

## Dauricine suppressed CsCl-induced early afterdepolarizations and triggered arrhythmias in rabbit heart *in vivo*<sup>1</sup>

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**KEY WORDS** dauricine; action potentials; cesium; arrhythmia

### ABSTRACT

**AIM:** To study the effect of dauricine on CsCl-induced early afterdepolarizations (EAD) and ventricular arrhythmias in rabbits. **METHODS:** Monophasic action potentials (MAP) of the left ventricle of the rabbit heart *in situ* were recorded with MAP recording technique. CsCl 1-2 mmol·kg<sup>-1</sup> iv was used to induce EAD and ventricular arrhythmias. **RESULTS:** CsCl resulted in decrease of MAP amplitude (MAPA,  $P < 0.05$ ) and prolongation of MAP duration at 90% repolarization (MAPD<sub>90</sub>,  $P < 0.01$ ), QRS, and R-R duration ( $P < 0.05$ ) compared with those before CsCl in the dauricine and control group. CsCl injection induced EAD that appeared within about 30 s and disappeared 5-15 min thereafter. EAD always preceded ventricular arrhythmias including ventricular premature beats and paroxysmal ventricular tachycardia. The EAD amplitude (EADA) in the dauricine group (26% ± 9% of MAPA) was smaller than that in the control group (52% ± 5% of MAPA,  $P < 0.05$ ) and the incidence of arrhythmias in dauricine group (28%) was lower than that in control group (80%,  $P < 0.05$ ). **CONCLUSION:** Dauricine exerted an antagonistic effect on EAD and suppressed triggered ventricular arrhythmias by decreasing EADA.

### INTRODUCTION

Triggered activity resulting from early after-

depolarizations (EAD) has been proposed as one of the mechanisms responsible for ventricular arrhythmias. Cesium chloride (CsCl) has been widely used in the induction of EAD *in vitro* and *in vivo* to study the mechanisms of arrhythmias and anti-arrhythmic drugs. In previous studies we demonstrated that dauricine, a bisbenzylisoquinoline alkaloid derivative, exerted an antagonistic action to early afterdepolarizations induced by quinidine<sup>[1]</sup> and delayed afterdepolarizations by many inducers such as phenylephrine, isoprenaline, onabain, and caffeine<sup>[2]</sup> in guinea pig papillary muscle. The effect of dauricine on EAD *in vivo* has not been reported. This study aimed to further study the effect of dauricine on EAD and ventricular arrhythmias induced by CsCl in rabbits.

### MATERIALS AND METHODS

**Drugs** Dauricine was a white powder supplied by Dr PAN Xi-Ping (Division of Plant Chemistry of this Institute,  $M_r$  624, mp 103-104 °C, purity > 98%). It was dissolved in normal saline to 0.5 g·L<sup>-1</sup>, pH 6.5-6.8. CsCl was purchased from Sigma Co and dissolved in normal saline to 0.5 mol·L<sup>-1</sup>.

**Experimental procedure** Rabbits of either sex weighing (2.3 ± 0.4) kg, provided by the Experimental Animal Center of Tongji Medical University (Certificate numbers of rabbits and animal house: 19-025 and 19-019), were randomly divided into two groups: (1) dauricine 0.5 mg·kg<sup>-1</sup>·min<sup>-1</sup> iv for 24 min; (2) normal saline (NS) 1 mL·kg<sup>-1</sup>·min<sup>-1</sup> iv for 24 min. When monophasic action potentials (MAP) and ECG recordings were obtained after intravenous infusion of dauricine or NS, CsCl 1-2 mmol·kg<sup>-1</sup> was administered into the femoral vein over a 15-30 s period. Similar recordings were made after iv CsCl for at least 20 min.

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**MAP recording** Rabbits were anesthetized with sodium pentobarbital ( $36 \text{ mg} \cdot \text{kg}^{-1}$ ). The femoral vein was cannulated for injection of drugs. After left sternotomy, the heart was exposed and suspended in pericardial cradle. A quadripolar contact electrode catheter (7F) for pacing and MAP recording (EP Technologies, Sunnyvale CA, USA) was introduced into the left ventricle through a tiny stab wound made in the free wall. The electrode tip was placed against the left ventricular anterior endocardium close to the apex. MAP signals were amplified by a high input impedance, MAP DC-coupled isolated, differential preamplifier (Model 300, EP Technologies)<sup>(3)</sup>. Together with surface ECG lead II, MAP signals were simultaneously displayed on oscilloscope and printed out on 8 channel physiologic recorder (Model RM 6000, Nihon Kohden) at paper speeds of  $25 - 100 \text{ mm} \cdot \text{s}^{-1}$ . The frequency response of the MAP recording system was DC to 5000 Hz.

**Definitions and measurement** (1) MAP amplitude (MAPA); the potential difference between the diastolic baseline and the crest of the plateau phase. (2) MAP duration at 90 % repolarization (MAPD<sub>90</sub>); interval in seconds from the onset of local activation to the time of 90 % repolarization. (3) EAD: either delay in repolarization or true depolarizations occurring during phase 2 or 3 of the MAP. (4) EAD amplitude (EADA); the difference between phase 4 and the first deviation or the crest of EAD from the smooth repolarization was defined as the percent of MAPA ( $\text{EADA}/\text{MAPA} \times 100 \%$ ). (5) EAD coupling interval (EADCI); the interval between phase 0 of the MAP and the peak or shoulder of the EAD that developed<sup>(4-6)</sup>.

**Data analysis** Data were expressed as  $\bar{x} \pm s$ . Statistical comparisons of results were performed with *t*-test or chi-square test.

## RESULTS

**Effect of CsCl on MAPA, MAPD<sub>90</sub>, QRS, and R-R duration** Before intravenous injection of CsCl, MAPA decreased and MAPD<sub>90</sub>, QRS duration prolonged in the dauricine group vs those in control group ( $P < 0.05$ ). CsCl  $1 - 2 \text{ mmol} \cdot \text{kg}^{-1}$  iv resulted in decrease of MAPA ( $P < 0.05$ ) and prolongation of MAPD<sub>90</sub> ( $P < 0.01$ ), QRS, and R-R duration ( $P <$

$0.05$ ) compared with before iv CsCl in the dauricine and control group (Tab 1).

**Tab 1. CsCl-induced changes of MAPA, MAPD<sub>90</sub>, duration of QRS, and R-R of rabbit heart.  $\bar{x} \pm s$ . <sup>a</sup> $P > 0.05$ , <sup>b</sup> $P < 0.05$ , <sup>c</sup> $P < 0.01$  vs control. <sup>d</sup> $P < 0.05$ , <sup>e</sup> $P < 0.01$  vs before iv CsCl.**

	Group	n	Before	After
MAPA/mV	Control	5	$22.7 \pm 2.8$	$17.6 \pm 3.2^c$
	Dau	7	$17.5 \pm 3.6^b$	$13.8 \pm 4.2^{bc}$
MAPD <sub>90</sub> /s	Control	5	$0.18 \pm 0.03$	$0.34 \pm 0.04^f$
	Dau	7	$0.23 \pm 0.06^b$	$0.34 \pm 0.07^c$
QRS/ms	Control	5	$51 \pm 8$	$60 \pm 20^c$
	Dau	7	$69 \pm 23^b$	$80 \pm 22^{bc}$
R-R/s	Control	5	$0.28 \pm 0.05$	$0.38 \pm 0.06^c$
	Dau	7	$0.33 \pm 0.09^b$	$0.45 \pm 0.15^b$

**Effect of dauricine on EAD and ventricular arrhythmias by CsCl** All MAP showed a smooth repolarization with no sign of EAD and no ventricular arrhythmias were present on ECG of all rabbits before CsCl was injected (Fig 1A). CsCl injection induced EAD that appeared within about 30 s and disappeared 5 - 15 min thereafter. EAD always preceded ventricular arrhythmias including ventricular premature beats and paroxysmal ventricular tachycardia (Fig 1B). There was no significant difference of EAD incidence between dauricine and control group ( $P > 0.05$ ). In contrast, the EADA in the dauricine group ( $26 \% \pm 9 \%$  of MAPA) was smaller than that in the control group ( $52 \% \pm 5 \%$  of MAPA,  $P < 0.05$ , Fig 1C) and the incidence of arrhythmias in the dauricine group (28 %) was lower than that in the control group (80 %,  $P < 0.05$ , Tab 2).

**Tab 2. Effects of dauricine ( $0.5 \text{ g} \cdot \text{L}^{-1} \cdot \text{min}^{-1}$  iv  $\times 24$  min) on EAD and triggered ventricular arrhythmias in the rabbit heart *in situ*.  $\bar{x} \pm s$ .**

<sup>a</sup> $P > 0.05$ , <sup>b</sup> $P < 0.05$  vs control.

	n	Incidence/%	EAD EADCI/s	EADA/%	Triggered/ %
Control	5	5/5 (100)	$0.20 \pm 0.04$	$52 \pm 5$	4/5 (80)
Dau	7	6/7 (86) <sup>a</sup>	$0.20 \pm 0.07^a$	$26 \pm 9^b$	2/7 (28) <sup>b</sup>

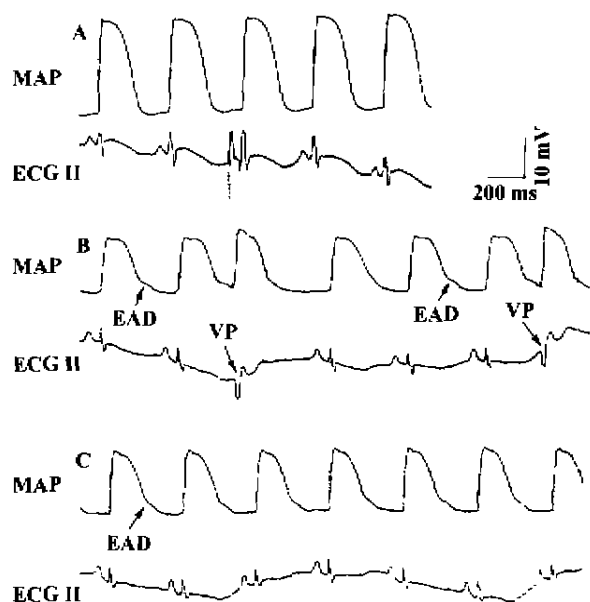


Fig 1. Effect of dauricine on early afterdepolarizations (EAD) and triggered ventricular arrhythmias induced by CsCl in rabbit heart. A) No EAD occurred before iv CsCl.  $n = 5$  rabbits. B) CsCl  $1 - 2 \text{ mmol} \cdot \text{kg}^{-1}$  iv-induced EAD and triggered ventricular premature (VP).  $n = 7$  rabbits. C) Dauricine  $12 \text{ mg} \cdot \text{kg}^{-1}$  iv pretreatment induced decrease of EAD amplitude and occurrence of triggered ventricular arrhythmias.  $n = 7$  rabbits.

## DISCUSSION

CsCl has been shown to depolarize the membrane potential and depress the plateau of the action potential<sup>[7]</sup>. It is primarily a blocker of the inward rectifying potassium current ( $I_{K1}$ ) and prolongs repolarization leading to generation of EAD<sup>[8]</sup>. In this study, CsCl  $1 - 2 \text{ mmol} \cdot \text{kg}^{-1}$  decreased MAPA and prolonged MAPD<sub>90</sub>, QRS, and R-R duration. The EAD were induced within about 30 s after CsCl injection. Ventricular arrhythmias were always preceded by the development of EAD and occurred only when EAD attained a certain amplitude. This present results are in accordance with those of Takahashi N, *et al*<sup>[3]</sup> and Di Francisco<sup>[9]</sup> and suggest that the EAD were closely related to arrhythmias.

EAD may occur when an inward depolarizing current exceeds an outward repolarizing current during phase 2 or phase 3 of the cardiac action potential. Increase of the former or decrease of the latter should facilitate EAD to develop. It was suggested that the

currents related to the induction of EAD were mainly slow inward calcium, sodium window current and repolarizing potassium currents. The present data demonstrated that dauricine decreased EADA and reduced the incidence of ventricular arrhythmias triggered by EAD. This may suggest that dauricine has an antagonistic effect on EAD and suppresses triggered ventricular arrhythmias by decreasing EADA. A recent study in guinea pig papillary muscles showed that dauricine could inhibit sodium and calcium currents<sup>[10]</sup>. This depressant effect of dauricine on EAD could be due to a decrease of the inward depolarizing currents.

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**蝙蝠葛碱抑制氯化铯诱发家兔在体心脏  
早后除极及心律失常<sup>1</sup>**

R972.2  
R965.2

夏敬生<sup>2</sup>, 屠洪<sup>3</sup>, 李真, 曾繁典 (同济医科大学临床药理研究所, 武汉 430030; <sup>3</sup>广东深圳红十字会医院心内科, 深圳 518029, 中国)

**目的:** 研究蝙蝠葛碱对氯化铯诱发家兔在体心脏早后除极及触发性心律失常的作用。 **方法:** 采用单向动作电位记录技术记录家兔在体心脏单向动作电位, 用氯化铯诱发家兔心脏早后除极及触发性心律失常。 **结果:** 静脉注射氯化铯 1-2 mmol·kg<sup>-1</sup>后 MAPA 降低, MAPD<sub>90</sub>, QRS 和 R-R 间期明显延长。 给氯化铯后 30 s 左右出现早后除极, 并由此触发室性早搏和室性心动过速。 蝙蝠葛碱降低早后除极幅度和心律失常发生率。 早后除极幅度对照组为 52% ± 5%, 蝙蝠葛碱组为 26% ± 9% (P < 0.05)。 心律失常发生率对照组为 80%, 蝙蝠葛碱组为 28% (P < 0.05)。 **结论:** 蝙蝠葛碱具有抗氯化铯所致早后除极及触发性心律失常作用。

**关键词** 蝙蝠葛碱; 动作电位; 铯; 心律失常

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药理

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