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肝硬化合并门静脉血栓形成机制

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摘　要

门静脉血栓(portal vein thrombosis, PVT)是肝硬化患者中的罕见并发症。肝硬化患者合并PVT可引起一系列并发症，通常指向肝硬化患者的不良预后。肝硬化患者并发PVT的机制涉及血流动力学因素、局部血管损伤、凝血功能变化、内皮功能障碍、炎症反应、肠道菌群失调、遗传因素、门静脉高压等方面。PVT的发生往往是隐匿的，探寻肝硬化合并PVT的机制有助于临床更好地诊断及治疗。现有的研究结果表明，PVT的形成是多因素共同作用的结果，其中门静脉高压和血流动力学因素是主要的驱动因素，而凝血功能变化、内皮功能障碍和炎症反应则是次要的促进因素。

关键词

肝硬化，门静脉血栓

The Mechanism of Portal Vein Thrombosis Combined with Liver Cirrhosis

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Abstract

Portal vein thrombosis (PVT) is an uncommon complication for patients with cirrhosis. PVT in patients with cirrhosis can lead to a number of complications, often pointing to a poor prognosis in patients with cirrhosis. The mechanism of PVT in cirrhotic patients involves hemodynamic factors, local vascular injury, changes in coagulation function, endothelial dysfunction, inflammatory response, intestinal

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flora disorder, genetic factors, portal hypertension and so on. The occurrence of PVT is often hidden, and exploring the mechanism of cirrhosis complicated with PVT is helpful for better clinical diagnosis and treatment. The existing research findings indicate that the formation of PVT is the result of the combined effects of multiple factors, with portal hypertension and hemodynamic factors serving as the primary drivers, while changes in coagulation function, endothelial dysfunction, and inflammatory responses act as secondary contributing factors.

Keywords

Liver Cirrhosis, Portal Vein Thrombosis

1. 前言

肝硬化(liver cirrhosis, LC)是临床常见的一系列由各种病因造成的慢性进行性肝脏疾病的终末阶段，常见病因有病毒性、酒精性、代谢及遗传相关性、自身免疫性、胆管性、血管性及药物相关性[1]，我国以病毒性为主。LC 往往提示疾病的不良预后，是第 11 位最常见的死亡原因，是 45~64 岁人群的第三大死亡原因[2]。门静脉血栓(portal vein thrombosis, PVT)是指门静脉主干或其分支内因血栓的形成而造成的部分或完全闭塞[3]，是 LC 一种少见的并发症，与小肠缺血、缺血性肝炎和胃肠道出血等主要临床不良预后事件相关[4]，LC 患者合并 PVT 的发病率在 10.42%~13.92% [5]，在 LC 患者中，PVT 的发生率增加 7.9 倍[6]。尽管肝硬化合并 PVT 并无明显的临床症状，PVT 的发现多于临床常规影像学检查中发现，随着影像学的发展和临床应用，肝硬化合并 PVT 的发病率呈增长趋势[7]。

PVT 的形成是否与 LC 的不良预后存在直接关系目前暂无明确定论，在有关 PVT 与 LC 患者死亡率的相关研究中，PVT 的形成与死亡率无关[8] [9]，PVT 可能是 LC 进展的标志而并非原因[9]。血栓形成的三大要素，即 Virshow 三要素：血液高凝、内皮损伤和血流瘀滞。LC 患者的血管、凝血功能、机体内环境等多方面因素发生变化，LC 合并 PVT 的机制考虑是多方面因素共同作用的结果，包括血流动力学因素、血管损伤及内皮功能障碍、炎症损伤等方面，关于基因相关因素方面的研究近年也取得了进展，为 PVT 的诊疗有极大的促进作用。

2. PVT 形成的临床表现及治疗方法

LC 患者合并 PVT 临床症状的具体类型与 PVT 类型(急性、亚急性、慢性)、部位(肝内、肝外)、闭塞程度(完全、部分)等因素相关，急性完全性闭塞性 PVT 可能会引发急性或进行性腹痛、发热、血性腹泻等症状，并伴有慢性失代偿性肝功能不全症状，如腹水的形成、静脉曲张、腹膜炎等。大多数肝硬化合并 PVT 无明显特异性临床症状，PVT 的发现也多在检查中偶然发现，但在失代偿表现加重的 LC 患者中应该怀疑 PVT 发生的可能性[7]。PVT 的进展与肠系膜血栓形成造成的肠梗死、门静脉海绵窦形成等相关[10]，在合并 PVT 的 LC 患者中，静脉曲张活动性出血手术失败风险增加 3 倍或手术时间延长[11] [12]，往往提示了 PVT 对于肝硬化患者的不良预后。

LC 合并 PVT 的治疗方式取决于血栓形成的范围、闭塞程度、肝移植状态及合并肝硬化失代偿症状进展程度等，主要适应症包括急性症状性 PVT、肝移植候选者和血栓延伸至肠系膜静脉的个体[13]，抗凝治疗是 PVT 患者的常规治疗方式，抗凝治疗可以降低肝硬化合并 PVT 的全因死亡率[14]，抗凝治疗后血

栓的再通率增加[15]，但有增加门静脉高压出血的风险[14]。经颈静脉肝内门静脉系统分流术(Transjugular intrahepatic portosystemic shunt, TIPS)是一种将支架置入门静脉，通过重新疏通门静脉并降低门静脉高压的手术。TIPS 主要适用于伴有严重门静脉高压、难治性腹水的早期患者，复发消化道出血患者[16]。随着介入技术的进展，PVT 不再是 TIP 手术的禁忌症[17]，并且对于难治性腹水患者的早期受益，减轻 PVT 患者的血栓负担[18] [19]。溶栓治疗通常在抗凝治疗无效或与 TIPS 治疗同时进行，包括经静脉溶栓及经超声溶栓治疗，通常只能实现血管的部分再通或作为其他治疗的辅助手段。机械取栓包括囊取栓、溶血性取栓或吸力取栓[20]，在 TIPS 放置期间或之后使用机械取栓可以成功解决 PVT [21]。

3. LC 患者 PVT 的形成机制

3.1. 门静脉高压(Portal Hypertension, PH)与血流动力学因素

肝门静脉起始于脾静脉和肠系膜上静脉的汇合处，收集来自小肠、大部分大肠和脾脏的血液，进入肝脏后分支成为小血管，最后形成肝窦。各类慢性进行性肝脏疾病再进展过程中，在各类致病因素如嗜肝病毒、酒精、脂肪等作用下肝脏组织失去原有的正常结构及功能，纤维化、细胞外基质的积累等因素造成肝脏结构改变，进一步导致肝窦内皮细胞(liver sinusoidal endothelial cells, LSECs)和肝星状细胞(hepatic stellate cells, HSCs)失调[22]，肝窦结构破坏压力升高，进一步造成门静脉高压(portal hypertension, PH)形成，PH 进一步造成全身血管的扩张，门静脉直径增加，造成门静脉血流的减少。PH 形成除了直接改变门静脉血流量，门静脉侧支血管的形成同时对门静脉的血流产生了影响，侧支血管使大量的血流直接进入体循环而并不经过肝脏[3] [13]，侧支循环的形成及肝门静脉直径的增加使肝脏血流减少，形成“窃血效应”[23]，在上述因素的共同作用下均可造成门静脉血流量的减少，研究表明门静脉直径的增加与 PVT 形成风险增加显著相关，门静脉直径 ＞12.5 mm 对预测 PVT 的发生高度敏感[24]。门静脉直径的增加及“窃血效应”在减少门静脉血流量的同时，减慢了门静脉的血流速度，血流速度的减慢及 PH 的严重程度均为 PVT 形成的独立危险因素[24] [25]。

非选择性 β 受体阻滞剂(nonselective β-blockers, NSBB)可以阻断 β1 和 β2 肾上腺素能受体，从而降低心率和心输出量，促进内脏血管收缩，从而减少门静脉血流，在预防 PH 和食管胃底静脉曲张出血中发挥一定的作用[26]。近年来，对于 NSBB 的使用逐渐增加，因 NBSS 减少门静脉血流量及减慢门静脉血流速度的作用，NBSS 是否与 PVT 的形成相关引起人们的重视。在现有的回顾性研究及荟萃分析中，接受 NSBB 治疗的肝硬化患者的 PVT 总患病率明显高于未接受 NBSS 治疗的患者[5]，NBSS 可能在 PVT 的形成过程中发挥一定作用[27]，具体关联及机制需要进一步研究探索。

3.2. 凝血功能变化

肝脏在凝血过程中发挥中心作用，LC 患者可发生复杂的凝血功能改变，包括血小板的减少、血小板功能的变化、血管性血友病因子(von Willebrand factor, vWF)和凝血因子 VIII (coagulation factor VIII, FVIII:c)水平的升高及功能改变、止血蛋白合成减少、抗凝因子(蛋白 C、蛋白 S 和抗凝血酶)合成减少[28] [29]，LC 患者的凝血功能变化更加倾向于止血功能平衡的紊乱而并非单纯的凝血功能的增强[30]，因此 LC 不仅存在出血风险，同时也存在血栓风险。vWF 和 FVIII 的升高直接促进了血小板聚集和血栓形成，尤其是在门静脉高压和血流缓慢的情况下，更进一步促进了血栓的生成。蛋白 C 和蛋白 S 的减少通过削弱抗凝机制，减少 FVa 和 FVIIIa 的降解，进一步加剧了高凝状态和血栓形成的风险。止血与出血功能之间的平衡一旦打破难以重建，常规的凝血指标监测无法正常评估 LC 患者的凝血功能，因此对于 LC 患者是否 PVT 高危的监测指标依旧是临床医务人员一项巨大的挑战。在发生 PVT 的 LC 患者中，蛋白 C、蛋白 S、抗凝血酶、可溶性 F1＋2 和 VIIa 因子等凝血因子的含量存在差异，但其差异并不能对 PVT 的发生

进行预测[31] [32]。在探究 PVT 相关凝血因素的回顾性研究中，凝血酶–抗凝血酶复合物(thrombin-antithrombin complex, TAT)、组织型纤溶酶原激活物抑制剂复合物(tissue plasminogen activator inhibitor complex, t-PAIC)、血管性血友病因子抗原(willebrand factor antigen, vWF:Ag)和 FVIII:c 与 PVT 的形成具有相关性，TAT、TAT/t-PACI 比值、FVIII:c 和 vWF:Ag 可作为预测肝硬化患者 PVT 的潜在生物标志物[33]。在 PVT 患者中，对血栓调节素抗凝作用的抵抗(resistance to the anticoagulant action of thrombomodulin, TM-R)是 PVT 形成的一项独立危险因素，可以作为意向预测 PVT 危险因素的因素[34]。LC 患者 D 二聚体(D-dimer, DDI)及 FVIII:c 水平升高，但并不能作为预测 PVT 发生的一项判别指标，在严重肝硬化中，正常的 DDI 和 FVIII:c 可以安全地排除无症状门静脉血栓的存在[35]。凝血功能的变化在 PVT 形成中发挥一定的作用，具体的作用机制尚未完全明确，在 PVT 患者中较多的与凝血相关的生化指标发生了变化，但具体相关性未被完全证实，在近期的重多研究中，凝血功能的变化可能在 PVT 中发挥一定作用，但不是关键性因素。

3.3. 血管损伤与内皮功能障碍(Endothelial Dysfunction, ED)

内皮细胞是血管内壁的单层细胞，将管壁与周围组织隔开，通过分泌一些促凝及抗凝的因子，包括一氧化氮(nitric oxide, NO)、前列环素、血栓调节素、组织因子途径抑制剂(tissue factor pathway inhibitor, TFPI)和蛋白 C 受体、vWF、组织因子(tissue factor, TF)、p-选择素、FVIII 和内皮素等，发挥阻止血小板的活化和级联、维持血流活动等作用[29] [36]。在正常的生理活动中，内皮细胞通过血小板抑制特性、肝素抗凝血酶 III 系统、组织因子通路、凝血酶受体、纤溶特性及凝血酶受体、凝血调节蛋白与蛋白 C/S 系统使促凝及抗凝作用达到一个平衡[36]，而在应激状态下，出现内皮依赖性血管舒张功能障碍，称为内皮功能障碍(endothelial dysfunction, ED) [37]，ED 在血栓的形成中发挥重要的作用，是血栓形成的一个危险因素[36]。LC 患者肝脏结构紊乱，肝内门静脉血流的阻力增加，形成 HP，且因血流淤滞造成细菌异位的发生引发感染，造成肝脏门静脉血管及内皮细胞的损伤，进一步造成 ED 的产生。p-选择素、vWF、前列腺素等标志物的升高，可以作为评估内皮细胞功能的指标，与 ED 发生引起 PVT 产生具有相关性[38] [39]，NO 与环氧酶(cyclooxygenase, COX)系统在 ED 的形成过程中发挥重要作用，增加肝内 NO 的可用性并阻断增加的血管收缩剂前列腺素途径，对 ED 有一定的改善作用[40]。改善血管内皮细胞功能的同时，成为一种治疗的方向，使用 COX 抑制剂增加 NO 利用率[40]、利用生长转化因子-β (Transforming growth factorbeta, TGF-β)修复血管内膜[41]、使用 miRNA-25-3p 修复门静脉内膜改善门静脉高压[42]等新型治疗手段成为了未来可能的方向。

3.4. 炎症与免疫反应

炎症在慢性肝病的进展过程中发挥重要的作用，组织损伤或感染进而引发凝血是一种机体防御机制。血栓与炎症可被视为一种互补的过程，血栓形成闭塞的血凝块，阻碍血液流经循环系统，炎症是作用于对有害刺激(如病原体、受损细胞或刺激物)的复杂保护性免疫反应[43]。肝脏拥有密集的吞噬细胞网络，能够迅速感知肝细胞应激及损伤信号，进一步激活炎症级联反应，在病毒、酒精等造成肝脏细胞损伤的因素长期作用下，白细胞迅速浸润肝实质，通过产生可激活其他免疫细胞和非实质细胞群的可溶性介质，促进炎症和纤维化。炎症介质可以激活 HSCs，活化的 HSCs 产生促炎介质，使肝脏炎症持续存在[44]。在对于系统性炎症与 PVT 关系的回顾性研究中，证实炎症激活与血栓形成具有相关性，PVT 患者炎症指标，包括白细胞介素-6 (interleukin-6, IL-6)、白细胞介素-8 (interleukin-8, IL-8)、肿瘤坏死因子 α (tumor necrosis factor-α, TNF-α)、降钙素原(procalcitonin, PCT)和 C 反应蛋白(C-reactive protein, CRP)水平显著升高，其中 IL-6 水平与 PVT 形成独立相关[45]。全身炎症导致一氧化氮介导的先前存在的内脏血管舒张的

加重，导致内源性血管收缩系统的过度激活，导致免疫介导的组织损伤[46]，对于肝脏的功能和结构具有严重损伤。单核/巨噬系统是机体炎症反应的重要环节，单核/巨噬细胞的数量与肝功能的分级密切相关[47]，在研究炎症反应与 PVT 相关性的研究中，CD169 作为一组独立的反映炎症指标的亚群，在反映机体炎症指标、免疫反应等方面存在价值[48]，在 LC 进展过程中，CD169 的亚群也在同步增殖，对 CD169 的耗竭处理后急性肝损伤的缓解表明炎症反应的抑制对于肝功能的改善有一定帮助[49]。

3.5. 肠道菌群失调

人类肠道存在丰富的菌群，菌群与人体保持平衡维持机体的正常生理功能，菌群的改变或失衡也被认为与疾病的发生或表型相关，随着基因组学等科学技术的发展，肠道菌群庞大的基因组成被逐步发现[50] [51]，肠道菌群对于健康及疾病的研究更进一步深入。肠道菌群的组成、分布、代谢产物等均对人体有复杂的作用[52]。肠道菌群的作用可以通过肝肠轴对肝脏产生影响，肝肠轴是肠道微生物与肝脏之间的细胞、产物相互影响的总和，肠道微生物及其代谢产物与肝脏的双向交流主要通过门静脉循环、内脏动脉和胆管系统进行，肠道微生物菌群的紊乱和代谢产物的异常可通过肝肠轴进一步影响肝窦的结构和功能，对 PH 的产生存在一定影响[53]。肠道菌群的失调可造成肠道屏障结构和功能的改变，人体肠道屏障包括黏液层、肠细胞屏障和血管层，防止肠道中的微生物及有害代谢产物进入血液循环，其中关键的结构包括粘附连接蛋白、紧密连接蛋白、间隙连接蛋白和桥粒[54]。肠道微生物群的改变或屏障功能的内在变化(如全身性炎症)或外源性因素(如酒精摄入滥用、非甾体抗炎药)可造成肠道通透性的改变[55]。病原菌的入侵对肠道内具有保护作用的代谢产物，包括短链脂肪酸(short-chain fatty acids, SCFAs)、由色氨酸微生物消化产生的吲哚和吲哚衍生物、胆汁酸代谢物、多胺和多酚[55]，代谢产物的改变造成肠道屏障功能和结构的破坏。肠道微生物群多样性的减少与机会性物种的相对或绝对增加等原因[56]可造成肠道生态的失调，造成肠道屏障的改变，同时脂多糖(lipopolysaccharides, LPSs)随着受损的肠道屏障进入肝脏[56] [57]，造成毒血症被认为是 PVT 产生的一种危险因素[58]。

3.6. 遗传因素

遗传及基因相关的因素在 PVT 的形成中发挥作用，自身免疫性疾病、JAK2 阳性骨髓增生性肿瘤(myeloproliferative neoplasms, MPN)、阵发性夜间血红蛋白尿(paroxysmal nocturnal hemoglobinuria, PNH)、恶性肿瘤、遗传性和获得性血栓形成疾病等都可能成为 PVT 的促发因素[59] [60]。在遗传性血栓性疾病对于 PVT 影响的研究中，往往受到样本量、诊断标准等多方面的影响导致结果不一致，其中因子 V Leiden (factor V Leiden, FVL)和凝血酶原 G20210A (prothrombin G20210A, PTHR)的突变[60]-[63]是目前有较多相关研究的，被认为是增加 LC 患者并发 PVT 的危险因素，且蛋白 S 和抗凝血酶的遗传缺陷可能不是 PVT 发病的主要易感因素[63]。然而，遗传性血栓性疾病在 LC 及 PVT 患者中少见，作为常规的筛查对于疾病的诊疗无明显收益，应结合患者个体情况进行相关疾病的筛查[64]。随着血栓形成倾向测试技术的发展，获得性嗜血栓因子(acquired thrombophilic factors, JAK2 V617F)的突变可能指向血栓的形成，JAK2 V617F 的突变在 PVT 患者中占比 14%~15.3% [65] [66]，JAK2 V617F 突变在费城染色体阴性的骨髓增殖性肿瘤中很常见，存在于 90%以上的真性红细胞增多症和 60%以上的原发性血小板增多症病例中，这一特性可能在血栓性并发症中起作用[67]。在血栓形成遗传因子的研究中，亚甲基四氢叶酸还原酶 C677T 和纤溶酶原激活物抑制剂-1 型 4G-4G 突变也被描述为 PVT 这些等位基因多态性可能会增加嗜血栓性疾病(如 LC)患者的血栓形成风险[68]。在 LC 合并 PVT 的患者中，狼疮抗凝标志物阳性比例增高[69] [70]，高危抗磷脂抗体(antiphospholipid antibody, aPL)谱的检测对于 LC 患者 PVT 发生危险性也有一定的指示作用[69]。在一些案例的分析中，蛋白 C 基因(PROC)突变引发的遗传性蛋白 C 缺乏(Hereditary protein C

deficiency, PCD)在一例 PVT 患者中发现[71]，指向 PVT 形成的基因遗传因素。

4. 总结

PVT 是肝硬化患者的一种罕见但严重的并发症，其形成机制复杂，涉及多种因素的相互作用。这些因素包括血流动力学的改变、血管损伤和内皮功能障碍、凝血功能的变化、炎症和免疫反应、肠道菌群失调以及遗传因素等。PVT 的形成是多方面机制共同作用的结果，关于某种机制的作用占比目前尚无定论，现有的研究结果表明，门静脉高压和血流动力学因素可能是 PVT 形成的主要驱动因素，而凝血功能变化和内皮功能障碍则可能是次要的促进因素。PVT 的发生往往是隐匿的，但其诊断对于肝硬化患者的临床治疗和预后评估至关重要。临床上需要综合考虑这些因素以实现更好地诊断和治疗。随着对 PVT 机制的进一步研究，未来可能会发现新的生物标志物和治疗靶点，从而改善肝硬化合并 PVT 患者的预后。

5. 未来展望

PVT 形成机制对于未来的研究方向的作用可以体现在以下几个方面，包括多种机制相互作用、肠道菌群与 PVT 的关系、新型生物标志物的探索、新型治疗靶点的开发、遗传因素与 PVT 的关系、PVT 的早期诊断和预防，以及 PVT 与肝移植的关系。通过这些研究，可以更深入地理解 PVT 的病理生理机制，并为临床诊断和治疗提供新的思路和方法。

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