·综　述·

急性 ST 段抬高型心肌梗死患者 PCI 术后冠脉无复流研究进展

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摘要：急性 ST 段抬高型心肌梗死（STEMI）是严重威胁人类生命健康的心血管疾病，起病凶险且死亡率高。随着经皮冠状动脉内介入（PCI）手术的开展，短期内尽快开通闭塞血管、恢复远端心肌血流灌注，能够显著降低 STEMI 患者病死率、改善临床预后。然而，相当部分 STEMI 患者 PCI 术后出现冠脉内无复流（CNR）现象，极大地阻碍了其临床治疗效果和远期预后改善。目前，CNR 的病理机制尚未完全清楚，临床上亦缺乏可靠的预测指标和治疗措施。部分药物和手术操作显示出一定预防和改善 PCI 术后 CNR 的疗效，但远期心血管获益尚有待研究。本文就 CNR 的定义与诊断、相关危险因素、预测评估及防治措施进行回顾，以提高临床对于 STEMI 患者 PCI 术后 CNR 的认知与重视，并对未来研究方向进行展望。

关键词：急性 ST 段抬高型心肌梗死；经皮冠状动脉介入治疗；冠脉无复流；危险因素；防治措施
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Current knowledge of no-reflow phenomenon after PCI in patients with acute ST-segment elevation myocardial infarction

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Abstract: Acute ST-segment elevation myocardial infarction (STEMI) is a catastrophic cardiovascular disease that threatens human health and life, with dangerous onset and high mortality. With the development of percutaneous coronary intervention (PCI), the revascularization of occluded arteries and the restoration of distal myocardial perfusion in short term can significantly reduce the mortality of STEMI patients and improve their clinical outcomes. However, a considerable number of STEMI patients may suffer from coronary no-reflow (CNR) phenomenon after revascularization, which greatly hinders the improvement of clinical therapy and long-term prognosis. Currently, the pathological mechanism of CNR is still unclear and there is a lack of reliable clinical predictors or treatment measures. Some medications and surgical procedures have shown certain efficacy in preventing and improving CNR after PCI, but the long-term cardiovascular benefits remain unknown. In this review, we focus on the definition and diagnosis, risk factors and predictors, and prevention and treatment measures, thus to improve clinical attention to CNR after PCI in STEMI patients and also to forecast future research directions.

Key words: ST-segment elevation myocardial infarction；percutaneous coronary intervention；coronary no-reflow；risk factors；theranostics

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急性 ST 段抬高型心肌梗死(ST-segment elevation myocardial infraction, STEMI)是冠状动脉性心脏病中最为凶险的类型,短期内尽快开通闭塞血管、挽救缺血坏死心肌对于患者临床预后和结局至关重要[1]。然而,即使在心外膜大血管开通情况下,仍有相当部分患者出现冠脉内无复流(coronary no-reflow, CNR)和心肌损伤加重现象。CNR 在 STEMI 患者冠脉血运重建后非常普遍,有报道 STEMI 患者行经皮冠状动脉介入(percutaneous coronary intervention, PCI)治疗后 CNR 发生率在 20% ~ 50%[2, 3]。CNR 的发生显著增加 STEMI 患者院内病死率和主要不良心血管事件(major adverse cardiovascular events, MACE)风险[4],并与急性心肌梗死 PCI 术后新发房颤发病风险增加有关[5]。

目前,对于 CNR 发病机制尚未完全清楚,认为可能与心肌缺血性损伤、再灌注损伤、远端微循环栓塞、血栓高负荷状态、个体易感性等多因素相关[1~3]。这导致了目前针对 CNR 术前和术中预防与治疗缺乏切实有效的手段和措施。术前应用抗血小板[6]、他汀类药物[7],术中冠脉内或静脉内给药[8],及血栓抽吸[9]、延迟 PCI 术[10] 等措施,被报道能够预防和改善 STEMI 患者急诊 PCI 手术中 CNR 发生。然而,上述研究普遍存在样本量较小、单中心研究,及选择偏倚等缺点,结论有待更确切的前瞻性、大样本临床研究证实。本文就 STEMI 患者 PCI 术后 CNR 发生情况、发病机制及治疗进展进行文献综述,并对未来可能研究方向进行展望。

1 CNR 的定义与诊断

CNR 是指冠状动脉机械性阻塞解除后,在没有残余狭窄、血栓、夹层或痉挛的情况下,冠脉前向血流显著减慢或完全无血流的现象[2,3]。文献报道中通常以冠状动脉心肌梗死溶栓(thrombolysis in myocardial infarction, TIMI)血流分级<3 或 TIMI 分级=3 而心肌显色分级<2 进行量化和诊断[11]。此外,术后心电图 ST 段回落程度也被用于间接反映急性心梗血管再通后远端心肌的灌注情况。近年来,随着心脏核磁共振显像 (cardiac magnetic resonance, CMR) 的发展,极大提高了血运重建后 CNR 评估的准确性[12]。

基于血管造影的 TIMI 血流评估虽然快速且易于执行,但其在不同观察者间变异性大,组间一致性差,因此引入了校正 TIMI 帧数(corrected TIMI frame count, CTFC)。通过计算造影剂到达标准远端标记所需的帧数,从而提供一种定量指标用以评估冠脉血流[1]。然而,以上指标均局限于解剖层面,无法准确反映心肌功能性灌注情况。研究显示,超过半数 TIMI 分级=3 血流正常的患者,其 CMR 检查上存在一定微血管栓塞[13]。心肌微循环阻力指数(index of microcirculatory resistance, IMR)不受血流动力学或心外膜血管狭窄程度的影响,能更直接反映心脏微循环阻力[1]。相比于 TIMI 血流分级,IMR 与冠脉微血管阻塞及临床结局关联性更为密切[14]。但由于 CMR 与 IMR 检查费用高昂及有创性,尚未能在临床实际中得到普遍应用。

2 CNR 的相关危险因素

STEMI 患者的病变特征和基础疾病与 PCI 术后 CNR 的发生有关。研究表明,高龄、糖尿病、罪犯血管病变长度、支架释放前 TIMI 血流分级、症状发作至血运重建时间等可能是 CNR 发生的重要危险因素[4, 15]。急性心梗患者术后发生 CNR 者年龄普遍偏高,且以女性多见[15, 16]。此外,CNR 组罹患高血压、糖尿病、高脂血症及心血管病史者更为常见[16]。糖尿病患者发生急性心肌梗死的风险显著升高,而合并糖尿病的 STEMI 患者血糖控制不佳可导致 PCI 术后 CNR 发生风险增加[17]。而非糖尿病患者发生 STEMI 后的应激性高血糖与 PCI 术后冠脉无复流、造影剂肾病、心源性休克和院内死亡相关[18]。高血压是诸多心血管疾病的一级危险因素,而入院时血压偏低 [收缩压<100 mmHg(1 mmHg = 0.133 kPa)] 同样也是 STEMI 患者血运重建后发生 CNR 的独立预测因素[16]。这可能间接反映了心肌梗死面积较大和心脏泵衰竭程度较重。肾功能不全可导致造影剂肾病发生,也是术后 CNR/慢血流发生的危险因素。慢性肾脏病史[19] 和肾小球滤过率下降[20] 与 PCI 术后 CNR 和心电图 ST 段回落不良有关。房颤患者术后 CNR 发生率远高于非房颤患者(29.1% *vs* 11.8%, *P*<0.01),入院时伴发房颤会增加 CNR 发生风险 81%(95% CI: 1.63 ~ 2.04)[19]。而病变血管复杂程度[21] 和支架植入长度[4, 19] 同样会增加 PCI 术后 CNR 发生率。术前罪犯血管前向血流缓慢 (TIMI 分级<3) 与术后 CNR 的发生直接相关[4, 15];循环中血栓负荷升高[22] 和蛋白 C 活性减低[23] 也与 PCI 术后 CNR 发生密切相关。

此外,STEMI 患者血管开通过程中部分手术操作也会增加 CNR 发生风险。研究发现,无论是 STEMI 还是 NSTEMI 的 AMI 患者,术中行血栓抽吸术会增加 CNR 发生风险[24]。支架释放后球囊后扩也与 CNR 发生风险升高有关[25],这可能与血栓破

碎后随血流冲击到远端导致微血管阻塞有关。此外，有报道延迟血管开通可减少 STEMI 患者急诊 PCI 术后 CNR 的发生[10]，但其他研究则发现罪犯血管开通时间>8 h 是 CNR 发生的危险因素之一[26]。有研究比较了在肾小球滤过率下降且行急诊溶栓治疗后的患者中，相比极早期血管开通(3 ~ 12) h，早期开通血管(12 ~ 24) h 组患者术后造影剂肾病和 MACE 发生无明显差异，而 CNR 的发生率更高[27]。急性心梗后早期开通血管(起病后<12 h)由于血栓负荷较重，可能导致急性血栓碎屑脱落，阻塞远端微血管，并且增加支架内急性血栓风险[10]；而延迟血管开通起病后(12 ~ 24) h 至(2 ~ 7) d，远端心肌缺血坏死时间过长，血运重建后造成再灌注损伤，导致短期并发症和院内死亡率的增加[28]。

近年来，有关 STEMI 患者血管开通后发生 CNR 的新型危险因素被不断发现。如经超声心动图测量的心包外脂肪厚度(⩾ 5 mm)，认为与 STEMI 患者 PCI 术后 CNR 发生和死亡风险相关[29]。冠状动脉扩张也被认为是 CNR 发生的独立危险因素[30]，冠脉扩张患者心梗后血运重建失败可能与冠脉远端栓塞和 CNR 有关[31]。诸如以上危险因素的发现，可帮助临床医生在术前更好地预测和评估 STEMI 患者 CNR 发生风险，从而做到早准备、早预防、早治疗。

3　CNR 的预测与风险评估

尽管 STEMI 术后 CNR 的病理生理机制非常复杂且尚未完全清楚，但目前仍可根据临床疾病特征进行预测。如支架植入前冠脉 TIMI 血流分级、病变长度、侧枝循环、动脉血压以及心电图 ST 段抬高导联数目等，从而对患者进行危险分层[32]。STEMI 患者既往心绞痛发作情况也与 PCI 术后 CNR 的发生相关。无心绞痛发作的患者，其心梗后行血运重建发生 CNR 的风险显著增加[33]，这可能与患者前期冠脉血管缺血预适应有关。

循环血中某些指标也可作为预测 CNR 发生的潜在生物标志物。血浆 N 端脑钠尿肽前体(NT-proBNP)和 D-二聚体升高是 STEMI 患者远期 MACE 的重要危险因素，被发现与 PCI 术后 CNR 相关，并能够独立预测 CNR 的发生[34]。近年来，新型炎症指标，如中性粒/淋巴细胞比值(NLR)[15]、血小板/淋巴细胞比值(PLR)[35]、C 反应蛋白/白蛋白比值(CAR)[36]及纤维蛋白原/白蛋白比值(FAR)[37] 等在预测 PCI 术后 CNR 的发生中显示出一定的潜在应用价值。而血浆动脉粥样硬化指数(AIP)作为冠状动脉性心脏病重要预测因子，也与 PCI 术后 CNR 发生密切相关[38]。Endocan 是由血管内皮细胞合成并分泌的一种胞外蛋白，与内皮功能障碍和炎症相关，被证实是 CNR 的独立预测因子(OR: 2.39, 95% CI: 1.37 ~ 4.15, P<0.01)[39]。循环中可溶性 sST2 水平升高与患者冠脉 Gensini 评分和多支病变相关，并能够一定程度上预测患者 PCI 术后 CNR 的发生[40]。血管内皮生长因子(VEGF)水平与 STEMI 患者微血管阻塞独立相关，可能成为 STEMI 患者预后分层的生物标志物[41]。微小 RNA 与冠心病、动脉粥样硬化之间相关性已有诸多报道，其在 CNR 的预测中亦具有重要价值。研究发现循环中 miR-660-5p 与 CNR 显著相关，高 miR-660-5p 组患者的 CNR 风险几乎是低 miR-660-5p 组的 6 倍(OR = 5.68, 95% CI: 1.40 ~ 23.07, P< 0.05)[42]。循环中的 miR-208a 水平可作为心肌梗死的诊断标志物，并且较肌钙蛋白 T 能够更好地预测 CNR 和院内 MACE 的发生[43]。

此外，入院时或术前心电图中某些心电指标，也可在一定程度预测 PCI 术后 CNR 的发生。T 波的峰值和终点之间的间隔 (T-peak-T-end, TPE)，代表心肌复极离散度，与 STEMI 患者恶性室性心律失常和心源性猝死增加有关，同时也与血管开通后灌注成功和 ST 段回落相关[44]。而随着血管腔内影像学的发展，也为术者评估和防治 CNR 提供了重要辅助工具。经血管内超声 (intravascular ultrasound, IVUS) 检测到斑块中较高的脂质坏死核体积是 STEMI 患者 PCI 术后发生冠脉内 CNR 的潜在危险因素[45]。而对于 IVUS 导丝无法通过的钙化病变，经冠脉内旋磨后 CNR 的发生率更高 (26.1% *vs.* 10.7%, P<0.05)[46]。

基于以上研究，学者们相继探索或开发出一系列临床评分，用于更加准确评估 STEMI 患者 PCI 术后 CNR 发生风险[32, 47]。除经典的评估冠脉病变狭窄程度的 SYNTAX 与 Gensini 评分[11] 以外，基于 PRECISE-DAPT 评分[48]、改良版 ATRIA 评分[49] 及 CHA(2)DS(2)-VASc 评分[50] 等在预测 CNR 的发生中均显示出良好的性能。另有学者开发出专门用于预测 CNR 的 PIANO 评分，纳入包括年龄 ⩾ 70 岁、梗死前无心绞痛、总缺血时间 ⩾ 4 h、左前降支病变、术前 TIMI 血流分级 ⩽ 1 及术前 TIMI 血栓评分 ⩾ 4 在内的六项指标 (总评分 0~14 分)，能够准确地对 STEMI 患者 PCI 术后 CNR 风险进行分层[51]。

4　CNR 的预防与治疗

目前，针对 STEMI 患者术后 CNR 尚缺乏广泛认可的防治措施。仅有少数单中心、小样本研究为 CNR 的防治提供了一定参考和思路。药物治疗方

面包括腺苷[52]、尼可地尔[8]、糖蛋白Ⅱb/Ⅲa受体抑制剂[53]、硝普钠[54]、钙离子通道拮抗剂[55]及山莨菪碱等。冠脉内腺苷给药能够预防STEMI患者CNR的发生,但并不能改善术后心律失常、左心功能及短期死亡率等临床结局[52]。尼可地尔能够显著降低再灌注后CNR与心律失常的发生,改善左室射血分数和收缩期末容积指数,减少MACE和心血管死亡,术中冠脉内给药与静脉联合给药治疗效果更佳[8]。血小板糖蛋白Ⅱb/Ⅲa受体拮抗剂替罗非班与依替巴肽均能够有效抑制血小板激活。替罗非班冠脉内给药联合硝酸甘油较单用替罗非班能够更有效预防CNR发生,且不增加出血事件[53]。而冠脉内或病变血管局部给予依替巴肽对STEMI患者PCI术后心肌灌注情况均被证实安全有效[56]。前列地尔作为一种前列腺素E1脂质体,具有舒张血管、抗血小板聚集和促进纤溶等作用。研究显示前列地尔冠脉内给药,相比硝酸甘油,能够有效改善STEMI患者术后心肌灌注,降低CNR的发生[57]。另有研究比较七种冠脉内给药(腺苷、山莨菪碱、地尔硫、尼可地尔、硝普钠、乌拉地尔和维拉帕米)在STEMI患者经PCI治疗后CNR中的疗效。结果发现,与其他药物相比,山莨菪碱能更有效改善患者的心肌再灌注水平、心功能和临床预后[58]。此外,与氯吡格雷相比,替格瑞洛负荷剂量能有效降低STEMI患者CNR和MACE的发生率,同时并不增加PCI术后出血的风险[6]。而作为新型抗凝药,冠脉内应用比伐卢定在预防STEMI患者术中CNR或慢血流方面获益并不显著[59]。

他汀类药物作为冠心病一线用药,降低血脂以外能够带来抗炎、抗氧化应激等潜在获益。心梗患者PCI术前阿托伐他汀负荷剂量能够显著降低术中CNR和远期MACE的发生[7]。传统中药,如参麦注射液、丹参注射液及通心络胶囊、丹红注射液、血塞通注射液等亦显示出改善和降低PCI术中CNR的作用[60]。长期服用复方丹参滴丸可以减少非糖尿病患者急性心梗PCI术后CNR现象[61]。然而,多数研究中人群样本量小且基线条件不明确,使得上述结论仍有待商榷。冠脉内应用脂联素能在腺苷联合替罗非班治疗基础上,进一步降低2型糖尿病合并急性心梗患者PCI术中无复流现象,这可能与其减轻心肌和内皮细胞损伤、抑制炎症反应和细胞凋亡有关。此外,动物实验表明西洋参皂苷能够抑制心肌炎症小体通路激活,改善心肌缺血再灌注损伤后CNR现象[62]。

此外,介入器械的发展与手术操作流程的改善也为PCI术后CNR防治带来新的曙光。研究人员开发出一种药物涂层导丝,将含有腺苷的药物层通过氢键与吸附于金属表面的聚乙二醇硅烷醇结合。猪在体实验表明,包被腺苷的导丝插入冠脉后,可显著提高冠脉内血流速度2.6倍,并能持续约30 min,且无全身血流动力学改变或心律失常发生[63]。而采用一种新型穿孔球囊技术实现冠脉内腺苷灌注,能够有效逆转急性冠脉综合征患者PCI术中CNR现象[64]。在经血管内超声证实的斑块长度≥5 mm的急性冠脉综合征患者中,采用过滤装置的远端栓塞保护能够降低CNR发生率,并且与常规PCI相比,严重心脏不良事件更少[65]。冠脉内血栓抽吸也为预防PCI术后CNR提供一种可能的解决方案[9]。此外,手术操作过程中的改进也为CNR防治提供了新的思路。延迟支架植入与较低的CNR发生率相关,但并未改善远期临床结局[10]。而支架植入过程中与快速收缩球囊相比,缓慢收缩能够改善STEMI患者再灌注后冠脉血流,减少心肌梗死面积[66]。另有研究评估了PCI术中快速自体输血逆转CNR的有效性与安全性,术中用10 mL注射器在(3~5)min内通过导引导管反复回抽血液(100~120) mL,再通过导管用力注射回血管内,能够在一定程度上改善CNR现象[67]。

5 总结与展望

急性STEMI患者的闭塞血管开通后CNR现象,严重限制和阻碍了STEMI患者临床治疗效果和远期预后改善。目前CNR的病理机制尚未完全清楚,患者既往基础病史和罪犯血管病变特征是CNR发生的重要危险因素。临床上已有较多生物标志物和疾病评分用于STEMI患者急诊PCI术后CNR发生风险的预测,但多数指标诊断效能较低且欠缺大样本验证。腺苷、尼可地尔、GP Ⅱb/Ⅲa受体抑制剂、硝普钠及传统中药复方在预防和改善PCI术后CNR中显示出较好的疗效,但对患者远期心血管获益和临床结局上有待研究。介入器械和手术操作的发展与改进也为CNR的防治提供强有力的支持。然而,多数研究普遍存在样本量较小,且基线条件不明确等问题,结果可能受多种混杂因素影响,尚未在临床实际中得到普遍认可和应用。未来,需要综合基础科研与临床研究,建立更好的CNR疾病动物模型,探究其发病机制与筛选潜在治疗药物;医疗机构将根据自身条件开展前瞻性队列或随机对

照试验，不仅要关注围手术期 CNR 的发生，同时要注重患者随访和远期心血管事件，从而使 STEMI 患者最大程度获益。

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