基础研究 论 著

生脉饮对劳力性热射病大鼠凝血功能障碍的预防作用

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[摘要] **目的** 探讨生脉饮口服液对劳力性热射病(EHS)大鼠凝血功能障碍的预防作用。**方法** SPF级雄性SD大鼠15只，均完成遥测温度胶囊植入术，术毕恢复1周后随机分为假手术组、热射病组、生脉饮组，每组5只。生脉饮组大鼠提前给予生脉饮0.02 ml/(g.d)灌胃5 d，热射病组及生脉饮组大鼠均在人工气候舱内(温度40 ℃，相对湿度70%)跑步，记录核心温度达到42 ℃时的运动时间及距离。采集3组大鼠血液，检测并比较其凝血酶原时间(PT)、活化部分凝血活酶时间(APTT)、血小板计数(PLT)及血乳酸(Lac)、血栓调节蛋白(TM)、凝血酶敏感蛋白-1(TSP-1)、血管性血友病因子(vWF)、纤溶酶原激活物抑制物-1(PAI-1)水平；观察3组大鼠肝、肾、肺、肠、心脏组织的病理改变。**结果** 生脉饮组大鼠核心温度达到42 ℃时的运动距离及运动时间均较热射病组明显延长[(456.3 ± 92.3) m *vs.* (282.8 ± 87.5) m，*P*<0.05；(36.3 ± 6.3) min *vs.* (21.7 ± 7.0) min，*P*<0.05]。与对照组比较，热射病组大鼠PT及APTT均明显延长[(13.8 ± 0.7) s *vs.* (9.9 ± 0.7) s，*P*<0.05；78.3(36.0，120.0) s *vs.* 19.0(16.6，22.5) s，*P*<0.05]，Lac明显升高[(10.5 ± 2.0) mmol/L *vs.* (4.0 ± 0.7) mmol/L，*P*<0.05]，PLT明显降低[(590.3 ± 80.2) × 10^9/L *vs.* (1750.3 ± 283.0) × 10^9/L，*P*<0.05]，血浆TM、vWF、TSP-1及PAI-1水平均明显升高[2.1(1.8，2.7) ng/ml *vs.* 1.6(1.5 ± 1.7) ng/ml，*P*<0.05；(953.1 ± 60.0) pg/ml *vs.* (462.3 ± 37.0) pg/ml，*P*<0.05；(78.1 ± 19.8) ng/ml *vs.* (59.3 ± 12.0) ng/ml，*P*<0.05；(1945.7 ± 74.5) ng/ml *vs.* (1487.6 ± 259.1) ng/ml，*P*<0.05]。与热射病组比较，生脉饮组大鼠APTT明显缩短[36.6(31.1，46.1) s *vs.* 78.3(36.0，120.0) s，*P*<0.05]，PLT明显增高[(980.5 ± 302.4) × 10^9/L *vs.* (590.3 ± 80.2) × 10^9/L，*P*<0.05]，血浆TM、vWF、PAI-1水平均明显降低[1.7(1.6，1.8) ng/ml *vs.* 2.1(1.8，2.7) ng/ml，*P*<0.05；(701.6 ± 32.0) pg/ml *vs.* (953.1 ± 60.0) pg/ml，*P*<0.05；(1582.8 ± 71.6) ng/ml *vs.* (1945.7 ± 74.5) ng/ml，*P*<0.05]。热射病组大鼠的肝、肾、肺、肠、心脏病理学检查均可见血栓形成，生脉饮组大鼠病理学检查未见明显血栓形成。**结论** 生脉饮可减轻EHS大鼠的血管内皮损伤，减少凝血因子与血小板的消耗，对凝血功能障碍有预防作用。

[关键词] 生脉饮；劳力性热射病；凝血功能障碍；大鼠；预防

Preventive effect of Shengmaiyin on exertional heatstroke induced coagulopathy in rats

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[**Abstract**] **Objective** To explore the preventive effect of Shengmaiyin on coagulation dysfunction of exertional heatstroke (EHS) in rat. **Methods** Fifteen SPF male SD rats were randomly divided into sham operation group, heatstroke group, and Shengmaiyin group (5 each group) after implantation of telemetry temperature capsule for one week. Rats in Shengmaiyin group

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were given Shengmaiyin at 0.02 ml/(g·d) by gavage for five days. The rats in the heatstroke group and Shengmaiyin group ran in the artificial climate chamber (40 ℃, 70% humidity). The running time and distance were recorded when the core temperature reached 42 ℃. Blood samples from the three groups of rats were collected to evaluate prothrombin time (PT), activated partial thromboplastin time (APTT), platelet count (PLT), blood lactic acid (Lac), thrombomodulin (TM), thrombin sensitive protein-1 (TSP-1), von Willebrand factor (vWF) and plasminogen activator inhibitor-1 (PAI-1). Pathological changes were examined in the liver, kidney, lung, intestine, and heart. **Results** When the core temperature reached 42 ℃, the running distance and running time of rats in the Shengmaiyin group were significantly longer than those in the heatstroke group [(456.3 ± 92.3) m *vs.* 282.8 ± 87.5) m, *P*<0.05; (36.3 ± 6.3) min *vs.* (21.7 ± 7.0) min, *P*<0.05]. Compared with the control group, PT and APTT in the heatstroke group were significantly prolonged [(13.8 ± 0.7) s *vs.* (9.9 ± 0.7) s, *P*<0.05; 78.3(36.0, 120.0) s *vs.* 19.0(16.6, 22.5) s, *P*<0.05], Lac was significantly increased [(10.5 ± 2.0) mmol/L *vs.* (4.0 ± 0.7) mmol/L, *P*<0.05], and PLT decreased significantly [(590.3 ± 80.2) × 10^9/L *vs.* (1750.3 ± 283.0) × 10^9/L, *P*<0.05], plasma TM, vWF, TSP-1, and PAI-1 levels increased significantly [2.1(1.8, 2.7) ng/ml *vs.* 1.6(1.5 ± 1.7) ng/ml, *P*<0.05; (953.1 ± 60.0) pg/ml *vs.* (462.3 ± 37.0) pg/ml, *P*<0.05; (78.1 ± 19.8) ng/ml *vs.* (59.3 ± 12.0) ng/ml, *P*<0.05; (1945.7 ± 74.5) ng/ml *vs.* (1487.6 ± 259.1) ng/ml, *P*<0.05]. Compared with the rats in heatstroke group, the APTT of the rats in Shengmaiyin group was significantly shortened [36.6(31.1, 46.1) s *vs.* 78.3(36.0, 120.0) s, *P*<0.05], and the PLT elevated significantly [(980.5 ± 302.4) × 10^9/L *vs.* (590.3 ± 80.2) × 10^9/L, *P*<0.05], plasma TM, vWF and PAI-1 levels were significantly reduced [1.7(1.6, 1.8) ng/ml *vs.* 2.1(1.8, 2.7) ng/ml, *P*<0.05; (701.6 ± 32.0) pg/ml *vs.* (953.1 ± 60.0) pg/ml, *P*<0.05; (1582.8 ± 71.6) ng/ml vs. (1945.7 ± 74.5) ng/ml, *P*<0.05]. Thrombosis was found in liver, kidney, lung, intestine, and heart in heat stroke group, while no appreciable thrombosis was observed in Shengmaiyin group. **Conclusion** Shengmaiyin can relieve vascular endothelial cell injury, reduce consumption of coagulation factors and platelets, and prevent coagulation dysfunction in rats with EHS.

[**Key words**] Shengmaiyin; exertional heatstroke; coagulopathy; rats; prevention

劳力性热射病(exertional heatstroke，EHS)是一种因高强度运动引起机体产热与散热失衡，导致核心温度>40 ℃并伴有多器官功能损伤的危重疾病[1]。流行病学调查显示，超过40%的EHS患者合并凝血功能障碍，此时患者的病死率超过50%[2-3]。热射病患者的核心温度明显升高可导致血管内皮细胞损伤，释放大量组织因子，激活凝血瀑布，造成凝血酶大量活化，凝血底物过度消耗，引起凝血功能障碍甚至弥散性血管内凝血(disseminated intravascular coagulation，DIC)[4-5]。因此，阻断EHS引起凝血功能障碍的病理生理途径是改善EHS相关凝血功能障碍患者预后的重要措施[6-7]。

中医学认为，热射病属“暑厥”范畴，EHS为阳暑，阳暑之极为毒热，易伤津耗气，致气虚血瘀。生脉饮出自《医学启源》，由人参(党参)、麦冬、五味子三味药物组成，具有益气生津的功效，常用于治疗心功能不全、心肌炎、心律不齐等疾病[8-9]。有研究报道，生脉散可降低热射病大鼠血浆炎性因子如白细胞介素-1、白细胞介素-6及肿瘤坏死因子等的水平，并延长热射病大鼠的生存时间[10]。但生脉饮对热射病相关凝血功能障碍是否有效尚未见报道。本研究探讨了生脉饮口服液(党参方)对EHS相关凝血功能障碍的预防作用。

1 材料与方法

1.1 实验动物与仪器 本研究经解放军联勤保障部队第908医院批准(动物伦理号：908yyLL031)，实验过程按照实验动物的管理及规定进行。15只SPF级雄性SD大鼠购于长沙天勤生物技术有限公司(动物生产许可证号：SCXK[湘]2019-0014)，适应性饲养7 d (5只/笼)，环境温度(25 ± 1) ℃，相对湿度40%~50%，大鼠自由摄食、摄水。Sv-223植入式遥测温度胶囊(深圳菲明格科技有限公司)，KW-PT动物跑步机、KW-PT-WS人工气候箱(南京卡尔文医疗科技有限公司)，BC-2600vet全自动动物血液分析仪(深圳迈瑞医疗科技有限公司)，ACL-TOP700全自动凝血分析仪、GEM premier 3500血气分析仪(美国沃芬公司)，汇松MB-530多功能酶标仪(深圳汇松公司)，Phenix-BMC100凤凰生物显微镜(江西凤凰光学科技有限公司)。

1.2 实验分组 15只SPF级雄性SD大鼠均完成遥测温度胶囊植入术，术毕恢复1周后，采用随机数字表法分为对照组、热射病组、生脉饮组，每组5只。生脉饮组大鼠提前给予生脉饮(北京同仁堂)0.02 ml/(g·d)灌胃5 d[11]，对照组及热射病组均以等量生理盐水灌胃5 d。模型复制前测定各组大鼠的体重及核心温度，差异均无统计学意义(*P*>0.05，表1)。

1.3 遥测温度胶囊植入术 15只大鼠均于造模前1周完成温度胶囊植入术[12-13]：术前24 h禁食，允许少量摄水，术前30 min刺激大鼠排便并称重。采用45 mg/kg戊巴比妥腹腔麻醉后将大鼠置于手术台，

表1 各组大鼠实验前基础数据比较($\bar{x}\pm s$，n=5)

Tab.1 Comparison of basic data of rats in each group before experiment ($\bar{x}\pm s$, n=5)

组别	体重(g)	核心温度(℃)
对照组	199.5 ± 2.3	36.8 ± 0.1
热射病组	200.8 ± 3.1	37.2 ± 0.3
生脉饮组	201.5 ± 2.7	37.1 ± 0.4
F	0.061	3.720
P	0.940	0.551

消毒后于腹部前正中线切开，切口长度为1~2 cm。将消毒后的遥测温度胶囊置入大鼠腹腔，逐层缝合关闭腹腔，消毒手术部位。术后每天观察大鼠伤口情况。

1.4 EHS大鼠模型制备 大鼠于造模前24 h禁食。将实验舱内环境温度设定为40 ℃，相对湿度为70%，大鼠放入动物跑步机中(坡度为0)以5 m/min的初速度开始跑步，速度达到15 m/min后持续。在每条跑道末端设置电极，电刺激强度为1 mA，迫使大鼠持续奔跑，以接受电刺激仍拒绝跑步5 s定义为疲劳。在大鼠运动过程中实时监测核心温度，以大鼠出现疲劳且核心温度达到42 ℃视为EHS造模成功[14-15]。

1.5 凝血指标检测 当热射病组与生脉饮组大鼠EHS模型复制成功时，立即使用乙二胺四乙酸(ethylene diamine tetraacetic acid，EDTA)管采集血液，采用全自动动物血液分析仪检测血小板计数(platelet count，PLT)；使用枸橼酸钠抗凝管(枸橼酸钠与血液比例为1∶9)采集大鼠血液，室温下3000 r/min离心10 min分离血清，采用全自动凝血分析仪检测凝血酶原时间(prothrombin time，PT)、活化部分凝血活酶时间(activated partial thromboplastin time，APTT)；使用肝素化注射器抽取0.5 ml大鼠血液，采用血气分析仪检测血乳酸(lactic acid，Lac)水平。采用酶联免疫吸附法检测大鼠血浆中血栓调节蛋白(thrombomodulin，TM)、凝血酶敏感蛋白-1(thrombin-sensitive protein-1，TSP-1)、血管性血友病因子(von Willebrand factor，vWF)、纤溶酶原激活物抑制物-1(plasminogen activator inhibitor-1，PAI-1)水平。取大鼠血浆/标准品100 μl加入反应孔，按照试剂说明书依次完成混匀、温浴、洗涤、加入抗体、温浴、显色等操作步骤，于酶标仪450 nm处测定吸光度值。对照组同时采血检测上述指标。

1.6 组织病理学检查 实验结束后取所有大鼠心脏、肝脏、肺、肾脏、十二指肠组织，置于4%甲醛溶液中固定48 h，常规石蜡包埋并切片(切片厚度约5 μm)，将切片用二甲苯、乙醇梯度脱蜡后苏木精染色5 min，蒸馏水冲洗后用盐酸乙醇分化30 s，温水复浴5 min，伊红复染5 min，常规脱水及封片。在400倍显微镜下观察，每个器官随机选择5个视野，观察组织中有无血栓形成。

1.7 统计学处理 采用SPSS 26.0软件进行统计学分析。以单样本S-W法对计量资料进行正态性检验，符合正态分布的计量资料以$\bar{x}\pm s$表示，多组间比较采用方差分析，进一步组间两两比较时，满足方差齐性者采用LSD-t法，不满足者采用Tamhane's T2法；非正态分布的计量资料以$M(Q_1, Q_3)$表示，组间比较采用秩和检验。P<0.05为差异有统计学意义。

2 结 果

2.1 热射病组与生脉饮组大鼠的状态及运动量比较 热射病组与生脉饮组大鼠跑步至核心温度达到42 ℃时均处于力竭状态，具体表现为精神萎靡、毛发耸立、呼吸急促，口腔或鼻腔出现大量粉红色泡沫状液体，四肢肿胀、发绀。生脉饮组大鼠核心温度达到42 ℃时的运动距离及运动时间均较热射病组明显延长，差异有统计学意义(P<0.05，表2)。

表2 热射病组与生脉饮组大鼠运动时间及运动距离比较($\bar{x}\pm s$，n=5)

Tab.2 Comparison of exercise time and distance between heatstroke group and Shengmaiyin group ($\bar{x}\pm s$, n=5)

组别	运动时间(min)	运动距离(m)
热射病组	21.7 ± 7.0	282.8 ± 87.5
生脉饮组	36.3 ± 6.3	456.3 ± 92.3
t	-3.083	-2.728
P	0.022	0.034

2.2 各组大鼠实验室指标比较 与对照组比较，热射病组PT、APTT、Lac明显升高，PLT明显降低，差异均有统计学意义(P<0.05)；与热射病组比较，生脉饮组大鼠PT、APTT、Lac明显降低，PLT明显增高，差异均有统计学意义(P<0.05，表3)。

2.3 各组大鼠凝血分子标志物水平比较 与对照组比较，热射病组血浆TM、vWF、TSP-1、PAI-1水平明显升高，差异均有统计学意义(P<0.05)；与热射病组比较，生脉饮组的血浆TM、vWF、PAI-1水平明显降低，差异均有统计学意义(P<0.05)，TSP-1水平虽然有降低趋势，但差异无统计学意义(P>0.05，表4)。

2.4 病理学检查结果 对照组大鼠的肺、肠、肾、肝脏及心脏组织切片均未见异常。热射病组大鼠肺组织的肺泡壁中度增厚，肺泡腔狭窄，有较多中性粒细胞浸润，局部血栓形成；肠管扩张，肠绒

表3 各组大鼠实验室指标比较(n=5)

Tab.3 Comparison of laboratory indexes of rats in each group (n=5)

组别	PT(s, $\bar{x}\pm s$)	APTT[s, $M(Q_1, Q_3)$]	Lac(mmol/L, $\bar{x}\pm s$)	PLT($\times 10^9$/L, $\bar{x}\pm s$)
对照组	9.9 ± 0.7	19.0(16.6, 22.5)	4.0 ± 0.7	1750.3 ± 283.0
热射病组	13.8 ± 0.7(1)	78.3(36.0, 120.0)(1)	10.5 ± 2.0(1)	590.3 ± 80.2(1)
生脉饮组	10.6 ± 0.5(2)	36.6(31.1, 46.1)(1)(2)	6.2 ± 2.0(2)	980.5 ± 302.4(1)(2)
F/H	47.610	7.785	16.035	23.489
P	<0.001	0.020	0.001	<0.001

PT. 凝血酶原时间；APTT. 活化部分凝血活酶时间；Lac. 血乳酸；PLT. 血小板计数；与对照组比较，(1)P<0.05；与热射病组比较，(2)P<0.05

表4 各组大鼠凝血分子标志物水平比较(n=5)

Tab.4 Comparison of coagulation molecular markers of rats in each group (n=5)

组别	TM[ng/ml, $M(Q_1, Q_3)$]	vWF(pg/ml, $\bar{x}\pm s$)	TSP-1(ng/ml, $\bar{x}\pm s$)	PAI-1(ng/ml, $\bar{x}\pm s$)
对照组	1.6(1.5, 1.7)	462.3 ± 37.0	59.3 ± 12.0	1487.6 ± 259.1
热射病组	2.1(1.8, 2.7)(1)	953.1 ± 60.0(1)	78.1 ± 19.8(1)	1945.7 ± 74.5(1)
生脉饮组	1.7(1.6, 1.8)(2)	701.6 ± 32.0(1)(2)	63.1 ± 5.5	1582.8 ± 71.6(2)
F	7.212	115.527	4.527	6.369
P	0.027	<0.001	0.048	0.016

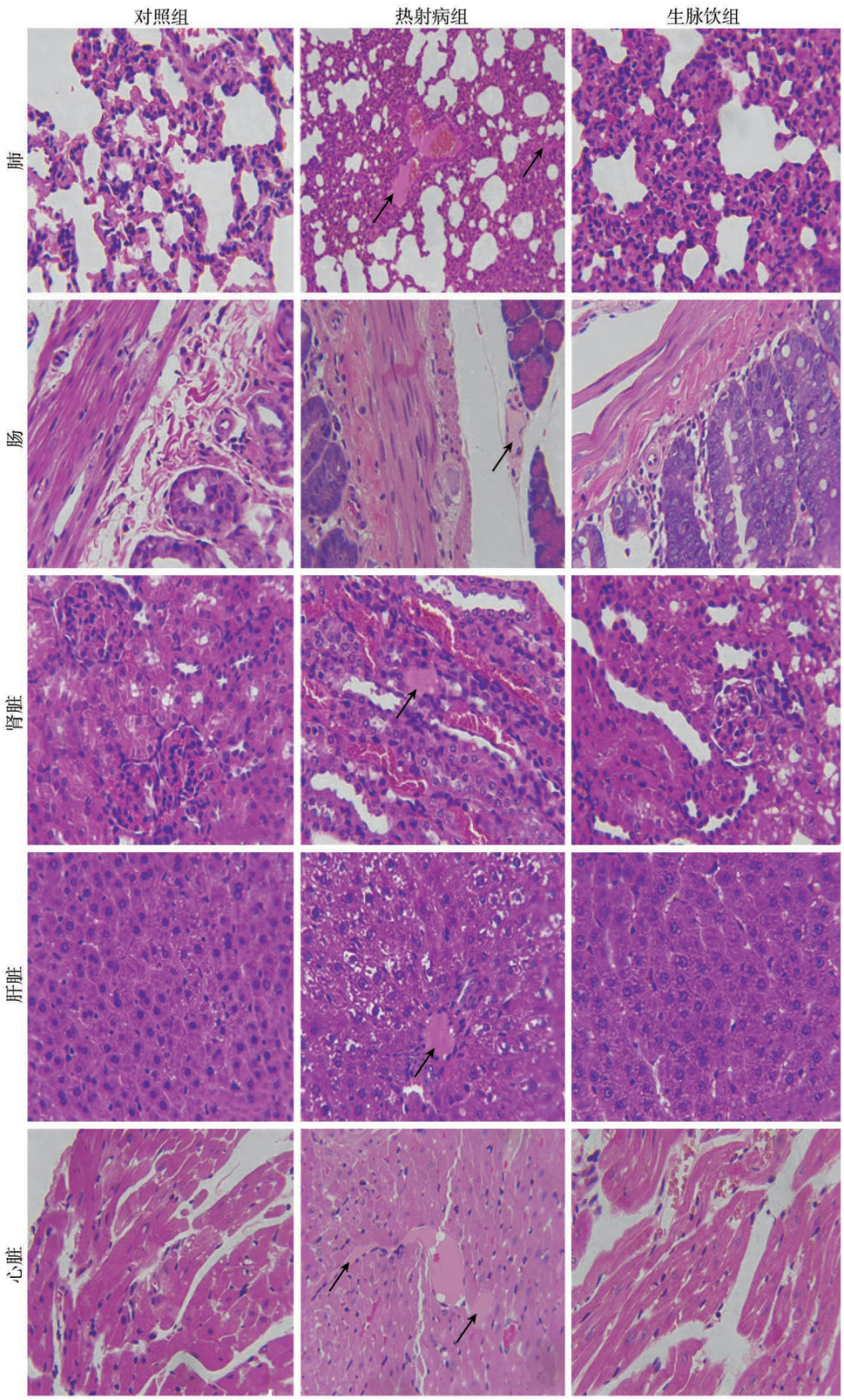
TM. 血栓调节蛋白；vWF. 血管性血友病因子；TSP-1. 凝血酶敏感蛋白-1；PAI-1. 纤溶酶原激活物抑制物-1；与对照组比较，(1)P<0.05；与热射病组比较，(2)P<0.05

毛结构被破坏，顶端可见空腔及嗜酸性物质，黏膜上皮与固有层分离，微血栓形成；肾小球及肾小管间质内毛细血管充血，微血栓形成，肾小管管腔明显扩张，腔内可见嗜酸性物质及中性粒细胞浸润；肝细胞肿胀明显，肝窦狭窄，可见吞噬黄色素的肝巨噬细胞，有大量炎性细胞浸润及微血栓形成；心肌细胞少量坏死，细胞核固缩、碎裂，可见空泡样变性及微血栓形成。生脉饮组大鼠肺组织的肺泡壁广泛轻度增厚，可见散在中性粒细胞浸润；肠组织可见毛细血管淤血，少量黏膜上皮细胞坏死、脱落；肾小管上皮细胞轻度水肿，毛细血管淤血，散在炎性细胞浸润；肝细胞空泡变性，部分呈脂肪样变，有少量炎性细胞浸润；少量心肌细胞呈现肿胀；各器官病理切片未见明显血栓(图1)。

3 讨　论

本课题组既往研究证实，EHS大鼠在高温环境下运动，当核心温度达到40 ℃时，可出现血管内皮损伤及PLT降低，且随着核心温度升高，凝血功能障碍会明显加重[16]。本研究中热射病组大鼠核心温度达42 ℃时，血管内皮细胞损伤标志物(如血浆TM、vWF、PAI-1)水平明显升高，凝血功能指标PT、APTT明显延长，Lac水平也明显升高，且病理结果显示心脏、肺、肝脏、肠、肾脏的小血管内均出现明显血栓。这表明热射病时血管内皮损伤可启动凝血系统活化，在实质器官广泛形成微血栓，导致微循环障碍及器官灌注不足，从而使无氧酵解增加，乳酸生成增多，局部酸中毒又加重了微循环障碍，促进微血栓形成，进而形成消耗性凝血病，直至发生DIC[17]。热射病时大量体液丢失，导致有效循环容量不足，也会造成组织低灌注，表现为Lac水平增高[18]。此外，肠道屏障破坏诱发的脓毒症也会加重凝血功能障碍[19]。因此，早期改善组织灌注、保护血管内皮功能及抑制凝血系统的显著激活可能是减轻凝血功能障碍的有效方法[20]。

中医学认为，中暑可分为阳暑与阴暑，阳暑系烈日暴晒或高强度劳动所致，其发病机制为暑邪伤人导致津液耗损、阴气枯竭[21]。生脉饮(党参方)由经典名方生脉饮改进而来，君药党参可平补肺气、养血生津，臣药麦冬可清热除烦、养阴生津，佐药五味子能益气生津、气阴双补。因此，理论上生脉饮可用于EHS的防治。既往研究显示，生脉饮可改善机体血液循环，增强细胞能量代谢，清除过多的活性氧(reactive oxygen species，ROS)，具有明显的抗疲劳功效[22]。本研究中生脉饮组大鼠在EHS制模前5 d接受生脉饮口服液干预，在制模时生脉饮组大鼠达到42 ℃核心温度的跑步时间及距离均明显延长，Lac水平明显下降，表明生脉饮可改善大鼠的热耐受能力，与既往研究应用生脉散汤剂延长经典型热射病大鼠生存时间的结果一致[23]。病理结果显示，尽管生脉饮组大鼠各器官仍存在较明显的细胞水肿及炎性细胞浸润，但未见明显的微血栓形成。与热射病组比较，生脉饮组大鼠的APTT明显缩短，PLT明显升高，提示生脉饮可减轻热射病大



黑色箭头为血栓形成

图1 各组大鼠器官病理学改变(HE染色 ×400)

Fig.1 Pathological changes of different organs of rats in each group (HE ×400)

鼠凝血因子及血小板的过度消耗。

热射病致凝血功能障碍的主要机制包括热打击造成内皮细胞损伤、热损伤相关的细胞死亡、肠源性感染继发脓毒性凝血功能障碍、循环衰竭导致组织缺氧引起凝血底物消耗等病理生理过程[24]。既往已有文献证实，生脉散或其注射液能减轻热射

病或循环衰竭时的炎性因子释放及氧化应激，上调糖皮质激素受体水平，改善重要器官(如脑、肾)的组织灌注[25-27]。本研究对血管内皮细胞分子标志物(TM、vWF、PAI-1)及血小板功能标志物(TSP-1)进行检测，结果显示，热射病组大鼠TM、vWF、PAI-1及TSP-1水平均较对照组明显升高，生脉饮组大鼠的TM、vWF及PAI-1水平较热射病组均明显降低，但TSP-1水平与热射病组比较差异无统计学意义。TM可辅助蛋白C发挥抗凝及抗血小板作用；vWF可激活血小板，促进血小板性血栓形成；PAI-1能抑制组织纤溶酶原激活物(tissue plasminogen activator，t-PA)的活性，发挥抑制纤溶的作用[28]。这提示生脉饮能通过减轻热射病时血管内皮细胞的损伤，调节内源性抗凝及抗纤溶活性，减轻血小板活化，进而减少微血栓形成。

本研究的不足之处主要有以下几个方面：(1)采用商品化的生脉饮口服液(党参方)，未对药物的具体活性成分进行详细鉴定；(2)通过制模前口服生脉饮来研究该药对EHS的预防作用，而未对其治疗作用进行探讨；(3)只对可发挥内源性抗凝、促血小板聚集及纤溶抑制的血管内皮损伤标志物进行检测，对生脉饮预防EHS的作用机制探讨不够深入。接下来的研究可深入探讨生脉饮预防热射病性凝血功能障碍的分子机制，并评估其在临床上预防热射病发生的实际效果。

综上所述，生脉饮可通过改善热射病大鼠的血管内皮功能来减少凝血底物的消耗及微血栓形成，减弱凝血时间延长及PLT减少的程度，从而缓解热射病大鼠的凝血功能障碍。

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