手段的出现使得探究 CMD 和微血管缺血病变成为可能[5]。Camici 和 Crea[6]将 CMD 分为 4 类：单纯性 CMD、CMD 伴心肌病、CMD 伴阻塞性冠心病和医源性 CMD。除导致心肌缺血的经典机制即动脉粥样硬化性疾病和冠状动脉大血管痉挛外，CMD 已成为心肌缺血的第 3 种潜在机制。本文就 CMD 的危险因素、发病机制和治疗手段的研究进展作一综述。

1　CMD 的危险因素

1.1　*糖尿病*　糖尿病是一种代谢性疾病，久坐、肥胖、过度饮食等均可促进糖尿病发病，约 80% 的糖尿病患者死于心血管疾病[7]。糖尿病不仅与心脏的微循环障碍有关，还与眼、肾脏和脑等器官的微循环功能改变密切相关[8]。糖尿病患者高血糖、胰岛素抵抗、高胰岛素血症、TNF-α 过度表达和炎症反应可通过下调一氧化氮（nitric oxide，NO）和升高内皮素 1，降低血流介导的内皮依赖性血管舒张，从而引起细胞内急性变化[9]。慢性高血糖与内皮依赖性或非依赖性冠状动脉血管舒张功能下降有关[10]。增强胰岛素敏感性可改善血管内皮细胞功能，进而改善无冠状动脉粥样硬化患者的心肌缺血症状[11]。然而也有研究显示，在排除其他混杂因素后，高胰岛素血症或胰岛素抵抗与 CMD 无相关性[12-13]。

1.2　*炎症反应*　炎症反应是一个相对较新的心血管疾病危险因素，其受重视程度越来越高。CRP 浓度升高是亚临床慢性炎症和急性炎症的标志，并与动态心电图检测的 MVA 患者心肌缺血发作频率增加有关，提示炎症反应可促进 CMD 的发生[14]。系统性红斑狼疮和类风湿关节炎患者 CMD 的发病率升高，其特征表现为冠状动脉血流储备与 CRP 浓度成反比，进一步表明炎症反应可能导致微血管功能异常[15-16]。Masi 等[17]给予牙周炎合并 2 型糖尿病患者牙周炎强化治疗 6 个月后，强化治疗组患者血浆 TNF-α 和干扰素 γ 浓度较标准治疗组显著降低，且其内皮功能障碍明显改善。

1.3　*衰老*　研究显示衰老是心脑血管疾病发生、发展的主要危险因素[18]。心脏随着年龄增长会发生改变，如心脏质量增加、心脏重构和心功能下降等。血管内皮结构和功能也会随着年龄增长而发生改变，血管收缩因子与血管舒张因子失衡可导致内皮舒张功能降低。NO 和前列环素等是内皮舒张功能改变的关键因素，内皮型一氧化氮合酶（endothelial nitric oxide synthase，eNOS）活性随着年龄增长而降低[19]。衰老会破坏内皮细胞黏附连接，这可能是老化血管出现舒张功能障碍的原因，而恢复内皮细胞黏附连接活性有望成为治疗血管老化的潜在靶点[20]。年龄相关的血管舒张功能和 CMD 可通过运动训练得到改善，运动训练对冠状动脉微血管功能的恢复作用可能与内皮功能改善有关[21]。

1.4　*血脂异常*　游离脂肪酸、非酯化脂肪酸和低密度脂蛋白是众所周知的心血管疾病的危险因素，这些指标异常也与很多代谢性疾病的发生关系密切。肥胖和血浆游离脂肪酸升高在动脉粥样硬化和心血管疾病发病过程中起着重要作用[22]。游离脂肪酸升高被认为与血管内皮功能紊乱有关，其损害内皮细胞的机制可能涉及 NO 产生受损、炎症反应、氧化应激和促进内皮细胞凋亡等[23]。三酰甘油和游离脂肪酸还可通过激活肾素－血管紧张素系统导致血管氧化应激损伤，引起心肌微循环功能障碍[24]。Tampakakis 等[25]报道静脉注射脂质可导致健康人体内皮细胞和单核细胞内质网应激、CMD，提示代谢紊乱与内质网应激和心血管疾病存在密切联系。氧化低密度脂蛋白诱导的内质网应激和内皮细胞凋亡是动脉粥样硬化发生、发展的关键因素[26]，而高密度脂蛋白具有抗氧化、抗凋亡、抗炎和抗血栓形成等功能，这也是其具有内皮细胞保护作用的原因[27]。多不饱和脂肪酸（如 omega-3）在降低人群肥胖、2 型糖尿病和冠心病的发病率方面具有重要作用[28]。

1.5　*女性*　因疑似心肌缺血性疾病而进行冠状动脉造影检查的患者中，60%～70% 的女性和 30% 的男性患有非阻塞性冠心病[29]。一般对女性缺血性心肌病的识别常被延误或推迟，这是由于女性特异的心血管疾病的病理生理机制不同于男性。女性出现心血管疾病症状的时间通常较男性晚 10～15 年，且其暴露于危险因素（如高血压、糖尿病、吸烟和血脂异常）的程度高于男性[30]。当评估患者心肌缺血的症状和体征时，女性非阻塞性冠心病患者较男性患者的症状更显著，心血管功能紊乱更严重，发病率更高[31]。2012 年美国心脏病学会基金会（American College of Cardiology

Foundation，ACCF）/ 美国心脏协会（American Heart Association，AHA）/ 美国医师学会（American College of Physicians，ACP）/ 美国胸外科学会（American Association for Thoracic Surgery，AATS）/ 预防性心血管护士协会（Preventive Cardiovascular Nurses Association，PCNA）/ 心血管造影和干预学会（Society for Cardiovascular Angiography and Interventions，SCAI）/ 胸外科医师学会（Society of Thoracic Surgeons，STS）稳定型缺血性心脏病患者的诊断和管理指南提示，在引起 CMD 和内皮功能异常的微血管疾病中，女性患者的心肌缺血程度高于男性[32]。

1.6 *心血管疾病* 急性心肌梗死、冠心病和高脂血症等与冠状动脉微血管功能紊乱密切相关。约 90% 冠状动脉血流供应发生在心室舒张期，冠状动脉血流对由间质或血管周围组织纤维化引起的血管外压增加、左心室舒张功能不全异常敏感[33]。由于冠状动脉血流量主要发生在心室舒张期，因此心室舒张期时长在冠状动脉血流供应中也起着至关重要的作用。冠状动脉内斑块可使冠状动脉管径减小，进而降低冠状动脉血流储备、损害心肌血流灌注。冠状动脉内斑块与劳力性或情绪性心绞痛、静息性心绞痛的发作密切相关。Moccetti 等[34]研究发现急性心肌梗死可引起外周血管一系列变化，包括上调内皮炎症黏附分子和血小板 - 内皮黏附因子。这些外周微血管改变在存在高脂血症的情况下持续时间更长，与促进斑块生长和炎症发生有关，并且可通过阻断还原型烟酰胺腺嘌呤二核苷酸磷酸（reduced nicotinamide-adenine dinucleotide phosphate，NADPH）氧化酶调控这一病理过程[34]。

此外，高血压、肥胖、腺苷、炎性因子、NO、内皮素、血管紧张素Ⅱ和雌激素等也对 CMD 发展起着重要作用[5]。

2 CMD 的发病机制

2.1 *冠状动脉痉挛* 心外膜冠状动脉痉挛的概念最初由 Prinzmetal 等[35]提出，Maseri 等[36]进一步将其完善。血管痉挛可发生于粥样硬化斑块所在部位或造影检查提示正常的血管，冠状动脉痉挛可致冠状动脉血流储备显著下降。Ford 等[37]研究发现全身性微血管功能异常在 MVA 和血管痉挛性心绞痛患者中较为常见，其机制涉及内皮素 1 表达改变、内皮功能紊乱和血管痉挛增强。冠状动脉内应用麦角新碱或乙酰胆碱可诱发冠状动脉痉挛，重现血管痉挛性心绞痛患者心绞痛发作时的症状和心电图表现[38-39]。有研究显示，因心绞痛行乙酰胆碱试验的患者中，约 1/4 存在微血管痉挛，且伴有典型的缺血性心电图表现、无明显的心外膜血管管径改变[39]。

2.2 *内皮细胞功能紊乱* 内皮细胞具有分泌 NO、前列环素、过氧化氢等物质的功能，内皮细胞释放的 NO 能有效抑制线粒体代谢、减少活性氧（reactive oxygen species，ROS）产生和抑制炎症反应[40-41]。NO 还可以降低血小板活化和黏附分子表达，从而抑制血栓形成和血管炎症[42-43]。在疾病或应激过程中发生内皮细胞功能障碍时，NO 释放减少，内皮素 1、血栓素 A2 和 ROS 释放增加，这些改变可引起组织炎症，还可抑制或激活细胞凋亡、调节心肌细胞的收缩能力[9]。在冠心病早期，局部内皮剪切力降低与微血管和外膜血管内皮细胞功能紊乱密切相关[44]。

2.3 *平滑肌细胞功能紊乱* 血管平滑肌细胞是阻力动脉和小动脉壁的主要效应器，通过调控血管平滑肌细胞的稳态舒缩或血管张力调节血管阻力。血管平滑肌细胞的细胞膜离子通道和内质网可调控细胞内钙离子浓度，后者在调节血管平滑肌细胞舒缩活性和血管张力方面有重要作用[45]。血管平滑肌细胞内 DNA 氧化损伤后碱基切除修复功能障碍可导致 8- 氧化鸟苷蓄积，进而促进血管内动脉粥样硬化斑块的形成与发展[46]。血管平滑肌细胞功能异常可破坏血管正常的收缩和舒张功能，改变血管阻力，最终引起心肌缺血性疾病。

2.4 *心肌水肿* 间质渗透压升高、血管通透性增加、离子转运异常和炎症等共同促进了心肌组织水肿的发生、发展[47]。冠状动脉微血管受压后可导致血小板 - 中性粒细胞聚集增多和冠状动脉微血管阻塞加重。心肌水肿也可进一步破坏急性 ST 段抬高型心肌梗死患者的冠状动脉血流量。

除此之外，心肌血管重构、毛细血管密度降低、血管周围纤维化、再灌注损伤、经皮冠状动脉介入相关的微栓塞和心脏移植术等也是 CMD 发生、发展的可能原因和潜在机制[48]。

3 CMD 的治疗现状

CMD 的治疗目标为改善或消除心肌缺血的危险因素，改善患者生活质量，改善患者预后，以及

鉴别并解决与临床预后不良相关的因素。

可通过改善内皮细胞功能紊乱、管理心血管疾病的危险因素及患者生活方式实现改善 CMD 症状的目的。CMD 合并 MVA 患者常伴有内皮细胞功能紊乱。积极管理所有可改变的传统危险因素（如高血压、糖尿病、肥胖、抽烟、久坐和高脂血症等）是改善 MVA 患者症状的重要措施[49]。单独应用他汀类药物或联合其他药物被证实对改善无冠状动脉阻塞性冠心病患者的内皮细胞或平滑肌细胞功能紊乱效果显著[50]。给予冠状动脉微血管痉挛患者 β 受体阻断剂时应有所警惕，因为此类药物可通过激活冠状动脉血管的 α- 肾上腺素能受体促进冠状动脉血管收缩。伊伐布雷定可通过降低心室率减少心肌氧耗，但是目前仅有较少的证据提示该药物对改善 MVA 患者症状有效[5]。曲美他嗪是一种心肌能量代谢调节剂，可在心肌缺血时通过使脂肪酸氧化减少改善心肌代谢，从而改善患者的症状和行动能力[51]。具有抑制心肌细胞动作电位晚期钠离子流作用的雷诺嗪，可改善非阻塞性冠心病女性患者和心肌缺血伴 CMD 患者的症状与冠状动脉血流储备[52]。Villano 等[53]报道雷诺嗪和伊伐布雷定联合应用常规抗缺血性药物可能对症状控制不良的 MVA 患者有治疗作用。由于异常的心脏伤害性感受可能是某些 MVA 患者胸痛的主要原因，三环类抗抑郁药丙咪嗪亦被学者推荐用于该病的治疗[54]。

4　小　结

目前评估 CMD 的手段分为侵入性（冠状动脉血流储备、微循环阻力指数等）和非侵入性（如 MRI、PET-CT、心脏超声等）方法，但是该病评估难度大、准确性差强人意。由于缺乏理想的 CMD 动物模型，探究其发病机制及筛选有效药物较为困难。为了更好地管理 CMD，要做到以下两点：一方面，CMD 大多隐匿起病、症状轻，但其危害大、疾病进程不可逆，患者和医务工作者应予以高度重视；另一方面，新技术、新手段和新设备的诞生会为科研工作者探索和研究 CMD 提供助力，需不断促进医疗辅助学科的发展。

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