Advances in Clinical Medicine 临床医学进展, 2023, 13(2), 2200-2205
Published Online February 2023 in Hans. https://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2023.132309

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肝癌血供特点及影响

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收稿日期：2023年1月14日；录用日期：2023年2月10日；发布日期：2023年2月17日

摘　要

肝脏是人体中重要的器官，肝脏疾病，影响人们健康状况，恶性肿瘤更是使其雪上加霜。肝脏自身血供特点，也决定了肝脏疾病的特殊性，肝脏疾病过程中，病理生理学的改变必然引起肝脏血流动力学的改变。探讨肝癌血流动力学的改变，从不同的角度为肝癌的诊断、治疗提供新的临床思路。

关键词

原发性肝癌，肝硬化，门静脉，血管生成，血流动力学，门静脉癌栓

Characteristics and Influence of Blood Supply of Liver Cancer

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Received: Jan. 14th, 2023; accepted: Feb. 10th, 2023; published: Feb. 17th, 2023

Abstract

The liver is an important organ in the human body, liver disease affects people's health, malignant tumors make it worse. The characteristics of the blood supply of the liver itself also determine the particularity of the liver disease. In the process of the liver disease, changes in the Pathophysiology will inevitably lead to changes in the Hemodynamics of the liver to explore the changes of liver cancer Hemodynamics, and to provide new clinical ideas for the diagnosis and treatment of liver cancer from different angles.

Keywords

Primary Liver Cancer, Cirrhosis, Portal Vein, Angiogenesis, Hemodynamics, Portal Vein Tumor

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文章引用: 叶艳霞. 肝癌血供特点及影响[J]. 临床医学进展, 2023, 13(2): 2200-2205.
DOI: 10.12677/acm.2023.132309

Thrombus

1. 引言

原发性肝癌是最常见的恶性肿瘤之一。作为最具有侵袭力和快速增长能力的恶性肿瘤，肝癌是仅次于肺癌和胃癌的全球第三大癌症相关死亡原因[1] [2] [3] [4]。在过去的时间，肝癌的发病率一直呈现上升趋势[5] [6]。根据世界卫生组织国际癌症研究机构 2020 年发布的全球最新癌症负担数据显示肝癌的发病人数占恶性肿瘤第六位，死亡人数占恶性肿瘤第三位，2020 年，全世界被新确诊为肝癌的人超过 90 万，因肝癌死亡的人超过 83 万，死亡人数接近新发病人数[7]。

2. 肝癌发病诱因

原发性肝癌(Hepatocellular Carcinoma, HCC)，病因不明，发病机制复杂，目前尚无一致的说法来阐述肝癌的发病机制。其诱发的危险因素主要包括：1) 病毒感染：慢性感染乙型肝炎病毒(Hepatitis B Virus, HBV)丙型肝炎病毒(Hepatitis C Virus, HCV)等；2) 长期的大量的酗酒；3) 黄曲霉毒素 B1 接触；4) 长期的化学、放射接触史；5) 遗传因素。流行病学的角度显示，全世界 80%以上的肝癌病例都有肝硬化病史；病理学的角度可见，80%~90%的肝癌患者有潜在的纤维化，三分之一的肝硬化患者将发展为肝癌[8]；分子学的角度分析，肝癌的侵袭性于基因相关，与侵袭性正相关的，这表明肝癌的早发现、早治疗的有效性受其生物学特性的限制[9]。无论肝损伤的病因如何，肝癌都与肝纤维化和肝硬化密切相关。慢性肝损伤、炎症和肝纤维化是 HCC 癌前微环境的特征[8]。

HBV 慢性感染是人类 HCC 中最常见的潜在因素，它会导致慢性肝损，伤诱发肝癌。最终导致肝硬化的慢性肝损伤可能以多种方式促进肝细胞转化，包括促进 HBV DNA 整合、易于获得细胞突变和产生突变性氧反应物种。通常在 HBV 感染的 HCC 患者中先检测到 DNA 整合。随后，整合的病毒 DNA 可以直接重排宿主染色体。乙型肝炎病毒 x 蛋白(Hepatitis B Virus, HBV X HBx)和截短的前 S/S 基因产物被认为在 HCC 中发挥致癌作用。HBx 可以转录激活多种病毒启动子以及细胞基因的启动子，可能与细胞增殖和转化有关[10] [11] [12]。

酒精蓄积，代谢物中的酒精会产生乙醛，乙醛会与 DNA 结合，从而引发癌症。此外，酒精诱导细胞色素 P450 2E1 生成游离氧，并增加环境前致癌物(如亚硝胺)的激活。相关报道称，长期饮酒会导致肝脏中的维甲酸减少，进而导致肝细胞再生，最终导致肝硬化[11] [13]。

黄曲霉毒素(Aflatoxin B_1 AFB1)是一种自然产生的真菌毒素，通过 p53 突变与肝癌发病率增加相关，尤其是在 HBV 感染患者中表现明显[14]。此外，AFB1 可能在 HBV 诱导的肝癌发生过程中发挥协同作用，产生肝硬化，并最终导致肝癌发生[15]。

3. 肝癌血供特点

肝癌是一种血管化良好的肿瘤，肝脏的双重血管供应，为肿瘤的生长提供了优渥的生存环境，使其生长快，预后差。血管生成在其发生、侵袭和转移中起着重要作用[16] [17]。HCC 的发展过程中，肝动脉供血比例逐渐增加，门静脉供血逐渐减少[18]。Saitoh 等人[19]观察到，在高分化肝细胞癌中，门脉血

流在动脉血流增加之前就消失了。当高分化肝细胞癌有门脉血流且无血管增生时，其生长缓慢，当它失去门脉血流并变得丰富时，就会迅速生长。Nakashima 等人[20]报告说，随着小 HCC 尺寸的增加；它们变得越来越去分化，门静脉束的数量明显减少，肿瘤内小动脉发育。随着动脉形成的增加，HCC 表现出明显的血管异常、血管扭曲、直径不均和分支不规则、功能性侧支动脉形成、肝窦毛细血管、微血管密度增加[21] [22] [23] [24]。

与典型的 HCC 不同，一些早期分化良好的 HCC 是由门静脉系统供血，而不是由肝动脉供血[25] [26] [27]。晚期 HCC 通常只有动脉样血管作为血液供应系统，并显示退化的门静脉[28]。病理生理学上，肝细胞癌结节的血流通过肝细胞癌包膜周围的门静脉分支流出。因此，肝癌的引流血管被认为位于门静脉系统[29] [30] [31]。临床观察表明，在肝癌影像辅助检查下，在肝细胞癌结节周围经常观察到流出恒定波形信号和流入脉动波形信号[32]。这些流出道信号通常在病理上对应于残余的门静脉分支[28]。临床动态 CTA 或彩色多普勒成像可将肝静脉识别为引流静脉。虽然这种 HCC 很少见，但静脉引流可能与肺转移或远处转移有关，这需要进一步的经验来证明这个假设是否成立。

4. 肝癌血流改变

在肝硬化的背景下的肝癌，不良结节－不典型变－典型小肝癌－进展期肝癌，不可逆的发展过程中，血供慢慢从以门静脉为主到以动脉为主的过度转变，有研究显示动脉血供可达 90%以上[33]。研究血流动力学在考虑动脉系统、毛细血管、静脉系统等整体的血供情况的同时，还要关注血管局部结构的变化情况。Hsieh 等[34]研究证实，肝癌血管内膜不完整，血管平滑肌相对较少，血管扭曲或呈囊状，血管走行丰富且杂乱无章。肿瘤新生血管一旦生成后，供血明显增加，同时由于微血管基底膜不完整性，使得毛细血管通透性增加[35]。故而，肝癌虽然富血性，但发育不良的肿瘤血管、动静脉短路的存在，加速了血液的流动，形成的涡流和层流对新生血管和门静脉的远端分支造成冲刷损害[36]。

肝癌的发生过程从增生性结节到早期 HCC，再到早期显性 HCC，最终发展为晚期显性高血管性 HCC [37] [38] [39] [40] [41]。在这个过程中，血管内血流动力学发生改变[26]，包括肝动脉和门静脉局部血管重构及其血流流场变化[42]。在癌变的初始阶段，血流动力学模式显示动脉血管丰富，伴有低血管和门静脉灌注(I 型)。下一步，动脉和门脉血供均减少(II 型)。随后，结节内动脉血管增加至等血管(III 型)，然后增加至高血管(IV 型)。另一个血液动力学转变发生在 I 型到 V 型(在门静脉灌注的低血管背景下，动脉血管与局部血管斑点) [26] [28]。早期高分化 HCC 中动脉和门脉血管密度降低的病理证据支持了动脉和门脉供应减少[43]。

由此可以看出肝癌的发展过程中，首先，肝癌结节中门静脉的血供逐渐减少，结节内动脉血供先减少后增加，而肝癌结节的引流从肝静脉到肝静脉窦，最后变成门静脉引流；随着肝癌的发展，肿瘤周围的微血管甚至较大的血管渐渐被肿瘤侵犯[42] [32] [43]。肿瘤边缘血流动力学改变反映其浸润程度、生长情况，从而判断其恶性程度。研究显示，与肿瘤中心相比，肿瘤边缘的肝血流、门静脉灌注量明显增多，而肝动脉灌注指数、肝动脉灌注量则呈递减趋势，提示肿瘤病灶向周围肝脏组织过渡浸润时血流动力学发生明显改变，血流动力学改变对肝癌的超声、CT 等影像学诊断有较大的意义[44] [45]。

5. 肝癌血流改变的意义

肝癌的进展依赖于新生血管生成，不同阶段所生成的血管密度、走向、血流量不完全一致。由于早晚期肝细胞癌在形态学和血流动力学方面存在显著差异，因此有学者认为通过观察肿瘤血管的密度和血流动力学，有助于评价肿瘤生长，对于诊断治疗及预后评估有重要价值[46]。

HCC 的进展过程中动－静脉瘘的形成，向肿瘤供血动脉阻力降低，进而导致血流灌注指数(Perfusion

Index, PI)，阻力指数(Resistance Index, RI)降低，收缩期峰值速度(Peak Systolic Velocity, PSV)升高[47]。HCC 生长过程中不断有新生血管生成，为其提供营养物质，尤其肿瘤复发组织受激产生新生毛细血管，导致肿瘤内血流异常丰富，出现异常的血流改变。这些改变在超声检测下表现为 PI、RI 降低，PSV 升高[48] [49]。肿瘤复发时，组织处于高代谢状态，需大量血供维持肿瘤细胞增殖，血流灌注升高，进而提升 PSV [50]。

有关这些改变的临床意义也得到了相应证实：Cabibbo [51]等认为肝动脉管径增宽对肝癌的诊断有一定帮助；Taylor [52]等则认为可以通过肝内肿瘤的血供丰富程度，鉴别肝脏良恶性肿瘤；梁丽[53]等认为 PI、RI 值与肝癌复发呈正相关，与 PSV 呈负相关，PI、RI、PSV 为影响肝癌复发的主要因素。

6. 结论

综上所述，对于肝脏血流动力学改变的探讨，可以为肝癌诊断和治疗选择提供颇具价值的理论依据。

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