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创伤性肝损的致伤机制和诊疗进展

张晓燕, 李 岩

张晓燕, 李岩, 上海交通大学附属第一人民医院危重症科 上海市 200080
张晓燕, 硕士, 主要从事危重病急救的研究.
作者贡献分布: 本文综述由张晓燕完成; 李岩审校.
通讯作者: 李岩, 副主任医师, 200080, 上海市松江区新松江路650号, 上海交通大学附属第一人民医院危重症科.
criticalcare@163.com
电话: 021-37798529
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Mechanisms and treatment of post-traumatic liver injury

Xiao-Yan Zhang, Yan Li

Xiao-Yan Zhang, Yan Li, Department of Emergency Medicine, the First People's Hospital Affiliated to Shanghai Jiaotong University, Shanghai 200080, China
Correspondence to: Yan Li, Associate Chief Physician, Department of Emergency Medicine, the First People's Hospital Affiliated to Shanghai Jiaotong University, 650 Xinsongjiang Road, Songjiang District, Shanghai 200080, China. criticalcare@163.com
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Abstract
Multiple organ failure is the leading cause of death in patients with severe multiple trauma in the early stage after injury. Hepatic insufficiency is common in intensive care unit (ICU), and about 27% of the patients with severe trauma suffer hepatic failure. However, the pathogenesis of traumatic liver damage is complicated due to the following main reasons: liver trauma, ischemia-reperfusion injury, severe sepsis, danger associated molecular patterns and so on. Clinically, trauma-induced liver injury can be managed conservatively or surgically, therefore, clarifying the mechanisms of traumatic liver damage, finding a new therapeutic target and improving its diagnosis and treatment are very important. This paper reviews the mechanism of post-traumatic liver injury and its diagnosis and treatment.

Key Words: Traumatic liver injury; Liver trauma; Ischemia-reperfusion; Severe infections; Danger associated molecular patterns

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摘要
严重多发伤患者创伤后早期阶段, 多脏器功能衰竭是死亡的主要原因. 重症监护室(intensive care unit, ICU)中创伤患者常伴有肝功能不全, 约27%的严重创伤患者发生肝功能衰竭. 然而创伤性肝损的发病机制复杂, 主要原因有: 肝脏创伤、缺血再灌注损伤、严重感染、危险相关分子模式等. 临床上对创伤性肝损患者常采用传统的保守治疗或手术治疗, 因此明确创伤性肝损的相关机制, 寻找新的药物治疗靶点, 规范合理地提高创伤性肝损的诊治水平至关重要. 本文主要针对创伤后导致肝功能损伤的机制及主要诊疗方式作一综述.

关键词: 创伤性肝损伤; 肝脏创伤; 缺血再灌注损

背景资料
严重多发伤是综合性重症监护室(intensive care unit, ICU)中的主要疾病之一, 由于近年来创伤及危重病患者救治能力的不断提高, 严重多发伤患者通常可以度过早期的危险阶段而存活下来. 但是接下来出现的单个或多个脏器功能不全, 会导致患者的死亡率增加、住院时间延长. ICU中肝功能不全很常见, 约27%的严重创伤患者发生肝功能衰竭.

同行评议者
王凯, 教授, 山东大学齐鲁医院肝病科

研发前沿

创伤性肝损的发病机制复杂, 主要包括: 肝脏创伤、缺血再灌注损伤、严重感染、危险相关分子模式. 而临床上对创伤性肝损患者常采用传统的保守治疗或手术治疗, 因此明确创伤性肝损的相关机制, 寻找新的药物治疗靶点, 规范合理地提高创伤性肝损的诊治水平至关重要.

伤; 严重感染; 危险相关分子模式

核心提示: 创伤性肝损的发病机制复杂, 主要包括: 肝脏创伤、缺血再灌注损伤、严重感染、危险相关分子模式. 对于创伤性肝损伤的诊治, 应根据患者实际情况合理选择, 除传统的保守治疗或者手术治疗外, 同时应积极寻找新的药物治疗靶点.

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0 引言

严重多发伤是综合性重症监护室(intensive care unit, ICU)中的主要疾病之一, 由于近年来创伤及危重病患者救治能力的不断提高, 严重多发伤患者通常可以度过早期的危险阶段而存活下来[1]. 但是接下来出现的单个或多个脏器功能不全, 会导致患者的死亡率增加、住院时间延长[2]. 在发达国家, 急性肝损伤常见于30岁左右的健康成年人[3], Laudi等[4]的研究表明严重创伤患者发生肝功能衰竭者占27%, 其中12.2%患者发生肝脏外伤. 由于肝脏在蛋白质合成、毒物和药物代谢以及免疫调节等方面具有重要的作用. 因此, 对于严重多发伤患者密切监测肝功能情况、早期发现肝功能损伤的情况并及时处理显得尤为重要. 在这里我们针对创伤后导致肝功能损伤的机制进行阐述.

急性肝损伤常见的原因主要为病毒感染(甲、乙和戊型肝炎)和药物诱导的肝损伤[3]. 尽管目前还缺乏一个统一的肝损伤的诊断标准, 但其通常表现为生化指标的升高, 包括: 天冬氨酸转氨酶、丙氨酸转氨酶、碱性磷酸酶、γ-谷氨酰转肽酶和胆红素等. 同时还存在血清白蛋白水平的降低以及国际标准化比值(international sensitivity index, INR)的延长. 创伤性肝损伤的发病率不高, 其发病原因有自己的特点, 主要为以下几方面: 肝脏创伤、缺血再灌注损伤、严重感染和危险相关分子模式(danger-associated molecular patterns, DAMPs)等.

1 肝脏创伤

肝脏是闭合性腹部外伤中最常见的损伤脏器, 也是穿透性腹部损伤中第2位的损伤脏器[5,6], 减速伤害是最常见的损伤机制[7]. 钝挫伤或穿透性损伤可导致肝实质裂伤和血肿、被膜下血肿、腹腔积血等, 美国创伤外科协会将肝脏损伤的严重程度分为六级[8], 将肝撕脱伤定为最严重损伤级别. 随着损伤严重程度的增加, 对肝脏本身功能的影响也明显增加. 目前随着B超、计算机断层扫描(computed tomography, CT)及磁共振成像(magnetie resonance imaging, MRI)等影像学技术对腹部脏器损伤严重程度评估水平的提高, 超过80%以上的钝性肝创伤患者可以采用保守治疗[9], 但应密切监测患者的血流动力学状态. Leppäniemi等[10]的研究表明在钝性腹部外伤中, 70%严重肝损伤的患者采用了保守治疗, 失败率仅为9%. 介入放射技术越来越广泛的被应用, 尤其适用于非手术治疗的患者[11], 主要包括: 肝动脉栓塞、肝动脉灌注技术、门静脉栓塞、肝内门体静脉支架分流、肝静脉的干预等[12]. 活动性CT造影剂外渗常常提示存在潜在性的威胁生命的出血, 需要及时动脉造影及血管内栓塞治疗[13]. 但对于血流动力学不稳定, 或需大量输液输血才能维持血流动力学稳定, 动态CT或B超提示肝脏病变扩大, 合并腹膜炎体征的患者, 仍需积极手术进行彻底清创、止血, 充分引流. 对于特别严重的肝损伤, 在条件允许的情况下可以考虑肝脏移植[14].

2 缺血再灌注损伤

肝脏作为一个高耗能的器官, 对低氧和缺氧环境非常敏感[15]. 缺血最常见的原因主要有移植、创伤、休克、选择性肝脏手术等[16]. 肝脏缺血再灌注损伤的基本机制主要是肝脏局部缺血导致供血不足, 随后出现的再灌注损伤[17]. 在缺血阶段, 发生在细胞水平上一系列功能的改变促进细胞的破坏[18], 由于腺嘌呤核苷三磷酸(adenosine triphosphate, ATP)消耗、体内钙离子平衡紊乱、氧化磷酸化过程受到抑制导致ATP生成减少, 促进了肝脏细胞凋亡[19]. 肝细胞缺血缺氧时可导致线粒体去能, 改变氢离子和钠离子的电解质平衡, 导致肝窦细胞和库普弗细胞肿胀[20]. 激活的库普弗细胞产生活性氧, 上调肝细胞诱生型一氧化氮合酶以及促炎细胞因子、趋化因子、黏附分子, 导致嗜中性粒

细胞的破坏, 从而产生炎症相关性损伤[21]. 在再灌注阶段, 肿瘤坏死因子-α和其他炎症介质激活细胞凋亡蛋白酶-3、细胞凋亡蛋白酶-8导致DNA破坏和细胞凋亡[22]. 发生缺氧性肝损伤的患者短期死亡率会高达50%以上[23], 目前还缺乏有效的治疗手段和预防措施. 最新研究[24]表明, 他汀类药物也许是新发的缺氧性肝损伤唯一的保护药物, 而且对于慢性肝病的患者仍有很好的耐受性和安全性[25]. 一些实验[26,27]也证明, 他汀类药物对于改善肝窦内皮细胞功能和微循环有潜在收益, 可以减少肝脏的缺血再灌注损伤, 尽管在研究中调整了年龄、性别等人口统计资料、疾病的严重程度、合并症以及基础疾病等, 他汀类药物仍然是缺氧性肝损伤一个独立的、保护性因素. 大量研究[28-30]发现, 和未使用他汀类药物治疗的患者相比, 使用他汀类药物治疗的患者脓毒性休克的发生率明显降低. 当然, 也有一些研究[31-33]认为他汀类药物不能降低严重脓毒症和急性肾损伤的发生率. 也许将来的研究方向应该是他汀类药物如何降低缺氧性肝损伤患者并发严重感染的发生率.

3 严重感染

严重多发伤患者通常伴随着严重的感染. 随着当今院前急诊网络的建立、院前与院内急救体系无缝连接的形成、院内急救技术水平的提升, 很多重症患者通常可以度过早期的休克阶段, 进入到后期的ICU救治阶段[34,35]. 在ICU中这类患者由于体表屏障以及体内黏膜屏障的破坏, 以及自身免疫功能的降低, 常常会并发严重的感染[36]. 由肝外细菌感染和脓毒症导致的肝功能异常和黄疸的发生率约为20%, 仅次于恶性肿瘤压迫性梗阻导致的肝功能异常. 研究[37]表明脓毒症患者早期发生黄疸是患者死亡的一个独立危险因素. 持续的肝功能损伤还会导致中性粒细胞吞噬功能的减弱并影响到后续的适应性免疫反应. 脓毒症会导致体内蛋白质组水平的显著改变, 其中就包括肝细胞合成的急性期蛋白. 其中有些是上调的, 例如C反应蛋白, 有些是下调的, 例如白蛋白. 通过对适应性免疫机制的研究有助于找到新的治疗手段. 最近的研究表明*S*-亚硝基化的α-1-酸性糖蛋白[38]和血管生成素-2[39]显示出抵抗多重耐药细菌的作用. 另外, 肝再生蛋白的增强子(augmenter of liver regeneration, ALR)可以促进肝细胞再生, 并可以维持脓毒症导致损伤的肝细胞活性[40]. ALR水平的升高意味着细胞活性的丧失或者DNA合成的抑制[41]. 早在2002年应用组学技术(包括蛋白质组学、转录组学和代谢组学)就测定了肝脏在脓毒症情况下的反应. 研究[42]表明在脓毒症动物模型中死亡的发生通常伴随着肝胆转运过程的异常, 进而导致肝细胞内胆汁酸、胆红素和外源性化学物质的滞留. 脓毒症情况下磷脂酰肌醇-3-激酶(phosphatidyl inositol 3-kinase, PI3K)的过表达抑制了参与生物转化过程的细胞色素和相关酶的表达, 影响了胆汁酸的代谢从而导致肝细胞损伤的发生. 因此, 通过抑制PI3K信号通路可以恢复损伤肝细胞的部分功能. 因此, PI3K可以作为肝损伤的潜在治疗靶点, 胆汁酸也比胆红素更适合作为脓毒症导致肝损伤的生物标志物[43].

4 DAMP

创伤后危重症患者的发病率及死亡率部分是由于炎症信号通路的过渡激活及随后发生的全身炎症反应综合症(systemic inflammatory response syndrome, SIRS)引起的. SIRS可引起机体多脏器功能衰竭, 甚至死亡. 众所周知, 没有感染、出血、缺血再灌注的组织损伤, 可引起DAMPs的释放. DAMPs可被体内初始免疫系统的模式识别受体识别, 从而触发创伤后炎症反应[44]. 这些DAMPs包括高迁移率族蛋白1(high-mobility group box 1, HMGB1)[45]、热休克蛋白、透明质酸、纤连蛋白、心磷脂和DNA片段等. 被DAMP分子活化后的初始免疫细胞进入到损伤区域并释放细胞因子和趋化因子, 进而导致组织产生无菌性炎症. 这些初始免疫细胞释放的可溶性产物一方面会加重组织损伤; 另一方面也可以促进组织愈合.

创伤、休克、手术破坏细胞的结构, 破碎细胞释放大量线粒体DAMPs(mitochondrial DAMPs, MTDs)进入血液循环, 研究[46]显示, MTDs在创伤、炎症、SIRS的关联中起着重要作用. MTDs主要包括线粒体DNA(mtDNA)和甲酰肽. 研究者检测了15例严重创伤患者复苏前的血液样本, 这些患者没有开放性伤口及消化系统损伤, 发现创伤患者血中的mtDNA与正常

创新盘点
系统的总结了近年来创伤性肝损的发病机制, 详细介绍了危险相关分子模式致创伤性肝损的机制, 并根据其相关机制针对性给予防治措施.

应用要点

应根据患者实际情况合理选择, 除传统的保守治疗或者手术治疗外, 可加用他汀类药物保护缺血再灌注的损伤肝组织. 同时应积极寻找新的药物治疗靶点, 如针对磷脂酰肌醇-3-激酶、甲酸基肽受体、丝裂原活化蛋白激酶的新型药物等. 力求规范合理地提高创伤性肝损伤的诊治水平.

对照组相比显著升高[46], 创伤组患者血mtDNA浓度为2.7 μg/mL±0.94 μg/mL, 比正常对照组患者高上千倍. Zhang等[46]静脉注射相当于大鼠肝脏5%的MTDs到动物体内, 结果显示注射后3 h动物就表现出明显的炎症反应和肺损伤, 中性粒细胞浸润导致肺组织基质金属蛋白酶8(matrix metalloproteinase 8, MMP-8)的含量增加, 并可浸润肝脏, 而对照组大鼠无肺或肝脏炎症浸润的证据.

mtDNA和甲酰肽可作用于G蛋白偶联受体(Toll-like receptor 9, TLR-9)和甲酸基肽受体(formyl peptide receptor 1, FPR-1), 活化中性粒细胞, 促进中性粒细胞Ca^{2+}流动、丝裂原活化蛋白激酶(mitogen-activated protein kinases, MAPKs)磷酰化, 从而导致中性粒细胞在体内外迁移、脱粒, 释放超氧化物和溶酶体酶等, 最终导致器官功能的损伤. 研究[47,48]显示, 缺血再灌注动物模型肝脏损伤、肝脏炎性因子浸润主要是通过TLR-9通路介导的. 研究发现来自人体或者小鼠肝脏、肌肉组织内的MTDs均可使中性粒细胞内Ca^{2+}消耗增多, 且与细胞是否破碎无明显相关性. FPR-1受体阻滞剂可抑制MTDs引起的Ca^{2+}消耗及内流, 环孢菌素H可以阻滞FPR-1受体, 抑制Ca^{2+}流动. 中性粒细胞利用分解酶, 如金属蛋白酶迁移到目标组织引起器官功能损伤, 研究[49]显示, FPR-1受体阻滞剂及环孢菌素亦可抑制中性粒细胞的迁移速度、干扰其迁移方向. 另外mtDNA可使中性粒细胞MAPKs磷酰化, 而抑制性寡聚脱氧核苷酸可阻滞MAPKs活化, 阻断mtDNA与TLR-9的相互作用[50]. 因此, 可为临床治疗创伤性肝损提供新的临床思路, 但仍需进一步研究.

5 结论

除肝脏创伤对肝功能造成的直接损伤外, 严重多发伤失血性休克时肝脏缺血再灌注损伤、肝外细菌感染和脓毒症导致的肝功能异常和黄疸、无菌性损伤组织释放的DAMPs均可对肝功能造成损伤. 对于创伤性肝损伤的诊治, 应根据患者实际情况合理选择, 除传统的保守治疗或者手术治疗外, 可加用他汀类药物保护缺血再灌注的损伤肝组织. 同时应积极寻找新的药物治疗靶点, 如针对PI3K、FPR-1受体、MAPKs的新型药物等. 力求规范合理地提高创伤性肝损伤的诊治水平.

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名词解释

危险相关分子模式：体内坏死的细胞可释放某些非特异性效应分子，即内源性“危险信号”，如高迁移率族蛋白1、热休克蛋白、透明质酸、纤连蛋白、心磷脂和DNA片段等.

同行评价

创伤性肝脏损伤发病机制复杂, 明确其发病相关机制并针对性给予防治措施有望提高创伤性肝损的现有诊治水平. 本综述总结了近年来创伤性肝损的发病机制进展, 对于提高创伤性肝损诊治水平的研究工作具有一定的学术价值.

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