J. Physiol. (1967), **192**, *pp.* 549–559
With 5 text-figures
Printed in Great Britain

DISTRIBUTION OF PERIPHERAL BLOOD FLOW IN PRIMARY TISSUE HYPOXIA INDUCED BY INHALATION OF CARBON MONOXIDE

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(*Received* 7 *April* 1967)

SUMMARY

1. The effects of primary tissue hypoxia induced by the inhalation of small concentrations of carbon monoxide in air on the distribution of blood flow in the portal, renal, muscle and skin beds have been studied in normal unanaesthetized rabbits, in animals without functioning autonomic effectors ('de-efferented' rabbits) and in animals with section of the carotid sinus and aortic nerves ('de-afferented' rabbits).

2. The pattern of blood flow distribution during CO hypoxia was similar in 'de-efferented' and 'de-afferented' animals, suggesting that the effects in the latter were determined by local mechanisms. The susceptibility of the various beds to the local dilator effects of CO hypoxia was markedly different, the greatest dilator effects being observed in the portal bed, followed by skin, kidney, and muscle. The pattern is somewhat different from that observed in arterial hypoxia.

3. In this type of hypoxia the arterial baroreceptors are probably the main afferent source of reflex activity. In normal animals reflex constrictor effects affect the portal and renal beds most, 'moderating' the local dilator effects of hypoxia in these beds. In muscle there is vasodilatation, probably the result of adrenaline secretion, but the response in skin is largely determined by the local effects of hypoxia. The total orthosympathetic activity evoked in this type of hypoxia appears to be less than in severe arterial hypoxia.

INTRODUCTION

In primary tissue hypoxia produced by inhalation of small concentrations of carbon monoxide in air, the arterial P_{O_2} remains normal but tissue hypoxia occurs as a result of reduction in oxygen carrying capacity of the arterial blood (Korner, 1959). The general circulatory effects differ from

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those of arterial hypoxia, mainly owing to differences in the primary source of reflex activity in each type of hypoxia. This is evoked through the arterial baroreceptors in primary tissue hypoxia, but through the chemoreceptors in arterial hypoxia (Korner, 1965*a*).

This paper describes the effects of inhalation of CO in air on the blood flow in the portal, renal, muscle and cutaneous beds of unanaesthetized rabbits. The role of reflex and local factors has been examined by contrasting the responses of normal animals with intact reflexes, with those of 'de-efferented' animals without functioning autonomic effectors. Comparison of the results of these two groups with findings in animals with section of the carotid sinus and aortic nerves permits evaluation of the role of the arterial baroreceptors in the response.

METHODS

New Zealand White rabbits cross-bred with the New Zealand Giant strain (mean body weight 2·6 kg; range 2·1–3·4 kg) were used in these experiments. The three groups studied were: (1) normal animals with intact reflexes; (2) 'de-efferented' animals following bilateral adrenalectomy, and sympathetic nerve block and depletion of tissue catecholamines after prolonged treatment with guanethidine, and administration of atropine on the day of the experiment; (3) 'de-afferented' animals with section of the carotid sinus and aortic nerves. Details of all preparations have been described elsewhere (Korner, 1965*b*; White, 1966; Korner & White, 1966; Chalmers, Korner & White, 1967*a*). The methods for measuring blood flow using local thermodilution techniques and Hatfield skin disks were as described by Chalmers & Korner, 1966; Chalmers, Korner & White, 1966; White, Chalmers, Hilder & Korner, 1967. Each experiment consisted of a control period of 16 min (breathing room air), a treatment period of 41 min (breathing 0·2 % + CO + 21 % O_2 + N_2), and a recovery period of 13 min (breathing room air) or of 43 min in some animals. The timing of the various measurements, and the statistical analysis of the results were as described in the accompanying paper (Chalmers *et al.* 1967*b*).

In two normal and two chronically adrenalectomized animals, maintained on cortical hormone replacement therapy, with implanted iliac vein catheters the effectiveness of guanethidine sympathetic nerve block to the limb was examined under chloralose-urethane anaesthesia (initial dose: chloralose 50 mg/kg + urethane 400 mg/kg I.V. supplemented with urethane 80 mg/kg I.V. after 60–90 min). The abdomen was opened, the left lumbar sympathetic chain exposed and cut at about L 3. The distal end was placed on platinum electrodes and stimulated using rectangular pulses of 500 μsec duration, 7·5 V amplitude, and frequencies ranging from 1 to 20/sec, and the effects on total limb blood flow were examined. Two rabbits were studied before and after injection of a single dose of guanethidine sulphate (Ismelin, Ciba) 12·5 mg/kg I.V., and two others after 5 days treatment with guanethidine sulphate at the usual dose of 12·5 mg/kg.day I.V.

RESULTS

Effects of carbon monoxide in normal animals. Inhalation of 0·2 % CO + 21 % O_2 produced a severe degree of tissue hypoxia, as estimated from reduction of the mixed venous P_{O_2} in seven normal rabbits from its normal value of 39 to 14 mm Hg (Table 1). The mean circulatory findings are

summarized in Fig. 1, and show that there was significant reduction in arterial pressure and in the renal blood flow ($P < 0{\cdot}001$), no significant change in ear flow, and hyperaemia in limb skin ($P < 0{\cdot}001$). The mean effects in portal blood flow were not statistically significant, and the average

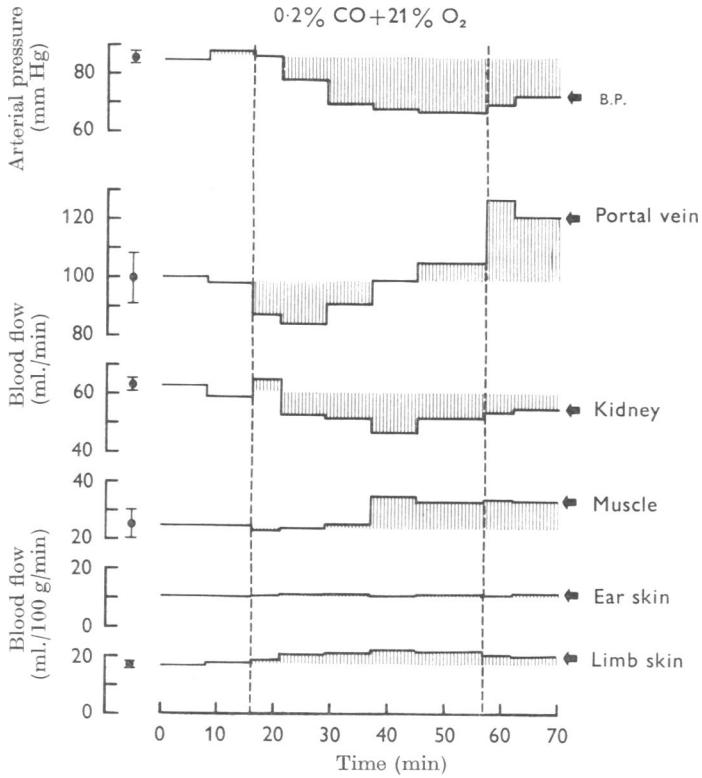

Fig. 1. Mean effects of severe primary tissue hypoxia induced by inhalation of 0·2 % CO + 21 % O_2 in seven normal rabbits on ear artery pressure (mm Hg), portal vein blood flow (ml./min), renal blood flow (ml./min), muscle blood flow (ml./100 g/min), ear and limb skin blood flows (ml./100 g/min). Hatching 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).

response in muscle blood flow of border-line significance ($P = 0{\cdot}05$), owing to greater variation in the responses of these regions between different animals (Fig. 2). In four rabbits, in which the venous P_{O_2} fell to 14–15 mm Hg, there was a small decrease in portal flow and marked hyperaemia in muscle (Fig. 2, left panel); in one rabbit with a mixed venous P_{O_2} of 16 mm Hg, neither portal nor muscle blood flow changed from their control values during CO hypoxia; in two rabbits, in which the mixed

venous P_{O_2} fell to 12 mm Hg, there was a large increase in portal blood flow, but reduction in muscle blood flow during the early part of the treatment period (Fig. 2, right panel). The circulatory effects in the latter group were associated with more profound arterial hypotension than in animals in which the portal blood flow either decreased or remained unchanged (Fig. 2).

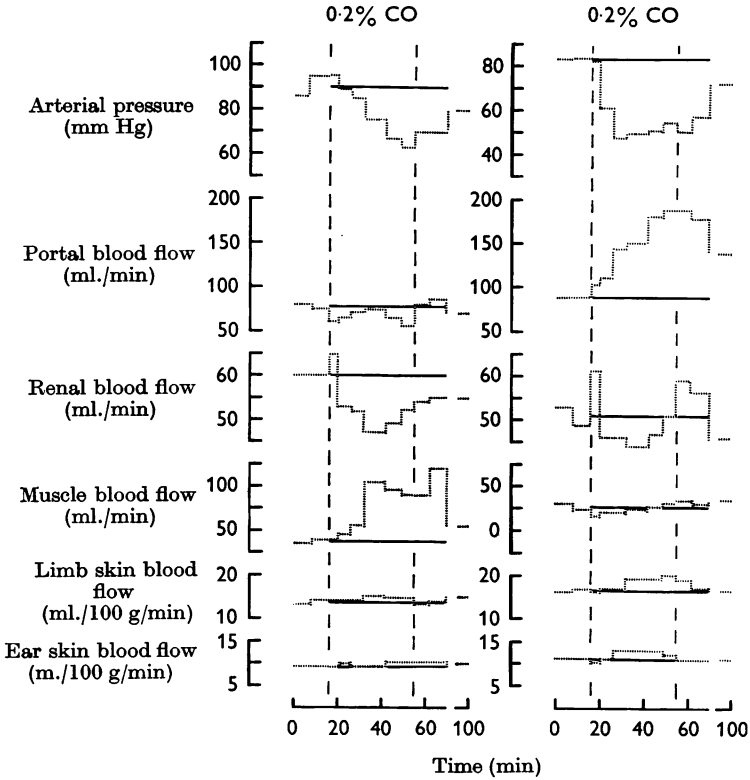

Fig. 2. Effects of severe primary tissue hypoxia induced by inhalation of 0·2 % CO + 21 % O_2 (between the vertical interrupted lines) in two different normal rabbits on ear artery pressure (mm Hg), portal vein blood flow (ml./min), renal blood flow (ml./min), muscle blood flow (ml./min), ear and limb skin blood flows (ml./100 g/min). The results show the variation in response that may occur in the portal and muscle vascular beds during this form of hypoxia. Details in text.

There was no significant change in respiratory minute volume, nor in arterial P_{O_2}, P_{CO_2} and pH, as expected in this type of hypoxia (Korner, 1965*a*), and there was a small but significant increase in heart rate (Table 1).

Effects of carbon monoxide in 'de-efferented' animals. Inhalation of 0·2 % CO + 21 % O_2 resulted in the same reduction in mixed venous P_{O_2} in three 'de-efferented' rabbits as in normal animals (Table 1). The circulatory response was uniform and consisted of a fall in blood pressure, a

striking increase in portal blood flow, no significant change in cutaneous blood flow, and reduction in kidney and muscle blood flow (Fig. 3, left panel). The blood flow pattern during CO hypoxia thus differs considerably from that observed in normal animals. The most striking difference in calculated vascular resistance between the two groups was the greater fall in the portal bed during hypoxia in 'de-efferented' animals (Fig. 4, left panel; Table 2). In the limb skin the calculated vascular resistance fell

TABLE 1. Results of heart rate and ventilation (l./min) in seven normal, three 'de-efferented' and three 'de-afferented' rabbits with section of the carotid sinus and aortic nerves; before, during and after inhalation of 0·2 % CO in air. Measurements of ventilation during the control period 16 min (C_1) and 8 min (C_2) before hypoxia; during treatment period 5 min (T_1), 13 min (T_2) and 38 min (T_3) after commencing inhalation of test gas; and 5 min (R_1) and 13 min (R_2) after resuming inhalation of air. Results given as mean ± S.E. of mean of a single time interval based on within animal comparisons. Blood analyses carried out at times C_1 and T_3 and given as mean ± S.E. of mean based on within animal comparisons

	Group							
	C_1	C_2	T_1	T_2	T_3	R_1	R_2	S.E.
Normal (7)								
H.R./min	288	282	300	302	300	306	310	±5·4
Ventilation (l./min)	0·99	1·08	1·10	1·00	1·04	1·10	1·08	±0·05
Arterial P_{O_2}	98	—	—	—	95	—	—	±1·3
Arterial P_{CO_2}	32	—	—	—	29	—	—	±1·2
Arterial pH	7·45	—	—	—	7·47	—	—	±0·01
Mixed venous P_{O_2}	39	—	—	—	14	—	—	±2·1
'De-efferented' (3)								
H.R./min	221	223	227	223	218	213	221	±4·6
Ventilation (l./min)	1·38	1·31	1·19	1·45	1·41	1·29	1·27	±0·17
Arterial P_{O_2}	94	—	—	—	93	—	—	±0·17
Arterial P_{CO_2}	30	—	—	—	26	—	—	*
Mixed venous P_{O_2}	38	—	—	—	15	—	—	±2·3
'De-afferented' (3)								
H.R./min	307	306	300	292	295	299	306	±4·9
Ventilation (l./min)	1·18	1·14	1·16	1·07	1·09	1·16	1·13	±0·04
Arterial P_{O_2}	95	—	—	—	87	—	—	±3·5
Arterial P_{CO_2}	31	—	—	—	31	—	—	±3·3
Mixed venous P_{O_2}	28	—	—	—	14	—	—	*

* Results obtained in only one animal.

more in the normal group, and in the renal bed it changed relatively little in either group (Fig. 4, left panel; Table 2). However, in muscle there was a marked difference between normal and 'de-efferented' rabbits, the calculated vascular resistance decreasing slightly in the former, but increasing significantly to 128 % of control in the latter group.

The increase in vascular resistance of muscle in 'de-efferented' rabbits was not expected, since no neurally mediated vasoconstriction seemed possible in these animals in view of the duration of treatment with guanethidine, and secretion of other constrictor substances seemed unlikely. Tests of completeness of the sympathetic block to hind limb and muscle vessels in anaesthetized rabbits following injection of a single dose

of guanethidine, and after a 5-day course of the drug (Fig. 5) indicate that the block was complete at physiological rates of sympathetic discharge.

There were no significant changes in heart rate in the 'de-afferented' group and the respiratory findings were the same as in normal animals (Table 1).

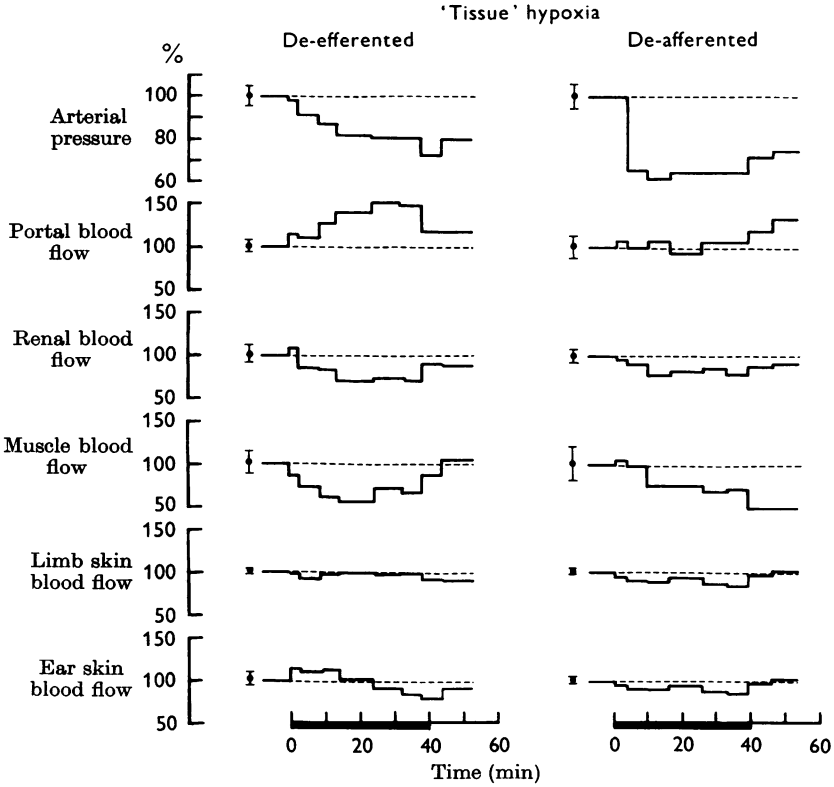

Fig. 3. Mean effects (expressed as % of control) on arterial pressure, and blood flow in portal, renal, muscle, limb and ear skin in three 'de-efferented' rabbits (left panel), and three 'de-afferented' rabbits (right panel). Primary tissue hypoxia was induced from 0–41 min shown by the black bar on each abscissa. S.E. of mean of a 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' animals.

Effects of carbon monoxide in 'de-afferented' animals. The control arterial pressure of rabbits with section of the carotid sinus and aortic nerves is higher than in 'de-efferented' animals (Chalmers *et al.* 1967*b*), accounting for the relatively larger fall in arterial pressure during CO hypoxia in three 'de-afferented' rabbits (Fig. 3). The blood flow remained unchanged during treatment in the portal bed but decreased slightly in skin and kidney, and more markedly in muscle (Fig. 3, right). The fall in calculated

vascular resistance was significantly greater than normal in portal and renal beds (Fig. 4, right panel; Table 2), and did not differ significantly from normal values in skin and muscle. The reduction in portal vascular resistance was the same as in 'de-efferented' rabbits during hypoxia, but in all other beds the calculated vascular resistance decreased further in

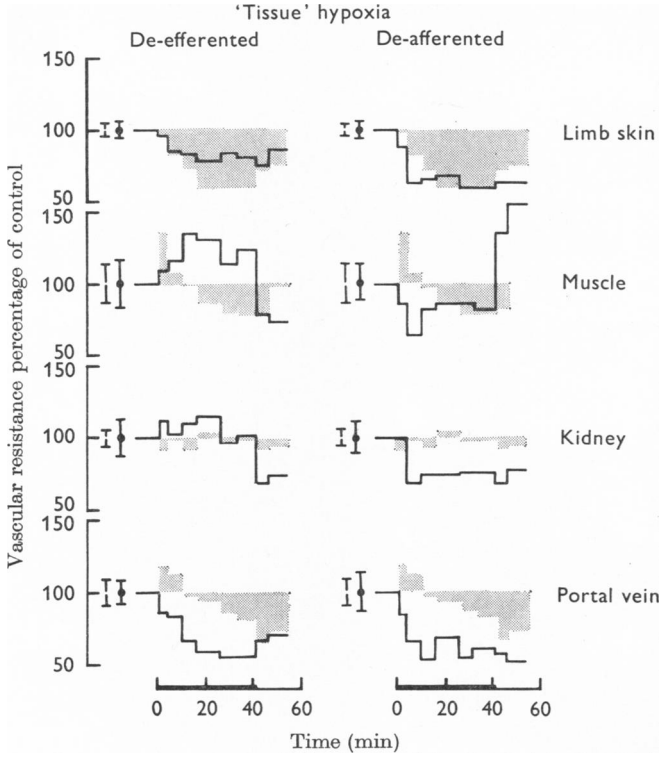

Fig. 4. Mean effects (expressed as % of control) on vascular resistance of limb skin, muscle, kidney and portal bed in three 'de-efferented' rabbits (left panel) and three 'de-afferented' rabbits (right panel). Results in each group are drawn as solid lines superimposed on the response of normal rabbits (shading). Notation as in Fig. 3.

the 'de-afferented' group (Fig. 4; Table 2), reflecting probably their higher resting vascular tone (cf. Chalmers *et al.* 1967*b*). As estimated from the changes in calculated vascular resistance, the portal bed was most susceptible to the dilator action of hypoxia, followed by the skin, kidney and muscle beds (Fig. 4; Table 2).

CO hypoxia did not produce significant effects on respiration and heart rate in these animals, and the reduction in mixed venous P_{O_2} was the same as in the other groups.

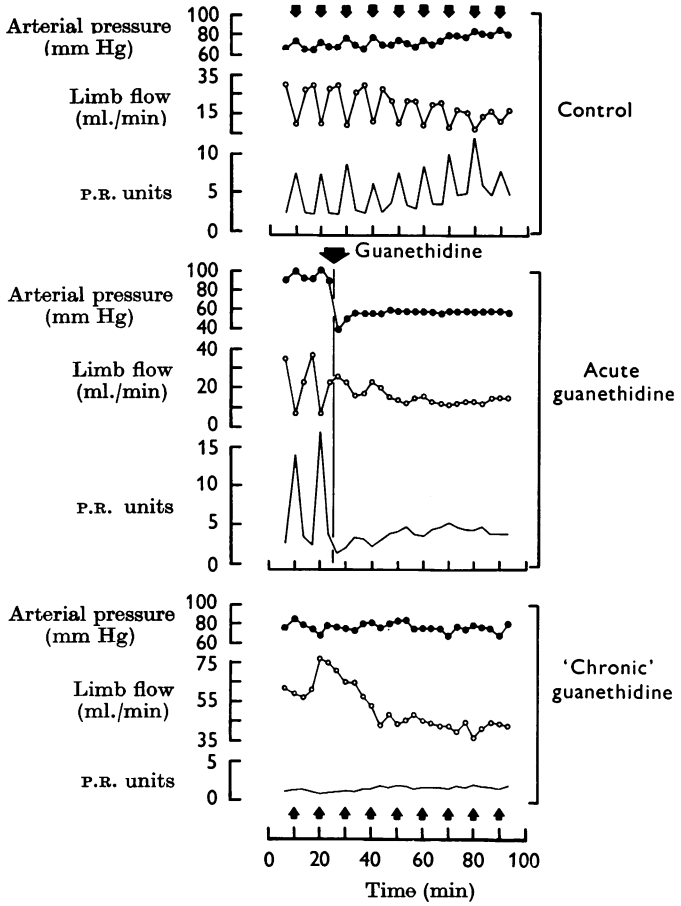

Fig. 5. Effects of electrical stimulation of the lumbar sympathetic chain on arterial pressure (mm Hg), total hind-limb flow (ml./min) and hind-limb vascular resistance in anaesthetized animals. Upper panel: normal rabbit; middle panel: adrenalectomized rabbit before and after a single dose of guanethidine sulphate 12·5 mg/kg I.V.; lower panel: adrenalectomized rabbit following 5 days of guanethidine sulphate 12·5 mg/kg.day I.V. Stimulus parameters: 10 c/s, 500 μsec, 7·5 V. Stimulation occurred at the arrows.

TABLE 2. Mean vascular resistance values (% of control) in the portal, kidney, skin and muscle beds for normal, 'de-efferented' and 'de-afferented' rabbits in the 'steady state' during inhalation of 0·2% CO in air. S.E. for difference between respective means are also given

Group: N = normal; D.E. = 'de-efferented'; D.A. = 'de-afferented'

Vascular bed	Normal	'De-efferented'	'De-afferented'	±S.E. N–D.E.	±S.E. N–D.A.	±S.E. D.E.–D.A.
Portal	89	59	59	6·3**	8·4**	8·1 (N.S.)
Kidney	97	106	75	7·2 (N.S.)	6·5**	8·7**
Skin	66	84	66	3·6**	3·9 (N.S.)	4·5**
Muscle	86	128	88	11·2*	10·5 (N.S.)	11·2**

** $P < 0.01$; * $P \leqslant 0.05$. N.S. = not statistically significant.

DISCUSSION

Local effects of CO hypoxia. The experiments suggest that the local dilator effects of primary tissue hypoxia are the chief determinants of the responses of the 'de-afferented' as well as the 'de-efferented' animals, since the relative susceptibility to hypoxia is the same in both groups. Vasodilatation is greatest in the portal bed, followed by skin, kidney and muscle. The susceptibility of the different beds to the local dilator effects of primary tissue hypoxia differs somewhat from those of arterial hypoxia. In both types of hypoxia the effects are greatest in the portal bed, and least in muscle. With CO hypoxia there is more pronounced vasodilatation in limb skin than in kidney, while the reverse obtains during arterial hypoxia. The reason for the difference is not clear: it does not depend on the differences in P_{CO_2} between the two types of hypoxia since it is maintained in 'de-afferented' rabbits in which the P_{CO_2} is the same in each type of hypoxia; the somewhat greater severity of CO hypoxia (estimated from reduction of the mixed venous P_{O_2}) may contribute to the apparently different susceptibilities (cf. Chalmers *et al.* 1967*b*).

The paradoxical rise in calculated vascular resistance in muscle in 'de-efferented' animals is not due to incomplete sympathetic nerve block by guanethidine. A possible explanation of this effect has been discussed in the accompanying paper (Chalmers *et al.* 1967*b*). Briefly, in such animals there is a progressive reduction in central venous pressure (Korner & White, 1966), due probably to sequestration of blood in the portal bed. This would lead to reduction in venous calibre and increased venous resistance to flow in muscle, the bed least susceptible to the local arteriolar dilator action of hypoxia.

Reflex effects of CO hypoxia. The experiments demonstrate that reflex activity is evoked in this type of hypoxia from the receptors of the carotid sinus and aortic arch regions, probably the arterial baroreceptors (Korner, 1965*a*). The most striking effects of reflex constrictor activity are seen in the portal bed and kidney. Although there is no increase in the vascular resistance in these beds, reflex activity 'moderates' the large local dilator effects. In the portal bed reflex constrictor effects are clearly evident in only about 70% (5/7) animals, whilst the massive portal dilatation in the remainder is indistinguishable from the effects in 'de-efferented' animals (Fig. 2). Possibly the greater severity of tissue hypoxia in the latter group overwhelms through its local action the constrictor effects of reflex orthosympathetic activity. Sympathetic nerve activity has been shown previously to play a part in the maintenance of the renal circulation during CO hypoxia, and its effects are potentiated by reflexly released adrenaline (Korner, 1963; 1967). The portal constrictor response probably has a similar basis.

In animals with the most adequate maintenance of the portal vascular resistance there is always a large increase in muscle blood flow. Since the local effects of hypoxia on this bed are small (cf. Haddy, 1966; Ross, Kaiser & Klocke, 1964) the increase in muscle blood flow is probably an 'active' vasodilatation owing to the β-adrenergic effects of reflexly secreted adrenaline, as described in the rabbit during arterial hypoxia (Chalmers *et al.* 1966).

There is little active constrictor control of the limb skin circulation probably owing to the opposing effects of strong local vasodilatation and somewhat weak neural discharge. In the rabbit and cat the skin vessels are relatively insensitive to the constrictor effects of adrenaline (Öberg, 1964; Chalmers *et al.* 1966), and less potentiation of neural constrictor activity would be expected in this bed than in the renal and portal beds.

The present findings suggest that in severe primary tissue hypoxia the total orthosympathetic discharge is relatively weak. Since the amount of adrenaline secreted is greater than in arterial hypoxia (Fukuda & Kobayashi, 1961; Korner & White, 1966), the sympathetic neural discharge must be considerably smaller. It seems likely, in view of the severity of tissue hypoxia and the magnitude of the arterial hypotension, that stimulation of sympathetic activity through the baroreceptors is nearly maximal (Heymans & Neil, 1958). The total orthosympathetic activity evoked in the rabbit during arterial hypoxia by strong stimulation of the arterial chemoreceptors is greater, as judged by the better maintenance of total peripheral resistance (Korner & White, 1966), and the larger regional constrictor effects (Chalmers *et al.* 1967*b*).

We are grateful to Miss J. Oliver, Mrs A. LeCouteur, Mrs R. Mather, D. Starr, G. Langsford and W. Ward for their assistance with the experiments. The work was supported by grants-in-aid from the National Heart Foundation of Australia, the Life Insurance Medical Research Fund, and the Australian Research Grants Committee.

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