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Hemodynamic actions of guan-fu base A in anesthetized rats

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ABSTRACT Guan-fu base A (GFA) is a terpenoid alkaloid isolated from the tuber of *Aconitum coreanum* in this institute. GFA exhibited anti-arrhythmic effects in various experimental arrhythmia animal models, and bradycardic actions. In this paper, the hemodynamic action of GFA was investigated. GFA 20 mg · kg^{-1} iv decreased in heart rate from 420 ± 51 to 305 ± 60 bpm ($P<0.05$). The changes of SBP, DBP, LVSP, $\pm dP/dt_{max}$, and LVEDP were much smaller or insignificant. GFA (1, 3, 10, 30, 60 mg · kg^{-1} cumulative iv) increased the heart periods (HP) and QT-intervals in a dose-dependent manner, accompanied by a small increase in PQ-interval, but did not affect QRS complex. The increase in HP from 138 ± 11 to 321 ± 48 ms ($P<0.01$) was mainly due to a prolongation of the diastolic period from 22 ± 12 ms to 156 ± 46 ms ($P<0.01$). The triple product of HR × LVET × SBP was also decreased with every dose of GFA.

This hemodynamic profile suggests that the bradycardic action of GFA can reduce myocardial oxygen consumption and improve myocardial blood supply, which may be of use in certain cardiac patients.

KEY WORDS guan-fu base A; propranolol; hemodynamics; bradycardia; aconite

Guan-fu base A (GFA) is a new alkaloid first isolated in China[1,2], and its chemical structure was revised in 1986[3]. GFA has been demonstrated to possess a potent anti-arrhythmic action in *in vivo* and *in vitro* studies[4-7]. The bradycardia effected by GFA is due to a direct action on sinoatrial node, which had a slight effect on the contractility of heart[4,8]. The purpose of this study was to describe the cardiovascular effects of GFA with respect to the specificity of the bradycardic action.

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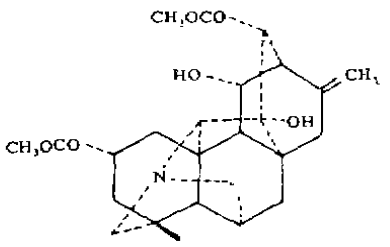

Guan-fu base A
mp 198℃, $[\alpha]_D^{22.8}$ +49° (chloroform)

MATERIALS AND METHODS

Drugs GFA hydrochloride (white crystal, MW 429, mp 290℃) was provided by the Department of Phytochemistry of this institute. Propranolol (Pro) was the product of Shanghai Second Pharmaceutic Factory.

Hemodynamic study Wistar rats (Shanghai Experiment Animal Center of Chinese Academy of Sciences) of either sex weighing 272 ± *s* 19 g were anesthetized by sodium pentobarbital 40 mg · kg^{-1} ip. For the recording of the left ventricular systolic pressure (LVSP) and the left ventricular end-diastolic pressure (LVEDP), a cardiac catheter (PE 50) filled with heparin 145 IU · ml^{-1} was introduced via the right carotid artery. The catheter was connected to a pressure transducer (P23XL, Statham, Nihon Kohden, Japan). The maximal velocity of pressure increase ($\pm dP/dt_{max}$) was determined by a differentiator (EQ 601G, Nihon Kohden, Japan). For the recording of blood pressure a catheter (PE 50) was inserted into the left femoral artery to measure the systolic (SBP), diastolic (DBP), and mean blood pressure (MBP). In some experiments, the pressure catheter was inserted

into the left carotid artery, and the ECG (limb lead II) was recorded simultaneously for measuring the left ventricular ejection time (LVET) and diastolic period (DP).

The heart period (HP) was determined from the PP-interval of ECG. QT-interval was measured from Q till the end of T wave. The LVET was determined from the carotid artery pulse wave (beginning of pressure rise to first incisura), the diastolic period was calculated from HP minus LVET and isovolumetric contraction period (peak of R wave to beginning of pressure rise)[9,10]. All the cardiovascular parameters were recorded on a polygragh (RM-6000, Nihon Kohden, Japan).

The drugs were given into one femoral vein 30 min after operation. For cumulative injections the dose was increased every 5 min and parameters were evaluated 2 min after each injection when the maximal effects were achieved.

Data analysis The data were presented as $\bar{x} \pm s$ and compared with t test.

RESULTS

Effects on ECG Cumulative iv GFA 1, 3, 10, 30, 60 mg · kg^{-1}, the maximal effects reached at 2 min after each iv (every 5 min). The most prominent effect of GFA on the ECG was the prolongation of HP (Fig 1). Up to 60 mg · kg^{-1}, GFA increased the PQ-interval by 43.4% but did not affect the QRS complex. However, GFA prolongation of HP and QT-interval by 133% and 108%, respectively.

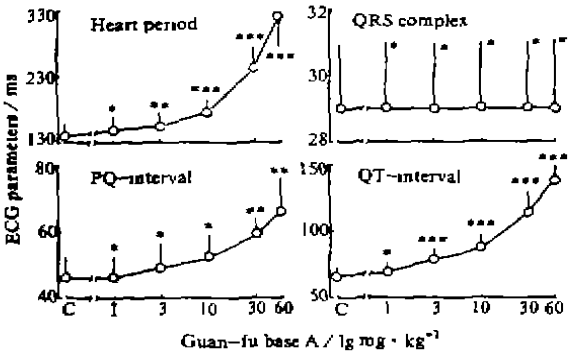

Fig 1. Effects of guan-fu base A on ECG in 6 anesthetized rats. Cumulative iv of GFA (every 5 min), limb lead II, recorded 2 min after each iv. $\bar{x} \pm s$. $^{*}P>0.05$, $^{**}P<0.05$, $^{***}P<0.01$ *vs* C (control).

Prolongation of diastolic period GFA 3 mg · kg^{-1} iv increased the LVET slightly and the diastolic period markedly. Whereas GFA 10 mg · kg^{-1} resulted in a LVET of 72 ± 4 ms ($n=5$, $P<0.05$ *vs* control value 65 ± 5 ms), but the greatest change was the prolongation of diastolic period (125%). The triple product of HR × LVET × SBP was also decreased by every dose of GFA, but MBP remained almost unchanged (Tab 1).

Tab 1. Effects of guan-fu base A iv on heart rate (HR), mean blood pressure (MBP), left ventricular ejection time (LVET), diastolic period (DP), and triple product (TP) of HR x LVET x SBP in 5 anesthetized rats. $\bar{x} \pm s$. $^{*}P>0.05$, $^{**}P<0.05$, $^{***}P<0.01$ *vs* control.

	Control	Guan-fu base A / mg · kg^{-1}				
		1	3	10	30	60
HR / bpm	436 ± 35	414 ± 33*	396 ± 26**	346 ± 31***	238 ± 18***	191 ± 32***
MBP / kPa	17.2 ± 1.2	17.2 ± 1.6*	17.1 ± 1.5*	17.2 ± 1.2*	16.7 ± 2.3*	16.0 ± 3.1*
LVET / ms	65 ± 5	65 ± 4*	66 ± 4*	72 ± 4**	83 ± 8***	100 ± 13***
DP / ms	24 ± 11	26 ± 12*	35 ± 15**	54 ± 11***	92 ± 13***	174 ± 16***
TP / bpm · ms · kPa	485 ± 37	463 ± 64*	447 ± 64*	431 ± 60*	365 ± 101**	311 ± 96***

The prolongation of diastolic period was accompanied by the increase of HP. These effects were maximal 2 min after GFA 40 mg · kg^{-1}, and gradually declined in 1 h. The effect of GFA on triple product was similar to that of Pro. (Fig 2).

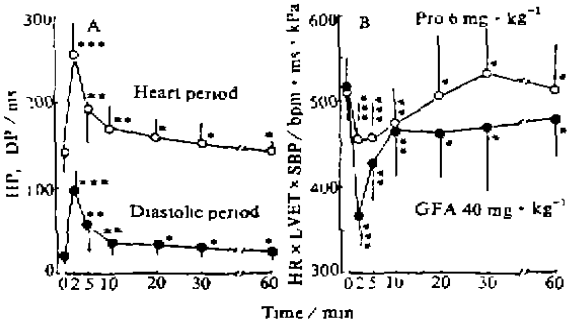

Fig 2. A) Effects of GFA (40 mg · kg^{-1} iv) on HP, DP. B) Effects of iv propranolol (Pro) and GFA on triple product. $n=5$, $\bar{x} \pm s$. $^{*}P>0.05$, $^{**}P<0.05$, $^{***}P<0.01$ *vs* **control.**

Effects on hemodynamic parameters GFA 20 mg · kg^{-1} iv induced a marked decrease in heart rate by 27%. A maximal reduction was obtained after approximately 2 min. the effect of lowering the heart rate declined to 2.9% of its maximum at 20 min.

The changes of SBP, DBP, LVSP, $\pm dP/dt_{max}$, and LVEDP were much smaller and statistically insignificant (Tab 2).

DISCUSSION

Our experiments confirmed that bradycardia was the prominent cardiovascular action of GFA in anesthetized rats.

GFA had no obvious effects on either blood pressure or myocardial contractility measured as left ventricular $\pm dP/dt_{max}$.

The duration of the diastolic period is proportional to the blood supply to the ischemic myocardial region[9]. The prolongation of diastolic period is expected to provide a richer myocardial blood supply even into

Tab 2. Effects of guan-fu base A (GFA) 20 mg · kg^{-1} iv and normal saline (NS) on hemodynamic parameters in 6 anesthetized rats. HR, systolic (SBP), and diastolic blood pressure (DBP), left ventricular systolic pressure (LVSP), maximal velocity of pressure increase ($\pm dP/dt_{max}$), and left ventricular end-diastolic pressure (LVEDP). $\bar{x} \pm s$. $^{*}P>0.05$. $^{**}P<0.05$, $^{***}P<0.01$ *vs* **control.**

		Control	Time after administration 2 min	5 min	10 min	20 min	30 min	60 min
HR, bpm	GFA	420 ± 51	305 ± 60**	363 ± 57**	380 ± 59*	408 ± 49*	421 ± 45*	444 ± 28*
	NS	458 ± 18	465 ± 21*	472 ± 25*	477 ± 18*	471 ± 29*	474 ± 25*	480 ± 14*
SBP, kPa	GFA	19.6 ± 2.7	19.8 ± 2.7*	20.1 ± 2.3*	19.3 ± 2.2*	19.1 ± 2.5*	18.7 ± 2.7*	17.8 ± 3.2*
	NS	20.0 ± 1.9	20.4 ± 1.9*	20.0 ± 2.3*	20.0 ± 2.4*	19.3 ± 1.9*	19.3 ± 2.8*	19.7 ± 1.4*
DBP, kPa	GFA	16.3 ± 1.2	15.7 ± 1.4*	16.0 ± 0.9*	16.0 ± 0.9*	16.1 ± 1.9*	15.6 ± 2.1*	14.6 ± 3.3*
	NS	14.0 ± 2.8	13.7 ± 1.4*	13.5 ± 1.2*	13.7 ± 1.4*	13.2 ± 1.7*	12.3 ± 2.3*	12.7 ± 0.9*
LVSP, kPa	GFA	20.4 ± 0.8	20.9 ± 3.1*	21.5 ± 2.4*	20.8 ± 2.7*	20.4 ± 2.0*	19.9 ± 2.8*	18.9 ± 3.3*
	NS	20.0 ± 1.9	20.7 ± 0.9*	20.0 ± 1.9*	20.0 ± 1.9*	19.6 ± 1.7*	19.3 ± 1.8*	19.7 ± 2.4*
$+dP/dt_{max}$, kPa · s^{-1}	GFA	656 ± 66	594 ± 116*	650 ± 89*	644 ± 91*	672 ± 91*	628 ± 108*	611 ± 117*
	NS	650 ± 28	650 ± 28*	651 ± 18*	651 ± 23*	650 ± 23*	617 ± 31*	620 ± 29*
$-dP/dt_{max}$, kPa · s^{-1}	GFA	617 ± 72	533 ± 82*	594 ± 80*	611 ± 78*	622 ± 89*	594 ± 112*	561 ± 141*
	NS	667 ± 47	683 ± 24*	666 ± 45*	680 ± 20*	650 ± 52*	616 ± 58*	627 ± 60*
LVEDP, kPa	GFA	0.5 ± 0.1	0.7 ± 0.5*	0.5 ± 0.4*	0.5 ± 0.4*	0.5 ± 0.4*	0.7 ± 0.4*	0.7 ± 0.5*
	NS	0.6 ± 0.1	0.7 ± 0.1*	0.5 ± 0.2*	0.6 ± 0.3*	0.8 ± 0.4*	0.7 ± 0.4*	0.7 ± 0.3*

region where blood flow was limited by coronary artery obstruction[10].

GFA not only increased the diastolic period but also decreased the triple product in the experiments. The triple product has been shown to the parallel to the myocardial oxygen consumption in animal experiments and myocardial oxygen demand in anginal patients[11,12].

The beneficial effects of GFA in potential use for the treatment of ischemic heart diseases can be explained by (1) the reduction of myocardial oxygen consumption and (2) the pronounced increase in diastolic period, which improves the myocardial blood supply.

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关附甲素对麻醉大鼠的血液动力学影响

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提要 本文研究了 GFA 对麻醉大鼠的血液动力学影响。GFA 20 mg · kg^{-1} iv 使大鼠心率从 420 ± 51 减慢至 305 ± 60 bpm ($P<0.05$)。对 SBP，DBP，LVSP，$\pm dP/dt_{max}$ 和 LVEDP 的影响很小。GFA 1，3，10，30，60 mg · kg^{-1} iv 使 HP，QT 间期和心室舒张期明显延长、三项乘积(心率 × 左室射血时间 × 动脉收缩压)降低。提示 GFA 可降低心肌氧耗量，改善血液供应。

关键词 关附甲素；普萘洛尔；血液动力学；心动过缓；乌头