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肝硬化门静脉血栓形成的研究进展

白莆荪，韩　文*

延安大学附属医院消化内科，陕西　延安

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摘　要

门静脉血栓形成是肝硬化的一种严重的并发症，可导致门脉高压和肝功能衰竭，进而引发严重后果，如食管胃底静脉曲张破裂出血、顽固性腹水和肝性脑病等，影响其预后和生活质量。过去几十年中，随着人们对门静脉血栓的逐渐重视，肝硬化门静脉血栓形成的研究也取得了一些进展，本文将从肝硬化门静脉血栓形成的发生机制、临床表现、相关因素、治疗及预后进行探讨，以期为临床预防和治疗提供科学依据。

关键词

肝硬化，门静脉血栓，机制，临床表现，研究进展

Research Progress on Portal Vein Thrombosis in Liver Cirrhosis

Puxi Bai, Wen Han*

Department of Gastroenterology, Affiliated Hospital of Yan'an University, Yan'an Shaanxi

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Abstract

Portal vein thrombosis is a serious complication of liver cirrhosis, which can lead to portal hypertension and liver failure, and then lead to serious consequences, such as esophageal and gastric variceal bleeding, refractory ascites and hepatic encephalopathy, which affect their prognosis and quality of life. In the past few decades, with the gradual attention to portal vein thrombosis, some progress has been made in the research of portal vein thrombosis in liver cirrhosis, and this article will discuss the pathogenesis, clinical manifestations and related factors of portal vein thrombosis in liver cirrhosis, in order to provide a scientific basis for clinical prevention and treat-

*通讯作者。

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ment.

Keywords

Liver Cirrhosis, Portal Vein Thrombosis, Mechanism, Clinical Manifestations, Research Progress

1. 引言

肝硬化门静脉血栓形成是肝硬化患者常见的严重并发症之一，其发生率逐年增加且具有高度致死性。一项较大规模回顾性研究中，PVT 患病率在代偿性肝病患者中为 1%，在肝细胞癌(hepatocellular carcinoma, HCC)患者中为 40%，在肝移植(liver transplant, LT)候选患者中为 8%~25% [1]。血栓形成导致门静脉系统的阻塞和压力升高，进一步加重肝脏功能损害，并可能引发严重的并发症，如肝性脑病、腹水感染等[2]。肝硬化患者血栓并发症的发生是隐匿的，发生率难以预测。常规凝血试验在估计止血平衡时价值有限，在评估危及生命的出血风险时甚至具有误导性[3]。鉴于血栓并发症对肝硬化的不良预后影响，确定可靠的预测因素对于临床决策和血栓预防管理至关重要[4]。尽管已有研究对肝硬化门静脉血栓形成的机制、相关因素进行了一定的探讨，但仍存在许多问题需要进一步研究和探索。因此，本文旨在通过综合分析现有文献，探讨肝硬化门静脉血栓形成的研究进展，并为临床预防管理该并发症提供科学的依据。

2. 发生机制

根据 Virchow 三联征，血流量减少、高凝状态和内皮损伤是血栓形成的主要危险因素[5]。在 PVT 的情况下，这些机制是门静脉高压症发展和维持的结果，因此门静脉高压症是慢性肝病中 PVT 发生的主要因素。

2.1. 血瘀

慢性肝病患者由于肝实质的组织学改变引起门静脉循环的许多变化：肝纤维化导致门静脉系统阻力的增加，同时，体循环血中释放更高水平的血管扩张剂，导致内脏小动脉的血管舒张从而使门静脉系统中血流重新分布，为了减少门静脉高压并绕过肝循环，门静脉内径扩大并门体分流形成，它们使血流量和门静脉血流速度降低[6]。已有很多研究证明低于 15 cm/s 的血流速度是 PVT 的预测因素[7]。这些机制导致血瘀，促进血小板的粘附和活化[8]，进而影响血栓的形成。

2.2. 内皮功能障碍

肝窦内皮细胞(LSEC)在肝细胞稳态中起着至关重要的作用，参与许多过程，包括调节血管张力、止血和炎症[9]。在健康条件下，LSEC 会产生多种物质，如一氧化氮(NO)、前列环素和血小板调节素，这些物质参与血管的完整性，并保证为肝细胞提供足够的血液支持和营养。据报道，肠道菌群失调和内毒素血症对内脏静脉血栓形成的发生有直接影响[10]。在慢性炎症和内毒素血症的情况下，内皮细胞损伤导致细胞外基质的暴露和内皮下促血栓形成成分的激活，进一步使门静脉高压症恶化[11]。

2.3. 高凝状态

肝功能障碍导致几种止血蛋白、促凝血剂(凝血酶原、凝血因子 V 和 X)和抗凝血因子(蛋白 C、蛋白

S 和抗凝血酶)的合成减少，导致大多数凝血途径成分的血浆水平降低，导致肝硬化患者止血系统的再平衡，但促凝血因子和抗凝血因子之间的这种重新平衡是脆弱的，因门静脉高压症出血的风险较高，血栓形成风险也随之增加[12]。几项研究描述了在比较发生 PVT 和未发生 PVT 的肝硬化患者时凝血因子的变化(蛋白 C、蛋白 S、抗凝血酶和因子 VIIa)；然而，他们都不能预测 PVT 的发展[13] [14]。在迄今为止发表的最大规模的前瞻性研究(369 例患者)和长期随访(长达 48 个月)中，许多生化标志物都发生了改变，但在与肝病阶段相关的随访期间，它们都没有与 PVT 的发展独立相关[6]。此外，基础获得性(骨髓增生性肿瘤、真性红细胞增多症)或遗传性(蛋白 C 和蛋白 S 缺乏、凝血酶原(G20210A)、凝血因子 V. Leiden 等突变)的血栓形成前疾病在肝硬化患者中的患病率非常低[15] [16]，进一步表明高凝状态在 PVT 发展中不起主要作用。

3. 临床表现

肝硬化中的 PVT 通常不易诊断[17] [18]，但在最近的一份报告中，约 57%的 PVT 肝硬患者有症状[19]。临床表现的存在可能取决于 PVT 形成的速度(急性 PVT)和血栓形成的扩展(位于不同躯干和/或闭塞性血栓形成)。急性 PVT 通常表现为 PVT 进展至肠系膜上静脉引起的小肠缺血或梗死[19] [20]；腹痛或腹胀、腹泻、直肠出血、恶心、呕吐、厌食、发热、乳酸中毒、脾肿大和败血症可能各不相同[21] [22]。如果梗阻不能迅速解决，还可能会发生肠穿孔、腹膜炎、休克和多器官衰竭导致的死亡[23]，慢性 PVT 更常表现为静脉曲张出血[19] [24]、皮肤侧支、腹水[25]或脾功能亢进导致的全血细胞减少症[26]，另一个临床特征是难治性腹水，但确切的机制尚不确定。PVT 与出血和肠梗死的致病关系表明，PVT 可能会降低肝硬化的生存率，但目前仍缺乏这方面的数据。此外，尚不清楚无症状 PVT 患者的生存率是否与无 PVT 的肝硬患者不同。这些问题值得进一步调查。

4. 相关因素

肝硬化 PVT 形成的发病机制尚不完全清楚。一些研究显示，门静脉血流速度(PBFV)降低到 15 厘米/秒以下[27]为 PVT 发展的主要危险因素。PVT 的其他危险因素是与肝病严重程度和门静脉高压症的存在相关的因素：血小板计数低[28]、低白蛋白[29]，食管静脉曲张[7]，和既往硬化疗法[30]，既往肝功能失代偿[28]，或存在大的门体侧支[31]。也有人提出全身炎症和全身炎症因子水平升高会加剧 PVT 形成的风险[32]。肝硬化可引起门静脉高压症、消化道血瘀、肠道屏障受损和肠道菌群失调。肠道菌群失调后共生厌氧菌的减少和病原菌丰度的增加，特别是革兰氏阴性肠杆菌科的增加，与 PVT 的发生密切相关[33]。细菌 LPS 是革兰氏阴性菌外膜上的糖脂，是肝硬化高凝状态的关键因素之一[34] [35]。细菌和病原体相关分子模式(PAMPs)的易位，特别是 LPS，会引起全身炎症，内毒素血症和血小板活化，同时，全身炎症和全身炎症因子水平升高会加剧 PVT 形成的风险[32] [36]。肝硬化患者通常由于肠道菌群失调而出现较高的内毒素血症和全身炎症。内毒素可以通过产生组织因子(TF)来增加血栓形成[37]。随着肠道通透性和细菌易位的增加，肝硬化患者血液中 LPS 水平显著升高。

5. 治疗

尽管文献报道了 PVT 的自发消退[38]，但必须采取特定的治疗措施来解决门静脉阻塞并避免严重并发症。急性和慢性 PVT 的治疗目标相似，包括纠正致病因素、预防血栓形成扩大和实现门静脉通畅。然而，在长期血栓形成的情况下，必须同时考虑门静脉高压症和门静脉胆管病相关并发症的处理[39]。如今，抗凝治疗是获得门静脉再通的最佳方法；然而，对其应用没有达成共识。只有在 PVT 部分消退或不存在的情况下，才应采用其他治疗方式[39]。在肝硬化 PVT 患者中普遍和长期使用抗凝剂不应被视为正确的

做法。然而，肠缺血或梗死的体征或潜在的血栓形成前疾病应被视为肝硬化患者使用抗凝剂的指征，但前提是必须充分预防静脉曲张出血。对于高危 PVT (门静脉阻塞超过 50%)的肝移植候选者，即使尚未评估预定的预防性治疗，也应推荐抗凝治疗。溶栓治疗，通过经颈静脉或经肝途径进入体静脉循环、肠系膜上动脉或门静脉，也可有效提供急性 PVT 的再通。然而，与保守治疗相比，接受溶栓治疗的患者疗效显着降低，死亡率增加。尽管副作用发生率很高，但当初始抗凝治疗失败时，应考虑溶栓，即使没有一致的证据证明在哪些情况下溶栓应优于抗凝治疗。其他方法，如经颈静脉肝内门体分流术，应仅用于肝移植前后发生急性 PVT 的患者，或抗凝失败时替代溶栓。它似乎能有效解决门静脉胆道病、腹水和门静脉高压，但如果门静脉不能置管或海绵状血管瘤静脉不能扩张，则不可行。分流手术可能作为最后的选择，并且仅在没有脾或肠系膜上静脉血栓形成的情况下应用[40]。

6. 预后

血栓复发率估计在 9%~42%之间。男性、既往接受过 PVT 治疗、Child-Pugh C 级和酒精性肝病可能与复发有关。此外，超过一半的门静脉阻塞(延伸或不延伸至肠系膜上静脉)的患者似乎增加了严重围手术期并发症的风险，死亡率更高，长期生存率降低。在患有 PVT 的肝硬化患者中，外科手术可能更困难，通常并发再血栓形成和再干预，但发病率和死亡率与非肝硬化患者相同[40]。

7. 结束语

肝硬化门静脉血栓形成是一种严重的并发症，其发生和发展受多种因素的影响。综合分析肝硬化门静脉血栓形成的机制、临床表现、相关因素、治疗及预后，可以发现肝硬化本身、肝功能不全、局部血流动力学改变以及其他因素如炎症反应、凝血系统异常和遗传因素等都与该并发症的发生密切相关。这些因素的综合作用导致了血栓形成的风险增加。深入研究这些因素的相互关系和作用机制，有助于医疗界更好地理解该病的发病过程，并为临床治疗和预防提供有效的策略和措施，有助于提高患者的生存率和生活质量，并为临床医生提供更好的指导和决策依据。

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