J. Physiol. (1967), **192**, *pp.* 537–548
With 3 text-figures
Printed in Great Britain

LOCAL AND REFLEX FACTORS AFFECTING THE DISTRIBUTION OF THE PERIPHERAL BLOOD FLOW DURING ARTERIAL HYPOXIA IN THE RABBIT

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(*Received* 7 *April* 1967)

SUMMARY

1. The effects of severe arterial hypoxia on the blood flow in the portal vein, and in kidney, muscle and skin beds have been determined in normal unanaesthetized rabbits, in animals without functioning autonomic effectors, and in rabbits with section of the carotid sinus and aortic nerves.

2. The resting blood flows in the above regions were not significantly different in the three groups.

3. The susceptibilities of the various beds to the local dilator effects of arterial hypoxia (assessed from the responses of animals without functioning autonomic effectors) were markedly different; vasodilatation was by far the greatest in the portal bed, followed in order by the renal, skin and muscle beds.

4. Section of the carotid sinus and aortic nerves completely abolished reflex activity, and the pattern of peripheral blood flow changes was similar to that of animals without functioning autonomic effectors. The findings suggest that the arterial chemoreceptors are the primary afferent source of reflex control of the peripheral circulation in arterial hypoxia.

5. In normal animals with intact reflexes there was sustained vasoconstriction throughout the treatment period in the portal and renal bed. The net vasomotor effects in muscle and limb skin were small owing to the operation of a number of factors, which opposed the effects of reflexly increased sympathetic nerve activity.

INTRODUCTION

The effects of severe arterial hypoxia on the peripheral circulation of the unanaesthetized rabbit are not uniform. For example, there is prolonged vasoconstriction in the renal bed (Korner, 1963), but vasodilatation or

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little change in blood flow in skeletal muscle (Chalmers, Korner & White, 1966). These findings could be the result of non-uniform reflex autonomic effects (Folkow, 1962; Folkow, Heymans & Neil, 1965), or could be due to differences in local susceptibility to hypoxia of the various regional beds. The reflex effects and their relation to the local effects of hypoxia have been studied in these experiments in normal unanaesthetized rabbits with intact reflexes, and in animals without functioning autonomic effectors. The effects of hypoxia were examined in the splanchnic bed drained by the portal vein, and the renal, muscle and skin beds. The role of the receptors of the carotid sinus and aortic arch regions in the reflex control of the peripheral circulation has been assessed in this type of hypoxia by studying the responses in animals with section of the carotid sinus and aortic nerves.

METHODS

Animals. New Zealand White rabbits cross-bred with the New Zealand Giant strain (mean body weight 2·4 kg; range 2·1–3·4 kg) were used in this study. The experiments were performed in: (1) normal rabbits; (2) 'de-efferented' rabbits without functioning autonomic effectors following bilateral adrenalectomy, prolonged treatment with guanethidine, and atropinization on the day of the experiment, as described previously (Korner & White, 1966; White, 1966; Chalmers, Korner & White, 1967*a*); (3) 'de-afferented' rabbits with section of the carotid sinus and aortic nerves (Korner, 1965*a*, *b*).

Operative procedures. Local thermodilution catheters were inserted into the left renal vein, portal vein, and left common iliac vein at a preliminary operation using sodium pentobarbitone anaesthesia (initial dose 30–40 mg/kg I.V. supplemented as required). The renal and portal catheters were inserted by direct puncture of the vessel wall, and were fixed by means of the tissue adhesive methyl 2-cyanoacrylate or isobutyl acrylate (Ethicon Inc. Sommerville, N.J., U.S.A.). Details of the operative procedure have been described elsewhere (Chalmers *et al.* 1966; White, Chalmers, Hilder & Korner, 1967). Experiments were carried out in normal animals 3–5 days after the preliminary operation when they had fully recovered. In 'de-efferented' rabbits bilateral adrenalectomy was carried out at the time of implanting the thermodilution catheters, and these animals were given in addition to the standard supportive steroid therapy (White, 1966) 0·0375 mg strophantin G (Ouabain, Arnaud) I.V. at the end of the operation; a 5-day course of guanethidine sulphate (Ismelin, Ciba) of 12·5 mg/kg.day I.V. was started on the 4th day after the operation. In the 'de-afferented' group implantation of the thermodilution catheters and section of the carotid sinus and aortic nerves were carried out at the same time.

Measurement of regional blood flow. Local thermodilution curves were recorded after rapid injection of room temperature injectate about 11–12 mm upstream from the thermistor using a mechanical injector. Flow in the various veins was calculated using the formulae and corrections described previously (Chalmers *et al.* 1966; White *et al.* 1967). Muscle blood flow was estimated as the difference between iliac vein flow (assumed to equal total hind-limb flow) and limb skin flow. The latter was estimated using a calibrated thermal conductivity method (Chalmers & Korner, 1966). The sampling of a representative area of hind-limb skin was improved in the present experiments by sampling from both limbs, since it was found (in separate perfusion experiments) that the variation in mean heat flow from the skin at a given blood flow was the same between different animals as between different limbs on the same animal. Ear skin blood flow was also measured in these experiments.

Other measurements. The ear artery pressure, heart rate and respiratory minute volume were measured as described previously (Korner, 1965*b*). Arterial P_{O_2}, P_{CO_2} and pH, together with mixed venous (right atrial) P_{O_2} were measured using a model 113 Instrumentation Laboratories Inc. Blood Gas Analyzer and pH Meter (Chalmers & Korner, 1966). The regional vascular resistance of each bed was calculated from the ratio Ear Artery Pressure/Regional Blood Flow and expressed in arbitrary units.

Conduct of experiment and statistical analysis. Minor operative procedures on the day of the experiment were carried out as described previously (Korner, 1965*b*; Chalmers *et al.* 1966). The rabbit rested without restraint inside a rabbit box for 1 hr before commencing the experiment, which consisted of a 16 min control period (breathing room air), a 41 min treatment period (breathing a low O_2 mixture), and a 13 min recovery period (breathing room air). The timing of the various measurements was the same in all animals. In each individual experiment 2–3 measurements of each parameter (except ventilation, see Table 2) were averaged for each of the selected time intervals (e.g. Fig. 1) of the experiment. In a given group of experiments the mean value for each time interval was determined for each parameter from the results of all the animals in the group, and the standard error of the mean of each time interval estimated by analysis of variance (Mather, 1949). In some instances the average effects of treatment in each group of experiments were expressed as the percentage of the mean control value (e.g. Fig. 2).

RESULTS

Resting blood flows in the different preparations. The mean circulatory findings in each group are summarized in Table 1. There were no significant differences in the mean blood flow values of normal, 'de-efferented' and 'de-afferented' animals in the portal bed, kidney, limb skin and muscle beds, but the ear blood flow was higher in 'de-efferented' animals. Since the differences in cardiac output between the three groups are small (Korner, 1965*b*; Chalmers, Isbister, Korner & Mok, 1965; Chalmers *et al.* 1967*a*, *b*; Korner & White, 1966), the results indicate that despite the considerable

TABLE 1. Normal resting values, expressed as means ±S.E. of mean, in thirteen normal rabbits with intact reflexes, nine 'de-efferented' rabbits (adrenalectomy + guanethidine + atropine), and eight rabbits with section of carotid sinus and aortic nerves. Results from each animal are the mean of 4 observations for each parameter

Group	Normal	'De-efferented'	Carotidsinus + aortic nerve section
Number	13	9	8
Body wt. (kg)	2·48 ± 0·03	2·38 ± 0·08	2·43 ± 0·08
Ear artery pressure (mm Hg)	87 ± 2·7	80 ± 3·8	112 ± 10·8
Heart rate (beats/min)	278 ± 15·5	211 ± 2·2	312 ± 7·0
Portal blood flow (ml./min)	100 ± 5·7	107 ± 9·0	84 ± 8·2
Renal blood flow (ml./min/kidney)	60 ± 6·3	58 ± 5·1	50 ± 4·1
Muscle blood flow (ml./100 g/min)	20·2 ± 2·7	16·0 ± 1·7	18·7 ± 1·3
Limb skin blood flow (ml./100 g/min)	17·4 ± 0·84	18·4 ± 1·34	16·6 ± 1·1
Ear skin blood flow (ml./100 g/min)	11·2 ± 1·21	17·5 ± 0·92	12·5 ± 1·3

range in resting autonomic tone there is relatively little difference in the regional blood flow distribution in these preparations under resting conditions. Possibly autoregulatory mechanisms (Johnson, 1964) compensate for any alteration in sympathetic nerve activity to a particular bed during the days following the initiation of the disturbance in tonic activity.

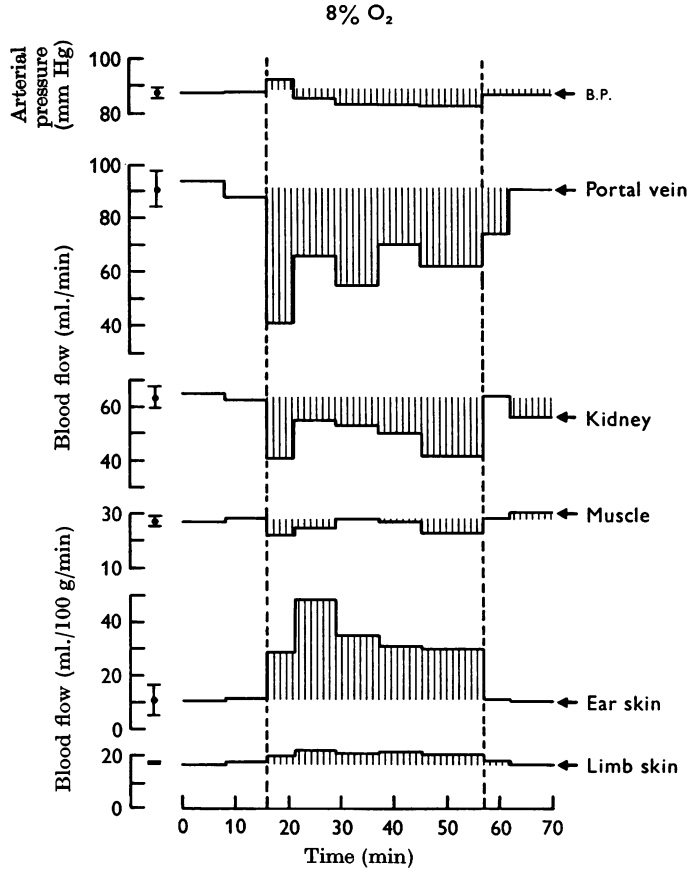

Fig. 1. Mean effects of severe arterial hypoxia induced by breathing 8 % O_2 in seven normal rabbits on ear artery pressure (mm Hg), portal vein blood flow (ml./min), renal blood flow (ml./min), muscle blood flow (ml./100 g/min), ear and limb skin blood flows (ml./100 g/min). Hatching denotes deviation from mean control value during treatment period (between vertical interrupted lines), and during recovery phase. The symbol on the left of each parameter is ± 1 S.E. of mean of a single time interval, measured from the mean control value (dot).

The differences in arterial pressure and heart rate between the groups were in agreement with previous findings (Korner & White, 1966; Chalmers *et al.* 1967*a*).

Effects of arterial hypoxia in normal rabbits. The circulatory findings in seven animals with intact reflexes are shown in Fig. 1. The arterial pressure was well maintained during hypoxia and there was marked reduction in portal and renal blood flows, no significant change in muscle blood flow, moderate hyperaemia in the limb skin ($P < 0{\cdot}001$), and a large increase in ear skin blood flow. Vasoconstriction was maximal soon after the onset of hypoxia when the portal and renal vascular resistance rose to 250 ± 10 (S.E. of mean) % and 193 ± 11 (S.E. of mean) % of their respective control values, but it was well maintained throughout the treatment period, the vascular resistance in each bed settling at 154 ± 5 (S.E. of mean) % and $122 \pm 5{\cdot}5$ (S.E. of mean) % respectively during the 'steady-state'.

Changes in heart rate, ventilation, and in arterial and mixed venous blood composition are summarized in Table 2.

Effects of arterial hypoxia in 'de-efferented' rabbits. The results in this group permit assessment of the local effects of arterial hypoxia, since the autonomic effectors are not functioning (Korner & White, 1966; Chalmers, Korner & White 1967, *c*). During reduction in arterial P_{O_2} of the same degree as in normal animals there was arterial hypotension, a large increase in portal blood flow, no significant change in renal blood flow, slight reduction in limb and ear skin blood flows, and somewhat more marked reduction in muscle blood flow (Fig. 2, left panel). The calculated portal vascular resistance fell to an average of 50 % of control ($P < 0{\cdot}001$), whilst the calculated vascular resistance in the kidney and limb skin fell to 80 % ($P < 0{\cdot}01$) and 90 % ($P < 0{\cdot}05$) of their respective control values (Fig. 3, left panel). However, the calculated vascular resistance in muscle did not change significantly during the treatment period, rising during the early period and falling slightly during the 'steady-state', a surprising finding in view of the well known local dilator effects of hypoxia observed in the denervated muscle bed studied under more controlled conditions (Crawford, Fairchild & Guyton, 1959; Haddy & Scott, 1964; Ross, Kaiser & Klocke, 1964; Haddy, 1966).

In these animals the ventilatory response to hypoxia was similar to that of normal rabbits, but the changes in heart rate were small and not statistically significant (Table 2).

Effects of arterial hypoxia in 'de-afferented' rabbits. The circulatory effects in three 'de-afferented' animals with section of the carotid sinus and aortic nerves (Figs. 2 and 3, right panels) differed from those of normal animals, but were similar to the findings in the 'de-efferented' rabbits. In the 'de-afferented' group arterial hypoxia induced a greater percentage change in arterial pressure than observed in 'de-efferented' animals, the difference probably reflecting the higher control value of the former group (Table 1). There was a large hyperaemia in the portal bed, no significant

TABLE 2. Results of heart rate and ventilation (l./min) in seven normal, three 'de-efferented' and three 'de-afferented' rabbits with section of carotid sinus and aortic nerves; before, during and after inhalation of low oxygen. Measurements of ventilation during control period 16 min (C_1) and 8 min (C_2) before hypoxia; during treatment period 1 min (T_1), 13 min (T_2) and 38 min (T_3) after commencing hypoxia, and 5 min (R_1) and 13 min (R_2) after resuming air breathing. Results expressed as mean ± S.E. of mean of single time interval based on within animal comparisons. At times C_1 and T_3 blood gas determinations carried out; results expressed as means ± S.E. of difference based on within animal comparisons

	Group							
	C_1	C_2	T_1	T_2	T_3	R_1	R_2	S.E.
Normal (7)								
Heart rate/min	289	286	189	227	235	297	300	±8·6
Ventilation (l./min)	1·01	0·96	2·13	1·91	1·79	1·54	1·45	±0·1
Arterial P_{O_2}	99	—	—	—	33	—	—	±2·0
Arterial P_{CO_2}	34	—	—	—	18	—	—	±1·0
Arterial pH	7·46	—	—	—	7·54	—	—	±0·01
Mixed venous P_{O_2}	41	—	—	—	17	—	—	±2·7
'De-efferented' (3)								
Heart rate/min	224	225	210	227	228	228	226	±11·4
Ventilation (l./min)	1·05	1·07	2·54	2·25	2·18	1·30	1·28	±0·13
Arterial P_{O_2}	95	—	—	—	29	—	—	±3·2
Arterial P_{CO_2}	33	—	—	—	16	—	—	±1·2
Arterial pH	7·48	—	—	—	7·73	—	—	±0·03
'De-afferented' (3)								
Heart rate/min	315	306	300	308	293	306	313	±6·5
Ventilation (l./min)	0·93	1·10	1·18	1·08	1·01	1·10	0·96	±0·1
Arterial P_{O_2}	91	—	—	—	34	—	—	±3·9
Arterial P_{CO_2}	32	—	—	—	30	—	—	±1·4
Arterial pH	7·38	—	—	—	7·39	—	—	±0·02

change in renal blood flow, and slight reduction in flow in muscle and skin beds (Fig. 2, right panel). The fall in the calculated vascular resistance during hypoxia was more marked in every bed in 'de-afferented' rabbits than in 'de-efferented' animals (Fig. 3). The 'steady state' values for the

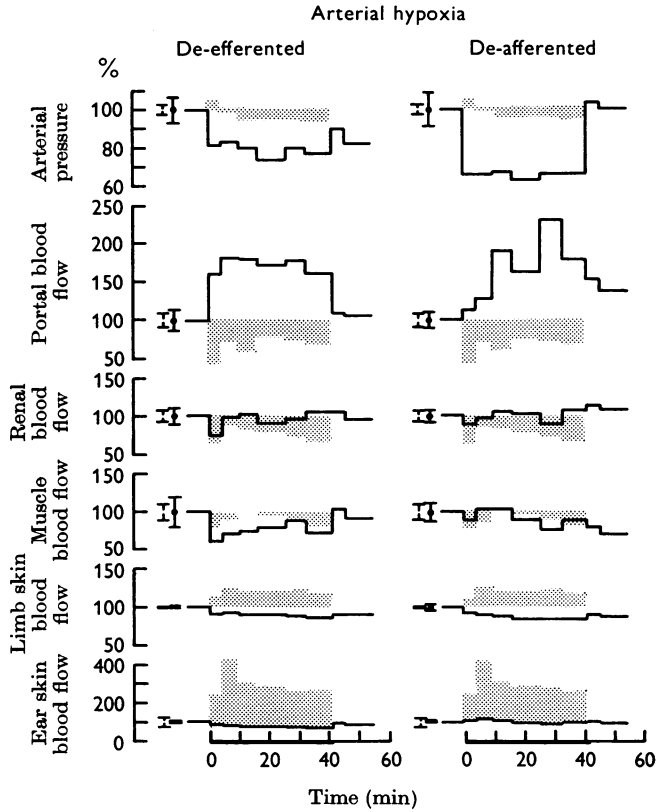

Fig. 2. Mean effects (expressed as % of control) on arterial pressure, and blood flow in portal, renal, muscle, limb and ear skin in three 'de-efferented' rabbits (left panel), and three 'de-afferented' rabbits (right panel). Results in each group are drawn as solid lines, and compared with the response of the group of normal animals (shading). Arterial hypoxia was induced from 0 to 41 min as indicated by the black bar on each abscissa. S.E. of mean of single time interval are given in the order (from left to right): S.E. of normal animals, then S.E. of either 'de-efferented' or 'de-afferented' rabbits.

calculated vascular resistance (expressed as % of control) in the 'de-afferented' group were: 36 ± 11 (S.E. of mean) % for the portal bed; 64 ± 7 (S.E. of mean) % for the renal bed; $77 \pm 8{\cdot}5$ (S.E. of mean) % for skeletal muscle; 79 ± 4 (S.E. of mean) % for limb skin.

The heart rate did not change significantly in these animals, and the respiratory findings (Table 2) were also in agreement with previous findings (Korner, 1965*a*).

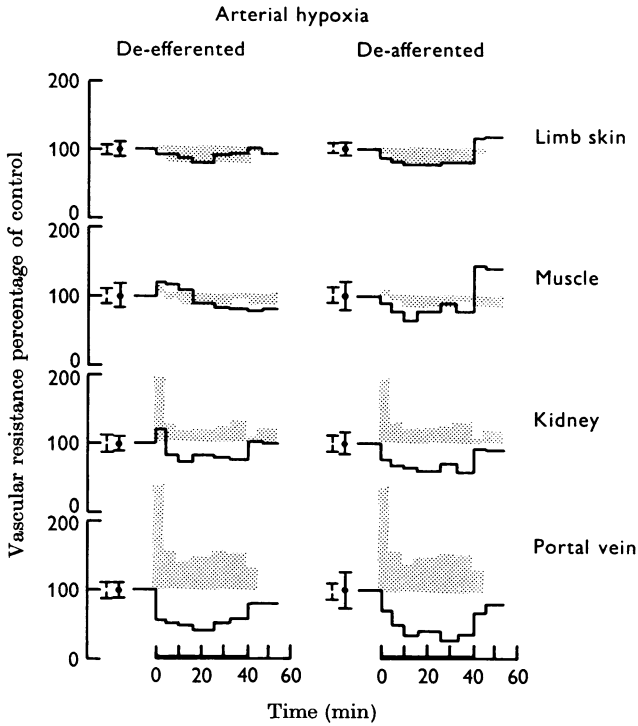

Fig. 3. Mean effects (expressed as % of control) on vascular resistance of limb, skin, muscle, kidney and portal bed in three 'de-efferented' rabbits (left panel) and three 'de-afferented' rabbits (right panel). Results in each group are drawn as solid lines, and compared to the response of normal rabbits (shading). Notation as in Fig. 2.

DISCUSSION

Local effects of arterial hypoxia. The present experiments indicate that the local effects of arterial hypoxia, assessed from the circulatory response of 'de-efferented' rabbits, differ markedly in the various beds studied. By far the greatest vasodilator response occurs in the portal bed, followed by the renal and cutaneous beds, but there is no obvious vasodilatation in the skeletal muscle bed as estimated from the change in calculated vascular resistance. In 'de-afferented' animals with section of the carotid sinus and aortic nerves the pattern of blood flow distribution during arterial hypoxia is similar to that found in 'de-efferented' animals without functioning autonomic effectors, although there is a greater fall in the vascular resistance in each bed. The similarity in flow patterns in the two groups

suggests that section of the carotid sinus and aortic nerves abolishes reflex activity during hypoxia, so that the circulatory effects are mainly produced by the local effects of hypoxia. The quantitative differences between the two groups can probably be explained by the higher resting vascular tone of the 'de-afferented' animals, by their higher P_{CO_2} levels which may potentiate selectively some of the peripheral dilator effects of hypoxia, (e.g. Sidky & Bean, 1951; Bean & Sidky, 1957) and by their better ability to maintain cardiac output (Korner & White, 1966).

The absence of an obvious dilator response in the muscle bed of 'de-efferented' animals is at variance with the findings in 'de-afferented' animals, with estimates of the local effects of hypoxia in perfusion studies (Crawford *et al.* 1959; Haddy & Scott, 1964, Ross *et al.* 1964; Haddy, 1966), and with results in the denervated limb of intact animals (Chalmers *et al.* 1966). Incomplete block has been excluded in 'de-efferented' animals (Chalmers *et al.* 1967*c*), and the production of other constrictor substances during hypoxia in amounts sufficient to account for the findings seems improbable. Differences in the shape of the pressure–flow curves of the various beds also cannot account for the paradoxical effect in muscle during hypoxia (Jones & Berne, 1964; Green & Rapela, 1964; Thurau, 1964; Johnson, 1964). It seems probable that the latter is due to a passive mechanical effect of differential susceptibility of the resistance vessels of the various beds, which in turn produces secondary changes in vascular capacity and in venous resistance. Previous findings in animals without sympatho-adrenal control have shown that during hypoxia the cardiac output is maintained relatively inadequately, and that there is progressive reduction in central venous pressure reflecting diminution in effective venous filling (Korner & White, 1966). In 'de-efferented' animals the latter effect probably results from sequestration of blood following the massive portal vasodilatation into the atonic, highly distensible gastro-intestinal veins. Filling of the capacity vessels of the beds less susceptible to hypoxia will be less than normal (Guyton, 1963 *a*, *b*), and the greatest reduction in vein calibre will occur in muscle, the bed least sensitive to hypoxia. This will increase the venous resistance to flow markedly in this bed, thus masking an arteriolar dilatation. The calibre of the small arteries may also become smaller in this bed owing to relatively poor mechanical filling. The absence of similar effects on central venous pressure in 'de-afferented' animals is probably due to avoidance of sequestration of blood in the gastro-intestinal veins by maintenance of normal venomotor tone (Korner, 1965*a*, *b*), despite abolition of reflex activity, and consequent avoidance of secondary changes in the capacity vessels of the less susceptible beds.

Reflex effects of arterial hypoxia. The present experiments indicate that the primary source of reflex control of the peripheral circulation comes

from the receptors of the carotid sinus and aortic arch region, probably mainly the arterial chemoreceptors (Korner, 1965*a*). The portal and renal vascular beds are the main sites of reflex vasoconstriction, but there are no apparent vasomotor effects in the limb skin and muscle beds, since the responses of the latter are similar in normal and 'de-efferented' animals.

The portal and renal vasoconstriction is well sustained during hypoxia, with a maximal effect during the early part of the treatment period. In the kidney the vasoconstriction is neurally mediated (Korner, 1963), and this probably applies also to the portal bed, since the small secretion rate of adrenaline in this type of hypoxia (Fukuda & Kobayashi, 1961) is unlikely to contribute greatly to vasoconstriction in this bed (Greenway & Lawson, 1966). The gastro-intestinal circulation must play an important part in the vasoconstriction of the portal bed, since the splenic + pancreatic component of portal blood flow is probably smaller in the rabbit than the value of 15% observed in the dog (Sapirstein, 1958). The present findings in unanaesthetized rabbits are at variance with the inability to sustain vasoconstriction in the isolated intestinal circulation of anaesthetized animals during direct and reflex sympathetic nerve stimulation ('autoregulatory escape' phenomenon—Folkow, Lewis, Lundgren, Mellander & Wallentin, 1964; Cobbold, Folkow, Lundgren & Wallentin, 1964; Dresel & Wallentin, 1966; Wallentin, 1966). It seems likely that a more reactive vasculature rather than species differences accounts for the difference in response.

TABLE 3. Average control values and 'steady-state' values during arterial hypoxia in normal rabbits, 'de-efferented' rabbits, and 'de-afferented' animals. Control cardiac output and peripheral blood flow are assumed to be the same in all preparations (Chalmers *et al.* 1967*a*, *b*), and changes in cardiac output during arterial hypoxia represent the mean effect of previous series (Korner, 1965*a*; Korner & White, 1966; Chalmers *et al.* 1966).

		'Steady-state' arterial hypoxia		
Flow (ml./min)	Control all groups	Normal	'De-effe-rented'	'De-affe-rented'
Cardiac output	600	600	600	650
Portal blood flow	100	70	175	200
Renal blood flow	120	90	115	120
Total body muscle	202	195	170	180
Total body skin	68	81	58	58
Other regions	110	164	82	92

Although there is no net vasomotor activity in muscle, previous analysis has shown that this is the result of a number of opposing factors, comprising on the one hand a well sustained neurally mediated vasoconstriction, and on the other vasodilatation due to local factors, and due to the β-adrenergic effects of adrenaline, the latter being quantitatively more important (Chalmers *et al.* 1966). In the skin the vasodilator response is

due to local effects, as a result of central inhibition of vasoconstrictor tone (Chalmers & Korner, 1966). During reflex activity in severe arterial hypoxia the increased sympathetic constrictor nerve discharge to the peripheral circulation appears to be distributed over most but not all the peripheral vascular beds, increasing to kidney, portal bed and muscle (where it is 'inhibited' peripherally by adrenaline), but decreasing in skin. The vasoconstrictor effects in the intact animal are effective in distributing the blood flow to the cerebral and coronary beds ('other regions' in Table 3), whilst in animals without adequate reflex control the viscera are perfused at the expense of the more vital regions despite maintenance of a relatively normal cardiac output.

We are grateful to Mrs A. LeCouteur, Miss J. Oliver, Mrs R. Mather, D. Starr, G. Langsford and W. Ward for their assistance with the experiments. We are indebted to Dr H. T. Goodman of Johnson & Johnson (A'sia) Pty. Ltd. for supplying the methyl 2-cyanoacrylate and isobutyl acrylate, and to Dr V. Balmer of Ciba Ltd. for supplying the guanethidine sulphate used in these experiments. This work was supported by grants-in-aid from the Life Insurance Medical Research Fund of Australia and New Zealand, the National Heart Foundation of Australia, and the Australian Research Grants Committee.

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