·文献综述·

视网膜中央静脉阻塞发病机制的研究进展

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摘要

视网膜中央静脉阻塞(CRVO)是致盲性视网膜血管疾病,其机制涉及多系统交互作用。文章系统综述 CRVO 病理机制,聚焦血管内皮功能障碍、动脉硬化、易栓症、炎症及氧化应激等核心环节。其病理机制包括动脉硬化通过机械压迫和内皮素-1 介导收缩双重机制阻碍静脉回流;内皮功能异常加剧血流紊乱;遗传性和获得性凝血异常破坏凝血稳态,促进血栓形成;炎症与氧化应激协同激活细胞因子,加重缺血和血管渗漏。文章创新性探讨了外泌体通过 miRNA 递送调控血管功能,肠道菌群失衡经“肠-眼轴”代谢通路影响视网膜微环境,进而通过多维度机制网络解析,阐明 CRVO 从局部病变到全身代谢紊乱的病理关联,强调眼-全身协同干预的重要性。本综述为疾病早期诊断标志物筛选、多靶点药物研发及个体化治疗提供理论依据,推动 CRVO 诊疗向整合医学模式转化。
关键词:视网膜中央静脉阻塞;机制;综述
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Research progress on the pathogenesis of central retinal vein occlusion

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Abstract

• Central retinal vein occlusion (CRVO) is a retinal vascular disorder that significantly impairs vision, with its underlying mechanisms involving complex interactions across multiple biological systems. This article provides a systematic review of the pathological mechanisms associated with CRVO, emphasizing critical factors such as endothelial dysfunction, arteriosclerosis, thrombophilia, inflammation, and oxidative stress. The pathological mechanisms of CRVO are characterized by arteriosclerosis, which obstructs venous return through a dual mechanism involving mechanical compression and endothelin-1-mediated contraction; endothelial dysfunction, which exacerbates disturbances in blood flow; genetic and acquired coagulation abnormalities that disrupt hemostatic balance and promote thrombosis; and the synergistic effects of inflammation and oxidative stress that activate cytokines, thereby aggravating ischemia and vascular leakage. Innovatively, this review explores emerging mechanisms such as miRNA-mediated vascular regulation *via* exosomes, gut microbiota-retina crosstalk through the "gut-eye axis," and systemic metabolic interactions that link local retinal lesions to broader dysregulation of CRVO. These insights underscore the importance of integrated eye-system interventions and provide a theoretical foundation for advancing early biomarker discovery, multitarget therapeutics, and personalized treatment paradigms. By bridging localized pathology and systemic mechanisms, this work promotes a transformative shift toward an integrative medicine model in the diagnosis and management of CRVO.
• KEYWORDS:central retinal vein occlusion; pathogenesis; review

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0 引言

视网膜静脉阻塞(retinal vein occlusion, RVO)是一种常见的视网膜血管疾病,也是导致单侧视力障碍和失明的重要原因之一。其发病率随年龄增长而逐渐增加,但也偶见于儿童患者[1]。RVO 的典型特征包括视网膜静脉充盈、近端血管闭塞、以及远端血管扩张,这些病理变化导致视网膜的缺血与缺氧、出血和水肿。根据阻塞的位置,

RVO 可以分为视网膜中央静脉阻塞(central retinal vein occlusion, CRVO)、视网膜半中央静脉阻塞(hemi-central retinal vein occlusion, HCRVO)和视网膜分支静脉阻塞(branch retinal vein occlusion, BRVO),并可进一步根据血流灌注状态区分为缺血型和非缺血型[2]。常继发于 CRVO 的玻璃体出血、新生血管性青光眼及黄斑水肿等是该疾病导致视力严重减退的重要原因[3]。与其他常见眼底疾病相比,CRVO 的治疗策略更注重以病因为导向,从疾病的发病机制出发,综合调控全身危险因素,同时积极预防和治疗继发性并发症,从而显著改善患者预后。随着影像学检查技术和眼内液代谢组学的进展,我们对 CRVO 的发病机制有了更深的理解。本综述旨在阐述 CRVO 发病机制的相关研究进展,以期为该类疾病的早期识别和合理治疗提供新的希望。

1 CRVO 与血管异常

1.1 血管内皮功能障碍和 CRVO 血管内皮功能障碍在 CRVO 的发生发展中具有重要作用。内皮细胞作为覆盖心脏、血管和淋巴管内表面的单层结构,既发挥半选择性屏障功能,又通过调控血管壁的通透性和张力维持生理平衡[4]。这类细胞能够感知物理与化学刺激,并通过释放多种血管活性物质动态调节血管稳态[5]。在病理状态下,内皮细胞功能的异常表现为一氧化氮(nitric oxide, NO)生成减少、血管通透性紊乱以及活性氧(reactive oxygen species, ROS)水平升高,进而引发血管舒缩功能障碍、促炎状态形成及血栓倾向增加,最终导致静脉回流受阻[6]。Gouliopoulos 等[7]的研究证实,RVO 患者经肱动脉血流介导的扩张(FMD)检测显示内皮功能显著受损(P = 0.002),且该异常与吸烟史及 RVO 分型无关。这些发现提示内皮功能障碍可能是 RVO 的危险因素,强调临床治疗需在控制局部病变基础上,同步加强系统性血管功能维护。

1.2 动脉硬化和 CRVO 视网膜动脉硬化既可通过直接压迫邻近静脉,也可间接通过诱导内皮素-1(endothelin-1, ET-1)产生,从而增加 CRVO 的发病风险。RVO 在高血压、糖尿病及高脂血症等患者中高发,此类代谢异常可引发血管内膜增厚和细胞外基质的沉积,进而削弱血管壁弹性[8]。在视网膜中,中央动静脉共享同一血管鞘,当动脉硬化压迫静脉时,可导致静脉血流速度下降及湍流形成,进而损害内皮细胞功能,触发中膜增生反应,最终形成血管腔狭窄,诱发局部栓塞和静脉回流障碍[9]。Gouliopoulos 等[7]采用颈-股动脉脉搏波传导速度(pulse wave velocity, PWV)检测技术评估主动脉弹性功能,研究显示 RVO 组 PWV 值显著高于对照组(P=0.004),经多因素校正分析证实,PWV 升高是 RVO 发生的重要预测因子。该发现提示,动脉壁结构完整性的破坏可能构成 PWV 升高的病理基础,为动脉硬化参与 RVO 发病的病理机制提供了新的血流动力学证据支持。

除机械性压迫机制外,动脉硬化引发的血管内皮损伤通过促进 ET-1 分泌增加,在 RVO 进展中发挥重要作用[10]。作为强效血管收缩剂和促炎因子,ET-1 不仅可引起静脉血管收缩和血流减慢,还能促进血小板聚集及炎症反应,最终导致血管阻塞[11-13]。List 等[14]研究显示,RVO 患者血清 ET-1 中位数(0.26 pmol/L)显著高于对照组(0.10 pmol/L,P<0.0001),且该升高与阻塞部位无关。即使在调整动脉高血压、糖尿病等混杂因素后,ET-1 水平的显著差异仍然存在,且不同 RVO 亚型间无统计学差异,研究者据此认为 ET-1 可能是所有类型 RVO 的潜在危险因素。动物模型研究中,Kida 等[10]发现 ET-1 可诱导自发性高血压大鼠出现视网膜静脉收缩及血流减少,同时该模型动物的 ET-A 受体与缺氧诱导因子-1 蛋白表达水平显著升高,这为 ET-1 参与 RVO 发病的假说提供了实验支持。

动脉硬化与 CRVO 的病理关联凸显系统性血管风险管理的重要性。现有治疗方案需强化高血压、高脂血症等基础疾病的综合干预,并加强动脉弹性功能评估。未来研究可重点研发 ET-1 受体拮抗剂等靶向药物,同时整合血流动力学监测技术构建动脉硬化早期预警体系,通过多学科协作建立涵盖全身血管健康管理的 CRVO 防治新路径。

2 CRVO 与易栓症

易栓症是以血栓形成及栓塞事件易发性为特征的病理状态。CRVO 的发生与视网膜静脉内的血栓形成密切相关,其阻塞机制符合 Virchow 提出的血栓形成三要素理论:血管内皮损伤、血流动力学异常及血液成分改变共同构成病理基础。任何导致上述三要素失衡的病理过程均可诱发易栓状态。其核心机制涉及凝血-抗凝血系统与纤溶-抗纤溶系统的动态失衡,最终引发血液高凝倾向。根据病因学差异,易栓症主要分为遗传性与获得性两种类型[15]。

2.1 遗传性易栓症和 CRVO

2.1.1 凝血-抗凝血失衡 遗传性易栓症主要源于抗凝血酶Ⅲ(antithrombin Ⅲ, ATⅢ)、蛋白 C(protein C, PC)、蛋白 S(protein S, PS)等生理性抗凝蛋白的基因突变,这些突变通过削弱抗凝功能参与发病机制。此外,促凝蛋白相关基因突变如因子 V Leiden(FV Leiden 突变)与凝血酶原(G20210A 突变),可增强促凝活性,进而促进血栓形成[16]。活化蛋白 C(activated protein C, APC)作为关键内源性抗凝物质,通过与 Ca^{2+} 和 PS 协同作用,特异性降解活化凝血因子Ⅴa 和Ⅷa,从而抑制凝血酶生成并增强纤溶活性。而 FV Leiden 突变可导致获得性 APC 抵抗现象,显著提升血栓事件风险[17]。Kuhli 等[18]研究发现,存在 APC 抵抗的个体更易发生 RVO,该结论经病例对照研究及 Meta 分析验证。Hara 等[19]临床观察显示,缺血性 CRVO 患者接受玻璃体内 APC 注射治疗后,最佳矫正视力(LogMAR 从 1.39 改善至 1.06)及中央视网膜厚度(1 090 μm降至 195 μm)均显著改善(均 P<0.001),提示该疗法可能改善视网膜灌注。Bucciarelli 等证实 PC、PS 和 AT 的缺失主要与 BRVO 相关,而 FV Leiden 突变与 CRVO 的关联性更为显著[20-21]。

2.1.2 纤溶-抗纤溶失衡 纤溶酶原激活物抑制物-1(plasminogen activator inhibitor-1, PAI-1)作为丝氨酸蛋白酶抑制剂家族的关键调节因子,通过灭活组织型纤溶酶原激活剂抑制纤溶系统活性。其表达水平或功能亢进可导致纤溶能力下降,成为血栓形成的潜在诱因。Christodoulou 等[20]采用多重 Logistic 回归模型证实,PAI-1 基因多态性与 RVO 发病存在显著关联。Ⅻ因子(factor Ⅻ, FⅫ)作为接触激活系统的核心成分,同时参与内源性凝血和纤溶调节[22]。该因子的缺乏在 45 岁以下 RVO 患者中呈高发特征,而 45 岁以上 RVO 患者与健康人群无显

著差异[23]。在叶酸代谢通路中,亚甲基四氢叶酸还原酶(methylene tetrahydrofolate reductase,MTHFR)的 C677T 突变可能导致酶活性降低,引发高同型半胱氨酸血症(hyperhomocysteinemia,HHcy),后者通过干扰凝血和纤溶的动态平衡,进而促进血栓形成[24]。Arthur 等[25]病例对照研究显示,HHcy 虽非 RVO 独立危险因素,但其水平与维生素 B12 及叶酸浓度呈负相关,提示针对性的营养干预可能通过调控同型半胱氨酸代谢降低 RVO 风险。

2.2 获得性易栓症和 CRVO 获得性易栓症多继发于特定病理状态或暴露因素,其特征性表现为促凝蛋白水平升高和抗凝蛋白活性降低的失衡状态,从而增加血栓栓塞风险[15]。临床常见诱因包括抗磷脂综合征、高同型半胱氨酸血症、妊娠期生理变化、口服避孕药使用、围手术期应激、肥胖相关代谢紊乱、肿瘤微环境和糖尿病血管病变等[17]。抗磷脂抗体综合征(antiphospholipid syndrome,APS)作为一种获得性自身免疫疾病,以持续存在的抗磷脂抗体(antiphospholipid antibody,APA)为血清学标志,临床表现为动静脉血栓形成和妊娠并发症[18]。Napal 等[26]对 170 例 RVO 患者的前瞻性研究显示,试验组中原发性高凝状态占比 13%,而获得性高凝状态显著高于对照组,其 APS 检出率达 10%。研究证据表明,高滴度抗磷脂抗体不仅是系统性血栓事件的关键预测因子,也是 RVO 发生的重要危险因素。

遗传性和获得性易栓因素之间存在交互作用。当这两种因素同时存在时,血栓栓塞性疾病的发生几率增加,同时也显著提高了 RVO 的风险。CRVO 与凝血功能异常的关联提示需重视血栓风险因素的系统评估。临床上应建立多学科协作机制,发展涵盖血栓预防、代谢调控及血管保护的综合干预体系,通过个性化方案提升 CRVO 防治的系统性和精准性。

3 CRVO 与炎症反应

CRVO 的发病机制涉及血管损伤与炎症介质间的复杂相互作用。研究指出,血管内皮生长因子(vascular endothelial growth factor, VEGF)在 RVO 病理进程中处于核心调控地位。其他参与因子包括白细胞介素(interleukin, IL)家族、细胞黏附因子(intercellular adhesion molecule, ICAM)、单核细胞趋化因子(monocyte chemoattractant protein, MCP)、基质金属蛋白酶(matrix metalloproteinases, MMPs)、内皮素-1(endothelin-1, ET-1)等[27-32]。Zhou 等[33]研究发现,CRVO 患者的房水和玻璃体液中 Flt-3 L、IL-8、IL-33 等炎症因子水平显著升高。KEGG 通路富集分析显示,炎症介质主要影响 PI3K-Akt、Ras、MAPK 和 Jak/STAT 等信号通路。PPI 分析表明,VEGF 是调控 IL-8、G-CSF 和 IL-33 表达的关键上游因子。高眼内炎症状态可激活视网膜血管内皮,引发凝血级联反应纤维蛋白异常沉积,最终导致病理性血栓形成[34]。同时,VEGF 等因子通过加剧炎症与氧化应激反应,促进 RVO 进展[35]。CRVO 与炎症反应的病理关联提示,未来需研发多靶点抗炎药物,并构建基于生物标志物的个体化诊疗体系,推动临床治疗从症状管理向靶向病理机制干预的策略转变。

4 CRVO 与氧化应激

氧化应激与 CRVO 的病理关联已获广泛证实。作为氧化应激的产物,氧化特异性表位可介导血管炎症反应和血栓形成过程。Posch-Pertl 等[36]的前瞻性研究显示,RVO 患者血清中针对铜氧化低密度脂蛋白和磷酸胆碱的 IgM、IgG 抗体水平显著降低,丙二醛修饰低密度脂蛋白相关 IgG 抗体亦呈现类似变化。该研究提示氧化应激和炎症反应在 RVO 及其并发症中具有协同致病作用。病理机制层面,氧化应激可直接损伤视网膜血管内皮,通过增加血管通透性与血液黏度提升 RVO 发生风险。ROS 通过改变红细胞膜流动性并促进丙二醛生成,导致膜刚性增加及微循环障碍,从而加剧 RVO 进展[37]。此外,氧化应激可激活炎症级联反应,通过趋化免疫细胞浸润加重组织损伤,并可能影响视网膜神经细胞功能,最终导致视力损害。因此,监测氧化应激标记物对 RVO 风险评估具有重要价值[38]。尽管现有研究明确二者关联,其分子机制仍需深入解析:丙二醛诱导的红细胞膜硬化是直接参与血栓形成,还是通过内皮信号通路间接影响凝血过程尚存争议;氧化应激与 IL-8 等炎症因子的相互作用虽存在理论推测,但体内动态互作证据仍需完善,开发同步示踪氧化与炎症信号的技术将有助于阐明协同机制。

5 CRVO 与眼部因素

5.1 高眼压和 CRVO 高眼压与 CRVO 的病理关联已被多项研究证实。流行病学数据显示,开角型青光眼与 CRVO 发病存在显著相关性[39-40]。其机制涉及机械压迫与血流动力学改变的双重作用:持续高眼压直接压迫视盘血管导致支撑结构破坏,同时筛板变薄及神经纤维层萎缩共同增加血管闭塞风险[41-43]。临床观察发现,杯盘比增大与 RVO 发生率呈正相关,可能与视盘区域血管弯曲度增加有关[44]。前瞻性队列研究显示,CRVO/HCRVO 患者中开角型青光眼的累积患病率为 19.6%(95% *CI*:8.7-30.5),通过降眼压药物(8 例)和小梁切除术(2 例)治疗后,眼压从 24.3±4.36 mmHg 显著降至 16.55±2.85 mmHg,降幅为 31.89%,且无青光眼进展,表明青光眼是 RVO 发生的危险因素,治疗高眼压可预防其进展[45]。长期高眼压还可能引发筛板肿胀、内皮损伤及血栓形成倾向,并通过降低眼内灌注压导致血流速度减缓,最终诱发静脉阻塞[41-42]。

5.2 短眼轴和 CRVO 短眼轴与 CRVO 的关联性已被多项研究关注。流行病学证据表明,远视眼及短眼轴状态与 RVO 发病风险存在相关性[46-48]。Kouser 等[48]病例对照研究显示,RVO 患者患眼眼轴长度(21.73±0.741 mm)显著短于未患眼(22.56±0.991 mm,$t=2.45$,$P=0.018$),未患眼眼轴长度也显著短于对照组(23.49±0.426 mm,$t=5.29$,$P=0.001$),认为短轴长可能是 RVO 的危险因素之一。解剖学机制方面,短眼轴可能导致眼球结构拥挤及巩膜管狭窄,当合并动脉硬化时,将进一步阻碍静脉回流,引发血流淤滞并升高 CRVO 风险,此结论与 Szigeti、Tsai 等[46-47]研究一致。但部分研究显示 RVO 患者眼轴长度与健康人群无统计学差异,提示其可能需协同高眼压、动脉硬化等因素共同致病[49]。当前争议集中于常规生物测量可能受 RVO 继发性脉络膜增厚干扰,导致眼轴测量值偏短。未来需借助高精度影像技术明确其独立作用。

6 CRVO 与全身因素

CRVO 与全身性危险因素存在明确关联。高龄、高血压、糖尿病及凝血功能异常均被证实与 CRVO 发病机制显著相关[50-51]。年龄增长与 CRVO 风险呈正相关,主要与

血管弹性下降及代谢异常相关,这些因素促进视网膜中央动脉硬化并压迫静脉,导致管腔狭窄和血流受阻[52-54]。高血压作为重要危险因素,通过长期内皮损伤和凝血系统激活增加血栓风险[55]。Kim 等[56]研究显示,与血压正常者相比,1 期及 2 期高血压患者的 RVO 风险显著升高。糖尿病则通过高血糖导致内皮功能障碍、炎症激活及血液流变学改变,增加 RVO 发生概率[57]。青年患者中凝血异常表现为红细胞氧化应激增强,加速纤维蛋白形成及血小板活化,干扰血管舒缩调节并破坏内皮稳态,从而参与 CRVO 病理进程[58-59]。

7 CRVO 与外泌体

近年研究揭示外泌体在 RVO 病理进程中发挥多维度调控作用。这类源自多泡体的纳米级膜泡结构,通过携带蛋白质、脂质及遗传物质等生物活性成分,介导细胞间通讯并调控靶细胞代谢过程[60-61]。具体而言,外泌体可调节视网膜血管内皮细胞功能,影响平滑肌细胞收缩性,并参与血管重塑[62]。在炎症微环境中,外泌体作为炎症介质载体,促进细胞因子释放并调控免疫细胞活化状态[63]。同时,其对视网膜神经节细胞的存活调控及突触可塑性调节作用已被证实。Wu 等[64]研究发现,接受抗 VEGF 治疗的 RVO 患者房水外泌体浓度显著降低,提示其可能参与缺血型 RVO 的病理生理机制。但该领域仍存争议:尽管观察到抗 VEGF 治疗与外泌体水平变化的相关性,其在缺血性 RVO 中的具体作用通路尚未完全阐明。后续研究需整合动态示踪与基因编辑技术,系统解析外泌体成分的分子作用机制。

8 CRVO 与肠道微生物组

近年研究提示肠道微生物群可能在 CRVO 病理进程中具有调控作用。作为宿主代谢与内稳态的关键调节者,肠道微生物群通过其代谢产物网络影响系统生理功能[65]。其生态失衡可能与高血压、血脂异常、肥胖及吸烟等 RVO 传统危险因素产生协同效应。基于“肠-眼轴”理论,肠道菌群可通过免疫调节与代谢物分泌途径影响眼部微环境[66-67]。Lincke 等[68]通过 16 S rRNA 测序联合液相色谱-质谱技术分析发现,RVO 患者粪便样本中特定菌属丰度与健康对照组存在显著差异,提示肠道菌群紊乱可能与疾病相关。基于这些发现,菌群调节策略或为 CRVO 管理提供新思路。但现有研究对菌群失调与 RVO 的因果关系仍存争议,其作为独立致病因素或代谢异常的伴随现象尚未明确。由于饮食结构、地域差异等混杂因素可能影响研究结论的可靠性,未来需通过纵向队列研究追踪菌群动态演变,结合动物模型验证关键菌种对视网膜血流的影响,并运用代谢组学解析菌群代谢物的分子调控机制。

9 小结与展望

本研究系统阐释了 CRVO 的病理机制,在传承经典理论框架的基础上,从以下维度拓展认知边界:(1)机制研究层面整合新证据。相较于李水等[69]聚焦血管、炎症及内皮素等传统机制的研究范式,本文创新性解析了外泌体介导的细胞间通讯及肠道菌群通过“肠-眼轴”调控疾病进程的新机制。(2)临床转化层面构建整合策略。突破孙佳等[70]局限于 BRVO 视盘区微血管量化分析的研究范畴,本文强调全身危险因素(易栓症、高血压等)与眼部特征(高眼压、短眼轴等)在 CRVO 中的多系统交互机制,为多靶点联合干预提供理论依据。相关机制详见图 1。

CRVO 的病理进程与血管内皮功能障碍、动脉硬化、易栓症及炎症-氧化应激网络等相关。其病理机制包括:动脉硬化的机械压迫和内皮素-1 介导收缩阻碍静脉回流,凝血稳态失衡促进血栓形成,炎症与氧化应激通过 VEGF、IL-8 等介质加剧缺血损伤等。本文突破性揭示外泌体 miRNA 调控血管功能及肠-眼轴代谢影响视网膜微环境的新机制,阐明局部与全身病理交互网络。未来研究需聚焦外泌体 miRNA 靶向递送技术、肠-眼轴关键生物标志物挖掘及多靶点药物开发,通过整合医学策略优化局部-全身协同干预路径,构建 CRVO 诊疗新体系,实现从单纯控制症状到针对病因精准治疗的根本性转变。

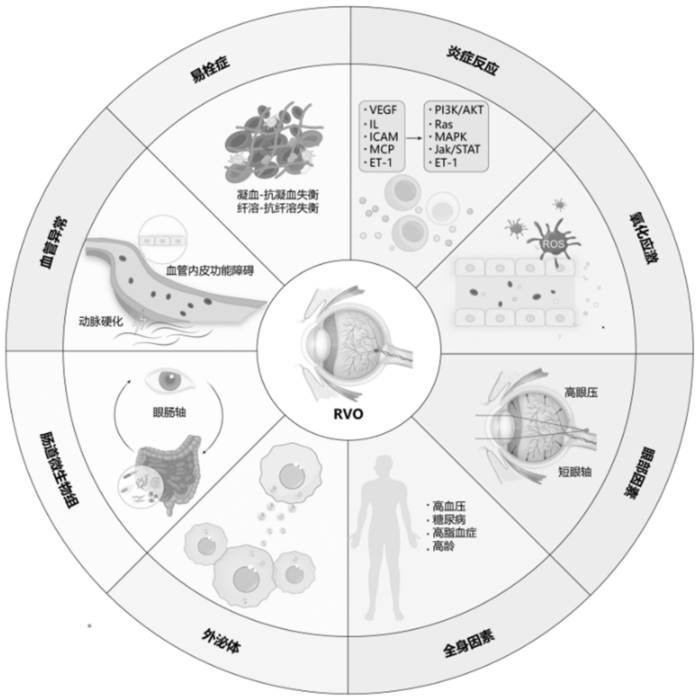

图 1　RVO 的相关发病机制。

利益冲突声明:本文不存在利益冲突。
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