论著·基础医学

高原、高寒、高热环境下致死性休克大鼠模型的建立与标准化造模方式筛选

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[**摘要**]　**目的**　基于本实验室已建立的常规环境大鼠失血性休克模型,建立高原、高寒、高热特殊环境大鼠致死性休克模型,为特殊环境下致死性休克救治相关研究提供动物模型。**方法**　864只12周龄、体质量(200±20)g SPF级雄性SD大鼠按不同预处理环境分为4组(n=216):高原环境组[低压氧舱模拟4 000 m海拔,(22±2)℃暴露48 h];高寒环境组(海拔200~300 m,-20 ℃暴露6 h);高热环境组(海拔200~300 m,35 ℃暴露12 h),常规环境对照组(不做环境预处理)。环境预处理后,采用4种脾损伤方式诱导腹腔自由出血制备非控制性失血性休克模型:①距脾实质末端3 cm处离断;②距脾实质末端3 cm和5 cm处分别离断;③脾尾端小动脉分支离断;④脾尾端小动脉分支离断联合距脾实质末端3 cm处离断,直至平均动脉压(mean arterial pressure,MAP)降至40 mmHg即判定模型制备成功。模型成功后,用乳酸林格氏液(lactated Ringer's solution,LR)低压维持MAP在50~60 mmHg 1 h,经脾动脉结扎彻底止血后,按出血量2倍体积LR进行确定性复苏。监测MAP、呼吸频率(respiratory rate,RR)、心率(heart rate,HR),检测心功能[肌钙蛋白I(troponin I, TnI)]、肝功能[谷草转氨酶(aspartate aminotransferase,AST)、谷丙转氨酶(alanine aminotransferase, ALT)]、肾功能[血尿素氮(blood urea nitrogen, BUN)、血清肌肝(serum creatinine,Scr)],观察大鼠存活时间及6 h存活率,筛选各环境适配的造模方式。用各环境组筛选出的造模方式分别在相应环境预处理的巴马香猪上制备失血性休克模型,并按前述治疗方案确定性复苏后,观察巴马香猪基础生理指标(MAP、RR、HR)、器官功能(心、肝、肾)及存活情况,以验证造模方式稳定性。**结果**　不同环境致死性休克模型的适配造模方式存在差异:常规环境优选重度血管联合实质损伤的方式④,高原环境优选重度血管损伤的方式③,高寒环境优选轻度实质损伤的方式①,高热环境优选中度双位点实质损伤的方式②,上述方式均满足休克后6 h致死率>70%、低压复苏后失血量>50%、确定性复苏后存活率>50%的模型标准。休克状态下,各组大鼠MAP显著降低(P<0.001),RR、HR异常改变,心、肝、肾器官功能指标(TnI、AST、ALT、BUN、Scr)显著升高(P<0.05),存活时间缩短;经LR低压复苏联合确定性复苏后,MAP显著回升(P<0.01),器官功能指标显著改善,存活时间延长。巴马香猪验证结果显示:休克组MAP降至约40 mmHg,RR显著降低,HR升高,6 h存活率为0,心、肝、肾器官功能指标(TnI、AST、ALT、BUN、Scr)显著升高(P<0.001);复苏组MAP显著升高至58.6~68.4 mmHg(P<0.01),器官功能明显改善,6 h存活率达50.00%~56.25%,模型可靠性得到确认。**结论**　成功建立了高原、高寒、高热环境下致死性休克模型,明确了各环境对应的标准化造模方式;经巴马香猪验证,模型稳定性与可靠性符合实验要求。

[**关键词**]　军事医学;高原医学;高寒;高热;致死性休克;动物模型

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Establishment and standardized modeling of lethal shock rat models in high-altitude, high-cold, and high-heat environments

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[**Abstract**] Objective To establish lethal shock models in high-altitude, high-cold, and high-heat environments based on the conventional environment hemorrhagic shock (HS) model established in our laboratory, in order to provide animal models for lethal shock treatment in special environments. Methods A total of 864 SPF-grade male SD rats (12 weeks old, weighing 200±20 g) were divided into high-altitude environment group (simulated 4 000 m altitude in a low-pressure oxygen chamber, exposed to 22±2 ℃ for 48 h), high-cold environment group (altitude 200 to 300 m, exposure to −20 ℃ for 6 h), high-heat environment group (altitude 200 to 300 m, exposure to 35 ℃ for 12 h), and conventional environment control group (no environmental pretreatment) according to different environmental pretreatment, with 216 animals in each group. After environmental pre-conditioning, 4 types of spleen injury methods were used to induce free intra-abdominal bleeding to construct corresponding uncontrolled HS model. The injury methods were as follows: ① Transverse transection at 3 cm away from the end of the splenic parenchyma; ② Transverse transection separately at 3 and 5 cm away from the end of the splenic parenchyma; ③ Transverse arteriotomy of a small arterial branch at the splenic tail; ④ Transverse arteriotomy of a small arterial branch at the splenic tail combined with transection at 3 cm away from the end of the splenic parenchyma. Free intra-abdominal bleeding was induced by above 4 methods until the mean arterial pressure (MAP) dropped to 40 mmHg, which was defined as successful establishment of the uncontrolled HS model. After successful modeling, lactated Ringer's (LR) solution was employed to maintain MAP at 50 to 60 mmHg at low pressure for 1 h. After the splenic artery was ligated for complete hemostasis, definitive resuscitation was obtained with LR solution of 2×blood loss volume. MAP, respiratory rate (RR) and heart rate (HR) were monitored, cardiac function [troponin I (TnI)], liver function [aspartate aminotransferase (AST), alanine aminotransferase (ALT)], and renal function [blood urea nitrogen (BUN), serum creatinine (Scr)] were evaluated, survival time was observed, and 6-hour survival rate was calculated to screeen the appropriate modeling methods for each environment. Then the obtained modeling methods were applied on Bama pigs to establish HS models for high-altitude, high-cold, and high-heat environments, respectively. After modelling, the pigs were resuscitated according to the aforementioned treatment regimens, and basic physiological indicators (MAP, RR, HR), organ functions (heart, liver, kidney), and survival status were observed to verify the stability of the modeling methods. Results There were differences in the appropriate modeling methods for different environments: the conventional environment preferred method ④, the high-altitude environment preferred method ③, the high-cold environment preferred method ①, and the high-heat environment preferred method ②. All the above methods met the model standards of a 6-hour mortality rate >70% after shock, a blood loss >50% after low-pressure resuscitation, and a survival rate >50% after definitive resuscitation. In the state of shock, the MAP of rats was significantly reduced in each group ($P<0.001$), RR and HR were abnormally changed, the indicators of cardiac, liver, and renal functions (TnI, AST, ALT, BUN, Scr) ($P<0.05$) were significantly increased, and the survival time was obviously shortened. After LR low-pressure resuscitation combined with definitive resuscitation, the MAP was notably recovered ($P<0.01$), the organ function indicators were significantly improved, and the survival time was greatly prolonged. The verification results in Bama miniature pigs showed that in the shock group, MAP was decreased to approximately 40 mmHg, RR was significantly reduced, HR was increased, the 6-hour survival rate was 0%, and the indicators of cardiac, liver, and renal

functions (TnI, AST, ALT, BUN, and Scr) were notbly elevated (P<0.001). In the resuscitation group, the MAP was significantly increased to 58.6 to 68.4 mmHg (P<0.01), the 6-hour survival rate reached 50.00% to 56.25%, and organ functions were significantly improved. All these findings confirmed the reliability of each model. **Conclusion** Lethal shock models under high-altitude, high-cold, and high-heat environments are successfully established, respectively, and the appropriate standardized modeling methods are identified for each environment. The modelling methods are further verified on Bama miniature pigs, and the constructed models have advantages of stability and reliability for laboratory requirements.

[**Key words**] military medicine; high-altitude medicine; high-cold; high-heat; lethal shock; animal model

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创伤失血性休克是战时和平时常见并发症,发生率和病死率均较高[1]。大多数早期可预防的失血性休克死亡都是由非控制性出血造成的[2],非控制性失血性休克具有持续性、活动性出血等特点,导致有效循环血容量急剧减少,组织灌注不足,若未能得到及时有效的治疗,迅速加重的缺血缺氧损伤会引起器官功能障碍,最终发展为致死性休克。我国未来的主要作战场景,多涉及高原、高寒、沙漠等特殊环境,这些环境因素会显著加剧失血性休克的病理进程。以往的研究表明,高原地区由于缺氧、寒冷等原因,同等程度的创伤或失血引起的休克,较平原地区休克程度重,发展快,死亡率高[3],持续的高热环境也会引起机体内环境紊乱,加剧失血性休克导致的器官功能损害,加速休克向致死性休克阶段进展[4]。因此,在这些特殊环境下发生失血性休克,复杂的环境因素使救治难度大大增加。目前针对常规环境失血休克的治疗尚有相关研究[5-8],但是对于高原、高寒、高热等特殊环境失血休克的研究相对较少,尤其缺乏可靠的、贴近特殊环境的致死性休克模型,严重制约了特殊环境下致死性休克针对性救治策略的研究和优化。因此,建立特殊环境致死性休克模型,对于后续的治疗方案研究具有重要意义。为解决这一问题,本研究开展了特殊环境下致死性休克模型建立的相关实验,为特殊环境下致死性休克的救治研究奠定模型基础。

1 材料和方法

1.1 实验动物

12周龄SPF级雄性SD大鼠864只,体质量(200±20)g,由陆军特色医学中心实验动物中心提供,自由饮水,实验前12 h禁食。动物许可证号[SCXK(渝)2022-0003]。8月龄巴马香猪288头,体质量(25.2±2.1)kg,购自重庆沃森生物技术有限公司,自由饮水,实验前12 h禁食。

1.2 实验试剂及仪器

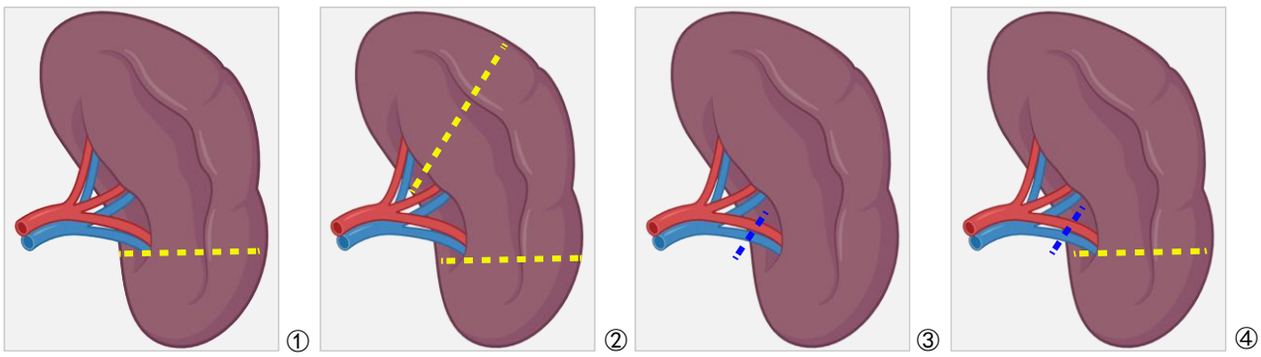
乳酸林格氏液(lactated Ringer's solution,LR)和氯化钠注射液均购自四川科伦药业股份有限公司;肝素钠注射液购自常州千红生化制药股份有限公司);戊巴比妥钠购自美国Merck公司;青霉素、链霉素购自山东鲁抗医药股份有限公司。生化分析仪购自美国Beckman Coulter。

1.3 实验方法

1.3.1 模型制备 常规及特殊环境非控制性失血性休克模型制备,具体如下:45 mg/kg戊巴比妥钠麻醉,腹部消毒,沿腹直线切腹,暴露脾脏,分成4种造模方式进行模型制作(图1):①距脾实质末端3 cm处离断;②距脾实质末端3 cm和5 cm处分别离断;③脾尾端小动脉分支离断;④脾尾端小动脉分支离断联合距脾实质末端3 cm处离断。手术结束后关闭腹腔,让血液从切口处自由流入腹腔,当平均动脉压(mean arterial pressure,MAP)降低至40 mmHg时达到休克标准。

常规环境组(不做环境预处理)、高原环境组[低压氧舱模拟4 000 m海拔,(22±2)℃暴露48 h]、高寒环境组(海拔200~300 m,-20 ℃低温环境箱暴露6 h)和高热环境组(海拔200~300 m,35 ℃高热环境箱暴露12 h)等环境预处理大鼠,均按上述4种造模方式复制非控制性失血性休克模型,实现常规及特殊环境非控制性失血性休克模型制备。

1.3.2 实验设计及指标观察 常规及特殊环境非控制性失血性休克模型制备成功后,根据低压复苏原则,采用LR进行低压复苏,将MAP维持在50~60 mmHg 1 h;然后进行彻底止血处理(即通过脾动脉结扎进行彻底性止血),彻底止血后测量腹腔内出血量,用2倍出血量LR进行确定性复苏。实验分3个批次,具体如下:



①: Parenchymal transection at 3 cm away from the end of spleen; ②: Parenchymal transection at both 3 and 5 cm away from the end of the spleen; ③: Transverse arteriotomy of a small arterial branch at the splenic tail; ④: Combination of ① and ③

图1 非控制性失血性休克模型中4种脾损伤相关造模方式的操作示意图

Figure 1 Schematic operation diagram of 4 spleen injury modeling methods for uncontrolled hemorrhagic shock

1.3.2.1 4种造模方式的休克模型制备及MAP和存活情况观察 实验分为4个组,分别为距脾实质末端3 cm处离断组(记为①)、距脾实质末端3 cm和5 cm处分别离断组(记为②)、脾尾端小动脉分支离断组(记为③)和脾尾端小动脉分支离断联合距脾实质末端3 cm处离断组(记为④),按上述方式复制常规及特殊环境下非控制性失血性休克模型。休克模型制备成功后,观察大鼠MAP和存活时间,计算6 h存活率。

1.3.2.2 LR低压复苏联合确定性复苏对非控制性失血性休克大鼠的干预效果评价 实验分为3个组,分别为假手术(Sham)组:只开腹,未进行手术;休克(UHS)组:制备休克模型,未进行复苏处理;乳酸林格氏液(UHS+LR)组:模型成功后,用LR进行低压复苏,维持MAP在50~60 mmHg 1h,低压复苏结束后彻底性止血,并用2倍失血量LR进行确定性复苏。观察大鼠MAP、失血量和存活时间,计算6 h存活率。

1.3.2.3 LR低压复苏联合确定性复苏对不同环境致死性休克大鼠的多器官保护效应评价及巴马香猪验证 实验分为3个组,分别为假手术(Sham)组:只开腹,未进行手术;休克(UHS)组:制备休克模型,未进行复苏处理;乳酸林格氏液(UHS+LR)组:模型成功后,用LR进行低压复苏,维持MAP在50~60 mmHg 1 h,并进行彻底性止血及2倍失血量LR确定性复苏。在第二批次实验结果的基础上,不同环境大鼠按达到致死性休克模型标准对应的方式复制致死性休克模型,LR低压复苏1 h,彻底性止血及2倍失血量LR确定性复苏,观察大鼠生命体征指标如MAP、呼吸频率(respiratory rate,RR)和心率(heart rate,HR),以及器官功能包括心损指标肌钙蛋白I(troponin I,TnI)、肝脏功能损伤指标[谷草转氨酶(aspartate aminotransferase,AST),谷丙转氨酶(alanine aminotransferase,ALT)]和肾脏功能损伤指标[血尿素氮(blood urea nitrogen,BUN),血清肌酐(serum creatinine,Scr)],并在巴马香猪上进行验证。

1.4 指标参数测定

1.4.1 生理参数监测 采用戊巴比妥钠(45 mg/kg)麻醉大鼠或氯胺酮麻醉巴马香猪后,行股动、静脉插管,实时监测动物MAP、RR和HR。

1.4.2 失血量检测 休克模型制备成功后,采用LR进行低压复苏1 h,用洁净干棉球吸干腹腔中的血,称量,计算失血量。

1.4.3 存活时间观察 液体复苏结束后,拔除股动脉和静脉的插管,结扎血管并缝合伤口,肌注抗生素(青霉素和链霉素),将实验动物放回观察室观察,给予正常饮食和水,观察存活情况,计算存活时间、存活率。

1.4.4 心、肝和肾脏功能测定 复苏结束后,取动物全血采用生化分析仪测定心功能指标(TnI)、肝脏功能指标(AST、ALT)和肾脏功能指标(BUN、Scr)。

1.5 统计学分析

采用SPSS 22.0统计软件进行数据处理与分析。符合正态分布的计量资料以$\bar{x}\pm s$表示,多组比较采用单因素方差分析,存活率和存活时间采用Kaplan-Meier生存分析和Log-rank检验。$P<0.05$为差异具有统计学意义。

2 结果

2.1 常规及高原、高寒、高热环境下致死性休克大鼠模型建立

大鼠休克模型制备后,在不止血的情况下观察大

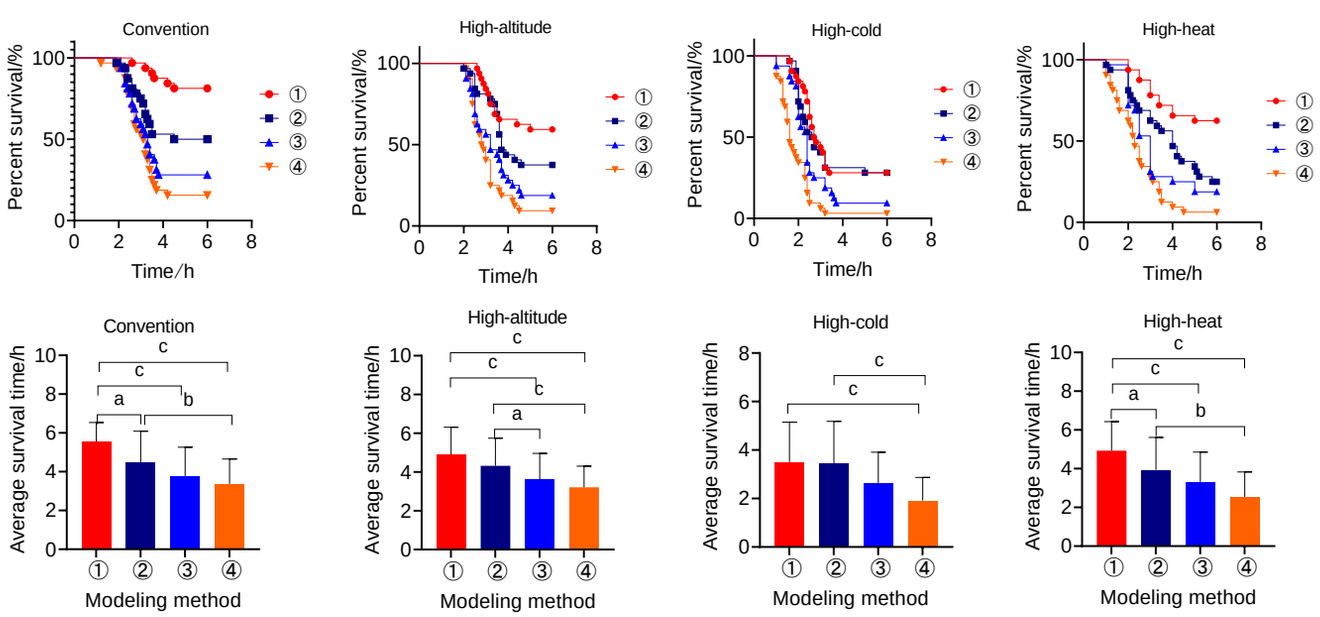
鼠的自然存活时间。结果显示:分别采用4种方式处理后,各环境下各组大鼠MAP在1 h内均能降至40 mmHg;在不进行液体复苏的情况下,常规环境①②③④种方式处理后6 h的存活率分别为81.250%、50.000%、28.125%和15.625%,其中③、④方式致死率>70%;高原环境6 h存活率分别为59.375%、37.500%、18.750%和9.375%,其中③、④方式致死率>70%;高寒环境6 h存活率分别为28.125%、28.125%、9.375%和3.125%,4种方式致死率均>70%;高热环境6 h存活率分别为62.50%、25.00%、18.75%和6.25%,其中②③④方式致死率>70%(图2)。

2.2　LR复苏对常规及高原、高寒、高热环境致死性休克大鼠、失血量和存活率的影响

大鼠失血量和确定性复苏后的存活时间结果显示:常规环境下①②③④方式复制休克模型,失血量分别为(29.9±1.3)%、(43.0±2.5)%、(46.9±2.2)%和(54.2±1.1)%,确定性复苏后6 h存活率分别为93.75%、87.50%、62.50%和50.00%;高原环境失血量分别为(40.6±1.9)%、(44.1±1.3)%、(53.7±2.4)%和(57.9±3.6)%,确定性复苏后6 h存活率分别为75.00%、68.75%、56.25%和37.50%;高寒环境失血量分别为(52.9±1.8)%、(55.8±1.7)%、(60.7±4.0)%和(62.2±3.4)%,确定性复苏后6 h存活率分别为56.25%、43.75%、37.50%和18.75%;高热环境失血量分别为(52.3±1.5)%、(53.1±3.0)%、(56.5±1.8)%和(61.5±2.1)%,确定性复苏后6 h存活率分别为68.75%、56.25%、43.75%和31.25%。结合前期致死率结果表明,常规环境下选择④方式,高原环境选择③方式,高寒环境选择①方式和高热环境选择②方式制备非控制性失血性休克模型,可达到致死率>70%,低压复苏后失血量>50%,彻底止血复苏后存活率>50%,满足致死性休克模型的标准(图3)。

2.3　LR复苏对常规及高原、高寒、高热环境致死性休克大鼠生命体征和器官功能的影响

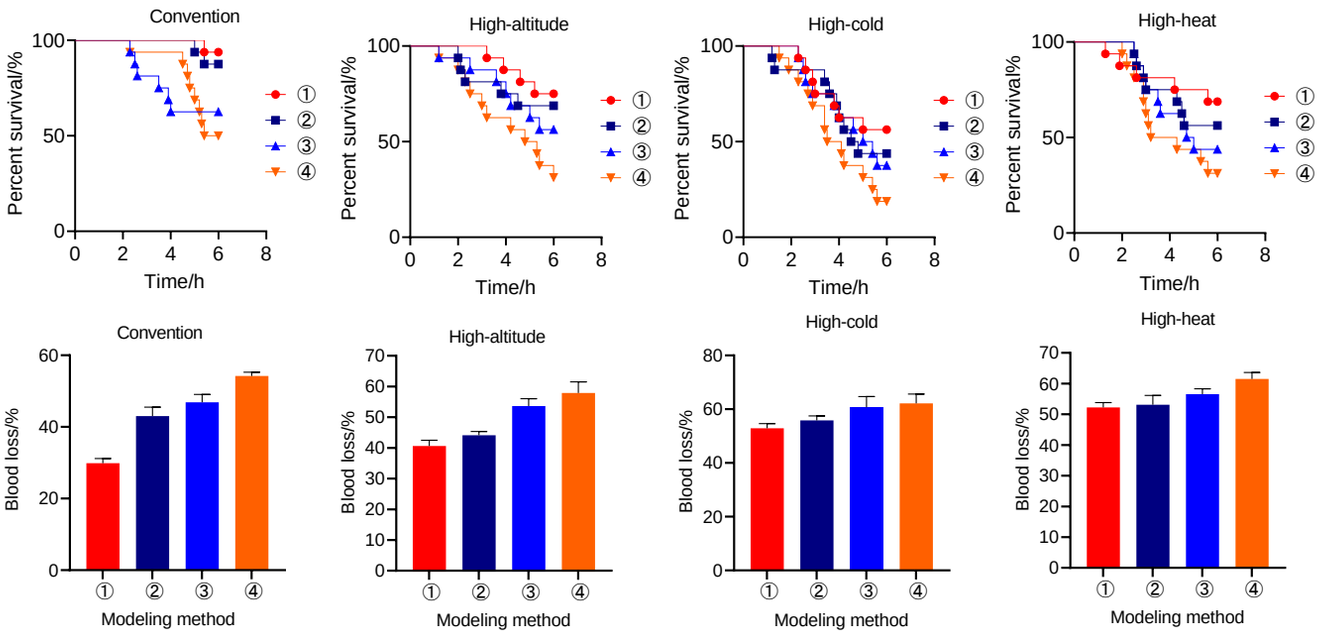
2.3.1　LR复苏对常规环境致死性休克大鼠生命体征及器官功能的改善效果　前期结果已经筛选出常规环境选择④方式造模,可满足致死性休克模型标准。后续研究按照④方式复制常规环境致死性休克模型,观察大鼠生命体征和器官功能的变化。结果显示:休克后大鼠MAP降低(P<0.001,图4A)、RR增加(P<0.001,图4B)、器官功能损伤,包括心功能指标TnI(P<0.001,图4D),肝功能指标AST(P<0.001,图4E)、ALT(P<0.01,图4F),肾功能指标BUN(P<0.01,图4G)、Scr(P<0.001,图4H)均表达增加;LR低压



①: Parenchymal transection at 3 cm away from the end of spleen; ②: Parenchymal transection at both 3 and 5 cm away from the end of the spleen; ③: Transverse arteriotomy of a small arterial branch at the splenic tail; ④: Combination of ① and ③. a: P<0.05; b: P<0.01; c: P<0.001

图2　常规及高原、高寒、高热环境不同造模方式复制非控制性失血性休克大鼠的存活情况(n=32,$\bar{x}\pm s$)

Figure 2　Survival status of uncontrolled hemorrhagic shock rats replicated using different modeling methods in conventional and high-altitude, high-cold, and high-heat environments(n=32,$\bar{x}\pm s$)



①: Parenchymal transection at 3 cm away from the end of spleen; ②: Parenchymal transection at both 3 and 5 cm away from the end of the spleen; ③: Transverse arteriotomy of a small arterial branch at the splenic tail; ④: Combination of ① and ③

图3　LR复苏对常规及高原、高寒、高热环境非控制性失血性休克大鼠失血量和存活的影响(n=16,$\bar{x}\pm s$)

Figure 3　Effects of lactated Ringer's solution resuscitation on blood loss, and survival in rats with uncontrolled hemorrhagic shock in conventional and high-altitude, high-cold, and high-heat environments(n=16,$\bar{x}\pm s$)

复苏1 h,彻底止血及确定性复苏后,生命体征指标得到改善,肝肾功能指标和心功能指标降低(P<0.05,图4D~H),器官功能显著增强。

2.3.2　LR复苏对高原环境致死性休克大鼠器官功能的改善效果　　前期结果已经筛选出高原环境选择③方式造模,可满足致死性休克模型标准。按③方式复制高原环境致死性休克模型,休克后大鼠的MAP降低(P<0.001,图5A),RR(P<0.001,图5B)和HR(P<0.01,图5C)增加,重要器官功能包括肝脏(AST、ALT,P<0.01,图5E、F)、肾脏(BUN、Scr,P<0.001,图5G、H)、心脏(TnI,P<0.001,图5D)均有较大程度损伤,用LR进行低压复苏及确定性复苏后AST(P<0.01)、ALT(P<0.05)、BUN(P<0.05)、Scr(P<0.05)、TnI(P<0.001)显著降低(图5D~H),器官功能显著改善。

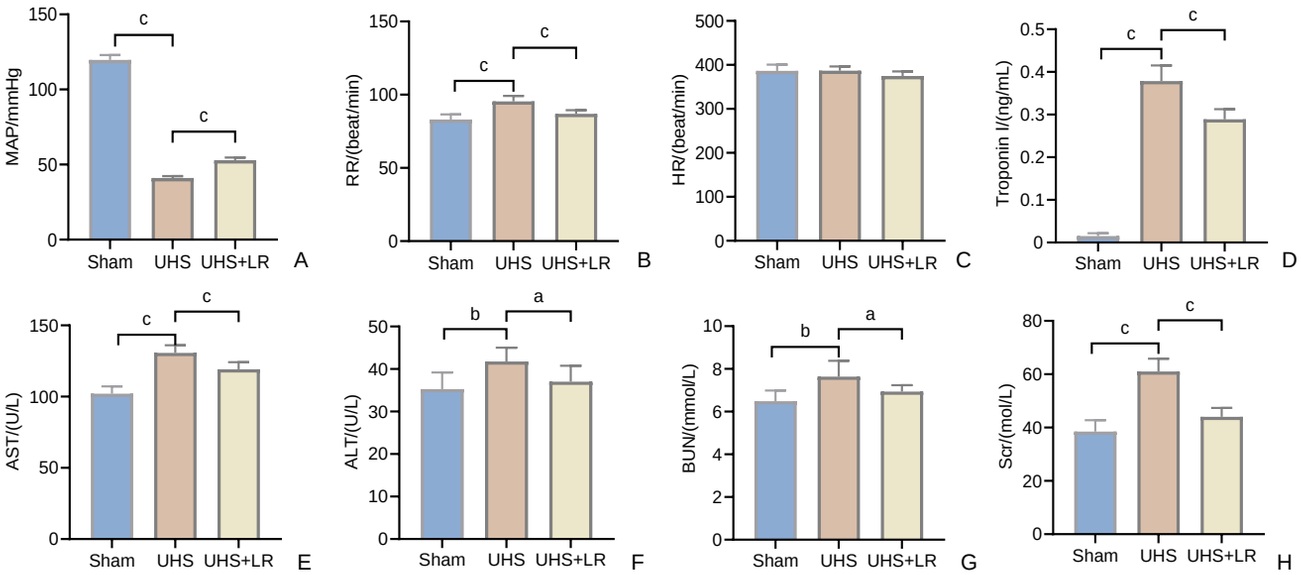
2.3.3　LR复苏对高寒环境致死性休克大鼠器官功能的改善效果　　根据前期结果显示,高寒环境致死性休克造模方式优选方式①,按①方式复制高寒环境致死性休克模型,休克后大鼠生命体征减弱,具体表现为MAP显著降低(P<0.001,图6A),RR显著降低(P<0.001,图6B),HR升高(P<0.05,图6C),重要器官功能指标包括心脏(TnI,P<0.001,图6D)、肝脏(AST、ALT,P<0.05,图6E、F)、肾脏(Scr,P<0.05,图6H)功能指标均有不同程度升高,用LR进行低压复苏及确定性复苏后重要器官功能损伤显著减轻,生命体征明显改善(图6)。

2.3.4　LR复苏对高热环境致死性休克大鼠器官功能的改善效果　　根据前期结果,按②方式复制高热环境致死性休克模型,休克后大鼠的基础生命体征指标发生明显变化,表现为MAP(P<0.001,图7A)和RR(P<0.001,图7B)显著降低,HR(P<0.05,图7C)显著增加,重要器官功能包括肝脏(AST、ALT,P<0.01,图7E、F)、肾脏(BUN、Scr,P<0.001,图7G、H)、心脏(TnI,P<0.001,图7D)功能指标均显著增加,用LR低压复苏并确定性复苏后重要器官功能损伤显著减轻,AST、ALT、BUN、Scr均显著降低(P<0.05,图7E~H),TnI显著降低(P<0.01,图7D),MAP显著回升(P<0.01,图7A),HR(P<0.05,图7C)也得到改善。

2.4　常规及高原、高寒、高热环境致死性休克模型在巴马香猪上的验证

2.4.1　LR复苏对常规及高原、高寒、高热环境致死性休克巴马香猪基础生理指标和存活情况的改善效果

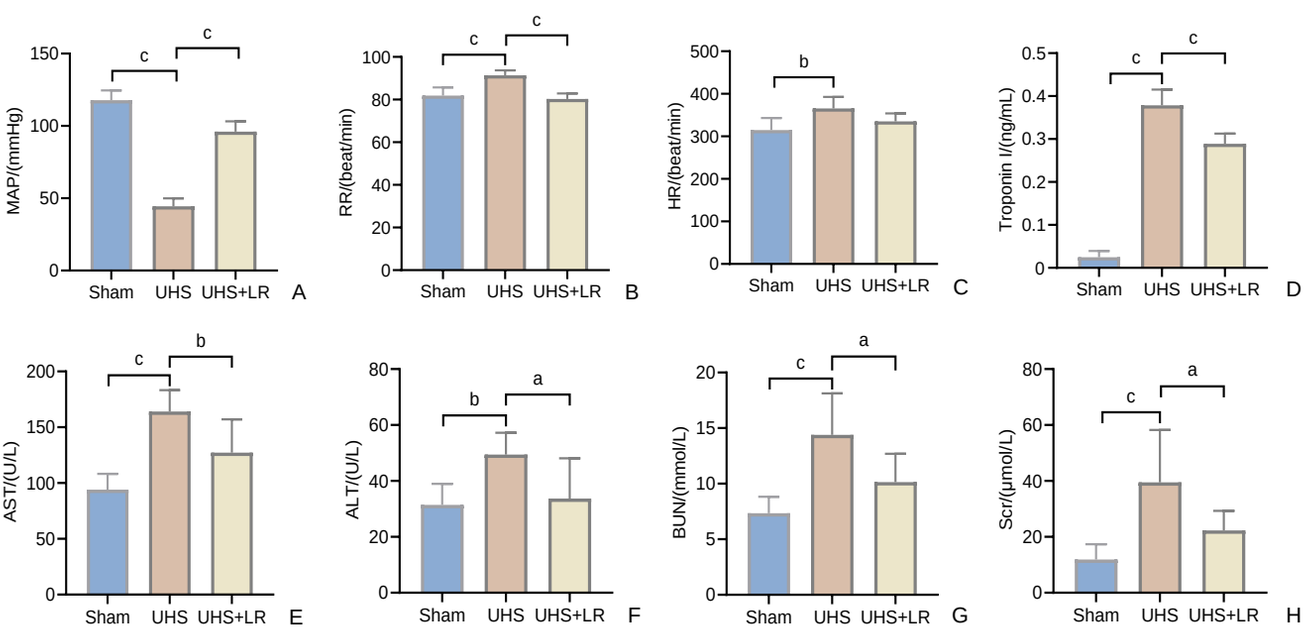
在大鼠实验结果基础上,用巴马香猪进行验证。取巴马香猪,不同环境选择相应可达致死性休克模型的造模方式制备非控制性失血性休克模型,模型成功后用LR进行低压复苏1 h,进行彻底止血和确定性复苏,观察动物基础生理指标和存活情况。结果发现非控制



Sham: Sham operation group; UHS: Uncontrolled hemorrhagic shock group; UHS+LR: Low pressure resuscitation of lactated Ringer's (LR) solution after UHS, followed by definitive resuscitation after complete hemostasis; MAP: Mean arterial pressure; RR: Respiratory rate; HR: Heart rate; AST: Aspartate transaminase; ALT: Alanine aminotransferase; BUN: Urea nitrogen; Scr: Serum creatinine. a: $P<0.05$, b: $P<0.01$, c: $P<0.001$

图4 LR复苏对常规环境致死性休克大鼠生命体征和器官功能的影响($n=8,\bar{x}\pm s$)

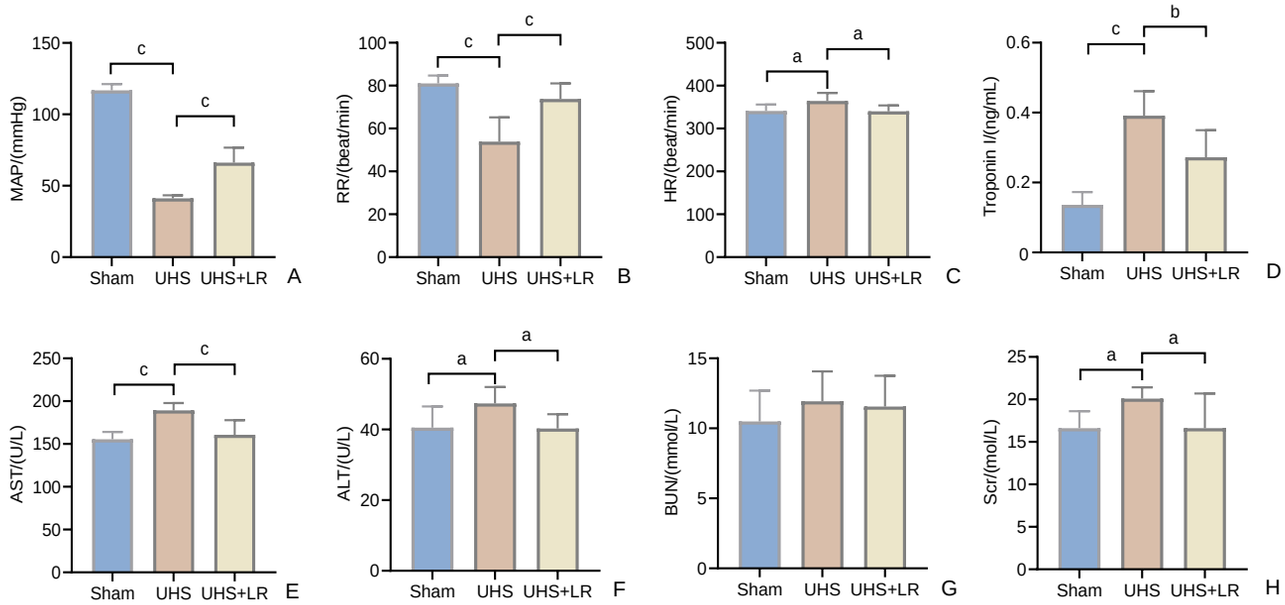
Figure 4 Effects of LR resuscitation on vital signs and organ functions in rats with lethal shock in a conventional environment($n=8,\bar{x}\pm s$)



Sham: Sham operation group; UHS: Uncontrolled hemorrhagic shock group; UHS+LR: Low pressure resuscitation of lactated Ringer's (LR) solution after UHS, followed by definitive resuscitation after complete hemostasis; MAP: Mean arterial pressure; RR: Respiratory rate; HR: Heart rate; AST: Aspartate transaminase; ALT: Alanine aminotransferase; BUN: Urea nitrogen; Scr: Serum creatinine. a: $P<0.05$, b: $P<0.01$, c: $P<0.001$

图5 LR复苏对高原环境致死性休克大鼠生命体征和器官功能的影响($n=8,\bar{x}\pm s$)

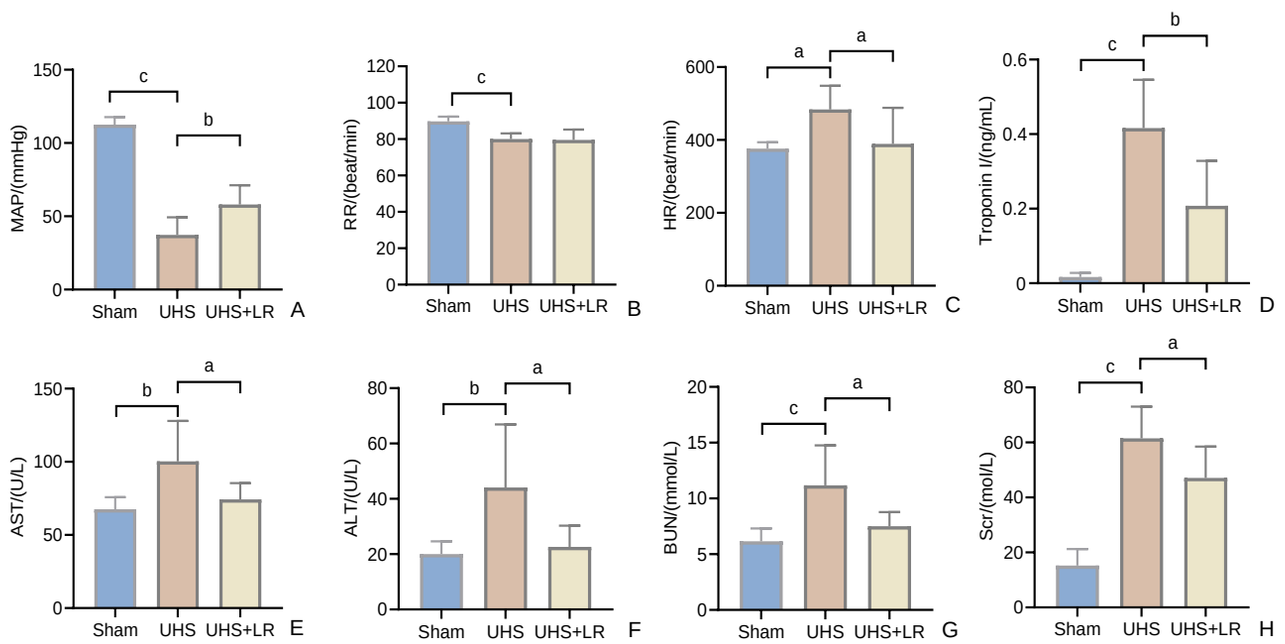
Figure 5 Effects of LR resuscitation on vital signs and organ function in rats with lethal shock in high-altitude environment($n=8,\bar{x}\pm s$)



Sham: Sham operation group; UHS: Uncontrolled hemorrhagic shock group; UHS+LR: Low pressure resuscitation of lactated Ringer's (LR) solution after UHS, followed by definitive resuscitation after complete hemostasis; MAP: Mean arterial pressure; RR: Respiratory rate; HR: Heart rate; AST: Aspartate transaminase; ALT: Alanine aminotransferase; BUN: Urea nitrogen; Scr: Serum creatinine. a: $P<0.05$, b: $P<0.01$, c: $P<0.001$

图6 LR复苏对高寒环境致死性休克大鼠生命体征和器官功能的影响($n=8, \bar{x}\pm s$)

Figure 6 Effects of LR resuscitation on vital signs and organ function in rats with lethal shock in high-cold environments($n=8, \bar{x}\pm s$)



Sham: Sham operation group; UHS: Uncontrolled hemorrhagic shock group; UHS+LR: Low pressure resuscitation of lactated Ringer's (LR) solution after UHS, followed by definitive resuscitation after complete hemostasis; MAP: Mean arterial pressure; RR: Respiratory rate; HR: Heart rate; AST: Aspartate transaminase; ALT: Alanine aminotransferase; BUN: Urea nitrogen; Scr: Serum creatinine. a: $P<0.05$, b: $P<0.01$, c: $P<0.001$

图7 LR复苏对高热环境致死性休克大鼠生命体征和器官功能的影响($n=8, \bar{x}\pm s$)

Figure 7 Effects of LR resuscitation on vital signs and organ function in rats with lethal shock in a high-heat environment($n=8, \bar{x}\pm s$)

性失血性休克后,不同环境巴马香猪的MAP(P<0.01,表1)均显著降低,在不进行复苏的情况下,平均存活时间均显著缩短(P<0.01),6 h内动物均全部死亡;确定性复苏后各环境巴马香猪的MAP(P<0.01)和平均存活时间(P<0.01)均显著延长,RR有所延长(P<0.01),各环境巴马香猪6 h存活率分别增加至56.25%、56.25%、50.00%、50.00%,均能达到50%及以上;不同环境表现出相同的结果趋势(表1)。

2.4.2 LR复苏对常规及高原、高寒、高热环境致死性休克巴马香猪器官功能的改善效果 在不同环境中,与Sham组相比,UHS组巴马香猪的TnI、AST、ALT、BUN及Scr水平均显著升高(P<0.001);LR复苏联合确定性复苏后,上述指标在不同环境中的具体变化虽有所差异,但均表现出LR对器官功能的改善效果。具体表现为:常规环境下,TnI、ALT、BUN及Scr水平较UHS组显著降低(均P<0.001);高原环境下,TnI(P<0.001)、AST(P<0.001)、BUN(P<0.001)及Scr(P<0.01)水平较UHS组显著降低;高寒环境下,TnI(P<0.01)、AST(P<0.01)、ALT(P<0.01)、BUN(P<0.05)及Scr(P<0.001)水平较UHS组显著降低;高热环境下,TnI(P<0.05)、ALT(P<0.001)及Scr(P<0.001)水平较UHS组显著降低(图8)。以上结果提示,不同环境下选择适配的造模方式在巴马香猪上制备致死性休克模型后,器官功能均显著损伤,LR复苏联合确定性复苏后,均能不同程度改善巴马香猪的器官功能。

3 讨论

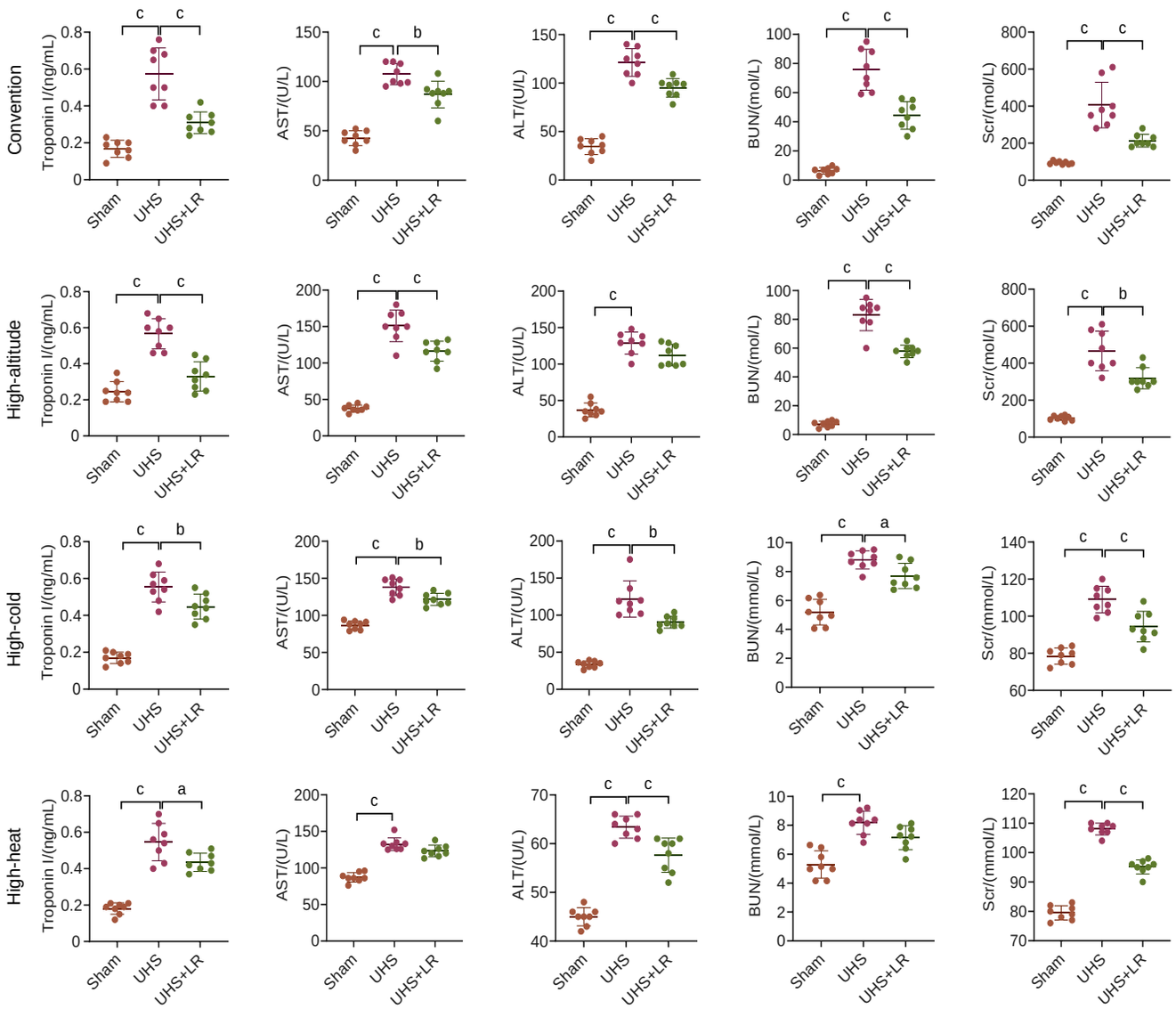
失血性休克是严重创伤后出现的严重并发症之一,是患者早期死亡的重要因素[9]。非控制性失血性休克是失血性休克的主要类型[10],大多数早期可预防的死亡都是由非控制性出血休克造成的[2]。徐乾等[10]研究了振动条件对大鼠非控制性失血性休克模型生理功能的影响,郑强等[11]研究了米诺环素对未控制性失血性休克大鼠肝组织的保护作用,郭淑芬等[12]和班定宏[13]也探讨了液体复苏策略对非控制性失血休克患者治疗效果的影响。由此可见,不管是动物模型还是临床研究,多以非控制性失血性休克模型为基础。因此,本研究采用了非控制性失血性休克为模型基础,更能模拟真实情况。值得注意的是,这些研究均是在常规环境下进行的,以往的研究表明,高原环境会加剧与失血性休克相关的生理和病理变化,导致更严重的器官损伤,增加患者的治疗难度[14]。低温失血性休克的特点是组织细胞缺血、缺氧更加严重[15],低温环境下的失血性休克患者处于低体温状态,会进一步加重凝血机制异常,病死率显著升高[16]。高热环境可诱发机体内环境紊乱,在发生失血性休克后呈现多种特殊的病理生理特征[17],高热环境下发生失血性休克还会导致线粒体过度分裂,导致线粒体功能障碍,进而导致器官功能障碍[18]。由此可见,高原、高寒、高热等特殊环境会加重休克程度。采用常规环境休克模型研究特殊环境休克的救治,缺乏系统性和代

表1 LR复苏对常规及高原、高寒、高热环境致死性休克巴马香猪基础生理指标和存活的影响(n=16,$\bar{x}\pm s$)

Table 1 Effects of lactated Ringer's (LR) solution resuscitation on basic physiological indicators and survival of Bama miniature pigs with lethal shock in conventional and high-altitude, high-cold, and high-heat environments(n=16,$\bar{x}\pm s$)

Environment type	group	MAP/mmHg	HR/(beat/min)	RR/(beat/min)	Average survival time/h	6-hour survival rate/%
Convention	Sham	111.3±4.7	154±11	50±3	6.0±0.0	100.00
	UHS	41.2±2.3^{b}	169±4	43±5^{a}	3.5±1.0^{b}	0
	UHS+LR	68.4±7.2^{c}	165±15	34±3^{c}	4.9±1.5^{c}	56.25
High-altitude	Sham	116.4±3.7	150±8	45±5	6.0±0.0	100.00
	UHS	41.5±3.2^{b}	169±6^{b}	27±5^{b}	3.2±0.8^{b}	0
	UHS+LR	66.0±6.7^{c}	154±7^{c}	37±4^{c}	4.9±1.4^{c}	56.25
High-cold	Sham	115.4±7.5	150±7	46±3	6.0±0.0	100.00
	UHS	40.1±3.6^{b}	168±7^{a}	38±4^{b}	2.6±1.1^{b}	0
	UHS+LR	64.8±6.2^{c}	159±12	41±3	4.8±1.4^{c}	50.00
High-heat	Sham	113.4±5.0	156±9	46±4	6.0±0.0	100.00
	UHS	41.6±1.6^{b}	173±12^{a}	38±3^{b}	2.4±1.0^{b}	0
	UHS+LR	58.6±5.5^{c}	166±10	43±3	4.7±1.5^{c}	50.00

Sham: sham operation group; UHS: uncontrolled hemorrhagic shock group; UHS+LR: Low pressure resuscitation of LR after uncontrolled hemorrhagic shock, followed by definitive resuscitation after complete hemostasis; MAP: Mean arterial pressure; HR: Heart rate; RR: Respiratory rate. a: P<0.05, b: P<0.01, compared with the Sham group; c: P<0.01, compared with the UHS group



Sham: Sham operation group; UHS: Uncontrolled hemorrhagic shock group; UHS+LR: Low pressure resuscitation of lactated Ringer's (LR) solution after UHS, followed by definitive resuscitation after complete hemostasis; AST: Aspartate transaminase; ALT: Alanine aminotransferase; BUN: Urea nitrogen; Scr: Serum creatinine. a: P<0.05, b: P<0.01, c: P<0.001

图8 LR复苏对常规及高原、高寒、高热环境致死性休克巴马香猪器官功能的影响(n=8,$\bar{x}\pm s$)

Figure 8 Effects of LR resuscitation on organ function of bama miniature pigs with lethal shock in conventional and high-altitude, high-cold, and high-heat environments(n=8,$\bar{x}\pm s$)

表性,严重制约了特殊环境休克针对性救治策略的研究。因此,本研究同时开展了常规环境、高原、高寒、高热环境的致死性休克模型建立的研究。

3.1 特殊环境致死性休克模型的构建及有效性验证

本研究大鼠分别进行环境预处理:高原环境[4 000 m海拔低压氧舱,温度(22±2) ℃]暴露48 h、高寒环境(-20 ℃)暴露6 h、高热环境(35 ℃)暴露12 h,常规环境作为对照,同时采用4种脾损伤方式诱导出血,即距脾实质末端3 cm处离断、距脾实质末端3 cm和5 cm处分别离断、脾尾端小动脉分支离断以及脾尾端小动脉分支离断联合距脾实质末端3 cm处离断复制特殊环境非控制性失血性休克模型,其中方式①和④参考了创伤失血性休克动物模型的经典文献[18-19],方式②和③则基于"分级损伤"设计原则优化,方式①~④出血强度梯度分别对应轻度、中度、中重度和重度,旨在模拟临床不同程度脾损伤所致失血场景,如包膜下破裂、车祸伤脾破裂、锐器刺伤及严重挤压伤等现实失血场景,同时兼顾模型的致死性梯度与操作重复性,为筛选最优造模方案提供依据。休克模型成功后,用LR低压维持MAP至50~60 mmHg 1 h,经脾动

脉结扎彻底止血后,按出血量2倍体积LR进行确定性复苏。通过监测基础生理指标及器官功能检测,观察存活时间及6 h存活率,结果显示不同环境下适配造模方式存在差异:常规环境优选重度血管联合实质损伤的方式④,高原环境优选重度血管损伤的方式③,高寒环境优选轻度实质损伤的方式①,高热环境优选中度双位点实质损伤的方式②,上述方式均满足休克后6 h致死率>70%、低压复苏后失血量>50%、确定性复苏后存活率>50%的模型标准。休克状态下,各组大鼠MAP显著降低,RR、HR异常改变,心、肝、肾器官功能指标显著升高,存活时间缩短;经LR低压复苏联合确定性复苏后,MAP显著回升,器官功能指标显著改善,存活时间延长。巴马香猪验证结果显示,休克组MAP降至40 mmHg左右,RR显著降低,HR升高,6 h存活率为0,心、肝、肾器官功能指标显著升高;复苏组MAP显著升高至58.6~68.4 mmHg,器官功能明显改善,6 h存活率达50.00%~56.25%,模型可靠性得到确认。不同环境下致死性休克模型诱导出血的方式有所差异,可能原因是与常规环境相比,高原、高寒、高热环境自身的环境因素差异,会加速休克的进程。本研究采用脾实质离断或联合小动脉分支离断的方式诱导出血,更贴近创伤或严重出血患者的临床表现,保证了模型的可靠性。金辰等[20]在研究结果中提到小动物主要用于研究失血性休克的发病机制,大型动物适合于临床前治疗效果的评价。本研究用大鼠作为研究对象复制休克模型研究不同特殊环境下休克动物的特点,用巴马香猪进行验证,更加确保模型的稳定性和可重复性。

3.2 研究局限性分析与未来展望

尽管本研究成功建立了高原、高寒、高热环境下致死性休克模型并完成验证,但仍存在一定的局限性与不足,需在后续研究中进一步完善。①环境模拟的单一性与局限性:本研究仅模拟了固定参数的特殊环境(高原4 000 m海拔、高寒-20 ℃、高热35 ℃),且环境预处理为静态暴露模式,未考虑自然特殊环境中常见的动态变化,如高原海拔的梯度升高、高寒环境的昼夜温差、高热环境的湿度波动等。此外,未纳入低氧与寒冷、高热与高湿等复合环境的干预,而实际战场或突发场景中,复合环境暴露更为常见,可能导致休克病理生理机制更复杂,现有模型难以完全模拟此类真实场景。②造模方式的理想化与临床场景脱节:本研究通过脾损伤诱导腹腔自由出血制备模型,虽能模拟非控制性出血,但创伤类型较为单一,未涵盖临床常见的多发伤、贯通伤、挤压伤等复杂创伤场景。此外,造模过程中出血部位固定、出血速度相对可控,而实际创伤失血性休克中,出血部位往往不确定、出血速度波动大,且可能伴随组织挫伤、感染风险等额外损伤因素,现有模型未能充分还原此类复杂创伤的病理生理特点。由于实验环境条件的限制,高原及高寒环境的造模手术及后续的指标观察未能全程在特殊环境中进行,可能未能充分还原真实场景。

综上所述,本研究利用大鼠成功建立了常规环境、高原、高寒、高热特殊环境致死性休克模型,采用生命体征、器官功能指标进行模型评价,并在巴马香猪上得到验证,更加客观、准确地模拟了临床患者进入致死性休克的状态,模型稳定可重复,为下一步特殊环境失血性休克的治疗措施研究提供了重要的模型基础。未来研究可针对上述局限性,进一步优化模型设计,如增加复合环境模拟、模拟复杂创伤类型等,以提升模型的临床相关性和实用性,为特殊环境失血性休克的精准救治提供更全面的实验支撑。

利益冲突 本文所有作者声明不存在利益冲突

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