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·论 著·

# 依达拉奉对大鼠失血性休克复苏后重要脏器功能及血浆炎症因子水平的影响

王 莹,王 飞,李金宝,邓小明*
第二军医大学长海医院麻醉科,上海 200433

[摘要] **目的** 探讨依达拉奉对大鼠失血性休克复苏后重要脏器功能及血浆炎症因子表达的影响。**方法** 24只SD大鼠随机分为假手术组(Sham组)、失血性休克复苏组(I/R组)、失血性休克复苏依达拉奉治疗组(I/R-ED组),每组8只。Sham组仅行股动、静脉置管。I/R、I/R-ED组经股动、静脉置管放血诱导休克,将平均动脉压(MAP)维持于35～45 mmHg(1 mmHg=0.133 kPa)60 min。休克期结束后,两组均给予60%的自体血和2倍的乳酸钠林格液复苏,分别在复苏即刻及结束时,I/R组给予生理盐水(2 ml/kg),I/R-ED组给予依达拉奉(2 ml/kg,2 mg/ml)。复苏后2、24 h取血,测定血浆ALT、AST、LDH、CK、BUN、Cr水平,采用ELISA法测定血浆TNF-α及IL-6水平。**结果** 复苏后2 h,I/R组血浆TNF-α、IL-6高于Sham组($P<0.05$),I/R-ED组与I/R组差异无统计学意义;复苏后24 h时,I/R组血浆TNF-α、IL-6仍高于Sham组($P<0.05$),而I/R-ED组低于I/R组($P<0.05$)。复苏后24 h时,I/R组血浆ALT、AST水平高于Sham组($P<0.05$),I/R-ED组低于I/R组($P<0.05$)。复苏后2 h及24 h时,I/R组血浆BUN、Cr均高于Sham组($P<0.05$),I/R-ED组低于I/R组($P<0.05$)。复苏后2 h及24 h时,I/R组CK、LDH高于Sham组($P<0.05$),I/R-ED组低于I/R组($P<0.05$)。复苏后24 h时,I/R组肝、肾、肺均有明显的病理改变,而I/R-ED组病理改变程度均有所减轻。**结论** 依达拉奉可降低失血性休克大鼠复苏后24 h血浆炎症因子(TNF-α、IL-6)水平,在一定程度上改善复苏后重要脏器的功能。

[关键词] 依达拉奉;出血性休克;复苏;肿瘤坏死因子α;白介素6
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## Influence of edaravone on major organ functions and plasma inflammatory cytokine level following hemorrhagic shock and resuscitation in rats

WANG Ying, WANG Fei, LI Jin-bao, DENG Xiao-ming*
Department of Anesthesiology, Changhai Hospital, Second Military Medical University, Shanghai 200433, China

[**Abstract**] **Objective** To investigate the effects of edaravone on the functions of major organs and plasma inflammatory cytokine levels following hemorrhagic shock(HS) and resuscitation in rats. **Methods** A total of 24 rats were randomly divided into 3 groups: the sham-operated control group (sham), the haemorrhage shock goup (I/R), and the haemorrhage shock plus edaravone injection (I/R-ED) group. Rats in the latter two groups were bled using a femoral artery catheter with MAP maintained within 35-45 mmHg(1 mmHg = 0.133 kPa) for 60 min to induce shock, and then resuscitaton was induced by reinjecting 60% autologous blood and 2 times of shed blood Ringer's. At the beginning and ending of resuscitation, I/R group and I/R-ED group were given the same dose (2 ml/kg) of normal saline and edaravone, respectively. The plasma levels of TNF-α, IL-6, ALT, AST, LDH, CK, BUN and Cr were measured at 2 and 24 h after resuscitation. **Results** (1)The plasma levels of TNF-α and IL-6 in I/R group were significantly higher than those of the sham group 2 h after hemorrhagic shock and resuscitation ($P<0.05$), with no significant difference found between I/R group and I/R-ED group ($P>0.05$). The plasma levels of TNF-α and IL-6 in I/R group were also significantly higher than those in the sham group after 24 h($P<0.05$), and the levels in I/R-ED group was significantly lower than those in the I/R group($P<0.05$). (2) The plasma levels of ALT and AST in I/R group were significantly higher than those in the sham group at 24 h ($P<0.05$), and the levels in I/R-ED group was significantly lower than that in the I/R group ($P<0.05$). The plasma levels of BUN and Cr in I/R group were significantly higher than those in the sham group after 2 h($P<0.05$), and the levels in I/R-ED group was significantly lower than those in the I/R group($P<0.05$). The plasma levels of BUN and Cr in I/R group were also significantly higher than those in the sham group ($P<0.05$); Cr level in ED group was significantly lower than that in the I/R group($P<0.05$); and the BUN level in I/R-ED group was similar to that in I/R group. (3) Great pathological changes were found in the liver, kidney, and lung of rats in I/R Group, and the pathological changes were slight in I/R-ED Group. **Conclusion** Our study suggests that edaravone can decrease the release of inflammatory factors (TNF-α and IL-6) after

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[作者简介] 王 莹,硕士,住院医师. E-mail: wangying81@163.com
*通信作者(Corresponding author). Tel: 021-81873484, E-mail: xmdeng@anesthesia.org.cn

induction of HS in rats, which can alleviate the pathological damage to major organs after HS.

[**Key words**] edaravone; hemorrhagic shock; resuscitation; tumor necrosis factor-α; interleukin-6

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尽管复苏和重症监护有了很大的进展，失血性休克仍然是导致患者死亡的重要原因之一[1-2]。传统复苏可以改善组织灌注，却不能阻止炎症因子的产生，复苏所引发的全身炎症反应可能比失血本身更加危险。绝大多数促炎因子，如肿瘤坏死因子-α(TNF-α)、白介素-6(IL-6)，可导致严重休克、多器官功能衰竭(MOF)甚至死亡[3-5]。依达拉奉(3-甲基-1-苯基-2-吡唑啉-5-酮，MCI-186)是一种新型的氧自由基清除剂[6]，可抑制脂质过氧化与血管内皮的损伤，具有清除氧自由基的功能，可改善大脑梗死引起的损伤[7-8]，主要用于临床改善急性脑卒中患者预后[9-10]。休克后即刻给予依达拉奉可提高失血性休克未复苏大鼠的生存率[11]，但对休克复苏后大鼠重要脏器功能的影响尚不清楚。因此，本研究观察依达拉奉对失血性休克复苏后大鼠重要脏器(心、肺、肝、肾)功能及血浆炎症因子(TNF-α、IL-6)表达水平的影响，探讨其可能的作用效果。

## 1　材料和方法

1.1　*主要试剂*　依达拉奉注射液(edaravone injection)购自南京先声东元制药有限公司，大鼠 TNF-α、IL-6 定量 ELISA 检测试剂盒购自美国 R&D 生物公司，生理盐水注射液购自上海百特医疗用品有限公司，乳酸钠林格液购自广东大冢制药有限公司。

1.2　*动物选择及分组*　纯系清洁级成年雄性 SD 大鼠购自上海西普尔-必凯实验动物有限公司，饲养于第二军医大学动物实验中心，体质量 220～300 g。24 只大鼠随机分为 3 组($n=8$)：假手术组(Sham 组)、失血性休克复苏组(I/R 组)、失血性休克复苏依达拉奉治疗组(I/R-ED 组)。

1.3　*休克模型的构建*　休克模型参照 Handrigan 等[12]的方法构建。实验前禁食 12 h，自由饮水。腹腔注射 1%戊巴比妥钠 45 mg/kg，麻醉后行右侧股动、静脉插管，右侧股动脉插入连有三通的套管并连接 M1205A 型心电监护仪(Philips 公司)，以备放血和监测复苏时血压变化。右股静脉置入连有三通的套管，以备给药及输液。插管后注入肝素钠生理盐水(500 U/kg)抗凝。稳定 15 min 后，经股动脉放血(15 min 内)使平均动脉压(MAP)达到 35～45 mmHg(1 mmHg=0.133 kPa)，而后通过间断放血和自体血回输使 MAP 维持在 35～45 mmHg，持续 60 min。I/R 组及 I/R-ED 组在休克期维持 60 min 后立即进行容量治疗，分别在 10 min 内回输 60%自体血及在 30 min 内以恒速输入 2 倍放血量的乳酸钠林格液，在复苏开始即刻及复苏结束时，分别给予生理盐水(2 ml/kg)和依达拉奉(2 ml/kg，2 mg/ml)。Sham 组仅行麻醉并右侧股动、静脉穿刺，未予失血性休克及复苏。

1.4　*血生化指标及血浆 TNF-α、IL-6 检测*　于失血前、容量复苏结束后 2、24 h 时经股动脉采集血样各 1 ml，离心后留血浆，－80℃冰箱保存。应用全自动生化分析仪(Olympus AU 2700)测定血浆丙氨酸转氨酶(ALT)、天冬氨酸转氨酶(AST)、尿素氮(BUN)、肌酐(Cr)、乳酸脱氢酶(LDH)和肌酸激酶(CK)等水平。采用 ELISA 法测定 TNF-α、IL-6 水平。检测方法严格按照试剂盒说明书操作。

1.5　*组织病理学观察*　在失血性休克复苏后 24 h，经心脏穿刺抽血快速处死动物，快速切取左肺、肝左叶、左肾并放入 10%甲醛固定 24 h，石蜡切片做 H-E 染色，分别在光镜下观察。

1.6　*统计学处理*　采用 SPSS 17.0 统计软件，数据以 $\bar{x}\pm s$ 表示，3 组参数的比较采用重复测量的方差分析，组间比较采用 Bonferroni 检验，检验水平($\alpha$)为 0.05。

## 2　结　果

2.1　*各组大鼠血浆生化指标的变化*　3 组大鼠血浆 ALT、AST 随时间的变化差异有统计学意义($P<0.01$)。复苏后 24 h 时，I/R 组血浆 ALT、AST 高于 Sham 组($P<0.05$)，I/R-ED 组低于 I/R 组($P<0.05$)。3 组大鼠血浆 BUN、Cr 随时间的变化差异有统计学意义($P<0.01$)。复苏后 2 h 时，I/R 组血浆 BUN、Cr 均高于 Sham 组($P<0.05$)，I/R-ED 组低于 I/R 组($P<0.05$)；复苏 24 h 时，I/R 组大鼠血浆 BUN、Cr 仍高于 Sham 组($P<0.05$)，I/R-ED 组血浆 Cr 明显低于 I/R 组($P<0.05$)，但其 BUN 与 I/R 组比较差异无统计学意义。3 组大鼠血浆 CK、LDH 随时间变化差异均有统计学意义($P<0.01$)，在复苏后 2 h 及 24 h 时，I/R 组高于 Sham 组($P<0.05$)，I/R-ED 组低于 I/R 组($P<0.05$)。此结果提示：在大鼠失血性休克复苏后 2 h，依达拉奉对心脏和肾脏功能有一定的改善作用，对肝脏功能改善不明显；而在复苏后 24 h 对心脏、肾脏和肝脏的功能均有显著改善作用。具体数据见表 1。

**表 1　各组大鼠血浆 ALT、AST、BUN、Cr 、CK、LDH 的变化**

**Tab 1　Changes of plasma ALT, AST, BUN, Cr, CK and LDH in different groups**

($n=8$, $\bar{x}\pm s$)

| Index | Before hemorrhagic shock | 2 h after resuscitation | 24 h after resuscitation |
|---|---|---|---|
| ALT $z$/(U·L$^{-1}$) | | | |
| Sham | 45.83±4.36 | 41.83±5.15 | 57.17±19.88 |
| I/R | 36.33±7.74 | 39.33±4.13 | 126.00±27.19* |
| I/R-ED | 38.67±8.96 | 35.50±3.27 | 68.00±15.53△ |
| AST $z$/(U·L$^{-1}$) | | | |
| Sham | 80.83±9.70 | 75.50±10.04 | 199.00±131.96 |
| I/R | 79.50±9.61 | 135.33±48.89 | 977.17±312.60* |
| I/R-ED | 72.83±12.35 | 100.17±25.20 | 223.50±123.10△ |
| BUN $c_B$/(mmol·L$^{-1}$) | | | |
| Sham | 4.22±0.74 | 4.68±0.85 | 4.52±0.69 |
| I/R | 4.25±0.52 | 6.20±1.16* | 8.92±2.99* |
| I/R-ED | 3.68±0.29 | 4.52±0.22△ | 6.17±0.33 |
| Cr $c_B$/(μmol·L$^{-1}$) | | | |
| Sham | 17.5 ±2.43 | 10.83±1.17 | 15.67±0.82 |
| I/R | 17.33±2.07 | 34.33±6.86* | 34.83±4.02* |
| I/R-ED | 16.67±1.63 | 17.33±2.58△ | 23.33±3.62△ |
| CK $z$/(U·L$^{-1}$) | | | |
| Sham | 315.67±73.29 | 311.83±82.63 | 284.67±167.71 |
| I/R | 264.17±83.84 | 1 204.83±694.00* | 5 051.00±940.36* |
| I/R-ED | 207.00±18.93* | 505.33±222.30△ | 314.67±74.96△ |
| LDH $z$/ (U·L$^{-1}$) | | | |
| Sham | 266.00±149.97 | 252.00±62.89 | 210.50±76.34 |
| I/R | 181.00±51.29 | 452.33±173.60* | 825.33±237.40* |
| I/R-ED | 197.50±56.30 | 258.00±59.59△ | 504.00±98.33*△ |

ALT: Glutamic-pyruvic transaminase; AST: Glutamic-oxal(o)acetic transaminase; BUN: Urea nitrogen; Cr: Creatinine; CK: Creatine kinase; LDH: Lactic dehydrogenase; I/R: Ischemia-reperfusion; I/R-ED: Ischemia-reperfusion+edaravone. * $P<0.05$ vs sham group; △ $P<0.05$ vs I/R group

2.2　各组大鼠血浆 TNF-α、IL-6 的变化　结果(表 2)表明:3 组血浆 TNF-α、IL-6 随时间的变化差异均有统计学意义($P<0.01$)。复苏后 2 h,与 Sham 组相比,I/R 与 I/R-ED 组血浆 TNF-α、IL-6 水平均增高($P<0.01$),而 I/R 与 I/R-ED 组间比较差异无统计学意义。复苏后 24 h,与 I/R 组相比,I/R-ED 组血浆 IL-6、TNF-α 水平均降低,差异有统计学意义($P<0.05$)。

**表 2　各组大鼠血浆 TNF-α、IL-6 的变化**

**Tab 2　Changes of plasma TNF-α and IL-6 in different groups**

[$n=8$, $\bar{x}\pm s$, $\rho_B$/(pg·ml$^{-1}$)]

| Index | | Before hemorrhagic shock | 2 h after resuscitation | 24 h after resuscitation |
|---|---|---|---|---|
| TNF-α | Sham | 81.29±6.82 | 112.44±8.81 | 86.73±6.75 |
| | I/R | 77.75±5.82 | 188.81±5.84** | 122.27±8.34* |
| | I/R-ED | 80.28±6.72 | 180.01±6.57** | 97.11±5.68*△ |
| IL-6 | Sham | 41.03±3.71 | 58.90±3.15 | 50.42±2.28 |
| | I/R | 40.53±2.55 | 82.08±4.42** | 55.58±2.97* |
| | I/R-ED | 39.20±3.96 | 83.19±3.61** | 49.55±2.44△ |

TNF-α: Tumor necrosis factor-α; IL-6: Interleukin-6; I/R: Ischemia-reperfusion; I/R-ED: Ischemia-reperfusion+edaravone. * $P<0.05$, ** $P<0.01$ vs sham group; △ $P<0.05$ vs I/R group

2.3　各组大鼠肝脏病理学改变　光镜下可见 Sham 组肝组织结构完整,肝小叶汇管区清晰,肝细胞形态完好,排列有序(图 1A)。I/R 组肝细胞索结构紊乱,肝细胞少量灶性坏死,肝窦狭窄,肝脏边缘区可见灶性水样变,大量炎性细胞浸润,中央静脉扩张充血(图 1B)。I/R-ED 组肝组织基本保持了正常结构,肝小叶、汇管区清晰,肝细胞水肿程度低于 I/R 组,肝窦仍然保持通畅,仅有少量炎性细胞浸润(图 1C)。

2.4　各组大鼠肾脏病理学改变　光镜下可见 Sham 组肾脏未见明显异常,肾小管排列整齐,管腔边缘清晰,间质无充血水肿(图 1D);I/R 组可见中度至重度肾小管上皮细胞损伤,部分细胞核凝固,甚至消失

(图 1E)；I/R-ED 可见轻微的肾小管上皮细胞损伤、肿胀(图 1F)。

2.5　各组大鼠肺脏病理学改变　光镜下可见 Sham 组肺泡结构清晰完整(图 1G)；I/R 组肺泡间隔明显增厚、肺间质水肿，肺间质、肺泡腔见大量炎性细胞浸润，部分肺泡壁断裂(图 1H)；I/R-ED 组肺间质轻度水肿及炎性细胞浸润(图 1I)。

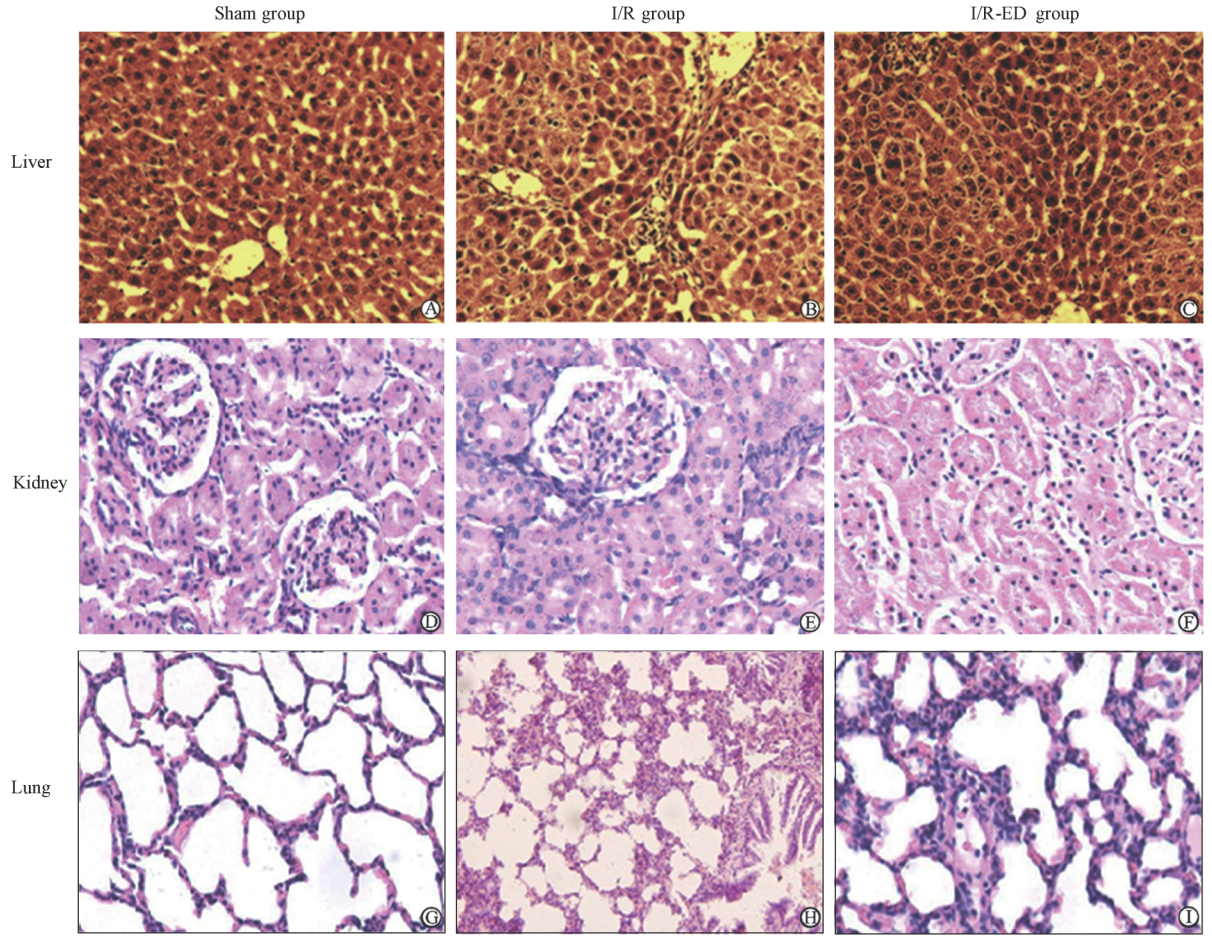


**图 1　各组大鼠失血性休克复苏后 24 h 肝脏(A～C)、肾脏(D～F)、肺脏(G～I)病理 H-E 染色**

**Fig 1　H-E staining results of rat liver(A-C), kidney (D-F) and lung(G-I) at 24 h after hemorrhagic shock and resuscitation in different groups**

I/R: Ischemia-reperfusion group; IR/ED: Ischemia-reperfusion+edaravone. Original magnification: ×200

## 3　讨　论

失血性休克后机体出现低灌注，微循环障碍，导致各个组织器官缺氧及代谢障碍，细胞功能受到损害，进而导致组织器官不可逆损伤。在失血性休克复苏后，自由基通过多种途径被激发产生，主要包括中性粒细胞呼吸爆发及线粒体氧化磷酸化功能障碍。自由基可与细胞各种成分，如蛋白质、核酸、膜磷脂等发生反应，造成细胞结构损伤及功能障碍[13]。复苏存活的患者往往会发生难以控制的全身性炎症反应综合征，最终导致终末器官损伤。

依达拉奉作为强效的新型氧自由基清除剂，主要通过抑制脂质自由基的生成及细胞膜脂质过氧化连锁反应，阻止氧自由基介导的蛋白质及核酸的不可逆破坏，有效地保护缺血再灌注所导致的细胞损伤，起到保护组织器官的作用[14]。依达拉奉可通过减少炎症因子和黏附因子的表达，从而减轻肝脏缺血再灌注导致的氧化应激和炎症反应损害[15]。依达拉奉同样对大鼠肾脏缺血再灌注损伤有保护作用，治疗后肾组织超微结构的损伤有明显减轻[16]。本研究结果也显示依达拉奉可降低缺血性休克复苏后升高的血浆 ALT、AST、BUN、Cr 水平，减轻肾失血性休克再灌注损伤。

在失血性休克复苏过程中，细胞核转录因子-κB (NF-κB)的不恰当表达是引起过度炎症反应和炎症损伤的关键因素。NF-κB 可以调节相关基因的表达，调节炎症因子 TNF-α、IL-6 的产生[2]。TNF-α 本身没有酶活性，其作用均表现为靶细胞对此细胞

因子的反应。过度分泌的 TNF-α 导致机体过强的炎症反应,引起血管通透性增强、血流动力学严重紊乱、微循环障碍及细胞功能障碍,最终导致各器官损伤及 MOF。因此该因子与疾病的严重程度和预后密切相关[17-18]。失血性休克后早期血浆 TNF-α、IL-6 水平显著升高[19-20]。应用单克隆抗 TNF-α 抗体可减轻休克导致的急性肺损伤[21-22]。另外,在猪失血性休克后,重组 IL-6 的应用减轻了肺炎症因子 TNF-α mRNA 水平[23]。依达拉奉可通过抑制 NF-κB 的活性,减轻内毒素诱导的肝部分切除术后的肝损伤及减少炎症因子的表达[24]。在心脏缺血再灌注损伤中,依达拉奉通过降低 TNF-α 的水平,减少心肌梗死面积,从而保护心脏功能[25]。依达拉奉通过降低 TNF-α 和 IL-6 的水平,达到减轻失血性休克复苏相关的组织损伤,此保护作用可能与依达拉奉的抗炎和抗氧化作用有关[26]。本研究发现依达拉奉可以降低失血性休克复苏后 TNF-α、IL-6 水平,在休克复苏后 24 h 降低得更加显著。依达拉奉可能是通过阻碍促炎因子的产生,缓解休克导致的组织损害及改善休克复苏后大鼠的预后。

综上所述,依达拉奉可降低失血性休克大鼠复苏后 24 h 血浆炎症因子(TNF-α、IL-6)水平,可一定程度上改善复苏后重要脏器的功能。

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