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Vasopressin induced myocardial depression is neurally mediated and not due to impaired coronary blood flow

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1 The mechanism of the cardiodepressant effect of vasopressin was studied by measuring simultaneously myocardial contractile force and coronary blood flow (with tracer microspheres) in anaesthetized open-chest rabbits.

2 Lysine-vasopressin administered at two dose levels (10 and 100 mu kg^{-1} infused in 2 min with a maintenance dose of 2 mu kg^{-1} min^{-1} between these two loading doses) to a group of 6 rabbits caused dose-dependent myocardial depression and also severely decreased coronary blood flow in a dose-dependent manner. Blood pressure remained almost unchanged but heart rate, cardiac output and total peripheral conductance were also decreased dose-dependently.

3 In another group of 6 rabbits treated in the same way with lysine-vasopressin, darodipine (PY 108-068, 30 and 100 $\mu g\,kg^{-1}$) was infused intravenously. It reversed the vasopressin-induced coronary constriction and cardiodepression. The high dose of vasopressin brought back cardiac depression but did not reduce coronary blood flow below baseline values. Myocardial depression could therefore not be adequately explained by the changes in coronary blood flow.

4 In a further group of rabbits which had been subjected to cervical vagotomy and β-adrenoceptor blockade (propranolol 1 mg kg^{-1} i.v.) before the experiment, vasopressin still caused coronary constriction which was reversed by darodipine, but had no effect on myocardial contractile force and heart rate.

5 The cardiodepressant effect of vasopressin can thus be explained fully by effects on the autonomic nervous system which are reversed by lowering blood pressure, whereas the severe reduction of coronary flow did not contribute to the vasopressin-induced myocardial depression.

Introduction

Vasopressin is a hormone with complex cardiovascular effects. It is now clear that even at blood levels found under physiological and pathophysiological conditions which were for a long time thought to influence only the water-salt homeostasis (Bie, 1980), it causes peripheral vasoconstriction (Möhring *et al.*, 1979; Montani *et al.*, 1980; Johnston *et al.*, 1981; Liard *et al.*, 1982). Interestingly the widespread peripheral vasoconstriction is associated with surprisingly small and often erratic changes in blood pressure (Liard, 1984). This is explained by an enhancement of the baroreflex, which buffers the blood pressure increase. Comparative studies with other constrictor agents indicate that cardiac output is decreased by vasopressin but not (or to a lesser extent) by other vasoconstrictors (Heyndrickx *et al.*, 1976; Hof, 1985a). Earlier experiments in our laboratory indicated that changes in cardiac output may have important repercussions on the peripheral circulation and that cardiodepression contributed much to the decrease in cardiac output (Hof, 1985a). Signs of myocardial depression have also been described by other investigators (Heyndrickx *et al.*, 1976; Wilson *et al.*, 1978; 1980; Cartheuser & Komarek, 1980).

Surprisingly few experiments concerning the mechanism(s) of these cardiac effects have been reported. Direct effects on the myocardium (Wilson *et al.*, 1980; Dominguez-Mon *et al.*, 1984) and, especially, coronary vasoconstriction causing myocardial ischaemia (Zito *et al.*, 1983) have been suggested as possible mechanisms. The present experiments were designed to investigate the myocardial effects of lysine-vasopressin, a synthetic vasopressin derivative used therapeutically. We studied, in anaesthetized rabbits, the relative contributions of vasopressin-induced coronary constriction and effects mediated by the autonomic innervation of the heart. Our results do not support either of the two mechanisms mentioned

above but instead show that myocardial depression is mediated mostly by effects of vasopressin on autonomic reflexes affecting the contractile function of the heart.

Methods

Experimental animals

Reliable haemodynamic measurements in open-chest rabbits depend critically on adequate and constant levels of anaesthesia and ventilation. We found phenobarbitone to be sufficiently longacting in rabbits to avoid the need of re-administration during the course of the experiments. However, during surgery a very deep level of anaesthesia is temporarily needed. The following procedure resulted in rapid induction, excellent tolerance of the open-chest surgery and a maintained anaesthesia with stable cardiopulmonary function for several hours. Large mongrel rabbits (body weight 2.5–4.5 kg) were anaesthetized by injection into an ear vein of 25 mg kg^{-1} pentobarbitone followed by 50 mg kg^{-1} phenobarbitone 10–15 min later. The animals were tracheotomized and ventilated with a Loosco MK2 infant ventilator using room air. The ventilation was adjusted to keep the end-expiratory CO_2 between 4.0 and 4.5 volume % (measured continuously with a Gould-Godart capnograph). A positive end-expiratory pressure was applied as soon as the thorax was opened. Catheters were placed in the lower abdominal aorta, the inferior vena cava and the right atrium. The anaesthesia was then deepened by a further 50 mg kg^{-1} phenobarbitone. Through a thoracotomy in the left 3rd intercostal space, the left atrium was cannulated for the injection of microspheres. The aortic root was cleaned of connective tissue and a flowprobe (Narco RT 500, inner diameter 3.5–4.5 mm) was fitted on it. The electromagnetic flow probe was calibrated *in vivo* by the reference flow method at the time of the last microsphere injection (Hof & Hof, 1981). A second thoracotomy in the fifth right intercostal space was used to sew a Walton-Brodie strain-gauge onto the right ventricle in parallel to the superficial muscle fibres.

Microspheres

The use of the microsphere method in our laboratory has been described in detail previously (Hof *et al.*, 1980; 1981; Hof & Hof, 1981). In brief: for each determination of regional blood flow we injected about 1.5×10^5 microspheres with one of the following labels: ^{125}I, ^{141}Ce, ^{51}Cr, ^{85}Sr or ^{46}Sc. In order to avoid systematic errors due to small differences between different batches of microspheres, spheres with different labels were rotated, so that each label was used for each measuring period. The spheres were injected into the left atrium with 1 ml of 0.9% saline. The reference sample was withdrawn from the lower abdominal aorta through the catheter in the femoral artery at a rate of approximately 6 ml min^{-1}.

At the end of the experiment the animals were killed with an overdose of pentobarbitone. The heart was dissected to obtain samples of the free wall of the left ventricle, which was then divided into 3 layers (Hof & Hof, 1982). The papillary muscles were weighed and counted together with the subendocardial layer. The radioactivity of the samples was determined in a Packard gamma counter (Model 5921) and the spectra processed on an OKI if-800 Model 30 microcomputer according to the method of Rudolph & Heymann (1967) with the modifications of the calculations described by Schosser *et al.* (1979).

Experimental protocols

After the preparative procedures were complete the rabbits were allowed to stabilize for 30–60 min. Fresh drug solutions were prepared immediately before the start of each experiment. Synthetic lysine-vasopressin (Sandoz) was diluted in 5% glucose to a concentration of 100 mu kg^{-1} ml^{-1}. Darodipine was dissolved in a mixture of ethanol and polyethyleneglycol 400, 1 ml each per mg of substance. This solution was diluted with 5% glucose to a concentration of 30 μg kg^{-1} ml^{-1} allowing use of the same infusion speed in all animals.

The experiments were carried out in 4 parallel groups. In a first group of 6 rabbits the effects were determined of two doses of darodipine (30 followed by 70 μg kg^{-1} infused over a period of 10 min each). In the figures the cumulative dose (100 μg kg^{-1}) is shown since the duration of action of darodipine is long compared to the duration of these experiments (Hof *et al.*, 1982). Darodipine or its vehicle was administered in the same way at the appropriate time in the 3 other groups, in which its interaction with vasopressin was studied.

The doses of vasopressin used for the interaction studies had been determined in experiments reported previously (Figure 5 in Hof, 1985a). Vasopressin was infused as a loading dose followed by a maintenance infusion, so that a constant level of peripheral vasoconstriction was achieved. This was verified in a parallel group (Group 2) where only vasopressin (and the vehicle of darodipine) was administered. Then the two doses of darodipine were administered to these vasopressin-treated animals. Finally a second and higher dose of vasopressin was rapidly infused in order to assess whether or not the effects of darodipine could be reversed by increasing the dose of vasoconstrictor.

Earlier experiments (Hof, 1985a) have shown that a loading dose of 10 mu kg^{-1} during the first 2 min followed by a maintenance infusion of 2 mu kg^{-1} min^{-1} resulted in vasopressin effects which remained constant over a prolonged time. During this time darodipine (Group 3) or its placebo (Group 2) was administered and measurements taken as described in the previous paragraph on the first group of animals. Following the second calcium antagonist dose, 100 mu kg^{-1} vasopressin was infused over 2 min and a last series of measurements was obtained immediately at the end of this infusion (Group 3). The 'placebo group' served to assess the time course of the vasopressin effects and was used for the statistical evaluation of the effects of darodipine on the changes induced by vasopressin in Groups 3 and 4.

The Group 4 rabbits were treated exactly like those of Group 3. However, in addition to the surgical procedures described under 'experimental animals' a cervical vagotomy was performed, and the animals were pretreated with an infusion of 1 mg kg^{-1} propranolol and then allowed to stabilize.

Systemic haemodynamic measurements and microsphere injections were performed before starting the first vasopressin infusion and then immediately at the end of each vasopressin or darodipine infusion period. The results shown are the changes from the baseline values presented in Table 1.

Statistical evaluation

The changes induced by vasopressin or darodipine alone as well as some selected within group changes (as indicated in the Results and Discussion sections) were evaluated using Wilcoxon's test for paired samples. In the figures significant differences ($P < 0.05$) found with this test are indicated by asterisks.

The interaction between vasopressin and the calcium antagonist was evaluated by comparing the changes induced by vasopressin alone in the placebo group (Group 2) with those induced by the combined vasopressin-darodipine administration in Groups 3 and 4 using the Kruskal-Wallis followed by the Dunn-Bonferroni test (Miller, 1966).

Results

All baseline values are given in Table 1. Figure 1 shows drug-induced changes from these baseline values again for all groups of animals, so that a side-by-side comparison of the drug actions and interactions under the various conditions is facilitated. The group number at the top of each block of results corresponds to the group number in Table 1 and in the description of the experimental protocols.

Haemodynamic effects of darodipine alone (Group 1)

The first columns in Figures 1 and 2 show the effects of the two doses of darodipine in the first group of rabbits. Mean arterial pressure and heart rate decreased dose-dependently, whereas cardiac output and central venous pressure increased. Contractile force tended to increase. Darodipine increased blood flow to the heart and redistributed it in the 3 layers of the left ventricular free wall. Flow increased dose-dependently in all layers but more so in the subepicardial (Epi) than in the subendocardial (Endo) layer. Since the baseline values were higher in the subendocardial

Table 1 Baseline values for the systemic haemodynamic variables and blood flow

	Group 1	*Group 2*	*Group 3*	*Group 4*
Systemic variables				
MAP (mmHg)	71 ± 2.4	75 ± 4.1	83 ± 2.6	62 ± 2.3
HR (beats min^{-1})	270 ± 7.9	282 ± 8.3	275 ± 10.4	205 ± 6.4
CVP (mmHg)	3.7 ± 0.5	3.3 ± 0.3	3.3 ± 0.4	3.9 ± 0.3
CF (g)	28 ± 3.0	36 ± 6.1	34 ± 2.9	22 ± 2.5
CO (ml min^{-1} kg^{-1})	92 ± 3.9	89 ± 4.9	87 ± 8.6	80 ± 7.0
Blood flow (ml min^{-1} 100 g^{-1})				
Heart total	143 ± 9.2	135 ± 10.7	125 ± 9.6	80 ± 8.0
Epi	156 ± 12.9	148 ± 10.1	141 ± 10.3	95 ± 11.5
Mid	179 ± 16.5	194 ± 11.7	191 ± 17.6	108 ± 18.5
Endo	198 ± 14.8	205 ± 13.8	185 ± 19.4	123 ± 17.9

Abbreviations: MAP: mean arterial pressure; HR: heart rate; CF; contractile force; CVP: central venous pressure; CO: cardiac output; epi, mid, endo: subepicardial, middle and subendocardial layer of the left ventricular free wall. The groups are defined in the text under 'experimental protocols'. The values are expressed as mean ± s.e.mean; $n = 6$ for each group of measurements.

layer (Table 1), absolute flow values were similar in all layers at the smaller dose of darodipine and the flow was only modestly higher in the subepicardium compared to the subendocardium after the high dose. Note that the effects of darodipine (or its vehicle in Group 2) are shown by open and hatched columns also for all the other experimental groups.

Haemodynamic effects of vasopressin alone (Group 2)

The animals infused with the vehicle for the calcium antagonists (placebo) show the effects of vasopressin alone through the time course of the entire experiment (Group 2 in Figures 1 and 2). The solid columns represent the effects of the first infusion (10 mu kg^{-1}) and these effects persisted or even tended to increase slightly during the maintenance vasopressin infusion i.e. during the two infusions of darodipine vehicle. Only the high dose of vasopressin (100 mu kg^{-1}) tended to increase mean arterial pressure and central venous pressure, but heart rate, contractile force and cardiac output were lowered dose-dependently. Vasopressin decreased coronary blood flow both dose-dependently and uniformly throughout the layers of the left ventricular free wall (Figure 2). Again the open and the hatched columns show that the effects persisted during the maintenance vasopressin infusion.

Interaction between vasopressin and darodipine in normal (Group 3) and β-adrenoceptor-blocked-vagotomized animals (Group 4)

The effects of the low dose of vasopressin were the

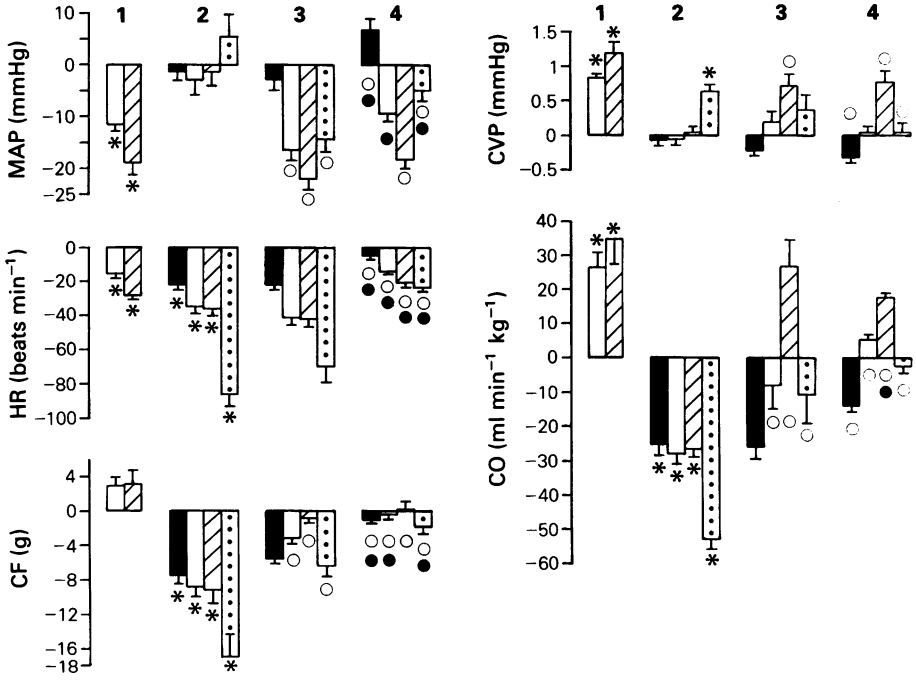

Figure 1 Haemodynamic effects of 3 different treatment schedules in 4 groups of anaesthetized rabbits. All effects are shown as changes (mean and s.e.mean) from the baseline values indicated in Table 1. Numbers above columns indicate the Group. Group 1: darodipine 30 (open column) and 100 μg kg^{-1} (hatched column) administered i.v. as the only drug. Groups 2–4: vasopressin administered at a loading dose of 10 (solid column), followed by a maintenance infusion of 2 mu kg^{-1} min^{-1} during which the two doses of darodipine or, in Group 2, their vehicle were administered (open and hatched columns, same doses as in Group 1). The stippled column shows the effects of the final dose of 100 mu kg^{-1} vasopressin. The animals of Group 4 were pretreated with propranolol 1 mg kg^{-1} and had undergone a bilateral cervical vagotomy.

Abbreviations: MAP: mean arterial pressure; HR: heart rate; CF: contractile force; CVP: central venous pressure; CO: cardiac output. Asterisks indicate changes from the pretreatment baseline values shown in Table 1. Selected other within-group comparisons are described in the text but not shown in the figures. Open circles indicate differences between corresponding columns of Group 2 and Groups 3 or 4, solid circles indicate those between Groups 3 and 4 (Kruskal-Wallis Dunn-Bonferroni test, $P < 0.05$, $n = 6$).

same as in the placebo group (as shown by the solid columns of the Group 3 results). The effects of darodipine, however, only partially resembled those seen in Group 1. The blood pressure effects were unaffected by the vasopressin pretreatment and significantly different when compared to placebo treatment in Group 2. The final high dose of vasopressin reduced the darodipine effect by just as much (7.6 mmHg) as it increased blood pressure in Group 2 (7.0 mmHg). The effects of vasopressin and darodipine on mean arterial pressure were thus additive. Similar additive effects were seen with respect to cardiac output and coronary blood flow to the outer and the middle layer of the left ventricle even though the additive effect was not quite as quantitative as it was with blood pressure.

Unlike results in Groups 2 and 3, vasopressin caused a significant increase in mean arterial pressure in Group 4, where the effector pathways of the baroreceptor reflex had been eliminated. The effects of darodipine remained similar to those seen in Group 2 and 3. The high vasopressin dose produced a significantly larger increase in mean arterial pressure (14.3 mmHg) than in Group 2 (7.0 mmHg) and Group 3 animals (7.6 mmHg). The effects of vasopressin on heart rate were not modified by darodipine in Group 3, i.e. the lowering of heart rate by darodipine no longer appeared in vasopressin-treated animals. Vasopressin had virtually no effects on heart rate in the β-adrenoceptor blocked and vagotomized animals. the Dunn-Bonferroni test indicates, that these changes were smaller in Group 4 than in the Groups 2 and 3.

Darodipine reversed the vasopressin-induced cardiodepression both dose-dependently and significantly in Group 3, this occurred even though the effects of darodipine alone had been neither dose-dependent nor

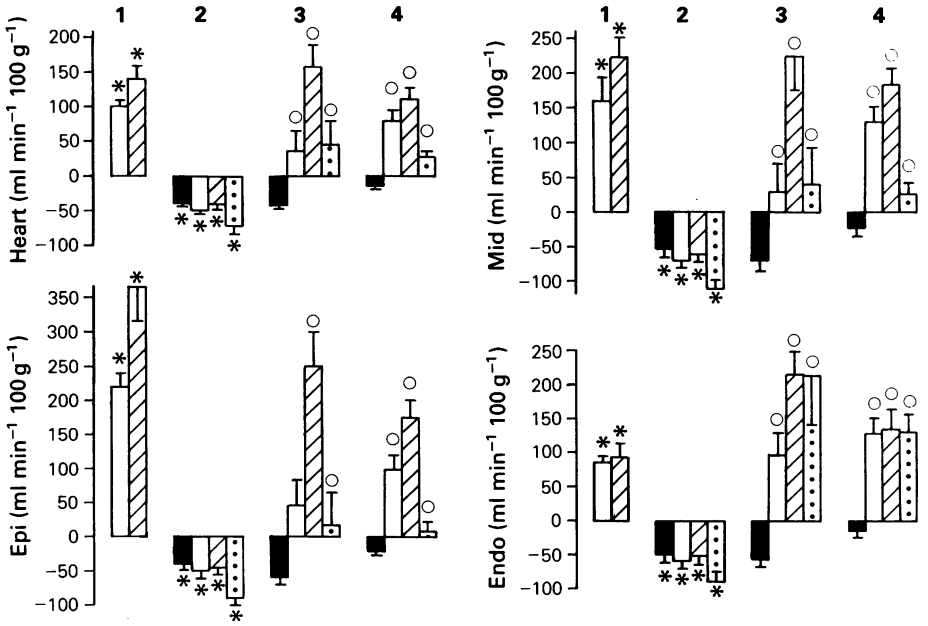

Figure 2 Effects of 3 different treatment schedules on regional and total coronary blood flow in 4 groups of anaesthetized rabbits. Same experiments as in Figure 1. All effects are shown as changes (mean and s.e.mean) from the baseline values indicated in Table 1. Group 1: darodipine 30 (open column) and 100 μg kg^{-1} (hatched column) administered i.v. a the only drug. Groups 2–4: vasopressin at a loading dose of 10 (solid column), followed by a maintenance infusion of 2 mu kg^{-1} min^{-1} during which the two doses of darodipine or, in Group 2, their vehicle were administered (open and hatched columns, same doses as in Group 1). The stippled column shows the effects of the final dose of 100 mu kg^{-1} vasopressin. The animals of Group 4 were pretreated with propranolol 1 mg kg^{-1} and had undergone a bilateral cervical vagotomy.

Abbreviations: epi, mid, endo: subepicardial, middle and subendocardial layer of the left ventricular free wall. Asterisks indicate changes from the pretreatment baseline values shown in Table 1. Selected other within-group comparisons are described in the text but not shown in the figures. Open circles indicate differences between corresponding columns of Group 2 and Groups 3 or 4, solid circles indicate those between Groups 3 and 4 (Kruskal-Wallis Dunn-Bonferroni test, $P < 0.05$, $n = 6$).

significant. After vagotomy and β-adrenoceptor blockade the cardiodepressant effect of vasopressin was absent and hence darodipine had no effect on contractile force. Even the high dose of vasopressin did not decrease contractile force to a relevant extent. The Kruskal-Wallis test indicated that the contractile force was significantly less affected than in Groups 2 and 3.

Central venous pressure was significantly decreased by the low dose of vasopressin only in the animals of Group 4. Darodipine increased central venous pressure significantly at the high dose. Interestingly the high dose of vasopressin increased central venous pressure when administered alone (Group 2) yet tended to decrease the darodipine effect in Group 3 and decreased it significantly in Group 4. There were no differences between the effects in Groups 3 and 4 indicating that nervous influences did not significantly modify venous return. The high dose of vasopressin increased central venous pressure (Group 2) and this effect was smaller after darodipine (Group 3 not significant but Group 4 significant).

The effects of vasopressin and darodipine on cardiac output were additive and β-adrenoceptor blockade plus vagotomy reduced all effects by half causing a significantly smaller increase at the high dose of darodipine.

The effects of the two agents on total coronary and various regional myocardial blood flows are shown in Figure 2, Groups 3 and 4. Except for flow to the subendocardial layer of the left ventricular free wall the interaction was additive. All effects tended to be attenuated slightly (not significant) by β-adrenoceptor blockade and vagotomy in Group 4. Interestingly, the high dose of vasopressin abolished the coronary dilator effects of darodipine in all parts of the myocardium except for the subendocardial layer. This is noteworthy since darodipine alone induced the least effects in the subendocardial layer (Group 1) and the flow reduction by vasopressin alone was comparable in all parts of the heart. β-Adrenoceptor blockade plus vagotomy did not alter any aspect of the interaction even though all effects were slightly smaller (not significant).

Discussion

High doses of vasopressin cause myocardial dysfunction (Cartheuser & Komarek, 1980; Kelly *et al.*, 1980; Wilson *et al.*, 1980; Zito *et al.*, 1983; Hof, 1985a). Cardiac side-effects in the form of coronary vasoconstriction, arrhythmias and myocardial dysfunction have been observed in man during the treatment of bleeding oesophageal varices, a situation where high doses of the agent are infused (Kelly *et al.*, 1980). Also in our experiments we saw striking negative inotropic effects as assessed by myocardial contractile force measured with a strain gauge. The mechanisms of these cardiac effects induced by vasopressin are controversial. At least three different mechanisms could possibly cause them or contribute to them: reflex mechanisms, direct myocardial effects and coronary vasoconstriction. Vasopressin-induced coronary constriction and direct myocardial effects have been investigated previously (Wilson *et al.*, 1980; Zito *et al.*, 1983) but reflex effects on myocardial function have received suprisingly little attention. The primary aim of our experiments was to investigate the contribution of coronary vasoconstrictor and of reflex effects to the negative inotropic actions of vasopressin.

Vasopressin severely decreases coronary flow in a variety of species (Barer, 1961; Nakano, 1967; Heyndrickx *et al.*, 1976; Zito *et al.*, 1983) but there is no agreement as to the importance of this effect for myocardial function (Wilson *et al.*, 1980; Zito *et al.* 1983). A decrease in coronary flow of the magnitude observed in our experiments might well be sufficient to cause cardiac depression (Downey, 1976; Banka *et al.*, 1977). Since the vasopressin-induced vasoconstriction depends on extracellular calcium and is inhibited by calcium antagonists (Fleckenstein, 1977; Altura & Altura, 1977; Hof, 1985a) we studied the interaction of vasopressin with a calcium antagonist having little cardiodepressant activity (darodipine, code name PY 108-068; Hof *et al.*, 1982; Hof & Scholtysik, 1983; Hof & Hof, 1985) at the doses used. This is discussed in more detail later. Our observation that darodipine reversed the vasopressin-induced cardiodepression, supports this concept superficially. However, the differences in dose-dependence of the interaction observed between the effects on contractile force and on myocardial blood flow clearly show that, in our experiments, the coronary vasoconstriction could not fully explain the negative inotropic effect of vasopressin even if we had not done the fourth group of experiments. With the high dose of vasopressin, myocardial depression recurred in Group 3 in the absence of coronary vasoconstriction. 27.6 g. Flow to the subendocardial layer of the left ventricle remained greater than baseline and this part of the myocardium is most susceptible to decreases in blood flow (Downey, 1976). The issue is complicated by indirect effects of vasopressin on myocardial oxygen demand, which must have been lowered sharply by the decrease in heart rate in Groups 2 and 3 but not 4. The heart rate × blood pressure product, which gives a rough estimate of the myocardial oxygen demand, is shown in Table 2. This product was indeed significantly lower than at the baseline time under all experimental conditions in Groups 2 and 3. Cardiodepression nevertheless occurred under these conditions in Groups 2 and 3. In Group 4, by contrast, vasopressin apparently did not decrease myocardial oxygen needs (the heart rate.blood pressure product

Table 2 Effects of vasopressin and darodipine on the heart rate × blood pressure product

Group	*Baseline*	*Vasopressin low dose*	*Derodipine 30 μg kg⁻¹ or placebo*	*Darodipine 100 μg kg⁻¹ or placebo*	*Vasopressin high dose*
2	21063 ± 1340	19150 ± 1229	17634 ± 871†	17947 ± 869†	15640 ± 971†
3	22891 ± 1184	20220 ± 1345†	15610 ± 950*	14228 ± 515*	14023 ± 904
4	12667 ± 711	13791 ± 727†	10017 ± 701*	7886 ± 499*	10355 ± 607*

Mean ± s.e.mean for $n = 6$. †Indicate significant differences from baseline. *Indicate significant differences from the preceding measurement. For details see Discussion.

was in fact significantly increased after the first loading dose), caused coronary constriction and yet did not decrease myocardial contractile force.

Vasopressin appears to have direct effects on myocardial cells in experiments performed *in vitro* (Wilson *et al.*, 1980; Dominguez-Mon *et al.*, 1984). This mechanism is unlikely to be important in the present experiments. Firstly, we would not expect darodipine to diminish direct myocardial effects of an agent because darodipine is rather 'vasoselective' (Hof & Scholtysik, 1983; Hof, 1985b). In experiments carried out *in vivo* we found no cardiodepressant effects in rabbits (present Group 1) cats (Hof & Hof, 1985) or dogs (Hof, 1985b). In all these studies myocardial contractile force was measured with a strain gauge to avoid the problems of contractility parameters derived from haemodynamic measurements. We therefore assume that the doses of darodipine used had no direct effects on the myocardium, and it appears unlikely that the calcium antagonist could have interfered with direct myocardial effects of vasopressin. Secondly, vasopressin did not have any cardiodepressant effects after vagotomy and β-adrenoceptor blockade, suggesting that cardiodepression was mediated by reflexes.

The reflex effects of vasopressin have been thoroughly investigated. This potent vasoconstrictor causes small and erratic changes in blood pressure because it strikingly enhances reflexes which buffer this increase (Cowley *et al.*, 1974; 1984; Liard *et al.*, 1981; Liard *et al.*, 1982; Rascher *et al.*, 1983). An enhancement of the baroreceptor reflex, causing sympathetic withdrawal, plus enhanced parasympathetic activity, resulting in bradycardia, will necessarily also decrease myocardial contractility. Darodipine as well as other coronary dilators (Zito *et al.*, 1983) lowers blood pressure, thus possibly reactivating the sympathetic system. In fact Cowley *et al.* (1984) have recently shown that vasopressin administered intravenously increased the gain of the reflex in response to decreases of carotid sinus pressure. In our Group 4 experiments we removed the two effector pathways important for the cardiac effects of the reflex. This resulted in a significantly greater increase in blood pressure which was reversed by darodipine as expected. Vasopressin completely lost its heart rate lowering effect and was no longer cardiodepressant even though coronary constriction was still present. We therefore conclude that, in experiments *in vivo*, the effects of vasopressin on the autonomic nervous system are responsible for the negative inotropic effects associated with vasopressin administration.

As is often the case, these experiments have not only answered questions but also brought up new ones. The unexpected behaviour of the subendocardial flow and also of central venous pressure in response to the two drugs cannot be adequately explained yet and might stimulate further investigations.

References

ALTURA, B.M. & ALTURA, B.T. (1977). Vascular smooth muscle and neurohypophyse hormones. *Fedn. Proc.*, **36**, 1853–1860.

BANKA, V.S., BODENHEIMER, M.M. & HELFANT, R.H. (1977). Relation between progressive decreases in regional coronary perfusion and contractile abnormalities. *Am. J. Cardiol.*, **40**, 200–205.

BARER, G.R. (1961). A comparison of the circulatory effects of angiotensin, vasopressin and adrenaline in the anaesthetized cat. *J. Physiol.*, **156**, 49–66.

BIE, P. (1980). Osmoreceptors vasopressin, and control of renal water excretion. *Physiol. Rev.*, **60**, 961–1048.

CARTHEUSER, C.F. & KOMAREK, J. (1980). Effects of vasopressin on the circulation, myocardial dynamics, and left ventricular oxygen consumption in the anaesthetized dog. *Basic Res. Cardiol.*, **75**, 668–682.

COWLEY, A.W., MONOS, E. & GUYTON, A.C. (1974). Interaction of vasopressin and the baroreceptor reflex system in the regulation of aterial blood pressure in the dog. *Circulation*, **34**, 505–514.

COWLEY, A.W., MARRIL, D., OSBORN, J. & BARBER, B.J. (1984). Influence of vasopressin and angiotensin on baroreflexes in the dog. *Circulation Res.*, **54**, 163–172.

DOMINGUEZ-MON, M., PONCE-HORNOS, J.E., GOMEZ, R.,

CANNATA, M. & TAQUINI, A.C. (1984). Energetic, metabolic and contractile effects of vasopressin in mammalian heart. *Meth. Find. expt. clin. Pharmac.*, **6**, 373–378.

DOWNEY, J.M. (1976). Myocardial contractile force as a function of coronary blood flow. *Am. J. Physiol.*, **230**, 1–6.

FLECKENSTEIN, A. (1977). Specific pharmacology of calcium in myocardium, cardiac pacemakers, and vascular smooth muscle. *A. Rev. pharmac. Tox.*, **17**, 149–166.

HENDRICKX, G.R., BOETTCHER, D.H. & VATNER, S.F. (1976). Effects of angiotensin, vasopressin and methoxamine on cardiac function and blood flow distribution in conscious dogs. *Am. J. Physiol.*, **231**, 1579–1587.

HOF, R.P. (1985a). Modification of vasopressin- and angiotensin II-indiced changes by calcium antagonists in the peripheral circulation of anaesthized rabbits. *Br. J. Pharmac.*, **85**, 75–87.

HOF, R.P. (1985b). PY 108-068: a calcium antagonist with an unusual pattern of cardiovascular activity. *Gen. Pharmac.*, **16**, 1–6.

HOF, R.P. & HOF, A. (1981). Very small microspheres are useful for the determination of cardiac output but not organ blood flow in conscious rabbits. *Experientia*, **37**, 438–439.

HOF, R.P. & HOF, A. (1982). A simple cutter for fresh tissue to facilitate the investigation of intramyocardial blood flow with tracer microspheres in cats and rabbits. *J. Pharmac. Methods*, **7**, 197–205.

HOF, R.P. & HOF, A. (1985). PY 108-068, a dihydropyridine derivative, and verapamil interact differently with the ouabain effects on the heart and the peripheral circulation. *Basic Res. Cardiol.*, **80**, 66–75.

HOF, R.P., HOF, A. & NEUMANN, P. (1982). Effects of PY 108-068, a new calcium antagonist, on general hemodynamics and regional blood flow in anesthetized cats: A comparison with nifedipine. *J. cardiovasc. Pharmac.*, **4**, 352–362.

HOF, R.P., HOF, A., SALZMANN, R. & WYLER, F. (1981). Trapping and intramyocardial distribution of microspheres with different diameters in cat and rabbit hearts *in vitro*. *Basic Res. Cardiol.*, **76**, 630–638.

HOF, R.P. & SCHOLTYSIK, G. (1983). Effects of the calcium antagonist PY 108-068 on myocardial tissues *in vitro* and on reflex tachycardia *in vivo*. *J. cardiovasc. Pharmac.*, **5**, 176–183.

HOF, R.P., WYLER, F. & STALDER, G. (1980). Validation studies for the use of the microsphere method in cats and young minipigs. *Basic Res. Cardiol.*, **75**, 747–756.

JOHNSTON, C.I., NEWNAN, M. & WOODS, R. (1981). Role of vasopressin in cardiovascular homeostasis and hypertension. *Clin. Sci.*, **61**, s129–s139.

KELLY, K.J., STANG, J.M. & MAKHJIAN, H.S. (1980). Vasopressin provocation of ventricular dysrhythmia. *Ann. Int. Med.*, **92**, 205–206.

LIARD, J.F. (1984). Vasopressin in cardiovascular control: role of circulating vasopressin. *Clin. Sci.*, **67**, 473–481.

LIARD, J.F., DERIAZ, O., SCHELLING, P. & THIBONNIER, M. (1982). Cardiac output distribution during vasopressin infusion or dehydration in conscious dogs. *Am. J. Physiol.*, **243**, H663–H669.

LIARD, J.F., DERIAZ, O., TSCHOPP, M. & SCHOUN, J. (1981). Cardiovascular effects of vasopressin infused into the vertebral circulation of conscious dogs. *Clin. Sci.*, **61**, 345–347.

MILLER, R.G. (1966). *Simultaneous statistical inference*. pp. 57–70. New York: McGraw-Hill.

MÖHRING, J., KINTZ, J. & SCHOUN, J. (1979). Studies on the role of vasopressin in blood pressure control of spontaneously hypertensive rats with established hypertension (SHR, stroke-prone strain). *J. cardiovasc. Pharmac.*, **1**, 593–608.

MONTANI, J.P., LIARD, J.F., SCHOUN, J. & MÖHRING, J. (1980). Hemodynamic effects of exogenous and endogenous vasopressin at low plasma concentrations in conscious dogs. *Circulation Res.*, **47**, 346–355.

NAKANO, J. (1967). Studies on the cardiovascular effects of synthetic vasopressin. *J. Pharmac. exp. Ther.*, **157**, 19–31.

RASCHER, W., LANG, R.E., GANTEN, D., MEFFLE, H., TAUBITZ, M., UNGER, T. & GROSS, F. (1983). Vasopressin in deoxycorticosterone acetate hypertension of rats: A hemodynamic analysis. *J. cardiovasc. Pharmac.*, **5**, 418–425.

RUDOLPH, A.M. & HEYMANN, M.A. (1967). The circulation of the fetus *in utero*: Methods for studying distribution of blood flow, cardiac output and organ blood flow. *Circulation Res.*, **21**, 163–184.

SCHOSSER, R., ARFORS, K.E. & MESSMER, K. (1979). Mic-II-A program for the determination of cardiac output, arterio-venous shunt and regional blood flow using the radioactive microsphere method. *Computer Progr. Biomed.*, **9**, 19–38.

WILSON, M.F., BRACKETT, D.J., ARCHER, L.T. & HINSHAW, L.B. (1980). Mechanisms of impaired cardiac function by vasopressin. *Ann. Surg.*, **191**, 494–500.

WILSON, M.F., BRACKETT, D.J. & MYERS, J.T. (1978). Myocardial depression by vasopressin without global ischemia. *Fedn Proc.*, **37**, 469.

ZITO, R.A., DIEZ, A.R. & GROSZMANN, R.J. (1983). Comparative effect of nitroglycerin and nitroprusside on vasopressin-induced cardiac dysfunction in the dog. *J. cardiovasc. Pharmac.*, **5**, 586–591.

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