Br. J. Pharmac. (1986), **88**, 161–171

The effect of clonidine on venous haemodynamics in cats and dogs

G.A. Bentley, L.K. Cullen*, J.A. Reynoldson* & R.E. Widdop[1]

Department of Pharmacology, Monash University, Wellington Road, Clayton, 3168, Victoria, Australia and School of Veterinary Studies*, Murdoch University, Murdoch, 6150, Western Australia

1 Experiments were undertaken to investigate a possible action of clonidine on venous haemodynamics, using cats and dogs with autoperfused hindquarters. This provided an arterial input to the region independent of cardiac output. Venous capacitance in the hindquarters was indicated by blood flow in the abdominal vena cava, as measured by an electromagnetic flow probe around this vessel.

2 It was found that in both cats and dogs, clonidine given intravenously (5 $\mu g\,kg^{-1}$ i.v.) or into the cisterna magna (1 $\mu g\,kg^{-1}$ i.c.m.) reduced mean arterial pressure and heart rate, but did not decrease hindquarter perfusion pressure. With the exception of dogs given i.v. clonidine, this drug caused a decrease in inferior vena cava (IVC) blood flow and this closely paralleled the hypotensive effect. However, when clonidine was given i.v. to dogs, the decrease in IVC blood flow preceded the hypotension. At the doses used, the reduction in IVC blood flow was larger following i.v. than i.c.m. clonidine in both species, and in all cases, it remained below control levels for at least 30 min, in spite of the constant arterial input to the region.

3 In cats, dose-response curves were constructed to noradrenaline and adrenaline given into the perfusion circuit (i.a.) before and after clonidine. Following i.v. and i.c.m. clonidine, there was a selective depression of the venoconstrictor actions of the catecholamines, but no change in the arterial pressor action.

4 Radiographic and latex studies in the dog and cat respectively were performed in order to visualize collateral blood flow that could account for the persistent decreases in IVC blood flow. In both species, intraspinal collateral flows were demonstrated which returned blood to the heart after ligation of the inferior vena cava below the renal veins. However, it was not possible to demonstrate radiographically any changes produced by clonidine in the collateral flow because of technical difficulties.

5 These results suggest that clonidine causes a selective reduction in sympathetic tone to the veins that is mediated at least partly by a central action, as well as an expansion of the collateral venous routes. This, together with the selective impairment of venoconstrictor responses to both noradrenaline and adrenaline, may account for the decrease in cardiac output that is most often reported following clonidine.

Introduction

It is generally accepted that the hypotensive action of the antihypertensive drug clonidine is due to the stimulation of α_2-adrenoceptors within the central nervous system (Kobinger & Pichler, 1982; Hausler, 1982), resulting in sympatho-inhibition and vagal facilitation (for reviews see Schmitt, 1977; Kobinger, 1978; 1984). In both clinical and animal studies the most consistently reported haemodynamic consequences associated with the hypotensive effect of clonidine are bradycardia and a decreased cardiac output. Somewhat surprisingly, decreases in total peripheral resistance have not been as consistently noted (see Schmitt, 1977). Similarly, regional haemodynamic studies have revealed analogous results. For example, clonidine, in doses that produce systemic hypotension when given intravenously or into the cisterna magna of anaesthetized cats with autoperfused hindquarters, has negligible effects on hindlimb peripheral resistance (Li & Bentley, 1970; Nolan & Bentley, 1978; Brazenor & Bentley, 1982).

In contrast, little work has been done on the effects of clonidine on venous haemodynamics, even though

[1]Author for correspondence.

the venous circulation stores the major portion of the total blood volume and is under reflex control (Hainsworth & Linden, 1979; Rothe, 1983a,b). Cardiac output is intimately related to venous return, and this emphasizes the need to analyse more closely the effects of clonidine on venous dynamics. Earlier work by Nayler *et al.* (1968) has shown that clonidine does produce venodilatation in dogs, and it has also been shown, in man, to increase venous capacity in the leg, and decrease central venous pressure (Ehringer, 1966; Barnett & Cantor, 1968; Brod *et al.*, 1972). The object of the present study was to investigate the effects of clonidine on the venous return from the hindquarters of cats and dogs in which the input of blood to this region was under the control of the perfusion pump, and was thus independent of drug-induced changes in cardiac output.

Methods

General procedures

Cats Cats of either sex weighing 3.5–5.5 kg were anaesthetized with α-chloralose (80 mg kg^{-1}) given intravenously following induction with halothane and nitrous oxide. A tracheal cannula was then inserted. Arterial blood pressure was recorded from the right brachial artery using a Statham P23AC pressure transducer, and heart rate was monitored by a cardiotachograph (Grass Model 7 P4) triggered by the pulse pressure wave. The right brachial vein was cannulated for intravenous (i.v.) injections.

Dogs Dogs of either sex weighing 8–27 kg were anaesthetized with thiopentone sodium (20–25 mg kg^{-1}) given intravenously. The animals were then intubated and connected to a close-circuit anaesthetic machine delivering oxygen and methoxyflurane from a vaporiser in circuit. Appropriate adjustments to the anaesthetic vapour concentration maintained an even depth of anaesthesia. Arterial blood pressure was recorded from the right brachial artery using a Statham P23ID pressure transducer. Heart period was recorded on a heart period meter as the interval between successive peaks of the arterial pressure signal. The brachial vein was cannulated for intravenous injections.

Autoperfused hindquarters

Both cats and dogs were prepared for constant flow autoperfusion using the method described by Li & Bentley (1969, 1970). Briefly, the procedure involved cannulation of the abdominal aorta just proximal to the origin of the inferior mesenteric artery after giving heparin (500 iu kg^{-1}) intravenously. Blood from the aorta was led through a constant-flow perfusion pump and back again to the aorta just distal to the first cannulation. Perfusion pressure was measured by a Statham (P23 AC or P23ID) transducer attached to the perfusion circuit close to its re-entry into the aorta, and was set equal to the systemic blood pressure by adjusting the blood flow to the perfused area. Since the supply of blood to the area is controlled entirely by the pump, any changes in the perfusion pressure must reflect changes in the peripheral resistance in the region.

Blood flow in the inferior vena cava (IVC) was measured with an electromagnetic flow meter. Two alternative transducer types were used for this. In most cases, a probe (1.5–3.5 mm i.d., Biotronex Series 5000) was placed around the vena cava at the same level as the arterial perfusion cannulae. Since this necessarily caused some constriction of the vena cava, other experiments were also performed in which the vena cava was cannulated and the blood was led through an extracorporeal flow transducer ($\frac{1}{8}$" Biotronex Series 2000C) and then returned via a second cannula to the vena cava. Mean blood flow, in all cases, was measured on a blood-flow meter (Biotronex BL 613). All variables were displayed on a Grass polygraph (Model 7D). In two experiments with cats, it was found that the effect of clonidine on venous outflow was essentially identical when measured with the extracorporeal flow transducer as that in other cats with the flow transducer around the vena cava. Therefore, these results have been grouped. In addition, in other experiments, similar results were obtained using both types of flow transducer to measure changes in venous outflow caused by other sympatho-inhibitory agents (Widdop & Bentley, unpublished). Thus the probe placed around the vena cava was usually preferred because it was less invasive. The choice of probe size was made to ensure good mechanical contact with the vessel wall. Since the input to the area is controlled, changes in blood flow in the vena cava reflect changes in capacitance.

Apart from ligating all visible arterial and venous side-branches in the exposed region, no other surgery was performed so as to maintain neural connections to the hindquarters.

Interaction of noradrenaline and adrenaline with clonidine in cats

The catecholamines were injected directly into the hindquarters perfusion circuit (in 0.1–0.5 ml volumes) and produced increases in the arterial perfusion pressure and IVC blood flow which indicated arterial and venous constriction, respectively. Three- or four-point dose-response curves were constructed to noradrenaline and adrenaline before, and approximately 15 min after, clonidine administration.

Radiographic and latex perfusion studies

In order to visualize collateral blood flow to and from the autoperfused area some latex perfusion and radiographic studies were performed using cats and dogs respectively. The animals were prepared as already described. In the dog studies, a cannula was inserted into the femoral vein for the injection of contrast medium (Angiographfin, Schering). An inflatable cuff was placed around the vena cava in the same position that the flow probe would occupy and when this was inflated it completely occluded the vena cava. Radiographs were taken of the abdominal and thoracic regions of the dogs, during a rapid infusion of 20 ml of the contrast medium. This was done before and after occlusion of the vena cava. Similarly, radiographs were taken before and after giving $5\,\mu g\,kg^{-1}$ clonidine i.v. to dogs with the vena cava unoccluded.

Other experiments were performed in which contrast medium was injected into the aorta via a cannula inserted into the left carotid artery and advanced so that its tip lay in the thoracic aorta. Radiographs were taken before and after switching off the perfusion pump in order to visualize possible arterial inflow to the hindquarters bypassing the perfusion pump.

In the cat studies, the left femoral vein and the vena cava at the level of the perfusion cannula were ligated and a cannula was inserted into the right femoral vein for the injection of 15–20 ml of coloured latex. The animals were overdosed simultaneously with pentobarbitone injected via the brachial vein, and 5% acetic acid was then applied over the perfused region. Post mortem inspection was performed 1–2 h later.

Experiments analogous to the dog aortic contrast medium experiments were performed on the cat. Latex was injected into the aorta via a cannula inserted into the left carotid artery with its tip in the thoracic aorta. The perfusion pump was switched off immediately before the injection.

Drugs

The following drugs were used: adrenaline bitartrate (Sigma); α-chloralose (BDH); clonidine hydrochloride (Boehringer Ingelheim); noradrenaline bitartrate (Sigma).

In both cats and dogs, clonidine was injected intravenously in a volume of $0.1\,ml\,kg^{-1}$ or into the cisterna magna in a volume of 0.1 ml. Intracisternal (i.c.m.) injections were performed by the insertion of a 22 gauge needle between the atlas vertebra and the occipitus. A free flow of cerebrospinal fluid indicated that the needle tip was within the cisterna magna. Clonidine was injected in a volume of 0.1 ml after a similar quantity of cerebrospinal fluid had been removed. Final dilutions of clonidine were made in 0.9% w/v NaCl solution (saline) before use. Final dilutions of noradrenaline and adrenaline were made up in saline containing $20\,\mu g\,ml^{-1}$ EDTA and $10\,\mu g\,ml^{-1}$ ascorbic acid. All concentrations are expressed in terms of the base substance and only one dose of clonidine was given to each animal. Saline was without effect in these experiments.

Statistical analysis

The effect of clonidine on all variables was compared with the control values using Student's paired t test, and significance was accepted at the 0.05 probability level.

The shifts in the dose-response curves of noradrenaline and adrenaline following clonidine were analysed for each experiment using a potency ratio programme which tested the two lines for parallelism and coincidence. This was done for the arterial (perfusion pressure) and venous (vena cava blood flow) vasoconstrictor reponses to noradrenaline and adrenaline. The dose-ratios were then pooled and averaged.

Results

Cat

The initial arterial inflow delivered by the pump to the hindquarters was $13.7 \pm 1.1\,ml\,min^{-1}$ ($n = 7$) for the i.v. clonidine group and $16.3 \pm 2.2\,ml\,min^{-1}$ ($n = 7$) for the i.c.m. clonidine group. These values were not significantly different from the venous outflows measured from the region, which were 15.5 ± 3.1 $ml\,min^{-1}$ and $18.9 \pm 2.9\,ml\,min^{-1}$ respectively (Table 1).

It was found that the intravenous injection of clonidine, $5\,\mu g\,kg^{-1}$, produced significant initial pressor responses in both the systemic (34 ± 6.2 mmHg, $n = 7$, $P < 0.05$) and hindlimb (16 ± 4.3 mmHg, $n = 7$, $P < 0.05$) circulations. Small transient increases in IVC blood flow were seen in 5 out of 7 cats ($1.9 \pm 0.3\,ml\,min^{-1}$, $n = 5$, $P < 0.05$). These responses were accompanied by an almost immediate bradycardia. Thereafter the hypotensive phase of the drug developed, with maximum systemic hypotension occurring within 5–10 min. The IVC blood flow followed a similar time course and in all cases it fell significantly below control levels for the remainder of the experiment (30–60 min). There was also a very small but significant decrease in perfusion pressure.

When clonidine, $1\,\mu g\,kg^{-1}$, was given by intracisternal injection, it produced a systemic hypotension similar to $5\,\mu g\,kg^{-1}$ i.v. but without the initial direct peripheral vasoconstrictor effects. The time course of the hypotension and bradycardia was slower, and

Table 1 Changes in mean arterial pressure (MAP), heart rate (HR), hindquarter perfusion pressure (PP), arterial inflow (AIn) and mean vena cava blood flow (VCBF) of chloralose-anaesthetized cats with autoperfused hindquarters in response to clonidine given intravenously (i.v.) or intracisternally (i.c.m.)

Treatment	*Variable*	*Initial value*	*Change*	*% Change*
Clonidine, 5 μg kg^{-1} i.v. ($n = 7$)	MAP (mmHg)	86 ± 11.0	−27 ± 5.8*	−30 ± 3.2
	HR (beats min^{-1})	199 ± 22	−36 ± 11.3*	−16 ± 4.0
	PP (mmHg)	107 ± 6.3	−6 ± 2.2*	−6 ± 1.9
	AIn (ml min^{-1})	13.7 ± 1.1†	—	—
	VCBF (ml min^{-1})	15.5 ± 3.1	−4.2 ± 0.8*	−29 ± 3.0
Clonidine, 1 μg kg^{-1} i.c.m. ($n = 7$)	MAP (mmHg)	87 ± 8.7	−22 ± 5.1*	−26 ± 5.2
	HR (beats min^{-1})	176 ± 10.9	−14 ± 3.7*	−7 ± 1.8
	PP (mmHg)	103 ± 5.8	−3 ± 1.8	−3 ± 1.7
	AIn (ml min^{-1})	16.3 ± 2.2†	—	—
	VCBF (ml min^{-1})	18.9 ± 2.9	−3.5 ± 0.3*	−20 ± 2.8

Data shown are means ± s.e.mean.
− Indicates decreases in the appropriate variable.
*Significantly different from control ($P < 0.05$).
†Arterial inflow delivered by the pump which was not significantly different from control VCBF ($P > 0.05$).

reached maximum within 15–20 min. Blood flow in the vena cava also decreased significantly and closely paralleled the fall in systemic blood pressure. Hindquarter perfusion pressure was not significantly decreased after intracisternal clonidine. These results are shown in Table 1.

Dogs

The initial arterial inflow delivered by the pump to the hindquarters was 120 ± 6.5 ml min^{-1} ($n = 5$) for the i.v. clonidine group and 147 ± 15.7 ml min^{-1} ($n = 5$) for the i.c.m. clonidine group. These values were not significantly different from the venous outflows measured from the region, which were 107 ± 7.7 ml min^{-1} and 133 ± 17.5 ml min^{-1} respectively (Table 2).

As in cats, the intravenous injection of clonidine, 5 μg kg^{-1}, caused significant initial pressor responses in the systemic (18 ± 1.8 mmHg, $n = 5$, $P < 0.05$) and hindlimb (82 ± 10.8 mmHg, $n = 5$, $P < 0.05$) circulations, accompanied by immediate bradycardia and decreased IVC blood flow. Maximum systemic hypotension developed within 5–10 min although, in contrast to cats, the hindquarter perfusion pressure remained significantly elevated (Table 2).

Intracisternal clonidine, 1 μg kg^{-1} caused haemodynamic changes similar to those seen in cats, and maximum hypotension and bradycardia occurred within 15–20 min. There was no change in the hindquarter perfusion pressure, while the IVC blood flow decreased in parallel with the systemic hypotension. The decreases in IVC blood flow produced by intravenous and intracisternal injection persisted for the period of observation (30–60 min) and, as seen in cats, with the doses used there were larger decreases in IVC blood flow following i.v. than i.c.m. clonidine. In contrast to the cat studies, the reduction in IVC blood flow preceded the hypotension produced by i.v. injection of clonidine by several minutes although this did not occur following i.c.m. injection (see Figure 1; Table 2).

Clonidine and catecholamines in cats

Noradrenaline (0.625–5.0 μg) injected into the perfusion circuit (i.a.) produced dose-related arterial and

Table 2 Changes in mean arterial pressure (MAP), heart rate (HR), hindquarter perfusion pressure (PP), arterial inflow (AIn) and mean vena cava blood flow (VCBF) of methoxyflurane-anaesthetized dogs with autoperfused hindquarters in response to clonidine given intravenously (i.v.) or intracisternally (i.c.m.)

Treatment	*Variable*	*Initial value*	*Change*	*% Change*
Clonidine, $5\,\mu g\,kg^{-1}$ i.v. ($n = 5$)	MAP (mmHg)	87 ± 8.1	-18 ± 4.4*	-20 ± 4.5
	HR (beats min^{-1})	130 ± 8.5	-21 ± 2.1*	-16 ± 1.3
	PP (mmHg)	93 ± 8.7	$+24 \pm 5.1$*†	$+26 \pm 4.5$
	AIn (ml min^{-1})	120 ± 6.5‡	—	—
	VCBF (ml min^{-1})	107 ± 7.7	-38 ± 5.0*	-36 ± 5.3
Clonidine, $1\,\mu g\,kg^{-1}$ i.c.m. ($n = 5$)	MAP (mmHg)	73 ± 3.8	-28 ± 3.9*	-39 ± 6.8
	HR (beats min^{-1})	127 ± 3.5	-19 ± 5.8*	-15 ± 4.7
	PP (mmHg)	87 ± 1.6	$+4 \pm 6.4$	$+5 \pm 7.5$
	AIn (ml min^{-1})	147 ± 15.7‡	—	—
	VCBF (ml min^{-1})	133 ± 17.5	-20 ± 3.1*	-15 ± 1.9

Data shown are means ± s.e.mean; + and − indicate increases and decreases respectively in the appropriate variable.
*Significantly different from control ($P < 0.05$).
†Recorded 30 min after clonidine.
‡Arterial inflow delivered by the pump which was not significantly different from control VCBF ($P > 0.05$).

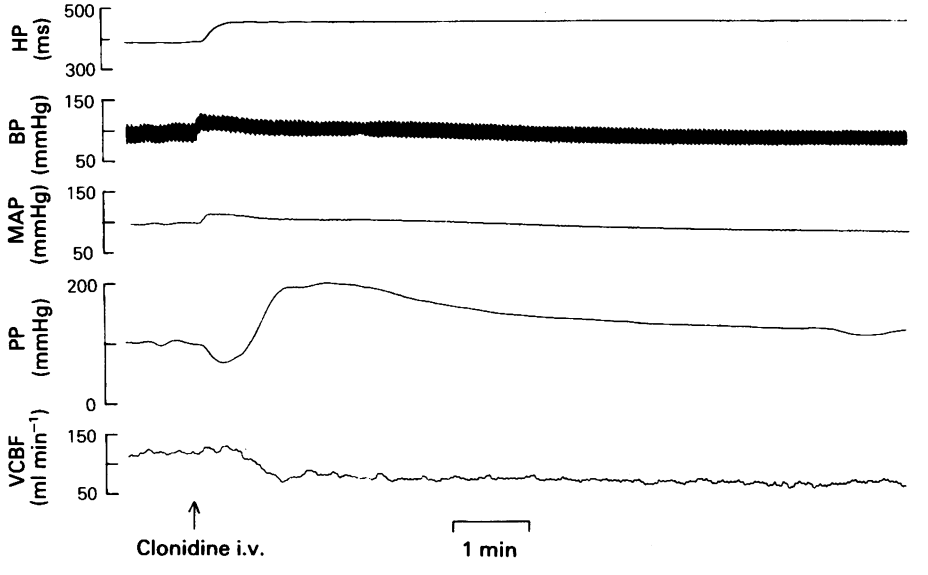

Figure 1 Recording from a methoxyflurane-anaesthetized dog with autoperfused hindquarters of heart period (HP), arterial pressure (BP), mean arterial pressure (MAP), hindquarter perfusion pressure (PP) and mean vena cava blood flow (VCBF) and the response to clonidine, $5\,\mu g\,kg^{-1}$ i.v. Note that VCBF decreased before, and was maintained during, the hypotensive phase of clonidine.

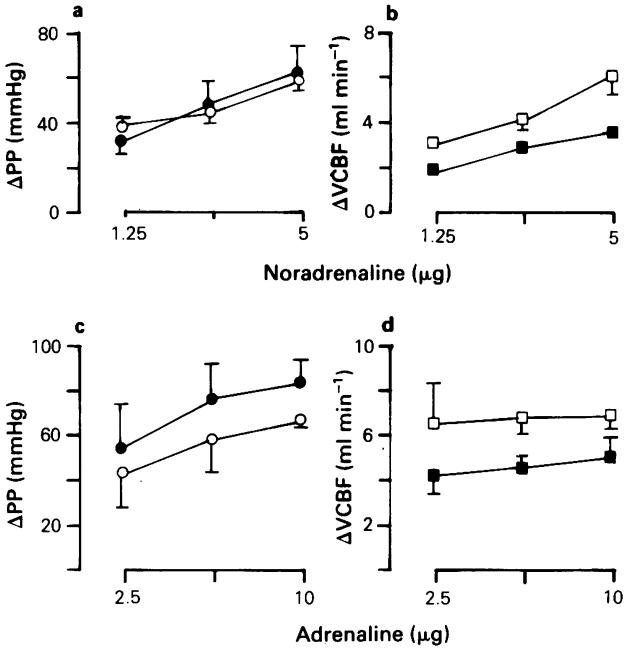

Figure 2 Dose-response curves for the increases in (a and c) perfusion pressure (PP) and (b and d) vena cava blood flow (VCBF) in response to noradrenaline (a and b) and adrenaline (c and d) given into the perfusion circuit before (open symbols) and after (closed symbols) clonidine, 5 $\mu g\,kg^{-1}$ i.v. The results show the means and the vertical lines s.e.mean of 4 (c and d) or 5 (a and b) experiments.

venous constriction as indicated by the increases in hindquarter perfusion pressure and IVC blood flow, respectively (Figures 2 and 3). These responses were followed by systemic pressor responses of 5–60 mmHg, depending on the dose. Heart rate responses were inconsistent and were not included in the analysis. The pressor response to i.a. noradrenaline in either the systemic circulation or the hindlimb perfusion pressure was not altered by the prior administration of clonidine 5 $\mu g\,kg^{-1}$ i.v. or 1 $\mu g\,kg^{-1}$ i.c.m. However, the venoconstriction caused by i.a. noradrenaline was depressed after clonidine given by either route. In both cases, after clonidine, the dose-response curves to the venoconstrictor effect of noradrenaline were shifted by at least a factor of two to the right (Figures 2 and 3), although in 2 experiments the maximum responses to noradrenaline were markedly depressed and hence the dose-response curves were not parallel (Table 3).

The effect of adrenaline injected into the perfusion stream was also tested. Adrenaline was usually more potent than noradrenaline in causing venoconstriction, but was less effective as an arterial constrictor. These effects were accompanied by both pressor or depressor responses in the systemic circulation. In the first (intravenous) series of experiments, the lowest dose of adrenaline tested (2.5 μg) caused a maximal increase in IVC flow, although doses up to 10 μg still gave dose-dependent increases in the perfusion pressure. Clonidine, 5 $\mu g\,kg^{-1}$ i.v. caused a reduction of about 30% in the response of the IVC blood flow to each dose of adrenaline but, in contrast, it potentiated the perfusion pressor responses. However, dose-ratios could not be calculated for these experiments (Figure 2).

For the experiments where clonidine was given i.c.m., lower doses of adrenaline (0.625–5.0 μg) were used, and these gave graded increases in IVC blood flow as well as in perfusion pressure. After clonidine 1 $\mu g\,kg^{-1}$ i.c.m. there was again a slight potentiation of the arterial response to adrenaline, although again, as for i.v. clonidine, there was a depression of the venous response to adrenaline (Figure 3, Table 3).

Collateral circulations

The possibility of collateral circulations was examined since in both dogs and cats clonidine caused a prolonged reduction in IVC blood flow in spite of a constant inflow to the hindquarters from the pump.

Injection of contrast medium into the femoral vein in dogs without occlusion of the vena cava, or with a

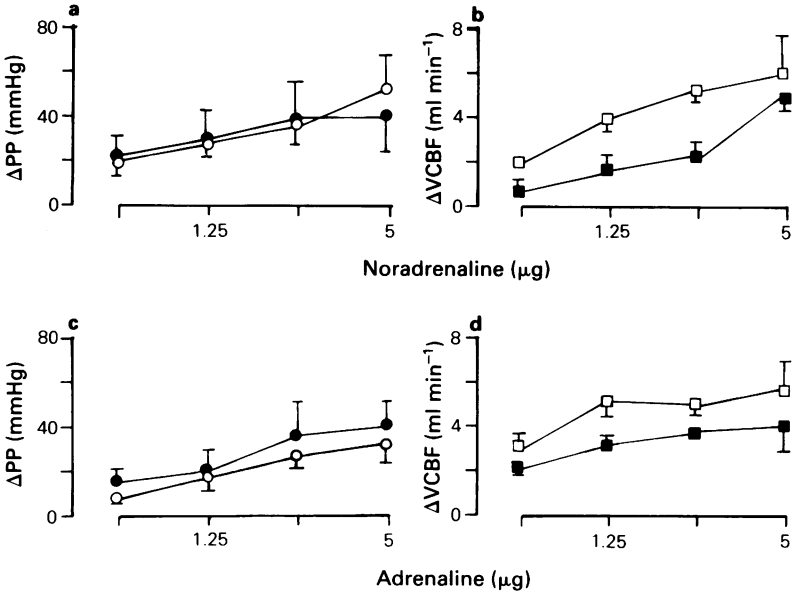

Figure 3 Dose-response curves for the increases in (a and c) perfusion pressure (PP) and (b and d) vena cava blood flow (VCBF) in response to noradrenaline (a and b) and adrenaline (c and d) given into the perfusion circuit before (open symbols) and after (closed symbols) clonidine, 1 $\mu g\,kg^{-1}$ i.c.m. The results show the means and the vertical lines s.e.mean of four experiments.

Table 3 Shifts of the dose-ratios in the constrictor response to noradrenaline and adrenaline measured simultaneously in the arterial (PP) and venous (VCBF) hindquarter circulations of chloralose-anaesthetized cats following clonidine pretreatment

Pretreatment	*Drug*	*n*	*PP**	*VCBF**
Clonidine, 5 $\mu g\,kg^{-1}$ i.v.	Noradrenaline i.a.	5	1.1 ± 0.2	2.3 ± 0.2 (4)†
	Adrenaline i.a.	4	Potentiated (see text, Figure 2)	Depressed (see text, Figure 2)
Clonidine, 1 $\mu g\,kg^{-1}$ i.c.m.	Noradrenaline i.a.	4	1.2 ± 0.4	2.1 ± 0.1 (3)†
	Adrenaline i.a.	4	0.8 ± 0.05	1.6 ± 0.2 (3)†

Data shown are means ± s.e.mean.
*Numbers greater than one indicate rightward shifts of the appropriate dose-response curve (depression) and numbers less than one indicate leftward shifts of the appropriate dose-response curve (potentiation).
†In each of these groups one experiment could not be included in the analysis, because there was a marked depression of the dose-response curve to the agonist in the venous circulation after clonidine resulting in a non-parallel rightward shift following the particular clonidine pretreatment.

flow probe around the vena cava, showed no significant entry of the medium into collateral veins. Unfortunately, after giving clonidine, 5 $\mu g\,kg^{-1}$ i.v., it was not possible to demonstrate unequivocally any increase in collateral blood flow when the vena cava was unoccluded. This was probably due, in part, to some technical difficulties encountered (see Discussion). However, when the vena cava was occluded there was clear indication of contrast medium entering intraspinal venous sinuses via connecting veins, and returning to the vena cava more proximal to the point of occlusion, largely via the azygos vein.

In one experiment, contrast medium was injected into the thoracic aorta before and after switching off the perfusion pump. No contrast medium could be detected at any point distal to the pump after it had been turned off, indicating that blood had not reached the hindquarters by collateral arterial routes.

Experiments were also performed using 5 cats which received an injection of about 15 ml coloured latex into the femoral vein after the vena cava had been ligated just below the level of the renal veins. Post mortem inspection revealed coloured latex in the vena cava below the ligature, and in some cases the renal veins and vena cava proximal to the ligation also contained a moderate amount of latex. In all cases, latex was seen within the thoracic spinal venous sinuses that fed into the azygos vein and superior vena cava. The right atrium, pulmonary arteries and lungs were usually coloured although there was no latex in the thoracic aorta. This would further indicate that the latex had moved forward within the vertebral venous sinuses and had rejoined the vena cava via more proximal spinal collaterals.

Latex was also injected into the thoracic aorta and in three cats no latex was detected at any point distal to the pump which had been turned off.

Discussion

The aim of this study was to investigate the effects of clonidine given either by i.v. or i.c.m. injection, on venous capacitance. Cats and dogs with autoperfused hindquarters were used in order to hold constant the blood flow to a discrete area of the body. Under these conditions, changes in perfusion pressure indicate changes in arterial resistance in this region. Venous outflow was also measured, and changes in IVC blood flow reflected changes in venous capacitance. Karim & Hainsworth (1976) have recently shown that venous outflow could be reliably measured from the abdominal region of dogs using a cannulating transducer with an electro-magnetic flowmeter. In their study, capacitance responses were determined by the integration of venous outflow from the abdominal circulation following peripheral sympathetic nerve stimulation.

In the present study and other studies (Widdop & Bentley, unpublished), consistent results were obtained using either an extracorporeal (cannulating) or a 'fish-hook'-type flow transducer, which was placed around the vena cava. Good mechanical contact was ensured in the latter case by securing a slot cover to confine the blood vessel within the transducer lumen and this was evident in some cases by the slight ballooning of the vena cava at each end of the probe. The advantages of measuring venous outflow, as compared to more conventional techniques of tissue weighing and plethysmography are that this method is used with the tissue *in situ* and so causes less trauma, and transient changes in blood flow can also be measured (Rothe, 1983a).

The pressure gradient along veins is flow-dependent and this has important consequences since 60–80% of total blood volume is contained in small veins and venules (Rothe, 1983a). For example, a decrease in arterial blood flow will cause a decrease in the transmural pressure distending small veins. This may produce passive mobilization of blood due to the elastic recoil of the compliant veins. This passive effect is more pronounced at low, rather than high, venous pressures (Oberg, 1967). Accordingly, the pressure that is distending all veins must be held constant and this is best achieved by perfusing the region at a constant blood flow (Hainsworth & Linden 1979; Rothe 1983a). Thus, in the present study, changes in venous capacitance were due only to active changes in the venous smooth muscle and were not influenced by changes in arterial resistance, as measured by changes in perfusion pressure. For these reasons, early work by Mellander (1960), who studied changes simultaneously in different series-coupled vascular sections, has been criticized (Karim & Hainsworth, 1976; Hainsworth & Linden, 1979) since, in those experiments, the hindquarters of cats were perfused at constant pressure rather than by constant flow perfusion.

In the present study, it was found that clonidine given by either route, selectively decreased blood flow in the vena cava in both cats and dogs for the duration of the experiments. This effect closely paralleled the hypotensive action of the drug. In contrast, clonidine had little effect on the hindquarters perfusion pressure in cats, and in dogs, caused a prolonged rise in pressure, at least after it was given i.v. This clearly indicates that dilatation on the arterial side of the circulation is not the primary cause of the hypotensive action of clonidine under these conditions. This work supports an earlier suggestion that clonidine may cause venodilatation by a selective reduction in sympathetic tone to the veins (Li & Bentley, 1970) and is consistent with the reports of other workers who demonstrated a similar venodilator action of clonidine. For example, Ehringer (1966) found that, in

man, i.v. clonidine increased the venous capacity of the leg. Also, under controlled flow conditions using dogs on cardio-pulmonary bypass, Nayler *et al.* (1968) found that clonidine caused systemic venodilatation; however, simultaneous resistance changes were note reported.

Although it had been shown that clonidine lowered IVC blood flow, it was puzzling that this decrease was so prolonged. Under constant inflow conditions, it could be expected that an increase in venous capacitance would reduce IVC blood flow only until this increased capacitance was filled. Thus the prolonged fall in IVC blood flow was probably due to either an increase in the formation of tissue fluid or, more likely, to clonidine opening up alternate venous pathways which by-passed the flow-probe. Another possibility was that the input of blood to the hindquarters was not exclusively via the pump, so that the reduced cardiac output caused by clonidine resulted in a reduction in the total blood supply to the region, despite the presence of the pump.

The injection of contrast medium into the thoracic aorta of dogs did not show any material by-passing the posterior aorta to reach the hindquarters. Similarly, infusions of latex into the thoracic aorta of cats failed to demonstrate any collateral arterial supply to the hindquarters. Thus, it seems unlikely that the lowered vena cava blood flow could be the result of a significantly reduced inflow to the hindquarters because of a reduced collateral arterial supply.

Since there were no signs of oedema in the hindquarters of these animals, it is most unlikely that increased extravasation of fluid could account for these discrepancies. Before giving clonidine, arterial inflow delivered by the pump and venous outflow from the hindquarters were approximately equal, with small differences between inflow and outflow in both directions noted in each group. These data suggested that, in the control state the main route of blood return was almost entirely via the inferior vena cava. This was confirmed, in part, by the radiographic studies using dogs, since when the IVC was not occluded, there were only traces of contrast medium observed in the intraspinal vessels. It seems probable that these collateral pathways are normally not patent, but provide an alternative route of flow when, for example, intra-abdominal pressure is raised and flow in the vena cava is diminished. However, after giving clonidine i.v., it was not possible to demonstrate radiographically, with certainty, whether there were any increases in collateral blood flow in the absence of vena cava constriction. This was probably due to the extremely rapid transit of contrast medium through both the main and the collateral vascular routes so that obtaining radiographs at the critical times was extremely difficult. In addition, the density of surrounding tissues, particularly bone, probably hindered the detection of small collateral vessels, although others have observed extensive linking between the caval and vertebral systems in patients without any caval obstruction (see Abrams, 1961).

However, when the vena cava was occluded at the level of the flow probe, contrast medium could clearly be seen leaving the vena cava to run via intra-spinal sinuses, which drained back into the vena cava via more anterior connections. This is an agreement with the anatomical study of Worthman (1956) who found that when the inferior vena cava was ligated below the renal veins, dogs could maintain an adequate supply of blood to the heart mainly via vertebral venous sinuses. Similarly, radiographic studies in human subjects both with, and without, obstruction to the inferior vena cava, have revealed extensive connections between vertebral venous and azygos systems (Abrams, 1961). In cats too, injections of coloured latex into the femoral vein, following ligation of the vena cava, provided a similar picture, with latex appearing as far proximal as the heart, lungs and sometimes even in the veins emptying into the superior vena cava. Thus it is obvious that there is a very effective venous shunt from the posterior vena cava via intraspinal routes. Although these studies are not dynamic, and therefore are not physiological, the use of radiography and latex perfusion has verified the existence of alternative pathways to the heart. Moreover, the unequivocal demonstration of collateral pathways, observed by the 'fixed' distribution of latex in and around the right atrium could not have been obtained unless the IVC had been obstructed.

It was also shown that in cats, i.v. or i.c.m. clonidine selectively depressed the action of noradrenaline and adrenaline to increase blood flow in the vena cava, although the arterial pressor responses to the catecholamines in the hindquarters were unaltered or even slightly potentiated. This unexpected interaction may, in part, be due to the increased collateral venous flow which ensured a wider distribution of the catecholamines and hence a reduced overall venoconstriction. This, in turn, would result in less venoconstriction being recorded at the probe site and a general dampening of the venoconstrictor signal. This would appear to be a function of the increased collateral flow per se since this phenomenon occurred after both i.v. and i.c.m. clonidine, although a peripheral α-adrenoceptor blocking action of clonidine in veins cannot be ruled out (Coupar & Kirby, 1972; Hepburn & Bentley, 1982).

However, if clonidine did in fact decrease the venoconstrictor action of neurally-released noradrenaline and circulating adrenaline this may further reduce the maintenance of IVC blood flow. This in turn, would amplify the more circuitous, and hence slower, route of blood return to the heart.

In both cats and dogs, when clonidine was given i.v.

it produced a greater reduction in IVC blood flow as compared with i.c.m. injection, for reasons which are not immediately obvious. Since i.c.m. clonidine decreased IVC blood flow, it is apparent that at least part of this response was of central origin. Differences between the effects of the two injection routes were probably due to local actions of clonidine after i.v. administration, such as an α-adrenoceptor blocking action of clonidine to decrease tonic venoconstriction (Coupar & Kirby, 1972). In addition, it is possible that i.v. clonidine, in producing initial venoconstriction, could, in effect, mimic the effect of partial mechanical occlusion of the IVC. This may divert venous outflow into collateral channels that remain patent due to the subsequent centrally-mediated inhibition of sympathetic tone which, in its own right, produces venodilatation and the opening of collateral channels.

In conclusion, the present study has shown that clonidine has caused a reduction in sympathetic tone to the veins, mediated at least partly by a central action, which results in both an increased venous capacitance in the hindquarters and an expansion of the collateral venous route via the intraspinal venous sinuses. This has also resulted in the selective impairment of venoconstrictor responses to both noradrenaline and adrenaline and the combination of these selective actions on the venous circulation may account for the decrease in cardiac output that is most often reported following clonidine.

We wish to thank Assoc. Prof. R.S. Wyburn and Mr G. Herd for their assistance with the radiographic studies and Mr R. Strack for his technical assistance. Clonidine was kindly supplied by Boehringer-Ingelheim, to whom we express our gratitude.

References

ABRAMS, H.L. (1961). The vertebral and azygos venous systems: their relationship to anomalies of systemic venous return. In *Angiography*. Vol. 1, ed. Abrams, H.L. pp. 407–427. London: J. & A. Churchill Ltd.

BARNETT, A.J. & CANTOR, S. (1968). Observations on the hypotensive action of 'catapres' (ST 155) in man. *Med. J. Aust.*, **1**, 87–91.

BRAZENOR, R.M. & BENTLEY, G.A. (1982). Central effects of α-adrenoceptor agonist and antagonist drugs on somatically evoked reflexes in cat systemic and hindlimb circulations. *Clin. exp. Pharmac. Physiol.*, **9**, 499–503.

BROD, J., HORBACH, L., JUST, H., ROSENTHAL, J. & NICOLESCU, R. (1972). Acute effects of clonidine on central and peripheral haemodynamics and plasma renin activity. *Eur. J. clin. Pharmac.*, **4**, 107–114.

COUPAR, I.M. & KIRBY, M.J. (1972). The effect of clonidine on human isolated smooth muscle. *Eur. J. Pharmac.*, **17**, 50–58.

EHRINGER, V.H. (1966). Die Wirkung von 2-(2,6-dichlorphenylamino)-2-imidazolin-hydrochlorid auf die Extremitatendurchblutung, den Blutdruck und die Venenkapazitat bie Normotonikern. *Arzneimittelforsch.*, **16**, 1165–1169.

HAINSWORTH, R. & LINDEN, R.J. (1979). Reflex control of vascular capacitance. In *Int. Rev. Physiol. Cardiovascular Physiology III*, 18. ed. Guyton, A.C. & Young, D.B. pp. 67–124. Baltimore: University Park press.

HAUSLER, G. (1982). Central α-adrenoceptors involved in cardiovascular regulations. *J. cardiovasc. Pharmac.*, **4**, S72–S76.

HEPBURN, E.R. & BENTLEY, G.A. (1982). Studies on the vasoconstrictor activities of imidazolidine derivatives in various vascular beds. *J. cardiovasc. Pharmac.*, **4**, 297–302.

KARIM, F. & HAINSWORTH, R. (1976). Responses of abdominal vascular capacitance to stimulation of splanchnic nerves. *Am. J. Physiol.*, **231**, 434–440.

KOBINGER, W. (1978). Central α-adrenergic systems as targets for hypotensive drugs. *Rev. Physiol. Biochem. Pharmac.*, **81**, 39–100.

KOBINGER, W. (1984). Central anti-hypertensives. In *Discoveries in Pharmacology*, Vol. 2, ed. Parnham, M.J. & Bruinvels, J. pp. 107–123. Amsterdam: Elsevier.

KOBINGER, W. & PICHLER, L. (1982). α-Adrenoceptor subtypes in cardiovascular regulation. *J. cardiovasc. Pharmac.*, **4**, S81–S85.

LI, D.M.F. & BENTLEY, G.A. (1969). The effect of St 155 on the active reflex vasodilatation induced by adrenaline, noradrenaline and veratrine. *Eur. J. Pharmac.*, **8**, 39–46.

LI, D.M.F. & BENTLEY, G.A. (1970). The effects of various anti-hypertensive drugs on the reflex responses to vasoactive substances. *Eur. J. Pharmac.*, **12**, 24–34.

MELLANDER, S. (1960). Comparative studies on the adrenergic neuro-hormonal control of resistance and capacitance blood vessels in the cat. *Acta physiol. scand.*, **50**, suppl. 176, 1–86.

NAYLER, W.G., PRICE, J.M., SWANN, J.B., McINNES, I., RACE, D. & LOWER, T.E. (1968). Effect of the hypotensive drug ST155 (catapres) on the heart and peripheral circulation. *J. Pharmac. exp. Ther.*, **164**, 45–59.

NOLAN, P.L. & BENTLEY, G.A. (1978). The effects of sympatholytic drugs on the cardiovascular response to tilting in anaesthetised cats. *Clin. exp. Pharmac. Physiol.*, **5**, 417–427.

OBERG, B. (1967). The relationship between active constriction and passive recoil of the veins at various distending pressures. *Acta physiol. scand.*, **71**, 233–247.

ROTHE, C.F. (1983a). Venous system: physiology of the

capacitance vessels. *Handbook of Physiol.*, **III,** Section 2, 397–452.

ROTHE, C.F. (1983b). Reflex control of veins and vascular capacitance. *Physiol. Rev.*, **63,** 1281–1342.

SCHMITT, H. (1977). The pharmacology of clonidine and related products. In *Handb. of exp. Pharmac.*, Vol. 39, ed. Cross, F. pp. 299–397. Berlin: Springer-Verlag.

WORTHMAN, R.P. (1956). The longitudinal vertebral venous sinuses of the dog. II Functional aspects. *Am. J. Vet. Res.*, **17,** 349–363.

(*Received October 22, 1985.*
Revised January 6, 1986.
Accepted January 11, 1986.)