

综述

肝硬化失代偿期门静脉高压症病理生理及分子机制改变的研究进展

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[摘要] 多种病因引起的肝硬化可导致门静脉高压症。处于肝硬化失代偿期的门静脉高压症患者预后显著不佳。由多种并发症引起的患者内环境紊乱通常会演变为肝内外器官功能衰竭。对于由不同病因引起的肝硬化, 在早期尚可应用一些缓解药物, 但目前关于肝硬化失代偿期门静脉高压症患者疾病进展的机制尚不明确, 也缺乏针对疾病进展的有效治疗方案。因此, 揭示肝硬化失代偿期门静脉高压症的病理生理机制, 以及寻找治疗疾病的有效药物靶点, 成为当前研究的重点。该文总结了在肝硬化失代偿期肝内外器官衰竭的病理生理改变, 简述了肝内血管阻力、门静脉系统、心血管系统及炎症介质等相关细胞分子调节机制。通过全面分析肝硬化失代偿期门静脉高压症的病理生理发展进程, 能够更好地理解引起病情恶化或缓解的潜在细胞分子机制, 有助于提高疾病的诊断准确性和对疾病分期的正确把握。此外, 发现阻断疾病恶化的药物靶点将指导临床工作者更好地应对难治性门静脉高压症, 改善患者预后。

[关键词] 肝硬化; 门静脉高压症; 病理生理机制; 治疗靶点

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Research progress in pathophysiological and molecular mechanism changes during decompensated phase of portal hypertension in liver cirrhosis

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[Abstract] Cirrhosis caused by multiple etiologies can lead to portal hypertension. The prognosis of patients with portal hypertension in decompensated cirrhosis is significantly poor. Disorders in the patient's internal environment caused by various complications often evolve into organ failure both inside and outside the liver. For cirrhosis caused by different etiologies, there are still some relief drugs used in the early stages, but the mechanism of disease progression in patients with decompensated cirrhosis and portal hypertension is currently unclear, and there is a lack of effective treatment plans for disease progression. Therefore, revealing the pathophysiological mechanisms of decompensated cirrhosis with portal hypertension and seeking effective drug targets for treating this disease have become the focus of current research. This article summarizes the pathological and physiological changes of intrahepatic and extrahepatic organ failure during the decompensated phase of liver cirrhosis, and briefly describes the cellular and molecular regulatory mechanisms related to intrahepatic vascular resistance, portal system, cardiovascular system, and inflammatory mediators. By comprehensively analyzing the pathological and physiological development process of decompensated cirrhosis with portal hypertension, the potential cellular and molecular mechanisms that cause disease deterioration or remission can be better understood, which can help improve the accuracy of disease diagnosis and the correct grasp of disease staging. In addition, identifying drug treatment targets to block the progression of the disease will guide clinical staff to better cope with refractory portal hypertension, and even improve the prognosis of patients.

[Key words] liver cirrhosis; portal hypertension; pathophysiological mechanism; therapeutic target

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肝硬化失代偿期门静脉高压症 (portal hypertension, PH) 的特点在于出现与肝硬化相关的严重并发症, 包括腹水合并细菌感染、肝性脑病以及静脉曲张破裂出血等。其中, 有30%的患者可能会进展至肝脏及肝外器官的衰竭。临床研究^[1]数据表明, PH患者在疾病发展至90 d时的死亡率可能高达14%。尽管关于PH的发生和发展已经开展了多项基础研究, 但仍有40%的病例其病理机制尚未明确阐明^[2]。疾病发展的不可预测性可能导致从最初的单纯肝内失代偿恶化为多器官衰竭。PH患者伴随多器官衰竭更凸显了该疾病的极大复杂性^[3-4]。早期研究^[5]结果认为, PH伴随全身血管扩张和高动力循环是失代偿发生的核心机制。然而, 近年来的研究结果^[3,6]认为, 全身性炎症、氧化应激以及代谢变化等共同病因导致的组织损伤和肝外多器官衰竭同样参与这一过程。本文在阐述肝硬化失代偿期PH发病机制的基础上, 从肝内血管及肝外血管系统 (以门静脉系统为主) 的变化出发, 结合全身其他器官及机体调节相关介质等对该疾病的诊断、治疗及研究现状做全面的总结。

1 肝硬化PH的病理生理改变

门静脉系统的压力梯度 (hepatic vein pressure gradient, ΔP) 由血流量与血管阻力的相互作用决定。根据欧姆定律, 该作用在血流动力学中表示为: $\Delta P = \text{血流量} \times \text{血管阻力}$ 。因此, 肝硬化PH是由血流量和血管阻力的综合作用引起的^[7]。

在生理条件下, 门静脉血流自然地注入肝脏。而在病理条件下, 肝内阻力增加, 门静脉血流回流受阻, 从而引起肝脏前性淤血。当 ΔP 升高, 同时血管内皮生长因子 (vascular endothelial growth factor, VEGF) 驱动的肝内微血管生成及门静脉-全身侧支形成时, 门静脉系统的血流会显著增加, 从而加剧PH。在肝硬化失代偿期PH, 建立的侧支循环排水量甚至可能超过门静脉总血流量的90%^[8]。当 ΔP 高于10 mmHg (1 mmHg=0.133 kPa) 时, 可被定义为临床显著的门静脉高压症 (clinically significant portal hypertension, CSPH)。CSPH患者通常伴随着门静脉-全身侧支形成、食管胃底静脉曲张、腹水以及肝性脑病等其他相应的症状^[9]。综上, 肝内阻力增加引起门静脉压力升高的同时, 代偿性增生的新生血管进一步加重了入肝血流量; 在肝内阻力未能得到有效

缓解的情况, 入肝血流量的增加反而加重门静脉压力的上升。

2 调节PH病理生理的细胞分子机制

2.1 肝内血管阻力

肝内血管阻力受到血管长度和血黏度的直接影响, 与血管内径 (相当于肝窦横截面积的总和) 呈负相关。由于病理改变, 正常肝窦组织明显减少, 其形成原因如下: ① 静态阻力 (结构阻力) 升高。肝内胶原沉积、纤维化及假小叶的形成, 使肝内血管扭曲, 促进血栓形成、肝窦毛细管化及肝星状细胞 (hepatic stellate cell, HSC) 激活。以上因素导致血管重构, 加重组织损伤^[10]。② 动态阻力增加。活跃的成纤维细胞及HSC激活促进肝内血管收缩, 导致血管阻力增加^[11]。此外, HSC可产生细胞外基质和胶原, 导致肝内纤维化加重。活化的HSC具有收缩性, 增加肝窦内皮细胞去分化的抗性, 导致内皮功能障碍, 间接参与肝损伤、氧化应激和炎症的发生过程。因此, HSC不仅涉及动态阻力的改变, 同时对结构阻力的加重也起着重要的作用^[12]。肝内组织结构变化及血管动力学改变互为助力破坏肝脏汇管区形态, 缩窄血管面积, 阻碍入肝血流的正常流通, 不断提高肝内阻力。

一氧化氮 (NO) 等内源性血管扩张剂的减少与血管收缩剂 (去甲肾上腺素、血管紧张素II、内皮素和血栓素A2) 增加引起的平衡失调也是肝内血管阻力增加的重要因素^[7]。研究^[13-15]表明, 某些药物如索拉唑嗪可扩张肝内血管, 但因其不良反应而无法单独应用于临床; 另有他汀类药物和环磷酸鸟苷 (cyclic guanosine monophosphate, cGMP) 激活剂可通过过表达转录因子Krüppel样因子2上调NO的肝内释放; 该转录因子亦被报道可调控多种血管保护基因。同时, 他汀类药物可抑制Ras同源基因家族成员A (RAS homologous gene family member A, RhoA) -Rho激酶 (可激活HSC并引起其收缩功能) 的激活, 有助于降低肝内阻力^[16-17]。他汀类药物还具有抗炎和抗纤维化作用, 在缓解肝内结构成分的病理性改变方面也起着重要作用^[18]。

2.2 门静脉系统

在生理状态下, 饮食引发内脏血管扩张, 增加门

静脉系统的血流量。相反,在低血容量休克和剧烈运动中,通过使用内脏血管收缩剂、抑制胰高血糖素分泌的药物(如生长抑素)或减少心输出量的药物(β 受体阻滞剂)引起血管收缩,门静脉血流随之显著减少^[19-20]。在肝硬化PH患者中,VEGF诱导内皮型一氧化氮合酶(endothelial nitric oxide synthase, eNOS)催化产生NO,NO促进内脏血管扩张。其他诱导血管扩张因子(一氧化碳、胰高血糖素、内源性大麻素等)作为NO的供体,进一步加强内脏动脉血管扩张,增加门静脉系统的血流量^[7,21-22]。内脏血管扩张引发全身血流动力学变化,外周阻力减少可能导致全身低血压,甚至引起全身多器官功能衰竭^[23]。因门静脉压力升高而代偿性增加的NO含量在缓解门静脉压力的同时也分泌至全身多处器官,这一变化引发了多器官血流供应改变(缺失)所致多器官衰竭。此外,门静脉结构也产生潜移默化的改变(肌层变薄),使其调节入肝血流的能力也显著降低。

2.3 心血管系统

由于PH疾病的发展,全身血管受到其分泌的调节因子干扰,导致内脏和肌肉血管扩张,有效循环血量减少,触发机体的以下补偿机制启动:①压力感受器反射性激活血管收缩因子及水钠调节系统,如肾素-醛固酮轴、交感神经系统和精氨酸-加压素的分泌^[24]。②水钠潴留导致体内血容量增加,肾上腺素受体刺激促进心输出量的增加。由于血流动力学失衡,心脏有效血容量降低^[25]。

PH患者的心脏持续高输出量最终未能满足机体需求。在这一过程中,交感神经系统的长期刺激导致心肌变性和心肌收缩力下降,尤其在PH合并肝肾综合征(hepatorenal syndrome, HRS)、HRS-急性肾损伤(HRS-acute kidney injury, HRS-AKI)和HRS-非急性肾损伤(HRS-non-acute kidney injury, HRS-NAKI)患者中表现得更为明显,最终导致心排出量急剧减少,无法满足机体脏器的需求^[26]。临床研究^[27]提示PH患者全身活性物质,尤其是血管紧张素II和去甲肾上腺素水平的升高,更加重心肌病的进展。在肝硬化失代偿期,组织内积聚大量炎症因子和氧化因子被认为是广泛的内皮激活和微血管功能障碍的主要原因,也是全身动脉血管扩张和多器官功能衰竭的前提因素。由此可见,PH患者体内发生的代偿性或非代偿性的病理生理改变(有效血容量减少、心

肌病发生率增加、微血管和内皮功能障碍等)可以增加PH相关并发症的发病率,从而加重疾病进展^[28]。此后,关于微血管功能障碍促肝性脑病发展的研究^[29]及心脏对血管收缩剂反应性降低促进休克发生,导致肝肺综合征的研究^[30-31]亦证实了这一观点。

2.4 炎症介质

众所周知,PH患者处于免疫过度激活状态。多中心临床研究^[32]证实,仅1%的PH患者体内炎症指标未上调。循环系统中炎症细胞因子水平的升高与疾病严重程度呈正相关。重要的炎症细胞因子,如肿瘤坏死因子 α (tumor necrosis factor- α , TNF- α)、白细胞介素-6(interleukin-6, IL-6)、IL-8和IL-10的表达,被认为是疾病预后不良的预测因子^[33]。

PH全身性炎症的触发因素主要有2个来源:①肠道通透性增加,导致肠道微生物组成和pH值的变化,使得病原体相关损伤因子(pathogen-associated molecular pattern, PAMP),如脂多糖、鞭毛蛋白、细菌或病毒RNA/DNA、真菌等,通过门静脉循环输送到肝脏的量增加^[34-35]。这种异常易位引起的全身炎症改变,不仅增强了肠系膜小动脉中eNOS的活性^[36],还增加了eNOS和诱导型一氧化氮合酶(inducible nitric oxide synthase, iNOS)在主动脉内壁上的表达,导致大量释放的NO引起周围动脉扩张^[37]。②病毒性肝炎、饮酒、代谢综合征等PH的常见病因而往往导致肝细胞和组织的持续损伤,进而释放肝脏内损伤相关分子(damage-associated molecular pattern, DAMP)^[33]。例如,坏死的肝细胞释放角蛋白18(cytokeratin 18, CK18),其数量与疾病进展及炎症的严重程度密切相关。

炎性小体是一种受损细胞的识别受体,其激活受到2个信号途径的调控:①诱导激活Toll样受体4(Toll-like receptor 4, TLR4)/脂多糖信号通路,增加促炎细胞因子(TNF- α 、单核细胞趋化蛋白-1、IL-6和IL-1 β)的释放^[38-39]。其中TNF- α 也可直接激活凋亡和坏死进程^[40]。TLR4在质膜上表达,通过识别细菌脂多糖诱导炎症产生^[41]。动物模型中,肝脏TLR4的上调导致脏器敏感性增加,内毒素驱动的组织损伤是导致后续脏器失代偿及衰竭的前提。相关研究^[42-43]发现,抑制TLR4信号通路可显著减少器官损伤。②炎性小体结合DAMP触发激活半胱氨酸蛋

白酶-1, 将人白细胞介素-1 β 前体 (pro-interleukin-1 β , proIL-1 β) 剪切成具有生物活性的 IL-1 β [44]。IL-1 β 诱导炎症和趋化因子的产生, 刺激免疫细胞聚集, 对局部感染和损伤产生免疫反应。在肝脏中, 表现为中性粒细胞及促炎单核/巨噬细胞浸润库普弗 (Kupffer) 细胞激活, 免疫调节功能失调, 促进全身炎症的产生; 这种持续的炎症反应加重组织损伤并导致脏器功能衰竭 [45]。

在PH患者长期炎症激活和氧化应激的微环境中, 白蛋白分子的结构和功能发生改变 (主要是半胱氨酸-34残基的可逆和不可逆氧化反应) [46-47]。血清中有效白蛋白比值降低, 削弱了机体对有害分子如PAMP和DAMP的全身扩散、持续炎症以及内皮和微血管功能障碍的抵御能力。临床研究 [48-49] 表明, PH患者中性粒细胞抗原的明显增加可诱导外周血单核细胞产生强烈的炎症反应, 因此白蛋白的氧化和结构改变是肝硬化失代偿期和肝衰竭中促进全身炎症的重要因素。

3 PH病理生理机制的研究现状及存在的争议

PH是一种逐步级联放大、危及肝内外多种器官的难治性疾病。本文总结的研究现状多针对多种病因引起的PH中趋于相同或相似的病理生理特征, 关于有效治疗疾病的切入点未见明确报道。以肝内病理生理改变而言, 病毒性、胆汁淤积性、自身免疫性、药物性等多种原因均可引起肝细胞损伤。以此为起点激活肝内多种病理生理学改变加剧了肝内结构不可逆的损伤, 这些损伤均可导致PH。致病原因的不同所致病理生理学机制的微妙差异成为PH治疗和研究的一大难点。此外, PH引发的全身多脏器功能异常亦加重了疾病的难治性和复杂性。PH在引发心脏和周围血管结构及功能改变中发挥核心作用。内脏血管扩张导致血容量充盈, 随之神经体液通路激活, 以代偿血运改变。待疾病发展到晚期严重阶段, 由于菌群紊乱 (以肠道为主), 系统性炎症成为主导, 代偿性机制失效, 进而导致器官衰竭。由于水钠潴留, 机体出现腹水及高钠血症, 继而代偿性出现血管收缩和心肌损伤, 最终导致微血管功能障碍和器官灌注减少的高动力状态。这是导致心血管功能障碍和肝功能衰竭的一个重要原因。激活的免疫系统不仅影响疾病进展, 还

可能导致心血管改变 (主要加速PH并发症的发展) 和代谢功能异常 (主要诱导组织损伤和器官功能障碍)。免疫系统为主导的激活不仅通过激活炎症途径直接诱导组织损伤, 还能将能量消耗主要场所从外围器官转移到免疫系统, 从而引起机体能量代谢异常, 最终导致器官功能衰竭。

尽管既往研究已经详尽总结了PH患者从代偿性过渡到失代偿期和肝衰竭的过程, 但仍存在争议, 需要进一步深入研究。例如, 目前尚不清楚炎症反应是否会影响门静脉压力, 从而成为PH出血等并发症的驱动因素。此外, 长期以来, 肝肾综合征被认为是灌注减少导致的肾脏的纯功能改变。但研究 [50] 发现, 随着PH的进展, 肾脏结构也发生变化, 其机制尚不明确。因此, 从病理生理学的角度深入研究PH, 对今后实现该疾病的个体化治疗具有重要意义。除此之外, 还需要了解何种诱导因素触发了PH向肝衰竭发展, 探索不同患者器官功能衰竭的类型及发生机制。

4 小结与展望

目前, 对于肝硬化PH的研究进展缓慢。针对PH这一全身性疾病, 可用于临床试验的药物治疗效果有限。比如, 针对门静脉压力增高采用的 β 受体阻滞剂等全身应用的降压药, 在显著降低门静脉压力的同时会带来心血管系统功能紊乱。再如, 针对引起门静脉压力增高的肝脏内原因 (代谢原因) 而应用的他汀类药物、胆汁酸代谢类药物, 早期应用可以延缓病情的发展, 但对于已经发展至肝硬化失代偿期的患者疗效则不够显著。从目前的相关研究结果来看, 对于失代偿期肝硬化PH这一全身多系统相关的疾病的探索尚处于起步阶段, 笼统地概述全身的改变或者片面地分析局部组织的病变不能从根本上获得减缓疾病进展的治疗靶点。进一步加速对于肝硬化失代偿期PH的病理生理机制的研究, 有助于更加深入了解此病, 挖掘靶向性的治疗手段, 从而帮助临床工作者全面提升肝硬化PH患者的诊断和治疗水平, 改善预后。

利益冲突声明/Conflict of Interests

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樊强、吴广博负责文献查询及文稿撰写、修改。赵劲博负责文稿格式修改。郑磊、罗蒙负责文稿思路设计及审核,提出修改意见等。所有作者均阅读并同意了最终稿件的提交。

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