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Hans汉斯

冠状动脉微循环障碍治疗进展

王　涵[1]，苏　立[2*]

[1]重庆医科大学，重庆
[2]重庆医科大学附属第二医院，重庆

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摘　要

心绞痛或者心肌梗死传统上被认为是由阻塞性冠状动脉疾病引起的。然而，大量心绞痛患者或者一部分急性心肌梗死患者在接受冠状动脉造影或冠状动脉CT血管成像技术检查未见冠状动脉大血管狭窄或狭窄 < 50%，这些患者中有很大一部分患有冠状动脉微血管功能障碍(Coronary Microvascular Dysfunction, CMD)。CMD已被确定为心脏缺血的原因之一，冠状动脉微血管功能障碍可以单独发生，也可以与阻塞性冠状动脉疾病一起发生。随着侵入性和非侵入性技术的出现，在过去的几年中，冠状动脉微血管系统得到了更广泛的研究。不幸的是，尽管已确定CMD在几种情况下的病理生理学和预后作用，但迄今为止，还没有针对CMD的特异性治疗方法，我们主要讨论目前临床研究产生的潜在的治疗策略。

关键词

冠状动脉，微循环障碍，治疗

Progress in the Treatment of Coronary Microvascular Dysfunction

Han Wang[1], Li Su[2*]

[1]Chongqing Medical University, Chongqing
[2]The Second Affiliated Hospital of Chongqing Medical University, Chongqing

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Abstract

Angina pectoris, or myocardial infarction, has traditionally been considered to be caused by obstructive coronary artery disease. However, in a large number of patients with angina pectoris or

*通讯作者。

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some patients with acute myocardial infarction, coronary angiography or coronary CT angiography showed no coronary artery stenosis or stenosis. 50%, a large proportion of these patients have coronary microvascular dysfunction. Coronary microvascular dysfunction has been identified as one of the causes of cardiac ischemia. Coronary microvascular dysfunction may occur alone or in conjunction with obstructive coronary artery disease. With the advent of non-invasive and invasive technologies, the coronary microvascular system has been studied more extensively in the past few years. Unfortunately, although the pathophysiological and prognostic role of coronary microcirculation disorders has been established in several conditions. However, to date, there is no specific treatment for CMD, and we mainly discuss the potential treatment strategies arising from current clinical studies.

Keywords

Coronary Artery, Microvascular Dysfunction, Treatment

1. 引言

冠状动脉微循环概述

冠状动脉微循环是指心脏中由微动脉(<300 μm)、毛细血管(平均 8 μm)和微静脉(<500 μm)构成的微循环系统。当冠状动脉微循环系统受到一种或多种因素影响后，即可出现冠状动脉微血管功能障碍(coronary microvascular dysfunction, CMD)。冠状动脉血流担负着为心肌供氧的任务，当氧需增加或在经体液因素的调节和药物作用下，冠状动脉会发生扩张，冠状动脉血流从静息状态增加到充血状态，这种冠状动脉血流增加的能力被称作冠状动脉血流储备(coronary flow reserve, CFR)，CFR 对临床判断血流灌注指导意义很强，CFR < 2.0 即可判定患者出现 CMD。

2. 机制及检查方法

CMD 的发生机制比较复杂，与多种因素相关，比如微循环栓塞和痉挛、缺血、再灌注损伤及个体差异等相关。现目前诊断主要分为侵入性和非侵入性检查方法。非侵入性方法主要有正电子发射断层扫描(positron emission tomography, PET)，心脏磁共振(cardiovascular magnetic resonance, CMR)，多普勒超声心动图，动态心肌灌注 CT；侵入性检查方法主要有 CFR，微血管阻力指数(index of microcirculatory resistance, IMR)，顺时无波形比值(Instantaneous Wave-free Ratio, iFR)，部分血流与储备(fractional flow reserve, FFR)。目前临床上比较公认的评价微血管功能的是侵入性方法检测的 CFR，一般认为 CFR < 2.0 即存在微循环障碍。但是对操作者的技术要求高、手术时间长且费用较昂贵，在临床并未广泛开展。对于需要行经皮冠状动脉介入治疗(percutaneous coronary intervention, PCI)治疗的患者，可直接通过导管技术评估冠状动脉微循环功能。使用非侵入性技术，只有在使用计算机断层扫描冠状动脉造影或者侵入性冠状动脉造影排除阻塞性冠状动脉疾病(coronary artery disease, CAD)后才能诊断 CMD。应用较多的非侵入性检查是 PET 或 CMR。PET 现在被认为是 CMD 无创评估的金标准参考，然而，由于可用性有限且成本高，其在临床实践中的使用受到限制。

3. 治疗方式

3.1. 药物治疗方式

3.1.1. 选择性钾通道开放剂

尼可地尔是一种选择性钾通道开放剂，具有双重作用，包括扩张冠状动脉和外周血管以及通过缺血预处理来保护心脏，以此来改善冠状动脉微循环。Kostic J 等[1]将 32 例接受直接经 PCI 的 ST 段抬高型心肌梗死患者纳入研究，分别在给予尼可地尔前后测量患者 IMR，发现尼可地尔给药后 IMR 显著降低。另外 Hirohata A 等[2]将 62 名接受 PCI 的稳定型心绞痛患者随机分配到对照组或尼可地尔组中，在 PCI 后立即测量 IMR 和 24 小时后检测肌酸激酶同工酶(creatine kinase-myocardial band, CK-MB)、心肌肌钙蛋白 I (cardiac troponin I, cTnI)，结果发现，对照组的 IMR 比尼可地尔组高；并且 cTnI 较尼可地尔组显著升高，另外对照组 cTnI 升高超过正常范围的发生率也明显高于尼可地尔组。

3.1.2. Rho 激酶抑制剂

Rho 激酶(Rho-associated kinases, ROCKs)属于丝氨酸/苏氨酸激酶家族，是小 GTP 结合蛋白 RhoA 的重要下游效应器。Rho 激酶有两种同工型，ROCK1 和 ROCK2，它们具有不同的功能，ROCK1 用于循环炎症细胞，ROCK2 用于血管平滑肌细胞。众所周知，RhoA/Rho-激酶通路在许多细胞功能中发挥重要作用，包括收缩、运动、增殖和凋亡，其过度活性会诱导氧化应激并促进心血管疾病的发展。此外，Rho 激酶的重要作用已在血管痉挛、动脉硬化、缺血/再灌注损伤、高血压、肺动脉高压和心力衰竭的发病机制中得到证实[3]。因此，Rho 激酶途径是心血管医学中一个重要的新治疗靶点。法舒地尔是一种 Rho 激酶抑制剂，将冠状动脉内给予法舒地尔，发现显着改善血管痉挛性心绞痛(vasospastic angina, VSA)患者的 IMR，另外发现它可有效预防 VSA 患者乙酰胆碱引起的冠状动脉痉挛和由此产生的心肌缺血[4] [5]，另外研究提出 Rho 激酶活性可用于 VSA 患者的预后分层，具有高 Rho 激酶活性的 VSA 患者的预后明显更差[6] [7]。

3.1.3. ACE-I 或者 ARB

血管紧张素 II 是一种较强的动脉血管收缩剂，血管紧张素转换酶抑制剂(angiotensin-converting enzymeinhibitors, ACE-I)可以通过反向重塑冠状动脉和改善微血管功能来改善冠脉动脉血流[8]。Pauly D.F 等[9]发现将 61 名有缺血症状和体征但没有 CAD 的女性随机分配在 ACE-I 组或者安慰剂组，16 周后 ACE-I 组的 CFR 有所改善，另 ACE-I 对基础 CFR < 2.0 的患者的冠脉改善更明显[10]。Higuchi，T 等[11]在一项前瞻性研究中发现在稳定性冠心病患者中，血管紧张素 II 受体拮抗剂(angiotensin II receptor blocke, ARB)可改善 IMR，微循环的改善先于血压的降低，这更表明了 ARB 对微血管功能有直接的有益影响。ACE-I 和 ARB 均会改善冠状动脉微循环，但是两种药物对冠脉的微循环改善程度上可能存在一些差异。有研究发现 2 型糖尿病患者的 IMR 在接受替莫卡普利治疗后得到改善大于坎地沙坦[12]；也有研究发现无症状的高血压引起的左心室肥厚患者在长期使用赖诺普利而不是氯沙坦后，心肌灌注储备和最大冠状动脉流量得到改善[13]，所以我们是否能得出 ACE-I 比 ARB 改善冠状动脉微循环的效果更好，未来可能进行更大规模、持续时间更长的对照试验来进一步验证。

3.1.4. 钙通道阻滞剂

钙通道阻滞剂(calcium channel blocker, CCB)不能改善 CMD 患者的 CFR 但可以通过扩张冠状动脉来改善心绞痛的发作时的症状[14]。一项 CCB 对 VSA 患者预后的影响荟萃分析显示贝尼地平、氨氯地平、硝苯地平或地尔硫卓是主要有效抑制 VSA 发作的 4 种主要 CCB，贝尼地平显示出比其他药物显着更有益的预后作用，贝尼地平的总事件、心血管事件和脑梗塞的发生率往往较低[15] [16]。

3.1.5. 脂肪酸氧化抑制剂

雷诺嗪是一种部分脂肪酸氧化抑制剂，它可以抑制线粒体的脂肪酸 β 氧化，增加心肌葡萄糖氧化，它还是一种选择性晚钠电流抑制剂，减少缺血心肌细胞内钙超载，改善舒张期心室壁张力和冠状动脉血流，现在有研究发现它可以改善冠状动脉微循环。Mehta P K 等[17]将 20 名患有心绞痛、无阻塞性 CAD 且腺苷负荷 CMR 成像显示 ≥ 10%缺血性心肌的女性进行了一项随机、双盲、安慰剂对照、交叉试验，研究发现使用雷诺嗪的患者比安慰剂组的西雅图心绞痛问卷(seattle angina questionnaire, SAQ)评分显着更好，雷诺嗪组的 CMR 心室中部定量心肌灌注储备指数(myocardial perfusion reserve index, MPRI)有更高的趋势，特别是对于那些 MPRI 更低的患者，它的改善更加明显，表明雷诺嗪可改善心绞痛，心肌缺血也可能得到改善；Rambarat C A 等[18]也证实了这一观点。但也有研究提出支持雷诺嗪会改善 CFR < 2.5 的患者的 MPRI、SAQ 心绞痛频率，但提出雷诺嗪不会改善 SAQ 心绞痛频率评分、侵入性微血管功能或峰值代谢当量、运动刺激的心肌血流或 CFR [19] [20] [21]，未来可能需要更多的研究。曲美他嗪可以通过阻断长链 3-酮酯酰辅酶 A 硫解酶抑制脂肪酸的 β-氧化促进葡萄糖氧化，当在细胞缺氧或者缺血情况，它可以通过增强葡萄糖氧化优化能量代谢，维持缺血中适当的能量代谢，Rogacka D 等[22]将曲美他嗪应用于 34 名 X 综合征，发现治疗 1 个月和 6 个月显着延长了患者运动的持续时间。

3.1.6. 抗血小板药物

血栓素 A2 合酶、血栓素 A2、血栓素前列腺素受体的激活会导致动脉收缩、血小板聚集和血管损伤。研究显示血栓素[23]。血栓素 A2 抑制剂(阿司匹林和 P2Y12 血小板抑制剂)可以通过抑制血小板的聚集、减少内皮血小板粘附来改善冠脉微循环。不同的抗血小板药物之间的改善能力可能存在差异，Park K 等[24]发现将需要支架植入的急性冠状动脉综合征患者随机分配到替格瑞洛或氯吡格雷组治疗 6 个月后，替格瑞洛组的 IMR 显着低于氯吡格雷组且 CFR 高于氯吡格雷，这可能与替格瑞洛可增加血浆腺苷水平有关。但最近的一项研究提出不同的观点，他们发现将接受纤溶的急性心肌梗死的患者随机分配至替格瑞洛组和氯吡格雷组，通过心肌造影超声心动图(myocardial contrast echocardiography, MCE)获得的整体心肌灌注评分指数评估冠脉微循环，发现与氯吡格雷相比，替格瑞洛对冠状动脉微循环没有改善，尽管替格瑞洛的血小板聚集到二磷酸腺苷(adenosine diphosphate, ADP)较低[25]，未来可能需要更多的临床研究炎症。

3.1.7. 降脂药物

他汀类药物可减少斑块富含脂质的核心、炎症、巨噬细胞和泡沫细胞的形成，促进纤维帽增厚，并降低血小板反应性。他汀类药物治疗对心脏综合征-X 中运动诱发的缺血和肱动脉血流介导的扩张均产生有益影响，这种有益作用的机制可能是内皮功能改善的结果[26]。既往研究表明微血管异常和内皮功能障碍是导致冠状动脉血流缓慢的原因。接受阿托伐他汀治疗 8 周后，CFR 值显着增加(1.95 ± 0.38 vs. 2.54 ± 0.56 ($p < 0.001$)，这一实验也证明了他汀类药物改善了内皮功能[27]。Pcsk 9 抑制剂(Several the use of proprotein convertase subtilisin/kexin type 9 inhibitors, PCSK9i)是一种目前来说降脂效果最好的降脂药物，目前对于它是否能改善冠状动脉微循环的研究尚少，未来需要更多的大型研究验证。

3.1.8. β 受体阻滞剂

在人体心脏的代谢刺激过程中，一氧化氮(nitric oxide, NO)的释放对微血管舒张有显着贡献，而心外膜血管的舒张主要依靠 NO 的释放。研究发现动脉粥样硬化或者具有动脉粥样硬化危险因素的患者在压力期间会降低 NO 生物利用度，从而通过限制心外膜和微血管冠状动脉舒张来导致心肌缺血[28]。奈必洛尔是一种高度选择性的 β1-肾上腺素能受体阻滞剂，Togni M 等[29]发现与对照组相比冠状动脉内注射奈必洛尔的试验组的 CFR 显着增加应该与奈必洛尔会增加基础及刺激内皮 NO 的释放有关。Galderisi M 等

[30]也提出第三代β受体阻滞剂(如卡维地洛和奈必洛尔)具有舒张血管的能力，它可以改善充血冠状动脉血流可能是由于α-肾上腺素能阻滞和/或NO介导使得血管阻力降低，这种改善显然对患有冠状动脉疾病的患者有益，并表明冠状动脉微血管功能得到改善。

3.1.9. 伊伐布雷定

伊伐布雷定是一种专门作用于窦房结的新型降心率药物可通过抑制 If 电流选择性地降低窦房结活动，从而改善心肌灌注和减少心肌需氧量，达到抗心绞痛和抗缺血作用[31]。Skalidis E.I 等[32]指出伊伐布雷定治疗可显着改善稳定型 CAD 患者的充血冠状动脉血流速度和 CFR。即使在心率校正后，这些效果仍然存在，表明微血管功能得到改善。

3.1.10. L-精氨酸

精氨酸是一种内皮源性 NO 的前体，它可以改善微血管性心绞痛患者冠状动脉微循环的内皮依赖性血管舒张[33]。一项双盲、随机研究发现口服 L-精氨酸的没有明显 CAD 的患者，在 6 个月后测量内皮依赖性冠状动脉血流储备较安慰组增加，这与血浆内皮素浓度的降低有关[34]。许多临床研究证明了浆果成分中含有精氨酸，证明了它在改善大血管和微血管功能方面的功效，由于目前没有旨在治疗 CMD 的使用浆果的临床研究，因此富含多酚类的食物可能在未来可以作为一种潜在的改善冠脉微血管循环的方式[35]。

3.1.11. 不对称二甲基精氨酸(Asymmetrical Dimethylarginine, ADMA)抑制剂

ADMA 是一种内源性内皮 NO 合酶抑制剂，它可与 L-精氨酸产生竞争，从而导致内皮功能障碍。研究发现冠状动脉疾病患者的 ADMA 水平高于健康对照组，多项荟萃分析结果表明，ADMA 水平升高与 CAD 疾病风险增加有关[36]。因此未来可以通过抑制 ADMA 来增加 NO，从而提高心肌的灌注。也有研究提出 ADMA 不光是通过简单抑制内皮 NO 合成来损伤血管，还可以通过上调血管紧张素转换酶和增加血管紧张素 II1 型受体导致氧化应激，造成血管的损伤[37]。

3.1.12. 选择性 ET(A)受体拮抗剂

内皮素-1 (endothelin-1, ET-1)是最有效的血管收缩剂之一，它使得微血管内皮功能障碍和血管收缩增强，在 CAD 的发病机制中起重要作用，选择性 ET(A)受体拮抗剂可以通过增加 NO，从而扩张冠脉，改善微循环[38] [39]，研究发现在 CMD 患者中的 ET-1 显着高于无 CMD 患者[40] [41]。阿曲生坦是一种选择性(ET(A))拮抗剂，CMD 患者使用阿曲生坦治疗 6 个月可减轻内皮功能障碍节段冠状动脉斑块的进展；它从基线起 6 个月时对乙酰胆碱的冠状动脉血流百分比变化比安慰剂组有显着改善，改善了冠状动脉微血管内皮功能，并支持内源性内皮素系统在人类早期动脉粥样硬化内皮功能调节中的作用[42] [43]。Halcox J.P 等[44]研究发现使用了选择性 ET(A)受体拮抗剂(BQ-123)的 CAD 患者的心外膜直径较安慰剂组增加，而 IMR 较安慰剂组下降，这表明它可能在治疗内皮功能障碍和动脉粥样硬化方面具有治疗潜力。

3.1.13. 叶酸和维生素 B12

一项研究同型半胱氨酸损害人类冠状动脉微血管扩张器功能的双盲交叉试验发现急性高同型半胱氨酸血症会由于 NO 生物利用度降低而损害人体冠状动脉循环中的微血管[45]。Bleie 等[46]发现长期联合叶酸和维生素 B12 治疗可增加基础和腺苷诱导的最大冠状动脉血流量，这可能反映了稳定型 CAD 患者微血管功能的改善。Tawakol A 等也发现[47]高剂量口服叶酸可显着降低冠状动脉疾病患者的血压并增强冠状动脉扩张。

3.1.14. 磷酸二酯酶(phosphodiesterase, PDE)抑制剂

1) 西洛他唑可以抑制由 ADP、肾上腺素导致的血小板聚集，抑制人体血小板中血栓 A2 的产生，产

生抗血小板作用，也可以通过选择性地抑制血管平滑肌内的磷酸二酯酶 III 的活性，发挥血管扩张作用。现西洛他唑目前主要用来改善因为慢性动脉闭塞症引起的溃疡、肢痛、冷感及间歇性跛行等缺血症状及预防脑梗死复发。在一项西洛他唑对血管痉挛性心绞痛患者血管舒缩反应性的影响研究中发现西洛他唑治疗组的 L-精氨酸和直径变化显着增加，西洛他唑增加了流量依赖性冠状动脉扩张；说明它可改善 VSA 患者的 CMD 和冠状动脉血流动力学[48]。另一研究也发现服用西洛他唑组的患者对比氨氯地平组发生胸痛的频率低和严重程度较轻，西洛他唑可能对常规氨氯地平治疗无法控制的 VSA 患者是一种有效的治疗方法[49]。

2) 西地那非是一种用于治疗勃起功能障碍的 PDE5 选择性抑制剂，目前已被发现可引起孤立的心外膜冠状动脉段的松弛。NO 通过刺激血管平滑肌中的鸟苷酸环化酶产生环磷酸鸟苷(Cyclic guanosine monophosphate, cGMP)引起血管舒张。由此产生的血管扩张作用受 cGMPPDE 家族的调节。在一项研究中发现西地那非可扩张心外膜冠状动脉，改善内皮功能障碍，抑制 CAD 患者的血小板活化，与硝酸异山梨酯和安慰剂相比，它对心肌缺血有中等效果[50]。在存在冠状动脉狭窄的情况下，西地那非抑制 PDE5 会导致冠状动脉阻力血管舒张，并增加运动期间流入缺血性心肌区域的血流量[51]；但西地那非不能改善冠心病患者的外周内皮依赖性血管舒缩或纤溶功能，不太可能逆转冠心病患者的全身血管功能障碍[52]。

3.1.15. 其他

自体 CD34+细胞具有微循环再生潜能和旁分泌抗炎作用，现已被证明可以促进血管修复并增强微血管系统中的血管生成，由此产生的微循环恢复改善心肌组织灌注，从而导致冠状动脉微血管功能的恢复。研究发现缺血性和非阻塞性冠状动脉疾病患者接受冠状动脉内输注 CD34+细胞治疗后，6 个月时 CFR 更高，心绞痛严重程度更低，生活质量更好。目前的研究支持 CD34+细胞在微血管心绞痛患者中的潜在治疗作用[53] [54]。一项随机、双盲、安慰剂对照研究二甲双胍对心绞痛和冠状动脉正常女性微血管功能和运动耐量的影响发现二甲双胍组显着改善了内皮依赖性微血管反应，说明二甲双胍可改善胸痛和冠状动脉造影正常的非糖尿病女性的血管功能并减少心肌缺血。但是未来可能需要进行更大规模、持续时间更长的对照试验[55]。目前的研究证明与男性相比，女性有更多非阻塞性冠状动脉疾病的心肌缺血。一项低剂量激素治疗无阻塞性冠状动脉疾病绝经后妇女心肌缺血的随机对照试验将受试者被随机接受 1 mg 炔诺酮/10 microg 炔雌醇或安慰剂治疗 12 周，结果发现低剂量激素治疗改善了胸痛症状、更年期症状和生活质量，但并未改善缺血或内皮功能障碍[56]，未来可能需要更多的大型研究验证。

3.2. 非药物治疗方法

减肥和间歇训练可以引起总胆固醇、甘油三酯、非高密度脂蛋白胆固醇和低度炎症的降低[57]。Olsen R.H [58]等发现有氧间歇训练和减肥改善了 CFR，因此我们可以得出这两种干预措施都可能通过改善冠状动脉微血管功能来影响 CAD 患者的预后。也有研究提出体育锻炼和放松训练可以减轻 X 综合征患者的心绞痛症状，可以提高患者的运动能力和生活质量[59] [60]。脊髓刺激(spinal cord stimulation, SCS)最初被提议作为一种治疗顽固性心绞痛的方法，用于治疗不适于经皮和手术血运重建的阻塞性冠状动脉疾病患者，现通过 SAQ 和生活质量视觉模拟量表评估心脏功能状态，发现难治性心脏综合征患者在 SCS 组的随访中得到改善，例如心绞痛发作的次数减少、持续时间减少和严重程度减轻[61] [62]。接受增强体外反搏(enhanced external counterpulsation, EECP)治疗的 X 型心脏综合征患者的 SAQ、每周心绞痛频率和三硝酸甘油酯使用、局部缺血均有初步改善，并且在长期的随访中也发现它是安全的一种治疗方式，故对于一些难治性的心绞痛，它可能是一种好的治疗方式[63] [64]。

4. 总结

CMD 是一种冠状动脉微循环结构和和功能出现异常的病变，衰老、吸烟、高血压、糖尿病、肥胖、

高脂血症以及炎症等均是 CMD 的高危因素。既往一些患者出现心绞痛或者心肌梗死的表现，但造影显示无明显异常或者异常程度不足以解释上述症状现在可以用 CMD 来解释。现目前 CMD 的机制及诊断较为清楚，但目前没有专门针对 CMD 的治疗方案，故现在需要进行更多该领域的研究。

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