

烧伤延迟复苏加重肠黏膜屏障功能损害的机制研究

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国家重点基础研究发展规划项目, No.G1999054202
国家杰出青年科学基金, No.30125040
全军医药卫生科研基金课题, No. 01L066
高等学校骨干教师资助计划项目基金, No.
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收稿日期: 2003-03-06 接受日期: 2003-04-03

Mechanism of delayed resuscitation in promoting loss of intestinal mucous membrane barrier function after rats scalding

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Supported by the National Key Basic Research Development Program, No. G1999054202; the National Outstanding Youth Scientific Foundation, No. 30125040; the Army Medicine and Sanitation Scientific Research Foundation, No. 01L066; the National High School Skeleton Teacher Supporting Program.
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Received: 2003-03-06 Accepted: 2003-04-03

Abstract

AIM: To investigate the effect of delayed resuscitation on intestinal mucous membrane barrier function and its relationship with neutrophil infiltration of local tissue after rats scalding.

METHODS: Rats with 40% full-thickness scald burn were randomly divided into two group: immediately resuscitation group (IR group) and delayed resuscitation group (DR group). The content of D-lactate, diamine oxidase (DAO) in plasma and myeloperoxidase (MPO), superoxide dismutase (SOD) and malondialdehyde (MDA) in intestinal mucous tissue were determined at different time points after burn. Apoptosis of mucous epithelial cells were identified by terminal deoxynucleotidyl-transferase mediated dUTP-biotin nick end labeling (TUNEL) histochemical methods.

RESULTS: The contents of D-lactate in plasma in DR group were much higher than those of IR group ($P < 0.01$ or 0.05), MPO activity in intestinal mucous tissue of DR group were dramatically increased accompanying with decrease of SOD activity and increase of MDA contents. Herein, we

found a close correlation between the contents of D-lactate and activity of MPO. Meanwhile, we also found an increase of the activity of DAO in plasma and number of TUNEL positive staining epithelial cells in DR group.

CONCLUSION: Delayed resuscitation promotes the loss of intestinal mucous membrane barrier function due to the increase of both cell necrosis and cell apoptosis, which may be related to increased neutrophil infiltration in local tissue.

Zhang JP, Huang YS, Yang ZC. Mechanism of delayed resuscitation in promoting loss of intestinal mucous membrane barrier function after rats scalding. *Shijie Huaren Xiaohua Zazhi* 2004;12(6):1329-1332

摘要

目的: 研究大鼠严重烧伤后延迟复苏对肠黏膜屏障功能的影响, 探讨中性粒细胞浸润在肠黏膜屏障功能损害中的作用及可能机制.

方法: Wistar 大鼠 40%TBSA III 度烫伤, 分立即复苏组和延迟复苏组, 于伤后不同时相点检测血中 D-乳酸、二胺氧化酶(DAO)及肠黏膜组织髓过氧化物酶(MPO)、超氧化物歧化酶(SOD)和丙二醛(MDA)含量; 肠黏膜组织石蜡切片黏膜上皮细胞凋亡原位检测.

结果: 延迟复苏组各时相点血中 D-乳酸含量明显高于立即复苏组 ($P < 0.05$), 肠黏膜组织局部 MPO 活性显著升高 (与立即复苏组比较, $P < 0.01$) 伴 SOD 活性降低和 MDA 含量升高. 两组血 DAO 含量以伤后 6 h 最高, 延迟复苏组约为立即复苏组的两倍 (1.40 ± 0.20 vs 0.78 ± 0.19 , $P < 0.01$), 伤后 24 h 比较, 二者仍具统计学差异. 各时相点两组动物均能检测到 TUNEL 染色阳性肠黏膜上皮细胞, 以伤后 12 h 为凋亡高峰, 延迟复苏组各时相点凋亡率均显著高于立即复苏组.

结论: 烧伤延迟复苏加重肠黏膜屏障功能损害, 黏膜上皮细胞坏死和凋亡共同构成早期屏障功能损害加重的病理学基础, 而组织局部中性粒细胞浸润增强可能在其中起重要作用.

张家平, 黄跃生, 杨宗城. 烧伤延迟复苏加重肠黏膜屏障功能损害的机制研究. *世界华人消化杂志* 2004;12(6):1329-1332

<http://www.wjgnet.com/1009-3079/12/1329.asp>

0 引言

临床观察表明, 严重烧伤延迟复苏患者往往易伴发全

身严重感染和多器官功能障碍(MODS). 延迟复苏是一休克-抗休克的过程, 而肠道是休克状态下受累最早、血流灌注恢复最晚的脏器. 近年研究表明, 肠缺血或再灌时肠黏膜屏障功能的损害是肠源性内毒血症、脓毒症发生的重要原因, 进入循环的内毒素成为启动 SIRS, MODS 的关键因素, 故也有学者认为肠道是 MODS 的启动器官^[1-9]. 因此, 探讨严重烧伤延迟复苏后肠黏膜屏障功能的改变及其病理学基础和发生机制对于防治、降低 MODS 的发生有积极的临床意义.

1 材料和方法

1.1 材料 Wistar 大鼠 80 只(200-250 g 雌雄不拘), 随机分成立即复苏组(IR 组)和延迟复苏组(DR 组). 实验前 12 h 禁食, 异戊巴比妥钠(30 mg/kg)麻醉, 背部 92 °C 烫伤 18 s 致 40% 总体表面积(TBSA)Ⅲ° 烫伤. IR 组伤后立即按 Parkland 公式补液(4.0 mL/kg⁻¹/TBSA⁻¹), DR 组伤后 6 h 开始按 5.33 mL/kg⁻¹/TBSA⁻¹ 补液. 各组均于伤后 8 h 内补入 24 h 计算补液量的 1/2, 余下 1/2 伤后 16 h 后匀速补入(颈静脉插管, 恒速输液泵补液). 大鼠于伤后 6, 8, 12, 18, 24 h 活杀, 腹主动脉取血, 制备血浆. 同时, 取回盲部小肠黏膜制备组织匀浆, -20 °C 保存. 另取 1 cm 长度小肠, 40 g/L 中性甲醛固定, 备作石蜡切片. D-乳酸标准品, D-乳酸脱氢酶(D-LDH)和辣根过氧化物酶均购自美国 Sigma 公司; MPO, SOD 和 MDA 检测试剂盒购自南京建成生物工程研究所; 细胞原位凋亡检测 POD 试剂盒购自美国罗氏公司.

1.2 方法

1.2.1 血浆 D-乳酸含量测定 参考文献[10], 略加修改. 制作标准曲线: 将 D-乳酸配成 15 mg/L、12 mg/L、9 mg/L、6 mg/L、3 mg/L 系列溶液(125 μL), 加 375 μL 尼克酰胺腺嘌呤二核苷酸(nicotinamide-adenine dinucleotide, NAD)缓冲液, 混匀, 按 30 KU/L 加入 D-LDH, 25 °C 水浴 90 min, 340 nm 处测 A 值, 求回归方程. 标本检测: (1)制备去蛋白血浆(PFP): 取 400 μL 血浆, 加入 5.8 mol/L 过氯酸 40 μL, 振荡混匀 20 s, 冰浴 10 min, 4 °C 5 000 r/min 离心 10 min. 取 200 μL 上清(PFP), 加 11.6 mol/L KOH 20 μL, 振荡混匀 20 s, 冰浴 10 min,

4 °C 5 000 r/min 离心 10 min, 上清为中和的 PFP-NPFP. (2)取 125 μL NPFP, 加 375 μL NAD 缓冲液, 混匀, 按 30 KU/L 浓度加 D-LDH, 25 °C 水浴 90 min, 测 A 值. 将值代入标准曲线计算 D-乳酸含量.

1.2.2 肠黏膜上皮细胞凋亡检测 TUNEL 法, 按操作说明书进行. 石蜡切片常规脱蜡、水化, 蛋白酶 K(10 mg/L)孵育 20 min, 30 mL/L H₂O₂ 甲醇封闭和 1 g/L Triton 处理后, 样品加 TUNEL 反应液 50 μL, 37 °C 湿盒孵育 60 min, PBS 轻洗 3 次, 加 Converter-POD 50 μL, 37 °C 湿盒孵育 30 min, PBS 轻洗 3 次, DAB 显色, 苏木素复染, 封片, 显微镜下观察照相. 各时相点每张切片随机数 5 个高倍镜(× 400)视野下凋亡的肠黏膜上皮细胞数和肠黏膜上皮细胞细胞总数, 二者比值为凋亡百分率.

1.2.3 肠黏膜组织 DAO 测定参考文献[20] 肠黏膜组织 MPO、SOD 及 MDA 测定按照试剂盒说明书操作.

统计学处理 数据以 mean±SD 表示, SPSS10.0 统计软件行单因素方差分析、 χ^2 检验和相关分析.

2 结果

2.1 血浆 D-乳酸及 DAO 变化 烧伤后大鼠血浆 D-乳酸及 DAO 含量显著增高, 两组均于伤后 6 h 达高峰. 组间比较, DR 组各时相点血浆 D-乳酸及 DAO 含量均显著高于 IR 组(见表 1).

2.2 肠黏膜上皮细胞凋亡变化 烧伤 6 h 起, 两组大鼠均检测到 TUNEL 染色阳性细胞. 阳性细胞表现为核呈棕或棕褐染色, 核形态一般较完整, 凋亡细胞多分布于黏膜上端或顶端(图 A、B). 组间比较, DR 组各时相点肠黏膜上皮细胞凋亡率显著高于 IR 组(见表 1).

2.3 肠黏膜组织 MPO、SOD 活力及 MDA 含量变化 烧伤后肠黏膜组织 MPO 活力升高, 伤后 8 h 达高峰. DR 组各时相点 MPO 活力均显著高于 IR 组($P < 0.01$); 烧伤后肠黏膜组织 SOD 活力下降, IR 组伤后 18 h 达低谷, DR 组伤后 12 h 达低谷, DR 组各时相点 SOD 活力显著低于 IR 组($P < 0.01$ 和 $P < 0.05$); 烧伤后肠黏膜组织 MDA 含量升高, IR 组伤后 8 h 达高峰, DR 组伤后 6 h 达高峰. 伤后 6-12 h, DR 组 MDA 含量显著高于 IR 组($P < 0.01$ 和 $P < 0.05$), (见表 2).

表 1 大鼠延迟复苏血浆 D-乳酸、DAO 及肠黏膜上皮细胞凋亡变化

指标	分组	正常值	伤后时间(h)				
			6	8	12	18	24
D-乳酸(mg/L)	IR 组	3.2±0.4	11.1±3.0	8.1±1.7	7.7±2.2	7.3±1.2	7.9±1.5
	DR 组		14.8±2.3 ^a	10.7±1.4 ^b	10.7±2.5 ^a	10.4±2.0 ^b	9.8±2.1 ^a
DAO(KU/L)	IR 组	0.28±0.04	0.78±0.19	0.66±0.10	0.41±0.07	0.43±0.06	0.41±0.08
	DR 组		1.40±0.20 ^b	1.035±0.15 ^b	0.69±0.13 ^b	0.65±0.10 ^a	0.61±0.06 ^a
细胞凋亡(%)	IR 组	1.1±0.3	3.7±1.6	4.2±1.5	8.2±2.5	6.6±1.7	5.2±2.0
	DR 组		6.0±1.9 ^b	7.4±2.7 ^b	15.3±3.1 ^b	10.5±2.2 ^b	11.8±2.4 ^b

^a $P < 0.05$, ^b $P < 0.01$ vs IR 组

表2 肠粘膜组织 MPO, SOD 及 MDA 含量变化

伤后 (h)	MPO (U/g)		SOD (KNU/g)		MDA($\mu\text{mol/g}$)	
	IR 组	DR 组	IR 组	DR 组	IR 组	DR 组
正常组	1.62 \pm 0.21		503.4 \pm 118.2		0.3 \pm 0.1	
伤后 6	5.5 \pm 1.0	9.4 \pm 1.7 ^b	344 \pm 63	268 \pm 43 ^b	1.2 \pm 0.2	2.8 \pm 0.7 ^b
伤后 8	5.7 \pm 1.8	8.6 \pm 2.3 ^b	281 \pm 80	146 \pm 43 ^b	1.3 \pm 0.2	2.5 \pm 0.4 ^b
伤后 12	4.7 \pm 0.5	7.3 \pm 2.0 ^b	186 \pm 51	92 \pm 25 ^b	1.1 \pm 0.2	1.4 \pm 0.3 ^a
伤后 18	3.8 \pm 1.1	6.3 \pm 1.1 ^b	165 \pm 45	95 \pm 20 ^b	0.8 \pm 0.1	1.0 \pm 0.2
伤后 24	2.2 \pm 0.5	5.9 \pm 1.7 ^b	174 \pm 48	137 \pm 35 ^a	0.6 \pm 0.1	0.7 \pm 0.1

^aP < 0.05, ^bP < 0.01 vs IR 组.

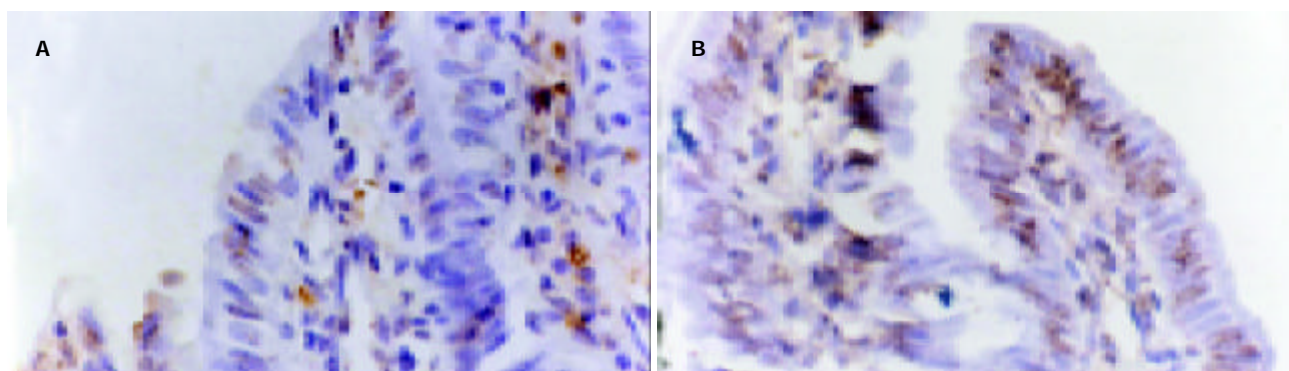


图1 肠黏膜上皮细胞凋亡变化. A: IR 组小肠黏膜上皮细胞凋亡(伤后 12 h) \times 400; B: DR 组小肠黏膜上皮细胞凋亡(伤后 12 h) \times 400.

3 讨论

肠黏膜屏障功能可通过新的血浆标志物D-乳酸定量评估^[11-14]. D-乳酸是细菌代谢、裂解的产物,肠道菌群中多种细菌均可产生,哺乳动物自身既不产生,也不能或仅能缓慢代谢D-乳酸.因此,检测血中D-乳酸的蓄积情况可反映严重创伤、感染或某些胃肠病变时肠黏膜通透性的增高,且较之传统方法更易于检测^[13-19].在本研究中,伤后两组大鼠血中D-乳酸含量均明显增多,6 h达高峰,组间比较,DR组升高更为显著,表明延迟复苏导致肠黏膜通透性进一步增高,加剧肠黏膜屏障功能障碍,类似结果见于孙晓庆和Li et al^[11-12]的研究.过去有观点认为,烧伤延迟复苏存在明显的缺血再灌注损伤,即意味着再灌注后的损伤应比缺血时的损伤重,对应到本研究,DR组血D-乳酸应该在复苏(伤后6 h)后进一步加重,但我们并未发现该现象,DR组血D-乳酸含量同IR组一样也于伤后6 h达高峰,提示延迟复苏后小肠并不存在明显的再灌注损伤,而仍主要是缺血性损害,可能的原因有二:(1)烧伤延迟复苏并非经典的缺血/再灌注过程.烧伤后6 h内尽管未补液,但肠黏膜并非经典意义上的完全缺血,因而复苏后未发生明显的再灌注损伤;(2)由于延迟复苏后循环系统中血容量增多,使D-乳酸浓度稀释,掩盖了事实上的再灌注损伤.

正常的细胞结构和细胞间连接是构成肠黏膜屏障的主要物质基础,细胞死亡势必造成屏障功能的破坏.DAO是小肠黏膜上层绒毛中具有高度活性的细胞内

酶,其他组织或细胞中几乎不存在,生理状态下血浆中DAO活性很低,当肠黏膜受损时,细胞释放的DAO大量入血,使血中DAO含量升高,故血中DAO含量可反映黏膜上皮细胞的坏死情况^[20].研究发现,烧伤后两组大鼠血中DAO含量均明显增加,6 h达高峰,各时相点DR组均显著高于IR组,表明延迟复苏加重了肠黏膜上皮细胞损伤.进一步,我们检测了细胞另一种死亡方式-凋亡在烧伤延迟复苏小肠黏膜上皮细胞中的变化,结果显示烧伤后两组大鼠肠黏膜上皮细胞凋亡率显著升高,12 h达高峰,其中DR组凋亡率显著高于IR组.上述结果说明,烧伤延迟复苏导致肠黏膜上皮细胞的两种死亡(坏死和凋亡)情况均显著加重.过往研究多只注意单一的细胞死亡方式在烧伤延迟复苏肠黏膜屏障功能中的作用^[21-23],本研究发现肠黏膜上皮细胞坏死和凋亡共同构成了烧伤延迟复苏肠黏膜屏障功能损害的病理学基础,且二者的变化规律不一致,其中,坏死高峰早于凋亡高峰,而凋亡的发生似乎更为持久.

在脏器缺血和/或再灌注损伤过程中,中性粒细胞浸润可能起关键作用^[24-26].活化的中性粒细胞(PMN)与血管内皮细胞黏附,产生多种影响血管舒缩的物质、蛋白酶和自由基等,导致微血管功能障碍;白细胞本身在毛细血管中嵌顿亦可导致无复流现象,加重缺血缺氧性损害;另外,活化的粒细胞通过跨膜运动迁移至组织间隙,通过释放自由基、细胞因子,或与实质细胞直接黏附进一步导致脏器损伤.研究表明,抑制粒细胞浸

润可显著减轻缺血或再灌注引起的肠损伤^[27-29]. 在本研究中, DR组肠黏膜组织中MPO(中性粒细胞中特异酶)活力在各时相点均明显高于IR组, 相关分析发现, 组织MPO活力与血中D-乳酸含量呈显著正相关($P < 0.01$, $r = 0.873$). 此外, DR组组织局部SOD活性显著下降伴MDA含量升高, SOD与MPO二者呈显著负相关($P < 0.05$, $r = -0.541$). 大量研究表明, 氧化应激不但可以引起细胞坏死, 同时也是诱导细胞凋亡的重要因素^[30-33]. 由此, 我们认为, 局部中性粒细胞浸润增多可能是烧伤延迟复苏加剧肠黏膜屏障功能损害的重要原因, 而氧化应激在其中起关键作用.

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