

159-163

氯化铯诱发猫在体心脏触发性活动及其药物终止

李翠兰¹, 解景田 (南开大学生物系生理学教研室, 天津 300071, 中国) R965.1

Triggered activities induced by cesium chloride and terminated by drugs in cat heart *in vivo*

LI Cui-Lan, XIE Jing-Tian
(Division of Physiology, Department of Biology, Nankai University, Tianjin 300071, China)

ABSTRACT Monophasic action potential (MAP) of the left ventricular epicardium *in vivo* in 58 cats were recorded by using a contact electrode. The results showed that early afterdepolarization, delayed afterdepolarization, oscillatory afterpotential, and some kinds of triggered arrhythmias were induced by CsCl (iv 0.5 mmol · kg⁻¹). that these afterdepolarizations and triggered arrhythmias were prevented by sodium valproate, and that ventricular tachycardias induced by CsCl was terminated by lidocaine, moricizine, and sodium valproate.

KEY WORDS electrophysiology; heart; cesium; arrhythmia; anti-arrhythmia agents; action potentials

提要 为探讨触发性心律失常的机制及治疗,用接触电极记录 58 只猫在体心脏左室外膜单相动作电位(MAP)证明,氯化铯(CsCl)可诱发在体心脏早期后去极化(EAD),延时性后去极化(DAD)、振荡性后电位(OAP)及多种触发性心律失常。丙戊酸钠对 CsCl 诱发的后去极化及触发性心律失常有预防作用;利多卡因、乙吗噻嗪和丙戊酸钠对 CsCl 诱发的室速有对抗作用。

关键词 电生理学; 心脏; 铯; 心律失常; 抗心律失常药; 动作电位

心脏的后去极化分为早期后去极化(early afterdepolarization, EAD)和延时性后去极化(delayed afterdepolarization, DAD)。当它们

达到阈电位时即可诱发心脏的触发性心律失常⁽¹⁾。多种因素可诱发心脏的触发性活动,其中氯化铯(CsCl)是实验中最常用的工具药⁽²⁾。本文用心外膜接触电极记录单相动作电位(monophasic action potentials, MAPs)的方法观察了 CsCl 诱发猫在体心脏的后去极化与触发性心律失常的特征以及 4 种抗心律失常药物利多卡因(lidocaine), 丙戊酸钠(sodium valproate, SV), 乙吗噻嗪(ethmozine)和乙胺噻嗪(ethacizine)对触发性心律失常的预防和/或终止作用,为临床治疗提供了实验基础。

MATERIALS AND METHODS

家猫 58 只, 雌雄兼有, 体重 2.8 ± 0.7 kg。ip 乌拉坦 1 g · kg⁻¹ 麻醉。背位固定后开胸, 钩制心包床以暴露和固定心脏, 行人工呼吸。

用自制心外膜接触电极^(3,4)引导左心室 MAP 输入 SME-8201 微电极放大器; 同时经 DSP-F 生理放大器引导 II 导 ECG。两个放大信号都经 HF-1 四道后置放大器输入超级微机记忆系统进行数据采集、测量和分析。

实验共分三组。(1) 对照组: 猫 10 只, 在 iv 生理盐水 1 ml · kg⁻¹ 后每隔 15 min 给予 CsCl 0.5 mmol · kg⁻¹, 记录首次注入 CsCl 后 10, 20, 30 s, 1, 3, 5, 10 min 的 MAP 变化, 并记录诱发室速的 CsCl 累积阈剂量。(2) SV 预防组: 猫 8 只, 在 iv SV 150 mg · kg⁻¹ 2 min 后每隔 15 min 注射同剂量的 CsCl, 其它记录同(1)。两组 CsCl 给药次数不超过 4 次⁽²⁾。如第 4 次给 CsCl 后仍无室速出现, 此时诱发室速的阈剂量以 >2.5 mmol · kg⁻¹ 计。(3) 药物终止组: 猫 40 只, 在 CsCl 诱发室速后 20 s 分别给予利多卡因 5 mg · kg⁻¹, 丙戊酸钠 150 mg · kg⁻¹, 乙吗噻嗪 5

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1 Now in Department of Cardiology of First Central Hospital of Tianjin, Tianjin 300050, China.

mg · kg⁻¹ 和乙胺嘧啶 1 mg · kg⁻¹, 记录从给药到室速终止的时间。

乌拉坦由北京西中化工厂生产; CsCl 为华美生物工程公司产品; 乙吗啉嘧啶和乙胺嘧啶由天津药物研究院提供; 丙戊酸钠由湖南湖中制药厂生产。

数据采用 $\bar{x} \pm s$ 表示, 进行成组 *t* 检验。

RESULTS

1 CsCl 诱发在体心脏触发性活动的特征

1.1 实验表明, CsCl 诱发猫在体心脏后去极化的种类有 EAD, DAD (Fig 1), 其中包括振荡性后电位 (oscillatory afterpotential, OAP) (Fig 2). 对 144 次 iv CsCl 的统计, EAD, DAD 的诱发率分别为 79.7%, 25.0%. 动物在第一次给 CsCl 后多出现明显的 EAD, 其振幅 EADA 为 5.6 ± 2.9 mV, 占 MAPA $31 \pm 16\%$. EAD 可表现为拖尾形、平台形和凸起形三种不同的形态⁽⁴⁾. 它们的发生机制并无

本质的区别, 有时在同一动物同一次给 CsCl 后在不同的时间可分别看到三种形态, 而在多数情况下只表现为一种或两种形态. DAD 多出现于重复注射 CsCl 之后, 或单独表现为 DAD, 或 DAD, EAD 并存. 实验中记录到在体心脏 OAP 现象, 证实 MAP 同 TAP 一样可以反映 OAP^(1,5,6).

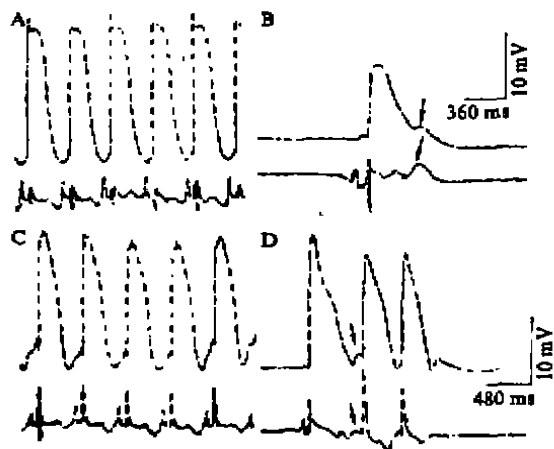


Fig 1. CsCl-induced afterdepolarization in cat heart *in vivo*. A) Control. B) EAD developed after iv CsCl (0.5 mmol · kg⁻¹), arrows show EAD and U waves. C) Control. D) DAD developed after iv CsCl (0.5 mmol · kg⁻¹); arrows show premature beats approximately at the peak of DAD. Upper tracing: left epicardial MAPs; Lower tracing: lead II of ECG

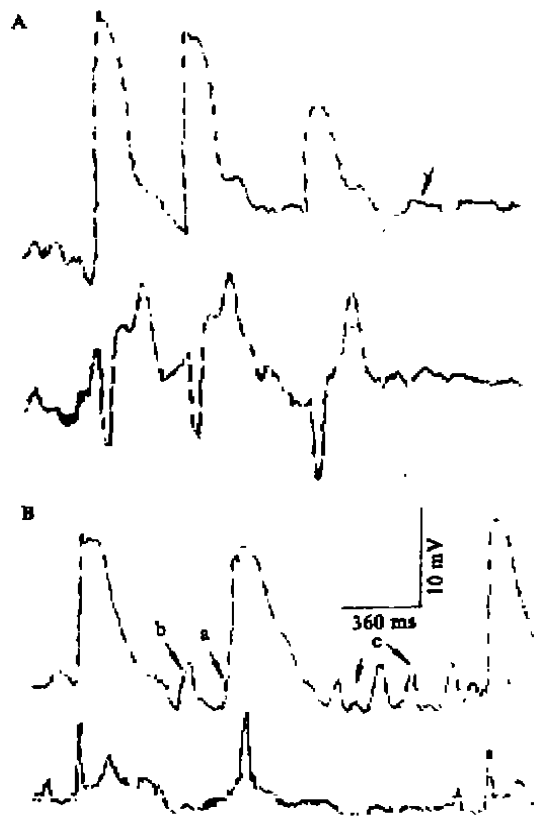


Fig 2. CsCl-induced oscillatory afterpotential in cat heart *in vivo*. A) Repolarization of the 1st MAP was interrupted by an EAD from which a premature beat arose. The 3rd MAP was followed by a DAD (arrow) which did not reach threshold and led to oscillatory afterpotentials followed by a quiescence at the depolarized level of potential. B) The afterdepolarization appearing in phase 4 showed either a premature beat (a) when it reached threshold, or a DAD (b) or OAP (c) when it was below the threshold. Upper tracing: left epicardium MAPs; Lower tracing: lead II ECG.

1.2 CsCl 可以诱发多种心律失常, 包括室性早搏、持续性单源及多源性室速, 扭转型室速及室颤等(Fig 3). 经室性早搏耦联间期(VB-CI)与 EAD 耦联间期(EAD-CI), DAD 耦联间期(DAD-CI)的比较提示, CsCl 诱发的心律失常可分为两类, 第一类: DAD-CI, EAD-CI 与 VB-CI 基本相同; VB-CI=0.76

DAD-CI + 126, $r=0.93$, $n=10$; VB-CI=0.93 EAD-CI + 37.8, $r=0.97$, $n=31$. 可见这种早搏发生在 DAD 或 EAD 的峰顶上, 此类心律失常可能由记录部位的后去极化所诱发. 第二类: VB-CI (577 ± 169 ms)较 EAD-CI (350 ± 109 ms)明显延长($P < 0.01$, $n=12$), 或无明显的后去极化仍有室性心律的出现, 推测第二类心律失常为非记录部位的后去极化所触发或由其它机制所引起.

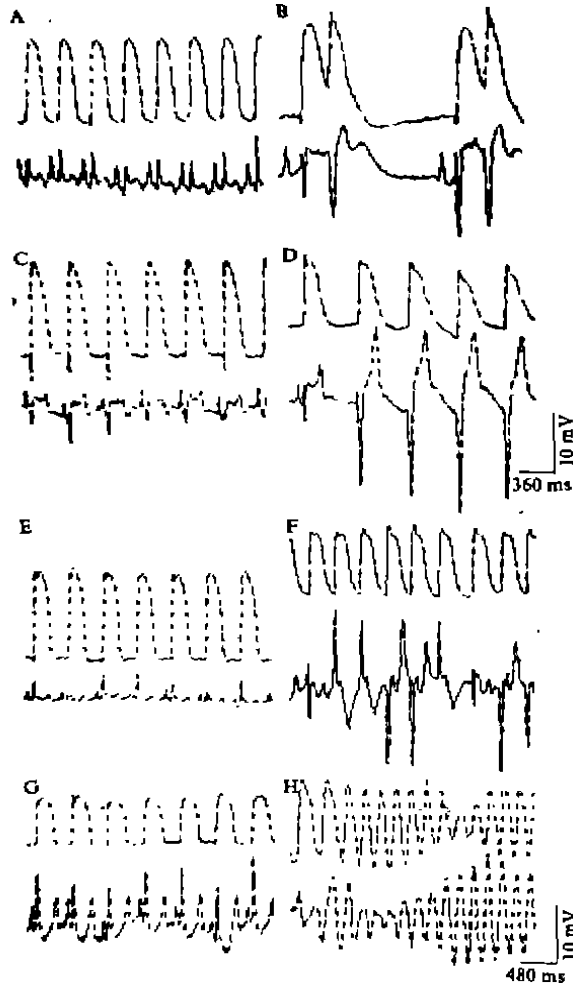


Fig 3. CsCl-induced triggered arrhythmias in cat heart *in vivo*. A, C, E, G were the controls of B, D, F, H respectively. B) Triggered ventricular bigeminy; D) Uniform ventricular tachycardia. F) Torsade de points. H) Ventricular fibrillation. Upper tracing: MAP; Lower tracing: ECG. A-D; E-H same scale.

1.3 CsCl 可使 MAPA 降低; V_{max} 减慢; MAPD₅₀ 与 MAPD₉₀ 延长(分别由对照值 164 ± 18 与 203 ± 19 延长至 271 ± 37 与 415 ± 115 ms, $P < 0.01$). 另外, 在 MAPD 延长的同时, 体表 ECG 上的 Q-T 间期也明显延长, 由对照组 0.23 ± 0.05 至 0.57 ± 0.09 s ($P < 0.01$). Q-T 间期的延长与 HR 的减慢, MAPD 的延长相一致, 故这种长 Q-T 现象具有心动过缓依赖性(bradycardia-dependent)⁽⁷⁾.

1.4 所有动物在给予 CsCl 后随着 EAD 的产生, 在 ECG 上同步出现对应的明显 U 波或 QTU 段改变. 且 U 波振幅随 EADA 的升高而升高, 不过明显的 U 波持续时间一般不超过 30 s, 之后代之以长 Q-T 现象, 但并不伴随 EAD 的迅速变化. 实验中没有观察到 DAD 与 U 波对应的现象.

2 抗心律失常药对 CsCl 诱发的触发性心律失常的预防和/或终止作用

2.1 丙戊酸钠对后去极化的影响及对心律失常的预防作用 与对照组相比, SV 对 CsCl 诱发的 EADA 无明显影响, 但却明显延长 EAD-CI. *iv* CsCl 后 10 s, EAD-CI 分别为: SV 组 352 ± 80 与对照组 259 ± 62 ms ($P < 0.05$). 另外, SV 不仅延长正常心机的 MAPD₅₀ (*iv* SV 之前为 176 ± 19 , 给药后为 203 ± 15 ms, $P < 0.05$), 而且还能在 *iv* CsCl 之后延长 MAPD₅₀, 由 176 ± 19 至 288 ± 35 ms, 而对照组仅由 164 ± 19 至 205 ± 23 ms

($P < 0.01$).

2.2 SV 预防组引起持续性室速的 CsCl 累积阈剂量($2.44 \pm 0.17 \text{ mmol} \cdot \text{kg}^{-1}$, $n=8$)比对照组($0.99 \pm 0.38 \text{ mmol} \cdot \text{kg}^{-1}$, $n=10$)明显提高($P < 0.01$), 而且 SV 预防组中只有 1 只动物在第 4 次给 CsCl 后出现室速, 未出现室速的动物占 89%; 而对照组全部在预定剂量内出现室速.

2.3 Tab 1 为 4 种抗心律失常药物终止室速时间的比较, 对照组不给予终止药物, 时间从室速出现到其自动终止计算.

Tab 1. Terminative time on CsCl-induced sustained ventricular tachycardias of 4 anti-arrhythmic drugs in cat heart *in vivo*. $\bar{x} \pm s$. * $P > 0.05$, *** $P < 0.01$ vs control.

	<i>n</i>	<i>t</i> / <i>s</i>
Control	11	76 ± 29
Lidocaine	14	$30 \pm 6^{**}$
Sodium valproate	12	$29 \pm 22^{***}$
Moricizine	11	$35 \pm 17^{**}$
Ethacizine	15	$73 \pm 27^*$

DISCUSSION

后去极化作为一种冲动起源异常的心律失常已日益受到重视. 本实验表明 CsCl 既可诱发 EAD, 又可诱发 DAD, 而以 EAD 居多. 我们还于在体心脏首次用 MAP 方法记录到 CsCl 诱发的 OAP. 本实验也进一步证实 CsCl 诱发 EAD 具有频率依赖性 or 心动过缓依赖性. 并于在体心脏上证明动作电位复极的延长是 CsCl 诱发 EAD 的先决条件之一⁽⁶⁾.

实验中观察到多例猫心电图的 U 波与 EAD 同步出现, 从它的波形变化和持续时间上可以发现 U 波的易变性⁽⁷⁾. 本实验看到明显的 U 波振幅随 EADA 增加而升高, 并提示 ECG 上异常 U 波能反映 MAP 上的 EAD⁽⁹⁾.

CsCl 可降低外向 K^+ 电流, 延缓动作电位

的复极过程, 在此基础上, 增加内向去极电流和 / 或降低外向复极电流都会促进 EAD 的发展⁽⁸⁻¹²⁾. 实验表明, 利多卡因, 乙吗噻啉和丙戊酸钠对 CsCl 诱发的持续性室速有明显终止作用. 利多卡因和乙吗噻啉的作用机制可能是抑制了 Na^+ 电流, 缩短了动作电位间期, 从而导致更快复极过程, 此为间接阻滞 EAD^(8,13). SV 有显著的抗实验性心律失常作用, 也有明显的临床疗效⁽¹⁴⁾. 本实验进一步证明 SV 具有明显的抗触发性心律失常的作用.

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163-166

间硝苯啶的高压液相色谱法测定及在兔体内的药物动力学

间硝苯啶
药物动力学
高压液相色谱法

梁颖彬、马小亚、武国杰、王莉芳、刘登科¹、邢建峰、赵更生 R969.1
(西安医科大学临床药理研究所, 西安 710004, 中国)

Determination of *m*-nifedipine and its pharmacokinetic study in rabbits by high-pressure liquid chromatography

LIANG Ying-Bin, MA Xiao-Ya, WU Guo-Jie, WANG Li-Fang, LIU Deng-Ke¹, XING Jian-Feng, ZHAO Geng-Sheng (Institute of Clinical Pharmacology, Xi'an Medical University, Xi'an 710004, China)

ABSTRACT A high-pressure liquid chromatographic method was developed for determination of *m*-nifedipine in plasma using a chemical bonded C-18 phase column (YWG-C₁₈, 10 μm, made in China) with nitrendipine as internal standard. To increase life of the YWG-C₁₈ column a mixture of methanol and 5 mmol · L⁻¹ phosphate buffer (70:30 vol/vol) was selected as mobile phase with a flow rate of 0.8 ml · min⁻¹. The method was sensitive to *m*-nifedipine 3

ng · ml⁻¹ plasma and the standard curve was linear from 10 to 1000 ng · ml⁻¹ with correlation coefficient of 0.99. The within-day and day-to-day precisions (CV) of this method were 4.5% and 7.0%, respectively, with recoveries of 95-102% (10-1000 ng · ml⁻¹). There was no interference with nifedipine, amiodarone, propranolol, and verapamil.

A pharmacokinetic study on *m*-nifedipine was carried out in 8 rabbits. A better computer fitted to a two-compartment model was observed using 3P87 program. The parameters obtained were as follow: V_c 6.3 L · kg⁻¹, Cl 0.021 L · kg⁻¹ · min⁻¹, $T_{1/2\alpha}$ 30 min, $T_{1/2\beta}$ 230 min, AUC 102 μg · min · ml⁻¹.

KEY WORDS high pressure liquid chromatography; *m*-nifedipine; pharmacokinetics

摘要 为分析生物样本中的间硝苯啶, 作者建立了用国产 YWG-C₁₈ 填充柱, 以含低浓度磷酸盐缓冲液和甲醇作流动相的 HPLC 法。方法准确、简捷、选择性强, 最低检测浓度 3 ng · ml⁻¹, 且色谱柱寿命大为延长, 间硝苯啶在兔体内代谢符合二室开放模型: V_c 6.3 L · kg⁻¹, Cl 0.021 L · kg⁻¹ · min⁻¹, $T_{1/2\alpha}$ 230

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¹Now in Tianjin Institute of Pharmaceutical Industry, Tianjin 300090, China.