论著·军事医学

ATP-柠檬酸裂解酶抑制剂贝派地酸通过调控心肌能量代谢延长非控制性失血性休克大鼠黄金救治时间窗

张千威[1],周远群[2],向鑫明[2],胡诗雨[3],曾埝琦[2,4],欧阳杏楠[2],刘良明[2],李涛[2],何海燕[1] 陆军军医大学(第三军医大学)大坪医院:[1]护理部,[2]战伤休克与输血研究室,[4]麻醉科,重庆;[3]重庆理工大学药学与生物工程学院,重庆

[**摘要**] **目的** ATP-柠檬酸裂解酶(ATP-citrate lyase,ACLY)是介导细胞能量代谢重塑的核心枢纽酶,其特异性抑制剂贝派地酸(bempedoic acid,BA)已在缺血损伤、代谢紊乱相关模型中证实具备多脏器保护作用。本研究旨在明确BA能否延长非控制性失血性休克大鼠的黄金救治时间窗、实现多脏器保护作用,并探究其机制。**方法** 8~10周龄、180~220 g的SPF级SD大鼠,共208只,雌雄各半。采用脾脏纵深切口法建立非控制性失血性休克(uncontrolled hemorrhagic shock,UHS)大鼠模型,大鼠平均动脉压(mean arterial pressure,MAP)降至40 mmHg即为模型建立成功。①48只大鼠采用简单随机抽样法分为3组(n=16),即乳酸林格液(lactated Ringer's solution,LR)组、10 mg/kg BA组(10 mg/kg BA+LR)、20 mg/kg BA组(20 mg/kg BA+LR)。造模成功后立即进行低压复苏,维持血压50~60 mmHg,观察各组大鼠血压变化、失血率、输液量及低压维持时间。②96只大鼠按简单随机抽样分为4组(n=24),即假手术(Sham)组、UHS组、LR组、BA组(20 mg/kg BA+LR)。造模成功后,UHS组不实施复苏,其余2组立即行低压复苏,1 h后结扎脾动脉彻底止血并补足2倍失血量的LR进行确定性治疗。检测各组大鼠存活情况、血气指标、肝肾肠血流量、重要器官功能损伤指标、肺脑含水量、心肌收缩功能、心肌组织游离脂肪酸(free fatty acid,FFA)和ATP的含量。**结果** ①LR组仅能将MAP稳定维持在50~60 mmHg约60 min,10 mg/kg BA组和20 mg/kg BA组均可稳定维持超过180 min。与LR组相比,20 mg/kg BA组失血率显著降低(63.7%±12.8% *vs* 73.8%±4.4%,P<0.05),输液量也显著减少[(6.8±4.9) *vs* (18.7±9.8) mL,P<0.05]。LR组大鼠的平均低压维持时间为(57±17)min,1 h维持率为68.8%;所有大鼠在80 min内死亡。10 mg/kg BA组和20 mg/kg BA组大鼠的平均低压维持时间分别延长至(138±60)min和(157±50)min,3 h低压维持率分别达50.0%和68.7%。②LR组失血率(55.6%±6.3%)显著高于UHS组(48.4%±5.3%,P<0.05)。BA组失血率较LR组显著降低(47.2%±6.0%,P<0.05),输液量显著减少[(4.5±2.9) *vs* (15.7±6.4)mL,P<0.05],大鼠72 h存活率由12.5%提升至25.0%(P<0.05)。与LR组相比,BA组大鼠血气相关指标包括Hb和PaO_2水平显著改善(P<0.05);肝、肾、肠血流量明显恢复(P<0.05),接近正常水平;心、肝、肾功能损伤也有所减轻,其中肌钙蛋白I(cardiac troponin I,cTnI)和谷丙转氨酶(alanine aminotransferase,ALT)的水平显著降低(P<0.05),但对肺脑含水量的影响无显著性差异。与LR组相比,BA组大鼠血清中的cTnI水平明显降低(P<0.05)。LR组大鼠心肌细胞的收缩幅度较UHS组有所恢复,但仅恢复至正常水平的25.8%,BA组大鼠心肌细胞的收缩幅度恢复至正常水平的54.6%(P<0.05)。与UHS组相比,LR组大鼠心肌组织中FFA和ATP水平无明显改善作用,BA组大鼠心肌FFA水平显著降低(P<0.05),ATP含量提高(P<0.05)。**结论** ACLY抑制剂BA能够有效延长非控制性失血性休克大鼠的黄金救治时间窗,其可通过改善机体氧合状态、恢复脏器血流灌注、提升心肌ATP含量以纠正能量代谢紊乱,减轻心肌及肝肾功能损伤,最终提高大鼠72 h存活率。

[**关键词**] 非控制性失血性休克;ATP-柠檬酸裂解酶;黄金救治时间窗;能量代谢

[**中图法分类号**] R322.11;R605.971;R972 [**文献标志码**] A

[**基金项目**] 国家自然科学基金重点项目(82430082)

[**通信作者**] 何海燕,E-mail:hehaiyan118@163.com

李 涛,E-mail:lt200132@tmmu.edu.cn

2097-0927/Copyright © 2026,陆军军医大学(第三军医大学)。这篇开放获取文章遵循CC BY许可协议(https://creativecommons.org/licenses/by/4.0/)

引用格式:张千威,周远群,向鑫明,等.ATP-柠檬酸裂解酶抑制剂贝派地酸通过调控心肌能量代谢延长非控制性失血性休克大鼠黄金救治时间窗[J].陆军军医大学学报,2026,48(17):2453-2464.DOI:10.16016/j.2097-0927.202604100.

Citation:Zhang Q W,Zhou Y Q,Xiang X M,*et al*.Bempedoic acid,an ATP-citrate lyase inhibitor,prolongs the golden therapeutic window *via* modulating myocardial energy metabolism in rats with uncontrolled hemorrhagic shock[J].J Army Med Univ,2026,48(17):2453-2464.DOI:10.16016/j.2097-0927.202604100.

Bempedoic acid, an ATP-citrate lyase inhibitor, prolongs the golden therapeutic window *via* modulating myocardial energy metabolism in rats with uncontrolled hemorrhagic shock

Zhang Qianwei[1], Zhou Yuanqun[2], Xiang Xinming[2], Hu Shiyu[3], Zeng Anqi[2,4], Ouyang Xingnan[2], Liu Liangming[2], Li Tao[2], He Haiyan[1] [1]Department of Nursing, [2]Department of Combat Shock and Transfusion, [4]Department of Anesthesiology, Daping Hospital, Army Medical University (Third Military Medical University), Chongqing; [3]School of Pharmacy and Bioengineering, Chongqing University of Technology, Chongqing, China

[**Abstract**] Objective ATP-citrate lyase (ACLY), a pivotal hub enzyme mediating the remodeling of cellular energy metabolism, and its specific inhibitor, bempedoic acid (BA), has been shown to exert multi-organ protective effects in models of ischemic injury and metabolic disorders. This study aims to determine whether BA could prolong the golden therapeutic window and exert multi-organ protection in a rat model of uncontrolled hemorrhagic shock (UHS), and to explore its underlying mechanisms. Methods A total of 208 SPF-grade SD rats (8 to 10 weeks old, weighing 180 to 220 g, half male and half female) were subjected. A rat UHS model was established by deep cutting the splenic parenchyma, with successful modeling defined as a mean arterial pressure (MAP) decrease to 40 mmHg. ①Forty-eight rats were randomly divided into a lactated Ringer's solution (LR) group, a 10 mg/kg BA group (10 mg/kg BA + LR), and a 20 mg/kg BA group (20 mg/kg BA+LR), with 16 animals in each group. Hypotensive resuscitation was initiated immediately after successful modeling to maintain MAP at 50 to 60 mmHg. Blood pressure profiles, blood loss rate, infusion volume, and duration of maintained hypotension were recorded. ② Ninety-six rats were randomly divided into (n=24): a Sham group, a UHS group, a LR group, and a BA group (20 mg/kg BA+LR). After successful modeling, the UHS group received no resuscitation, while the other 2 groups underwent immediate hypotensive resuscitation. In 1 h later, the splenic artery was ligated for definitive hemostasis, followed by definitive fluid therapy with LR equivalent to twice the total blood loss volume. Outcome measurements included survival status, blood gas parameters, hepatic, renal and intestinal blood perfusion, biomarkers of vital-organ injury, pulmonary and cerebral water contents, myocardial contractile function, as well as myocardial levels of free fatty acid (FFA) and adenosine triphosphate (ATP). Results ① In the LR group, MAP was stably maintained within 50 to 60 mmHg for approximately 60 min, whereas both 10 and 20 mg/kg BA combined with LR solution sustained the target blood pressure for more than 180 min. Compared with the LR group, the 20 mg/kg BA group exhibited a significantly lower blood loss rate (63.7%±12.8% *vs* 73.8%±4.4%, P<0.05) and reduced infusion volume [(6.8±4.9) *vs* (18.7±9.8) mL, P<0.05]. The mean duration of maintained hypotension in the LR group was (57±17) min, with a 1-hour maintenance rate of 68.8%, and all animals died within 80 min. The mean hypotension- maintenance durations were extended to (138±60) min in the 10 mg/kg BA group and (157±50) min in the 20 mg/kg BA group, with 3-hour maintenance rates of 50.0% and 68.7%, respectively. ② The blood loss rate in the LR group was markedly higher than that in the UHS group [(55.6%±6.3%) *vs* (48.4%±5.3%), P<0.05]. The BA group demonstrated a significantly lower blood loss rate compared with the LR group (47.2%±6.0%, P<0.05), along with a markedly reduced infusion volume [(4.5±2.9) *vs* (15.7±6.4) mL, P<0.05], and the 72-hour survival rate increased from 12.5% to 25.0% (P<0.05). Compared with the LR group, BA intervention resulted in significant improvements in blood gas parameters including hemoglobin (Hb) and arterial partial pressure of oxygen (PaO_2) (P<0.05), and restored hepatic, renal and intestinal blood perfusion close to normal levels (P<0.05). BA treatment also mitigated cardiac, hepatic and renal injuries, with significantly decreased levels of cardiac troponin I (cTnI) and alanine aminotransferase (ALT) (P<0.05), while no significant difference was observed in pulmonary and cerebral water contents. Serum cTnI levels were significantly lower in the BA group than the LR group (P<0.05). Cardiomyocyte contraction amplitude in the LR group recovered to only 25.8% of the normal level, whereas BA treatment restored it to 54.6% of normal (P<0.05). Compared with the UHS group, the LR group showed no significant

improvement in myocardial tissue FFA and ATP levels, whereas the BA group exhibited significantly decreased myocardial FFA levels and increased ATP content (both $P<0.05$). **Conclusion** The ACLY inhibitor BA effectively prolongs the golden therapeutic window in UHS rats. Its mechanism may be related to improving systemic oxygenation, restoring visceral perfusion, and enhancing myocardial ATP content to reverse energy metabolic disturbance, thereby alleviating myocardial and hepatic-renal function injuries and ultimately improving the 72-hour survival rate.

[**Key words**] uncontrolled hemorrhagic shock; ATP-citrate lyase; golden therapeutic window; energy metabolism

Supported by the Key Program of National Natural Science Foundation of China (82430082). Corresponding authors: He Haiyan, E-mail: hehaiyan118@163.com; Li Tao, E-mail: lt200132@tmmu.edu.cn

非控制性失血性休克(uncontrolled hemorrhagic shock,UHS)是严重创伤后早期死亡的主要原因,相关死亡占创伤早期死亡的50%左右[1]。液体复苏是失血性休克早期救治(即院前急救阶段)的关键措施,允许性低压复苏、延迟复苏等复苏策略的应用,在一定程度上提升了失血性休克的早期救治水平[2-4]。现有的研究表明,在休克发生后的1 h内,进行早期复苏和止血治疗是挽救生命的关键,这一时间被称为"黄金1小时"救治时间窗。一旦超过此时间窗,即使成功复苏,也难以逆转线粒体功能障碍、多器官功能衰竭综合征(multiple organ dysfunction syndrome,MODS)及高乳酸血症,导致病死率急剧上升。然而,在偏远及复杂地区,伤员往往无法在1 h内转运至有能力救治的医院获得院内治疗。目前常用的复苏液体如乳酸林格液(lactated Ringer's solution,LR)等低压维持时间较短,不支持长时程后送转运,无法为后续院内治疗赢得时间[5]。此外,现有救治策略多侧重于循环容量的补充,缺乏对休克状态下机体代谢紊乱的调控,这在很大程度上限制了复苏效果。因此,探索新的治疗策略以延长失血性休克患者的黄金救治时间窗并提高复苏效果,具有重要意义。

研究表明,在失血性休克的代谢病理进程中,组织ATP耗竭和底物利用障碍处于核心地位[6-7]。休克引发的持续组织低灌注与缺氧状态,可导致细胞线粒体功能受损、氧化磷酸化过程受阻,进而造成能量生成严重不足、代谢紊乱,并最终诱发细胞损伤与多器官功能障碍[8]。ATP-柠檬酸裂解酶(ATP-citrate lyase,ACLY)是连接线粒体三羧酸循环与细胞质代谢的关键枢纽酶,其主要功能是将线粒体产生的柠檬酸转运至细胞质后催化裂解为乙酰辅酶A和草酰乙酸。乙酰辅酶A不仅是脂肪酸和胆固醇合成的必需前体,还是组蛋白及非组蛋白乙酰化修饰的重要供体,通过表观遗传调控方式影响基因的转录,从而调控多种细胞功能。因此,ACLY在协调能量代谢与表观遗传调控中发挥关键作用,其活性变化可能深刻影响应激状态(如缺血-再灌注或休克)下细胞的存活与损伤走向[9]。有研究发现,脓毒症患者血浆ACLY水平与其血管内皮损伤指标和炎症水平呈正相关,ACLY抑制剂贝派地酸(bempedoic acid,BA)可通过调控糖脂代谢显著改善肺、肾、肝的病理损伤[10-11]。但BA能否干预休克诱导的全身代谢紊乱、缓解脏器损伤,尚无相关实验佐证。

本课题组前期预实验证实,失血性休克模型大鼠心肌ACLY表达水平显著上调。因此,本研究通过建立非控制性失血性休克大鼠模型,观察ACLY抑制剂BA对休克大鼠低压维持时间、失血率、输液量、血气指标、重要器官功能以及大鼠存活的影响,旨在为失血性休克院前低压复苏提供新型代谢干预方案。

1 材料与方法

1.1 实验动物与药物试剂

208只8~10周龄的成年SPF级SD大鼠,体质量180 g~220 g,雌雄各半,由陆军特色医学中心实验动物中心提供。动物许可证号:SCXK(渝)2022-0011。本研究方案已获陆军军医大学实验动物福利伦理审查委员会批准(AMUWEC-2023-0290)。所有大鼠饲养于温度22~24 ℃、相对湿度50%~60%、每12小时光照/黑暗交替的环境下,自由摄食、饮水。实验操作全程遵循3R原则[12],以减少动物痛苦。当大鼠持续平均动脉血压(mean arterial pressure,MAP)<20 mmHg、自主活动完全消失、口唇四肢发绀、大量腹腔活动性出血无法控制任一出现时,即实施安乐死。本研究全程无动物意外死亡、切口感染、额外创伤等不良实验事件发生。

BA购自美国MCE公司(HY-12357),规格1 g;LR购自四川美大康华康药业股份有限公司(H20043897);肝素钠注射液购自常州千红生化制药股份有限公司(H32022088),规格2 mL∶12 500 U;ATP检测试剂盒(S0026)和FFA检测试剂盒(S0215M)购自上海碧云天生物技术有限公司。

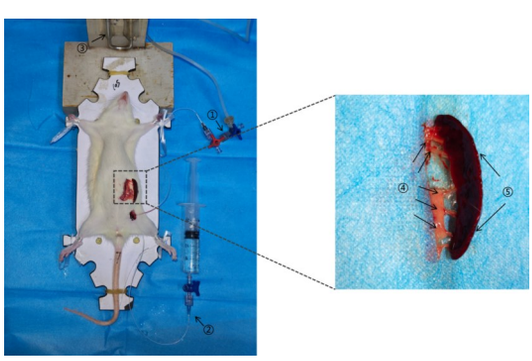
1.2 心肌细胞收缩检测实验相关溶液配制

无钙台氏液:NaCl 137 mmol/L、KCl 5.4 mmol/L、

NaH_2PO_4 1.2 mmol/L、$MgCl_2$ 1.2 mmol/L、HEPES 3.3 mmol/L、Glucose 11 mmol/L,NaOH调节pH至7.3~7.4;含钙台氏液:在无钙台氏液中加入$CaCl_2$ 1.8 mmol/L,NaOH调节pH至7.3~7.4;KB液:L-Glutamic acid 120 mmol/L、KOH 120 mmol/L、KCl 110 mmol/L、KH_2PO_4 10 mmol/L、Taurine 10 mmol/L、$MgSO_4 \cdot 7H_2O$ 1.8 mmol/L、K-EGTA 0.5 mmol/L、HEPES 10 mmol/L、Glucose 20 mmol/L、BSA 0.2%,KOH调节pH=7.2;消化液:无钙台氏液40 mL、Ⅱ型胶原酶24 mg、BSA 40 mg。

1.3 脾脏纵深切口法构建非控制性失血性休克大鼠模型

采用本实验室常规方法建立非控制性失血性休克模型[13]:SD大鼠术前禁食12 h,自由饮水,腹腔内注射3%戊巴比妥钠0.3 mL进行麻醉,仰卧固定动物,于大鼠左侧股动脉、股静脉插管,用于采血、监测MAP和输液。插管完成后注入100 U肝素钠,稳定15 min。沿腹正中线切开腹腔并暴露脾脏,于脾脏第2、3支与第4、5支脾动脉分支间行脾脏纵深切口(图1),使血液在非控制情况下自由流入腹腔,30~40 min后,大鼠MAP降至40 mmHg时即造模成功。若大鼠MAP无法自主降至40 mmHg,则经股动脉导管进行匀速控制性放血,直至MAP降至40 mmHg。假手术组不做脾脏深切口,其他操作同模型组。



① Femoral artery blood pressure monitoring catheter; ② Femoral vein fluid infusion catheter; ③ Mercury sphygmomanometer; ④ The 1st-5th branches of the splenic artery; ⑤ Deep cutting of the spleen

图1 非控制性失血性休克大鼠模型手术效果示意图

Figure 1 Surgical schematic diagram of rat model of uncontrolled hemorrhagic shock (UHS)

1.4 实验分组与复苏方案

实验分为2部分。第一部分,将48只SD大鼠按简单随机抽样法分为(n=16):LR组、10 mg/kg BA组(10 mg/kg BA+LR)和20 mg/kg BA组(20 mg/kg BA+LR)。造模成功后,各组大鼠立即用相应液体进行低压复苏,输液速度为25 mL/h,维持血压至50~60 mmHg(若血压稳定维持在目标区间时暂停输液,血压下降则恢复输液)。LR组大鼠用LR进行低压复苏;BA组分别用10 mg/kg、20 mg/kg BA加入5 mL的LR中进行低压复苏(若5 mL液体输注完,后续维持用单纯LR)。观察各组大鼠低压维持时间、输液量和失血量,以明确BA是否能延长休克大鼠的黄金救治时间窗。第二部分,将96只SD大鼠按简单随机抽样法分为(n=24):Sham组、UHS组、LR组、BA组(20 mg/kg BA+LR复苏)。同前造模成功后(记为休克期末,Phase Ⅰ),UHS组不进行复苏。LR组和BA组立即用相应液体进行低压复苏,输液速度和方式同前。低压复苏至1 h(记为低压复苏期末,Phase Ⅱ),结扎脾动脉分支阻断活动性出血,用无菌脱脂棉球充分吸附腹腔内积血并统一收集称重计算失血量,记录输液量。随后,补足2倍失血量的LR进行确定性治疗(输液完成记为彻底复苏期末,Phase Ⅲ),输液速度为25 mL/h。2 h后进行器官功能等指标检测(n=8)。在存活实验中,分组、造模及给药同前(n=16),UHS组不进行复苏,观察自然死亡率;LR组和BA组在彻底复苏完成后,结扎股动、静脉,放回饲养笼,观察72 h存活情况。存活观察结束后,大鼠腹腔注射过量戊巴比妥钠以安乐死。以明确BA低压复苏1 h对休克大鼠重要器官功能的保护作用。

1.5 指标检测方法与仪器

1.5.1 称重法检测大鼠失血量 称量收集血液的容器和无菌棉球的初始质量,在低压复苏结束后收集大鼠腹腔内血液,再次称重二者差值即为血液的净重量,按血液密度1.05 g/mL换算,即可得出失血量的毫升数,加上控制性放血量即为总失血量,计算失血率,失血率(%)=总失血量÷(体质量×7%)×100%。

1.5.2 全自动血气分析仪测定动脉血气指标 分别于造模前(Baseline)、休克期末(Phase Ⅰ)、低压复苏期末(Phase Ⅱ)及彻底复苏期末(Phase Ⅲ)经大鼠腹主动脉采集各组大鼠动脉血0.5 mL,使用GEM3500型全自动血气分析仪测定血气指标,包括pH、Hb、Lac、PaO_2、$PaCO_2$、SO_2。

1.5.3 激光多普勒血流监测仪测定肝肾肠血流量 在彻底复苏完成后,剪开大鼠腹部,充分暴露大鼠肝脏、肾脏及肠道组织,使用激光多普勒血流监测仪对各组大鼠上述器官进行血流成像分析。仪器配套的数据分析软件可直接输出监测期内(2~3 min)微血流动力学参数数值,选取较平稳时段(1 min)的均数进行统计学分析。相对血流量(%)=(UHS组平均血流量÷Sham组平均血流量)×100%。

1.5.4 生化分析仪测定心功cTnI、肝功AST、ALT和肾功Urea和Crea 于血流量测定结束后,经大鼠腹主动脉取各组大鼠全血,3 000×g、25 ℃离心10 min,取血清,使用生化分析仪测定其心损指标cTnI、肝脏功能损伤指标AST和ALT以及肾脏功能损伤Urea和Crea。

1.5.5　细胞微张力仪检测心肌细胞收缩功能　　采血后,取大鼠心脏组织,按照本实验室前期研究的方法[14],采用Langendorff灌流系统制备单个心肌细胞,并用浓度梯度法复钙,最后将细胞重悬于1 mL含钙台氏液中。取50 μL上述心肌细胞悬液于细胞微张力仪(美国IonOptix LLC)的刺激浴槽中,加入含钙台氏液至淹没刺激电极。显微镜下找到收缩正常、肌节较清晰的单个心肌细胞,置于视野中央,调整光圈大小至孔径只包含一个心肌细胞,以减少运动伪影的干扰。以心肌细胞肌节收缩幅度反映收缩能力,收缩幅度(%)=(静息肌节长度-收缩末肌节长度)÷静息肌节长度×100%。肌节长度标准化为每组静息肌节平均长度,其余肌节长度除以其平均值。相对收缩幅度(%)=处理组收缩幅度÷正常组收缩幅度×100%。

1.5.6　烘干称重法检测肺脑含水率　　提取大鼠心肌组织后,取各组大鼠肺组织和脑组织,清理表面血迹后称重,记为湿重;将肺、脑组织置于55 ℃恒温烘箱持续烘烤72 h后再次称重,记为干重。脑、肺含水率的计算方法为:含水率(%)=[(湿重-干重)÷湿重]×100%。

1.5.7　试剂盒检测心肌组织FFA和ATP含量　　取各组大鼠心肌组织,严格参照对应游离脂肪酸(free fatty acid,FFA)、ATP检测试剂盒配套说明书完成心肌组织样本前处理与指标定量检测。

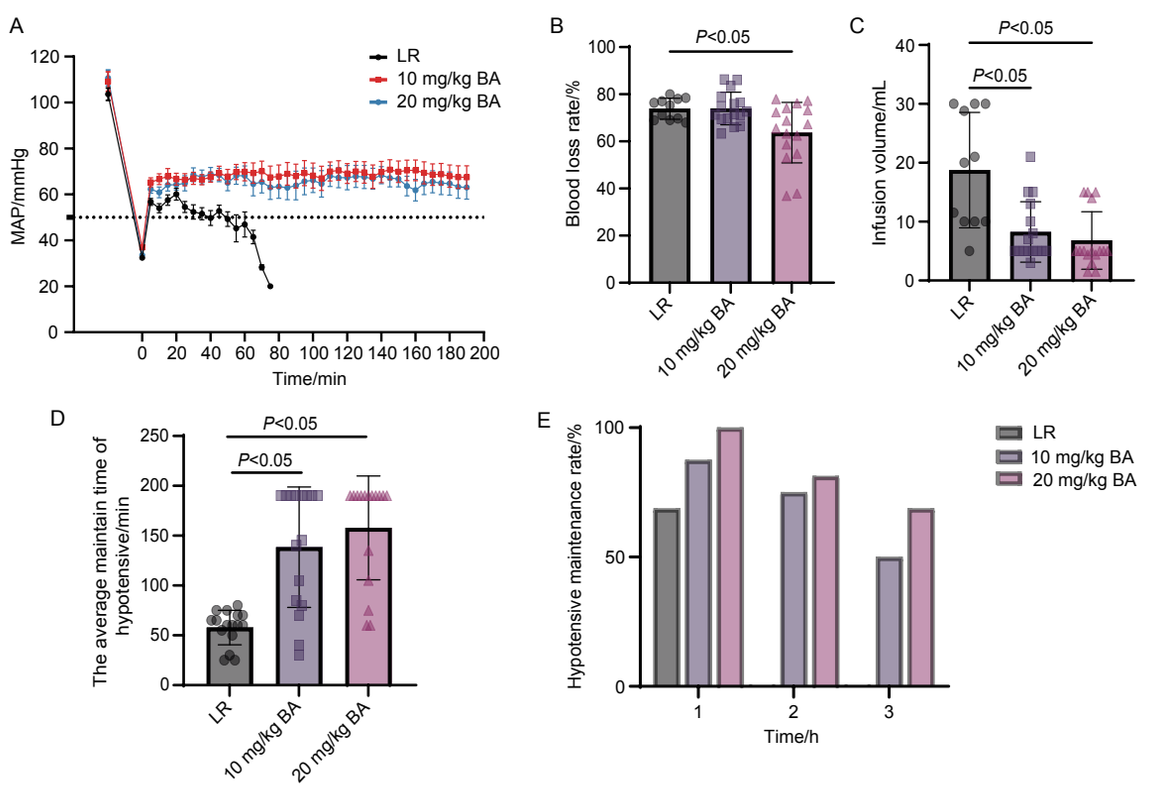
1.6　统计学分析

采用GraphPad Prism 9.5统计软件分析。数据均以$\bar{x}\pm s$描述,多组间比较采用单因素方差分析,涉及多因素时的组间比较采用双因素方差分析,生存分析采用Kaplan-Meier法绘制生存曲线,组间比较采用Log-rank检验。$P<0.05$表示差异具有统计学意义。

2　结果

2.1　BA联合LR复苏延长休克大鼠黄金救治时间

2.1.1　BA联合LR低压复苏可以长时间维持休克大鼠的MAP　　大鼠初始血压水平为(107±13)mmHg。造模后,大鼠血压降至40 mmHg。采用LR或LR+BA进行低压复苏,但不进行止血处理。结果发现,单纯LR复苏能使MAP在50~60 mmHg维持约60 min,随后MAP开始下降。80 min后,LR组大鼠血压降至20 mmHg。10 mg/kg BA和20 mg/kg BA联合LR应用,均可使MAP在50~60 mmHg稳定维持180 min以上(图2A),提示BA联合LR应用能够更长时间维持低压复苏。



A: Time-course changes in MAP during hypotensive resuscitation. The dotted line represents the target hypotensive level; B: Comparison of blood loss rate across groups; C: Comparison of total infusion volume during the resuscitation period; D: Average duration of hypotensive resuscitation in each group; E: Proportion of rats maintaining target hypotension at 1, 2 and 3 h after resuscitation initiation

图2　BA联合LR复苏对休克大鼠MAP、失血率和输液量的影响(n=16,$\bar{x}\pm s$)

Figure 2　Effects of bempedoic acid (BA) combined with lactated Ringer's (LR) resuscitation on mean arterial pressure (MAP), blood loss rate and infusion volume in hemorrhagic shock rats(n=16,$\bar{x}\pm s$)

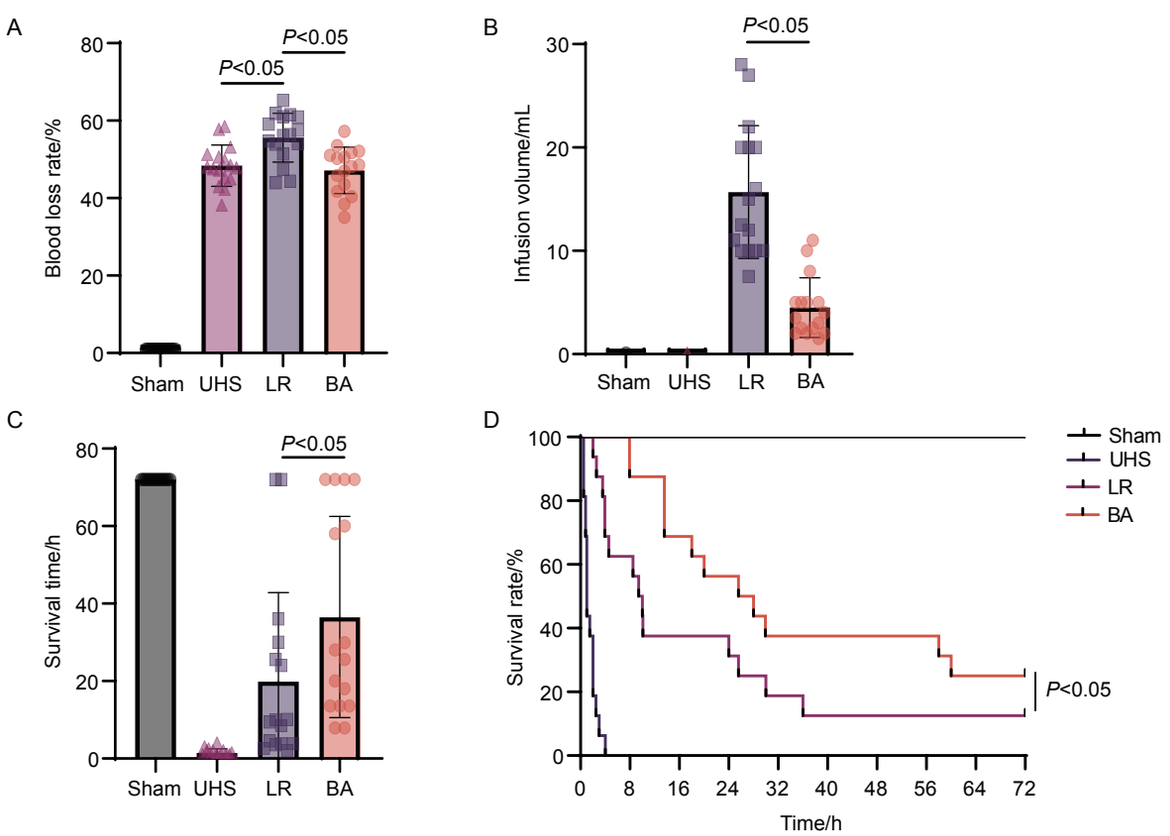
2.1.2　BA联合LR低压复苏显著降低大鼠失血率并减少输液量　　LR组失血率为73.8%±4.4%。与LR组相比，10 mg/kg BA组失血率无明显差异，而20 mg/kg BA组失血率显著降低至63.7%±12.8%（P<0.05，图2B）。同时，LR组输液量为（18.7±9.8）mL，10 mg/kg组和20 mg/kg BA组液体输注量较LR组均显著降低，分别为（8.2±5.1）mL和（6.8±4.9）mL（P<0.05，图2C）。

2.1.3　BA联合LR低压复苏明显延长休克大鼠的低压维持时间　　LR组休克大鼠的平均低压维持时间为（57±17）min，低压维持至1 h后有11只大鼠可维持目标血压，维持率为68.8%（11/16）。所有大鼠在80 min内全部死亡。与LR组相比，10 mg/kg BA组与20 mg/kg BA组大鼠的平均低血压维持时间显著延长，分别为（138±60）min和（157±50）min。在低压维持1 h时间点，2组大鼠的维持率分别达到87.5%（14/16）与100.0%（16/16）。在10 mg/kg BA组中，75.0%（12/16）的大鼠低压维持时长超过2 h，50.0%（8/16）超过3 h；在20 mg/kg BA组中，81.2%（13/16）大鼠低压维持时长超过2 h，68.7%（11/16）超过3 h（图2D、E）。这些结果表明，BA联合LR低压复苏可以明显延长休克大鼠的黄金救治时间。其中，20 mg/kg BA的效果更好。因此，后续实验采用20 mg/kg的剂量。

2.2　BA联合LR低压复苏1 h对休克大鼠的保护作用

2.2.1　BA联合LR低压复苏1 h降低休克大鼠的失血率并减少输液量　　大鼠造模成功后，立即采用LR或BA联合LR进行低压复苏。复苏1 h后，结扎脾动脉止血并进行确定性治疗。UHS组未进行复苏，失血率为48.4%±5.3%。与UHS组相比，LR组失血率明显升高，为55.6%±6.3%。BA组失血率较LR组显著降低，为47.2%±6.0%（P<0.05，图3A）。同时，LR组输液量为（15.7±6.4）mL，BA组液体输注量较LR组显著减少，为（4.5±2.9）mL（P<0.05，图3B）。

2.2.2　BA联合LR低压复苏1 h延长休克大鼠存活时间并提升72 h存活率　　UHS组大鼠平均存活时间为（1.5±1.0）h，所有大鼠在4 h内死亡。LR组大鼠的平均存活时间为（19.9±23.2）h，72 h存活率仅为12.5%（2/16）。BA组大鼠的平均存活时间延长至（36.5±25.0）h（P<0.05，图3C），其72 h存活率为25.0%（4/16，



A: Blood loss rate in each group; B: Total infusion volume during resuscitation; C: Survival time of rats in each group ; D: Kaplan-Meier survival curves showing the probability of survival over 72 h post-resuscitation

图3　BA对休克大鼠彻底止血复苏后失血量、输液量和存活时间的影响（n=16，$\bar{x}\pm s$）

Figure 3　Effects of BA on blood loss, infusion volume and survival time in hemorrhagic shock rats after definitive hemostasis and resuscitation（n=16，$\bar{x}\pm s$）

P<0.05,图3D)。

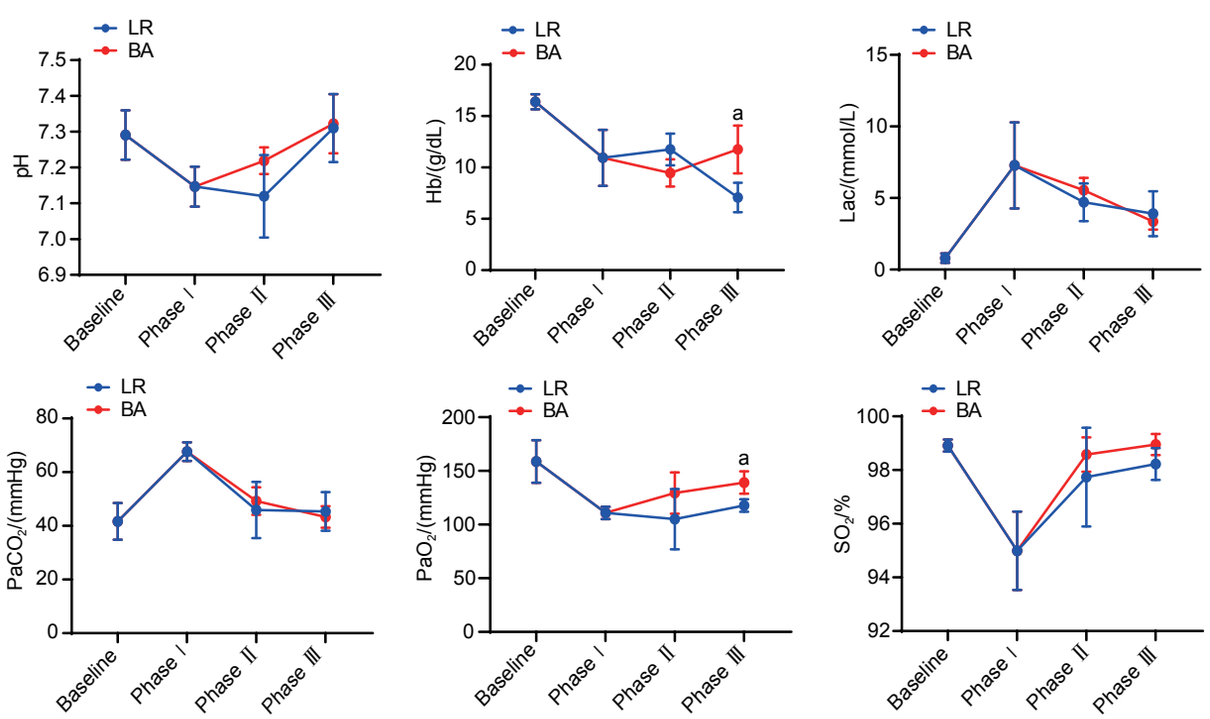
2.2.3　BA联合LR低压复苏1 h显著改善休克大鼠的血气指标　　与造模前相比,大鼠休克期末的pH、Hb、PaO_2、SO_2均降低,而Lac和$PaCO_2$增加。应用LR或BA联合LR均可以改善休克大鼠pH、Lac、$PaCO_2$、SO_2指标,但2组没有统计学差异。与LR组相比,BA组休克大鼠的Hb和PaO_2水平增加(P<0.05,图4)。

2.2.4　BA联合LR低压复苏1 h改善休克大鼠的肝、肾、肠血流量　　UHS组大鼠肝、肾、肠道的血流灌注明显减弱,各脏器高血流红色区域范围较Sham组显著缩小;LR组和BA组肝、肾、肠的血流灌注情况明显改善(图5A)。定量分析结果显示,UHS组大鼠肝脏血流量仅为正常水平的36.9%,LR组大鼠肝脏血流量提升至(162.7±26.5)U/min,而BA组大鼠肝脏血流量提升至(212.6±25.3)U/min,接近正常水平(图5B)。UHS组大鼠肾脏血流量为正常水平的11.6%,LR组大鼠和BA组大鼠肾脏血流量分别提升至(154.0±46.1)U/min和(233.9±67.1)U/min(图5C)。UHS组大鼠的肠道血流量为正常水平的18.1%,LR组大鼠和BA组大鼠肠道血流量分别提升至(42.2±8.6)U/min和(71.8±19.3)U/min(图5D)。BA联合LR复苏对休克大鼠肝、肾、肠血流量的改善作用均明显优于单纯LR复苏(P<0.05)。

2.2.5　BA联合LR低压复苏1 h改善休克大鼠的肝脏和肾脏功能　　与Sham组相比,UHS大鼠的肝脏功能损伤指标AST、ALT显著升高(P<0.05,图6A、B)。LR组和BA组大鼠血清中AST的水平没有显著改变(图6A)。与UHS组相比,LR组大鼠血清中的ALT水平显著降低(P<0.05),而BA组大鼠血清中ALT的水平较LR组进一步降低(P<0.05,图6B)。与Sham组相比,UHS组大鼠的肾脏功能损伤指标UREA和CREA水平显著升高(P<0.05,图6C、D)。BA组大鼠UREA和CREA水平有一定下降,但无统计学差异。

2.2.6　BA联合LR复苏1 h不影响休克大鼠的肺、脑含水量　　相较于Sham组,UHS组大鼠肺、脑含水率显著升高(P<0.05,图7)。LR组和BA组大鼠肺、脑组织含水量均轻度降低,但各组间差异无统计学意义。

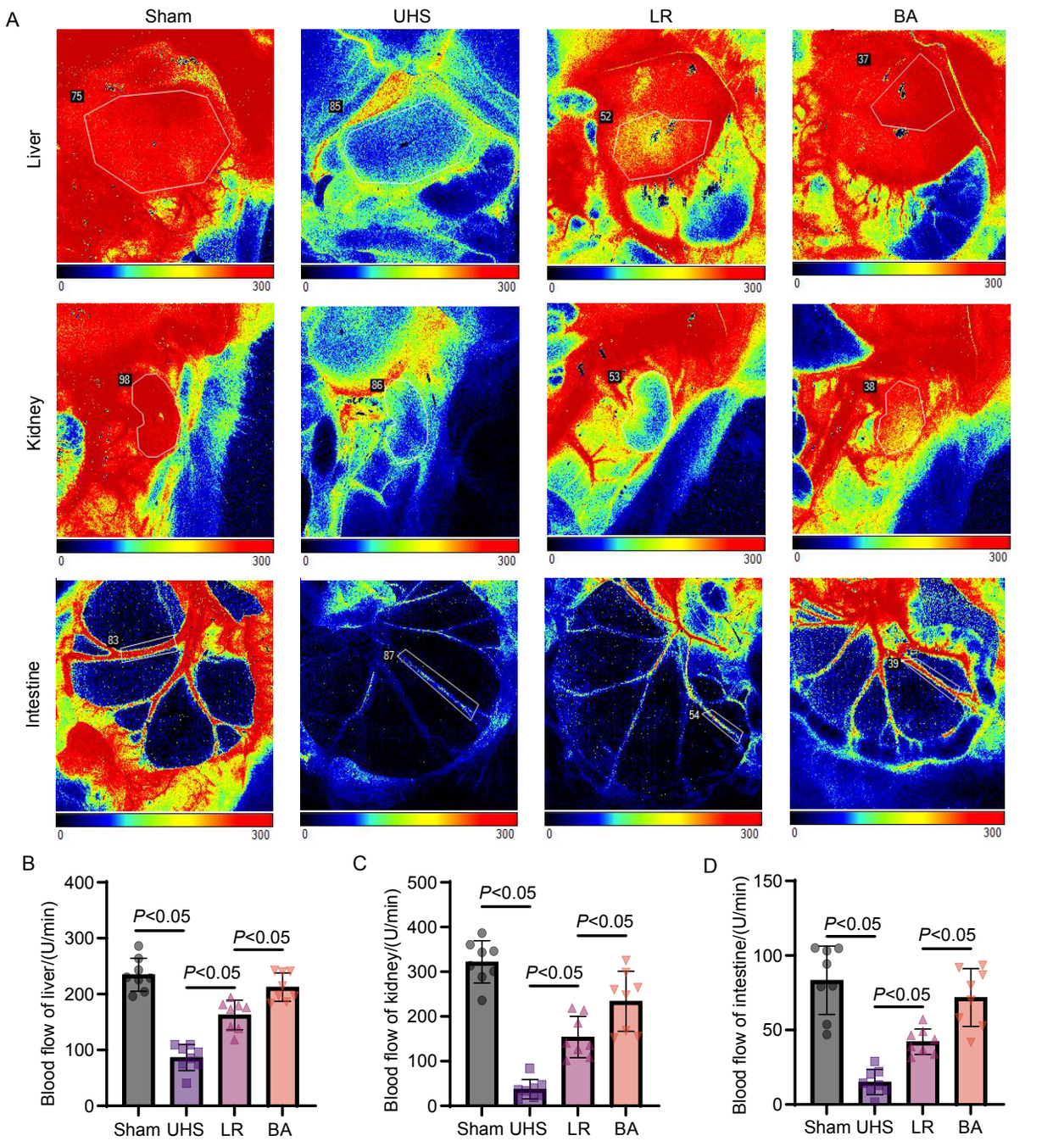
2.2.7　BA联合LR复苏1 h改善休克大鼠的心脏功能、降低心肌FFA水平并提升心肌ATP含量　　与Sham组相比,UHS组大鼠血清中的心肌损伤标志物cTnI的水平显著升高,表明心脏功能明显损伤,LR组大鼠cTnI的水平反而使其升高。与LR组相比,BA组



Baseline: Before modeling; Phase Ⅰ: After successful modeling; Phase Ⅱ: End of hypotensive resuscitation; Phase Ⅲ: End of definitive resuscitation. pH: potential of hydrogen; Hb: hemoglobin; Lac: lactic acid; PaO_2: arterial partial pressure of oxygen; $PaCO_2$: arterial partial pressure of carbon dioxide; SO_2: arterial oxygen saturation. a: P<0.05, compared with LR

图4　BA对休克大鼠不同复苏阶段动脉血气指标的影响(n=8,$\bar{x}\pm s$)

Figure 4　Effects of BA on arterial blood gas parameters at different resuscitation stages in hemorrhagic shock rats(n=8,$\bar{x}\pm s$)



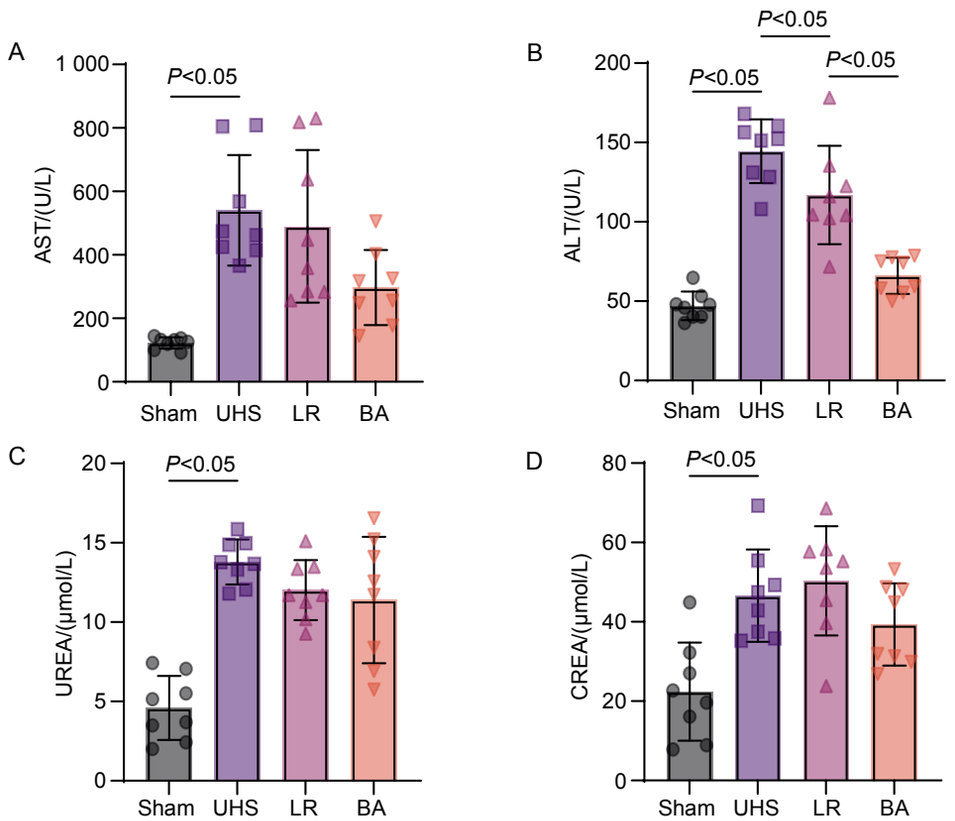
A: Representative laser speckle contrast images (LSCI) of liver, kidney, and intestinal microperfusion in each group. The color scale bar (0 to 300 U) represents blood flow intensity, with red indicating high perfusion and blue indicating low perfusion; B to D: Quantitative analyses of blood flow in the liver (B), kidneys (C), and intestine (D)

图5 BA对休克大鼠肝、肾和肠血流量的影响(n=8,$\bar{x}\pm s$)

Figure 5 Effects of BA on hepatic, renal and intestinal blood flow in hemorrhagic shock rats (n=8,$\bar{x}\pm s$)

大鼠血清中的cTnI水平显著降低(P<0.05,图8A),表明BA应用可以明显减轻休克导致的心肌损伤。

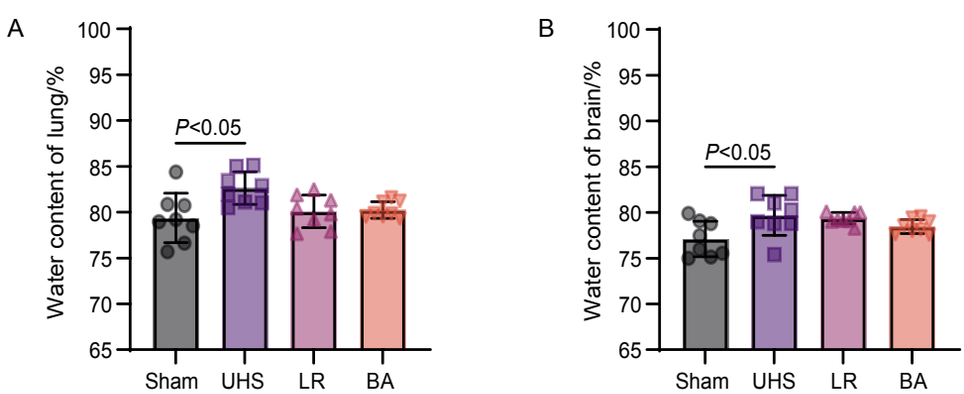
为进一步观察BA对休克大鼠心脏功能的改善作用,分离心肌细胞并采用细胞微张力仪检测单个心肌细胞的收缩功能变化。结果显示,与Sham组相比,UHS组大鼠心肌细胞的收缩幅度显著下降,下降了89.4%,LR组大鼠心肌细胞的收缩幅度较UHS组有所恢复,但仅恢复至正常水平的25.8%(P<0.05),而BA组大鼠心肌细胞的收缩幅度恢复至正常水平的54.6%(P<0.05,图8B、C)。同时,UHS组大鼠心肌细胞的最大收缩速度和最大舒张速度较正常组均显著减慢,BA组大鼠心肌细胞的最大收缩速度和最大舒



A to D: Serum levels of aspartate aminotransferase (AST, A), alanine aminotransferase (ALT, B), urea (UREA, C) and creatinine (CREA, D)

图6 BA对休克大鼠肝肾功能的影响(n=8,$\bar{x}\pm s$)

Figure 6 Effects of BA on liver and kidney functions in UHS rats (n=8,$\bar{x}\pm s$)



A and B: Tissue water contents in the lung (A) and brain (B) in each group

图7 BA对休克大鼠肺脑含水量的影响(n=8,$\bar{x}\pm s$)

Figure 7 Effects of BA on pulmonary and cerebral water contents in UHS rats (n=8,$\bar{x}\pm s$)

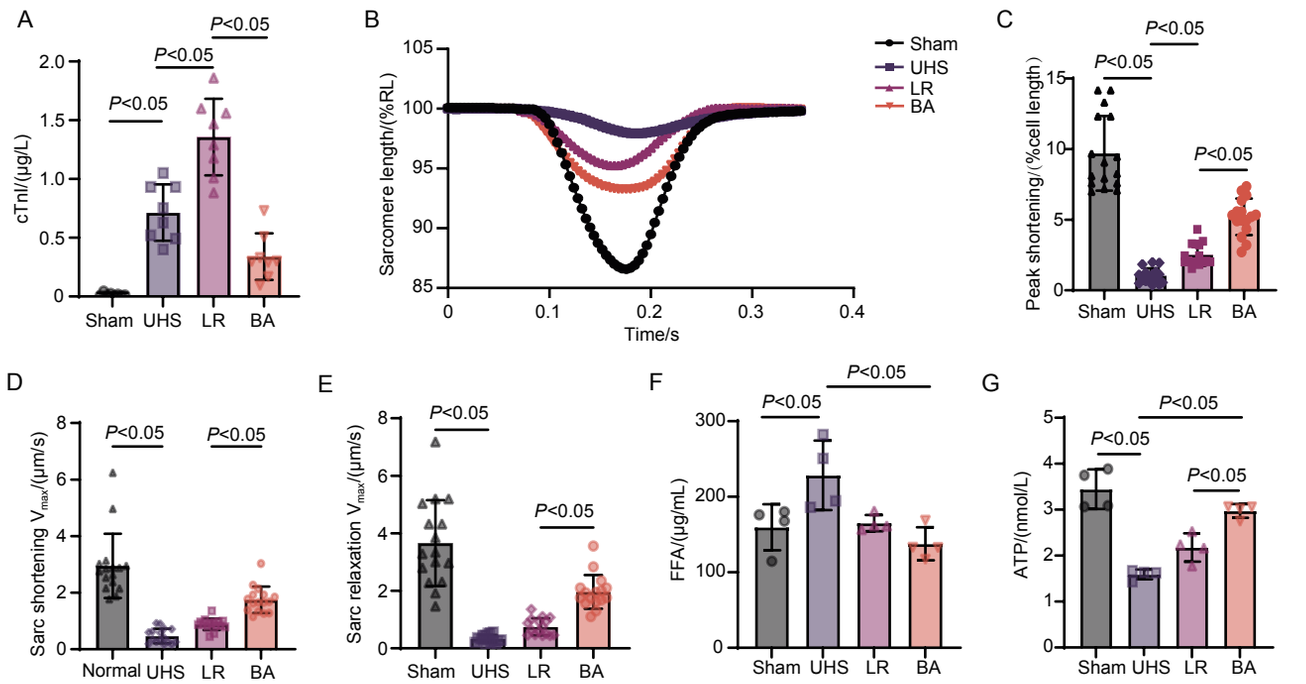
张速度较LR组明显提升(P<0.05,图8D、E)。这些结果表明BA可显著改善休克大鼠心脏的收缩功能。

与Sham组相比,UHS组大鼠心肌组织中FFA水平显著升高,ATP水平显著降低(P<0.05),单纯LR复苏对心肌FFA、ATP含量均无明显调控作用。与UHS组相比,BA联合LR干预后,可显著下调心肌FFA水平、提升ATP含量(P<0.05,图8F、G)。

3 讨论

3.1 BA可有效延长非控制性失血性休克的黄金救治时间窗

UHS是创伤致死的首要原因,其早期救治面临的核心难题在于:在确定性手术止血之前,有限的"黄金1小时"救治时间窗与长时程转运需求之间存在根本



A: Serum cardiac troponin I (cTnI) levels; B: Sarcomere length changes in acutely isolated single cardiomyocytes under continuous electrical stimulation; C: Sarcomere contraction amplitude in acutely isolated single cardiomyocytes; D: Maximum sarcomere shortening velocity in acutely isolated single cardiomyocytes; E: Maximum sarcomere relaxation velocity in acutely isolated single cardiomyocytes; F: Myocardial free fatty acid (FFA) levels; G: Myocardial adenosine triphosphate (ATP) levels

图8 BA对休克大鼠心肌收缩功能、心肌损伤及心肌组织FFA和ATP的影响(n=16,$\bar{x}\pm s$)

Figure 8 Effects of BA on cardiomyocyte contraction function, myocardial injury, and FFA and ATP levels in myocardial tissues of UHS rats (n=16,$\bar{x}\pm s$)

性矛盾。在偏远地区或大规模伤亡事件中,转运时间往往超过1 h,现有院前急救阶段的常用液体复苏策略难以维持患者生命体征直至到达确定性医疗中心[15]。此外,大量液体复苏常诱发稀释性凝血病与再灌注损伤,进一步加重患者伤情,反而缩短了伤员等待确定性手术止血治疗的窗口期[16-17]。本研究通过建立非控制性失血性休克动物模型,评估了BA联合LR进行低压复苏对血压的维持效果,结果显示,该策略能将有效低压维持时长从单纯LR复苏的60 min显著延长至180 min以上,同时减少了液体输注总量与继发性失血量。这一发现意味着可能将院前救治的"黄金时间窗"由1 h扩展至3 h,为偏远地区、复杂灾害救援条件下的伤员争取更多后送时间与手术机会。

3.2 BA通过改善循环与氧合状态,协同限制性低压复苏显著提升复苏效果

限制性低压复苏旨在通过维持较低的MAP(通常为50~60 mmHg),避免冲脱尚未形成的血栓,同时保证心、脑等重要器官的最低灌注[18]。然而,单纯的限制性液体复苏在长时间转运中面临代偿失效的风险,根本原因在于其仅依靠扩容维持组织灌注,易引发血液稀释、血氧携带能力下降,继而造成内脏微循环持续低灌注,难以遏制休克进展[19]。本研究发现,在常规晶体液低压复苏基础上联用BA能够显著提升血红蛋白水平与动脉血氧分压,优化全身氧合供给;同时有效提升肝、肾、肠道等脏器的微循环血流量,逆转重要器官灌注不足的局面。循环稳定性的提升可减少活动性出血,避免容量超负荷带来的二次损伤,最终减轻器官功能损害,提高休克动物短期生存率。乳酸林格氏液作为平衡盐溶液,相较于生理盐水具有更佳的酸碱平衡维持能力,但其单独使用无法解决代谢根源问题[20]。BA与LR的联合,实现了"物理容量限制"与"生物代谢调控"的良好互补:LR提供基础的离子平衡和微量容量支持,而BA则从细胞层面提升了组织对低灌注和低氧的耐受阈值。这种协同效应不仅减少了继发性出血量,还降低了因大量输液引起的腹腔间隔室综合征和呼吸功能障碍风险。综合来看,相较于仅依靠补液的传统复苏方案,BA联合LR低压复苏干预可有效改善其复苏效果受限的问题,兼顾循环稳定、氧合改善与出血控制,弥补了传统液体复苏只扩容、不纠正内环境紊乱的短板,是一种具备临床转化

潜力的理想复苏措施。

3.3 BA调控能量代谢、恢复能量供应是脏器保护的核心机制

传统观点认为,休克早期的循环衰竭主要源于血容量不足,因此治疗重点在于快速补充晶体液以恢复血压[21]。然而,现代病理生理学研究表明,休克本质上是细胞代谢危机,即组织氧气输送无法满足代谢需求,导致细胞转向无氧糖酵解并产生大量乳酸[22]。ACLY作为连接三羧酸循环与脂质合成、表观遗传修饰的关键节点酶,正常状态下负责将线粒体产生的柠檬酸裂解为胞质内的乙酰辅酶A。在缺血缺氧应激下,ACLY过度激活可能加剧代谢紊乱和炎症反应。本研究中使用的ACLY抑制剂BA,其作用机制并非直接提升血压,而是通过阻断ACLY介导的代谢通路,调控糖脂代谢、改善线粒体呼吸功能、维持细胞能量稳态、抑制细胞过度炎症反应,从而发挥多器官保护效应[23-24]。有研究发现,在脑缺血再灌注损伤中,抑制ACLY能够减少氧化应激并增强线粒体功能[25-26]。在本研究的UHS模型中,BA干预可以显著降低心脏FFA水平,提高ATP生成。这可能源于BA抑制了过度的糖酵解通量和脂质合成需求,从而减轻低氧环境下细胞的代谢负担,延长细胞在低灌注状态下的存活时间[27-28]。这种“代谢休眠”或“代谢保护”效应,使机体能够在更低的血压水平下维持基本器官功能,也为BA联合LR低压复苏能在极低液体输入下维持长达180 min的循环稳定提供了合理解释。

3.4 研究局限性与后续研究展望

本研究仍存在一定的局限性:首先,本研究仅证实BA可改善心肌能量代谢与收缩功能,BA调控ACLY介导的心肌线粒体修复、脂代谢重编程的上下游分子通路,仍需进一步验证;其次,BA联合LR早期应用的救治效果仍需通过大动物实验或临床研究继续验证;最后,因实验设计限制,暂未设置更长观察周期,无法评价BA对失血性休克大鼠长期存活的作用。

综上所述,ACLY抑制剂贝派地酸可通过恢复ATP生成,改善重要器官功能,延长非控制性失血性休克的黄金救治时间窗。

利益冲突 本文所有作者声明不存在利益冲突

参考文献:

[1] 刘良明. 战创伤休克早期救治研究进展与思考[J]. 陆军军医大学学报, 2022, 44(20): 2025-2029. DOI: 10.16016/j.2097-0927.202205151.
Liu L M. Advances and thinking for early treatment of war wound and traumatic shock[J]. J Army Med Univ, 2022, 44(20): 2025-2029. DOI: 10.16016/j.2097-0927.202205151.

[2] Chi Y F, Jiang X, Chai J K, *et al*. Protective effect of restrictive resuscitation on vascular endothelial glycocalyx in pigs with traumatic hemorrhagic shock[J]. Ann Transl Med, 2022, 10(4): 177. DOI: 10.21037/atm-21-7004.

[3] 刘良明. 创伤失血性休克早期救治规范解读[J]. 创伤外科杂志, 2017, 19(12): 884-887. DOI: 10.3969/j.issn.1009-4237.2017.12.002.
Liu L M. Interpretation of norms for early treatment of traumatic hemorrhagic shock [J]. J Trauma Surg, 2017, 19(12): 884-887. DOI: 10.3969/j.issn.1009-4237.2017.12.002.

[4] 李涛, 胡平, 胡弋, 等. 院前适度低压复苏对严重创伤出血患者器官功能保护作用观察[J]. 创伤外科杂志, 2018, 20(8): 595-599. DOI: 10.3969/j.issn.1009-4237.2018.08.009.
Li T, Hu P, Hu Y, *et al*. Effects of permissive hypotensive resuscitation during pre-hospital for severe traumatic patients [J]. J Trauma Surg, 2018, 20(8): 595-599. DOI: 10.3969/j.issn.1009-4237.2018.08.009.

[5] Xu J, Lan D, Li T, *et al*. Angiopoietins regulate vascular reactivity after haemorrhagic shock in rats through the Tie2-nitric oxide pathway[J]. Cardiovasc Res, 2012, 96(2): 308-319. DOI: 10.1093/cvr/cvs254.

[6] D' Alessandro A, Moore H B, Moore E E, *et al*. Early hemorrhage triggers metabolic responses that build up during prolonged shock [J]. Am J Physiol Regul Integr Comp Physiol, 2015, 308(12): R1034-R1044. DOI: 10.1152/ajpregu.00030.2015.

[7] Jia B, Ye J J, Gan L B, *et al*. Mitochondrial antioxidant SkQ1 decreases inflammation following hemorrhagic shock by protecting myocardial mitochondria[J]. Front Physiol, 2022, 13: 1047909. DOI: 10.3389/fphys.2022.1047909.

[8] Andrianova N V, Buyan M I, Brezgunova A A, *et al*. Hemorrhagic shock and mitochondria: pathophysiology and therapeutic approaches[J]. Int J Mol Sci, 2025, 26(5): 1843. DOI: 10.3390/ijms26051843.

[9] Morrow M R, Batchuluun B, Wu J H, *et al*. Inhibition of ATP-citrate lyase improves NASH, liver fibrosis, and dyslipidemia[J]. Cell Metab, 2022, 34(6): 919-936.e8. DOI: 10.1016/j.cmet.2022.05.004.

[10] Uddin N, Syed A A, Ismail S M, *et al*. Clinical efficacy and safety of bempedoic acid in high cardiovascular risk patients: a systematic review and meta-analysis of randomized controlled trials[J]. Curr Probl Cardiol, 2023, 48(12): 102003. DOI: 10.1016/j.cpcardiol.2023.102003.

[11] Samsoondar J P, Burke A C, Sutherland B G, *et al*. Prevention of diet-induced metabolic dysregulation, inflammation, and atherosclerosis in *Ldlr*$^{-/-}$ mice by treatment with the ATP-citrate lyase inhibitor bempedoic acid[J]. Arterioscler Thromb Vasc Biol, 2017, 37(4): 647-656. DOI: 10.1161/ATVBAHA.116.308963.

[12] Lewis D I. Animal experimentation: implementation and application of the 3Rs[J]. Emerg Top Life Sci, 2019, 3(6): 675-679. DOI: 10.1042/ETLS20190061.

[13] Zhou Y Q, Li Q H, Xiang X M, *et al*. Low-dose norepinephrine in combination with hypotensive resuscitation may prolong the golden window for uncontrolled hemorrhagic shock in rats[J]. Front Physiol, 2022, 13: 1004714. DOI:10.3389/fphys.2022.1004714.

[14] 王志华, 周远群, 向鑫明, 等. 左旋肉碱对脓毒症心肌收缩功能障碍的改善作用及机制[J]. 陆军军医大学学报, 2025, 47(21): 2630-2640. DOI: 10.16016/j.2097-0927.202507037.
Wang Z H, Zhou Y Q, Xiang X M, *et al*. Effect and underlying mechanism of L-carnitine improving myocardial systolic dysfunction in sepsis mice[J]. J Army Med Univ, 2025, 47(21): 2630-2640. DOI: 10.16016/j.2097-0927.202507037.

[15] Pusateri A E, Moore E E, Moore H B, *et al*. Association of prehospital plasma transfusion with survival in trauma patients with hemorrhagic shock when transport times are longer than 20 minutes: a post hoc analysis of the PAMPer and COMBAT clinical trials[J]. JAMA Surg, 2020, 155(2): e195085. DOI:10.1001/jamasurg.2019.5085.

[16] Sperry J L, Guyette F X, Brown J B, *et al*. Prehospital plasma during air medical transport in trauma patients at risk for hemorrhagic shock[J]. N Engl J Med, 2018, 379(4): 315-326. DOI:10.1056/NEJMoa1802345.

[17] Tubert P, Kalimouttou A, Bouzat P, *et al*. Are crystalloid-based fluid expansion strategies still relevant in the first hours of trauma induced hemorrhagic shock?[J]. Crit Care, 2024, 28(1): 416. DOI:10.1186/s13054-024-05185-7.

[18] Sims C A, Holena D, Kim P, *et al*. Effect of low-dose supplementation of arginine vasopressin on need for blood product transfusions in patients with trauma and hemorrhagic shock: a randomized clinical trial[J]. JAMA Surg, 2019, 154(11): 994-1003. DOI: 10.1001/jamasurg.2019.2884.

[19] 张连阳. 战伤休克复苏首选血液制剂[J]. 创伤外科杂志, 2026, 28(4): 275.
Zhang L Y. Blood preparation is the first choice for resuscitation of war injury shock[J]. J Trauma Surg, 2026, 28(4): 275.

[20] Hu Y, Fang H, Tan L, *et al*. The mitochondrial division inhibitor mdivi-1 protected organ function and extended the treatment window in rats with uncontrolled hemorrhagic shock[J]. Shock, 2025, 63(3): 474-486. DOI: 10.1097/SHK.0000000000002459.

[21] Bickell W H, Wall M J Jr, Pepe P E, *et al*. Immediate versus delayed fluid resuscitation for hypotensive patients with penetrating torso injuries[J]. N Engl J Med, 1994, 331(17): 1105-1109. DOI:10.1056/NEJM199410273311701.

[22] Cannon J W. Hemorrhagic shock[J]. N Engl J Med, 2018, 378(4): 370-379. DOI:10.1056/nejmra1705649.

[23] Nicholls S J, Nelson A J, Lincoff A M, *et al*. Impact of bempedoic acid on total cardiovascular events: a prespecified analysis of the CLEAR outcomes randomized clinical trial[J]. JAMA Cardiol, 2024, 9(3): 245-253. DOI:10.1001/jamacardio.2023.5155.

[24] Banach M, Duell P B, Gotto A M Jr, *et al*. Association of bempedoic acid administration with atherogenic lipid levels in phase 3 randomized clinical trials of patients with hypercholesterolemia[J]. JAMA Cardiol, 2020, 5(10): 1124-1135. DOI:10.1001/jamacardio.2020.2314.

[25] Sun X N, Zhao R, Zhou Q D, *et al*. ACLY alleviates cerebral ischemia/reperfusion injury by reducing oxidative stress and enhancing mitochondrial function *via* histone acetylation[J]. Cell Death Dis, 2026. DOI:10.1038/s41419-026-09021-4.

[26] 刘绍源, 高茸, 宋凡, 等. 基于网络药理学和分子对接技术探讨黄连解毒汤治疗心肌缺血再灌注损伤的分子机制[J]. 空军军医大学学报, 2025, 46(8): 1081-1089, 1096. DOI:10.13276/j.issn.2097-1656.2025.08.018.
Liu S Y, Gao R, Song F, *et al*. Exploring the molecular mechanism of Huanglian Jiedu Decoction in treating myocardial ischemia/reperfusion injury based on network pharmacology and molecular docking techniques[J]. J Air Force Med Univ, 2025, 46(8): 1081-1089, 1096. DOI:10.13276/j.issn.2097-1656.2025.08.018.

[27] Duarte Lau F, Giugliano R P. Adenosine triphosphate citrate lyase and fatty acid synthesis inhibition: a narrative review[J]. JAMA Cardiol, 2023, 8(9): 879-887. DOI: 10.1001/jamacardio.2023.2402.

[28] Butera E, Termite F, Esposto G, *et al*. Exploring the role of bempedoic acid in metabolic dysfunction associated steatotic liver disease: actual evidence and future perspectives[J]. Int J Mol Sci, 2024, 25(13): 6938. DOI: 10.3390/ijms25136938.

(**收稿**:2026-04-28;**修回**:2026-07-13)
(编辑 黄 晟)