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基于残余炎症风险评估的冠心病二级预防

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摘　要

冠心病是常见的心血管疾病，长期的炎症反应促使患者病情进展与死亡风险增加，残余炎症风险是比低密度脂蛋白胆固醇更强的主要心血管不良事件预测因子。本文从炎症与冠心病的关系入手，结合国内外抗炎治疗方面的最新研究进展，探讨建立残余炎症风险评估指导下的冠心病二级预防策略。

关键词

冠心病，残余炎症风险，秋水仙碱，主要心血管不良事件

Secondary Prevention of Coronary Heart Disease Based on Residual Inflammatory Risk Assessment

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Abstract

Coronary heart disease is a common cardiovascular condition. The long-term inflammatory response of patients contributes to the progression of the disease and an increased risk of death. Residual inflammatory risk is a stronger predictor of cardiovascular adverse events than low density lipoprotein cholesterol. The secondary prevention strategies of coronary heart disease under the guidance of residual inflammation risk assessment were discussed according to the relation-

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ship between inflammation and coronary heart disease as well as the latest clinical research advances in the anti-inflammatory treatment.

Keywords

Coronary Heart Disease, Residual Inflammatory Risk, Colchicine, Major Adverse Cardiovascular Events

1. 引言

我国心血管疾病现患病人数 3.3 亿，且仍呈上升趋势，已成为重大公共卫生问题[1]。冠心病是常见的心血管疾病，长期的炎症反应促使动脉粥样硬化进展与患者死亡风险增加[2]。残余炎症风险(RIR)是指持续的炎症反应引发心血管事件的风险，它是比低密度脂蛋白胆固醇(LDL-C)更强的主要心血管不良事件(MACE)预测因子[3]。

近年来多项大型临床试验研究发现，长期使用低剂量的秋水仙碱对急性冠脉综合征(ACS)和慢性冠状动脉综合征(CCS)的心血管结局均有改善[4]。在全球范围内冠心病发病率持续上升的背景下[5]，秋水仙碱作为防治 MACE 事件的新药物，具有巨大临床获益和广泛的经济可行性[6] [7]。本文从炎症与冠心病的关系入手，结合国内外抗炎治疗临床研究的最新研究进展，探讨建立基于 RIR 评估的冠心病二级预防方案。

2. 冠心病与炎症反应的相关性

冠状动脉粥样硬化的发生发展与炎症反应密不可分，涉及单核细胞、巨噬细胞、T 淋巴细胞、B 淋巴细胞等多种免疫细胞[8] [9]。氧化型低密度脂蛋白(Ox-LDL)和胆固醇结晶可诱发炎症反应，促进巨噬细胞内的核苷酸结合寡聚域(NOD)样受体家族吡啶结构域 3 (NLRP3)炎症小体的生成与活化，通过 IL1β、IL-6 和 C 反应蛋白炎症反应轴增加下游炎症因子的表达[10]。

单核细胞趋化蛋白-1 (MCP-1)、血管细胞粘附分子-1 (VCAM-1)和细胞间粘附分子-1 (ICAM-1)通过募集单核细胞和巨噬细胞发挥重要作用[11]。巨噬细胞可分为 M1 (促炎)和 M2 (抗炎)两种类型细胞，两者之间的平衡状态影响动脉粥样硬化疾病的进展或好转[12]。

淋巴细胞异常是促进动脉粥样硬化进展的独立危险因素[13]。某些不同亚群(如 Th1、Th2 和 Th17) T 淋巴细胞释放具有促炎或调节炎症活动的特定细胞因子[8]。$CD8^+$ T 细胞通过限制 Th1 细胞和巨噬细胞发挥保护作用[14]。B 淋巴细胞通过产生白细胞介素(IL)-10 来调节炎症，$IL\text{-}10^+$ B 淋巴细胞也与动脉粥样硬化患者的炎症反应有关。

胆固醇晶体诱导中性粒细胞释放中性粒细胞胞外诱捕网(NET)，引起与促进炎症反应等作用[8]。NLRP3 炎症小体通过促进血管炎症和干扰脂质代谢，在冠心病的发生和发展中起关键作用[15]。肥大细胞、自然杀伤细胞和树突状细胞也通过各种机制促进动脉粥样硬化[16]，如酶促降解、泡沫细胞形成和细胞因子产生等[17]。此外，炎症和血栓级联反应紧密相关，炎症促凝反应导致特定病理条件下的血栓形成[18] [19]。

3. 冠心病患者残余炎症风险评估

冠心病患者可根据 RIR 与 LDL-C 分为四大类[20] [21]：第一类是指仅存在残余胆固醇风险(RCR)的患者，需接受进一步的降低 LDL-C 治疗；第二类是指仅存在 RIR 的患者，虽然其 LDL-C 水平已达标，但仍存在炎症活动风险；第三类为 RCR 与 RIR 共存患者；第四类为既无 RCR 也无 RIR 的患者。

近年来发现可根据白细胞亚型的比率来评估机体炎症状态，这些新型炎症标志物包括[22]全身免疫炎症指数(SII)、全身炎症反应指数(SIRI)、全身炎症聚合指数(AISI)，后者也称为全身免疫炎症反应指数(SIIRI)或泛免疫炎症值(PIV)。

SII 用来评估 CCS 的发生及其严重程度的危险因素[23] [24]，并与心血管[25] [26]和全因死亡率[27] [28]，以及与 ACS 患者出现心力衰竭[29] [30]或 MACE [31] [32]独立相关。SIRI 与 CCS 患者发生 ACS 的风险程度相关[23]，被认为是 ACS 患者 PCI 术后 MACE 的独立危险因素[33]。AISI 被确定为接受 PCI 术的 ACS 患者不良结果的独立预测因子[34]。它们在预测冠心病的临床结局方面具有一定的实用性[22] [35]，但敏感性较低[36]。

LoDoCo [37]、CANTOS [38]、COLCOT [39]、LoDoCo2 [40]、PROMINENT、REDUCE-IT 和 STRENGTH 等临床研究证实[3] [41]，炎症反应参与冠心病事件链的全过程，即使患者的 LDL-C 水平已低于目标值，却仍会因为机体的炎症反应而出现 MACE，表明 RIR 客观存在[42]。此前已发现多种生物标志物可用于检测和评估冠心病患者的 RIR，其中 hs-CRP 是最广泛可及的有效生物标志物，hs-CRP 水平在多个前瞻性流行病学队列中可独立预测新发和复发心血管事件[43]。

炎症反应使动脉硬化斑块的风险增加，RIR 体现了冠心病患者的血管炎症状态，且与 MACE 密切相关[20] [44]。尽管越来越多的患者接受了血运重建、抗栓、他汀类强化降脂等综合治疗，但其住院死亡率和远期死亡率仍居高不下，单纯 RIR (上述第二类患者)比单纯 RCR (第一类患者)的发生率更高，并且 hsCRP 评估的 RIR 比 LDL-C 评估的 RCR 更能预测未来心血管事件和死亡的风险[3]。

RIR 是指持续的炎症反应引发心血管事件的风险，也可被理解为冠心病患者血浆 LDL-C 水平 < 1.8 mmol/L 且 hsCRP 水平 ≥ 2.0 /L 这一目标值时，存在的持续性血管损害风险[3]。在排除急性感染后，稳定的 hs-CRP 水平通常低于目标值 2.0 mg/L。如果患者已控制了 LDL-C 但 hs-CRP 水平仍升高，则应考虑干预与降低 RIR (如抗炎药物治疗)。

4. 冠心病抗炎治疗临床研究现状

抗炎治疗改善冠心病 MACE 事件的第一个证据来自 CANTOS 试验[45]，该研究发现，白细胞介素-1 (IL-1)特异性抑制剂卡那单抗可将 hs-CRP > 2.0 mg/L 的慢性冠状动脉疾病患者心血管死亡、心肌梗死和卒中的复合结局的风险降低 15% [45]，但卡那单抗价格昂贵，且使患者严重感染的风险增加[38]。

临床试验发现可改善冠心病患者预后的抗炎治疗药物包括三大类[38] [46]-[49]：NLRP3 炎症小体抑制剂(秋水仙碱、别嘌呤醇)、IL-1 受体拮抗剂(阿那白滞素、卡那单抗)、IL-6 抑制剂(如托珠单抗、泽伟奇单抗)。在标准治疗的同时服用低剂量(0.5 mg/日)的秋水仙碱，可将稳定的 CCS 患者的 MACE 降低 31 [50]，还可将 ACS 患者的 MACE 降低 23% [39] [51]。

秋水仙碱作为一种药物使用至少已有 3500 多年的历史[52]。70 年前它已被用于预防痛风和家族性地中海热发作[53] [54]，它被用于治疗和预防心包炎也有近 50 年历史[55]。最近的多项随机对照试验的荟萃分析验证了秋水仙碱联合标准冠心病治疗方案的疗效与安全性[56]-[58]。

秋水仙碱主要通过抑制中性粒细胞和巨噬细胞功能而发挥抗炎和抑制免疫作用。Phelps P 等人发现，在体外，0.1 nM 秋水仙碱可以抑制中性粒细胞的趋化性，抑制中性粒细胞中趋化因子 S100A8 和 S100A9 的释放[59]，Cronstein B 等人发现秋水仙碱还可以通过抑制微管合成和促进微管解聚来抑制中性粒细胞

粘附和募集[60] [61]。此外，秋水仙碱可通过抑制 P2X7 诱导的 K^+通道开放，减少 K^+外流，细胞内高浓度的 K^+会阻止 NLRP3 炎症小体的组装和激活，并可通过抑制 caspase-1，最终降低 IL1β 的水平，从而抑制动脉粥样硬化中的炎症反应[62]。

5. 冠心病抗炎药物二级预防策略

欧洲及多国最新的冠心病治疗指南建议将 LDL-C 降至 1.0 mmol (40.0 mg/dL)以下，仅建议对已发生 MACE 的患者谨慎使用秋水仙碱[63]。2023 年 6 月，秋水仙碱获得美国食品和药品监督管理局(FDA)批准，成为全球第一个用于 CCS 的抗炎治疗药物[41]。目前在欧洲及亚洲多国，秋水仙碱的临床适应证仅限于发生 MACE 时 ACS 的治疗，并未推荐用于 CSS 患者[63] [64]。

为了有效地制定防治方案，临床医生需要评估患者的总体风险与收益比，积极使用生物标志物来评估 RIR，从而在 MACE 发生之前的 CCS 阶段尽早起始管控机体炎症反应的治疗[65]。非侵入性或侵入性成像技术，例如冠状动脉计算机断层成像、颈动脉超声、正电子发射断层扫描、血管内超声、近红外光谱和光学相干断层扫描，均可以显示粥样硬化的动脉血管，RIR 评估也可以识别出动脉粥样硬化高风险患者[21]。

一旦患者 LDL-C 达到目标值，建议同时使用生物标志物(如 hs-CRP 等)来评估 RIR，而不是仅采取 MACE 发生后的救治方法。虽然目前尚没有哪一种药物被证明更有效，但考虑到先前的研究与临床经验、最近 FDA 的批准通过，秋水仙碱或许是目前最好的药物选择[66]。因此，将 hs-CRP 作为首选 RIR 生物标志物，将秋水仙碱作为冠心病二级预防首选抗炎药物是合理的[41] [67]。

6. 面临的问题与展望

建立该防治方案需要解决几个问题，例如 LDL-C 达到目标水平后，检测 hs-CRP 的时间和频率、肾衰竭或胃肠道不耐受患者的处理措施、秋水仙碱处方持续时间以及降低 RIR 后的随访策略等。上述方案并未解决同时具有低 hs-CRP 与低 LDL-C 水平的 MACE 防治问题。对于合并艾滋病、肝炎和结核病的患者，还必须解决药物之间相互作用方面的挑战[17] [68]。

尽管评估秋水仙碱在冠心病二级预防中的研究排除了肌酐清除率为<50 mL/min 的患者，但这些研究的持续时间不到 3 年[50]，同时秋水仙碱半衰期长、治疗窗口窄且需经肾代谢，因此应避免用于晚期肾病患者(eGFR < 30 mL/min/m^2)。美国用于冠心病患者二级预防的秋水仙碱剂量为每日 0.6 mg，但已发表的临床研究使用的剂量为每日 0.5 mg [69]，其长期疗效和安全性以及最适宜的治疗人群等仍需进一步观察与研究[65] [70]。

秋水仙碱被认为是一种治疗指数较小的药物，其有效剂量与可能导致严重不良反应的剂量之间只有很小的差异。秋水仙碱由细胞色素 P450 3A4 和 p-糖蛋白代谢，容易发生药物相互作用，因此监测不良反应至关重要。鉴于此，需要制订高度个性化精准给药方案，并将秋水仙碱的使用限制在处于高风险的冠心病人群中[65]。

预防冠心病高风险人群的 MACE 一直是许多创新疗法研究者关注的焦点。许多突破性的临床试验已经表明，降低 RIR 可为患者带来实质性的益处。ACS 与 CCS 发生的不良心血管事件仍严重威胁着患者生命，RIR 正是这一风险的关键驱动因素。阐明 RIR 的病理生理机制，聚焦 RIR 评估的受益人群，研发低成本且可更广泛应用的 RIR 抑制性药物可能是未来该领域的主要研究目标。

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