Vascular Responses after Alpha Adrenergic Receptor Blockade

II. RESPONSES OF VENOUS AND ARTERIAL SEGMENTS TO ADRENERGIC STIMULATION IN THE FORELIMB OF DOG

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ABSTRACT The effects of nerve stimulation and of intraarterial injections of norepinephrine on arterial and venous resistances were studied in the perfused forelimb of dog before and after administration of the alpha adrenergic receptor blocker phenoxybenzamine.

Pressures were recorded from the perfused brachial artery and a small metacarpal vein in the forepaw. Blood flow to the whole forelimb was maintained constant. Changes in perfusion pressure in the brachial artery reflected primarily changes in arterial resistance and changes in small vein pressure reflected changes in resistance of venous segments downstream from the point of pressure measurement.

Alpha receptor blockade reduced vasoconstrictor responses to both nerve stimulation and norepinephrine. Responses to angiotensin, used in these experiments as an internal control, were not blocked consistently in a dose-related manner indicating that the effects of phenoxybenzamine were specific to adrenergic stimuli.

Increases in venous pressure in response to norepinephrine and to nerve stimulation were blocked almost completely whereas increases in arterial pressure were reduced only in part by the blocker. The more effective reduction of pressor responses in the small vein was not caused by a passive reduction in blood flow through the paw nor was it caused by a reduction in the concentration of norepinephrine in the venous effluent reaching the venous segments.

This differential effect of alpha receptor blockade on increases in venous and arterial resistances may account for the beneficial effect of phenoxybenzamine in shock.

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INTRODUCTION

It was shown in the preceding experiment (1) that blockade of alpha adrenergic receptors antagonizes venous responses to norepinephrine more effectively than arterial responses in man. The venous responses that were measured, however, were changes in venous compliance. Information on changes in venous resistance is important since venous resistance is one of the determinants of capillary hydrostatic pressure (2). Several experimental observations suggest that changes in both venous compliance and venous resistance may be similar in response to a variety of stimuli (3–7).

It has been suggested also that alpha adrenergic receptor blockers may be more adrenolytic than sympatholytic or in other words they antagonize the constrictor effect of circulating amines more completely than the constrictor action of nerve stimulation. Convincing evidence of this selective antagonism has been lacking (8, 9).

The present experiments were carried out on the perfused foreleg of the dog to determine changes

in both venous and arterial resistances in response to norepinephrine and to nerve stimulation before and after alpha adrenergic receptor blockade.

METHODS

Male mongrel dogs weighing 14–20 kg were anesthetized with chloralose, 50 mg/kg, and urethane, 500 mg/kg. Decamethonium bromide, 0.3 mg/kg, was given intravenously to prevent contraction of skeletal muscle. The dogs were ventilated artificially through a cuffed endotracheal tube connected to a respiratory pump. A small polyethylene cannula (PE 10, 0.6 mm o.d.) filled with normal saline was manipulated through a superficial dorsal metacarpal vein upstream for a distance of 2–3 cm in the paw and tied in place. Blood could be aspirated and saline infused freely through the cannula indicating adequate collateral connections (10). After intravenous injection of heparin, 5 mg/kg, the brachial artery was ligated, transected partially, and its distal segment was perfused with blood from the femoral artery by means of a pump (Sigmamotor, Inc., Middleport, N. Y.). Ligatures were tied around muscle groups high in the leg to prevent collateral circulation. The pump was adjusted initially so that perfusion of the foreleg was at a pressure approximately equal to systemic arterial pressure. The same flow was maintained throughout the experiment. Fluctuations in systemic arterial pressure and changes in perfusion pressure over the range encountered did not alter the rate of blood flow through the pump. Flow rates ranged from 64 to 120 ml/min and averaged 80 ml/min with a standard error of 3.0 ml in 14 experiments. Pressures in the perfused brachial artery and the small vein of the forepaw were measured with transducers (Statham Instruments, Inc., Los Angeles, Calif.) and recorded with a direct-writing oscillograph (Sanborn Co., Waltham, Mass.). A tranducer having a small volume displacement of 0.01 mm^3/100 mm Hg (Statham P23Gb) was used for pressure measurements in small veins. The distal ends of the severed median, ulnar, radial, and musculocutaneous nerves which had been exposed high in the foreleg were stimulated. 10-msec square waves were delivered at supramaximal or maximal voltage (25 v) to the nerves at rates of 3, 6, and 12 cycles/sec for periods of 20 sec using an S_4 (Grass Instruments Co., Quincy, Mass.) stimulator and a bipolar electrode. The maximal voltage was necessary to ensure stimulation of most of the fibers in the thick nerves of the brachial plexus. In previous experiments vascular responses to stimulation of these nerve trunks were similar to those observed with stimulation of sympathetic nerves extending from the stellate ganglion to supply the vasculature of the foreleg (11).

Norepinephrine bitartrate and angiotensin were injected into the distal tubing of the pump close to the brachial artery. Fresh dilutions in 5% glucose in water were made at the beginning of each experiment. The doses of norepinephrine ranged from 0.5 to 4.0 μg of base and those of angiotensin were 1.0 and 2.0 μg. Random order was followed for nerve stimulation and injections of drugs. Pressures were allowed to stabilize between interventions. Observations on the effects of norepinephrine, nerve stimulation, and angiotensin were repeated once after intraarterial injection of 0.25 mg of phenoxybenzamine and again after an additional 0.5 mg of phenoxybenzamine. Angiotensin was used in these experiments as an internal control to test specificity of blockade and responsiveness of the preparation. The time required to set up the experiment was approximately 45 min and the responsiveness of the preparation was maintained for an additional 90 min to 2 hr.

Since blood flow to the foreleg was constant and systemic venous pressure also was constant during the interventions, the changes in perfusion pressure in the brachial artery reflected changes in total vascular resistance of the forelimb. Changes in small vein pressure in the paw reflected changes in resistance of the venous segments draining the paw downstream from the point of pressure measurement. These venous segments form the tributaries of the cephalic vein (12). Small veins in the paw were selected for study in preference to other muscular veins in the foreleg because previous observations indicated to us that the veins draining the paw were more reactive to adrenergic stimuli (13). Changes in perfusion pressure and in small vein pressure caused by the interventions were compared before and after phenoxybenzamine.

Constancy of blood flow through the paw. The accuracy with which small vein pressure in the paw reflects venous resistance depends on the constancy of blood flow through the paw. Redistribution of flow between the paw and more proximal muscular parts of the foreleg is possible despite a constant total blood flow to the forelimb. In these parallel-coupled vascular beds blood could be diverted from a site of marked vasoconstriction to a less constricted bed. Blood flow through the paw was estimated by measurement of venous return from the paw. Anatomically the cephalic vein drains the paw while the brachial vein drains the muscular parts and deeper structures of the foreleg (12). The cubital vein which joins the brachial and cephalic veins was ligated. A Shipley-Wilson rotameter (Clifford Wilson Instruments, Indianapolis, Ind.) was interposed between the proximal and distal segments of the transected cephalic vein high in the foreleg; it caused little resistance to flow and increased small vein pressure only slightly (11, 13). Zero flow base line was established frequently throughout each experiment by shunting blood flow past the rotameter. At the end of each experiment, blood was allowed to flow through the rotameter into a graduated cylinder for calibration. Calibrations were made at two levels of flow. The responses of the rotameters were linear within the range of flows encountered. In previous experiments (11, 13) both nerve stimulation and administration of norepinephrine reduced venous return through the cephalic vein and augmented venous return through the brachial vein at constant brachial arterial inflow. This was caused by a greater constriction of resistance vessels in the paw than in more proximal parallel-coupled segments in response to the adrenergic stimuli. In the present experiments we needed to determine the effect of phenoxybenza-

mine on this redistribution of flow in order to interpret changes in small vein pressure in the paw correctly.

Autobioassay of norepinephrine in venous effluent. The concentrations of norepinephrine to which the veins draining the paw are exposed after intraarterial injections of norepinephrine into the brachial artery determine the venous response in the paw. These concentrations could change either with changes in blood flow through the paw or with changes in the amount of norepinephrine taken up by the tissues on the arterial side in the paw. After phenoxybenzamine, the decrease in blood flow through the paw in response to intraarterial norepinephrine could be less pronounced causing a relatively higher flow and therefore a lower concentration of norepinephrine to reach the venous segment after the blocker. On the other hand the uptake of norepinephrine on the arterial side would be blocked in part after phenoxybenzamine allowing more norepinephrine to reach the veins. The opposite effects of these two factors might cancel each other and the concentration of norepinephrine reaching the veins would be the same before and after the blocker. In order to interpret correctly differences in venous responses it seemed important to estimate the concentration of the catecholamine in the venous effluent. This was done by perfusing a portion of the cephalic vein effluent into the hind paw of the same dog at a constant rate of flow with a small Sigmamotor pump. The hind paw thus served as an autobioassay organ. Changes in perfusion pressure in the hind paw reflected changes in concentration of vasoactive substances in the venous return from the forepaw.

A cannula was used to divert the venous return from the ligated and transected cephalic vein into the jugular vein. The proximal tubing of the small Sigmamotor pump was connected to this cannula close to its exit from the cephalic vein. The distal tubing of the pump was inserted into the anterior tibial artery supplying the hind paw and ligated. Thus a portion of the cephalic venous return averaging 13.0 ml/min (range 9–16 ml/min in 14 experiments) was perfused into the hind paw which was denervated by section of the sciatic and anterior tibial nerves. Collateral circulation to the hind paw was minimized by ligating the femoral artery. The interventions had no detectable systemic effect that could influence significantly the responses in the hind paw.

The transit time from the cephalic vein to the hind paw was approximately 20 sec. Responses of the hind paw to direct intraarterial injections of norepinephrine into the perfused tibial artery provided the standard dose-response curves which permitted us to estimate the concentration of norepinephrine in the venous effluent. Perfusion of the hind paw was arrested temporarily for a period of 30 sec when phenoxybenzamine was injected into the brachial artery to prevent the blocker from reaching the hind paw in possibly a significant concentration after its initial circulation through the forelimb. Dose-response curves of the perfused hind paw to norepinephrine were obtained after each dose of phenoxybenzamine and the responses were found to decrease only slightly.

RESULTS

Perfusion pressure. At constant arterial inflow perfusion pressure reflects total vascular resistance of the foreleg and represents predominantly arterial resistance. The increases in perfusion pressure which were observed after the administration of norepinephrine and during nerve stimulation were reduced slightly after 0.25 mg of phenoxybenzamine (Tables I and II and Fig. 1). A significant rise in perfusion pressure in response to both norepinephrine and nerve stimulation still persisted after the second dose (0.5 mg) of the blocker (Figs. 1 and 2). There was no consistent reduction of the response to angiotensin (Table III and Figs. 2 and 3).

Small vein pressure. Increases in small vein pressure observed after the administration of norepinephrine during nerve stimulation were reduced significantly after the low dose of phenoxybenzamine and were blocked almost completely

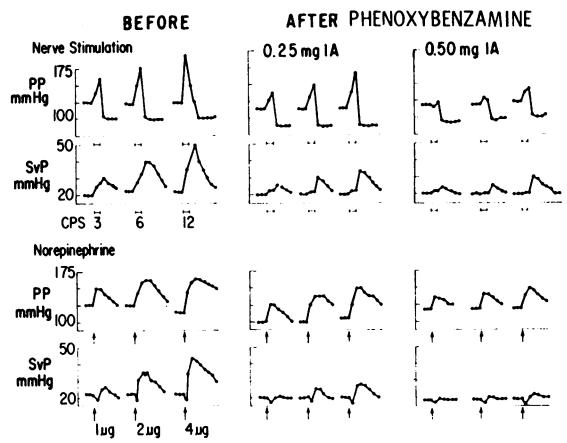

FIGURE 1 Changes in pressure in the perfused brachial artery (*PP*) and in a small metacarpal vein (*SvP*) in response to nerve stimulation and to norepinephrine. The duration of nerve stimulation was 20 sec. Note that both arterial and venous pressures rise during nerve stimulation. At the end of stimulation arterial pressure falls abruptly but venous pressure continues to increase sharply for 5–10 sec. This poststimulation increase in pressure (seen also in Fig. 2) is caused by a poststimulation increase in blood flow through the paw and through the cephalic vein as a result of dilatation of small vessels in the paw. The dilatation is reflected also by the fall in perfusion pressure below control levels and has been reported previously (18). The entries for venous pressure in Table II represent peak responses before the overshoot. After phenoxybenzamine the arterial responses to norepinephrine and to nerve stimulation were reduced but venous responses were nearly abolished.

TABLE I

Increases in Perfusion Pressure and in Small Vein Pressure in Response to Norepinephrine (1, 2, and 4 μg) Injected into the Perfused Brachial Artery before and after Phenoxybenzamine

Expt. No.	Δ Perfusion pressure (mm Hg)									Δ Small vein pressure (mm Hg)								
	Before phenoxybenzamine			After phenoxybenzamine						Before phenoxybenzamine			After phenoxybenzamine					
				0.25 mg			0.5 mg						0.25 mg			0.5 mg		
	Norepinephrine, μg																	
	1	2	4	1	2	4	1	2	4	1	2	4	1	2	4	1	2	4
1	35	60		35	50		42	47		8	18		3	9		1	2	
2	85	100		82	105		90	105		0	6		0	0		0	0	
3	77	102		68	100		70	75		2	4		2	1		0	0	
4	56	75		55	71		55	75		4	11		1	1		1	1	
5	55	60		50	53		47	62		0	2		0	0		0	0	
6	87	140		90	100		64	70		8	16		4	5		0	3	
7	68	85		60	87		73	90		18	31		13	16		7	10	
8	105	140		67	85		35	58		9	17		5	6		3	4	
9	80	105		55	87		43	60		0	3		0	1		2	3	
10	95	125		95	110		55	91		20	48		18	20		4	6	
11		43	80		30	32		25	40		6	15		1	3		1	3
12		75	80		40	80		55	60		7	6		1	3		1	4
13	20	35	50	25	30	45	17	22	27	4	12	19	1	5	7	1	1	2
14	35	47	60	20	25	35	23	25	45	1	9	12	0	3	8	0	0	1
15	67	86	85	45	60	70	25	43	55	1	8	11	1	2	4	0	1	2
16	57	60	100		70	97		75	98	3	4	6		3	2		2	2
17	27	28	55	17	22	35	4	7	10	3	4	8	0	0	0	0	0	0
18	105	112	128	70	110	125	38	52	67	4	15	18	2	8	10	0	0	4
19	70	90	165	75	75	105	75	85	100	5	15	23	5	8	20	1	4	7
Mean	66.1	82.5	89.2	56.8	68.9	69.3	47.2	59.0	55.8	6.0	13.5	13.0	3.7	5.3	6.3	1.2	2.1	2.7
SE	6.3	7.7	12.4	6.0*	6.9‡	11.5*	5.9‡	6.0‡	10.0‡	1.6	2.7	1.8	1.5‡	1.4‡	1.8‡	0.6‡	0.6‡	0.6‡

* and ‡ indicate that the responses observed after phenoxybenzamine were significantly different from responses observed before phenoxybenzamine using paired *t* test analyses (* = $P < 0.05$ and ‡ = $P < 0.01$). The absence of a symbol indicates a lack of significant difference.

TABLE II

Increases in Perfusion Pressure and in Small Vein Pressure in Response to Nerve Stimulation (3, 6, and 12 cycles/sec) before and after Phenoxybenzamine

Expt. No.	Δ Perfusion pressure (mm Hg)									Δ Small vein pressure (mm Hg)								
	Before phenoxy-benzamine			After phenoxybenzamine						Before phenoxy-benzamine			After phenoxybenzamine					
				0.25 mg			0.5 mg						0.25 mg			0.5 mg		
	Nerve stimulation, *cps*									Nerve stimulation, *cps*								
	3	6	12	3	6	12	3	6	12	3	6	12	3	6	12	3	6	12
1	25	30	45			50			15	3	7	7			2			0
2	75	105		60	87		50	87										
3		102	142		75	87		−18	−8		2	9		0	0		0	0
4		55	73		55	80		45	47		10	26		0	0		0	0
5		50	92		65	73		54	68		6	13		0	0		0	0
6	115	150		82	130		72	90		3	6		2	5		0	3	
7	103	140		55	93		43	67		3	10		3	6		2	6	
8	105	130		85	95		32	40		18	22		8	10		0	1	
9	110	125		77	80		36	50		8	12		0	1		0	1	
10	95	127		42	65		40	50		26	35		23	28		9	11	
11		40	53		20	30		8	20		2	3		1	4		1	2
12		77	90		60	70		43	72		5	12		1	12		2	6
13	30	55	65	22	35	51	0	5	20	10	15	27	6	10	14	5	6	10
14	35	60	85	25	65	80	15	35	40	0	12	17	0	11	17	1	0	1
15	87	90	130	60	62	95	35	55	70	6	7	24	0	0	4	1	2	4
16		85	110		75	105		2	32		5	8		0	0		0	0
17	67	85	95	62	60	92	32	34	35	0	3	0	0	0	0	0	0	0
18	80	105	150	104	127	135	75	112	130	8	19	23	2	9	20	0	1	8
19	70	100	135	32	60	90	35	47	50	6	12	15	3	4	8	1	3	6
Mean	76.7	90.0	97.3	58.8	72.7	79.8	38.8	44.8	45.5	7.5	10.3	14.1	4.3	5.0	6.2	1.7	2.2	2.8
SE	8.5	8.1	9.5	7.4‡	6.4‡	7.4‡	6.0‡	7.7‡	9.6‡	2.1	1.9	2.3	1.9‡	1.7‡	2.0‡	0.8‡	0.7‡	0.9‡

For ‡ see footnote to Table I.

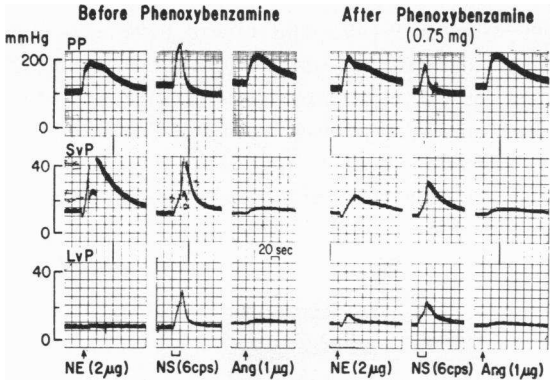

FIGURE 2 Tracings of responses to norepinephrine (*NE*), nerve stimulation (*NS*), and angiotensin (*Ang*). Large vein pressure (*LvP*) was obtained in this experiment from a point 3–4 inches above the carpus. The rise in LvP during NS has been reported (16) and indicates that significant venous constriction occurs in larger veins further downstream from the point of pressure measurement. Note that phenoxybenzamine caused little or no change in resting levels of pressure. Perfusion pressure (*PP*) averaged 136.2 ± (SE) 7.75 mm Hg before phenoxybenzamine and 127.9 ± 11.3 mm Hg after 0.75 mg of the blocker. Corresponding values for resting small vein pressure were 16.9 ± 1.3 and 18.2 ± 1.6 mm Hg. The peak rise in arterial pressure in response to NE was practically unaltered by the blocker in this experiment but the simultaneous venous response was reduced drastically. The arterial response to NS was reduced by the blocker indicating an antagonism of neurogenic stimulation of alpha receptors which in this experiment appeared more effective than the antagonism of circulating amines. Venous responses to angiotensin were negligible.

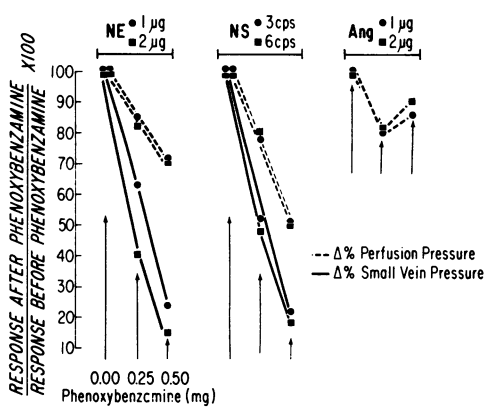

FIGURE 3 Graphic representation of more effective antagonism of venous than arterial responses to NE and NS. Percentages were calculated from the average data in Tables I, II, and III. The response to angiotensin in contrast to that of NE or NS was not reduced after phenoxybenzamine in a dose-related manner supporting the specificity of alpha adrenergic blockade in this experiment.

TABLE III

Increases in Perfusion Pressure (mm Hg) in Response to Angiotensin Injected into the Perfused Brachial Artery before and after Phenoxybenzamine

Expt. No.	Before phenoxybenzamine		After phenoxybenzamine 0.25 mg		After phenoxybenzamine 0.5 mg	
	Angiotensin, μg					
	1	2	1	2	1	2
2	34	52	35	72	65	80
3	60	75	55	70	60	65
4	45	61	35	47	45	75
5	50	65	55	60	45	65
6	27	47	30	43	34	47
7	48	67	55	80	65	90
8	45	55	18	35	20	35
9	30	55	25	45	22	34
12	37	62	27	35	25	45
14	42	47	25	40	10	40
15	53	55	25	35	20	37
16	60	110	40	53	48	70
17	18	26	10	10	12	17
Mean	42.2	59.8	33.4	48.1	36.3	53.8
SE	5.2	5.3	4.0	5.2	5.6	6.0
*P**			<0.05	<0.05	>0.2	>0.2

* refers to significance of difference between responses observed before and after phenoxybenzamine. The reduction in response to angiotensin after 0.25 mg of phenoxybenzamine was neither sustained nor accentuated after the additional dose of 0.5 mg of phenoxybenzamine. The reduction in response was transient and unrelated to the dose of blocker.

after the high dose (Tables I and II and Figs. 1 and 2). Increases in small vein pressure during the administration of angiotensin were not significant statistically either before or after the blocker (Fig. 2).

Changes in cephalic vein flow. Venous return through the cephalic vein (Table IV) decreased in response to norepinephrine (Fig. 4) and to nerve stimulation. Increases in small vein pressure despite the decreases in flow must indicate marked constriction of veins downstream from the point of small vein pressure measurement. After the administration of phenoxybenzamine decreases in blood flow through the paw were less (Table IV) and yet the increases in small vein pressure were nearly abolished (Tables I and II). This indicates a significant antagonism of venous constriction.

Concentration of norepinephrine in venous effluent. Increases in perfusion pressure in the hind paw were observed approximately 20 sec after the injection of norepinephrine into the perfused brachial artery (Figs. 4 and 5). The concentration of norepinephrine in the venous effluent through

TABLE IV

Effect of Norepinephrine and Nerve Stimulation on Venous Return through the Cephalic Vein

Expt. No.	Before phenoxybenzamine			After 0.75 mg of phenoxybenzamine		
	Norepinephrine					
	C	LD	HD	C	LD	HD
		ml/min			*ml/min*	
28	50	38	33	50	45	39
29	32	13	12	36	34	21
30	43	26	25	35	27	25
31	45	39	39	45	39	46
33	35	23		35	29	
Average	41.0	27.8	27.2	40.2	34.8	32.7
	Nerve stimulation					
Expt. No.	C	LF	HF	C	LF	HF
		ml/min			*ml/min*	
28	48	22	20	54	37	37
29	26	10	10	40	10	10
30	37	19	17	35	33	
31	46	35	39	43	37	35
33	35	25	16	35	29	29
Average	38.4	22.2	20.4	41.4	29.2	27.7

C refers to blood flow immediately before the intervention. LD and HD refer to low dose (0.5 μg) and high dose (1.0 μg) of norepinephrine respectively. LF and HF refer to nerve stimulation at low frequency (1.5–6 cps) and high frequency (3–12 cps) respectively. Experiments were paired so that the same frequencies of stimulation were used before and after the blocker in each experiment.

the cephalic vein following intrabrachial injections of norepinephrine as estimated from responses observed in the hind paw was not altered significantly by the administration of phenoxybenzamine (Table V).

DISCUSSION

Two observations were made during these experiments. The first concerns the effect of blockade of alpha adrenergic receptors on responses to circulating catecholamines as compared to responses to nerve stimulation and the second concerns the relative effects of the blockade on venous and arterial segments.

It is believed that the alpha adrenergic blocking drugs antagonize more readily the responses to circulating amines than those to nerve stimulation and a distinction is made between sympatholytic and adrenolytic agents (8, 9). The evidence for such distinction does not seem conclusive and the problem deserved investigation particularly since Moran and Perkins (14) made the observation, which we (15) and others have also confirmed, that beta adrenergic blocking drugs antagonize the nerve-mediated responses of the heart as well as the responses to injected amines. Our present results indicate that in the perfused foreleg of the dog the constrictor response to nerve

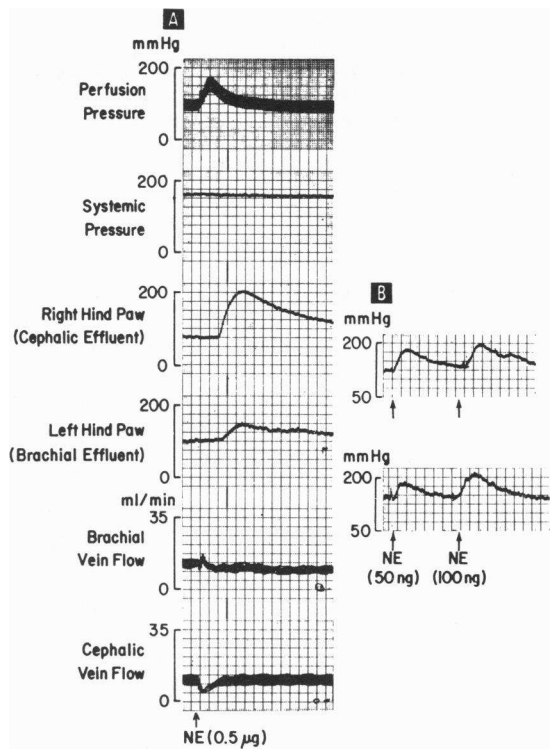

FIGURE 4 A. Changes in cephalic and brachial vein flows (lower 2 tracings) and estimate of concentration of NE in venous effluents (middle 2 tracings) in response to injection of NE (0.5 μg) into the perfused brachial artery. A portion of the venous return through the cephalic vein was perfused into the right hind paw and the remaining venous return was directed through the rotameter to the jugular vein. Cephalic vein flow decreased in response to NE and 20 sec later a pressor response was observed in the right hind paw; the magnitude of this response is directly related to the concentration of NE in the venous effluent. The same procedure was followed for the brachial venous effluent in several experiments and the changes in flow were directionally opposite those of the cephalic vein. We omitted reporting on changes in brachial vein flow or responses in the hind paw perfused with brachial vein effluent for the sake of brevity since we are concerned with venous responses measured in a tributary of the cephalic vein.

B. Responses of right (upper frame) and left (lower frame) hind paws to direct intraarterial injections of NE. These responses were used to estimate concentrations of NE in venous effluents.

stimulation is antagonized just as effectively if not more than the constrictor response to circulating norepinephrine. This antagonism was not restricted to constriction of arterial segments which is reflected primarily by the rise in perfusion pressure in the foreleg but included also constriction of venous segments. The absence of dose-related reductions of the response to angiotensin after the blocker supports the specificity of adrenergic blockade.

In previous experiments (13, 16) we emphasized a difference between effects of nerve stimulation and of norepinephrine on vascular segments in the foreleg of dog. Nerve stimulation constricts predominantly large arterial segments and large venous segments (16, 17) whereas norepinephrine constricts smaller metacarpal and muscular arteries and veins (16). The reduction of responses to both nerve stimulation and to norepinephrine seen after the blocker would suggest that alpha adrenergic receptors in both large and small vessels are accessible to the antagonist.

The vasodilator response which is seen after the end of nerve stimulation both before and after phenoxybenzamine in Figs. 1 and 2 did not appear to be exaggerated by the blocker. This post-stimulation dilatation was not blocked by beta adrenergic receptor blockers (18) and the constrictor effect which is seen during nerve stimulation was not reversed by the intraarterial administration of up to 13 mg of phenoxybenzamine in one experiment. The question of whether there is a neurogenic vasodilatation mediated through beta receptors is an important one and the evidence thus far has failed to demonstrate such a response (19).

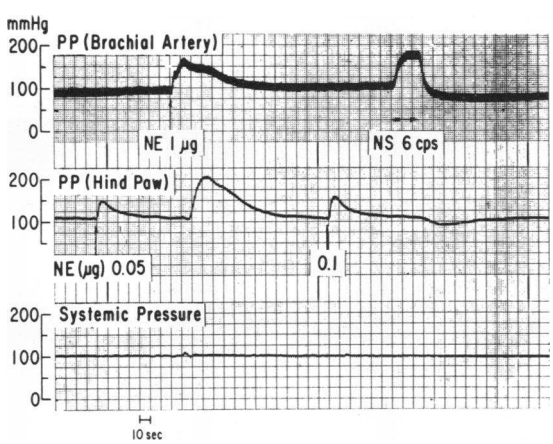

FIGURE 5 Changes in forelimb perfusion pressure (*PP*) and hind paw PP in response to intrabrachial NE and to nerve stimulation. The pressor response to NE in the forelimb was followed 20 sec later by a pressor response in the hind paw. There was no vasoconstriction in the hind paw during or after NS; instead a vasodilator response was seen in 50% of the experiments. The nature of this humoral dilator factor is not known. The amount of NE released from the paw during NS must be too small to be detected by this assay.

TABLE V

Estimate of Concentration of Norepinephrine in Cephalic Venous Blood after Intraarterial Injections of Norepinephrine (NE) into Perfused Brachial Artery in Doses of 0.5, 1, 2, and 4 µg*

	Before phenoxybenzamine				After 0.75 mg of phenoxybenzamine			
NE, µg.....	0.5	1	2	4	0.5	1	2	4
Expt. No.								
21	0.18	0.27			0.20	0.35		
23	0.17	0.24			0.14	0.20		
28	0.12	0.35			0.12	0.30		
29	0.05	0.07			0.03	0.07		
30	0.10	0.29			0.10	0.13		
27	0.07	0.16	0.23		0.08	0.15		
31		0.05	0.17			0.10	0.20	
35			0.20				0.22	
26			0.23	0.35			0.28	0.56
Average	0.12	0.20	0.21	0.35	0.11	0.19	0.23	0.56

* Entries represent doses of norepinephrine in µg which if injected directly into the perfused hind paw would give the same pressor response as that observed in the hind paw 20 sec after injection of doses of norepinephrine shown at the top of the table into the perfused brachial artery. Values for entries obtained by plotting the response observed in the hind paw after intrabrachial norepinephrine ("test responses") on the dose-response curve obtained with direct injections of norepinephrine into the hind paw ("standard responses"). The average responses of the hind paws to 0.025, 0.05, 0.1, and 0.2 µg of norepinephrine were 17 ± 1.2 mm Hg (n = 4), 34 ± 4.1 (n = 12), 42 ± 3.0 (n = 19), and 54 ± 3.8 (n = 11) respectively. A "standard dose-response curve" was obtained also after phenoxybenzamine.

The relative effects of drugs that block alpha adrenergic receptors on responses of venous and arterial segments were demonstrated in this study. The results extend the conclusions reached from observations made in man and reported in the preceding paper (1). In man, the administration of phentolamine antagonized very effectively the constrictor action of norepinephrine on capacitance vessels without reducing significantly the constrictor effect on resistance vessels. In the foreleg of dog the increase in venous resistance in response to norepinephrine and to nerve stimulation was completely antagonized but the increase in

total resistance which reflects primarily the arterial response was only partly reduced. It was difficult from the experiments done in man to relate the change in distensibility of capacitance vessels to changes in venous or postcapillary resistances and to changes in capillary pressure and filtration. The results of the present experiments however would indicate that the administration of alpha adrenergic receptor blockers can, by antagonizing the increase in postcapillary venous resistance and by preserving an increase in precapillary arterial resistance, prevent the excessive capillary filtration which may occur during adrenergic stimulation. On the other hand, the responses observed with intraarterial norepinephrine and with nerve stimulation may not closely simulate those which occur after a naturally evoked sympathico-adrenal discharge.

The reason for the more effective blockade of venoconstriction is unclear. We have found that the decrease in pressor responses in the veins was not caused passively by a decrease in blood flow through the paw. In fact blood flow through the paw during adrenergic stimulation was higher after than before phenoxybenzamine. Furthermore the concentrations of norepinephrine reaching the venous segments were similar before and after the blocker. The marked reduction in responsiveness of veins represents therefore a very effective inhibition of active constriction of smooth muscle in the walls of veins.

The findings in this and in the preceding study (1) in man are relevant only to the doses of norepinephrine that were used. These doses gave venous and arterial responses which appeared to be in the upper part of the respective dose-response curves. In both the human and animal experiments the slope of the dose response curve of veins appeared steeper than that of arteries. The steeper slope on the venous side could explain the greater reduction in venous response to the same dose of norepinephrine.

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