Br. J. Pharmac. Chemother. (1967), **31**, 407–419.

ADRENOCEPTIVE SITES IN THE VEINS

BY

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(*Received June* 8, 1967)

Since the introduction of new, potent β-receptor blocking agents (Black & Stephenson, 1962 ; Black, Duncan & Shanks, 1965), there has been renewed interest in learning more about the existence and function of β-adrenoceptive sites. In the last few years, an impressive number of papers has accumulated dealing with various β-receptor blocking agents and their therapeutic use (Harrison, Braunwald, Glick, Mason, Chidsey & Ross, 1964 ; Honey, Chamberlain & Howard, 1964 ; Schröder & Werko, 1965 ; Rowlands, Howitt & Markman, 1965 ; Keelan, 1965), as well as with the importance of β-adrenoceptive sites as mediators of various haemodynamic and metabolic events (Moran, 1963 ; Zsotér, Tom, Kraml & Dvornik, 1966). The role of β-receptors in the venous system, indeed whether those receptors are present in the veins at all, is controversial. Kaiser, Ross & Braunwald (1964) reported that isoprenaline causes venoconstriction. Others have found that isoprenaline dilates veins (Folkow, 1960) or has a biphasic action on venous strips (Sutter, 1965). No data were found on the effect of β-receptor blocking agents on veins.

Veins can actively participate in the regulation of venous pressure. Furthermore, several vasoactive materials are known to have a quantitatively or qualitatively different effect on the resistance and on the capacitance vessels (Haddy, 1960). Consequently, the fact that stimulation of α-adrenoceptive sites constricts and that of β-receptors dilates arteries does not mean necessarily that those receptors, when present at all, would have the same effect on the veins. When resistance in capacitance vessels is altered, this is of utmost importance in the regulation of venous return and hence of cardiac output. Resistance changes may also alter the cross-capillary pressure gradient and hence the capillary filtration. For these reasons experiments were conducted in an attempt to clarify the role of β-receptors in the venous system. The effects of various drugs, considered as stimulating or blocking agents of the α- or β-adrenoceptive sites, on segmental pressure and blood flow were investigated in animals.

METHODS

Mongrel dogs weighing 14–28 kg and cats weighing 4–4.8 kg were anaesthetized with sodium pentobarbitone ; 30 mg/kg was given intravenously and 15 mg/kg intramuscularly, followed by additional intravenous doses of 5 mg/kg as required. The animals received 5 mg/kg heparin intravenously (150 U.S.P. u./mg heparin sodium, Wilson Laboratory).

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Blood flow was measured by a Medicone K-200 sinewave electromagnetic flowmeter. One and a half to 3 mm flow probes were used, depending on the size of the vessel. Each flow probe was calibrated *in vitro* by perfusing saline from a container to a graduated cylinder over a wide range of flow. The sensitivity factor, in ml./min/0.1 V, for every probe was calculated from several tests. For calibration of the flowmeter, before each experiment, the Instruction Manual of Medicone was followed. Zero line was established by clamping the artery upstream from the probe. When flow was measured in the femoral artery the probe was placed 1 cm below the inguinal ligament. When blood flow was recorded in the inferior mesenteric artery the probe was placed about 4 cm below the origin of the vessel.

Intra-arterial infusion of solutions of various drugs or 0.9% NaCl was given through a No. 22 needle, inserted into the artery 1 cm distal from the probe. About 5 cm more distal, a No. 20 needle was placed into the artery and connected to a Statham P23 AC transducer. A similar needle was inserted into the femoral vein, about 5 cm below the inguinal canal, or into the inferior mesenteric vein just above the origin. Pressure in the small veins was recorded *via* a 1/20 in. o.d. polyethylene tube connected to a transducer. This catheter was introduced with a metal leader into the paw vein and manipulated distally through the valves ; when wedge position was obtained, the catheter was withdrawn 1 cm. When the mesenteric vessels were studied, a similar polyethylene catheter was introduced into a small branch of the vein to the wall of the intestine and then withdrawn 1 cm from the wedge position. For venous pressure measurements a Statham P23 BC transducer was used. All pressures were referred to right atrial level, taken as 10 cm above the table. Pressures and blood flow were simultaneously recorded by a Grass Model 7 Recorder during the entire experiment, either with a 2.5, 1 or 0.5 mm/sec paper speed.

Solutions of drugs or 0.9% NaCl were infused into the artery with a Harvard infusion pump, at a rate of 0.5 ml./min. The following drugs were used: (−)-noradrenaline bitartrate (Levophed, Winthrop Laboratory), isoprenaline hydrochloride U.S.P. (Winthrop Laboratory), propranolol hydrochloride (Inderal, Ayerst), pronethalol hydrochloride (Nethalide, Ayerst), dichloro-isoprenaline (DCI, Aldrich Chemical Company), phenoxybenzamine hydrochloride (Dibenzyline, Smith, Kline and French) and acetylcholine bromide (Eastman Organic Chemicals). Stock solutions, 1 or 10 mg/100 ml. were prepared fresh each day and further diluted with 0.9% NaCl solution. Details of doses are given in Results. The infusion of drugs was preceded and followed by the infusion of 0.9% NaCl solution at the same rate. In some experiments two drugs were simultaneously administered by connecting the outlets of two infusion pumps by a Y tube and infusing the two solutions through a common needle. The drugs were administered intravenously as single injections, not as infusions.

In six dogs the femoral artery was cannulated and perfused at a constant flow rate by a Sigmamotor pump with blood from the contralateral femoral artery. Isoprenaline and (−)-noradrenaline were administered into the tube before and after propranolol. The drugs were infused in doses similar to those in the experiments with varying blood flows. In addition to pressures in the femoral artery, femoral vein and small vein of the paw, pressure was also recorded in a small vein of the quadriceps muscle.

Vascular resistance for all experiments was calculated in resistance units (RU), as pressure gradient (mm Hg) divided by blood flow (ml./min). Pressure difference between artery and small vein was used for calculation of " arterial " resistance, while pressure difference between small and large veins was used for calculation of " small vein " resistance. For calculation of resistance in large veins pressure was divided by flow values. Right atrial pressure was then assumed to remain unaltered by the drugs.

RESULTS

Effects of infusion of isoprenaline and noradrenaline into the femoral artery of the dog

Femoral arterial flow in 40 dogs during intraarterial infusion of 0.9% NaCl solution before any drug was given was 34.1 ± 1.6 ml./min (mean ± S.E. ; range 19.6–64.6 ml./min.). The corresponding pressure in the artery was 141 ± 2.5 mm Hg (range 112–173 mm Hg),

in the small vein of the paw 20.3 ± 1 mm Hg (range 9.5–33 mm Hg) and in the femoral vein 7.2 ± 0.3 mm Hg (range 4.8–11 mm Hg). These values remained remarkably constant during a 3 hr long infusion of 0.9% NaCl solution (Fig. 1).

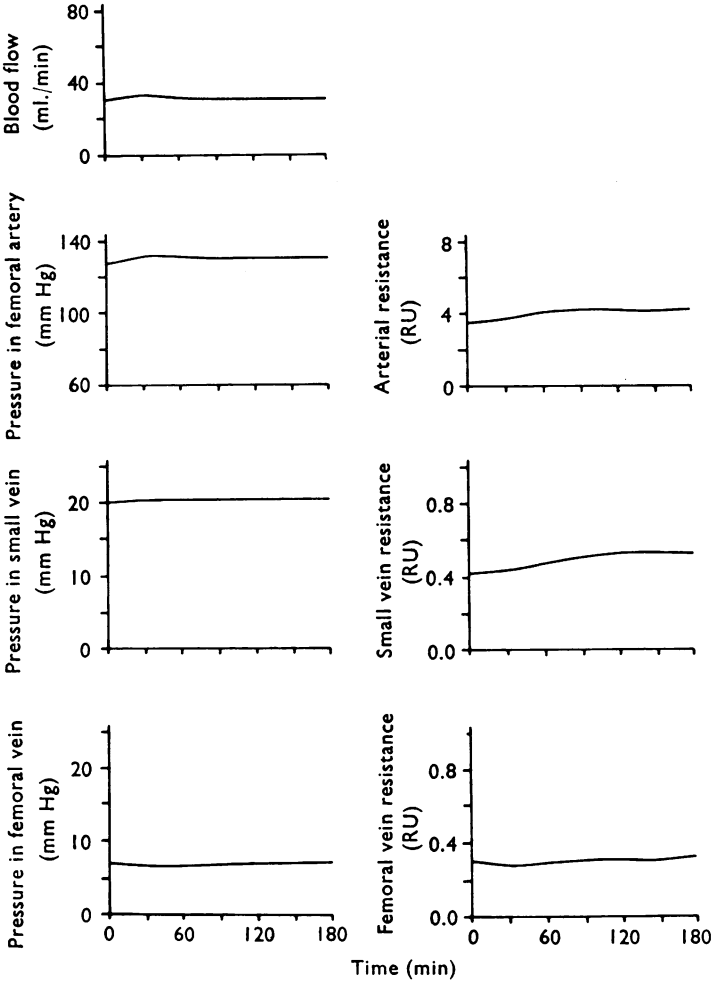

Fig. 1. Effects of prolonged infusion of 0.9% NaCl solution (0.5 ml./min) into the femoral artery on blood flow in the femoral artery and on pressures and vascular resistances in the femoral artery, a small vein of the paw and the femoral vein. Mean values of observations in 4 dogs.

Isoprenaline was infused into the femoral artery of 11 dogs in gradually increasing doses (0.3, 1 and 3 μg/min), each level for 5 min. The lowest dose (0.3 μg/min) was sufficient to produce the characteristic changes; at higher doses alterations were only slightly more pronounced (Fig. 2). After 0.3 μg/min isoprenaline blood flow increased in every animal, the mean value being about three times greater than that of the controls. Pressure in the perfused artery slightly decreased, indicating a diminished arterial resistance. Pressure in the small vein of the paw was increased, but to a lesser extent than

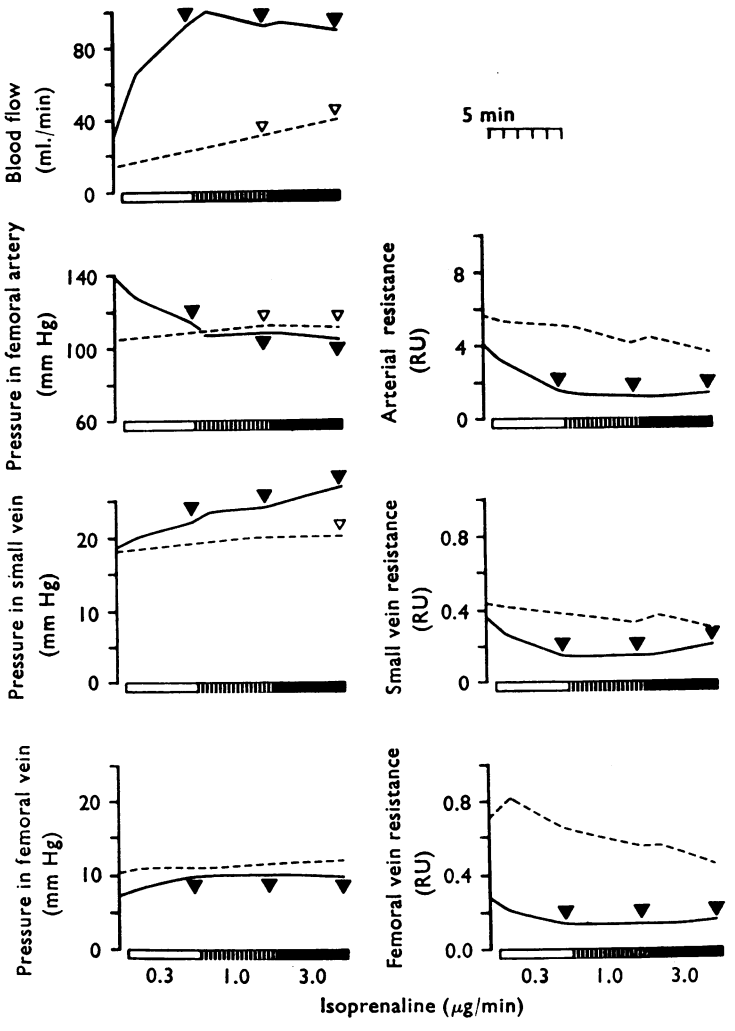

Fig. 2. Effects of intra-arterial infusion of isoprenaline, 0.3, 1 and 3 μg/min, each dose level for 5 min. In this and all subsequent figures only values obtained after 1 and 5 min of infusion are shown. ——, isoprenaline alone (11 dogs); - - - -, isoprenaline 15–45 min after intravenous injection of propranolol 10 μ-mole/kg (4 dogs). ▽, $P<0.05$, ▼, $P<0.01$ when values at 5 min infusions were compared with values obtained before isoprenaline was infused.

blood flow. This means that resistance in the small vein was diminished ($P<0.01$). The effect on the pressure and resistance in the femoral vein was similar (Fig. 2).

When in 4 dogs the infusions of isoprenaline were repeated 15 to 45 min after intravenous injections of propranolol, 10 μ-mole/kg, the effects of isoprenaline were almost entirely blocked (Fig. 2). In other animals pretreatment with 10 μ-mole/kg DCI or pronethalol had a similar blocking effect. On the other hand, phenoxybenzamine

(10 μ-mole/kg), given intravenously to 4 dogs did not alter significantly the responses of either arteries or veins.

The pressure gradient between small vein and femoral vein was calculated for each experiment. This gradient increased after isoprenaline but the effect was statistically significant only after infusion of 3 μg/min (Table 1).

TABLE 1

EFFECTS OF ISOPRENALINE AND NORADRENALINE (a) AND OF α- AND β-BLOCKING AGENTS (b) ON THE PRESSURE GRADIENT BETWEEN A SMALL VEIN OF THE PAW AND THE FEMORAL VEIN

The drugs were infused into the femoral artery for periods of 5 min at each dose level. Values of the pressure gradients are those obtained at the end of each period.

(a)

Drug	Dogs (no.)	Pressure gradient (mm Hg) Control	After 0·3 μg/min	After 1 μg/min	After 3 μg/min
Isoprenaline	11	11·2	12·3	14·1	16·1*
Noradrenaline	10	11·4	9·0†	15·9	22·5*

(b)

Drug	Dogs (no.)	Pressure gradient (mm Hg) Control	After 0·3 μ-mole/min	After 1 μ-mole/min	After 3 μ-mole/min
DCI	8	11·8	22·4†	25·8*	24·5*
Pronethelal	4	10·9	12·7*	14·5*	17·4†
Propranolol	4	7·7	5·9	6·0	6·1
Phenoxybenzamine	4	12·3	12·4	10·2	9·5

* $P<0·05$; † $P<0·01$; all other values not significantly different from the control values.

The effects of intra-arterial infusion of noradrenaline in 10 dogs are demonstrated in Fig. 3. Increasing doses, 0.3, 1 and 3 μg/min, were infused in three successive periods of 5 min. The diminution of blood flow was dose-related. Although the pressure in the femoral artery was raised only after infusion of the highest dose, arterial resistance increased after infusion of the lowest dose in every animal. Pressure in the small veins of the paw slightly decreased with the lowest dose of noradrenaline but increased sharply with the highest dose. In contrast, pressure in the femoral vein diminished slightly. Resistance increased in both large and small veins; with the two larger doses of noradrenaline the rise was greater in the small than in the large vein. The pressure gradient from small to large vein decreased after a small dose of noradrenaline and increased after a large dose (Table 1).

In 4 dogs effects of noradrenaline on pressures and resistances were blocked 30–60 min after intravenous injection of phenoxybenzamine (10 μ-mole/kg) (Fig. 3). On the other hand, propranolol, in equimolecular dose, did not affect significantly the changes produced by noradrenaline.

Effects of infusion of α- and β-receptor blocking agents into the femoral artery of the dog

Intra-arterial infusion of DCI (0.3 μ-mole/min) augmented flow markedly in all 8 dogs (Fig. 4). Pressure and resistance in the femoral artery decreased but, in the small vein, the pressure increased without change in resistance. The pressure in the femoral

vein was only slightly raised. Larger doses of DCI did not produce any further increase in blood flow. After intravenous injection of either propranolol (10 μ-mole/kg) or phenoxybenzamine (10 μ-mole/kg) the effects of intra-arterial infusion of DCI were much reduced. Pronethalol, infused intra-arterially at rates similar to those used with DCI, increased the blood flow in the femoral artery and the pressure in a small vein of the paw less than DCI (Fig. 5). The increase of flow was partly prevented by pretreatment with propranolol (10 μ-mole/kg). Propranolol infused into the femoral artery had no effect other than an increase in blood flow lasting for less than a minute. Intra-arterial infusion of phenoxybenzamine did not cause any changes in blood flow or pressures (Fig. 5). The pressure gradient between a small vein of the paw and the femoral vein was increased by DCI or pronethalol, but not by propranolol or phenoxybenzamine (Table 1).

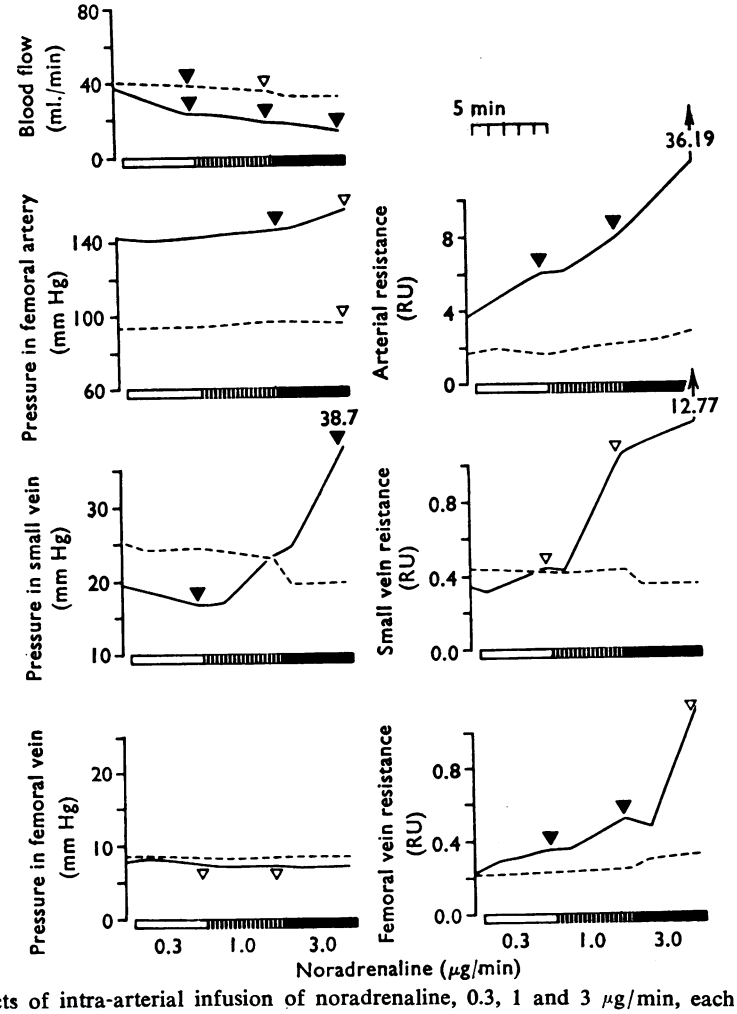

Fig. 3. Effects of intra-arterial infusion of noradrenaline, 0.3, 1 and 3 μg/min, each dose level for 5 min. ——, noradrenaline alone (10 dogs); - - - -, noradrenaline 30–60 min after intravenous phenoxybenzamine, 10 μ-mole/kg (4 dogs). ▽, $P<0.05$, ▼, $P<0.01$ when values at 5 min infusions were compared with values obtained before noradrenaline was infused.

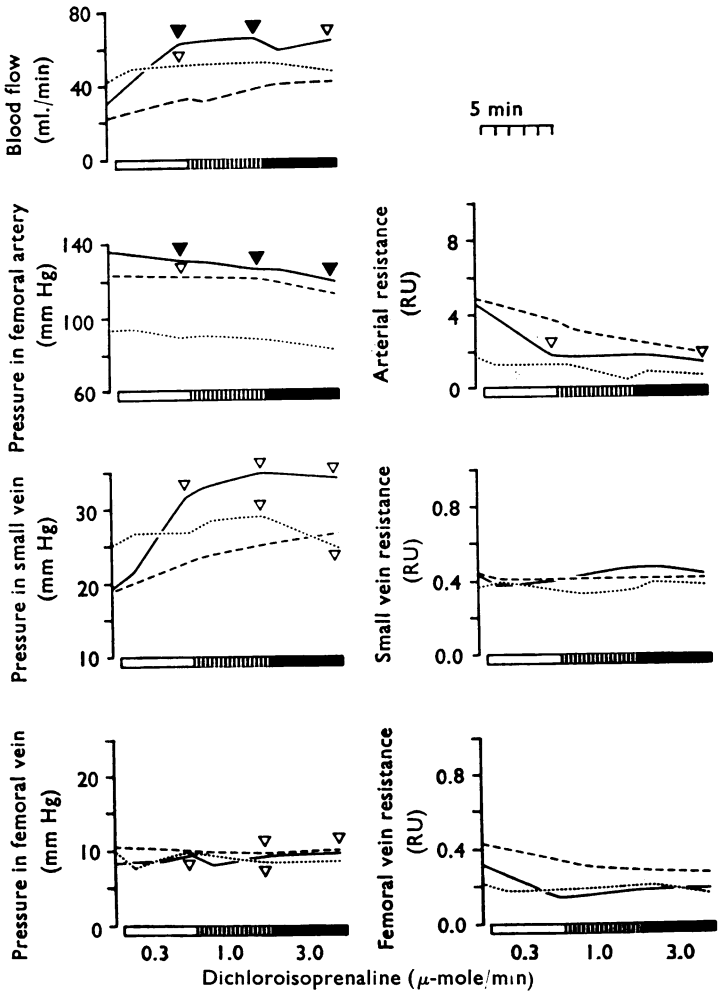

Fig. 4. Effects of dichloroisoprenaline (DCI) infusion, 0.3, 1 and 3 μ-mole/min, into the femoral artery. ——, DCI alone (8 dogs); - - - -, DCI after intravenous propranolol, 10 μ-mole/kg (4 dogs); . . . . ., DCI after intravenous phenoxybenzamine, 10 μ-mole/kg (4 dogs). ▽, $P<0.05$, ▼, $P<0.01$ when values at 5 min infusions were compared with values obtained before DCI was infused.

Effects of infusion of isoprenaline, noradrenaline and DCI into the mesenteric artery of the dog

In 7 dogs isoprenaline, noradrenaline and DCI were infused into the cranial mesenteric artery. The blood flow in the mesenteric artery was higher and the resistances in the artery and small vein were lower than in the femoral vascular bed. While the effects of isoprenaline and noradrenaline on the mesenteric vessels were similar to those observed in the femoral vessels DCI produced no increase in blood flow (Fig. 6). Pretreatment with propranolol (10 μ-mole/kg; 4 dogs) prevented the effects of isoprenaline and

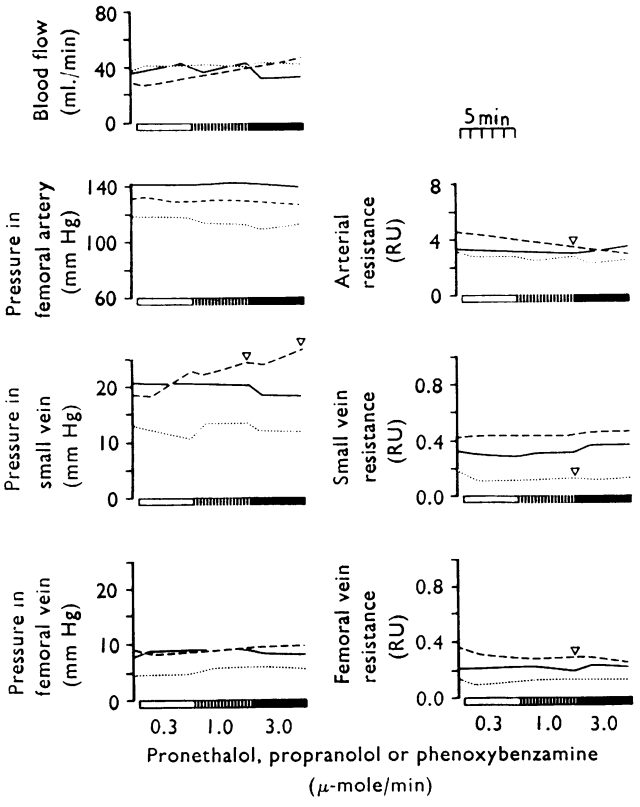

Fig. 5. Effects of intra-arterial infusions of receptor blocking agents, 0.3, 1 and 3 μ-mole/min, each dose level for 5 min. – – – –, pronethalol (4 dogs); ·····, propranolol (5 dogs); ——, phenoxybenzamine (4 dogs). ∇, $P<0.05$ when values at 5 min infusions were compared with values obtained before the blocking agent was infused.

pretreatment with phenoxybenzamine (10 μ-mole/kg; 3 dogs) blocked the effects of noradrenaline.

The effects of infusion of isoprenaline and noradrenaline into the femoral artery of the cat

In 5 cats intra-arterial infusion of isoprenaline increased the blood flow in the femoral artery and decreased arterial and small vein resistance. Noradrenaline, on the other hand, decreased the blood flow and increased arterial and small vein resistance (Fig. 7). The effects of isoprenaline were blocked by intravenous injection of propranolol (10 μ-mole/kg) and those of noradrenaline by phenoxybenzamine (10 μ-mole/kg).

Effects of intravenous injection of propranolol

When propranolol was injected in a dose (10 μ-mole/kg) sufficient to block β-receptors, it produced no significant change in the pressures of femoral vessels or in the femoral blood flow. Consequently, the resistance in the femoral artery, vein and small vein remained practically unaltered.

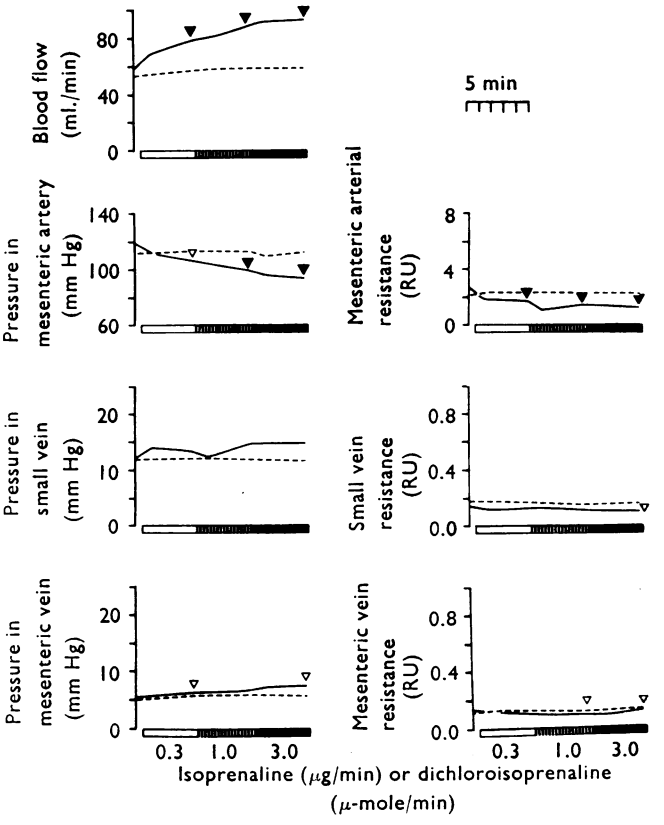

Fig. 6. Effects of isoprenaline and DCI infusions into the mesenteric artery. ——, isoprenaline, 0.3, 1 and 3 μg/min (7 dogs); - - - , DCI, 0.3, 1 and 3 μ-mole/min (7 dogs). ▽ , $P<0.05$, ▼, $P<0.01$ when values at 5 min infusions were compared with values obtained before the drugs were infused.

Effects of infusion of isoprenaline and noradrenaline into the femoral artery perfused at a constant rate

When the arterial blood flow was kept constant, intraarterial infusion of isoprenaline caused a decrease in the pressures in the artery, the small vein of the paw and, to a lesser extent, the small veins of the muscle. There was no significant fall in the pressure in the femoral vein. Propranolol (3 μ-mole/kg) injection intravenously prevented these effects of isoprenaline (Fig. 8). Noradrenaline raised the pressures in the artery and small vein of the paw; these effects were not blocked by propranolol. The sensitivity of various vessels to noradrenaline, in descending order, was: arteries, small veins of the paw, small veins of skeletal muscle and finally large veins.

DISCUSSION

Several of our conclusions are based on pressure measurements in the small veins. These pressure values are meaningful only when the polyvinyl catheters remained in the same position during the entire test. Although spontaneous variations were occasionally

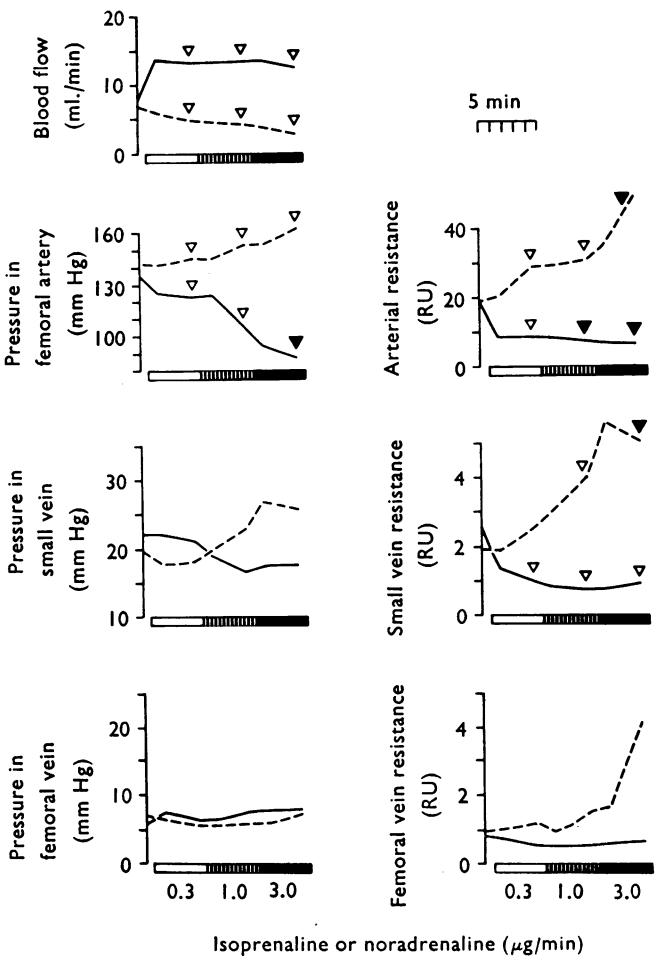

Fig. 7. Effects of infusions of isoprenaline and noradrenaline into the femoral artery in cats. ——, isoprenaline, 0.3, 1 and 3 μg/min (5 cats); - - - -, noradrenaline, 0.3, 1 and 3 μg/min (5 cats). ▽, $P<0.05$, ▼, $P<0.01$ when values at 5 min infusions were compared with values obtained before isoprenaline and noradrenaline were infused.

observed, similar to those described by Haddy, Richards, Alden & Visscher (1954), small vein pressure was remarkably stable in our experiments over prolonged periods.

Arterial flow values were used for calculation of vascular resistance in the veins. It was assumed, then, that arterial inflow at any given time was characteristic for flow values in the veins. This should be correct provided no redistribution of blood flow occurs during the experiments, with consequent alteration of flow rate through the vein in which the pressure was measured. The possibility could not be excluded that some of the drugs caused such a redistribution. When blood flow was kept constant the decrease in pressure after isoprenaline was smaller in small veins of the skeletal muscle than in small veins of the paw. This observation might reflect some redistribution of blood from the cutaneous to the muscular vessels, in agreement with data that isoprenaline

dilates muscular vessels more than skin vessels (Allwood, Cobbold & Ginsburg, 1963). However, isoprenaline diminished venous resistance in both types of veins.

Femoral blood flow in dogs is increased by the infusion of acid or alkaline buffers (Zsotér, Banderman & Chappel, 1961). As all the drug solutions used in this study were acid, local pH changes cannot be the cause of the different effects of α- or β-receptor-stimulating and blocking agents.

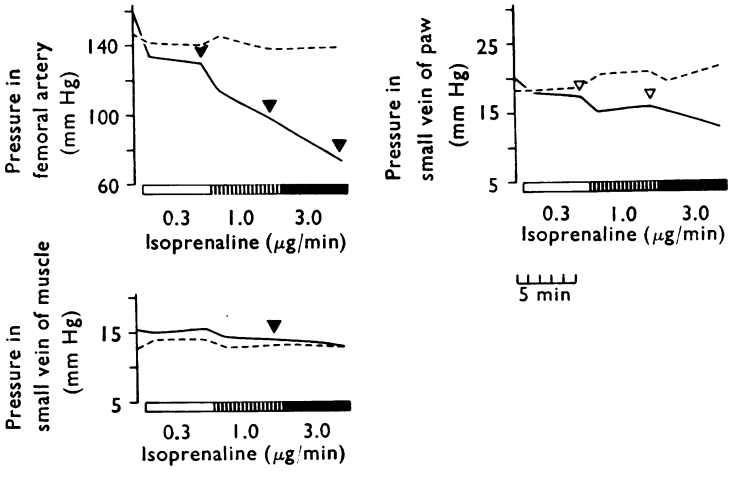

Fig. 8. Femoral artery perfused from contralateral femoral artery at a constant rate, adjusted to maintain the initial arterial pressure at time of the cannulation. Effects of isoprenaline on pressures in femoral artery, small veins of muscle and paw. ——, isoprenaline alone (6 dogs); - - - -, isoprenaline after intravenous injection of propranolol (3 μ-mole/kg). ▽, $P<0.05$, ▼, $P<0.01$ when values at 5 min infusions were compared with values before isoprenaline was infused.

Pressure in small veins generally tended to become higher when blood flow had been increased and to become lower when flow had been decreased after administration of various vasoactive drugs. This might suggest that venous pressure reflects consequences of arterial dilatation or constriction. While this mechanism may operate in some cases, pressure changes in veins did not seem to follow flow alterations in a passive manner, in our experiments or in those reported by Haddy, Molnar & Campbell (1961). This was perhaps best demonstrated with noradrenaline, which in a small dose decreased and in a large dose increased the pressure in small veins, while arterial flow was markedly reduced after both doses. The initial decrease in pressure might be explained by diminished flow consequent upon arterial constriction; the subsequent rise in pressure, however, would indicate an active venoconstriction. Dichloroisoprenaline in femoral vessels decreased arterial resistance, but left venous resistance unaltered. These, and other examples in which venous and arterial resistance were affected to a different extent, suggest that resistance in veins and arteries can be altered independently.

Noradrenaline, which stimulates α-receptors, consistently increased resistance in small veins. This finding is in agreement with those of Haddy, Fleishman & Emanuel (1957). Isoprenaline, which stimulates β-receptors, decreased the resistance in small veins. This

effect of isoprenaline in the hind limb of the dog was evident whether the blood flow was allowed to vary or kept constant. Experiments on the mesenteric vessels of the dog and on the vessels of the limbs of the cat corroborated these results. They disagree with the conclusion of Kaiser *et al.* (1964) that stimulation of β-receptors causes venoconstriction. These authors found that isoprenaline increased venous return and they interpreted this observation as a sign of venoconstriction. In our study the pressure gradient between small and large veins became greater after large doses of isoprenaline (Table 1), but this was not associated with venoconstriction, indeed resistance in veins decreased.

The effects of noradrenaline on the arteries and on the veins were abolished by pretreatment with phenoxybenzamine and those of isoprenaline were blocked by pretreatment with propranolol, pronethalol and DCI. This would then justify the conclusions that stimulation of β-receptors dilates, while stimulation of α-receptors constricts the veins.

Not all effects of the β-receptor blocking agents on blood vessels can be explained by their action on adrenoceptive receptors. Recently Shanks (1967) reported that the transient vasodilator effects of propranolol, pronethalol and DCI, observed also by us, are not prevented by blocking β-receptors. In our study, however, the effect of propranolol was more transient than that of pronethalol and DCI. The difference between the findings of Shanks (1967) and our results may be due to the fact that Shanks administered the drugs as single injections whereas we used continuous infusions. The slight increase in femoral blood flow produced by intra-arterial infusion of pronethalol was diminished, but not prevented, by propranolol. Similarly, arterial dilatation induced by DCI in the hind limb was not prevented by pretreatment with either propranolol or phenoxybenzamine. These results would suggest that DCI and pronethalol, in addition to their intrinsic sympathomimetic activity (Moran & Perkins, 1958; Zsotér *et al.*, 1966) seem to have a direct effect on blood vessels, not mediated by the adrenoceptive receptors.

Since neither intravenous injection of propranolol nor intra-arterial infusion of propranolol, pronethalol and DCI has any significant effect on pressures and resistances in the small and large veins, it is likely that adrenoceptive receptors, at least in " normal " resting conditions, play a relatively unimportant role in the regulation of venous resistance.

SUMMARY

1. The role of β-adrenoceptive receptors in the regulation of venous resistance was investigated in anaesthetized dogs and cats by studying the effects of isoprenaline, noradrenaline and α- and β-receptor blocking agents on pressure and flow in the femoral and mesenteric arteries and pressures in small and large veins.

2. When infused into the femoral artery isoprenaline decreased and noradrenaline increased resistance in a small vein of the paw and the femoral vein. The effects of isoprenaline were prevented by pretreatment with the β-receptor blocking agents, propranolol, pronethalol and dichloroisoprenaline, while noradrenaline was without effect after injection of phenoxybenzamine. Similar results were obtained on the mesenteric vessels of the dog and the femoral vessels of the cat. These findings were corroborated by the results of experiments with constant-flow perfusion of the femoral artery of the dog.

3. Intra-arterial infusion of dichloroisoprenaline and pronethalol raised the pressure, but not the resistance, in the veins. Propranolol or phenoxybenzamine, infused intra-arterially or injected intravenously, had no effect on the resistance in large or small veins.

4. It is concluded that stimulation of β-receptors diminishes resistance in small and large veins, while stimulation of α-receptors has the opposite effect. In " normal " resting circumstances, however, adrenoceptive receptors seem to play only a minor role in the regulation of venous resistance.

The competent technical assistance of Mr. H. Kiliaan is gratefully acknowledged.

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