Responses of Saphenous and Mesenteric Veins to Administration of Dopamine

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ABSTRACT Others have observed that dopamine (3,4-dihydroxyphenylethylamine) constricts resistance vessels in skin, but dilates these vessels in the mesentery. We studied the effects of dopamine on cutaneous and mesenteric veins of dogs to see if this agent also produced qualitatively different effects on the tone of capacitance vessels (veins) in these vascular beds. The lateral saphenous or the left colic vein was perfused at constant flow with blood from a femoral artery. Pressures at the tip of the perfusion cannula and at the tip of a catheter 15 cm downstream were recorded continuously. Increases in the pressure gradient between these two points indicated venoconstriction; decreases indicated venodilatation. Dopamine and norepinephrine injected into the perfusion tubing caused constriction of both veins. The constriction was antagonized by blockade of alpha receptors. A dilator action of dopamine was not seen, even after alpha receptor blockade or in the presence of increased venous tone produced by serotonin, norepinephrine, or nerve stimulation. Reserpine and cocaine did not alter responses to dopamine in the saphenous vein; this suggests that the venoconstrictor action of dopamine results mainly from a direct effect on alpha receptors and that uptake into sympathetic nerve endings may not be important in regulating the amount of dopamine available to receptors in the saphenous vein.

INTRODUCTION

Few if any stimuli produce qualitatively different effects on tone of capacitance vessels (veins) in different vascular beds. We considered the possibility that dopamine might be an exception since its effects on resistance vessels differ in the limb and the mesentery (1, 2). If the effects of dopamine on veins resemble its

effects on resistance vessels, its administration would produce venoconstriction in the limb but venodilatation in the mesentery.

The experiments reported here were done to study the actions of dopamine on the lateral saphenous and the left colic veins of dogs.

METHODS

Methods. Dogs weighing 17–26 kg were anesthetized with chloralose (75 mg/kg) and urethane (500 mg/kg). An endotracheal tube was inserted and the dogs were given decamethonium bromide (0.3 mg/kg) intravenously and ventilated. Heparin sodium (500 U/kg) was given intravenously when the operative procedures were completed.

We measured responses of the lateral saphenous vein using a modification of the method described recently by Webb-Peploe and Shepherd (3). The dorsal branch of the left lateral saphenous vein was cannulated at the ankle and perfused at constant flow, 56–72 ml/min, with blood from the right femoral artery using a Harvard peristaltic pump. The two major tributaries, the plantar branch and the calcaneal branch, were ligated and a small polyethylene catheter was inserted through one of these into the lateral saphenous vein so that the tip was 15 cm downstream from the perfusion cannula. Pressure at the tip of the perfusion cannula (perfusion pressure) and at the tip of the catheter downstream (downstream pressure) were measured continuously with Statham transducers and recorded with a Sanborn direct-writing oscillograph. With flow constant, changes in the pressure gradient between these two points reflected changes in venous tone. Increases in the pressure gradient indicated venoconstriction; decreases indicated venodilatation.

The validity of this method rests on the assumption that changes in the pressure gradient between the perfusion and the downstream catheters are caused by changes in venomotor tone and not by changes in flow through this segment of vein. As indicated above, we ligated the two major tributaries, but did not expose and ligate smaller tributaries. To exclude the possibility that flow through the saphenous vein changed because of flow in or out of small tributaries, we measured flow just downstream from the tip of the downstream catheter (outflow) using an electromagnetic flowmeter in preliminary experiments on four dogs. Outflow approximated pump flow in the resting state when the femoral artery on the same side was temporarily occluded to reduce the possibility of inflow through tributaries. In
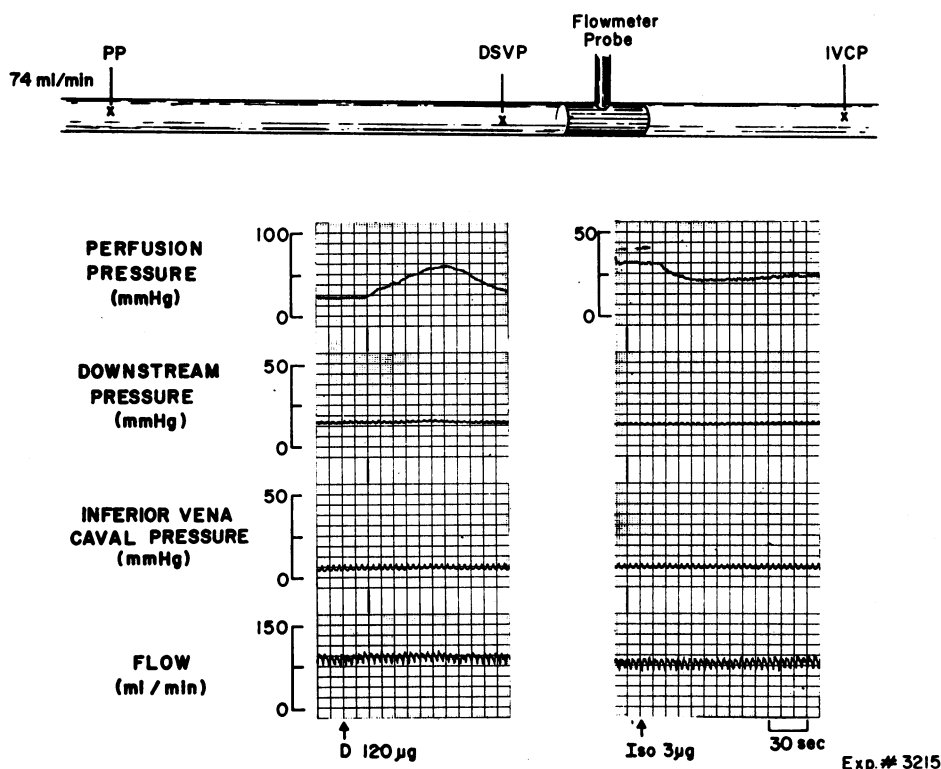
FIGURE 1 Study of the method. The lateral saphenous vein was perfused at 74 ml/min while perfusion pressure (PP), downstream pressure (DSVP), and inferior vena caval pressure (IVCP) were monitored. An electromagnetic flowmeter measured "outflow" (bottom panel) just downstream from the downstream catheter. Increases in the pressure gradient with dopamine (D 120 μg, left panel) and decreases with isoproterenol (Iso 3 μg, right panel) occurred without changes in outflow. The left (ipsilateral) femoral artery was temporarily occluded during responses in these experiment to reduce the possibility of inflow through tributaries.

addition, in three of the four dogs responses to various drugs occurred without changes in outflow (Fig. 1). In the fourth animal, small transient increases in outflow occurred a few seconds after peak responses to venoconstrictor agents. These increases may have resulted from flow into the vein through small tributaries, but it should be noted that similar increments in flow produced by increasing pump flow did not change the pressure gradient. These experiments indicate that changes in the pressure gradient reflect changes in venomotor tone. There was little or no change in downstream pressure during most interventions; this is consistent with the report by Webb-Peploe and Shepherd (3) that there is a sudden transition from responsive to unresponsive vein approximately 8–12 cm downstream from the perfusion cannula at the point where the lateral saphenous vein receives its first large branch draining muscle.

We also examined in preliminary experiments the possibility that perfusing with arterial, as opposed to venous, blood might alter responses and resting venous tone. Veins were perfused alternately with blood from the femoral vein and femoral artery. Resting venous tone and responses to the agents studied were similar while perfusing with arterial or venous blood.

In separate experiments we studied responses of the left colic vein using a similar method. Through a midline ab-

dominal incision the vein was cannulated and perfused at constant flow, 50–68 ml/min, with blood from the right femoral artery. All visible tributaries were ligated and a small catheter was inserted through one of these into the left colic vein so that the tip was 15 cm downstream from the perfusion cannula. Perfusion and downstream pressures were recorded continuously. Changes in the pressure gradient between these two points indicated changes in tone in this segment of left colic vein.

The resting pressure gradient averaged 4 mm Hg (range 1–17 mm Hg) in the saphenous vein and 5 mm Hg (range 1–13 mm Hg in the colic vein. The gradient was not altered appreciably by phentolamine, phenoxybenzamine, or cocaine.

Drugs used as agonists were dopamine hydrochloride,[1] 1-norepinephrine bitartrate, isoproterenol hydrochloride, tyramine hydrochloride, and serotonin creatinine sulfate. Doses of these agents are expressed in terms of base. Fresh solutions were prepared for each experiment using 5% dextrose in water. These drugs were injected into the perfusion tubing upstream from the peristaltic pump in volumes of

0.1–0.4 ml; injection of these volumes of dextrose solution alone had no effect. Other drugs used in some of these experiments were phentolamine mesylate, phenoxybenzamine hydrochloride, cocaine hydrochloride, and reserpine.

Design. The plan of this study was first, to see if dopamine caused constriction or dilatation of saphenous and colic veins; second, to determine if a dilator response to dopamine could be unmasked by blocking the constrictor response; third, to see if dopamine exerted an indirect as well as direct sympathomimetic effect on the saphenous vein by studying responses after reserpine; fourth, by using cocaine to see if uptake of dopamine into sympathetic nerve endings was an important factor regulating the availability of dopamine to receptor sites in the saphenous vein; and fifth, to establish the relative venoconstrictor potency of dopamine and norepinephrine.

Initially we studied saphenous responses in eight dogs. In each experiment, four doses of dopamine (60, 120, 240, and 480 μg) and four doses of norepinephrine (3, 6, 12, and 24 μg) were given at 5- to 7-min intervals at a time when pressures had returned to control levels. A modified Latin square determined the order of administration. After these injections, serotonin (30 μg) was given as an internal control. To study the effect of alpha receptor blockade, we then gave phenoxybenzamine (7.5 mg) in four experiments and saline (control) in the other four. Fifteen min later, injections of dopamine (120 and 240 μg), norepinephrine (12 μg) and serotonin (30 μg) were repeated.

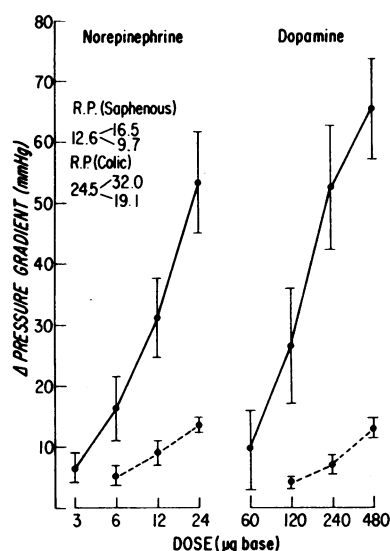FIGURE 2 Responses to norepinephrine (left) and dopamine (right) in saphenous (solid lines) and colic (broken lines) veins. Entries are mean values ±SEM for eight experiments in saphenous vein and six experiments in colic vein. Responses in the saphenous vein exceeded responses in the colic vein. Parallel line bioassay (Table I) indicated that the relative potency (R.P.) of dopamine compared with norepinephrine in the saphenous vein was 12.6 (95% confidence limits 9.7–16.5). The relative potency indicates the ratio of the dose of dopamine required to produce a given response to the dose of norepinephrine required to produce the same response. The relative potency of dopamine to norepinephrine in the colic vein was 24.5 (95% confidence limits 19.1–32.0) (Table II).

Similar studies were done on the colic vein in six other dogs. The three highest doses of dopamine and norepinephrine were given, and phentolamine (3–4 mg) was used as the alpha receptor antagonist.

In other experiments on the saphenous or the colic vein, dopamine, isoproterenol, and nitroglycerin were administered in the presence of increased venous tone produced by serotonin, norepinephrine, or nerve stimulation.

Finally, the effects of reserpine and cocaine on saphenous vein responses were studied in 12 dogs divided into two equal groups. One group received reserpine (0.25 mg/kg intraperitoneally) 24 and 48 hr before study; the other group was not treated with reserpine. In each experiment, responses to tyramine (500 and 1000 μg), dopamine (30 and 120 μg), and norepinephrine (1.5 and 6.0 μg) were obtained before and after cocaine (6–10 mg) was administered into the perfusion tubing.

Statistical comparisons were made using analysis of variance and, in appropriate instances, the parallel line bioassay (4, 5). Responses to the various agents were taken as peak changes in the pressure gradient.

RESULTS

Saphenous vein responses to dopamine, norepinephrine, and serotonin. Dopamine, norepinephrine, and serotonin caused constriction of the lateral saphenous vein. Increases in the pressure gradient with the four doses of dopamine (60, 120, 240, and 480 μg) averaged 9.4 ±6.5 (SEM), 26.5 ±9.5, 52.6 ±10.1, and 65.4 ±8.3

TABLE I

Responses to Norepinephrine and Dopamine in the Saphenous Vein
(Analysis of Variance)

| Source of variation	Degrees of freedom	Sum of squares	Mean square	F
Doses	7	27,462	3,923	23.35*
Preparations	1	2,186	2,186	13.01*
Regression	1	24,430	24,430	145.41*
Parallelism	1	300	300	1.78
Quadratic	1	64	64	0.38
Difference of quadratic	1	280	280	1.66
Cubic	1	88	88	0.52
Difference of cubic	1	112	112	0.66
Dogs	7	16,336	2,334	13.89*
Order	7	2,179	311	1.85
Error	42	7,043	168	
Total	63	53,025		

Parallel line bioassay using a symmetrical 8-point design according to methods described by Finney (4). The two preparations are dopamine and norepinephrine. F values were calculated using the error mean square as divisor. Significant F value for regression and nonsignificant F value for parallelism indicate that the chief requirements for a parallel line bioassay are satisfied.
* $P < 0.01$.

mm Hg, respectively (Fig. 2). Increases with norepinephrine (3, 6, 12, and 24 µg) were 6.5 ±2.4, 16.1 ±5.4, 31.2 ±6.6, and 53.3 ±8.3 (Fig. 2) and with serotonin (30 µg) were 33.6 ±9.3 mm Hg. Parallel line bioassay indicated that the dose of dopamine required to produce a given response was 12.6 times the dose of norepinephrine needed to produce the same response (Fig. 2 and Table I) (4, 5).

Phenoxybenzamine reduced responses to dopamine (120 and 240 µg) and norepinephrine (12 µg) by 91,
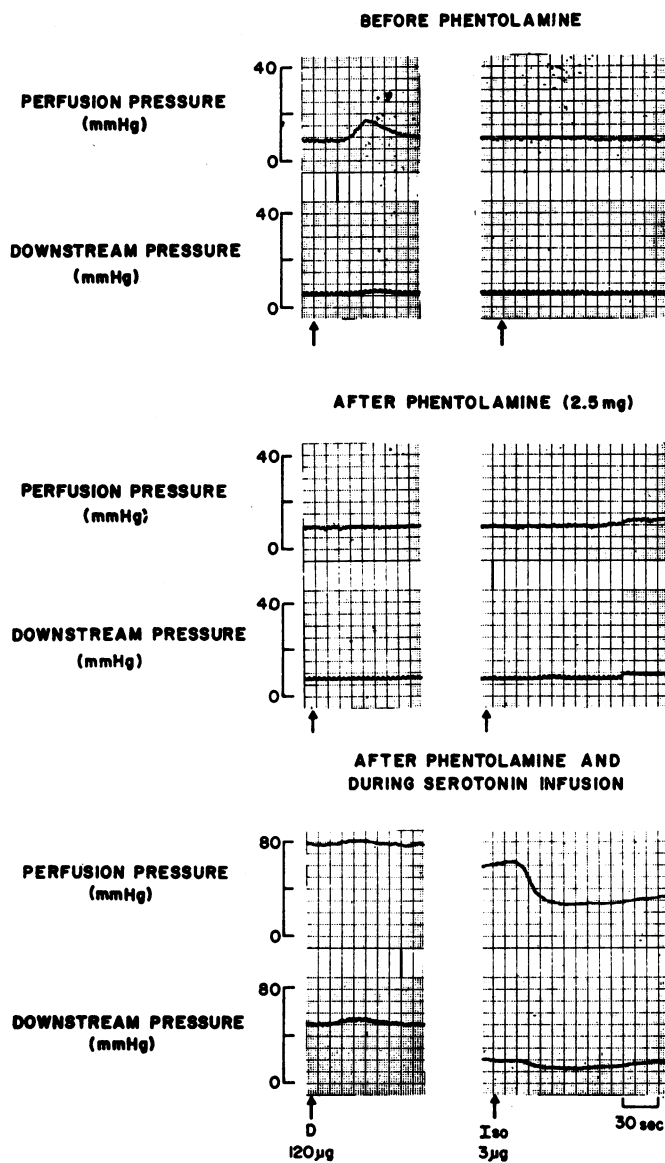
FIGURE 3 Responses to dopamine (D), 120 µg, and isoproterenol (Iso), 3 µg, before and after phentolamine in lateral saphenous vein. Before phentolamine (upper panels), dopamine caused constriction and isoproternol produced no effect. After phentolamine (middle panels), neither agent produced a response. After phentolamine and during serotonin infusion (15 µg/min) (lower panels), dopamine did not change the gradient while isoproterenol caused venodilatation.

78, and 83%, respectively, but did not reduce responses to serotonin (30 µg). Administration of saline in the control group did not decrease responses to these agents. In four separate experiments, phentolamine decreased the constriction with dopamine by 98%, whereas the constriction with serotonin was reduced only by 13%.

Although phenoxybenzamine or phentolamine frequently abolished the constriction with dopamine, reversal to a dilator response was not seen. But under the same conditions isoproterenol (0.75–3.0 µg) also failed to produce dilatation, and the possibility was considered that the vein was incapable of relaxing further. Accordingly after blockade of alpha receptors, serotonin (6–30 µg/min) was infused into the perfusion tubing in six experiments to increase venous tone and the injections of dopamine and isoproterenol were repeated. Under these conditions, dopamine in doses of 7.5–240 µg failed to decrease the gradient, while isoproterenol, 0.75–6.0 µg, and nitroglycerin, 65 µg, caused decreases of 6–30 mm Hg (Fig. 3).

Effects of reserpine and cocaine on responses of saphenous vein. Responses of the reserpinized group were compared with those of the group not pretreated. Reserpine virtually abolished the constriction with tyramine, but did not alter significantly responses to dopamine and norepinephrine (Fig. 4).

In the nonreserpinized dogs, a dose of cocaine which reduced responses to tyramine also potentiated responses
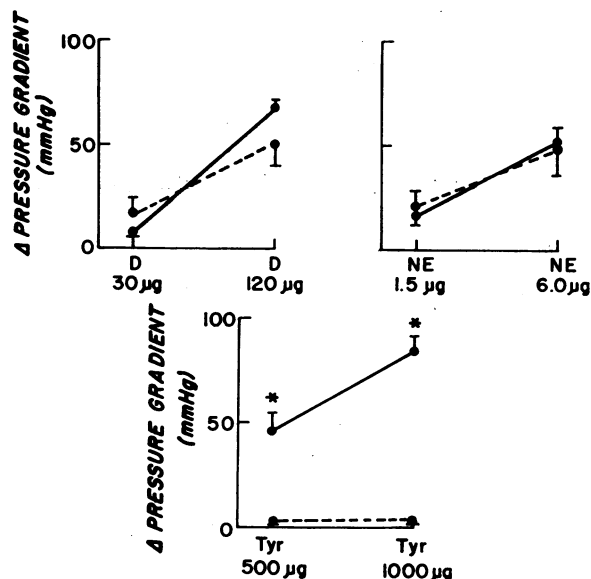

FIGURE 4 Effects of reserpine on responses of the saphenous vein. Responses of six reserpinized dogs (solid lines) were compared with those of six nonreserpinized dogs (broken lines) using analysis of variance. Entries are mean values ±SEM for each group. D represents dopamine, NE represents norepinephrine, and Tyr represents tyramine.* *P* < 0.05.
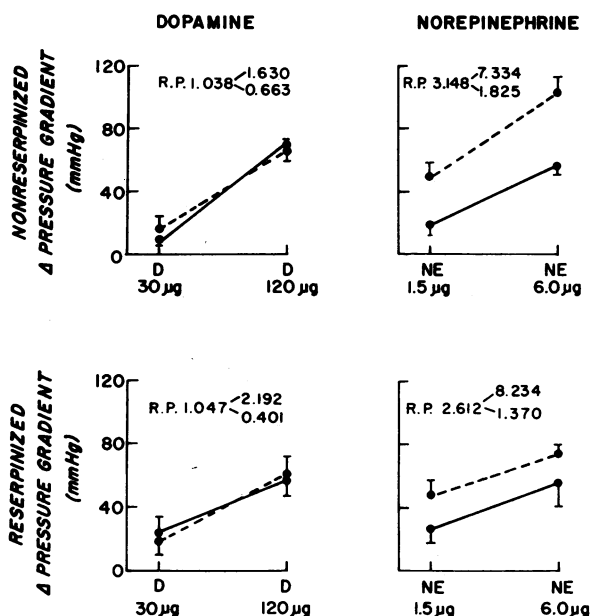

FIGURE 5 Effects of cocaine on responses of saphenous vein in nonreserpinized dogs (top panels) and reserpinized dogs (bottom panels). Entries represent mean values ±SEM of responses before cocaine (solid lines) and after cocaine (broken lines) for each group. Responses to dopamine (D) or norepinephrine (NE) before cocaine were compared with responses after cocaine using parallel line bioassay. This was done by regarding injections of dopamine or norepinephrine before cocaine as standard preparations and injections after cocaine as test preparations. R.P. represents the relative potency with 95% confidence limits; this indicates the ratio of the dose required to produce a given response before cocaine to the dose required to produce the same response after cocaine. The effect of either agent was considered to be significantly greater after cocaine if a potency ratio of 1.0 was not included in the confidence limits.

to norepinephrine, but did not significantly change responses to dopamine (Fig. 5, top panels). Cocaine also potentiated the constrictor responses to norepinephrine in the reserpinized group, but again did not alter responses to dopamine (Fig. 5, bottom panels).

Colic vein responses to dopamine and norepinephrine. Both dopamine and norepinephrine caused constriction of the colic vein. Increases in the pressure gradient with the three doses of dopamine (120, 240, and 480 µg) averaged 4.0 ±0.8 (SEM), 7.1 ±1.6, and 13.0 ±1.7 mm Hg, respectively (Fig. 2). Corresponding increases with norepinephrine (6, 12, and 24 µg) were 5.3 ±1.6, 9.0 ±2.1, and 13.6 ±1.3 mm Hg (Fig. 2). Parallel line bioassay indicated that the dose of dopamine required to produce a given response was 24.5 times the dose of norepinephrine needed to produce the same response (Fig. 2 and Table II) (4, 5).

In eight experiments dopamine was administered in the presence of increased venous tone induced by sero-

TABLE II

Responses to Norepinephrine and Dopamine in the Colic Vein
(Analysis of Variance)

Source of variation	Degrees of freedom	Sum of squares	Mean square	F
Doses	5	474.59	94.91	17.81*
Preparations	1	14.04	14.04	2.63
Regression	1	450.66	450.66	84.55*
Parallelism	1	0.88	0.88	0.17
Quadratic	1	6.60	6.60	1.24
Difference of quadratic	1	2.13	2.13	0.40
Dogs	5	260.24	52.04	9.76*
Order	5	80.11	16.02	3.01‡
Error	20	106.53	5.33	
Total	35	921.47		

Parallel line bioassay using a symmetrical 6-point design according to methods described by Finney (4). See legend for Table I.
* $P < 0.01$.
‡ $P < 0.05$.

tonin, norepinephrine, or splanchnic nerve stimulation. Dopamine in doses of 7.5–480 µg caused further constriction in this situation, while nitroglycerin or isoproterenol led to venodilatation with decreases in the gradient of 4–8 mm Hg (Fig. 6).

Phentolamine reduced responses to dopamine by 84% and to norepinephrine by 87%. As in the saphenous vein phentolamine frequently abolished the constriction with dopamine, but reversal to a dilator response was not seen. Serotonin did not consistently constrict the colic vein in these experiments, either before or after alpha receptor blockade. In the one experiment in which serotonin produced venoconstriction after phentolamine,

dopamine (30 and 120 µg) and isoproterenol (20 µg) did not alter the increased venous tone.

DISCUSSION

In these experiments administration of dopamine caused constriction of capacitance vessels in both the limb (lateral saphenous vein) and the mesentery (left colic vein). As discussed below these results indicate that the effects of dopamine on capacitance vessels differ from its effects on resistance vessels.

In Eble's experiments, dopamine, injected into the mesenteric artery, produced transient constriction of resistance vessels followed by more sustained dilatation (2). The constriction was blocked by alpha receptor antagonists, but the dilatation usually was not affected by blockade of beta receptors. Eble suggested that specific dopamine receptors might mediate this dilatation. In our experiments on the colic vein, dopamine caused only venoconstriction. We considered the possibility that this agent stimulates dilator receptors in the colic vein, but that dilatation did not occur because the vein was maximally dilated in the control state. Accordingly, dopamine was administered in the presence of increased venous tone produced by nerve stimulation or infusions of norepinephrine or serotonin. Dopamine, given over a wide range of doses, caused further constriction in these experiments, while nitroglycerin or isoproterenol produced dilatation. Another possibility which we considered was that dopamine might have a dual action, stimulating both constrictor and dilator receptors with the constriction masking the dilatation. To examine this possibility phentolamine was administered to abolish the constriction. When this was done reversal to a dilator response with dopamine was not seen.

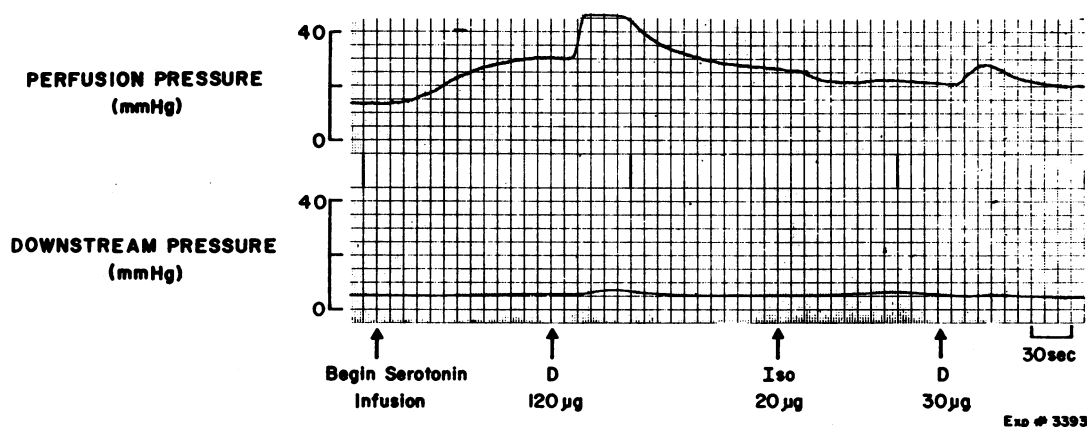McNay, McDonald, and Goldberg (1) demonstrated that close arterial injections of dopamine caused con-

FIGURE 6 Responses of colic vein to dopamine (D), 30 and 120 µg, and isoproterenol (Iso), 20 µg, during serotonin infusion (229 µg/min). Dopamine caused further constriction while isoproterenol produced venodilatation.

striction of resistance vessels in the hindlimb. This effect was abolished by phenoxybenzamine unmasking a very weak dilator action mediated through stimulation of beta receptors (6). Since dopamine caused predominant alpha receptor stimulation in the limb, it was not surprising that it produced constriction of the lateral saphenous vein in our experiments. Phenoxybenzamine or phentolamine blocked the constriction of the saphenous vein, but reversal to a dilator response was not observed even in the presence of increased venous tone induced by infusion of serotonin. Isoproterenol or nitroglycerin decreased venous tone under these conditions.

The venoconstrictor action of dopamine appeared to result from a direct effect on alpha receptors. An indirect effect of dopamine, resulting from release of endogenous norepinephrine from sympathetic nerve endings, was not apparent. Reserpine reduced the constriction with tyramine, but did not alter responses to dopamine significantly (Fig. 4). Other investigators demonstrated both direct and indirect sympathomimetic effects of dopamine on the cat nictitating membrane (7, 8) and the guinea pig atria (7) but Guimarães and Osswald (9) reported recently that reserpine does not influence the responses of strips of lateral saphenous vein to dopamine.

It may be noted also that reserpine did not augment the venoconstriction with norepinephrine. This is consistent with an earlier report by Abboud and Eckstein that the veins do not participate in the increased vascular responsiveness to norepinephrine occurring after reserpine (10).

Administration of cocaine potentiated the responses to norepinephrine, but did not potentiate the constriction with dopamine, even in dogs treated with reserpine. Considerable evidence supports the view that cocaine causes supersensitivity to l-norepinephrine by preventing uptake into nerve endings so that more amine becomes available to the receptor site (11). The results of these experiments suggest, therefore, that uptake into sympathetic nerve endings may not be important in regulating the concentration of dopamine at receptor sites in the lateral saphenous vein. In contrast, these and other experiments (12) support the view that uptake into nerve endings is an important factor regulating the amount of norepinephrine available to receptors in the saphenous vein.

Responses to all of the agonists used in these studiies were greater in the saphenous than in the colic vein. These differences may result from differences in vessel geometry. Because of this reservation, a statistical analysis comparing responses of the two veins to a given agent was not made. The relative potencies which are cited in Fig. 2 compare responses to two agents, dopamine and norepinephrine, in a single vein. In both

the saphenous and the colic veins, more dopamine than norepinephrine was needed to produce a given venoconstrictor response. Specifically, the ratio of the dose of dopamine to the dose of norepinephrine needed to cause a given response was 12.6 in the saphenous vein and 24.5 in the colic vein. These ratios are lower than those reported by investigators studying the effects of dopamine and norepinephrine on resistance vessels in the limb (1), the rabbit aorta (13), and the dog heart (14). For instance, McNay et al. demonstrated that the dose of dopamine causing a given decrease in femoral blood flow was 44 times the dose of norepinephrine causing the same response (1). Kohli found a similar ratio in the rabbit aorta where 50 times more dopamine than norepinephrine was needed to produce a given level of alpha receptor stimulation (13). In the dog heart-lung preparation Holmes and Fowler observed that 100 times more dopamine than norepinephrine was needed to produce comparable cardiac responses (14). The difference in the relative potency of the two drugs on the veins and the heart probably results from the fact that alpha receptors mediate the responses in the veins and beta receptors in the heart. The reasons for the difference in relative potency on arteries and veins are not clear. Whatever the reasons, these observations suggest that *when compared to norepinephrine* the venoconstrictor action of dopamine is greater than its effects on the heart and on resistance vessels in the limb. This relatively greater venoconstrictor action may be important since dopamine is used to treat patients with hypotension and shock; the venoconstriction would tend to increase venous return and cardiac filling pressure.

ACKNOWLEDGMENTS

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