介入术后冠脉无复流的危险因素识别与药物治疗

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摘要:冠脉无复流现象(NRP)作为经皮冠状动脉介入治疗(PCI)过程中的常见并发症,尤其高发于急诊 PCI 术中。无复流区范围随血运重建时间延长而扩大,是一种影响预后的独立危险因素,可导致梗塞面积扩大,左心室重塑,心律失常或复发胸痛等主要不良心脏事件(MACE)发生率显著增加。目前已有多种药用方案来预防无复流,主要包括硝普钠、维拉帕米、替罗非班、腺苷、尼可地尔、山莨菪碱等,其疗效各有优劣,现就无复流的判断及治疗做一综述。

关键词:无复流;经皮冠状动脉介入治疗;诊断;药物治疗;给药方式

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Identification of Risk Factors and Drug Therapy for Postoperative Coronary Artery No-reflow

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Abstract:Coronary no-reflow (NRP) is a common complication in percutaneous coronary intervention (PCI), especially in emergency PCI. The extent of no-reflow area expands with prolonged revascularization time and is an independent risk factor for prognosis, which can lead to an enlarged infarct size, left ventricular remodeling, arrhythmia or recurrent chest pain and other major adverse cardiac events (MACE). A significant increase. At present, there are a variety of medicinal programs to prevent no-reflow, mainly including sodium nitroprusside, verapamil, tirofiban, adenosine, nicorandil, and anisodamine. Now I will review the judgment and treatment of no reflow.

Key words:No reflow; Percutaneous coronary intervention; Diagnosis; Medical treatement Mode of administration

经皮冠状动脉介入术(PCI)治疗后,尽管心外膜冠状动脉成功血运重建,但是有时心肌的大部分区域仍未得到足够的灌注,从而使心肌持续缺血、缺氧,最终导致不可逆的心肌细胞损害,即是冠脉无复流现象(NRP)。关于其具体机制尚未完全阐明,可能系因多种因素引起冠脉微循环功能障碍和阻力小血管痉挛所致。支架置入或血管机械扩张后不仅使斑块破裂,且支架材料抑制平滑肌细胞增殖;再灌注时激活细胞释放如内皮素、白介素 6、肿瘤坏死因子和粘附 VCAM-1 等分子[1],造成内皮细胞肿胀、细胞凋亡和坏死,最终微血管栓塞形成,导致无复流。有研究显示 NRP 是 5 年死亡率的强预测因子[2],介入术后及早恢复心肌灌注是关乎患者预后的重要因素,因此预防和治疗 NRP 是术者最为关心的工作。本文通过查阅当前关于冠脉无复流的药物治疗等文献,并将从事临床及医疗工作一线的人员的用药经验进行分析和总结,为临床决策提供相关理论和依据。

1 冠脉无复流的危险因素与识别

1.1 危险因素 Poon K[3]等的研究发现一些病变特征如血管病变长、钙化、存在血栓、复杂病变和任何残余狭窄,是无复流发生的独立危险因素。年龄大、吸烟的患者血管内皮功能减退、易于凝块形成。有学者通过相干光断层扫描及血管内超声观察到其更多发生于血管斑块负荷重,且伴脂质核心的患者[4]。

1.2 临床评估技术手段 通过评估心肌梗死溶栓治疗血流分级(TIMI)、校正 TIMI 血流帧数(CTFC)、心肌灌注血流分级(TMP)、心肌呈色分级(MBG)、心肌声学造影、核素心肌灌注显象、多普勒组织成像、心电图 ST 段回落指数等指标来发现 NRP。其中临床常用的是 TIMI 血流帧数(TFC)计算法:即造影剂开始进入血管起始部位接触到两侧血管边界并向前血流动为第 1 帧,造影剂开始进入靶血管末端分支及界标(类似于第 3 级分支)的第 1 帧为末帧(所有冠状动脉造影资料均校正为 30 帧/s 采集数据);以及校正的 TIMI 帧数计算:参考 Gibson[5]等的方法,将左前降支的平均帧数除以 1.7 作为 CTFC,将 CTFC=40 定义为 TIMI 血流 2、3 级的分界线。

2 常用治疗药物

2.1 硝普钠 硝普钠不需细胞代谢即可直接产生一氧化氮(NO),发挥扩冠脉效应,不仅能够降低心脏的前后负荷,改善心排及心功能不全,且促进前列环素合成、增加血小板内环磷酸鸟苷浓度,抑制血栓素 A2 及血小板聚集,降低其活性,具有扩张动静脉平滑肌的双重作用[6]。有研究发现[7],推荐的冠状动脉内硝普钠应用剂量为 50~200 μg,最大值剂量为 1000 μg。有 2 项关于冠脉内注射硝普纳治疗无复流 Meta 分析[8,9]均提示了硝普钠在 PCI 期间对无复流有明显益处,且安全有效。

2.2 山莨菪碱 山莨菪碱是毒蕈碱胆碱能拮抗剂,调节交感和迷走神经活动间的平衡,缓解微血管痉挛、减少血栓形成,增加血压和心率,保证冠脉灌注压;

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其次可预防细胞内钙超载导致的再灌注心律失常，减少脂质过氧化，降低缺血-再灌注心肌肿胀，抑制心肌细胞凋亡，提供心脏保护作用[10]。而最新一项 Meta 分析显示[11]，山莨菪碱可改善 STEMI 患者 PCI 术后心肌梗塞溶栓血流分级（TFG）且提高 STR 与左心室射血分数（LVEF）。Shiru Bai 等[12]在分别给予介入术后无复流患者 1000 μg、2000 μg、4000 μg 山莨菪碱，发现高剂量更能降低 CTFC，且越高剂量越可能提供心脏保护作用越强。

2.3 腺苷　可拮抗血小板和嗜中性粒细胞，减少钙超负荷和氧自由基，并诱导 NO 致血管舒张；通过增加血流中组织纤溶酶原激活物释放而限制梗死面积。Niccoli G[13] 等于无复流患者中病灶远端给予腺苷获得明显疗效，随访 1 年与对照组相比并未提高不良心血管事件；Polimeni A 等[14]研究提示冠脉内给予腺苷能改善 LVEF，降低心衰发生，尽管增加短暂性房室传导阻滞发生率，但并不显示明显的致命性心律失常。另有研究显示[15]单支闭塞血管的 STEMI 患者冠脉内给予高剂量腺苷（2~3 mg）或硝普钠（500 μg）预处理并未减少梗塞面积或 MVO，且随访心衰发生风险较高，提示腺苷可能不需预防性使用。

2.4 尼可地尔　尼可地尔是具有独特的双重作用机制的 K^+-ATP 通道开放剂，可增加细胞中 K^+外流，致细胞膜超极化，抑制 Ca^{2+}的内流，减少 Ca^{2+}过载，从而减少心律失常发生。尼可地尔可发挥硝酸酯类作用，较小的冠状动脉（<100 μm）可更明显。Feng C[16] 发现，尼可地尔（冠脉内注射 2 mg，可重复至多 3 次）改善冠脉术后微循环及心肌灌注，减轻早期无复流。Yamada K[17] 给心梗患者以尼可地尔 2.0 mg/h 静脉注射降低肌酸激酶同工酶 CK-CM 峰值和 MVO，减少梗死面积。齐琪[18]等发现闭塞病变远端给药同样疗效显著，降低无复流发生率且随访预后良好。

2.5 维拉帕米　维拉帕米是非二氢吡啶钙通道阻滞剂，不仅可以产生内皮依赖性血管舒张，还通过选择性抑制 L 型钙通道受体，阻止离子钙内流，减少心室细胞内钙过载，减缓房室传导，降低心率、血压，但不影响 LVEF[19]。Wang L 等[20]发现冠状动脉内维拉帕米降低了 NRP，改善 MACE，其在降低室壁运动指数方面表现出一定优势。Abdelaziz 等[21]予病灶远端推注维拉帕米 750 μg 预处理并获得更好的 CTFC、MBG 等级，MVO 率更低；Abu Arab 等[22]尝试病灶远端给予肾上腺素 5~200 μg 与维拉帕米 100~200 μg/次（最多 7 次）发现血流恢复更佳。

2.6 替罗非班　替罗非班致使血小板 GPⅡb/GPⅢa 受体占有率水平升高，使血小板聚集过程不稳定，其可抑制纤维蛋白原和血管性血友病因子交联，诱发血小板及心外膜动脉血管的血栓解聚还具有抗炎作用。Ali-Hasan-Al-Saegh 等[24]分析比较了冠脉内和静脉给予 GPⅡb/Ⅲa 抑制剂的疗效，发现冠脉内给药可增加 LVEF 及 TIMI 等级，降低心衰发生率。Sun B[25]等学者发现病灶处给药在改进心肌组织再灌注方面疗效显著，理论上可达到更高的局部药物浓度和生物利用度，产生较好的血栓解聚效果和较少的微栓塞[31]。

2.7 其他　肾上腺素作为 β_2 受体激动剂，产生血管扩张作用，可能是肾上腺素治疗无复流的一种机制；无复流通常表现为低血压，可以由肾上腺素发挥的 α 激动剂活性纠正。最近一个关于难治性无复流患者中的回顾性研究中，病变远端给予 200~450 μg 肾上腺素，导致 9 例患者有所改善[26]。其可导致心率增加，但并无致命性心律失常。外源性脂联素在无复流中的应用也有报道，据称可减轻心肌与内皮损伤，并抑制炎症和细胞凋亡[27]；前列腺素 E_1 在冠脉病变的应用也有报道[28]，其副作用小，安全有效。

3 总结及展望

无复流的规范化治疗是当前冠脉介入领域研究的热点。关于山莨菪碱治疗无复流临床价值的荟萃分析今年首次被发表，研究发现其可以显着改善心肌再灌注和心脏功能，预后优良，耐受良好且经济，在当前主流抗无复流药物中居首位。其实用性值得进一步研究评估。及时纠正无复流是现下介入工作者的首要任务，本文总结了目前临床常用药物给药方式、安全或有效剂量及其可能不良后果，以期为当前临床工作提供一定诊疗思路。冠脉无复流的药物治疗研究仍有大量工作需要落实，如无复流的机制、相关微血管结构功能异常的基础研究及大型循证医学证据支持的相对安全的药物等。无复流更深层次研究以及器械水平的改良，将为更多冠脉无复流的患者提供思路，改善其长期预后。

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