Spinal cord blood flow in dogs¹

2. The effect of the blood gases

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SUMMARY The effect of CO₂ on the spinal cord blood flow was investigated in nine dogs. The flow was closely correlated with the paCO₂ and at about 85 mmHg was double the normocarbic flow. The effect of pO₂ was studied in a further nine dogs. Hypoxia markedly increased the flow which was maximal at paO₂ 30-40 mmHg. The vasoconstrictor effect of hypocarbia was absent or decreased in hypoxia. The response of the cord vessels to the blood gases was very similar to that of the brain.

The effects of blood gases on the cerebral circulation have been studied extensively (Harper, 1965, 1969 for reviews). It is accepted that the cerebral blood flow (CBF) is increased in hypercarbia and decreased in hypocarbia. Hypoxia also increases CBF. The effect of these blood gases on the spinal cord blood flow (SCBF) has been studied by relatively few workers. Wüllenweber (1968) and Palleske and Herrmann (1968) have studied the SCBF, using heat clearance techniques. Flohr, Brock, Christ, Heipertz, and Pöll (1969) and Smith, Pender, and Alexander (1969) have investigated the effects of carbon dioxide (CO₂) on the spinal circulation. This paper presents the results of investigations into the effect of paCO₂ and paO₂ on SCBF.

METHODS

Eighteen unselected dogs were used in the experiments, nine being used to study the effects of paCO₂ on SCBF and nine to study the effects of paO₂. For the studies with CO₂, anaesthesia was induced with thiopentone (25 mg/kg) and maintained on 70% nitrous oxide/oxygen mixture and either 0.5-1% trichlorethylene or 0.5% halothane. For the studies with hypoxia, anaesthesia was induced with pentobarbitone (25 mg/kg) and maintained with 70% N₂O/O₂ mixture. The anaesthetic-gas mixture was delivered through a Palmer pump

with ventilation adjusted to maintain normocarbica during surgical preparation and measurements. End tidal CO₂ concentration was monitored with an infra-red analyser.² The inspired oxygen concentration was measured with an oxygen analyser.³ A femoral artery was cannulated and mean arterial blood pressure (BP) measured with a damped mercury manometer. This cannula also allowed collection of arterial samples for blood gas analysis. During each blood flow estimation, blood pH, pCO₂, and pO₂ were measured using standard electrodes.⁴ Any base deficit was corrected with 8.4% sodium bicarbonate. The packed cell volume (PCV) was measured using the microhaematocrit method and the result used in the selection of λ (tissue/blood partition coefficient).

Pharyngeal temperature was measured with a mercury thermometer and heating lamps were used to maintain the temperature between 37-38°C.

Dorsal laminectomies were performed to expose the required spinal cord segments (T12 and T13) with the dura mater intact. Hypercarbia was produced by adding CO₂ to the inspired gases until the capnograph showed a constant inspired concentration of 7-9%. Hypocarbia was produced by hyperventilation (increase in pump volume/same rate) until the end tidal CO₂ concentration was reduced to 3-4%.

Graded hypoxia was achieved by reducing the inspired oxygen concentration and increasing the N₂O to maintain a fixed total volume.

² Capnograph Godart.

³ Servomex Controls Ltd.

⁴ Radiometer Copenhagen.

¹ This work was performed at the Wellcome Surgical Research Institute, University of Glasgow.

After any alteration in any blood gas tension, at least 10 minutes elapsed before a blood flow estimation. The clearance of ^{133}Xe after direct injection into the spinal cord was monitored with an uncollimated scintillation counter, coupled through a ratemeter to a linear recorder. The recording was transposed onto semilogarithmic paper for calculation of $T_{\frac{1}{2}}$.

The blood flow was calculated from the formula:

$$\text{SCBF (ml./100 g/min)} = \frac{\lambda \times \log_e 2 \times 60}{T_{\frac{1}{2}}} \times 100$$

The technique for measuring the blood flow, the results at normoxia and normocarbica and the influence of certain anaesthetics have been fully described previously (Griffiths, 1972a). (It should be emphasized that the flows have been calculated from the slow component of biexponential clearances which accounted for 40% of curves. The other 60% were monoexponential.)

RESULTS

pACO₂ AND SCBF Spinal cord segments T12 and T13 in nine dogs were used to study the effects of

pCO₂ on SCBF when the paCO₂ was varied between 20 mmHg, and 140 mmHg. The influence of hypercarbia is presented in Table 1. Hypercarbia caused a significant increase in flow with both trichlorethylene and halothane anaesthesia, the significance being slightly greater with halothane. There was no significant difference between the hypercarbic flows using halothane and

TABLE 1
EFFECT OF HYPERCARBIA ON SCBF

Anaesthetic	Observations (no.)	pCO ₂ (mmHg) M ± SD	BP (mmHg) M ± SD	SCBF (ml./100 g/min) M ± SD
Trilene	17	38 ± 5.9	140 ± 12.32	16.9 ± 8.0
		66 ± 9.6	152 ± 11.49	29.8 ± 15.2*
Halothane	13	42.9 ± 4.6	114 ± 17.5	14.8 ± 4.0
		80 ± 21.4‡	121 ± 24.2	23.3 ± 9.8†

* P < 0.02.

† P < 0.01.

‡ P < 0.001.

FIG. 1. Percentage change in blood flow in response to changes in paCO₂ (nine dogs). The flow at paCO₂ 40 mmHg was taken as 100%.

FIG. 2. Percentage change in blood flow in response to hypoxia (nine dogs). The flow at paO_2 100 mmHg was taken as 100%.

in flow occurs reaching maximal levels at paO_2 of 30–40 mmHg. The change in absolute blood flow as a result of decreasing paO_2 is shown in six dogs (Fig. 3). When the percentage change in SCBF was plotted against blood oxygen satura-

tion the maximal flows occurred at a saturation of approximately 60% and the change in SCBF between 100% and 60% saturation was logarithmically correlated ($r = -0.811$, $P < 0.001$). Below 60% saturation, there was a decrease in the SCBF response. In one dog the paO_2 was lowered to 20 mmHg from normoxia (paO_2 165 mmHg) resulting in an 8% increase in flow. The paO_2 was then raised to 31.5 mmHg resulting in a 130% increase in flow from normoxia.

In four dogs the effect of hypocarbia coexistent with hypoxia was studied (Table 4). It is

TABLE 4
EFFECT OF COMBINED HYPOXIA AND HYPOCARBIA
ON SCBF

Dog	Run	SCBF (ml./100 g/min)	$PaCO_2$ (mmHg)	PaO_2 (mmHg)
40	1	15.2	42.5	134
	2	31.6	47	35
	3	18.2	26	22
	4	11.5	24.5	192
41	1	17	40	160
	2	39.2	36	31.5
	3	29.7	21.5	52
	4	12.6	27.5	162
44	1	13.4	38	168
	2	23.78	37	31.5
	3	24.8	20	22
	4	12.4	24	59
	5	6.7	21	138
45	1	14.6	45	163
	2	30	45	44
	3	19.1	20.5	56

FIG. 3. Absolute changes in blood flow in response to hypoxia in six dogs.

evident that the usual vasoconstrictor action of hypocarbia was absent or severely reduced in hypoxia. In all investigations, except one (dog 44, run 4), the hypoxic, hypocarbic flow was greater than the flow at normoxia and normocarbia. The effect of hypocarbia varied with the degree of hypoxia, having a greater vasoconstrictor effect with higher paO_2 levels.

DISCUSSION

It is apparent that CO_2 has a similar action on the SCBF as on the CBF. This similarity has been noted by previous workers. Wüllenweber (1968) using a heat clearance technique demonstrated an increase in SCBF to hypercarbia and Palleske and Herrmann (1968) using the same method confirmed these observations in pigs. The heat clearance technique allows only qualitative results but nevertheless demonstrates clearly the vasodilator effect of CO_2 .

Smith *et al.* (1969) presented quantitative results to demonstrate the increase in SCBF during hypercarbia and the decrease in hypocarbia. The present results confirm the previous publications and suggest that the flow response in the white matter of the cord is similar to that found in the cerebral cortex. Harper, Glass, and Glover (1961) showed that raising the paCO_2 from 30–70 mmHg doubled the cortical flow and in the present experiments a comparable response was obtained. The overall results (Fig. 1) suggest a continuous change in SCBF between pCO_2 20 and 80 mmHg and compare with Harper and Glass's (1965) results for CBF. These authors suggest an upper limit of paCO_2 above which no further increase in flow occurs. This is stated to be 80–90 mmHg. Increases in SCBF occurred for paCO_2 levels above these figures but the number of observations at extreme hypercarbia are too few to draw definite conclusions. The sensitivity of the cord vessels to paCO_2 has been investigated by Flohr *et al.* (1969) in cats, using a particle distribution method. They found a linear correlation between thoracic cord blood flow and paCO_2 ($r=0.5$) and an absolute sensitivity of 0.54 ml./100 g/min/mmHg. Smith *et al.* (1969) found areas of high and low sensitivity (0.617 and 0.154 ml./100 g/min/mmHg). The present results show a mean sensitivity of 0.36 ml./100 g/min/mmHg. The variations in

results probably depend to some extent on variations in experimental technique. It was apparent, however, in the present experiments that the sensitivity to paCO_2 could vary in the same dog under apparently constant conditions. There was no obvious evidence of the dichotomy observed by Smith *et al.* (1969). It would appear both from the present observations and from those of Smith *et al.* that on occasions only very small increases in flow occur which may not even exceed the coefficient of variation for the method. It has also been observed in the present experiments that these small increases may be followed by a much larger increment in a subsequent observation, even when the experimental conditions remain constant. It is possible that some of these very low sensitivities could be attributed to experimental errors.

Flohr *et al.* (1969), comparing the absolute sensitivity to paCO_2 in various areas of the central nervous system, suggest that it is related to the blood flow, being greater in areas with a high initial blood flow. In the present experiments an attempt was made to determine if the sensitivity of the thoracic cord to CO_2 was related to the flow at normocarbia. The greatest sensitivity to CO_2 was noted in the dog with the highest SCBF, at normocarbia (Table 3, dog 4) but this tendency was not seen in other dogs. A similar lack of correlation between flow and sensitivity in the thoracolumbar cord was demonstrated by Smith *et al.* (1969).

It is well known that hypoxia induces vasodilatation of the cerebral circulation resulting in an increased blood flow. It is important, however, to control ventilation to ensure that no concurrent hypercarbia occurs. In the hypoxic normocarbic situation, it has been shown by McDowall (1966) that below a paO_2 of 50 mmHg there is a sharp increase in CBF, and at 30 mmHg, the flow is about 120% greater than at normoxia. Haggendal and Johansson (1965) showed that CBF increased by about 100% when the arterial oxygen saturation was reduced from 90 to 20 or 30%. They suggested that hypoxia has a weaker dilator action on cerebral vessels than hypercarbia.

In the spinal cord Palleske and Herrmann (1968) have shown, qualitatively, the increase in SCBF accompanying hypoxia. This increase occurred even in the presence of decreasing

cardiac output and blood pressure. Flohr, Pöll, and Brock (1971) found no change in SCBF when the paO_2 was varied between 55 and 160 mmHg at normocarbica and normotension.

These results suggest that the effect of hypoxia on the spinal cord is very similar to that on the brain. The present experiments support this suggestion. The blood flow remains constant above a paO_2 of approximately 60 mmHg below which, there is a sharp increase in flow. It is suggested that hypoxia of paO_2 , 30–40 mmHg is equally effective as paCO_2 , 80–90 mmHg in causing spinal vasodilatation.

A feature shown in the present experiments, which has not been commented upon by other workers, is the decrease in SCBF, below a paO_2 of approximately 30 mmHg (saturation of approximately 60%). The reason for this is not obvious at present. In a minority of cases it was possibly due to hypotension developing. Although the blood pressure did not fall below the normal autoregulatory range, it has been shown that effective autoregulation is eliminated in hypoxia, both in the brain (Haggendal and Johansson, 1966; Freeman and Ingvar, 1968) and in the spinal cord (Griffiths, 1973b). In the other dogs, however, there was no significant decrease in blood pressure. It is probable that this decline in SCBF below paO_2 , 30 mmHg is quite genuine, as illustrated in the dog, where the paO_2 was initially reduced to 20 mmHg and then gradually raised.

It has also been clearly demonstrated in the present experiments that hypoxic vasodilatation takes precedence over hypocarbica vasoconstriction. The effect is graded, the vasodilatation being greater at lower oxygen tensions. A similar situation was found in goats (Alexander, Marshall, and Angoli, 1968), where the CBF increased with combined hypoxia and hypocarbica.

Flohr *et al.* (1971) have studied the effects of increasing hypoxia at hypercarbica. They found that the SCBF showed an increase at a higher paO_2 than at normocarbica. The threshold at hypercarbica was a paO_2 of about 70 mmHg.

It is interesting to contrast the response to paCO_2 and paO_2 . Whereas there is a continuous response to changes of paCO_2 , there is a definite threshold for paO_2 (approximately 60 mmHg)

above which large alterations in oxygen tension have no effect on flow.

The mechanism by which the blood gases alter the CBF has been investigated in some detail, particularly with respect to CO_2 . Evidence has been presented to suggest that paCO_2 acts on a brain-stem centre (Shalit, Reinmuth, Shimojyo, Lockhart, and Scheinberg, 1968). However, this is not widely accepted and most workers suggest that CO_2 acts directly on the cerebral vessels. Gotoh, Tazaki, and Meyer (1961) have demonstrated an increase in CBF when 35% CO_2 in air was applied locally to the cortex. It would appear that CO_2 also acts locally on the cord vessels as Kindt, Ducker, and Huddleston (1971) demonstrated the usual vasodilator response to CO_2 in cords subject to high cervical transection. Gotoh *et al.* (1961) also demonstrated a fall in CBF when 100% oxygen was applied locally to the cortex.

It is thought that one main factor affecting CBF is the extracellular pH of the brain around the arterioles (Lassen, 1968). CO_2 can diffuse rapidly from the blood through the vascular endothelium which acts as an effective barrier to hydrogen and bicarbonate ions. The tissue pH is, therefore, a function of the paCO_2 and tissue bicarbonate concentration. This hypothesis was outlined by Gotoh *et al.* (1961) and has been supported by other workers. Lassen, Wahl, Deetjen, Thureau, and Ingvar (1971) have demonstrated the changes in vessel diameter, as a result of periarteriolar injection of mock cerebrospinal fluid (CSF) at varying pH. Bicarbonate free fluid caused dilatation, whereas higher concentration of bicarbonate caused constriction.

It is known that in hypoxia there is an increase in tissue and CSF lactate and the lactate/pyruvate ratio (Kaasik, Nilsson, and Siesjö, 1968; Leusen, Weyne, and Demeester, 1968; Mines and Sørensen, 1969). This tissue lactate is thought to be the origin of the hydrogen ions causing vasodilatation.

It has also been demonstrated (Harper and Bell, 1963) that neither acute metabolic acidosis nor alkalosis produced by intravenous infusion of lactate or bicarbonate, at a constant paCO_2 , alters the CBF. Alteration of the pH of the CSF has been reported to have varying correlations with CBF. Skinkøj (1968) and Angoli (1968)

claimed a convincing correlation, whereas this was not found by McDowall and Harper (1968) and Plum, Posner, and Zee (1968). The reason for these discrepancies is not clear but several factors may have influenced results, such as the degree of acuteness of the pH change in the CSF or tissue damage, etc. These relationships have been discussed by Severinghaus (1968).

It would appear that the effect of the blood gases on SCBF is similar to the effect on CBF in both magnitude and direction and, in view of this and the other available information, it would be surprising if there were any major differences between the control of blood flow in either organ.

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