Circulation 1989; **80** : 23–30.
6 Kass RS, Tsien RW. Fluctuation in membrane current driven by intracellular calcium in cardiac Purkinje fibers. *Biophys J* 1982; **38** : 259–69.
7 Kass RS, Tsien RW, Weingart R. Ionic basis of transient inward current induced by strophanthidin in cardiac Purkinje fibers. *J Physiol* (Lond) 1978; **281** : 209–26
8 Cranefield PF. Action potentials, afterpotentials, and arrhythmias. *Circ Res* 1977; **41** : 415–23.
9 Struyker-Boudier HAJ, Smits JFM, De Mey JGR. The pharmacology of calcium antagonists: a review. *J Cardiovasc Pharmacol* 1990; **15** Suppl 4 : 1–10.

间尼索地平对犬浦肯野氏纤维迟发性后除极化的影响

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提要 利用细胞内微电极技术，观察了间尼索地平(*m*-Nis)预防给药或诱发 DAD 后再给予 *m*-Nis (0.5–4 $\mu mol \cdot L^{-1}$)，对 DAD 和 TA 均有明显的抑制作用。DAD 的幅度由 15.3±2.7 减小到 2.3±2.0 mV，DAD 时程由 980±45 减小到 130±27 ms，TA 的发生也明显减少或完全被抑制，*m*-Nis 这些效应可能与其阻断钙通道、减轻细胞内钙超载有关。

关键词 间尼索地平；电生理；浦肯野纤维；微电极

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Antithrombotic activity of verapamil

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ABSTRACT The antithrombotic activity of verapamil (Ver) was assessed in an arterial thrombosis model and an *ex vivo* thrombosis model. Ver 2 and 4 $mg \cdot kg^{-1}$ ip markedly prolonged the time of thrombotic occlusion in rat carotid artery induced by electric stimulation. The weight of thrombus formed *ex vivo* was reduced by Ver 0.2 $mg \cdot kg^{-1}$ iv. However, Ver showed no effects on blood viscosity.

KEY WORDS verapamil; thrombosis; blood viscosity

The incidence of reocclusion following successful reperfusion in acute myocardial infarction (AMI) by thrombolytic therapy was reported of 15–30% or more[1]. A subsequent adjunctive treatment to intervene thrombosis and to prevent the reocclusion remains a requisite[2]. Thromboxane A_2 (TXA_2) and / or epoprostenol (Epo) play an important role in thrombosis, and calcium channel blockers show antiplatelet effects[3] and beneficial actions on TXA_2 and / or Epo formation[4]. But their action on reocclusion after AMI is not yet identified, nor have the data of the agents on thrombosis been found. Here we report the effects of verapamil (Ver), a calcium channel blocker on thrombosis and the influence of Ver on blood viscosity.

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MATERIALS AND METHODS

Arterial thrombosis Lewis rats (♀ and ♂, wt 271 ± *s* 24 g) were anesthetized by sodium pentobarbital 1 h after saline or Ver ip. The right carotid artery was isolated up to 15 mm long. Thrombosis was induced by electric stimulation of 1.6 mA, which lasted 7 min[5]. The thrombosis was indicated by occlusion

time (OT) which was determined by the sudden decrease of the artery surface temperature after blocking the blood flow by thrombus induced.

Ex vivo **thrombosis** The *ex vivo* thrombosis of New Zealand rabbits was performed on Chandler's rotating loop system[6]. On d 7 after blood was taken by cardiac puncture for measurement as self-control, Ver 0.2 mg · kg^{-1} was injected into a central vein of ear. A second blood sample was drawn 30 min later.

Blood viscosity measurement Blood viscosity of rabbits (2.3 ± 0.6 kg) was determined by cone-plate viscometer (Model NXE-1, Chengdu Instrument Factory, China) at the low shear rate of 23 Hz and the high shear rate of 230 Hz. Under anesthesia, the right carotid artery and vein were isolated for blood collection and drug administration respectively. Blood (5 ml) was drawn from the artery for base test, then saline (5 ml) or Ver (0.2 mg · kg^{-1} in 5 ml saline) was injected iv slowly. After 30 min, a second blood sample was collected.

RESULTS

Antithrombotic activity In the arterial thrombosis model, Ver potently prolonged the OT at the doses of 2 and 4 mg · kg^{-1} (Tab 1). In Chandler's loop system, Ver 0.2 mg · kg^{-1} iv also showed an *ex vivo* antithrombotic activity. The weight of thrombus decreased from 53.4 ± 16.7 mg to 48.7 ± 14.6 mg ($P<0.05$).

Tab 1. Effects of verapamil ip on artery thrombosis *in vivo* in rats. $\bar{x}\pm s$. $^{***}P<0.01$ *vs* saline

Drug		n	Occlusion time / min
Saline	2 ml · kg^{-1}	10	15.7 ± 1.2
Verapamil	2 mg · kg^{-1}	10	17.9 ± 1.4***
	4 mg · kg^{-1}	8	18.4 ± 1.6***

Effects of Ver on blood viscosity There were no statistically significant differences in the blood viscosity decrease between the control and the Ver groups ($P>0.05$) (Tab 2).

Tab 2. Effects of Verapamil iv 0.2 mg · kg^{-1} on blood viscosity at shear rates of 230 Hz and 23 Hz. $n=10$, $\bar{x}\pm s$. $^{*}P>0.05$ *vs* saline.

	Blood viscosity / mPa · s^{-1} Pre-treatment	Post-treatment
23 Hz		
Saline	6.5 ± 1.1	5.7 ± 0.9
Verapamil	6.3 ± 1.4*	5.5 ± 1.2*
230 Hz		
Saline	4.7 ± 0.6	4.2 ± 0.5
Verapamil	4.2 ± 0.5*	4.6 ± 0.8*

DISCUSSION

In the procedure of blood viscosity measurement, physiological mechanism and 5 ml of saline may theoretically cause hemodilution and the increase of blood volume and subsequently influence the blood visicosity. It may be reflected by the decrease of the hematocrit which indicated that the declining was very small and no significant difference was detected between the control and the Ver.

Platelet aggregation definitely contributes to and may be the primary mechanism underlying reocclusion in AMI receiving effective thrombolytic therapy[7]. Theoretically, antiplatelet agents in combination with thrombolytic drugs may show a favorable effect on the rethrombosis and reocclusion. In this study, we found a potent antithrombotic effect of Ver both *in vivo* and *ex vivo*. It is in accordance with the hypothesis that a calcium blocker may be an important adjunctive remedy following thrombolysis[2]. Moreover, we noticed that the antithrombotic activity of Ver was more potent *in vivo* than *ex vivo*. This may be due to the effects of Ver on Epo production[8] and on vasodilation[9].

As in AMI, hemoconcentration, increased plasma fibrinogen level and decreased blood cell filterability do occur. These changes all tend to increase the blood viscosity[10], and may play a role in its pathological and clinical outcome[11]. So if the antithrombotic agents show an effect of decreasing blood viscosity, it may be better in conjunction with thrombolytic agents. But we did not find this action of Ver.

REFERENCES

1 Cox JL, Gotlieb AI. Review of antiplatelet drug use in preventing restenosis following percutaneous transluminal coronary angioplasty. *Can J Cardiol* 1988; **4** : 201–10.

2 Roberts R. Thrombolysis and its sequelae — calcium antagonists as potential adjunctive therapy. *Circulation* 1989; **80** Suppl 6 : IV93–101.

3 Liu JT, Qiu PL. Effect of calcium antagonists on platelet functions. *Prog Physiol Sci* 1988; **19** : 273–5.

4 Zadionchenko VS, Kamenker ES, Chikvashvili IA. Changes in the platelet–vascular system of hemostasis in patients with ischemic heart disease and hypertension after the treatment. *Kardiologiia* 1989; **29** : 51–4.

5 Dong ED, Shi S. Effects of the combination of aspirin and nifedipine on platelet aggregation and thrombogenesis. *Chin J Cardiol* 1990; **18** : 301–3.

6 Chandler AB. *In vitro* thrombotic coagulation of the blood. *Lab Invest* 1958; **7** : 110–4.

7 Gold HK, Coller BS, Yasuda T, Saito T, Fallon JT, Guerrero JL, *et al.* Rapid and sustained coronary artery recanalization with combined bolus injection of recombinant tissuetype plasminogen activator and monoclonal antiplatelet GPIIB / IIIa antibody in a canine preparation. *Circulation* 1988; **77** : 670–7.

8 Weiss K. Calcium antagonists: anti–athero–sclerotic effect by modification of the prostaglandin system. *Wien Klin Wochenschr* 1988; **100** : 718–20.

9 Saine RK. Calcium antagonists. In: Antonaccio MJ, editor. *Cardiovascular pharmacology* 2nd ed. NY: Raven Press, 1984: 415–43.

10 Dormandy JA, Ernst E, Matrai A, Flute PT. Hemorheologic changes following acute myocardial infarction. *Am Heart J* 1982; **104** : 1364–7.

11 Dormandy JA. Cardiovascular diseases. In: Chien S, Dormandy JA, Drnst E, Matrai A, editors. *Clinical hemorheology — applications in cardiovascular and hematological disease, diabetes, surgery and gynecology*. Dordrecht: Martinus Nijhoff, 1987 : 165–94.

维拉帕米对血栓形成的影响

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提要 利用大鼠在体动脉血栓形成模型和兔体外血栓形成模型观察维拉帕米对血栓形成的影响. 结果表明维拉帕米 2 mg · kg^{-1} 和 4 mg · kg^{-1} ip 均能使电刺激诱导大鼠颈动脉血栓形成时间显著延长，0.2 mg · kg^{-1} iv 亦使兔体外形成的血栓重量明显减轻. 但维拉帕米对血液粘度无明显影响.

关键词 维拉帕米；血栓形成；血液粘度

第三届全国生物医药学色谱学术会议征稿通知

会议定于 1992 年 11 月 17–20 日在上海召开. 应征论文应为色谱法及有关技术、理论及其在生物、医药等方面的应用. 应征论文应为 1500 字左右的详细摘要(包括必要的数据、图表). 长江以北，请寄 100850 北京市太平路 27 号中国军事医学科学院放射医学研究所马立人；长江以南，请寄 200031 上海市岳阳路 319 号中国科学院上海药物研究所徐修容. 截稿日期：1992 年 4 月 30 日.