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Progress in the Treatment of Coronary Microvascular Dysfunction

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Abstract

Obstructive diseases of the epicardial coronary artery have been considered to be the leading cause of angina in the past two centuries. In addition, sudden epicardial coronary thrombotic occlusion has been considered to be the cause of acute myocardial infarction for nearly 100 years. However, in recent years, dysfunction of the coronary microvasculature has emerged as a further mechanism for myocardial ischemia. Coronary microvascular dysfunction (CMD) refers to impaired coronary flow reserve due to abnormalities in the function or structure of coronary microvasculature. Patients with CMD often present with recurrent angina pectoris 1, which may eventually develop into serious adverse events such as ischemic cardiomyopathy, acute coronary syndrome, and sudden cardiac death. Among patients with suspected coronary heart disease, the incidence of CMD was 41% in male patients and 54% in females. However, the criteria for the diagnosis and treatment of coronary microvascular dysfunction have not been clarified. This article reviews the research progress of coronary microvascular dysfunction in recent years.

Keywords

Coronary Microvascular Dysfunction, Acute Coronary Syndrome, Arteriosclerosis

冠状动脉微血管功能障碍治疗的研究进展

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摘 要

在过去的2个世纪，心外膜冠状动脉的阻塞性疾病被认为是心绞痛的主要原因。此外，近100年来，突发的心外膜冠状动脉血栓性闭塞被认为是急性心肌梗塞的原因。然而，近年来冠状动脉微血管系统的功能障碍作为心肌缺血的另一种机制出现在临床工作者的视野中。冠状动脉微血管功能障碍(Coronary microvascular dysfunction，CMD)是指由于冠状动脉微血管的功能或结构的异常导致的冠状动脉血流储备受损。CMD患者常表现为反复发作的心绞痛，最终可能会发展为缺血性心肌病、急性冠脉综合征、心源性猝死等严重不良事件。在可疑冠心病患者中，男性患者CMD的发病率为41%，女性发病率为54%。然而，冠状动脉微血管功能障碍的诊治标准尚未明确，本文对近几年冠状动脉微血管功能障碍治疗的研究进展做一综述。

关键词

冠状动脉微血管功能障碍，急性冠脉综合征，冠状动脉粥样硬化性心脏病

1. 正常冠状动脉的结构

冠状动脉系统是由三种具有不同功能的部分组成。心外膜冠状动脉是指直径约为 500 μm 至 5 mm 的大血管，发挥容量血管的作用，并且对血流的阻力很小。在心脏收缩期末期，心外膜冠状动脉扩张，其血液含量可增加将近 25%。扩张的同时，心外膜冠状动脉可积聚弹性能量，这种弹性能量在心脏舒张开始时即转化为血液的动能，有助于使心脏收缩时收缩的心肌血管迅速重新舒张[1] [2] [3]。前动脉是指直径约为 100~500 μm 的血管。作为心脏大动脉与微动脉的桥接部分，其血压随长度的延伸而逐渐下降。前动脉的功能是根据冠状动脉灌注压力或冠状动脉内血流量的变化，调节其下游血管的压力维持在一个相对稳定的范围内。近端前动脉对血流量的变化最为敏感，而远端前动脉则对压力的变化最为敏感。远端动脉是由直径 < 100 μm 的小动脉组成，随着长度的延伸，小动脉的血压明显下降。小动脉的紧张度受心肌代谢产物的影响，如腺苷、过氧化氢等心肌代谢产物。因此，小动脉对心肌血流量发挥代谢性调节的作用[4]。此外，小动脉还具有调节心肌血液供应和需氧量的特殊功能。

由此我们可以了解到，不同直径的冠状血管动脉对心肌血流有不同的调节作用。与心外膜冠状大动脉相比，前动脉和小动脉均低于目前冠状动脉血管的造影系统的分辨率，无法通过现有的血管造影技术显示[3]。自 20 世纪 50 年代生理学家发现冠状动脉微血管系统对维持适当的心肌血流灌注的重要性以来，近 30 年来已有足够的实验证据支持冠状动脉微血管的功能和结构的异常可以引起心肌灌注不足和心肌缺血，这种情况便被称为冠状动脉微血管功能障碍(CMD) [5]。

2. CMD 的治疗

2.1. 调节生活方式

CMD 的危险因素与冠状动脉疾病大致相似，包括高血压、糖尿病、高龄、高脂血症及吸烟等。研究显示，持续吸烟状态会使心肌血流储备分数下降 20%以上[6]。而良好的生活方式如戒烟、减重、平衡膳食(富含纤维，水果和蔬菜的饮食方式)、适量的有氧运动等[7] [8] [9] [10]不仅可以改善患者血管内皮功能、增加运动耐量，而且可以降低冠状动脉疾病的发病率，减少缺血性心肌病患者的胸痛发作频率，降低胸痛程度，进而改善患者的生活质量。因此，更应鼓励老年以及冠状动脉疾病患者培养良好的生活方式。

2.2. 药物疗法

2.2.1. K 通道开放剂

尼可地尔在结构上属于硝酸酯类药物，是三磷酸腺苷敏感性钾通道的开放剂。尼可地尔既可以扩张心外膜冠状大动脉，也可以舒张冠状动脉小动脉。临床随机对照试验研究结果显示，尼可地尔可以改善 CMD 患者的心绞痛症状，并可以改善患者心电图运动试验的结果[11]。

2.2.2. 他汀类药物

内皮功能障碍在 CMD 的发生中扮演重要角色。他汀类药除了调脂作用外，还具有改善血管内皮功能[12]抗炎、保护血管的功能[13]。根据目前的脂质管理指南，适当强度和剂量的他汀类药物对改善内皮功能障碍发挥着极其重要的作用[14]对于内皮功能障碍引起的缺血性心肌病和持续性心绞痛患者，他汀类药物获益明显[12] [15]。

2.2.3. 血管紧张素转换酶抑制剂及血管紧张素受体阻滞剂

血管紧张素转换酶抑制剂(angiotensin-converting-enzyme, ACEI)和血管紧张素受体拮抗剂(angiotensin-receptor blocker, ARB)具有改善心肌血流储备的功能[16]，同时也具有保护血管内皮的功能[10]。ACEI、ARB 可增加患者的运动耐量，改善心绞痛症状。对于左心室舒张末压升高的 CMD 患者，可加用依普利酮或螺内酯。然而，一项女性 CMD 临床试验却发现 ACEI 与盐皮质激素受体拮抗剂的联合治疗并不能改善患者内皮功能或心肌血流储备[17]。

2.2.4. β 受体阻滞剂

β 受体阻滞剂可缓解 CMD 患者的持续性心绞痛的症状[17] [18]。对于有心肌缺血的症状与体征的患者，β 受体阻滞剂的耐受性良好[19] [20]。研究表明，β 受体阻滞剂可以减少患者的胸痛发作次数[21]，并具有改善血管内皮细胞功能的作用[22]。因此，服用 β 受体阻滞剂(如卡维地洛，拉贝洛尔或奈比洛尔)，对 CMD 患者可有获益[17] [23]。

2.2.5. 钙通道阻滞剂

钙通道阻滞剂通过阻断钙离子进入血管平滑肌细胞发挥舒张平滑肌的功能，可缓解 CMD 患者的胸痛程度并减少其发作频率[17] [18]。如果怀疑心外膜冠状动脉痉挛可能，则首选钙通道阻滞剂联合硝酸酯类药物治疗[17]。对于平滑肌功能障碍的患者，尤其是伴有心外膜冠状动脉或微动脉痉挛时，亦可首选钙通道阻滞剂，例如氨氯地平，地尔硫卓或维拉帕米等药物[24] [25]。

2.2.6 硝酸盐类药物

硝酸盐类药物可通过减小心脏前后负荷、降低心脏变时变力效应，从而减少心肌耗氧量而发挥抗心绞痛的疗效。如舌下含服硝酸甘油、硝酸甘油贴剂或长效硝酸盐口服药，是辅助治疗心绞痛的药物，可

缓解 CMD 患者的临床症状与体征。

2.2.7. 雷诺嗪

雷诺嗪是一种哌嗪衍生物[26]，已被 FDA 批准作为心绞痛治疗的辅助或一线治疗药物。特别是对于难治性心绞痛的患者、对传统抗心绞痛药物反应差或有禁忌症的患者，或伴低血压或心率缓慢等血流动力学不稳定的患者，可考虑使用雷诺嗪[26] [27]。然而，雷诺嗪的具体作用机制尚不明确，可能与抑制心脏动作电位的晚期钠电流而促使钠和钙浓度达到稳态水平有关[28]。此外，雷诺嗪可以在不影响心率或血压的情况下缓解心绞痛[7] [29]。心电描记压力测试显示雷诺嗪是改善心肌缺血的有效药物[30] [31] [32] [33] [34]。此外，研究表明，对于有心肌缺血症状和体征而无明显冠状动脉狭窄的女性患者，雷诺嗪治疗可明显改善其西雅图心绞痛评分量表结果[35]。以往认为雷诺嗪对女性患者的疗效不明显，但近年来的研究表明，使用雷诺嗪治疗时患者心绞痛症状的改善与心电图运动试验结果的变化无明显性别差异[36]。

2.2.8. 伊伐布雷定

伊伐布雷定通过阻断窦房结内的 If 电流而降低心率。研究显示，伊伐布雷定可改善稳定性 CMD 患者的心肌血流储备[37]。此外，亦有研究表明，伊伐布雷定可减轻 CMD 患者及无心外膜冠状动脉狭窄患者的心绞痛严重程度[38]。

2.2.9. 三环类药物

对于难治性心绞痛患者，除现存治疗方案之外，亦可选用非传统药物治疗。例如，若心绞痛的患者疼痛反应较强烈，使用低剂量三环类药物(如阿米替林、丙咪嗪或去甲替林)治疗可能是有效的[7] [29]。三环类药物治疗心绞痛的作用机制目前尚未明确，但可能与其对去甲肾上腺素摄取的调节作用、抗胆碱能以及 α-肾上腺素能受体拮抗作用有关。

2.2.10. 腺苷

腺苷是介导心脏疼痛的媒介，因此腺苷受体拮抗剂如黄嘌呤衍生物氨茶碱被用于治疗心绞痛和心肌缺血，其机制可能与抑制磷酸二酯酶有关。已有研究表明，对于持续性胸痛或有心肌缺血的症状和体征，而心电图未见明显冠状动脉狭窄的患者，腺苷受体拮抗剂疗效显著[39]。此外，表现为持续性胸痛或心肌缺血症状而无明显冠状动脉狭窄患者，其血管舒张能力明显受损，因此 α-肾上腺素能受体阻滞剂(如 α1 受体选择性阻断剂－多沙唑嗪)可能有效。然而，使用多沙唑嗪的患者心电图运动试验并未提示胸痛缓解或运动耐量有改善[40] [41]。尚需进一步研究明确 α-肾上腺素能受体阻滞剂对 CMD 的疗效。

2.2.11. 其他

法舒地尔，一种可以抑制血管平滑肌收缩的 Rho 激酶抑制剂，可增加心肌缺血阈值和运动耐量[42]，可能有抗心绞痛的疗效，目前正在研究之中。此外，磷酸二酯酶-5 抑制剂，如西地那非和他达拉非，可延长一氧化氮生物利用度。以上这些药物也作用于微血管，通过调节微血管舒缩而增加 CFR，可用于难治性心绞痛患者的治疗[43]。

2.2.12. 中药复方制剂

国内研究表明，丹红注射液可以有效改善 CMD 患者的心肌血流储备，改善心肌缺血症状，其机制可能与通过降低血清 ET-1 水平而保护内皮功能有关[44]。此外，多项中药复方制剂及单体成分的研究结果显示，茱萸、牡丹皮、川芎嗪、葛根素、姜黄素、黄芪多糖等可以通扩张冠状动脉微血管、改善心肌血流灌注，其机制可能与影响 NF-κB 等炎性信号通路相关[45] [46] [47] [48]。

2.3. 非药物治疗

CMD 的非药物治疗包括增强型体外反搏[17] [49]，神经刺激[50]和认知行为治疗[51]。增强型体外反搏可明显减少心绞痛发作次数并改善局部心肌缺血。神经刺激疗法适用于患有难治性心绞痛的患者[52]。有研究表明，脊髓刺激疗法可以明显减少患者心绞痛的持续时间、发作频率[53]。认知行为疗法可以作为心绞痛的辅助治疗。研究显示，自体认知行为疗法可以明晰减少患者缺血症状的发作频率和严重程度[54] [55]。

3. 结论

综上所述，CMD 与缺血性心肌病及非狭窄性冠状动脉疾病的发生发展密切相关，且可发生严重不良心血管事件，预后不良。CMD 的治疗方式包括改善生活方式、抗动脉粥样硬化、抗炎、改善血管内皮功能、舒张血管平滑肌等。近年来，中药复方制剂对 CMD 的治疗有一定进展，然而其具体有效成分、有效剂量、作用时间及作用机制仍需进一步探索。

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