

Differential Effects of Catecholamines on the Distribution of Aortic Blood Flow

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During continuous intravenous infusion of isoproterenol, epinephrine, and norepinephrine, in the intact dog under barbiturate anesthesia, mean aortic blood flow was measured at the aortic root (RAF) and in the descending (thoracic) aorta (TAF). With graded doses of isoproterenol, RAF increased markedly while TAF increased more moderately and then decreased at higher doses. With infusion of epinephrine the dose-effect curves of RAF and TAF were more nearly parallel, rising with lower doses and declining at higher infusion rates. With infusion of norepinephrine there was little change in either flow at any dose. During infusion of isoproterenol and norepinephrine there were definite changes in the distribution of flow: with isoproterenol the greater portion of flow was shifted toward the head and forelimbs, with norepinephrine toward the viscera and lower limbs (despite the small variation in RAF and TAF with norepinephrine). Epinephrine infusion induced a slight redistribution in the same direction as that produced by isoproterenol. Partial or complete autonomic block prior to catecholamine infusion had no important effect on the responses elicited by any of the three amines. (Key words: Catecholamines; Aortic blood flow;

Isoproterenol; Epinephrine; Norepinephrine; Blood flow redistribution.)

THE INFLUENCE of catecholamines on blood flow in specific organs and tissues has been extensively investigated,^{1,2,3} but there seem to have been few studies of the effects of these amines on the gross distribution of cardiac output in the intact organism.

These experiments grew out of an incidental observation made during graded infusions of isoproterenol. Blood flow was measured in the thoracic aorta (TAF), assuming that flow here adequately represented cardiac output. However, there was only modest enhancement of TAF even with large doses of isoproterenol, a finding contrary to the many reports of marked increases in cardiac output with this agent.⁴⁻⁸ When the position of the flow probe was changed to the root of the aorta, flow measured here (RAF) increased substantially with even small doses of isoproterenol. These unexpected and previously unreported differential effects of isoproterenol on aortic blood flow led to a study of the effects of graded doses of not only isoproterenol, but also epinephrine and norepinephrine, on flow distribution. The studies presented here describe and compare the dose-related effects of the three catecholamines on two broad divisions of aortic flow: that to the viscera and lower limbs and that to the head and forelimb regions.

Since the effects of an administered catecholamine may be altered or modified by the release of endogenous neurohumors or by reflex activity, the effects of isoproterenol were determined first in the presence of anesthesia only and then after the influence of the autonomic nervous system had been partially or wholly eliminated by one of several blocking procedures. In the studies with epinephrine and norepinephrine, which were fewer, the autonomic blocks were limited to two with the former amine and one with the latter.

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Methods

Nineteen mongrel dogs weighing between 10 and 21 kg (average 15.4 kg) were anesthetized by intravenous administration of thiopental sodium (approximately 20 mg/kg) without prior medication. Anesthesia was maintained with sodium pentobarbital, the total doses ranging from 200 to 1,000 mg, iv. (The dose range was wide because the group of dogs with epidural spinal block required little supplementary anesthesia and some experiments were of longer duration than others.) After endotracheal intubation through a tracheostomy, dogs were ventilated with a constant-volume piston pump with 100 per cent oxygen; the rate and volume were adjusted to give an arterial pH between 7.45 and 7.60, which would tend to produce respiratory alkalosis and thus insure an optimal response of the heart to catecholamines.⁹

A polyethylene catheter was introduced into the thoracic aorta by way of a femoral artery for measurement of blood pressure. Similar catheters were placed in a femoral vein for injection of drugs and solutions and in the superior vena cava (by way of a jugular vein) for the infusion of catecholamine. A lumbar laminectomy was sometimes performed and a large-bore (1.68 mm ID) polyethylene catheter threaded into the epidural space in preparation for a later epidural spinal block, similar to that described by Brewster *et al.*¹⁰

The chest was opened by a midline incision and two electromagnetic flow probes (Nycotron, Model 372) were placed on the aorta, one at the root and another in the thoracic region 3 to 4 cm above the diaphragm, for measurement of mean blood flow. The flow probes were calibrated for each experiment as previously described.¹¹

Pressure was measured by a transducer (Sanborn, Model 267B). Mean aortic blood flows and pressure, and an electrocardiogram originating from leads clipped to the pericardium (Lead I), were continuously registered with a Hewlett-Packard recorder (Model 7700). Arterial pH was obtained with a standard glass microelectrode (Radiometer). Esophageal temperature, measured with a mercury thermometer, was kept at or near 37°C with a heating pad placed under the dog.

After preparation and a 30-minute interval for baseline stabilization, one of the following procedures for blocking the autonomic nervous system was generally carried out: 1) for parasympathetic block, intravenous injection of atropine sulfate, 1.0 mg/kg; 2) for spinal (sympathetic) block, epidural injection of lidocaine hydrochloride, 1.0 per cent, in three or four divided doses, totaling 100 to 150 mg; 3) for combined parasympathetic and sympathetic block, the first and second procedures together; 4) for ganglionic block (HEX block), intravenous injection of hexamethonium chloride, 7.5 or 10.0 mg/kg. In addition, there was a group (5) which received none of these pretreatments (no block). The numbers of infusions under the various conditions were:

Block	Isoproterenol	Epinephrine	Nor-epinephrine
None	6	3	2
Parasympathetic	4	3	3
Sympathetic	4	—	—
Parasympathetic + sympathetic	3	—	—
HEX	3	3	—

Since the object of the experiments was to compare qualitative differences among drug-response patterns, there appeared no need to have these groups of equal size.

Sympathetic block was verified when, after occlusion of the carotid arteries, the pre-block pressor response was abolished. Parasympathetic block was ascertained when bradycardia after electrical stimulation of the right vagus nerve was eliminated. The presence of ganglionic block was tested by both of these procedures. The circulatory effects of spinal and ganglionic block were reductions in heart rate, mean aortic blood pressure and, to a lesser degree, mean aortic blood flow. In some cases an infusion with no, parasympathetic, or sympathetic block was followed (after a return to baseline conditions) by an additional block, prior to an infusion of the same or another agonist. (The original block was maintained and again tested before the second infusion.)

Following the establishment of autonomic block(s), if any, when all variables had stabilized, measurements were made which served as the precatecholamine level ("0"). Isoproterenol hydrochloride, epinephrine hydrochloride,

TABLE 1. Mean Slope and ED₅₀ of Dose-Effect Curves from Graded Continuous Infusion of Catecholamines (\pm SE)

	Blood Flow at Aortic Root		Blood Flow in Thoracic Aorta		Heart Rate		Mean Aortic Blood Pressure	
	Slope* (μ g/kg/min)	ED ₅₀ (μ g/kg/min)	Slope* (μ g/kg/min)	ED ₅₀ (μ g/kg/min)	Slope* (μ g/kg/min)	ED ₅₀ (μ g/kg/min)	Slope* (μ g/kg/min)	ED ₅₀ (μ g/kg/min)
Isoproterenol (20 infusions)	23.3 \pm 3.58	0.51 \pm 0.229	18.1 \pm 2.61	0.16 \pm 0.024	27.4 \pm 3.00	0.27 \pm 0.033	-28.4 \pm 3.58	0.98 \pm 0.182
Epinephrine (9 infusions)	24.9 \pm 4.24	1.12 \pm 0.316	24.8 \pm 6.67	0.90 \pm 0.242	25.1 \pm 1.57	3.12 \pm 0.766	36.0 \pm 2.85	1.91 \pm 0.302
Norepinephrine (5 infusions)	27.8 \pm 10.07	1.12 \pm 0.345	43.5 \pm 16.56	0.90 \pm 0.267	25.1† \pm 3.23	6.33† \pm 2.025	37.3 \pm 3.98	2.64 \pm 0.572

* Units for slopes: per cent of maximum effect μ g/kg/minute.

† Three infusions with atropine.

ride, or norepinephrine bitartrate, was then given by continuous intravenous infusion, with a constant-volume pump, in the following doses (calculated from the salt): 0.04, 0.1, 0.2, 0.4, 1.0, 2.0, 4.0, and 10.0 μ g/kg/min; infusions were generally carried to rates of 20.0, and occasionally to 40.0, μ g/kg/min. There were 20 infusions of isoproterenol, nine infusions of epinephrine, and five of norepinephrine; 12 dogs received only isoproterenol, two, only epinephrine, and one, only norepinephrine; three dogs received two different agonists each, while one dog was given an infusion of each of the three catecholamines.

Drug was infused at a given rate until all variables being measured had reached steady levels (times ranged from 6 to 8 minutes for small doses to 1 or 2 minutes for the highest). After 2 to 4 minutes at the steady level, the pump speed was changed to a higher rate. Measurements were taken from recordings made just before a change in infusion rate. The total volume of each infusion was roughly 20 ml. When more than one catecholamine infusion was given, time was allowed between infusions for a return to the initial baseline state, aided, in some cases, by administration of 20 to 50 ml of dextran. Doses of agonist were not randomized, since in earlier work¹² it was found that the dose-response patterns to be described were not altered with successive graded infusions of catecholamines.

Differences in catecholamine effects stemming from the autonomic blocking procedures

were determined by comparison of dose-effect curves. The slope of the dose-effect curve for each variable of an infusion was obtained by the method of least squares, from points lying on the steep portion of the individual plots of logarithm of dose against effect, expressed as percentage of maximum. This conversion to percentage allowed the slopes for all variables to be given in common units. From the slope and mean of X and Y, derived from the calculation of the regression line, the dose necessary for half-maximal effect (ED₅₀) was then determined.¹³ The slope, ED₅₀, and maximum or plateau level (the intrinsic activity) of the dose-effect curves for each variable, after a given catecholamine, were then compared: the values from the various treatment groups were individually tested against those from the no-block group, using the non-parametric rank test of Wilcoxon.

Under the conditions of these experiments and with these sample sizes, the autonomic blocks led to no differences in effect with a given catecholamine that were qualitatively consistent or statistically significant. Since the null hypothesis could in almost no case be rejected (see Results), the data from all groups were necessarily pooled for each amine.

Blood flow measured at the root of the aorta (RAF) was considered representative of total aortic blood flow (excepting flow to the coronary vessels). Blood flow to the viscera and lower extremities (V flow) was flow to the thoracic aorta (TAF), expressed as percentage

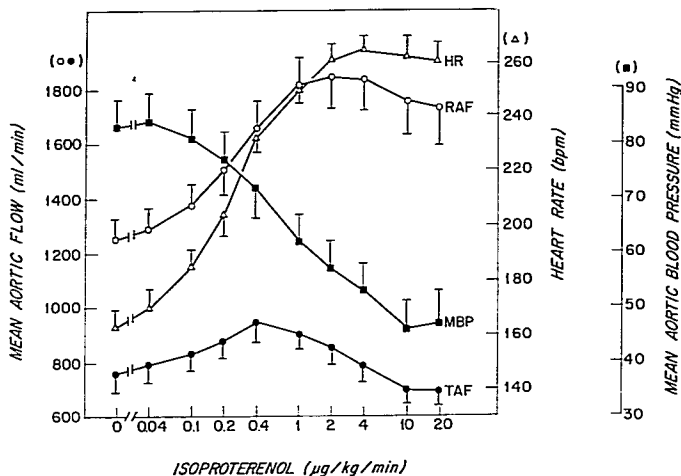


FIG. 1. Effects of graded continuous infusions of isoproterenol on: heart rate (HR, open triangles), mean blood flow at the aortic root (RAF, open circles), mean blood flow of the thoracic aorta (TAF, closed circles), and mean aortic blood pressure (MBP, closed squares). Each point represents the mean (and SE) of 20 infusions except that at 20.0 $\mu\text{g/kg/min}$, which is the mean of 13 infusions.

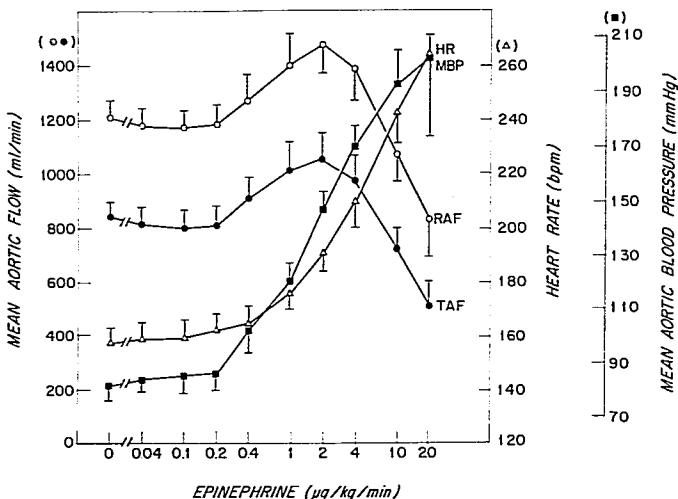


FIG. 2. Effects of graded continuous infusions of epinephrine. Symbols and abbreviations as in figure 1. Each point represents the mean (and SE) of nine infusions except that at 20.0 $\mu\text{g/kg/min}$, which is the mean of five infusions.

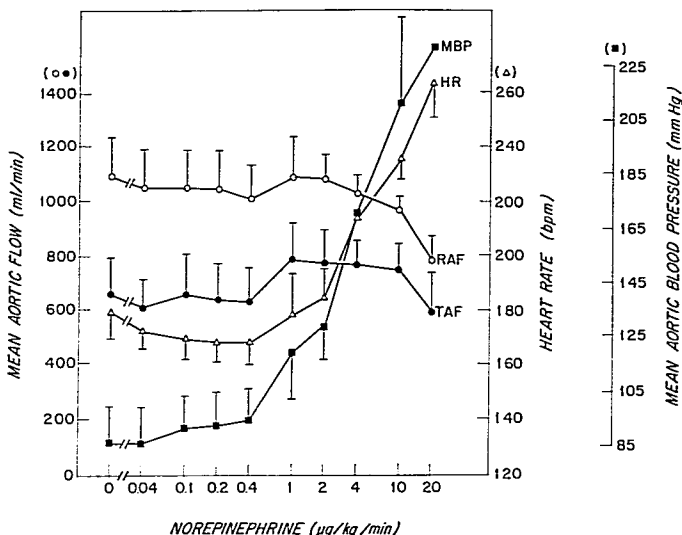


FIG. 3. Effects of graded continuous infusions of norepinephrine. Symbols and abbreviations as in figure 1. Each point is the mean of five infusions except for heart rate, which gives the means from three infusions with parasympathetic block. The RAF, TAF, and MBP at 20.0 µg/kg/min are the means of four infusions. The standard errors for HR and MBP at 4.0 µg/kg/min are ± 15.1 beats/min and ± 29.0 mm Hg, respectively; that for MBP at 20.0 µg/kg/min is ± 26.1 mm Hg.

of total flow ($\text{TAF}/\text{RAF} \times 100$), while rostral (Rs) flow was taken as total flow less thoracic flow, again expressed as percentage of total flow ($\text{RAF} - \text{TAF}/\text{RAF} \times 100$). Resistance peripheral to the thoracic flow probe (VR) was calculated by dividing mean aortic (thoracic) blood pressure by TAF; resistance in the circulatory beds of the head and forelimbs (RsR) was obtained similarly, using RAF less TAF. The derived blood flows (V and Rs) and resistances (VR and RsR) were determined at each dose of each infusion of a catecholamine. The mean values for all infusions of a given amine were then computed for each dosage level. Further details on methods and procedures may be found in reference.¹²

Results

Activity of the autonomic nervous system, seemingly, had no influence on the blood-flow effects of any of the amines to be described, for various autonomic blocks (see Methods)

established prior to catecholamine infusion led to no changes of statistical significance of the flow or flow distribution effects induced by each agent. This was also true of heart-rate (HR) effects (except for norepinephrine with no block) and nearly always so for mean aortic blood pressure. Since groups with parasympathetic or sympathetic block, or the two combined, or ganglionic block, did not differ from the group with no block in their responses to a catecholamine, the effects of each amine were pooled in reporting results. Unless stated otherwise, the results presented refer to the mean values from all infusions of a given catecholamine.

The infusion of isoproterenol in increasing graded concentrations led to increases in mean aortic blood flow at both the aortic root (RAF) and the thoracic aorta (TAF), beginning at the lowest dosage given (0.04 µg/kg/min). The dose-effect curves for each of the two flows, however, differed in pattern with every infusion of isoproterenol (fig. 1). The curve

for RAF climbed fairly steeply with increasing dose (infusion rate), reaching a maximum and plateau level of 1,840 ml/min at 2.0 $\mu\text{g/kg/min}$. In contrast, the TAF dose-effect curve rose only slightly at lower doses, reached a peak (943 ml/min) at 0.4 $\mu\text{g/kg/min}$, and then declined at higher rates (fig. 1). TAF at 0.4 $\mu\text{g/kg/min}$ differed from the preinfusion ("0") values at a significance level of only 0.1. When "0" was compared with maximum TAF for each infusion (peak TAF did not occur at the same dose with all infusions), the increase was significant at the 0.05 level. Mean aortic blood pressure (MBP) during isoproterenol infusion began decreasing at a dose of 0.1 $\mu\text{g/kg/min}$ and continued to fall with each succeeding dose, reaching a minimum (47 ± 6.1 mm Hg) at 20.0 $\mu\text{g/kg/min}$ (fig. 1); when infusions were carried to a higher rate (40.0 $\mu\text{g/kg/min}$), there was generally no further decrease in MBP. Heart rate (HR) increased during isoproterenol infusion with every increase in dose, reaching a maximum (264 beats/min) and steady level at 2.0 or 4.0 $\mu\text{g/kg/min}$ (fig. 1). The mean slope and dose for half-maximal effect (ED_{50}) for each of these variables (obtained by combining the slopes and ED_{50} determined from the individual infusions) are given in table 1.

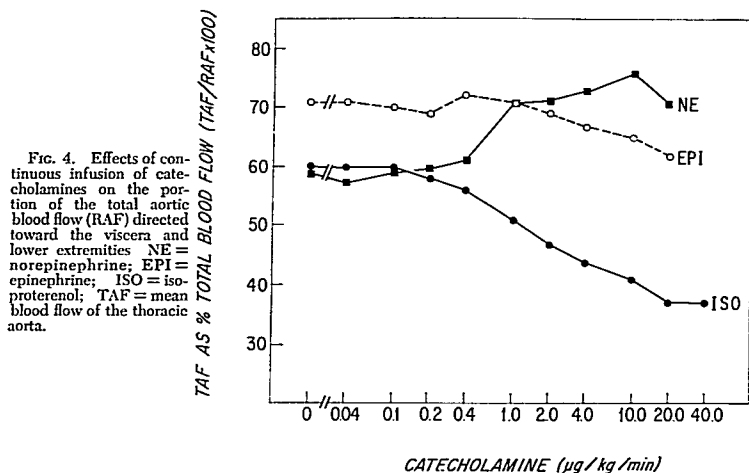
The dose-effect curves for RAF and TAF after epinephrine infusion were more nearly parallel than those after isoproterenol. There were very small increases in both flows at 0.2 $\mu\text{g/kg/min}$, maxima at 2.0 $\mu\text{g/kg/min}$, then marked decreases at higher infusion rates (fig. 2). MBP, however, beginning at 0.2 $\mu\text{g/kg/min}$, rose at each dose but failed to come to a steady level by 20.0 $\mu\text{g/kg/min}$ (202 ± 28.1 mm Hg at this dose) and usually had not attained a steady level at an infusion rate greater than those depicted (40.0 $\mu\text{g/kg/min}$). The heart rate during epinephrine infusion rose slightly at lower infusion rates, then markedly at higher rates, coming to a maximum of 264 beats/min at 20.0 $\mu\text{g/kg/min}$. This last dose level was administered in only five of the nine epinephrine infusions, but in two of the five, a plateau was reached at 10.0 $\mu\text{g/kg/min}$. Thus, the intrinsic activity of epinephrine with respect to heart rate appeared to be very near to that of isoproterenol.

In the five infusions of norepinephrine, there was very little change in mean aortic blood flow, RAF, or TAF at any infusion rate. In the dose-effect curves for norepinephrine (fig. 3), the only definite increases in blood flow occurred between the doses of 0.4 and 1.0 $\mu\text{g/kg/min}$; in no case, however, did flow increase to significantly above the preinfusion level. Both RAF and TAF declined at higher infusion rates. The MBP, after very minor increases between 0.1 and 0.4 $\mu\text{g/kg/min}$, climbed steeply to even greater levels than with epinephrine (232 ± 26.1 mm Hg at 20.0 $\mu\text{g/kg/min}$), and in only one case reached a steady level (at a dose of 20.0 $\mu\text{g/kg/min}$). In the three infusions of norepinephrine in the presence of parasympathetic (atropine) block, heart rate did not increase until an infusion rate of 1.0 $\mu\text{g/kg/min}$; then it climbed to a maximum of 264 beats/min at a dose of 20.0 $\mu\text{g/kg/min}$ (fig. 3); although in none of the three was a plateau HR reached, in these few dogs the intrinsic activity of norepinephrine was at least as great as that of isoproterenol or epinephrine. In two other infusions of norepinephrine with no autonomic block, hence intact buffer reflexes, HR did not vary appreciably from the preinfusion level (3 beats in one case and 6 in the other).

The lack of parallelism in the dose-effect curves for the mean blood flows, RAF and TAF, particularly with isoproterenol and norepinephrine infusion, suggested that there may have been changes in the overall distribution of blood flow during graded infusions of these agents. Therefore, the portion of the total blood flow (RAF) being sent to the regions below the thoracic flow probe (V flow) was determined for each catecholamine by expressing TAF as a percentage of RAF (fig. 4).

During isoproterenol infusion V flow showed a dose-related decline, beginning at 0.2 $\mu\text{g/kg/min}$ and continuing to about 20.0 $\mu\text{g/kg/min}$, when it neared a minimum. Conversely, the portion of total flow moving rostrad (Rs flow) during isoproterenol infusion gave dose-effect curves identical in slope but opposite in sign (i.e., positive).

With infusion of epinephrine, V flow changed little at first, but at 1.0 $\mu\text{g/kg/min}$ it began to decline as dose increased, although



not so steeply as with isoproterenol (fig. 4); indeed, V flow at 20.0 µg/kg/min was not significantly lower than the preinfusion level. Infusion of norepinephrine, however, had an effect on V flow opposite to that of isoproterenol: starting at a dose of 0.1 µg/kg/min, it climbed moderately with increasing dose, and then at 1.0 µg/kg/min, more steeply, reaching a peak at 10.0 µg/kg/min.

In an effort to elucidate the nature of the changes in the distribution of aortic blood flow, resistance in the circulation distal to the thoracic probe (VR) and in the head and forelimb regions (RsR) was determined (fig. 5). With infusion of isoproterenol, at the two lowest rates the VR and RsR fell to about the same degree, but at subsequent doses the resistance peripheral to the thoracic probe tended to decline less steeply, and leveled out at about 2.0 µg/kg/min. RsR declined more rapidly and to a greater extent than VR and did not reach a minimum level until a dose of 10.0 µg/kg/min. With infusion of epinephrine the two resistances were essentially the same at all infusion rates but 10.0 µg/kg/min, when VR was 384 per cent and RsR, 367 per cent above the preinfusion level. The two resistances during infusion of norepinephrine did

not differ markedly until a dose of 1.0 µg/kg/min was reached; then, however, VR rose to a much lesser degree than RsR, 320 as opposed to 944 per cent at the final dose.

Discussion

The effect of a catecholamine on overall blood flow distribution may reflect the distribution of *alpha* (vasoconstrictor) and *beta* (vasodilator) receptors among the individual vascular beds. While the three amines studied here, isoproterenol, epinephrine, and norepinephrine, all may stimulate both types of receptors, only epinephrine results in notable dual excitation, for norepinephrine acts predominantly upon the *alpha*, and isoproterenol primarily upon the *beta*, receptor.¹⁴⁻¹⁵ The relative order of increasing activity of the three agents given by Ahlquist¹⁴ for effects mediated by the *beta* receptor was norepinephrine-epinephrine-isoproterenol; that for effects mediated by the *alpha* receptor was (isoproterenol)-norepinephrine-epinephrine. Ginsburg and Cobbold¹⁹ found the former progression to obtain for cardiovascular, respiratory, and metabolic (oxygen consumption) effects in man. In the studies reported here, heart rate (HR) was the only measurement reflecting stimulation of a

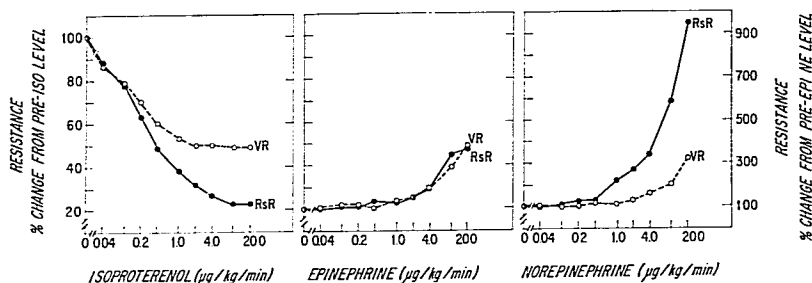


FIG. 5. Resistance peripheral to the thoracic flow probe (VR) and in the circulation of the head and forelimb regions (RsR) during catecholamine infusion. The scale on the right for epinephrine and norepinephrine is ten times that on the left for isoproterenol.

single type of receptor (*beta*), and here the expected order of potency was found: the dose for half-maximal effect (ED_{50}) of norepinephrine was $6.5 \mu\text{g/kg/min}$; epinephrine, $3.1 \mu\text{g/kg/min}$; isoproterenol, $0.3 \mu\text{g/kg/min}$ (table 1). The parallel slopes and similar maxima of the dose-effect curves would be in keeping with agents acting upon the same receptor²⁰; however, with epinephrine and norepinephrine a plateau HR was not always reached, so that the actual intrinsic activity of the two amines in these experiments remains uncertain. If vascular changes induced by catecholamines are the sum of combined *alpha* and *beta* effects, it is unlikely that the dose-effect curve components for blood flow and pressure could be as easily interpreted. Nonetheless, with MBP the similar slopes for epinephrine and norepinephrine allowed comparison of potencies, and this disclosed a greater ED_{50} for norepinephrine than for epinephrine, and order consistent with *alpha* receptor stimulation (table 1). The RAF and TAF effects, however, could not be categorized with respect to their actions upon receptors, which may well have stemmed from gradations of *alpha* and *beta* activity among the three agents. The net result of changes in the two flows, however, placed epinephrine effects intermediate between those of isoproterenol and norepinephrine. Thus, with isoproterenol the preponderance of flow was shifted toward the head and forelimbs, with norepinephrine infusion toward the viscera and lower limbs, while with epinephrine there

were less marked changes in overall distribution, although at higher infusion rates there was some shift in flow, as with isoproterenol, toward the head regions.

The infusion of a high dose of isoproterenol has been shown to reduce flow in the renal¹⁷ and superior mesenteric²¹ arteries of the dog. Since the kidney and mesenteric artery normally receive 46 per cent of the canine cardiac output,¹⁵ a decrease in flow to these regions may account, at least in part, for the redistribution seen with this agent. Diminution in flow to these areas may be the result of a paucity of *beta* receptors¹⁵ combined with the weak *alpha* receptor stimulation of high doses of isoproterenol.^{18, 22} The relative lack of vasodilatation in some visceral beds may then have been compounded by the low mean arterial (driving) pressure induced by isoproterenol,¹⁷ suggesting that blood flow to these tissues may have been reduced markedly, perhaps critically, at doses of isoproterenol which were high enough to bring about redistribution of flow. In any case, comparison of VR and RsR (fig. 5) suggests that active vasodilatation in the regions beyond the thoracic probe proceeds more slowly and diminishes, or ceases, at a lower dose of isoproterenol than that in the regions of the head and forelimbs. In the dog, the decrease in flow to the kidneys with isoproterenol may be reversed and increased, by maintaining a moderate arterial pressure (100 mm Hg)²³ or by pretreatment with an *alpha* blocking agent.²⁴ In addition, other experi-

ments in our laboratory¹² suggest that holding blood pressure constant during graded infusion of isoproterenol prevents redistribution of flow. Thus, if these results were applicable to man, transfusion of blood to counter the fall in mean blood pressure during infusion of isoproterenol would probably eliminate or reduce the decline in blood flow to the viscera which occurs with higher doses.

Infusion of norepinephrine, in contrast to isoproterenol, seemed to shift the greater portion of cardiac output away from the head and towards the lower regions. Comparison of peripheral resistances in the two areas (RsR and VR) suggests that vasoconstriction in the head and forelimbs was proportionately greater than that in the circulation below the thoracic probe (fig. 5), even though a number of visceral beds, particularly the renal, have been found to be those most responsive to α receptor stimulation.¹⁵

In a given vascular bed, epinephrine may elicit either vasoconstriction or vasodilatation or combinations of the two, depending, among other things, on the dose and state of the circulation in question.²⁵ It is perhaps to be expected, then, that the effect of epinephrine on the gross allocation of cardiac output would be less well defined than those of isoproterenol or norepinephrine. The parallel course of the resistances, RsR and VR, would seem to indicate that the mixed peripheral effects of epinephrine tended to keep the Rs and V flows more nearly balanced, so that overall redistribution was minimal.

There was no great change in flow distribution with any of the three catecholamines at infusion rates of less than 1.0 $\mu\text{g/kg/min}$. These lower rates would probably encompass the usual range of clinical doses, so that ordinarily, if man and dog respond alike, redistribution induced by these agents may rarely proceed to any extent. In the results presented here, these relatively slow infusion rates of isoproterenol and epinephrine gave nearly maximal enhancement of aortic blood flow and norepinephrine gave little or no increase in flow at any dose, suggesting that the therapeutic usefulness of the former agents may lie only at low concentrations of drug. Bendixen *et al.*¹¹ came to a similar conclusion in an earlier study

on the effects of single injected doses of epinephrine and norepinephrine. Johnson and Parkins²¹ have also emphasized the importance of selecting the proper dose of isoproterenol or norepinephrine for optimal effects on blood flow; further, they pointed out that an increase in total systemic flow does not necessarily ensure the most favorable flow distribution.

The results presented here underscore that it cannot be taken for granted that aortic blood flows in the ascending and thoracic aorta bear a constant relationship to one another; nor that a single dose or infusion rate of a catecholamine will adequately describe its flow effects; experiments in which just one of these flows is measured during catecholamine administration^{11,26} or but one dose is given^{6,7} could lead to spurious interpretations of drug effects.

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Obstetrics

FETAL MONITORING AND CHROMOSOMAL DAMAGE Continuous monitoring of the fetal heart rate utilizing ultrasound has become increasingly popular. According to this study, ultrasound radiation at diagnostic frequencies and power levels used clinically produce no chromosomal damage. Leukocytes obtained from blood of ten mothers and cord blood of the newborn infants were cultured

and scored for chromosomal damage after two to ten hours of monitoring fetal heart rates during labor. When the irradiated samples were compared with controls, no increase in chromosomal damage was found. (Watts, P. L., and Stewart, C. R.: *The Effect of Fetal Heart Monitoring by Ultrasound on Maternal and Fetal Chromosomes*. *J. Obstet. Gynecol. Br. Comm.* 79: 715, 1972.)