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THE USE OF RADIOACTIVE MICROSPHERES TO COMPARE THE EFFECTS OF HYDRALAZINE, GUANETHIDINE AND SK&F 24260 ON THE REDISTRIBUTION OF CARDIAC OUTPUT IN ANAESTHETIZED RABBITS

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1 The use of radioactive microspheres is described for the measurement of cardiac output in anaesthetized rabbits and its redistribution after the administration of drugs which lower blood pressure.

2 Hydralazine increased peripheral vascular conductance by 123%. The vascular beds in which it had most effect were those of the carcass (mainly muscle) and the kidneys.

3 SK&F 24260, (1,4 dihydro-2, 6-dimethyl-4-(2-trifluormethylphenyl)-3,5,-pyridine-dicarboxylic acid diethyl ester), had similar vasodilator actions. Its effect in the carcass contributed relatively more to the increase of total peripheral conductance. It also caused a remarkable degree of cerebral vasodilatation.

4 Guanethidine had a relatively small effect on total peripheral conductance and lowered blood pressure mainly by reducing stroke volume and cardiac output.

Introduction

Drugs used to lower arterial blood pressure may do so by interference with a variety of physiological mechanisms, and hence cause a redistribution of cardiac output which may differ qualitatively or quantitatively. Until recently it has been possible to study this redistribution only by the tedious assembly of information on blood flow to different organs or tissues from many separate experiments. The isotope-labelled microsphere method (Rudolph & Heymann, 1967), combined with direct sampling of arterial blood during microsphere injection (Jarai, 1969; Duncan, 1969), now makes it relatively easy to obtain a complete quantitative profile of blood flow to the major organs and tissues. Repeated injections may be made of γ-emitting isotopes whose energy spectra are sufficiently distinct.

In order to test the possibilities of this method for the analysis of the cardiovascular properties of drugs, it was decided to compare the effects of hydralazine, which acts by precapillary vasodilatation (Stunkard, Wertheimer & Redisch, 1954; Ablad, 1963) with those of SK&F 24260 (1,4 dihydro-2, 6-dimethyl-4-(2-trifluormethyl-phenyl)-3,5,-pyridinedicarboxylic acid diethyl ester) (Loev, Ehhreich & Tedeschi, 1972) with similar properties (Fielden, Owen & Taylor, 1974). Their circulatory effects are contrasted with those of the adrenergic neurone blocking drug, guanethidine.

Methods

Adult male Chinchilla rabbits weighing 2.0-3.9 kg (mean 2.97 ± 0.07 kg; s.e.) were anaesthetized with sodium pentobarbitone (Abbott Laboratories) 30 mg/kg intravenously. The trachea was cannulated and catheters were inserted into both femoral arteries, one for measuring arterial pressure and the other for blood sampling for cardiac output determination. The left ventricle was catheterized via the right carotid artery for the injection of microspheres. Arterial and ventricular pressures (1 mmHg = 1.333 mbar) were measured with strain gauge manometers (Devices, Ltd.), and

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were recorded on a Schwarzer Polygraph. Heart rate was recorded with a heart rate meter (Wyatt, 1957) actuated by the arterial pulses.

The rabbit was placed in a supine position on a warm table, and the intensity of a light above it was adjusted to maintain the rectal temperature at 38.5° C. When the depth of anaesthesia was stable, arterial pH, P_{CO_2} and P_{O_2} were measured using 0.6 ml blood samples (Radiometer). The values were corrected for the difference between electrode and body temperatures. The method of measuring both organ blood flow and cardiac output by the use of radioactive microspheres was as described by Duncan (1969). The exact composition of these microspheres has not been released but the manufacturers describe them as 'carbonized plastic spheres of uniform size and shape'. The nominal diameter was 25 μm ± 5. Measurement of small samples from each batch showed the mean diameter in different batches ranged from 22 ± 5 μm to 27 ± 6 μm. The density of the microspheres is between 1.1 and 1.6 (mean 1.4) and when injected into the heart they are uniformly mixed with the blood. Approximately 60,000-100,000 25 μm microspheres (3M Company, Minnesota) labelled with ^{46}Sc and homgeneously suspended by ultrasonic agitation in 1 ml NaCl 0.9% w/v solution, containing a drop of Tween 80, were injected into the left ventricle from a polyethylene syringe. Withdrawal of blood from the femoral artery was begun at 5 ml/min about 10 s before the injection of the microspheres, and was continued throughout and for 15-20 s afterwards. The suspension of microspheres was injected over a period of 20-30 s, the syringe being continuously agitated to maintain an even dispersion. Fifteen to twenty minutes after the first injection of microspheres arterial pH and blood gas tensions were measured once more to ensure that the animal was in a normal physiological state, and the appropriate dose of either hydralazine (Apresoline, Ciba Laboratories) SK&F 24260 or guanethidine (Ismelin, Ciba Laboratories) was then given. Doses and routes of administration were chosen to produce a gradual fall in pressure over a 20-30 min period.

When the pressure had stabilized at a lower level the pH and blood gas tensions were measured again. A second injection of microspheres, labelled with ^{85}Sr, was given as described previously. The rabbits were then killed with an overdose of pentobarbitone.

The radioactivity of the whole animal was measured with a small total body γ-counter (Johnson & Warner, unpublished observations). The animal was then dissected and various organs were removed and weighed. The radioactivities of the large organs, hind legs, skin, large and small intestines, stomach and liver, and of the carcass were measured in the total body counter. The hind limbs were measured rather than the fore limbs since they are larger and contain more skeletal muscle. Although both femoral arteries were tied the collateral circulation was sufficient to give a normal blood flow; not only was there a good correlation in flows between left and right leg, but statistically significant changes in flow after administration of guanethidine and SK&F 24260 were seen. Smaller organs and blood samples were placed in vials and counted in an automatic well-type scintillation counter (Phillips P.W. 4520/00S). The design of this counter had been modified so that the geometrical error of counting with varying position within the vial was less than 5% (Bruce, N.W., Johnson, P. & Wyatt, D.G., personal communication).

The errors due to self-absorption and varying geometry, when counting organs or whole animals of different sizes in the small total body counter, were calculated by injection of ^{46}Sc or ^{85}Sr microspheres of measured radioactivity into rats, guinea-pigs or rabbits of different weights (25 g-4 kg) which were then counted. The necessary corrections (varying as negative exponentials with weight) were incorporated into a computer programme, which also introduced corrections for the overlap of Sc counts on the Sr channel in each counter, for the different sensitivities of the two counters and for variations in background counts. This was used to calculate from raw data the corrected cardiac output, organ blood flows in ml/min and ml/mm^{-1} 100 g^{-1} and vascular resistances.

Cardiac output was calculated as

$$\frac{R_{Total}}{R_{Femoral}} \times Q_F$$

where Q_F is the rate of flow into the femoral syringe (5 ml/min) and R_{Total} and $R_{Femoral}$ are the total radioactivity injected and the radioactivity of the femoral syringe respectively. The blood flows to individual organs were calculated in a similar fashion. Vascular peripheral resistances were calculated, in arbitrary units, as

$$\frac{\text{arterial pressure (mmHg) x body weight (kg)}}{\text{blood flow (ml/min)}}$$

'Conductance' is the reciprocal of resistance. All results are expressed as mean ± s.e. mean. The limits for the differences between the means were calculated using a paired Student's *t*-test.

Validation

Sufficient microspheres were injected to ensure

that every organ examined received at least 400 (Buckberg, Luck, Payne, Hoffman, Archie & Fixler, 1971) and that the radioactivity of each organ was several times the background count in whichever detector it was measured. The numbers injected, therefore, were increased to take account of the isotopic decay of the stock microsphere suspension.

The mean calculated proportion of total injected radioactivity arrested in the lungs was 3.9 ± 0.4% (s.e.). This must have included bronchial arterial flow. The relatively low proportion indicates that most microspheres were trapped in the first capillary bed downstream from the site of injection. The homogeneity of microsphere distribution in the circulation was demonstrated by simultaneous estimations of cardiac output from femoral and brachial arterial samples ($r = 0.97$, $n = 6$), and by the close correlation between blood flows to right and left kidneys ($r = 0.981$, $n = 63$). There was also a highly significant correlation between flows to all organs estimated after simultaneous injection of ^{46}Sc and ^{85}Sr labelled microspheres. Hence the number of microspheres used and the femoral arterial sampling rate were adequate to provide reliable estimates of blood flows.

Occasionally, in about 5% of rabbits, injection of microspheres caused an immediate large fall of heart rate and blood pressure presumably attributable to coronary infarction; such experiments have been excluded from these results.

Results

Table 1 shows the changes in cardiac output and organ blood flows in 12 rabbits in which microspheres labelled with different isotopes were injected on two occasions at 30-45 min intervals without drug administration. Only mean arterial pressure and blood flow to the stomach fell significantly. These observations agree with those of Duncan (1969) and Leduc (1972) who found that the injection of microspheres 30-45 min apart in anaesthetized pregnant rabbits had little effect on cardiac output or its distribution. There were no significant changes in blood gas values, heart rate, or total peripheral resistance. The fall in arterial pressure is attributed to the effect of anaesthesia and time; a similar decrease is seen in anaesthetized rabbits which have not been given microspheres.

The relative proportion of organ or tissue to body weight in adult rabbits is approximately constant. Hence for economy of space organ weights are only given in Table 4 (observations on guanethidine), in which group of experiments measurement of organ weights was most detailed.

Table 1 Control observations (no drug given) on two microsphere injections 30-45 min apart on 12 rabbits

	^{46}Sc	^{85}Sr
Cardiac output (ml kg^{-1} min^{-1})	133.6 ± 8.7	129.3 ± 8.9
Arterial pressure (mmHg)	98 ± 2.9	89 ± 2.6*
Heart rate (beats/min)	320 ± 11	335 ± 13
Total peripheral resistance	0.771 ± 0.06	0.734 ± 0.06
P_{O_2} (mmHg)	74 ± 5.3	77 ± 4.7
P_{CO_2} (mmHg)	28.6 ± 2.1	27.4 ± 1.9
pH	7.46 ± 0.018	7.45 ± 0.018
Organ	*Flows (ml/min)*	
Carcass	110.4 ± 13.7	108.6 ± 12.6
Skin	22.5 ± 4.0	20.2 ± 4.0
Right hind leg	12.7 ± 2.2	11.3 ± 2.0
Left hind leg	11.3 ± 2.0	10.9 ± 2.1
Intestines	64.0 ± 10.1	56.2 ± 10.2
Stomach	15.2 ± 2.5	9.5 ± 1.9*
Liver	14.0 ± 2.4	14.1 ± 2.7
Right kidney	45.8 ± 5.3	43.2 ± 4.5
Left kidney	45.3 ± 5.4	43.0 ± 4.4
Heart	14.5 ± 1.7	15.0 ± 1.5
Brain	3.1 ± 0.28	3.5 ± 0.17

* $P < 0.002$.

Hydralazine

Nine rabbits of 2.6 ± 0.12 kg body weight were injected with microspheres before, and 20-30 min after, administration of hydralazine 200 μg/kg intravenously (Table 2). There was a large fall in arterial pressue to 45 mmHg (by 46%). Total peripheral resistance was reduced by 55% on average, cardiac output increased by 20% and heart rate by 11%. The change in stroke volume was insignificant.

The vascular resistances of the carcass, heart, brain ($P < 0.001$), legs, kidneys ($P < 0.01$) and skin ($P < 0.05$) fell significantly. It is interesting to note that calculated skin vascular resistance fell in spite of the reduction in skin blood flow. It is remarkable that in spite of the large reduction in arterial pressure there was no evidence of compensatory vasoconstriction in the organs selected for flow measurement.

Table 2 also shows that administration of hydralazine in the dose used caused an increase in ventilation which was noticeable at the time and is shown by the rise of PaO_2 and fall in $PaCO_2$. This is probably due to peripheral arterial chemoreceptor stimulation consequent on the fall in arterial pressure. Once again the absence of concomitant vasoconstriction in the peripheral circulation (so far as this was analysed) is interesting. The evidence suggests that hydralazine had caused very widespread, overriding and non-selective vasodilatation.

SK&F 24260

Fourteen rabbits of 2.8 ± 0.12 kg were injected with microspheres before and 20-30 min after administration of SK&F 24260 200 μg/kg subcutaneously. The mean arterial pressure fell to 52 mmHg (by 38%, Table 3). Total peripheral resistance was reduced by 39%. There was no significant change in heart rate, cardiac output or blood gas values.

Among the changes in the distribution of cardiac output was a two-fold rise in cerebral flow, due to a 72% fall in cerebral vascular resistance. The vascular resistances of the carcass, legs, brain, large intestines ($P < 0.001$) and heart ($P < 0.05$) also were reduced. Those of other organs were not altered significantly.

Guanethidine

Eleven rabbits, of 2.69 ± 0.18 kg, were injected with microspheres before and 20-30 min after administration of guanethidine 500 μg/kg intramuscularly. The mean arterial pressure fell to 75 mmHg (by 23%, Table 4). Total peripheral resistance was reduced by 15%. There was a small increase in heart rate; the mean reduction in cardiac output was not significant but there was a significant decrease in stroke volume ($P < 0.01$). Blood gas values did not change significantly.

As Table 4 shows, administration of guanethidine caused a widespread reduction in the

Table 2 Effects of hydralazine (200 μg/kg, i.v.) in nine rabbits

	Initial	*After drug*	P<
Cardiac output (ml kg^{-1} min^{-1})	119.4 ± 5.6	143.4 ± 10.5	0.01
Arterial pressure (mmHg)	84.3 ± 4.2	45.1 ± 3.8	0.001
Heart rate (beats/min)	308 ± 14.8	343 ± 21.1	0.01
Total peripheral resistance	0.76 ± 0.04	0.34 ± 0.02	0.001
PO_2 (mmHg)	70 ± 2.5	84 ± 3.1	0.01
PCO_2 (mmHg)	29 ± 1.1	26 ± 1.2	0.05
pH	7.45 ± 0.02	7.48 ± 0.01	NS
Organ	*Flows (ml/min)*		
Carcass	89.0 ± 10.1	103.5 ± 12.6	0.05
Skin	21.8 ± 3.1	13.6 ± 2.4	0.01
Right hind leg	10.6 ± 1.9	9.8 ± 2.5	NS
Left hind leg	10.3 ± 1.8	8.5 ± 2.0	NS
Intestines	49.5 ± 4.2	54.0 ± 9.9	NS
Stomach	9.4 ± 1.0	4.2 ± 0.6	0.002
Liver	15.2 ± 3.2	14.1 ± 2.3	NS
Right kidney	35.6 ± 2.8	53.0 ± 5.8	0.002
Left kidney	35.1 ± 2.9	55.8 ± 4.6	0.001
Heart	12.1 ± 1.9	31.1 ± 6.7	0.01
Brain	3.6 ± 0.5	3.8 ± 0.5	NS

NS = Not significant.

blood flow to organs and tissues. None of the changes in vascular resistances was statistically significant, except that of the thyroid, which was increased more than three-fold.

The results of the four sets of experiments are shown in Figure 1. It is evident that administration of the three drugs caused much larger changes in arterial pressure and in the redistribution of

Table 3 Effects of SKF 24260 (200 μg/kg, s.c.) in 14 rabbits

	Initial	*After drug*	P<
Cardiac output (ml kg^{-1} min^{-1}	154.0 ± 5.7	153.3 ± 10.7	NS
Arterial pressure (mmHg)	84.1 ± 3.8	52.3 ± 4.1	0.001
Heart rate (beats/min)	321 ± 11.8	320 ± 11.8	NS
Total peripheral resistance	0.596 ± 0.031	0.364 ± 0.4	0.001
P_{O_2} (mmHg)	71 ± 2.8	69 ± 3.0	NS
P_{CO_2} (mmHg)	29 ± 1.6	28 ± 2.2	NS
pH	7.46 ± 0.009	7.41 ± 0.023	NS
Organ	*Flows (ml/min)*		
Carcass	140.0 ± 12.1	160.4 ± 16.0	NS
Skin	25.9 ± 3.3	18.6 ± 3.0	NS
Right hind leg	14.4 ± 0.87	17.6 ± 2.2	NS
Left hind leg	13.8 ± 0.75	17.0 ± 2.1	NS
Small intestine	38.8 ± 4.2	28.5 ± 3.1	0.05
Large intestine	30.0 ± 2.5	32.1 ± 3.6	NS
Stomach	16.6 ± 1.98	12.2 ± 1.6	NS
Liver	20.2 ± 3.4	20.6 ± 2.7	NS
Right kidney	51.6 ± 3.8	35.4 ± 4.2	0.002
Left kidney	50.7 ± 3.6	35.6 ± 4.2	0.002
Heart	17.9 ± 1.8	25.1 ± 3.1	0.05
Brain	3.9 ± 0.47	8.7 ± 1.8	0.02
Spleen	4.06 ± 1.2	1.9 ± 0.44	0.05

Table 4 Effects of guanethidine (500 μg/kg, i.v.) in 11 rabbits

		Initial	*After drug*	P<
Cardiac output (ml kg^{-1} min^{-1})		167.7 ± 12.4	144.9 ± 8.9	NS
Arterial pressure (mmHg)		97.0 ± 2.9	74.6 ± 3.7	0.001
Heart rate (beats/min)		340 ± 13.9	370 ± 13.9	0.001
Total peripheral resistance		0.612 ± 0.04	0.522 ± 0.02	0.02
P_{O_2} (mmHg)		75 ± 5.2	78 ± 4.1	NS
P_{CO_2} (mmHg)		28.2 ± 2.1	25.6 ± 1.8	NS
pH		7.46 ± 0.19	7.43 ± 0.02	NS
Organ	*Weights (g)*	*Flows (ml/min)*		
Carcass	1275 ± 12	118.1 ± 5.8	109 ± 9.5	NS
Skin	391 ± 36	31.9 ± 2.4	20.3 ± 2.6	0.002
Right hind leg	208 ± 14	16.5 ± 1.1	13.2 ± 1.0	0.05
Left hind leg	203 ± 13	16.2 ± 1.1	13.2 ± 1.0	0.05
Small intestine	108 ± 6	45.6 ± 4.1	37.2 ± 5.1	0.05
Large intestine	201 ± 9	34.1 ± 2.9	32.1 ± 3.3	NS
Stomach	82 ± 11	16.1 ± 3.0	11.1 ± 2.0	0.05
Liver	119 ± 7	13.6 ± 1.2	17.3 ± 3.5	NS
Right kidney	10.4 ± 0.6	42.9 ± 7.0	33.7 ± 6.4	0.05
Left kidney	10.5 ± 0.6	43.2 ± 6.9	33.0 ± 6.4	0.05
Heart	7.5 ± 0.4	17.5 ± 1.7	16.8 ± 1.7	NS
Brain	7.8 ± 0.3	4.0 ± 0.43	3.72 ± 0.2	NS
Spleen	1.06 ± 0.08	3.3 ± 0.56	2.8 ± 0.86	NS
Thyroid	0.192 ± 0.02	0.225 ± 0.07	0.052 ± 0.017	0.02
Adrenals	0.235 ± 0.03	0.230 ± 0.045	0.319 ± 0.06	0.05

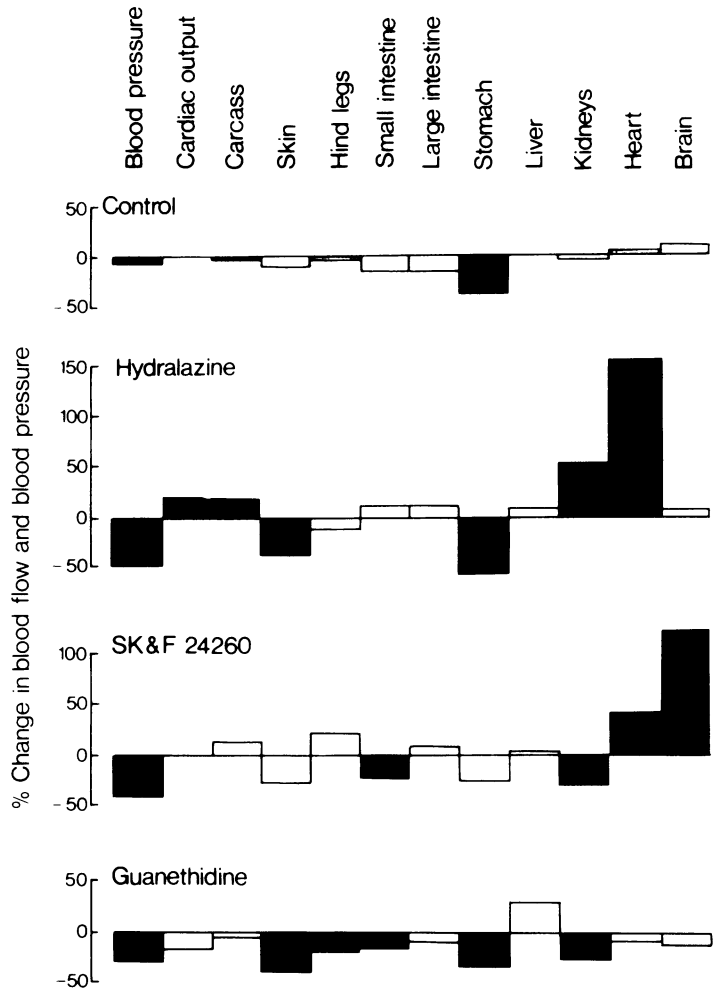

Figure 1 Percentage change from resting blood flow to all organs 30 min after hydralazine, guanethidine and SK&F 24260 compared with the fall in blood pressure. Note: (1) Shaded areas are those in which the changes in blood flow were statistically significant. (2) The controls show the change in flow and pressure between two microsphere injections 30 min apart.

cardiac output than occurred spontaneously in the group of rabbits which received no drug. The changes in arterial pressure in the three experimental groups were different, and the consequential homeostatic physiological responses (through activation of the baroreceptor and chemoreceptor reflexes and of the renin-angiotensin system) may well have differed. Nevertheless the doses were selected on the basis of those used clinically, and from this point of view, but bearing in mind species differences, are comparable.

With these reservations the results show a remarkable difference in the cardiovascular responses to hydralazine and SK&F 24260 (Figure 1), especially as regards the coronary, cerebral and renal blood flows. Comparison between the effects of these two drugs and that of guanethidine is even more striking.

Discussion

The results show that the radioactive microsphere method for measuring cardiac output and its

Table 5 Percentage distribution of cardiac output in adult rabbits

	Chalmers et al. *(1967a)*	*Neutze* et al. *(1968)*		*Warren (1973)*		*Present Paper*
	Local thermodilution	*Microspheres*		*Microspheres*		*Microspheres*
	Unanaesthetized	*Unanaesthetized*	*Halothane*	*Unanaesthetized*	*Pentobarbitone*	*Pentobarbitone*
Total body muscle	33.6					
Carcass		39.6*	36.5*	29.0	39.6	29.2
Limbs				12.9	15.1	6.7†
Skin	11.3	7.4	5.8	5.0	7.1	6.5
Small intestine		11.5	11.1	7.3	5.6	10.0
Large intestine	16.6‡	9.3	11.6	7.8	5.9	8.1
Stomach		3.4	4.3	3.9	1.9	3.5
Kidneys	20.0	16.2	16.6	14.7	12.0	21.0
Heart		2.8	3.7	2.9	2.1	4.1
Brain		1.2	1.8	0.9	0.5	0.9
Spleen		1.8	1.9	1.1	0.3	0.8
Liver		3.4	5.4	2.9	2.9	3.8

* Including hind limbs. † Hind limbs only. ‡ Portal venous.

distribution is useful for detecting changes simultaneously in many organs, and that different drugs which lower arterial pressure cause very different cardiovascular changes. Figure 1 shows that the reduction in blood pressure varied with the different drugs and while this may influence the cardiovascular changes that were seen, the aim of the experiment was to select drug dose on the basis of those used clinically.

The cardiac output in the present experiments on rabbits under light pentobarbitone anaesthesia (145 ± 4.9 ml $kg^{-1}min^{-1}$) was less than in unanaesthetized rabbits (175-250 ml $kg^{-1}min^{-1}$) as estimated by direct Fick or indicator dilution methods (Korner & Darian Smith, 1954; Edwards, Korner & Thorburn, 1959; Korner, 1963, 1965; Chalmers, Korner & White, 1967a, b, c; Warren, 1973) but greater than in some previously reported series under pentobarbitone (e.g. 110 ml $min^{-1}kg^{-1}$.; Neutze, Wyler & Rudolph, 1968). Within the present series there were large variations in the mean initial cardiac outputs (119 ± 6 ml $min^{-1}kg^{-1}$ in those which subsequently received hydralazine; 168 ± 12 ml $min^{-1}kg^{-1}$ in those which later were given guanethidine) for no apparent reason (size or source of rabbits, thermal, anaesthetic dose, duration of experiment, season). Nevertheless the proportionate distribution of cardiac output to different organs and tissues did not vary significantly. The distribution was very similar to that observed by others in unanaesthetized or anaesthetized rabbits (Table 5), although Warren (1973) found a greater proportion of cardiac output distributed to skeletal muscle and less to the viscera. This is probably because his rabbits were larger; the carcass carried a greater proportion of the extra weight than the abdominal organs.

The effect of hydralazine on cardiac output and on the blood flow to many organs is well documented in both animals and man. The increase in cardiac output observed in rabbits using microspheres agrees with that in clinical studies by Wilkinson, Backman & Hecht (1952), Fries, Rose, Higgins, Finnerty, Kelley & Partenope (1953) and Stein & Hecht (1955). Similarly the large increases in renal and coronary flows agree with those found in man by Reubi (1950), Wilkinson *et al.* (1952), Stein & Hecht (1955) and Crumpton, Rowe, Crosley, Maxwell & Huston (1953). Hydralazine is believed to lower blood pressure by dilatation of the pre-capillary resistance vessels (Ablad, 1963). Although the vascular resistance fell in the heart and brain, even if these organs were maximally dilated they would not contribute greatly to the fall observed in total peripheral resistance; in rabbits the heart normally only receives about 4-5% and the brain 1% of cardiac output. The simplest way of expressing the contribution of the vascular beds of different organs and tissues to the total, is to consider it in terms of vascular conductances. Table 6 shows the changes in total systemic vascular conductances on administration of hydralazine and SK&F 24260. It also shows the relative contributions of the principal organs to the mean change, where this contribution is equal to, or exceeds 10% of the total change. For hydralazine the greatest effects are in the carcass and kidneys.

Like hydralazine, SK&F 24260 has been described as a pre-capillary vasodilator (Fielden, Owen & Taylor, 1974). The present observations show that it causes a large fall in blood pressure, due to a decrease in total peripheral resistance with no change in cardiac output. Although the increases in blood flow to the carcass and hind legs were not statistically significant, increases in vascular conductance were significant and large (Table 6). Together they contributed to nearly 63% of the observed increase in total peripheral conductance. As with hydralazine, SK&F 24260 caused a significant increase in vascular conductance to the heart. Similarly, SK&F 24260

Table 6 Changes in systemic vascular conductance in rabbits given hydralazine or SKF 24260

	Hydralazine	*SKF 24260*
Total systemic conductance	1.32	1.68
Change	+ 1.63 (123%)	+ 1.07 (63%)
% of total change* in:		
Carcass	+31	+48
Hind limbs		+12
Intestine	+15	+10
Kidneys	+38	
Heart	+13	+10

* Only those changes which were statistically significant, and which, for different organs, accounted for 10% or more of the total.

also caused a significant increase in vascular conductance in the large intestines. Yet the increases in conductance in the heart and intestine each contribute only 10% of the total, so the major site of action of SK&F 24260 is in skeletal muscle. The very large increase in cerebral flow produced by SK&F 24260 is interesting and seems worth further investigation, although it contributes very little to the overall lowering of blood pressure.

The cardiovascular changes produced by guanethidine were very different from those caused by hydralazine or SK&F 24260. Guanethidine is thought to have a selective action on the post-ganglionic nerves (Maxwell, Mull & Plummer, 1959; Maxwell, Plummer, Schneider, Povalski & Daniel, 1960) by interfering with the synthesis of noradrenaline (Abercrombie & Davies, 1963) or by otherwise depleting the local stores. Fielden & Green (1967) concluded that guanethidine also had a strong adrenergic neurone blocking action distinct from the depleting action. It has been suggested that a reduction in total peripheral resistance (by blocking the sympathetic nervous system) is the mechanism by which guanethidine lowers blood pressure (Chamberlain & Howard, 1964). In the present experiments the total peripheral conductance was only increased by 17% after guanethidine; there was no significant change in any individual organ. Guanethidine caused a significant fall in stroke volume, and it is likely that this is the principal means by which blood pressure was reduced. Sympathetic vasoconstrictor nerves are distributed not only to the arterioles but also to the venules and veins. Therefore a decrease in sympathetic tone would increase the venous capacity of the peripheral vascular beds and so reduce venous return.

Guanethidine is very different from hydralazine and SK&F 24260 because it did not cause vasodilatation in any vascular bed. The widespread fall in systemic blood flow after guanethidine (Table 4) is small and must be a passive result of the lowered blood pressure, because the calculated vascular conductances to all organs were not changed significantly in the conditions of these experiments.

In the group of rabbits which received guanethidine it was also decided to look at the effects of the drug on certain endocrine glands, namely the thyroid and the adrenal. As Table 4 shows they reacted very differently from the other organs; the blood flow to the thyroid was much reduced, the resistance being significantly increased. The adrenal glands were the only organs to show a significant increase in flow. These results were unexpected and deserve further investigation.

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