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雷尼替丁和西咪替丁对早期缺血心肌室颤阈及不应期离散度的影响

罗晓星、谭月华 (第四军医大学药理教研室，西安 710033，中国)

Effects of ranitidine and cimetidine on ventricular fibrillation threshold and dispersion of refractory period in early myocardial ischemia

LUO Xiao-Xing, TAN Yue-Hua

(Department of Pharmacology, Fourth Military Medical University, Xi-an 710033, China)

Abstract The effects of two H_2-receptor antagonists, ranitidine (Ran) and cimetidine (Cim), on the ventricular fibrillation threshold (VFT) and dispersion of the refractory period in animals with early acute myocardial ischemia induced by coronary artery ligation (CAL) were studied. The measurement of VFT was obtained in anaesthetized rats. The control group showed a decrease in VFT from 6.7±0.4 to 3.1±0.7 V 5 min after CAL, while Ran (15 mg/kg iv) and Cim (40 mg/kg iv) increased VFT from 2.8±0.7 to 5.4±1.7 V and from 3.1±0.8 to 8.1±2.7 V, respectively. By means of suction electrodes, FRP in different ischemic zones were recorded in anaesthetized rabbits, and differences between FRP in different zones were taken as the dispersion of FRP. After CAL, the control group exhibited a prolongation of FRP in central ischemic zone and a shortening of FRP in boundary zone, i. e., a dispersion of FRP was increased. Both Ran (5 mg/kg iv) and Cim (25 mg/kg iv) markedly decreased the extent of dispersion of FRP. It is concluded that the anti-arrhythmic effects of Ran and Cim may be attributable to increases in VFT and decreases in dispersion of FRP.

Key words ranitidine; cimetidine; histamine; myocardial infarction; ventricular fibrillation; myocardial refractory period

提要 结扎大鼠冠状动脉(CA)可降低室颤阈(VFT)，iv雷尼替丁(Ran) 15 mg/kg或西咪替丁(Cim)40 mg/kg，可分别使VFT自2.8±0.7，3.1±0.8 V提高至5.4±1.7，8.1±2.7 V。给兔结扎CA前iv Ran 5 mg/kg或Cim 25 mg/kg，可防止缺血中央区功能不应期(FRP)的延长和缺血边缘区FRP的缩短，降低不应期离散度。上述作用可能为Ran与Cim抗心律失常的电生理学基础。

关键词 雷尼替丁；西咪替丁；组胺；心肌梗塞；心室纤颤；心肌不应期

心脏组胺(histamine, H)含量丰富[1]，急性心肌缺血时，H大量释放是心律失常发生的诱因之一[2,3]。H所致急性缺血性快速型心律失常主要由H_2受体介导[4,5]。H_2受体拮抗剂雷尼替丁(ranitidine, Ran)和西咪替丁(cimetidine, Cim)抗早期缺血性心律失常的作用已得到证实[6]。本文进一步观察Ran、Cim对大鼠缺血心肌室颤阈(VFT)的影响，并采用吸引电极技术[7,8]，在兔在体缺血心肌上分析Ran和Cim的可能机理。

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Materials

Ran 为西南制药一厂产品，系微黄色结晶；Cim 为江苏武进制药厂产品。上述药品配成母液放冰箱中保存，临用前生理盐水(NS)稀释至所需浓度。

Methods and results

Ran 和 Cim 对大鼠缺血心肌 VFT 的影响 Sprague-Dawley 大鼠 18 只，体重 208±SD 24 g，♀♂不拘。戊巴比妥钠 60 mg/kg ip 麻醉，气管插管，正压呼吸(通气量 2 ml/100 g，频率 102 bpm)，示波器监视 II 导程 ECG。胸骨左缘开胸，暴露心脏，于冠脉前降支下穿线[6]，以备结扎。将两根铜制电极分别置于房室环和心尖处，并连于 FX-3 型电生理刺激器，施以波宽 0.7 ms，频率 50 Hz 的方波连续刺激。电压自 1 V 起，逐渐增加，直至出现室颤，此时电压记作 VFT。实验分 3 组：对照组，Ran 组，Cim 组。先分别测 3 组的 VFT，10 min 后，结扎 CA，再测 VFT。然后 iv 试药，对照组 iv NS 2 ml/kg，Ran 组 iv Ran 15 mg/kg，Cim 组 iv Cim 40 mg/kg，10 min 后再测 VFT。实验结果采用配对 t 检验法处理(Tab 1)。Ran 和 Cim 均可显著提高大鼠缺血心肌的 VFT。

Tab 1. Effects of ranitidine (Ran) and cimetidine (Cim) on ventricular fibrillation (VF) threshold of ischemic myocardium induced by coronary artery ligation (CAL) in anaesthetized rats. $n=6$, $\bar{x}\pm SD$. $^{***}P<0.01$ *vs* pre-CAL; $^{\dagger}P>0.05$, $^{\dagger\dagger\dagger}P<0.01$ *vs* post-CAL.

Drug (mg/kg)	VF threshold (V)		
	Pre-CAL	Post-CAL	Post-drug
NS (2 ml/kg)	6.7±0.4	3.1±0.7***	3.1±0.7†
Ran 15	6.3±0.7	2.8±0.7***	5.4±1.7†††
Cim 40	7.4±1.4	3.1±0.8***	8.1±2.7†††

Ran 和 Cim 对兔急性缺血心脏不同区域 FRP 的影响 兔 21 只，体重 2.3±SD 0.2 kg，♀♂不拘。戊巴比妥钠 30 mg/kg iv 麻醉，正压呼吸，开胸，右室起搏，冠脉左室支下穿线[8]，并套一细塑料管，拉线阻断血流 15-20 s，确定缺血范围，安置电极。刺激电极分别安置于缺血中央区(central zone)，边缘区(boundary zone)和非缺血区(nonischemic zone)，吸引电极安放于边缘区。FX-3 型刺激器提供起搏刺激(波宽 2 ms，强度 10 V，频率 4 Hz)和早搏刺激(波宽 2 ms，2 倍舒张阈电压)。8 个起搏刺激触发一个早搏刺激，吸引电极引出单向动作电位(monophasic action potentials，MAP)输入 SJ-42 型多道记录仪描记，纸速 50 mm/s。以 MAP 上升支起点至刚引起早搏刺激伪迹的距离为 FRP。

实验分 3 组：对照组(NS 组)，Ran 组和 Cim 组。结扎 CA 前先测定 3 个区域的 FRP，然后分别 iv NS 2 ml/kg，Ran 5 mg/kg 及 Cim 25 mg/kg，5 min 后结扎 CA。4 min 后，再分别测上述 3 个区域的 FRP。以同一时间内两不同区域的 FRP 之差值作为不应期离散的指标。Ran 和 Cim 均可防止兔心脏缺血中央区 FRP 的延长，以及缺血边缘区 FRP 的缩短。非缺血区 FRP 变化不明显(Tab 2)。从而使缺血心肌不应期离散的程度降低(Fig 1)。

Tab 2. Functional refractory period (ms) in different myocardial zones influenced by iv NS 2 ml/kg, Ran 5 or Cim 25 mg/kg in anaesthetized rabbits with coronary artery ligation (CAL). $n=7$, $\bar{x}\pm SD$. $^{*}P>0.05$, $^{***}P<0.01$ *vs* NS.

Zone	Drug	Before CAL	After CAL
Central	NS	127±13	174±16
	Ran	129±15*	137±11***
	Cim	128±8*	126±11***
Boundary	NS	117±14	86±16
	Ran	120±8*	130±12***
	Cim	123±6*	119±9***
Nonischemic	NS	119±7	121±5
	Ran	121±10*	131±10*
	Cim	121±8*	126±8*

Discussion

急性实验性心肌缺血早期，缺血区 FRP 变化表现为两种相反趋向。边缘区的 FRP 与

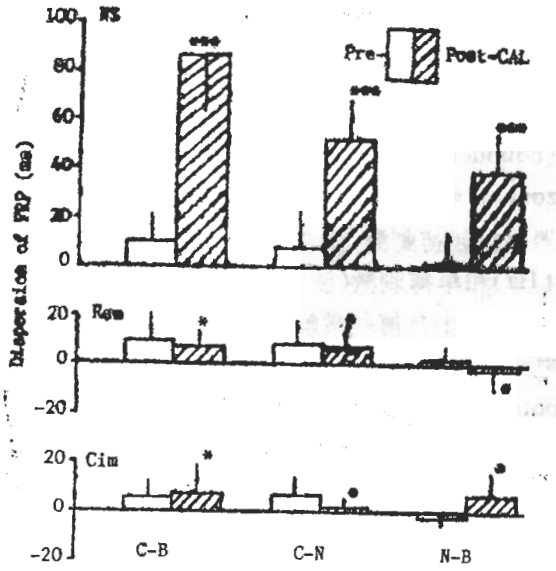

Fig 1. Dispersion of functional refractory period (FRP) after iv NS 2 ml/kg, Ran 5 or Cim 25 mg/kg. C-B: FRP_{CZ}-FRP_{BZ}; C-N: FRP_{CZ}-FRP_{NZ}; N-B: FRP_{NZ}-FRP_{BZ}. CZ = central zone, BZ = boundary zone, NZ = nonischemic zone. $^{*}P>0.05$, $^{***}P<0.01$ *vs* pre-CAL.

动作电位时程呈平行缩短，中央区的FRP延长，并可超过动作电位时程出现复极后不应性(PRR)，致不应期离散[9]。不应期离散在折返性心律失常形成中起重要作用[10]。急性心肌缺血2-6 min时，不应期离散最明显，这与心律失常的发生时间一致[8,9]。本实验观察结扎CA 4 min后的FRP，结果表明，NS组FRP变化与文献[8,9]相近。Ran与Cim则可明显防止边缘区处FRP缩短及中央区FRP的延长，降低不应期的离散度，进而有助于消除折返。提高缺血心肌VFT和降低不应期的离散度，可能是Ran与Cim抗心律失常作用的电生理学基础。

急性缺血心肌对H敏感性增加[5]，H可通过H_2受体增加心肌慢Ca^{2+}内向电流[11,12]。Ran和Cim则可选择性地阻断H_2受体，因此可能通过抑制Ca^{2+}内向电流，防止H所致心律失常。

Ran拮抗心肌H_2受体的强度约为Cim的10倍[13]。若两药的上述作用均系阻断H_2受体所致，则欲获相等效应，Cim的剂量应为Ran剂量的10倍。而本实验中Cim的剂量仅为Ran剂量的2.6或5倍。在此剂量下，Cim提高VFT的作用强于Ran，降低FRP离散度的作用与Ran相当。提示Cim对VFT和FRP的影响除阻滞H_2受体外，可能尚有其它机理参与。

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