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残余胆固醇在动脉粥样硬化性心血管疾病中的研究进展

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摘　要

动脉粥样硬化性心血管疾病是全球公共卫生领域的主要致死致残病因，每年造成重大疾病负担。其病理生理基础与脂代谢紊乱高度相关，尽管当前指南推荐的他汀类药物可有效控制低密度脂蛋白胆固醇至目标范围(如<1.8 mmol/L)，仍面临较高心血管残余风险。近年循证医学证据表明，这种残余风险可能与新兴脂质标志物——残余胆固醇密切相关。残余胆固醇作为富含甘油三酯的脂蛋白残粒(如极低密度脂蛋白和中密度脂蛋白)的核心成分，可通过促炎、促氧化及内皮功能障碍等多途径加速动脉粥样硬化斑块进展。本文系统综述近年来残余胆固醇的定义、标准化检测方法、在斑块易损性中的分子机制，以及大规模队列研究中的最新进展。

关键词

残余胆固醇，动脉粥样硬化性心血管疾病，脂质代谢，降脂药物

Research Progress of Remnant Cholesterol in Atherosclerotic Cardiovascular Disease

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Abstract

Atherosclerotic cardiovascular disease (ASCVD) is a leading cause of morbidity and mortality in the field of global public health, imposing a significant disease burden annually. Its pathological basis

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is closely associated with lipid metabolism disorders. Although current guidelines recommend statins to effectively control low-density lipoprotein cholesterol (LDL-C) to target levels (e.g., <1.8 mmol/L), patients still face a high residual cardiovascular risk. Recent evidence-based medical studies suggest that this residual risk may be closely linked to an emerging lipid marker—remnant cholesterol (RC). As a core component of triglyceride-rich lipoprotein remnants (such as very low-density lipoprotein and intermediate-density lipoprotein), RC can accelerate the progression of atherosclerotic plaques through multiple pathways, including pro-inflammatory, pro-oxidative, and endothelial dysfunction mechanisms. This article systematically reviews recent advances in the definition of RC, standardized measurement methods, its molecular mechanisms in plaque vulnerability, and findings from large-scale cohort studies.

Keywords

Remnant Cholesterol, Atherosclerotic Cardiovascular Disease, Lipid Metabolism, Lipid-Lowering Drugs

1. 引言

动脉粥样硬化性心血管疾病(atherosclerosis cardiovascular disease, ASCVD)的病理进程与脂代谢紊乱呈显著相关性。临床实践表明，通过生活方式干预和药物治疗，患者可有效控制低密度脂蛋白胆固醇(low-density lipoprotein cholesterol, LDL-C)水平、血糖稳态维持、血压优化并预防血栓形成。然而，即使严格遵循指南将 LDL-C 浓度降至目标区间(如<1.8 mmol/L)并优化糖尿病、高血压等传统危险因素管理，仍有约 40%的患者存在持续性心血管事件风险[1]。这一现象提示，除传统指标外，血清甘油三酯(triglyceride, TG)及其代谢产物——富含甘油三酯的脂蛋白(triglyceride-rich lipoprotein, TRL)的病理作用亟待重视[2]。研究证实，TRL 代谢后衍生的残余胆固醇(remnant cholesterol, RC)因富含胆固醇成分且具有促炎特性，可通过诱导内皮功能障碍和斑块不稳定，成为 ASCVD 残余风险的核心驱动因素[3]。本综述整合最新循证证据，系统阐述 RC 在 ASCVD 中的研究进展，旨在为优化 ASCVD 防治策略提供理论依据。

2. 定义和测量方法

RC 的概念最早由 Nordestgaard 团队定义为源自甘油三酯富集脂蛋白(TRL)代谢产物的胆固醇组分。其生化本质涵盖空腹状态下经脂蛋白脂肪酶水解产生的极低密度脂蛋白(VLDL-C)和中间密度脂蛋白(IDL-C)残粒，以及非空腹时乳糜微粒(CM)分解后的胆固醇成分[4]。

当前 RC 的定量分析主要基于两种技术路径：间接推导法与直接检测技术。前者通过公式 RC=TC−(LDL-C)−(HDL-C)计算得出。值得注意的是，LDL-C 的获取需根据 TG 水平实施差异化计算策略：当 TG ≥ 4.52 mmol/L (400 mg/dL)时，推荐采用 Martin-Hopkins 方程($R^2 = 0.96$)，该模型通过非线性回归优化 VLDL-C 估算[5]；当 TG < 4.52 mmol/L 时，则优先采用 Friedewald 方程(VLDL-C = TG/5)进行估算[6]。得益于操作简便与成本效益优势，间接推导法占据临床实践的主导地位(应用率 > 85%)。后者包括直接酶法、磁共振波谱法、密度梯度超速离心法和免疫分离法。直接酶法通过使用酶和表面活性剂从其他脂蛋白中去除胆固醇，定量剩余 CM 和 VLDL 中的胆固醇含量。但有研究发现，该方法检测值仅为计算值的 13% ± 5% [7]。超速离心法通过分离血清 ApoB48 脂蛋白颗粒实现外源性 RC 定量[8]。免疫

分离法则通过使用抗 ApoB-100 和 ApoA1 的单克隆抗体去除两者的某些亚型后特异性捕获 CM/VLDL 残粒[9]。尽管这些方法具有较高的理论特异性，但其操作复杂性及高昂成本限制了临床推广，目前多局限于科研场景。值得注意的是，不同检测手段间存在显著差异性。大规模队列研究显示，约 5%的受试者在直接检测中未被识别，此类人群不仅 RC 水平显著升高，且残余甘油三酯浓度较低，心肌梗死发生风险增加至 1.8 倍[10]。这提示临床实践中需根据研究目的合理选择检测策略，并关注不同方法学的局限性。

当前 RC 检测体系存在方法学的标准化不足与技术复杂性，临床实践中亟待建立自动化程度高、操作流程统一的规范化检测方案。研究显示，不同检测体系间的结果异质性导致学界尚未就 RC 的病理阈值达成共识(如直接法测得参考值多低于 0.8 mmol/L，而间接法结果可能存在 30%以上偏差)，迫切需要基于多中心研究制定与心血管风险分层对应的 RC 干预阈值标准。

3. 致动脉粥样硬化作用机制

RC 致动脉粥样硬化(atherosclerosis, AS)作用机制主要涉及血管内膜损伤及炎症反应相关通路。病理状态下升高的 RC 水平可诱导血管内皮通透性异常增高，促进其跨膜迁移并在内膜下蓄积，进而被巨噬细胞与平滑肌细胞吞噬，经 CD36 清道夫受体介导形成泡沫细胞[11] [12]。不同于 LDL 需氧化修饰后才能被吞噬，RC 可不经髓过氧化物酶(MPO)修饰直接启动胞吞过程[13]。临床队列研究证实，RC 水平升高与慢性低度炎症状态具有显著相关性，其特征性标志物包括 C 反应蛋白(CRP)水平持续升高[14] [15]。脂蛋白脂酶(LPL)介导 TRL 水解过程可生成大量氧化型游离脂肪酸(FFA)等分解产物[16]，此类代谢中间体通过激活 NF-κB 等信号转导通路，促进炎症反应、凝血功能异常及细胞凋亡。RC 还可通过上调促凋亡因子(如 TNF-α、IL-1β)及活性氧(ROS)的生成，进一步加剧内皮屏障功能障碍，促进白细胞黏附和内皮细胞程序性死亡[16]-[20]。在凝血调控方面，RC 通过促进凝血酶原复合物生成，同时上调纤溶酶原激活物抑制剂-1 (PAI-1)及其抗原表达，协同增强血小板活化与纤维蛋白沉积[21]。值得注意的是，RC 通过干扰 HDL 介导的胆固醇逆转运过程，削弱其抗动脉粥样硬化及抗炎效应。TRL 的核心载脂蛋白 ApoC3 不仅干扰极低密度脂蛋白(VLDL)与细胞受体的正常结合，还可直接诱导促炎因子表达，促进单核细胞活化、黏附和凋亡进程[22]。上述多途径协同作用加速动脉粥样硬化斑块的形成与进展。

4. RC 与心血管疾病

心血管疾病已成为全球公共卫生领域的首要致死致残因素，其疾病流行趋势与健康负担持续加重。流行病学数据显示，全球每年约 1800 万例死亡归因于心血管系统病变。截至 2019 年，NHANES 队列研究[23]纳入了共 13,383 名 ≥ 20 岁受试者(平均年龄 45.7 岁，女性占比 52%)。在中位随访 26.6 年间，共记录 1741 例心血管相关死亡事件(缺血性心脏病 1409 例，卒中 332 例)。数据分析证实，RC ≥ 29.80 mg/dL 组相较对照组(<14.26 mg/dL)显示全因死亡风险增加 23% (HR = 1.23, 95% CI 1.07~1.42)，其中缺血性心脏病死亡率升高 32% (HR = 1.32, 95% CI 1.03~1.69)，但卒中死亡率未见显著统计学差异。值得注意的是，高 RC 水平与全因死亡及缺血性心脏病死亡的关联性独立于社会经济因素、基础疾病史等混杂因素。

在急性心血管事件方面，多项研究证实 RC 水平与急性冠脉综合征(ACS)和急性脑梗死(ACI)的发生发展密切相关。对于 ACS 患者，流行病学证据显示 RC 不仅是其发病的独立风险因素，其动态变化对心血管不良事件(如再梗死、血运重建需求)的预测效能优于传统血脂指标[24] [25]。值得注意的是，这种关联性在绝经后女性及老年患者中尤为显著[26] [27]，提示特定人群需强化 RC 监测。然而，曹等[28]通过多因素回归模型校正血糖、肾功能等混杂因素后，RC 并不能作为 ACS 不良预后的独立预测因素。在合并糖尿病的 ACS 患者中，Shao 团队[29]观察到随访 2.5 年期间高 RC 组 MACE 发生率增加 57.2% (P < 0.001)；而叶等[30]的研究则表明 RC 仅对非糖尿病亚组的远期预后具有预测价值，但不是 ACS 合并糖尿

病的预测因子。这种矛盾结果可能与样本量及基线 RC 截断值设定差异有关。

在脑血管疾病方面，多项回顾性队列研究证实 RC 在 ACI 发生发展中具有独立风险属性，其特异性预测效能已得到多中心数据支持[31]-[35]。亚组分析发现不同亚组之间高 RC 组的 ACI 发病风险显著高于低 RC 组，RC 水平越高，ACI 发病风险越大[33]。在一项涉及 112,512 人的大型前瞻性研究中[36]，高 RC 与高缺血性卒中风险相关，至 80 岁时累积发病率从 7.3% (RC < 0.5 mmol/L)递增至 11.5% (RC ≥ 1.5 mmol/L)。将 RC 与传统危险因素相结合可能会提高对脑血管疾病的预测价值。郝团队[32]构建的联合预测模型在 ACI 合并 2 型糖尿病人群中展现优异判别能力(AUC = 0.904)，以 2.30 mmol/L 为截断值时灵敏度达 89%。值得注意的是，在 NIHSS 评分较高的重症 ACI 患者中，RC 联合甲状腺功能指标(FT3, FT4)预测 ACI 不良预后效果最佳[34] [37]。鉴于临床实践中多病共存的复杂性，建立包含 RC 在内的多维度生物标志物评估体系，可为制定个体化防治策略提供循证依据。

PREDIMED 研究[38]针对 6901 例超重/肥胖高危个体开展干预分析，随访期间共 263 例发生主要不良心血管事件(MACE)。结果表明，TG 和 RC 水平独立预测主要心血管不良事件(MACE)风险(P < 0.05)，而传统指标 LDL-C 与 HDL-C 未显示显著相关性。此外，两项 Meta 分析[39] [40]整合 41 项研究显示，RC 每升高 1.0 mmol/L，ASCVD 发病风险增加 27% (95% CI 1.19~1.36)，且该关联独立于糖尿病、空腹状态及载脂蛋白 B (ApoB)水平。当前证据表明，RC 作为新型生物标志物，其临床价值不亚于传统血脂指标。临床实践中需将 RC 纳入常规血脂管理指标，以实现更精准的心血管风险评估。未来研究需进一步明确 RC 的最佳干预阈值及靶向治疗策略。

RC 作为心血管疾病的重要风险因素，与其他心血管风险因素的交互作用成为近年研究的热点。代谢综合征(Metabolic Syndrome, MetS)是心血管疾病的重要危险因素，其核心特征包括肥胖、胰岛素抵抗、高血压和血脂异常。研究表明，RC 水平与 MetS 和 MetS 的每个成分的患病率独立相关。MetS 部分介导了 RC 水平与 CVD 风险之间的关联[41]。慢性低度炎症是动脉粥样硬化的重要病理机制之一。RC 与炎症标志物(如 C 反应蛋白、IL-6、中性粒细胞/高密度脂蛋白胆固醇比值 NHR、全身免疫炎症指数 SII 等)之间存在显著相关性[42]。此外，研究还发现 RC 与糖尿病、肾功能异常等均存在密切联系。

5. 治疗

ASCVD 的综合管理需基于生活方式干预与药物联合治疗的双轨策略。在非药物干预领域，通过控制体重、优化血压管理、戒烟限酒、限制添加糖及饱和脂肪摄入(如动物油脂、加工食品)，并增加膳食纤维与不饱和脂肪酸比例(如深海鱼类、坚果)，可显著降低 RC 水平[43]。药物干预方面，LDL-C 作为 ASCVD 一、二级预防的核心靶标，市面上大多药物主要针对降低其水平来达到控脂效果。目前尚无相关指南和专家共识推荐的特异性降 RC 药物，但经典降脂药(他汀类、贝特类、Omega-3 脂肪酸类和 PCSK9 抑制剂类等)均可不同程度降低 RC 水平。

多项研究证实，他汀类药物在降低 RC 水平方面具有显著作用[44]。PREVAIL US 研究[45]显示，在同等剂量下(匹伐他汀 4 mg vs 普伐他汀 40 mg)，前者对 RC 的调控效能更为突出，两组中位降幅分别达 34%和 23% (P < 0.05)。一项开滦队列研究表明[46]，接受他汀治疗的高 RC 患者心梗风险较未干预组降低 55% (HR = 0.89 vs 2.13)。贝特类是过氧化物酶体增殖物激活受体 α (PPARα)激动剂，可有效降低 TG 水平及 2 型糖尿病病人 RC 水平。新型选择性 PPARα 调节剂(如 Pemafibrate) [47] [48]可以降低高 TG 和低 HDL-C 血脂异常患者中的 RC 水平。John 等[49]发现，与对照橄榄油组相比，Omega-3 脂肪酸(OM3-FFA)的 3 个亚组 RC 水平均显著降低。ω-3 脂肪酸制剂(如二十碳五烯酸乙酯)在 MARINE 和 ANCHOR 的 III 期随机对照试验[50] [51]中实现 RC 水平下降 29.8% (P = 0.004)和 25.8% (P = 0.0001)，其机制可能与抑制肝脏 VLDL 合成有关。此外，PCSK9 抑制剂阿利西尤单抗(Alirocumab)可使 RC 水平降低 42.1%~52.5%

[52]，提示其具有多靶点调控脂蛋白代谢的潜力。

相较于常规降脂方案，基于基因调控的创新疗法展现出更精准的靶向优势。基因沉默技术[53]主要涵盖反义寡核苷酸疗法[54]与 siRNA 介导的两大技术类别，通过降解致病基因 mRNA 阻断蛋白表达，进而调控脂代谢异常。例如以 ApoB 为靶点的米泊美生(mipomersen)、ANGPTL3 单克隆抗体依维苏单抗(Evinacumab)、ApoC3 抑制剂 Volanesorsen 以及通过沉默 APOC3 基因的 siRNA 药物 Plozasiran 等均可以有效降低脂蛋白水平[55]-[58]。然而，针对这些新型靶点的药物仍需要大规模临床试验验证其长期疗效与安全性。

6. 总结

当前心血管病学领域正经历血脂管理范式的重大革新。RC 作为富含甘油三酯脂蛋白的代谢终产物，其致动脉粥样硬化效应已获多中心研究证实。然而，当前临床实践面临双重挑战：其一，RC 检测方法尚未形成统一标准，间接推导法易受 TG 水平干扰，而直接检测技术操作复杂且成本高昂；其二，RC 的致病阈值存在争议，不同指南对理想范围的定义差异显著。在治疗领域，尽管他汀联合依折麦布可部分降低 RC 水平，但针对其特异性调控的靶向药物仍需大规模临床试验验证。因此，未来研究应聚焦于 RC 检测技术的标准化、炎症通路机制解析，以及个体化降脂策略的优化，从而为 ASCVD 残余风险管理提供循证依据。

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