

抗心律失常药对截肢大鼠炎症因子表达及心肌电活动的影响

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【摘要】 目的:观察抗心律失常药对截肢大鼠炎症因子表达及心肌电活动的影响。

方法:选取 30 只健康清洁级雄性 SD 大鼠,随机分为 A 组、B 组、C 组、D 组和 E 组,每组 6 只,建立左后肢截肢手术创伤模型,其中 A 组给予生理盐水,B 组、C 组、D 组和 E 组分别给予利多卡因(2 mg/kg)、普萘洛尔(7 mg/kg)、胺碘酮(200 mg/kg)和维拉帕米(20 mg/kg),记录并比较手术前后大鼠心率、QT 间期、PR 间期、单相动作电位(MAP)振幅、左室收缩压(LVSP)变化,及肿瘤坏死因子- α (TNF- α)、白细胞介素-6(IL-6)和 C 反应蛋白(CRP)水平。 **结果:**C 组、D 组和 E 组术后 15 min、30 min、60 min 时心率明显低于 A 组和 B 组($P < 0.05$);B 组、C 组、D 组和 E 组术后 15 min、30 min、60 min 和 120 min 时 PR 间期、QT 间期高于 A 组($P < 0.05$);B 组术后 15 min、30 min、60 min 和 120 min 时 MAP 振幅明显低于 A 组、C 组、D 组和 E 组($P < 0.05$);B 组、C 组、D 组和 E 组术后 15 min、30 min、60 min 和 120 min 时 LVSP 明显低于 A 组($P < 0.05$);A 组、B 组、C 组、D 组和 E 组术后 2 h 时血清 TNF- α 、IL-6 和 CRP 比较差异均无统计学意义。 **结论:**抗心律失常药有助于减轻截肢创伤对大鼠心肌电活动的影响,但对炎症因子水平无明显作用。

【关键词】 抗心律失常药;截肢大鼠;炎症因子;心肌电活动

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Effects of antiarrhythmic drugs on the expression of inflammatory factors and the electrical activity of myocardium in amputated rats ZHAO Guixiang, LIU Jia Department of Cardiology, the Sixth Affiliated Hospital, Xinjiang Medical University, Urumuqi 830000, China

【Abstract】 Objective: To investigate the effect of antiarrhythmic drugs on the expression of inflammatory factors and the electrical activity of myocardium in amputated rats. **Methods:** A total of 30 healthy and clean-grade male SD rats were randomly divided into group A, group B, group C, group D and group E, with 6 rats in each group. The model of left hindlimb amputation injury was established in each group. The rats in the group A were given normal saline, and rats in the group B, group C, group D and group E were given lidocaine (2 mg/kg), propranolol (7 mg/kg), amiodarone (200 mg/kg) and verapamil (20 mg/kg), respectively. The heart rate, QT interval, PR interval, monophasic action potential (MAP) amplitude, left ventricular systolic pressure (LVSP), and the level of tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6) and C-reactive protein (CRP) were measured before and after the operation. **Results:** The heart rate of group C, group D and group E at 15 min, 30 min and 60 min after surgery were significantly lower than that of group A and group B (all $P < 0.05$). The PR interval and QT interval of group B, group C, group D and group E at 15 min, 30 min, 60 min and 120 min after surgery were higher than that of group A (all $P < 0.05$). The amplitude of MAP at 15 min, 30 min, 60 min and 120 min after surgery in group B was significantly lower than that

in group A, group C, group D and group E (all $P < 0.05$). In group B, group C, group D and group E, LVSP at 15 min, 30 min, 60 min and 120 min after surgery was significantly lower than that in group A (all $P < 0.05$). There was no statistically significant difference in level of serum TNF- α , IL-6 and CRP between group A, group B, group C, group D and group E at 2 hours after surgery (all $P > 0.05$).

Conclusions: Antiarrhythmic drugs could reduce the effect of amputation on the myocardial electrical activity in rats, but have no obvious effect on the expression of inflammatory factors.

【Key words】 Antiarrhythmic agents; Amputated rats; Inflammatory factor; Myocardial electrical activity

截肢创伤患者手术前后均会发生应激反应,已证实心血管事件是截肢手术围手术期并发症及术后死亡的主要原因,其中心律失常是常见的并发症之一^[1]。心肌电活动异常和炎症因子的异常表达是预测心血管事件的重要指标,传统临床治疗心律失常的主要药物包括钠通道阻滞剂、 β 受体拮抗剂、延长动作电位时程药物及钙通道阻滞药,其中代表药物分别是利多卡因、普萘洛尔、胺碘酮和维拉帕米。对截肢手术患者术后相关心肌电及炎症反应的研究很少^[2-3],本研究利用单相动作电位技术观察了抗心律失常药对截肢大鼠炎症因子表达及心肌电活动的影响。

1 材料与方法

1.1 实验动物

30 只健康清洁级雄性 SD 大鼠,8 周龄,250~300 g,购自于新疆医科大学基础研究室,许可证号 [SYXK(新)2016-0008],适应性喂养 1 周,饲养环境温度 22~25 °C,湿度 50%~60%,自然光照条件下,大鼠自由摄食饮水。

1.2 方法

将大鼠随机分为 5 组,每组 6 只,建立左后肢截肢手术创伤模型。使用 3%异戊巴比妥钠 80 mg/kg 对大鼠进行腹腔麻醉,仰卧位固定后切开左侧腹股沟皮肤,将股动静脉游离并于腹壁牵动下进行镜面结扎,于膝关节上 1.3 cm 处,将除股动脉和股静脉之外所有结构完全切除,最后将股动脉和股静脉剪断建立截肢创伤模型^[4]。A 组给予等量生理盐水,B 组、C 组、D 组和 E 组分别给予利多卡因(2 mg/kg)、普萘洛尔(7 mg/kg)、胺碘酮(200 mg/kg)和维拉帕米(20 mg/kg)。使用生理信号采集系统,皮下插入针型电极,记录标准 II 导联心电图,扫描速率设定 200 ms,

频率设定 10 kHz,观察大鼠的心率、QT 间期和 PR 间期变化。使用 MedLab U/4CS 生物信息采集处理系统(南京美易科技公司)实时记录(MAP),彩色多普勒超声检测大鼠左室收缩压(LVSP)并观测是否存在室性心律失常。于术前、术后 2 h 取尾静脉血 3 mL,静置 30 min 后,3 000 转/min 离心 10 min;分离血清,将血清转移至 EP 管中,保存于 -80 °C 的冰箱备用;酶联免疫法检测血清肿瘤坏死因子- α (TNF- α)、白细胞介素-6(IL-6)和 C 反应蛋白(CRP),酶标仪(美国 BD 公司)检测 450 nm 波长读数。

1.3 统计学分析

数据整理分析采用 SPSS 22.0 软件,TNF- α 、IL-6、CRP 等计量资料以均数 \pm 标准差表示,组间比较使用方差分析。 $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 各组大鼠手术前后心电图相关指标比较

C 组、D 组和 E 组术后 15、30、60 min 时心率明显低于 A 组和 B 组;B 组、C 组、D 组和 E 组术后 15、30、60、120 min 时 PR 间期、QT 间期高于 A 组($P < 0.05$)。见表 1。

2.2 各组大鼠手术前后 MAP 比较

B 组术后 15、30、60、120 min 时 MAP 振幅明显低于 A 组、C 组、D 组和 E 组($P < 0.05$),见表 2。

2.3 各组大鼠手术前后 LVSP 比较

B 组、C 组、D 组和 E 组术后 15、30、60、120 min 时 LVSP 明显低于 A 组($P < 0.05$),见表 3。

2.4 各组大鼠手术前后炎症因子比较

各组大鼠术后 2 h 血清 TNF- α 、IL-6 和 CRP 较术前均升高($P < 0.05$),但各组间比较差异均无统计学意义,见表 4。

表 1 各组大鼠心电图相关指标比较

指标	组别	术前	术后 15 min	术后 30 min	术后 60 min	术后 120 min
心率/次·min ⁻¹	A 组	203.55 ± 12.19	220.49 ± 13.84 ⁽¹⁾	231.15 ± 14.42 ⁽¹⁾	233.03 ± 17.65 ⁽¹⁾	203.50 ± 14.11
	B 组	202.80 ± 15.52	215.54 ± 15.51 ⁽¹⁾	227.41 ± 15.51 ⁽¹⁾	230.03 ± 18.82 ⁽¹⁾	205.56 ± 13.22
	C 组	204.45 ± 14.49	194.33 ± 14.45 ⁽¹⁾⁽²⁾	202.15 ± 15.60 ⁽¹⁾⁽²⁾	211.15 ± 15.56 ⁽¹⁾⁽²⁾	198.55 ± 10.22
	D 组	203.35 ± 13.30	195.51 ± 15.50 ⁽¹⁾⁽²⁾	203.36 ± 16.62 ⁽¹⁾⁽²⁾	208.89 ± 16.60 ⁽¹⁾⁽²⁾	200.15 ± 12.21
	E 组	205.51 ± 12.22	194.43 ± 16.60 ⁽¹⁾⁽²⁾	201.15 ± 17.80 ⁽¹⁾⁽²⁾	209.55 ± 17.50 ⁽¹⁾⁽²⁾	199.50 ± 13.31
	F	1.032	8.154	10.154	12.365	0.877
	P	0.565	<0.001	<0.001	<0.001	0.664
PR 间期/ms	A 组	67.51 ± 12.03	64.45 ± 12.10	66.40 ± 13.30	66.81 ± 12.21	68.03 ± 12.25
	B 组	68.41 ± 11.55	77.24 ± 10.03 ⁽¹⁾⁽²⁾	78.03 ± 11.50 ⁽¹⁾⁽²⁾	76.62 ± 13.12 ⁽¹⁾⁽²⁾	77.81 ± 12.12 ⁽¹⁾⁽²⁾
	C 组	67.90 ± 12.21	79.91 ± 12.25 ⁽¹⁾⁽²⁾	79.50 ± 15.11 ⁽¹⁾⁽²⁾	77.87 ± 13.31 ⁽¹⁾⁽²⁾	78.00 ± 16.10 ⁽¹⁾⁽²⁾
	D 组	68.11 ± 13.03	80.11 ± 11.54 ⁽¹⁾⁽²⁾	79.51 ± 16.60 ⁽¹⁾⁽²⁾	79.55 ± 14.11 ⁽¹⁾⁽²⁾	78.47 ± 12.33 ⁽¹⁾⁽²⁾
	E 组	67.94 ± 12.50	79.40 ± 12.11 ⁽¹⁾⁽²⁾	80.12 ± 17.15 ⁽¹⁾⁽²⁾	79.41 ± 16.64 ⁽¹⁾⁽²⁾	78.06 ± 13.55 ⁽¹⁾⁽²⁾
	F	1.101	8.977	12.214	12.248	15.154
	P	0.541	<0.001	<0.001	<0.001	<0.001
QT 间期/ms	A 组	190.41 ± 12.66	178.87 ± 11.44 ⁽¹⁾	175.51 ± 13.21 ⁽¹⁾	177.54 ± 15.12 ⁽¹⁾	189.51 ± 16.55
	B 组	191.31 ± 13.70	162.21 ± 12.26 ⁽¹⁾⁽²⁾	160.04 ± 14.11 ⁽¹⁾⁽²⁾	159.11 ± 14.22 ⁽¹⁾⁽²⁾	164.41 ± 12.80 ⁽¹⁾⁽²⁾
	C 组	189.46 ± 14.22	170.54 ± 12.60 ⁽¹⁾⁽²⁾	168.87 ± 15.80 ⁽¹⁾⁽²⁾	163.34 ± 12.11 ⁽¹⁾⁽²⁾	170.15 ± 19.33 ⁽¹⁾⁽²⁾
	D 组	190.41 ± 13.55	170.11 ± 13.60 ⁽¹⁾⁽²⁾	169.94 ± 16.88 ⁽¹⁾⁽²⁾	162.64 ± 14.80 ⁽¹⁾⁽²⁾	172.24 ± 17.80 ⁽¹⁾⁽²⁾
	E 组	190.70 ± 16.67	172.21 ± 12.89 ⁽¹⁾⁽²⁾	170.10 ± 17.90 ⁽¹⁾⁽²⁾	165.51 ± 16.70 ⁽¹⁾⁽²⁾	174.41 ± 15.90 ⁽¹⁾⁽²⁾
	F	1.006	8.114	9.687	11.547	13.344
	P	0.612	<0.001	<0.001	<0.001	<0.001

注:与术前比较,⁽¹⁾P<0.05;与 A 组比较,⁽²⁾P<0.05

表 2 各组大鼠 MAP 指标比较

指标	组别	术前	术后 15 min	术后 30 min	术后 60 min	术后 120 min
MAP 振幅/mv	A 组	15.20 ± 1.10	15.06 ± 1.09	14.32 ± 1.01 ⁽¹⁾	13.34 ± 1.01 ⁽¹⁾	10.50 ± 0.89 ⁽¹⁾
	B 组	15.11 ± 1.09	12.20 ± 1.00 ⁽¹⁾⁽²⁾	11.41 ± 0.97 ⁽¹⁾⁽²⁾	11.03 ± 0.87 ⁽¹⁾⁽²⁾	9.88 ± 0.90 ⁽¹⁾⁽²⁾
	C 组	15.08 ± 1.11	15.01 ± 1.01	14.20 ± 0.99 ⁽¹⁾	13.30 ± 0.97 ⁽¹⁾	10.68 ± 0.94 ⁽¹⁾
	D 组	15.12 ± 1.14	15.02 ± 1.03	14.11 ± 0.98 ⁽¹⁾	13.25 ± 0.96 ⁽¹⁾	10.55 ± 0.93 ⁽¹⁾
	E 组	15.09 ± 1.22	15.00 ± 1.00	14.08 ± 0.95 ⁽¹⁾	13.31 ± 0.95 ⁽¹⁾	10.60 ± 0.97 ⁽¹⁾
	F	1.216	10.544	15.541	14.458	11.846
	P	0.512	<0.001	<0.001	<0.001	<0.001

注:与术前比较,⁽¹⁾P<0.05;与 A 组比较,⁽²⁾P<0.05

表 3 各组大鼠 LVSP 相关指标比较

指标	组别	术前	术后 15 min	术后 30 min	术后 60 min	术后 120 min
LVSP/mmHg	A 组	87.54 ± 6.99	87.03 ± 5.97	88.03 ± 6.80	87.20 ± 8.15	85.12 ± 9.11
	B 组	88.03 ± 7.10	80.40 ± 7.21 ⁽¹⁾⁽²⁾	78.84 ± 6.22 ⁽¹⁾⁽²⁾	81.11 ± 9.02 ⁽¹⁾⁽²⁾	80.18 ± 7.22 ⁽¹⁾⁽²⁾
	C 组	89.03 ± 8.06	77.54 ± 6.90 ⁽¹⁾⁽²⁾	78.03 ± 5.54 ⁽¹⁾⁽²⁾	78.84 ± 9.11 ⁽¹⁾⁽²⁾	79.10 ± 5.64 ⁽¹⁾⁽²⁾
	D 组	88.00 ± 8.10	77.42 ± 7.11 ⁽¹⁾⁽²⁾	77.10 ± 6.10 ⁽¹⁾⁽²⁾	79.31 ± 9.11 ⁽¹⁾⁽²⁾	78.44 ± 6.10 ⁽¹⁾⁽²⁾
	E 组	87.59 ± 7.92	77.10 ± 6.94 ⁽¹⁾⁽²⁾	77.04 ± 6.03 ⁽¹⁾⁽²⁾	78.41 ± 8.22 ⁽¹⁾⁽²⁾	79.40 ± 5.87 ⁽¹⁾⁽²⁾
	F	1.201	10.154	10.787	13.654	13.021
	P	0.503	<0.001	<0.001	<0.001	<0.001

注:与术前比较,⁽¹⁾P<0.05;与 A 组比较,⁽²⁾P<0.05

表 4 各组大鼠手术前后炎症因子比较

组别	TNF/ng · mL ⁻¹		IL-6/pg · mL ⁻¹		CRP/mg · dL ⁻¹	
	术前	术后 2h	术前	术后 2h	术前	术后 2h
A 组	0.35 ± 0.10	0.75 ± 0.11 ⁽¹⁾	154.15 ± 14.14	215.56 ± 23.36 ⁽¹⁾	0.16 ± 0.05	0.20 ± 0.07 ⁽¹⁾
B 组	0.34 ± 0.09	0.76 ± 0.10 ⁽¹⁾	153.30 ± 13.20	220.10 ± 25.51 ⁽¹⁾	0.17 ± 0.06	0.21 ± 0.06 ⁽¹⁾
C 组	0.33 ± 0.12	0.78 ± 0.12 ⁽¹⁾	150.41 ± 15.51	218.45 ± 26.10 ⁽¹⁾	0.15 ± 0.04	0.22 ± 0.07 ⁽¹⁾
D 组	0.35 ± 0.08	0.76 ± 0.13 ⁽¹⁾	152.26 ± 16.03	219.44 ± 24.80 ⁽¹⁾	0.16 ± 0.07	0.21 ± 0.05 ⁽¹⁾
E 组	0.36 ± 0.12	0.77 ± 0.14 ⁽¹⁾	154.44 ± 13.80	217.71 ± 20.65 ⁽¹⁾	0.15 ± 0.07	0.20 ± 0.06 ⁽¹⁾
F	1.411	1.506	1.425	1.544	1.606	1.745
P	0.322	0.254	0.313	0.224	0.214	0.188

注:与术前比较,⁽¹⁾P<0.05

3 讨论

国内外学者对截肢手术并发症的研究主要集中在术后并发症的预防与处理,如残端出血、感染、皮肤坏死、深静脉血栓、继发性骨筋膜室综合征、残肢疼痛以及截肢后远端脏器继发损伤等。对截肢创伤导致心律失常的机制缺乏深入认识^[5-10]。本研究动态观察术前、术后不同时间点应用抗心律失常药物大鼠的心电图、右心室内膜 MAP 振幅和 LVSP 的变化。结果发现抗心律失常药物均可有效改善患者 PR 间期、QT 间期,其中普萘洛尔、胺碘酮和维拉帕米较利多卡因降低心率更明显。利多卡因较其他抗心律失常药物更有助于降低 MAP 振幅,其机制可能是利多卡因可通过阻断钠通道,延长动作电位及不应期,还可镇静神经系统,提高兴奋阈值,稳定神经细胞膜,减少病灶高频放电的扩散^[11-12]。

本研究提示抗心律失常药有助于减轻截肢对大鼠心肌电活动的影响,降低患者血压。截肢大鼠由于严重创伤刺激且易感染,导致炎症指标升高,而引起心肌电活动异常,进而出现高血压和心血管不良事件。利多卡因属于钠通道阻滞剂,对缺血或强心苷中毒所致的除极化型心律失常具有较强的抑制作用,可与强心苷竞争 Na⁺/K⁺-ATP,抑制强心苷中毒所致的滞后除极,进而发挥抗室性心律失常的作用^[13-14]。

手术前后炎症因子比较结果显示,各组大鼠术后 2 h 血清 TNF-α、IL-6 和 CRP 较术前升高,但组间比较无显著差异,提示抗心律失常药物对炎症因子并无明显作用。

综上所述,抗心律失常药有助于减轻截肢对大鼠心肌电活动的影响,但对炎症因子无明显作用。

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