

脓毒症急性肾损伤的血管加压药物选择

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摘 要

脓毒症急性肾损伤(S-AKI)是重症监护病房中的常见疾病, 死亡率高, 目前的研究表明仅靠单纯的液体复苏难以逆转其带来的循环衰竭, 所以血管加压药物对于患者的循环管理有着重大意义。本文回顾了脓毒症急性肾损伤的流行病学及发病机制, 探讨了去甲肾上腺素及其他不同血管加压药物在脓毒症急性肾损伤患者治疗中的应用情况, 为临床脓毒症急性肾损伤患者的循环管理提供新思路。

关键词

脓毒症急性肾损伤, 休克, 去甲肾上腺素, 血管加压药物

Selection of Vasopressors for Sepsis-Associated Acute Kidney Injury

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Abstract

Sepsis-associated acute kidney injury (S-AKI) is a common condition in intensive care units with a high mortality rate. Current research indicates that fluid resuscitation alone is often insufficient to reverse the circulatory failure caused by S-AKI, making vasopressors critically important for circulatory management in these patients. This article reviews the epidemiology and pathogenesis of sepsis-associated acute kidney injury, explores the application of norepinephrine and other vasopressors in

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the treatment of patients with sepsis-associated acute kidney injury, and provides new insights for the circulatory management of clinical S-AKI patients.

Keywords

Sepsis-Associated Kidney Injury, Shock, Norepinephrine, Vasopressors

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1. 引言

脓毒性急性肾损伤(S-AKI)是一种在危重症患者及住院患者中的常见并发症,特征是与脓毒症相关的肾功能迅速恶化,发病率在脓毒性休克中居高不下。一项包括 1243 例脓毒性休克患者的多中心随机对照试验(RCT)的辅助分析显示,50.4%的入组患者出现 AKI,另有 18.7%的患者在 7 天内出现 AKI,其中约三分之二的 AKI 患者被分类为 CKD 2 期或 3 期[1]。Ignacio 等人一项纳入 1490 名患者的前瞻性多中心队列研究表明,对于老年患者,在使用了相关复苏策略后,它仍与高达 60%的高死亡率相关[2]。血清肌酐升高和/或尿量减少仍然是其主要诊断标准[3],但与 AKI 一样,由于受到通常缺乏患者血清肌酐值基线,以及血清肌酐的滞后性和利尿剂的使用等各方面因素的影响,其存在一定局限性。

2. 脓毒症急性肾损伤的病理生理

2.1. 肾缺血及肾脏血流重新分配

传统的病理生理学通常将 S-AKI 归咎于肾血流减少和缺血再灌注损伤,缺血性损伤可导致广泛的细胞死亡。然而相关研究表明,在没有肾灌注不足和血流动力学不稳定的情况下,患者仍然能发生 S-AKI [4]-[6],在某些患者中,甚至观察到存在肾血流增加的现象[5] [7]-[9]。面对这种肾脏血流灌注增加的 S-AKI 病人,一个可能的机制是肾脏血流的重新分布。在健康人群中,肾血流量约占心输出量的 20%,但是肾脏内的血流分布具有明显的差异性,大约 90%的肾血流流向进行肾小球滤过功能的皮质,其余 10%的肾血流流向肾髓质周围的肾小管微循环。但是脓毒症期间,肾内血流灌注被重新分配,流向肾髓质的血流明显减少,同时肾髓质对缺血缺氧的耐受性极差,引起氧化应激导致发生炎症级联反应,从而损伤肾功能[10] [11]。在一项对绵羊的 S-AKI 动物实验研究中,对绵羊诱发 S-AKI 后,发现绵羊肾皮质的血流并未明显降低,但肾髓质的灌注血流却明显下降[12]。遗憾的是,缺少相关类似的人体研究以进一步证明其影响。

2.2. 炎症反应失调

炎症反应是宿主抵御入侵病原体的主要防御机制。然而,正如新的脓毒症定义所暗示的那样,失调的炎症反应可能是器官功能障碍和不良预后的原因。在脓毒症中,大量炎症介质被释放到血管内,这些分子可与免疫细胞表面的膜结合模式识别受体(例如 toll 样受体)结合,启动下游信号级联,导致促炎分子的合成和释放。人肾小管上皮细胞也同样表达 toll 样受体,尤其是 TLR2 和 TLR4。当炎症介质与近端肾小管上皮细胞相关受体结合,便会产生氧化应激,活性氧生成增多,线粒体损伤的风险大大增加[13]-[15],最终导致血栓形成和血流连续性改变,从而影响肾功能。

许多炎症介质已被证明与 S-AKI 有关[16]-[18]。可表现为免疫过度反应和免疫抑制两种不同的特征分类。在高炎症反应的病人中,免疫抑制干预方案未能改善脓毒症的预后,免疫抑制类病人受到了更多的关注[19][20]。这种类似“免疫麻痹”的特征是免疫系统中的各种异常,包括抗原呈递细胞上 HLADR 的表达减少,体外刺激的白细胞产生的促炎细胞因子减少,以及细胞因子谱不平衡,典型的抗炎细胞因子 IL-10 水平较高,而促炎介质如 TNF- α 和 IL-6 的水平较低[19][21]。从而加大感染源的清除难度,增加了继发感染的风险,并导致高死亡率的发生[20]。

3. 去甲肾上腺素在脓毒症急性肾损伤中的应用

S-AKI 的具体病理生理机制尚未完全彻底揭露。因此,仍然缺乏特异性的治疗手段,对症治疗依旧是主流方案。仅靠液体复苏不足以恢复足够的平均动脉压(MAP),需要额外使用血管加压剂。目前常用的药物有去甲肾上腺素、肾上腺素、加压素、多巴胺和苯肾上腺素等。另外,来自临床和实验研究的新证据表明,血管紧张素 II 也可能对其有效[22]。其中去甲肾上腺素因为其独特的药理作用而被推荐作为脓毒症的首选药物[23],去甲肾上腺素主要具有 α , β_1 肾上腺素能特性,可收缩动静脉血管,升高动脉压,并能增加静脉回流。同时刺激心脏 β_1 肾上腺素能受体,对心肌产生正性肌力作用,但其 β_2 肾上腺素能的效果较弱,对心率和心肌耗氧量的影响不明显。去甲肾上腺素对肾脏作用也非常复杂,可以增加肾小球滤过率,增加钠的过滤和重吸收,增加肾血流量和肾氧耗。同时,去甲肾上腺素对肾血管阻力、肾过滤分数、尿量等没有明显影响[24][25]。

许多研究结果也支持去甲肾上腺素作为首选血管加压药,与多巴胺相比,去甲肾上腺素可小幅降低全因死亡率(相对风险[RR] 0.89, 95%置信区间[CI] 0.81~0.98)[26]。并可减少心率失常的风险。另一项对脓毒性休克患者的荟萃分析得出了相同的结论,去甲肾上腺素相比多巴胺在住院死亡率或 28 天死亡率方面具有优势(RR 0.91, 95% CI 0.83~0.99, $P = 0.028$)。相较于多巴胺,接受去甲肾上腺素治疗患者的心律失常发生率也显著降低(RR 0.43, 95% CI 0.26~0.69, $P \leq 0.001$)[27]。一项前瞻性多中心观察性研究 CHASERS 评估了脓毒性休克后最初 6 h 和 24 h 内血管加压药的给药强度对 30 天病死率的影响[28]。结果提示前 6 h 内较高剂量的去甲肾上腺素等效物与 30 天病死率增加的比值比(OR)相关。在整个 24 h 期间,维持 MAP 所需的每 10 $\mu\text{g}/\text{min}$ 去甲肾上腺素等效物与 30 天病死率增加相关(调整后的 OR 1.33, 95% CI 1.16~153)。休克时尽早使用去甲肾上腺素对于患者可能更加有利,一项随机对照试验(CENSER 试验),在脓毒性休克患者的早期分配给去甲肾上腺素治疗组或安慰剂组[29]。早期去甲肾上腺素治疗组和安慰剂组的休克控制率分别为 76.1%和 48.4% ($P < 0.001$),但生存率差异并不明显[29]。在脓毒性休克发病后 ≥ 2 小时开始进行去甲肾上腺素治疗,脓毒性休克患者的死亡率更高。事实上,前 6 h 每延迟 1 h 去甲肾上腺素使用,28 天死亡率就会增加 5.3% [30]。综上所述,这些数据印证了去甲肾上腺素作为一线血管加压药物的优势,并强调了早期使用去甲肾上腺素的必要性。

虽然目前去甲肾上腺素被广泛用于脓毒症休克的主要治疗,但其使用仍存在争议,人们认为去甲肾上腺素可能会导致肾血管收缩导致肾功能进一步恶化[31][32]。最近的研究表明,在 S-AKI 发生之前,组织缺血和缺氧可能发生在髓质,而不是皮质。在这类实验模型中,去甲肾上腺素恢复血压进一步加重了髓质缺血缺氧程度,去甲肾上腺素使得肾髓质组织氧分压降低 50%,并使得肾髓质血流灌注减少。由于去甲肾上腺素增加 GFR,使得钠的重吸收增加。这意味着需要消耗更多的氧气,从而加重了髓质缺氧[33]。相关实验通过测量舌下血流量的方法来评估微循环血流情况,结果表明去甲肾上腺素虽然可恢复全身血流动力学,但对改善脓毒症休克患者的微循环异常收效甚微[34]-[36]。另外,不能忽视去甲肾上腺素可能会加重免疫麻痹带来的风险,相关实验证明去甲肾上腺素减弱了促炎细胞因子 IFN- γ 诱导蛋白的释放,同时减少了活性氧的产生,并增加了抗炎因子 IL-10 的产生。上述因素增加了细菌向脾脏、肝脏和血液的播散风险[37][38]。综上所述,去甲肾上腺素作为升压药物并不完美,仍然存在相应的局限性,去甲肾上

腺素的局限性主要源于其非选择性受体激活和全身性血管收缩效应。未来的解决方案需从多靶点药物设计、精准剂量调控、器官保护修饰等方向突破,结合人工智能、纳米技术和基因编辑等新技术,实现升压治疗从“粗放型血压维持”向“精准化器官灌注优化”的转型。

4. 新型血管活性药物进展

4.1. 加压素

脓毒症生存运动国际指南建议,如果脓毒症休克患者 MAP 不足,则在去甲肾上腺素输注的基础上可以应用加压素[23]。加压素(vasopressin)可以通过 V1a 受体介导的直接加压作用,以及间接地增强对肾上腺素能药物(如去甲肾上腺素)的敏感性,所以当加用 VP 时,在升高患者动脉压的同时减少对去甲肾上腺素的剂量需求[39]。在绵羊 S-AKI 模型中,与去甲肾上腺素相比,加压素升高平均动脉压并持续改善肾功能,而且不会加重肾髓质缺血缺氧或将肠系膜血流量降低到基线值以下[40]。在一项以去甲肾上腺素或 VP 作为初始单一药物进行去甲肾上腺素抢救的随机开放实验中,VP 与去甲肾上腺素输注需求减少、降低心率和心输出量、全身血管阻力增加、肌酐清除率增加有关[41]。以上证据让人们对于 VP 的应用前景充满信心,但是在 VASST 和 VANISH 研究中,结果显示加压素对去甲肾上腺素缺乏优越性,并不能降低患者死亡率[42][43],仍然还需要寻找更多的证据来证明 VP 在 S-AKI 中的应用价值。目前 VP 及其合成类似物诸如特利加压素等的相关研究正在逐步增多,遗憾的是,尚未有鼓舞人心的发现。

4.2. 血管紧张素 II

血管紧张素 II(AT-II)是一种活性八肽,由血管紧张素转换酶切割血管紧张素 I 衍生而来,AT-II 刺激血管紧张素 II 受体 1(AGTR1),它与血管收缩、醛固酮分泌、水钠潴留、加压素分泌和促凝血有关[44]。此外,AT-II 刺激血管紧张素 II 受体 2(AGTR2),上调肾内黏附分子(如 ICAM-1、VCAM-1),促进中性粒细胞和单核/巨噬细胞浸润,这会进一步加重局部炎症损伤。Ang II 可能通过氧化应激激活 NLRP3 炎症小体,导致 IL-1 β 和 IL-18 释放,放大炎症反应。Ang II 通过 AT1 受体激活 NADPH 氧化酶(NOX),增加活性氧(ROS)生成,导致脂质过氧化、DNA 损伤及线粒体功能障碍。Ang II 还可以下调超氧化物歧化酶(SOD)和谷胱甘肽(GSH)等抗氧化分子来加剧氧化损伤。输注 AT-II 对特定休克患者的影响将是这一系列相互作用的平衡[45]。实验研究表明,在脓毒症患者中,AT-II 受体表达下调,同时出现受体对 AT-II 刺激敏感性下降。脓毒症休克患者血浆 AT-II 水平也相对降低,这可能是因为 AT-II 酶缺乏与脓毒症诱导的内皮损伤有关[46]。162 例接受 AT-II 治疗的难治性分布性休克患者的多中心回顾性分析报告称,在 0~20 分钟内 MAP 平均增加 9.3 mmHg (95% CI 6.4~12.1, $P < 0.001$),输注的去甲肾上腺素等效剂量减少(平均减少 0.16 $\mu\text{g/kg/min}$, 95% CI 0.10~0.22, $P < 0.001$) [47]。他们得出结论,在去甲肾上腺素等效剂量超过 0.2~0.3 $\mu\text{g/kg/min}$ 之前,应在休克过程的早期使用 AT-II 以维持 MAP。一项多中心随机双盲安慰剂对照研究(ATHOS-3)比较了 321 例患者 AT-II 与安慰剂对 MAP 的影响,这些患者尽管进行了充分的液体复苏并给予大剂量去甲肾上腺素后,仍有血管扩张性休克。与安慰剂相比,AT-II 在降低儿茶酚胺剂量的同时可以达到预定的 MAP 目标,但不会降低 7 天和 28 天的死亡率[48]。对于脓毒症休克患者,尤其是在最严重的病例和/或需要肾脏替代治疗的急性肾损伤患者中,AT-II 似乎是一种有前途且相对安全的血管升压剂。但是,仍需进一步实验以确定预计将从 AT-II 治疗中获益最多的脓毒症休克患者;AT-II 的最佳应用剂量也有待进一步研究。

4.3. 右美托咪定

一项大型动物 S-AKI 模型实验中,作为辅助治疗的右美托咪定(DEX)降低了恢复基线 MAP 所需的去

甲肾上腺素的剂量,缓解了肾髓质低灌注和缺氧,并显著降低循环血浆中炎症介质的水平[49]。在大鼠 S-AKI 模型的研究中,同样证明了 DEX 可以减少炎症反应,保护肾功能,减轻肾损伤[50] [51]。因此, Dex 有望成为治疗 S-AKI 的重要新治疗靶点,在 S-AKI 中提供肾脏保护。而最近的一项在 ICU 病房的随机对照试验结论似乎也支持这一说法,试验证明 DEX 组前 6 天的血清肌酐水平较非右美托咪定[non-DEX] 组显著降低($P=0.04$)。同时 DEX 组的 28 天死亡率和住院死亡率也显著低于非右美托咪定组(22% vs. 42%, $P=0.03$; 28% vs. 52%, $P=0.01$) [52]。但上述实验仍有其相对局限性,缺乏相关对长期的肾功能影响以及相关的髓质氧合改善证据,需要更多的随机对照试验来确认这些药物的效用、剂量、组合和给药顺序。

5. 总结与展望

治疗 S-AKI 存在多种药物选择,但选择有限。在 S-AKI 中早期使用去甲肾上腺素已得到充分证实是可靠的,在 S-AKI 中早期权衡使用 VP 或 AT-II 似乎也是合理的。不幸的是,仍然缺乏多个随机对照试验来证明其优越性,也相对缺乏药物之间的比较试验和关于应该在什么时候加用药物的循证数据,去甲肾上腺素目前依旧被推荐作为脓毒性休克患者的一线血管加压药,有着其余药物无法比拟的优势。新一代的血管加压药物可以通过精准受体调控以及双重或多靶点选择来进一步强化效果,另外现有药物的药代动力学也有优化的空间,例如超短效制剂依靠其更加可控的半衰期来实现药物的精准滴定,研发长效缓释制剂来减少频繁给药需求。进一步改善脓毒性休克患者的管理,并减少与血管加压药相关的不良反应。

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