Spinal cord blood flow in dogs¹

1. The 'normal' flow

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SUMMARY The spinal cord blood flow has been measured in anaesthetized dogs using an inert radioactive gas (¹³³Xenon) clearance technique. The ¹³³Xe was placed in the cord by direct injection. This study has demonstrated that the flows obtained from the white matter are reproducible and that there is little variation in blood flow in the white matter between different thoracolumbar segments in the same dog. No difference was found in blood flow between dogs anaesthetized with halothane, trichlorethylene, or pentobarbitone.

In comparison with the brain, relatively little work has been devoted to the blood flow in the spinal cord. Field, Grayson, and Rogers (1951), using a thermocouple technique, were early workers in this field but certain of their results are at variance with current concepts. Several workers (Margolis, Griffin, Kenan, Tindall, Laughlin, and Phillips, 1957; Otomo, Wolbarsht, Van Buskirk, and Davidson, 1960) have used direct observation of the response of spinal pial vessels to various agents or measurement of the velocity of the flow using intravascular indicators. More recently, Palleske and Herrmann (1968) in pigs and Wüllenweber (1968) in the human have used heat clearance techniques to obtain qualitative information regarding spinal cord blood flow (SCBF).

As a result of increasing clinical interest in the spinal circulation, in both medical and surgical conditions, it has become evident that quantitative measurements of SCBF are necessary. Landau, Freygang, Roland, and Sokoloff (1955) and Flohr, Brock, Christ, Heipertz, and Pöll (1969) have developed techniques for single measurements of cord blood flow. Smith, Pender, and Alexander (1964) using an inert gas radioactive isotope clearance technique measured the flow in goats. This present study has been undertaken in dogs as a prelude to investigating the physiological control of the cord circulation.

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THEORY OF THE METHOD

The technique involved is based on the Fick principle, which states that, in the steady state, the quantity of an indicator taken up or released by an organ is the product of the blood flow and the arteriovenous difference of the indicator.

The indicator, ¹³³Xenon (¹³³Xe) dissolved in saline, is introduced into the cord by direct injection. Diffusion into the peri-injection site tissues will occur and the partial pressure of ¹³³Xe at a particular site will depend solely on diffusion and solubility. ¹³³Xe will diffuse into the capillaries and be removed by the blood flow, thus allowing further diffusion of indicator. It follows that the greater the blood flow, the faster will be the isotope clearance from the tissue. In a homogeneously perfused tissue the isotope will clear in a monoexponential manner but in a heterogeneously perfused tissue a bi-exponential or multiexponential clearance will be obtained, depending on the number of tissues with different flows present in the organ under study.

¹³³Xe is suitable for this technique because it is an inert, highly diffusible gamma-emitting isotope and is far more soluble in air than blood. On reaching the lungs, a high proportion is exhaled and any remaining isotope is so diluted that the effective arterial recirculation is nil. Thus only the clearance of the isotope from the tissues is monitored.

METHODS

Unselected dogs were used. In the majority, anaesthesia was induced with thiopentone (25 mg/kg) and maintained with a 70% nitrous oxide/oxygen mixture and 0.5-1% trichlorethylene or 0.5% halothane.

FIG. 1. Semilogarithmic plot of a monoexponential clearance curve.

In addition to these animals maintained on anaesthetic-gas mixtures, several dogs were also anaesthetized with pentobarbitone (25 mg/kg) and maintained on 70% N₂O/O₂. The anaesthetic-gas mixture was delivered through a Palmer pump with ventilation adjusted to maintain normocarbida during surgical preparation and measurements. End tidal carbon dioxide concentration was monitored continuously with an infra-red analyser.²

A femoral artery was cannulated and mean arterial blood pressure 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, pO₂ were measured using standard electrodes.³ Any base deficit was corrected with 8.4% sodium bicarbonate. The packed cell volume (PCV), was estimated by the microhaematocrit method (Fisher, 1962).

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 cord segments, with the dura mater intact.

Approximately 1–2 µl. ¹³³Xe dissolved in saline (activity 1 mC/ml.) was drawn into a Hamilton syringe, care being taken not to include air bubbles. (The actual amount injected was arranged to give a maximum count rate of 300/sec.)

The recording apparatus consisted of an uncollimated scintillation counter with a one inch (2.2 cm) sodium iodide crystal coupled through a ratemeter to a linear recorder. The count range was 0–300/sec, with a one second time constant. The paper speed was 2 cm per minute.

The scintillation counter was positioned 1 to 2 cm above the cord and the background count measured. The injection of ¹³³Xe was made obliquely into the mid-line through the intact dura mater. The clearance curve was recorded for 20 minutes or until the background count was reached. In certain measurements 0.2 µl. congo red was included in the syringe to identify the site of injection.

Approximately 20 minutes elapsed between measurements, during which time the dura mater was covered with a swab soaked in saline at 37°C.

ANALYSIS OF CLEARANCE CURVES After subtraction of background activity the clearance curves were transposed onto semilogarithmic paper. Those curves showing more than one component were analysed by compartmental analysis (Lassen, Høedt-Rasmussen, Sørensen, Skinhøj, Cronquist, Bodforss, and Ingvar, 1963) dividing them into fast and slow components. The blood flow was calculated from the formula:

$$\text{SCBF} = \frac{\lambda \times \log_e 2 \times 60}{T_2^1}$$

SCBF = spinal cord blood flow
(ml./100 g/min)

² Capnograph Godart.

³ Radiometer. Copenhagen.

where λ = partition coefficient: tissue/blood.
(This varies with the haematocrit (Veal and Mallett, 1965). The values for λ were considered to be the same as those obtained for grey and white matter in the brain.

$T_{\frac{1}{2}}$ = time in seconds for the activity to decrease to one half of the initial value and is calculated from the semilogarithmic plot.

RESULTS

Approximately 60% of clearances were mono-exponential. Figure 1 illustrates the semi-logarithmic plot of a monoexponential clearance and the site of the cord injection for this clearance is illustrated in Fig. 2. The remainder of the curves were biexponential (Fig. 3) and from these latter the fast component, or flow in the grey matter and the slow component, or white matter flow, were extracted (Fig. 4). The site of injection for the curve obtained in Fig. 3 is also illustrated in Fig. 2. (See discussion for the validity of these assumptions.)

Table 1 demonstrates the reproducibility of the flows in the white matter over a period of six hours in three dogs. (In each dog the runs not mentioned were used to investigate the effects of $p\text{CO}_2$ on flow.) The flows in Tables 1 and 2 have been corrected to a $p\text{aCO}_2$ of 40 mmHg (see discussion).

The results for a larger series are presented in Table 2. The mean blood flow in the white matter in eight dogs (25 observations) was 15.7 ± 6.6 ml./100 g/min.

FIG. 2. (Upper) Drawing of the cord from which the trace in Fig. 1 was obtained. (Lower) The cord from which the curve in Fig. 3 was obtained. The solid marking indicates maximum intensity of congo-red dye, while the hatched area demonstrates the maximum limits of the dye diffusion.

FIG. 3. The biexponential clearance curve obtained from the cord shown in Fig. 2 (lower).

TABLE 1
FLOWS IN WHITE MATTER (THREE DOGS)

Dog no.	Run	$p\text{CO}_2$ (mmHg)	SCBF	SCBF corrected to
				$p\text{CO}_2$ 40 mmHg (ml./100 g/min)
4	1	35.5	18.2	19.4
	3	32	19.1	21.0
	7	37	18.2	19.2
5	1	40	15.7	15.7
	2	36	12.4	13.4
	3	34.5	13.9	14.7
	7	42	11.21	10.8
13	1	48.5	12.75	11.48
	2	42	14.97	11.68
	3	46	11.17	10.39
	4	47	11.17	10.28

The mean deviation of each flow from the average at its site was 7.3% and 80% of measurements had a variation of less than 10% from the mean flow for the cord segment.

The variation in flow rates in the white matter between different thoracolumbar segments in the same dog was studied by injecting two segments and recording the clearance from each simultaneously. The segments were shielded from each other by lead. The results are presented in Table 3.

TABLE 2
BLOOD FLOW IN WHITE MATTER STANDARDIZED TO A $p\text{CO}_2$ OF 40 MM HG

Dog	Estimations (no.)	SCBF (ml./100 g/min) $M \pm SD$	Cord segment
3	3	13.8 ± 0.92	L ₁
4	3	19.8 ± 0.98	T ₁₃
5	4	13.6 ± 2.12	T ₁₃
6	4	15.2 ± 2.5	L ₂
7	3	29.4 ± 3.3	L ₃
9	2	11.1 ± 0.84	T ₁₂
10	2	11.25 ± 0.5	L ₁
13	4	10.95 ± 0.72	T ₁₃

A comparison of the effects of trichlorethylene, halothane, and pentobarbitone anaesthesia on the flow in the white matter was studied using segments T12 and T13 (Table 4). There was no significant difference in SCBF between dogs anaesthetized with any of the three methods. There was, however, a significant difference in mean arterial blood pressure between dogs anaesthetized with trichlorethylene or pentobarbitone and those anaesthetized with halothane ($P < 0.01$).

A much smaller number of estimations of the flows in fast component were made and the results are presented in Table 5. The mean blood

FIG. 4. The semilogarithmic plot of the curve in Fig. 3 demonstrating the fast and slow components.

TABLE 3
FLOWS IN WHITE MATTER AT DIFFERENT
SPINAL CORD SEGMENTS IN SAME DOG

Dog	Segments	Estima- tions (no.)	pCO ₂ (mmHg) M ± SD	SCBF (ml./100 g/min) M ± SD	P
22	T ₁₂	3	45.5 ± 3.2	9.2 ± 1.2	<0.05
	L ₃	3		20.5 ± 5.3	
23	T ₁₂	4	45.0 ± 4.9	16.7 ± 1.3	NS
	L ₂	4		15.0 ± 2.5	
24	T ₁₃	4	36.5 ± 1.6	14.92 ± 2.2	NS
	L ₄	4		17.6 ± 5.3	
32	T ₁₃	4	49 ± 7.8	23.4 ± 6.9	NS
	L ₃	5	52.0 ± 8.3	18.6 ± 3.8	

P = significance of difference in flows.
NS = not significant.

TABLE 4
COMPARISON OF SCBF, IN WHITE MATTER
USING TRICHLORETHYLENE, HALOTHANE, AND
PENTOBARBITONE AS ANAESTHETICS (SEGMENTS T₁₂/T₁₃)

Anaesthetic	Observa- tions (no.)	pCO ₂ (mmHg) M ± SD	SCBF M ± SD	BP (mmHg) M ± SD
Trichlorethylene (0.5–1%)	17	33 ± 5.9	16.9 ± 8.0	140 ± 12
Pentobarbitone (25 mg/kg)	14	40.6 ± 3.6	14.7 ± 5.3	138 ± 24
Halothane (0.5%)	13	42.9 ± 4.6	14.8 ± 4.0	114 ± 17

* P < 0.01.

flow, calculated from the fast component, for all the observations was 48.4 ± 23.7 ml./100 g/min, and this is significantly greater than the flow in the white matter (P < 0.001).

The mean deviation of each flow from the average at its site was 16% and 50% of clear-

TABLE 5
ESTIMATIONS OF FLOW IN FAST COMPONENT

Dog	Estima- tions (no.)	Blood flow calculated from fast component		Segment
		Arterial pCO ₂ (mmHg) M ± SD	SCBF (ml./100 g/min) M ± SD	
2	4	33 ± 1.4	86 ± 20	L ₅
3	1	37	85	L ₁
5	3	39 ± 3.0	31.5 ± 4.2	T ₁₃
6	3	35.3 ± 2.0	51 ± 8.8	L ₂
7	3	46 ± 1.0	84 ± 24	L ₃
19	1	36	74	L ₁
13	5	45.7 ± 2.0	26.7 ± 2.0	T ₁₃

ances had a variation of greater than 10% from the mean flow at the segment.

Figure 5 illustrates the failure of ¹³³Xe clearance after cardiac arrest, thus showing that the major part of the isotope clearance is by the bloodstream and not by diffusion into adjacent structures.

FIG. 5. This curve demonstrates the failure of ¹³³Xe clearance after cardiac arrest.

DISCUSSION

The anatomical identification of the fast and slow components of the clearance curve has been studied in relation to cerebral blood flow. There is good evidence that the slow component represents the flow in the white matter. Espagno and Lazorthes (1966) obtained a monoexponential slow clearance after injection of ^{133}Xe into the cerebral white matter. It has also been demonstrated by autoradiographic techniques that the slow component represents the flow in the white matter (Lassen, 1968). The flows obtained from monoexponential clearances in the present experiments were very similar to those obtained from the slow component in the same dog and the congo-red marking suggested that these monoexponential clearances resulted from an injection into the white matter (Figs 1 and 2). It has, therefore, been assumed, on reasonable evidence, that the monoexponential clearances and the slow component of biexponential clearances represent the flow in the white matter. Espagno and Lazorthes (1966) found that the slow component of the biexponential curves, after cortical injection, is faster than the monoexponential clearance after direct injection of deep white matter. They suggest that this faster flow arises from the subcortical white matter. In the present study there was no significant difference between the flows calculated from the slow component and those from monoexponential clearances recorded from the same dog.

It is known that alterations in paCO_2 affect the SCBF (Smith *et al.*, 1964; Flohr *et al.*, 1969; Griffiths, 1973a), and for this reason a correction must be applied when comparing flows at slightly varying paCO_2 . The change in blood flow in response to a change in paCO_2 was measured (Griffiths, 1973b) and, from this graph, the flows at normocarbica were corrected to a standard paCO_2 of 40 mmHg, as suggested by Harper, Glass, and Glover (1961). These corrections are illustrated in Table 1, which demonstrates how the flows may be under- or overestimated, if allowance is not made for variations in paCO_2 . This correction also allows valid comparison between the flows in different dogs (Table 2).

The results demonstrate that, in apparently identical situations, there is a marked variation

in flows between different dogs varying from approximately 10 ml./100 g/min to 30 ml./100 g/min. In spite of the wide range of flows between different dogs, the flows at one segment in the same dog were reasonably reproducible over a period of six hours in constant experimental conditions (Tables 1 and 2). Smith *et al.* (1964), in the goat, also found a marked variation in flows at the same segment, between different animals and, in distinction from the present study, found variations between lumbar and thoracic segments in the same animal. This discrepancy is probably due to the fact that the present author was measuring flow in the white matter, whereas Smith *et al.* (1964) were estimating the average cord blood flow, which takes into account flow in the grey matter.

Only one of four dogs in the present experiments showed a significant variation in the white matter flow between different segments of the cord (Table 3). Fieschi, Issacs, and Kety (1968) have shown that the blood flow is approximately the same in numerous areas of subcortical white matter and that it is homogeneously perfused, unlike the grey matter. It is, therefore, reasonable to suppose that there is constancy of flow through the white matter of all the thoracolumbar cord segments in the anaesthetized dog, as suggested in the present experiments.

It is known that in the anaesthetized animal the cerebral cortex is heterogeneously perfused in common with most areas of grey matter so far examined. This has been shown by beta clearance curves using Krypton⁸⁵ (Harper *et al.*, 1961) and autoradiography (Fieschi *et al.*, 1968). However, Harper and Jennett (1968) have shown a good correlation between the fast component of the gamma clearance curves and the average cortical blood flow measured by beta clearance. The fast component has been assumed to represent the flow in the grey matter, at the site of injection.

The flows in the grey matter are, as expected, significantly greater than those in the white matter. There has, however, been difficulty in obtaining reproducible results in the same dog under constant conditions. There are several possible reasons for this:

1. The initial portion of the clearance curve, which contains the fast component, could not be accurately recorded due to removal of the needle

from the cord and the ^{133}Xe remaining in the syringe affected the count rate.

2. There is the possibility of intercompartmental diffusion of ^{133}Xe , especially from white to grey matter, as discussed by Gillespie (1968).

3. As stated previously, the grey matter is heterogeneously perfused and the actual flow measured in these experiments would depend on the siting of the injection in the cord. It is, therefore, possible that if consecutive injections were placed so that clearances were obtained from different areas of grey matter the flows would not be the same.

Smith *et al.* (1964) surmounted this problem by calculating the average cord blood flow. They used a micromanipulator to ensure subsequent injections were made into the same area. The present author could not achieve consistent results by calculating the average blood flow and this is probably due to the fact that the injections were made freehand. Approximately 60% of all clearances were monoexponential and it would obviously not be possible to calculate the average blood flow in these cases. For these reasons it has been decided to study SCBF, in relation to the slow component and it has been found that this shows similar responses to changes in pCO_2 , pO_2 , and blood pressure, as are found in the brain (Griffiths, 1973a, b).

Perhaps one major criticism of the method is the necessity to inject the indicator into the spinal cord, thus causing at least some injury to the tissue.

The reasons for using a method utilizing intramedullary injection have been given by Smith *et al.* (1964). It is suggested that the degree of

trauma is insufficient to invalidate the results for a number of reasons:

1. There is the precedent of the direct injection technique to measure blood flow in muscle (Lassen, Lindbjerg, and Hunck, 1964) and brain (Espagno and Lazorthes, 1966) and in both situations the method has proved satisfactory.

2. Histological sections of the cords taken after six to eight injections into one segment revealed only small focal haemorrhages. The trauma at one area of the cord was minimized by moving the needle to different locations in the same segment for subsequent injections.

3. The results obtained in these experiments compare favourably with those obtained by other workers (Table 6).

4. It has been shown by this method that autoregulation is present in the spinal cord (Griffiths, 1973b) and as demonstrated by Reivich, Marshall, and Kassell (1969) and Fog (1968) autoregulation in the brain may be lost after trauma.

In order to ascertain whether any leakage of isotope along the injection tract occurred, any blood or cerebrospinal fluid (CSF) that accumulated on the dura mater in initial experiments, was removed but showed no radioactivity. Its removal did not result in any drop in count rate.

The choice of anaesthetic has been shown to affect cerebral blood flow (Landau *et al.*, 1955; McDowall, 1965; McDowall and Harper, 1965). McDowall, Harper, and Jacobson (1964) have shown that 0.4–0.9% trichlorethylene did not cause a significant alteration in cerebral blood flow compared with control values using light nitrous oxide anaesthesia. In a later study, McDowall (1967) showed that during the first 20 minutes of anaesthesia with 0.5% halothane, a flow increase of 16% occurred but after 20 minutes flows returned to control values. As no measurements were made in this present study until two hours after administration of 0.5% halothane, it is likely that the latter conditions apply. Landau *et al.* (1955) using a short acting barbiturate anaesthetic, thiopentone, noted no difference in SCBF in the white matter from values obtained in unanaesthetized cats. In this present study, using pentobarbitone, no significant difference was noted when compared with

TABLE 6
SUMMARY OF PREVIOUS QUANTITATIVE
INVESTIGATIONS OF SCBF

Author	Method	Species	SCBF (ml./100 g/min)	Area of cord
Landau <i>et al.</i> (1955)	Auto-radiography	Feline	14	White matter
Flohr <i>et al.</i> (1969)	Particle distribution	Feline	20.3 16.5 23.7	Cervical Thoracic Lumbosacral
Smith <i>et al.</i> (1969)	^{133}Xe clearance	Caprine	17.6	Lumbar

the two volatile anaesthetics. The difference in blood pressure in dogs anaesthetized with either trichloroethylene or pentobarbitone and those anaesthetized with halothane should not have influenced flows. It has been shown by Kindt (1971) and Griffiths (1973b) that changes in pressure over the range encountered in this study do not alter SCBF. To date no detailed studies have been made on the effect of anaesthetics on SCBF.

Finally, the method has proved straightforward and reliable in investigating physiological parameters influencing SCBF, in the experimental animal.

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