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Cardiovascular effects of elgodipine and nifedipine compared in anaesthetized rats

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Abstract

The cardiovascular effects of elgodipine were studied and compared with those of nifedipine in the presence or absence of ganglion blockade. A bolus of elgodipine (5–25 μg/kg) or nifedipine (60–120 μg/kg) was given and sequential cardiovascular effects in rats were recorded. Both dihydropyridines induced a dose-dependent decrease in mean arterial pressure but, whereas nifedipine induced reflex tachycardia, elgodipine induced a dose-dependent bradycardia. Both substances induced decreases in left ventricular dP/dt_{max} without significant changes in central venous pressure. Good linear correlation was observed between the elgodipine-induced decrease in mean arterial pressure and those of heart rate and left ventricular dP/dt_{max}. The profile of the decrease in mean arterial pressure in animals pretreated with hexametonium chloride (20 mg/kg) was the same but the nifedipine-induced tachycardia was abolished without changes in elgodipine-induced bradycardia. These characteristics of elgodipine makes this dihydropyridine a potentially beneficial therapeutic agent in the case of severe hypertension accompanied by obstructive coronopathy. © 1997 Elsevier Science B.V.

Keywords: Elgodipine; Blood pressure; Tachycardia, reflex; Dihydropyridin

1. Introduction

The effectiveness of the first generation Ca^{2+} channel antagonists (nifedipine, verapamil and diltiazem) in the treatment of a large number of cardiovascular disorders has led to the development of a new generation of Ca^{2+} entry blockers, with more selective properties. Several reviews have appeared which comment that dihydropyridines must be used with caution in patients with coronary heart disease because of the increased mortality observed in patients treated with these drugs (Furberg et al., 1995, 1996; Psaty et al., 1995; Poole-Wilson, 1996). One of the most discussed undesirable effects to which some authors attribute the mortality is the reflex tachycardia produced by dihydropyridines (specially those of the first generation) (Bala Subramanian et al., 1982).

Elgodipine is a recent example of the dihydropyridine structural family of Ca^{2+} channel antagonists (Tamargo et al., 1991) which has potent coronary dilator properties in the anaesthetized pig without significant depression of cardiac contractility (Sassen et al., 1990). Also, elgodipine does not show a tachycardiac effect in dogs and pigs (Sassen et al., 1990; Drieu la Rochelle et al., 1994). However, to our knowledge, the effect of elgodipine on cardiac function has not been studied in rats.

We have, therefore, designed the present study to compare the effects of elgodipine and nifedipine on arterial pressure, heart rate and cardiac contractility in rats in the presence or absence of ganglion blockade.

2. Materials and methods

Experiments were carried out in female Wistar rats weighing about 250 g (IFFA-CREDO, France), fed on a standard diet and water ad libitum. All the experiments were performed according to the guidelines for the ethical treatment of the experimentation animals by the European Community and the Spanish Ministerio de Agricultura, Pesca y Alimentación.

The animals were anaesthetized with sodium pento-

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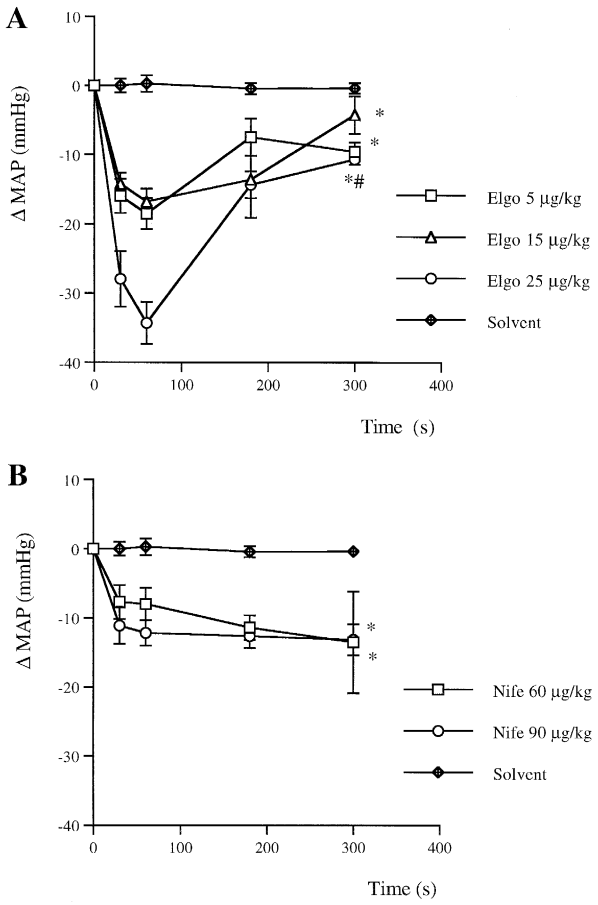

Fig. 1. Effect of different doses of elgodipine (A) and nifedipine (B) on mean arterial pressure (MAP). Data are shown as means ± S.E.M. of the changes from basal. Symbols are: * $P < 0.01$ vs. solvent. # $P < 0.05$ vs. elgo 5 μg/kg (one-way ANOVA).

barbital (50 mg/kg, i.p.), rectal temperature was monitored by thermometer and maintained at 37°C. Firstly, a tracheotomy was performed to facilitate breathing throughout the experiment. A polyethylene PE-10 catheter was then inserted in the right carotid reaching to the left ventricle to record intraventricular pressure. Another catheter was introduced into the right auricle through the left jugular vein, and was used to record central venous pressure. The same route was used to infuse physiological salt solution at a constant rate of 1 ml/h to make up for the loss of fluid produced by surgery. In addition, a femoral artery was cannulated for mean arterial pressure recording.

The three catheters were connected to pressure transducers (Statham instruments, Hato Rey, Puerto Rico), and to a digital data recorder (Mac Lab, AD Instruments, Australia) to record mean arterial pressure, central venous pressure, intraventricular pressure and heart rate. Left ventricular dP/dt_{max} was calculated from the intraventricular pressure curve as a measure of cardiac contractility.

After 30 min of recovery, and once the mean arterial pressure and heart rate had stabilized, 0.5 ml of solvent solution was injected through the jugular vein and a recording was made to be used as a control. Then, the rats were injected through the same route with elgodipine or nifedipine.

Solutions were prepared by dissolving nifedipine in equal parts of water, ethanol and propylene glycol, and elgodipine in ethanol. The solutions were diluted with physiological saline solution, so that the maximum infused concentration of ethanol and propylene glycol was 1%. The doses used were 5 ($n = 20$), 15 ($n = 10$) and 25 ($n = 10$) μg/kg for elgodipine and 60 ($n = 20$), 90 ($n = 10$) and 120 ($n = 10$) μg/kg for nifedipine.

Half of the animals treated with the lower doses of each drug received hexametonium chloride (20 mg/kg) for ganglion blockade. The efficacy of the sympathetic blockade was proven by the lack of a reflex tachycardiac response to the removal of 1 ml of blood. After replacement of the blood and some minutes allowed for stabilization, hemodynamic parameters were recorded and the ex-

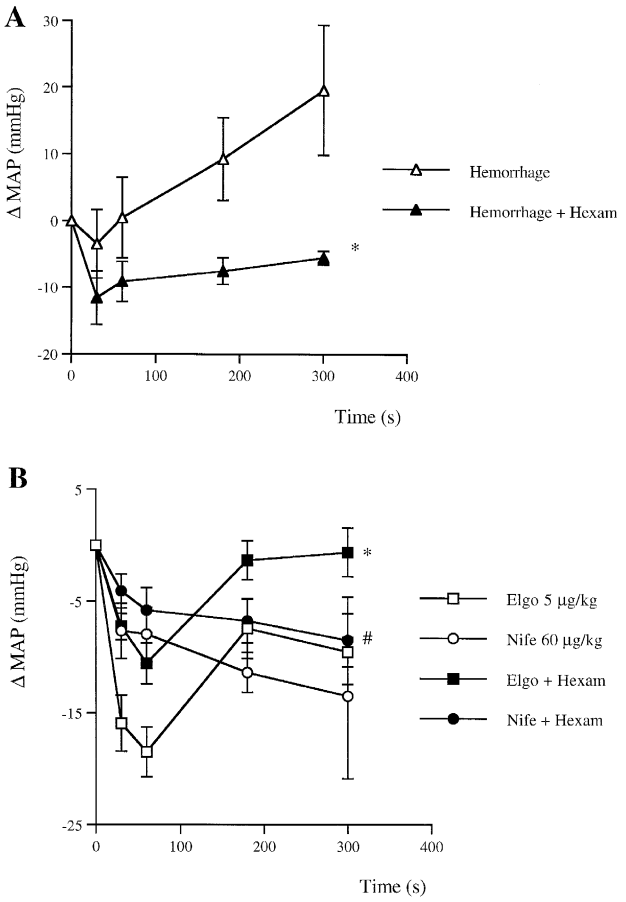

Fig. 2. Effect of ganglion blockade on mean arterial pressure in rats with removal of 1 ml of blood (A) and rats treated with the lower doses of nifedipine or elgodipine (B). Data are shown as means ± S.E.M. of the changes from basal. Symbols are: * $P < 0.01$ vs. the same group without hexamethonium. # $P < 0.05$ vs. the same group without hexamethonium (one-way ANOVA).

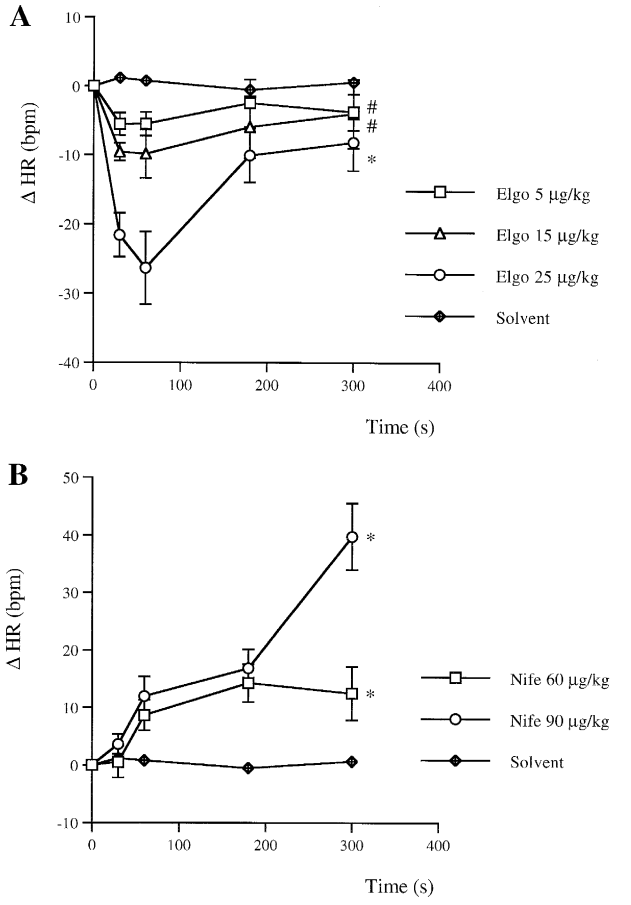

Fig. 3. Effect of the different doses of elgodipine (A) and nifedipine (B) on heart rate. Data are shown as means ± S.E.M. of the changes from basal. Symbols are: * $P < 0.01$ vs. solvent. # $P < 0.05$ vs. solvent (one-way Anova).

periments were immediately repeated with nifedipine and elgodipine.

Results are presented as means ± S.E.M. Statistical analysis of the data was carried out with one way analysis of the variance for repeated measurements followed by comparison of all means by the Scheffé test. A P value lower than 0.05 was considered as significant.

3. Results

Fig. 1 shows the effect of the different doses of nifedipine and elgodipine on mean arterial pressure. Elgodipine induced an acute, dose-dependent decrease in mean arterial pressure with a maximum fall after about 1 min. Afterwards, the decrease in mean arterial pressure was stable at about 10 mmHg. Nifedipine also induced a dose-dependent decrease in mean arterial pressure with the two lower doses. The dose of 120 μg/kg (not shown) did not induce further decreases in mean arterial pressure. The decrease in mean arterial pressure induced by nifedipine also stabilized at 12 mmHg.

Fig. 2 shows the effect of ganglion blockade on the decrease in mean arterial pressure induced with nifedipine and elgodipine. The decrease in mean arterial pressure in the groups pretreated with hexametonium had the same profile as that in the groups without pretreatment, although the decrease was lower. In panel A we can see the effect of ganglion blockade in mean arterial pressure after 1 ml blood loss. Whereas under basal conditions removal of 1 ml blood induces an increase in mean arterial pressure, after hexamethonium infusion removal of 1 ml blood induced a decrease in mean arterial pressure.

Fig. 3 presents the changes in heart rate after nifedipine and elgodipine infusion. Nifedipine and elgodipine both induced dose-dependent changes in heart rate but, whereas nifedipine induced an increase, elgodipine produced bradycardia. Treatment with hexamethonium (Fig. 4) significantly decreased the tachycardia induced by nifedipine or

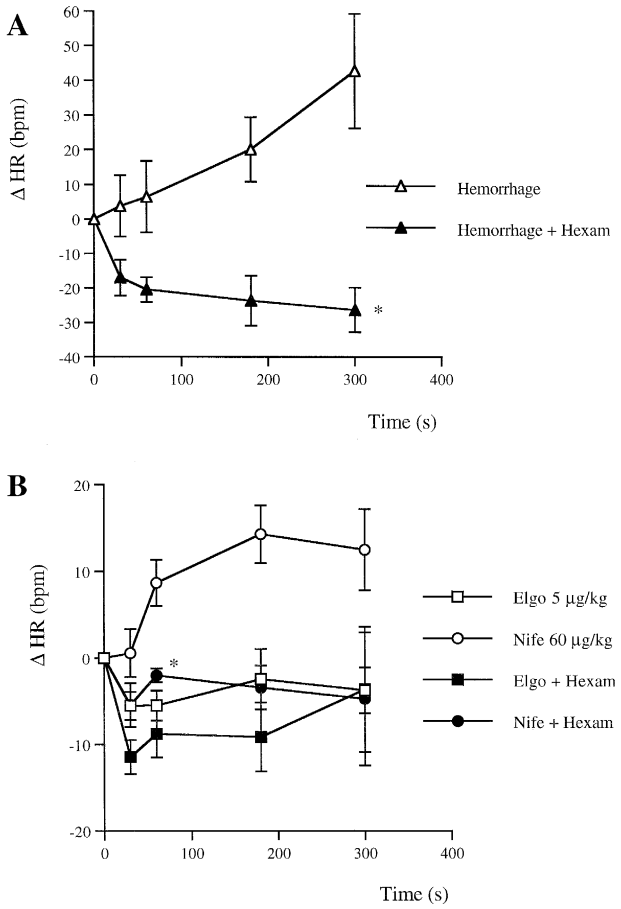

Fig. 4. Effect of ganglion blockade on heart rate in rats with removal of 1 ml (A) and rats treated with the lower doses of nifedipine or elgodipine (B). Data are shown as means ± S.E.M. of the changes from basal. Symbols are: * $P < 0.01$ vs. the same group without hexamethonium (one-way ANOVA).

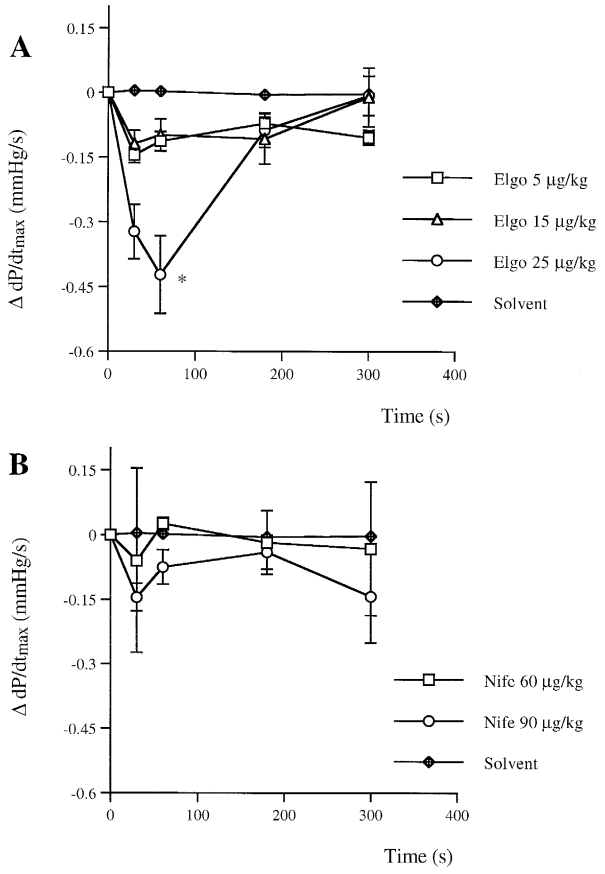

Fig. 5. Effect of the different doses of elgodipine (A) and nifedipine (B) on the left ventricular dP/dt_{max}. Data are shown as mean ± S.E.M. of the changes from basal. Symbols are: * $P < 0.01$ vs. solvent (one-way ANOVA).

removal of 1 ml blood without changes in elgodipine-treated animals. The additive effect of hexametonium and elgodipine in the decrease in heart rate observed is not statistically significant. However, it can be explained because of the basal nervous stimulation of heart rate. When we abolished this stimulus with hexametonium, heart rate diminished. After this, addition of elgodipine leads to an additive effect in heart rate, diminishing it to more low levels.

Fig. 5 shows the effect of nifedipine and elgodipine on left ventricular dP/dt_{max}. Elgodipine induced a significant decrease in left ventricular dP/dt_{max} that was not observed after nifedipine. Pretreatment with hexamethonium (Fig. 6) did not have any significant effect on left ventricular dP/dt_{max}. However, the increase in left ventricular dP/dt_{max} observed after removal of 1 ml blood was abolished by ganglion blockade.

In Fig. 7 we can see the effect of nifedipine and elgodipine on central venous pressure. Neither elgodipine nor nifedipine induced significant changes in central venous pressure. Treatment with hexamethonium induced an increase in central venous pressure in rats treated with elgodipine and also in rats that had been bled (Fig. 8).

Fig. 9 shows a significant linear correlation between decreases in left ventricular dP/dt_{max} and mean arterial pressure and between heart rate and mean arterial pressure in rats infused with elgodipine.

4. Discussion

In our experimental model, elgodipine induced a dose-dependent decrease in mean arterial pressure, which was not associated with cardiac stimulation of reflex origin: tachycardia or inotropism. In fact, elgodipine induced a dose-dependent decrease in heart rate and in left ventricular dP/dt_{max}, which correlated significantly with the decrease in arterial pressure. These results are compatible with previous data obtained from anesthetized dogs (Drieu la Rochelle et al., 1994) and pigs (Sassen et al., 1990). Thus, when infused i.v. in pigs, elgodipine caused dose-de-

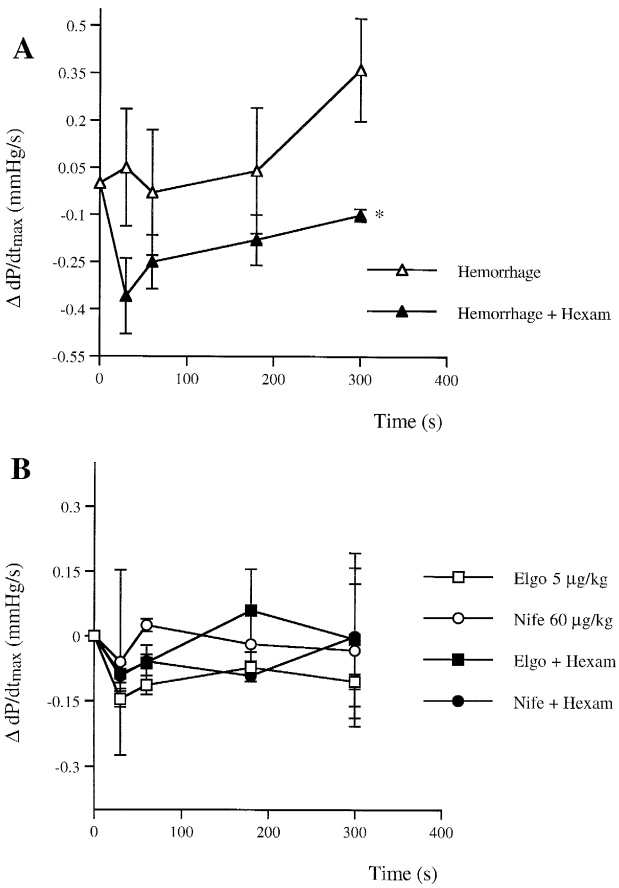

Fig. 6. Effect of ganglion blockade on left ventricular dP/dt_{max} in rats with removal of 1 ml (A) and rats treated with the lower doses of nifedipine or elgodipine (B). Data are shown as means ± S.E.M. of the changes from basal. Symbols are: * $P < 0.01$ vs. the same group without hexamethonium (one-way ANOVA).

pendent decreases in arterial blood pressure and systemic vascular resistances, whereas heart rate and left ventricular dP/dt_{max} did not change (Sassen et al., 1990). In anesthetized dogs, elgodipine produced a decrease in arterial blood pressure, with increases in dP/dt_{max} and little or no reflex tachycardia (Drieu la Rochelle et al., 1994). Nifedipine, the typical dihydropyridine, has a different profile: a decrease in arterial pressure to the same degree as that induced by elgodipine was accompanied by a significant reflex tachycardia and reduction in dP/dt_{max}.

The studies performed in the presence of ganglion blockade with hexamethonium showed that elgodipine not only has a marked inhibitory effect on sinus rate, but also acts on neurogenic reflex genesis or transmission, as hexamethonium, which was able to block volume depletion-induced tachycardia, did not affect the heart rate after infusion of elgodipine.

The mechanism responsible for the direct decelerator effect of elgodipine seems to involve blockade of L-type Ca^{2+} channels, which plays an important role in impulse

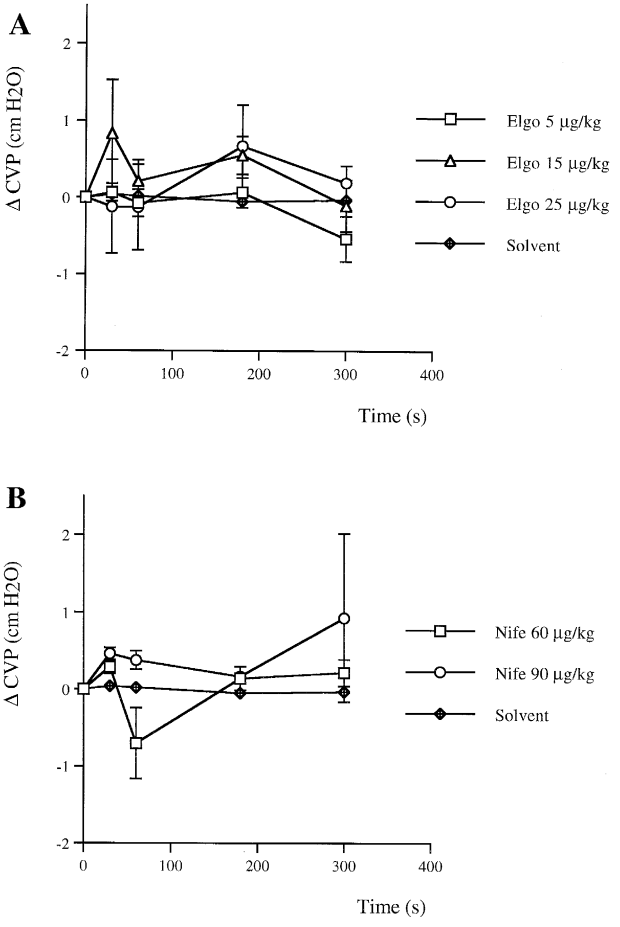

Fig. 7. Effect of the different doses of elgodipine (A) and nifedipine (B) on central venous pressure. Data are shown as means ± S.E.M. of the changes from basal.

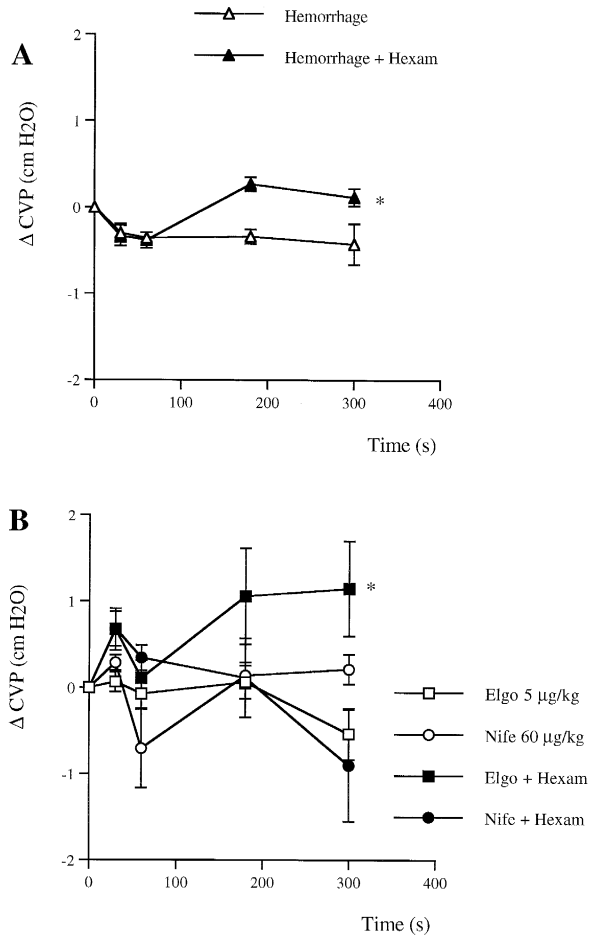

Fig. 8. Effect of ganglion blockade on central venous pressure in rats with removal of 1 ml (A) and rats treated with the lower doses of nifedipine or elgodipine (B). Data are shown as means ± S.E.M. of the changes from basal. Symbols are: * $P < 0.01$ vs. the same group without hexamethonium (one-way ANOVA).

generation and conduction in nodal tissues. In addition to blocking L-type Ca^{2+} channels, elgodipine has been shown to posses antagonistic activity at T-type Ca^{2+} channels in rat portal vein (Lepetre et al., 1994). Similar T-type Ca^{2+} channels seem to play a role in pacemaker function (Hagiwara et al., 1988). Drieu la Rochelle et al. (1994) have also suggested that elgodipine possesses an anti-accelerator property of neurogenic origin which comes rapidly into operation to reduce the reflex elevation of the heart rate. One possible explanation for this effect would be an inhibitory effect of elgodipine on the baroreceptor function. Changes in baroreceptor sensitivity have been reported to follow the administration of several Ca^{2+} channel antagonists (Heesch et al., 1983; Waltier et al., 1984).

Hemodynamics studies with elgodipine in pigs have shown that elgodipine-induced vasodilatation is not associated with significant depression of cardiac contractility

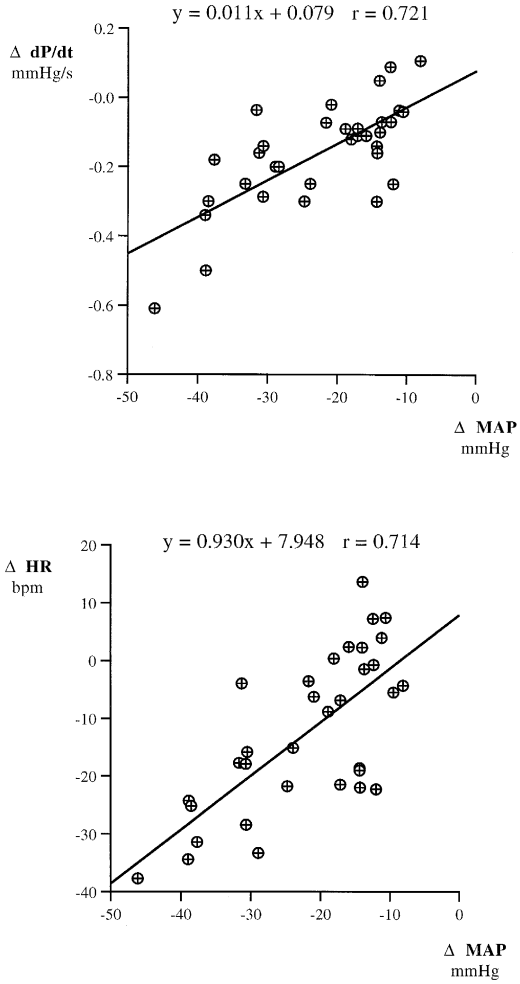

Fig. 9. Linear correlation between elgodipine-induced changes in mean arterial pressure and heart rate (A) and elgodipine-induced changes in mean arterial pressure and left ventricular dP/dt_{max} (B).

(Sassen et al., 1990; Van Woerkens et al., 1991). However, our data and those of Drieu la Rochelle et al. (1994) indicate that elgodipine decreased dP/dt_{max} in presence or absence of autonomic blockade.

When viewed in the context of angina, the hemodynamic profile of elgodipine appears rather attractive. Reflex tachycardia is an undesired consequence of acute vasodilatation induced by most dihydropyridines when used in monotherapy, and this can be one of the causes of the pro-ischemic properties of these drugs in coronary artery disease patients (Furberg et al., 1995, 1996; Gheorghiade et al., 1989). Thus, elgodipine, by not causing reflex tachycardia, and not increasing myocardial oxygen consumption (Drieu la Rochelle et al., 1994), seems to have a favorable effect on the myocardial oxygen supply/demand ratio. In hypertensive patients with coronary artery disease, the use of elgodipine could decrease arterial pressure without increasing cardiac muscle work and, thus, oxygen demand. Due to this fact, the probability of an ischemic insult is reduced.

However, whether elgodipine offers clinically significant advantages over other dihydropyridines remains to be established by adequately designed clinical studies.

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