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Autoregulation of cerebral blood flow: influence of the arterial blood pressure on the blood flow through the cerebral cortex

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Until fairly recently it 'was believed that cerebral blood flow followed more or less passively the mean arterial blood pressure, and the stability of the cerebral circulation under physiological conditions reflected only the relative constancy of the arterial pressure maintained by the homeostatic pressor reflex mechanism' (Sokoloff, 1959). That there might also be an intrinsic regulation of cerebrovascular tone was suggested by Fog (1934, 1938) and by Forbes, Nason, and Wortman (1937). These workers observed that the blood vessels of the pia mater constricted in response to a rise in arterial blood pressure and dilated in response to a fall in pressure.

Although more recent studies in man (summarized by Lassen, 1959) seem to refute the idea of a passive pressure/flow relationship for the cerebral circulation, there is still conflict on the precise role of the arterial blood pressure in the control of the cerebral blood flow.

The experiments reported in this paper were undertaken to measure the effect of gradual reduction of the mean arterial blood pressure on the blood flow through the cerebral cortex under 'normal' respiratory conditions (that is a $PaCO_2$ of 40 mm. Hg) and under conditions of hypercapnia (CO_2 being added to the respiratory mixture).

METHOD

One hundred and seventeen measurements of blood flow through the cerebral cortex were made on 12 unselected mongrel dogs. The animals were anaesthetized with thiopentone. A cuffed endotracheal tube was inserted and connected to a Starling respiratory pump, through which a 4:1 mixture of N_2O and oxygen was delivered in open circuit. Suxamethonium chloride was administered at intervals. Repeated small doses of thiopentone were given during the actual operation. A cannula was inserted into the femoral artery and connected to a damped mercury manometer for the measurement of the systemic blood pressure. This cannula was also used for the withdrawal of arterial blood samples.

The thyroid branch of the common carotid artery was cannulated centripetally, the distal end being tied. The temporal muscle was excised and a trephine hole made over the perietal bone. A cruciate incision was made in the dura and the exposed brain cortex was covered with a plastic membrane (Melinex) 6μ in thickness. A thin lead shield was placed over the surrounding dura and bone, leaving exposed only the area of cortex covered by the membrane. An end window Geiger counter, mounted 1 mm. above the exposed cortex, was connected to a rate meter and a direct writing recorder. After the operation was completed, thiopentone administration was discontinued and the preparation remained undisturbed for one hour before the first measurements of blood flow were made. Plasma substitute (Dextran), saturated with 85 Krypton, was injected, rapidly at first and then more slowly, into the carotid artery over two to three minutes. The blood flow through the cerebral cortex was calculated from the half-life of the initial slope of a semi-logarithmic plot of the clearance curve using the formula of Lassen and Ingvar (1961), Ingvar and Lassen (1962). After each measurement of blood flow, blood samples were taken from the femoral artery for the measurement of $PaCO_2$ and *p*H on the micro-Astrup apparatus. Arterial oxyhaemoglobin saturation was measured at intervals on a Kipp haemoreflector. Pharyngeal temperatures were measured with a mercury thermometer.

The experiments were divided into two groups:

GROUP 1: BLOOD PRESSURE REDUCTION DURING NORMOCAPNIA The mean arterial blood pressure was gradually lowered in eight dogs by bleeding the animals into a reservoir flask. The $PaCO_2$ was held between 30 and 40 mm.Hg by adjusting the respirator.

GROUP 2: BLOOD PRESSURE REDUCTION DURING HYPERCAPNIA The PCO_2 was raised to, and maintained at, 68-86 mm.Hg (mean values) by adding carbon dioxide to the anaesthetic mixture in four dogs. The arterial blood pressure was then gradually lowered by bleeding them into the reservoir flask.

RESULTS

GROUP 1: BLOOD PRESSURE REDUCTION DURING NORMOCAPNIA The results are given in Table I and Figure 1. The mean initial blood pressure from

TABLE I

HYPOTENSION AT NORMOCAPNIA

Experiment No.	*Mean Arterial Blood Pressure (mm.Hg)*	*pH*	*pCO_2 (mm.Hg)*	*Blood Flow (ml./g./min.)*
B.1	165·0	7·32	32	0·90
	160·0	7·33	33	0·97
	150·0	7·33	32	0·99
	140·0	7·34	31	0·83
	130·0	7·32	32	0·88
	120·0	7·31	32	0·90
	105·0	7·29	33	0·92
	90·0	7·24	37	0·77
	52·5	7·18	30	0·71
	32·5	7·11	26	0·44
Mean and S.D.			31·8±2·8	
B.2	150·0	7·33	35	0·91
	135·0	7·25	34	0·73
	120·0	7·28	32	0·71
	125·0	—	—	0·76
	110·0	7·22	32	0·67
	90·0	7·20	29	0·77
	77·0	7·15	31	0·64
	57·0	7·00	31	0·43
	37·0	6·92	31	0·34
Mean and S.D.			31·9±1·9	
B.3	155·0	7·26	42	0·70
	150·0	—	—	0·74
	135·0	7·20	44	0·84
	110·0	7·15	41	0·86
	97·0	7·12	43	0·80
	95·0	7·14	41	0·70
	90·0	7·18	41	0·71
	83·0	7·15	43	0·66
	83·0	—	—	0·63
	75·0	7·16	41	0·57
	70·0	—	—	0·50
	65·0	7·13	42	0·52
	57·5	7·11	42	0·50
	50·0	7·09	41	0·49
	42·5	7·05	39	0·43
	35·0	6·98	36	0·28
	22·5	6·93	36	0·21
Mean and S.D.			40·9±2·4	
B.4	127·0	7·26	38	0·74
	130·0	7·27	38	0·73
	110·0	7·23	35	0·66
	80·0	7·22	34	0·57
	70·0	7·16	39	0·58
	60·0	7·11	39	0·51
	45·0	6·88	39	0·51
	40·0	6·83	41	0·48
	25·0	6·92	—	0·30
Mean and S.D.			37·9±2·3	
B.5	150·0	7·31	34	0·72
	155·0	7·33	32	0·72
	120·0	7·32	29	0·71
	105·0	7·32	28	0·59
	105·0	7·28	31	0·66
	92·0	7·27	30	0·46
	82·0	7·23	35	0·57
	72·0	7·22	33	0·49
	57·0	7·21	31	0·47
	42·0	7·19	32	0·46
	28·0	7·14	25	0·32
Mean and S.D.			30·9±2·9	
B.6	135·0	7·28	35	0·71
	155·0	7·30	36	0·83
	145·0	7·33	34	1·05
	135·0	7·33	33	0·87
	125·0	7·31	33	0·81
	112·0	7·29	32	0·85
	100·0	7·24	34	0·96
	90·0	7·22	35	0·96
	80·0	7·19	38	0·86
	60·0	7·17	37	0·85
	40·0	7·02	30	0·56
Mean and S.D.			34·3±2·3	
B.7	180·0	7·39	34	0·82
	170·0	—	—	0·83
	155·0	7·38	35	0·89
	130·0	—	—	0·82
	120·0	7·35	37	0·95
	100·0	—	—	0·91
	85·0	7·29	38	0·71
	60·0	—	—	0·52
	40·0	7·12	38	0·26
Mean and S.D.			36·4±1·8	
B.8	170·0	7·30	39	0·84
	155·0	7·32	37	1·18
	140·0	7·32	37	0·80
	125·0	7·30	37	0·98
	110·0	7·27	40	0·95
	100·0	7·26	44	0·95
	90·0	7·28	38	0·90
	80·0	7·27	39	0·98
	70·0	7·25	39	0·86
	62·5	7·21	37	0·84
	50·0	7·08	37	0·71
	35·0	7·02	37	0·63
	12·5	7·18	35	0·24
Mean and S.D.			38·2±2·2	

the experiments in this group was 155 mm.Hg. (The $PaCO_2$ was held within fairly narrow limits for each dog.) The mean $PaCO_2$ was 35·3 mm.Hg and the average standard deviation of $PaCO_2$ in individual dogs was 6·6%.

From Fig. 1 it can be seen that the blood pressure could be lowered to approximately 90 mm.Hg without any marked change in blood flow. At lower blood pressures, however, blood flow declined with blood pressure.

Over a fairly wide range of blood pressure (from 90 to 180 mm.Hg) the blood flow remained relatively constant, despite a varying blood pressure. This phenomenon will hereafter be referred to as 'autoregulation'.

GROUP 2: BLOOD PRESSURE REDUCTION DURING HYPERCAPNIA The results are given in Table II. A 'blanket' graph of all the results in this group is shown on Figure 2.

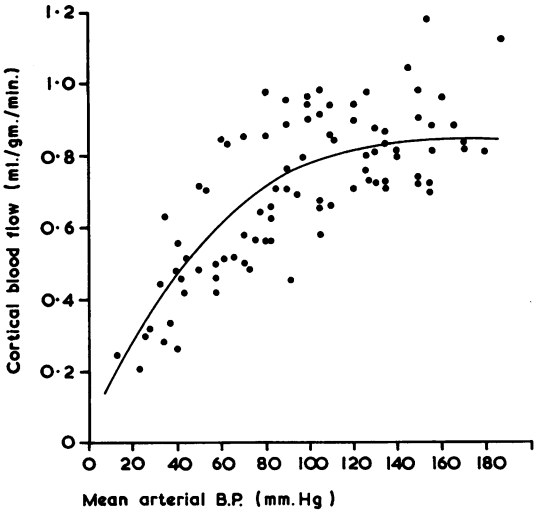

FIG. 1. *Response of cortical blood flow to changes in mean arterial blood pressure in normocapnic animals. Line is best polynomial fit.*

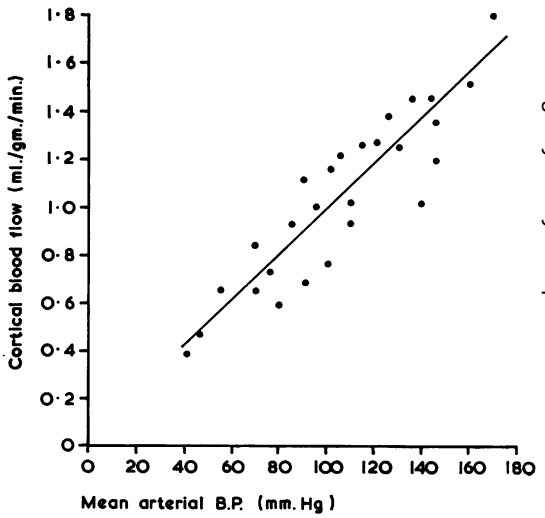

FIG. 2. *Response to cortical blood flow to changes in mean arterial blood pressure in hypercapnic animals. Line is calculated linear regression.*

TABLE II

HYPOTENSION AT HYPERCAPNIA

Experiment No.	*Mean Arterial Blood Pressure (mm.Hg)*	*pH*	*pCO_2 (mm.Hg)*	*Blood Flow (ml./g./min.)*
B.9	145·0	7·10	68	1·20
	140·0	7·00	70	1·02
	110·0	7·07	72	0·93
	100·0	7·05	71	0·76
	80·0	7·00	66	0·58
Mean and S.D.			69·4±2·4	
B.10	135·0	7·02	83	1·89
	120·0	7·02	83	1·28
	105·0	7·02	78	1·22
	100·0	6·97	83	1·16
	90·0	6·97	88	1·11
	85·0	6·99	84	0·93
	70·0	7·01	79	0·84
	55·0	6·98	85	0·65
	40·0	6·93	86	0·39
Mean and S.D.			74·9±3·2	
B.11	143·0	7·04	68	1·45
	135·0	7·03	68	1·45
	125·0	7·01	71	1·37
	115·0	6·94	71	1·26
	95·0	6·83	68	0·99
	75·0	6·81	63	0·73
Mean and S.D.			68·2±2·9	
B.12	170·0	7·13	80	1·80
	160·0	7·15	73	1·51
	145·0	7·10	82	1·35
	130·0	7·04	91	1·26
	110·0	7·03	91	1·02
	90·0	7·02	91	0·69
	70·0	6·97	91	0·65
	45·0	6·90	90	0·47
Mean and S.D.			86·1±6·9	

The mean values for $PaCO_2$ for each of the four dogs in this group are 69, 83, 68, and 86 mm.Hg. From Fig. 2 it can be seen that blood flow declined linearly with blood pressure.

DISCUSSION

It would appear that the experiments shown on Fig. 1 indicate the existence of 'autoregulation' of blood flow in response to moderate changes in the arterial blood pressure. This is in agreement with studies by Carlyle and Grayson (1955) who used a heat clearance technique to obtain a qualitative index of the blood flow through the cerebral cortex in anaesthetized rabbits. These workers found that if the blood pressure was lowered from the control level of approximately 90 mm.Hg to approximately 45 mm.Hg, there was no change in the heat clearance and, by inference, the blood flow. More recently Rapela and Green (1964) estimated cerebral blood flow in dogs by measuring the venous outflow from the brain and found a marked autoregulatory response over the pressure range 90–50 mm.Hg.

However, other workers using isolated head perfusion techniques have denied the existence of autoregulation and have claimed that the cerebral blood flow is passively dependent on the perfusion pressure (Geiger and Magnes, 1947; Sagawa and Guyton, 1961). Factors which could have 'masked' autoregulation in these studies must be considered.

Figure 2 shows that autoregulation is abolished by hypercapnia. Presumably the explanation for this

is that vessels already maximally or nearly maximally dilated by hypercapnia are unable to dilate further in response to a lowered blood pressure. A passive pressure/flow relationship will then be observed. In the papers cited above, very extensive surgical trauma was inflicted in isolating the cerebral circulation and fairly deep anaesthesia must have been required. In neither study was the $PaCO_2$ reported, but if it was elevated the resultant hypercapnic cerebral vasodilatation may have been sufficient to abolish or obscure autoregulation.

Rapela and Green (1964) observed autoregulation in autoperfused isolated cerebral circulations but not in artificially perfused preparations. The authors state that 'the absence of [autoregulatory] response in some experiments may be explained by the vulnerability of blood vessel responses to traumatic, surgical, or artificial perfusion procedures which appear to induce a near-maximal dilatation'.

It would appear then that, in the experimental animal, under 'normal' physiological conditions, the calibre of the cerebral blood vessels can be adjusted to maintain a constant blood flow in the face of fairly wide fluctuations in the arterial blood pressure. However, under certain abnormal conditions, hypercapnia for instance, or probably any condition which produced an existing near-maximal dilatation, autoregulation is reduced or absent.

MECHANISM OF AUTOREGULATION In the studies of the pial blood vessels by Fog (1938), in which vasoconstriction was demonstrated on raising the blood pressure and vasodilatation on lowering the blood pressure, the response was not affected by sectioning of the vagi, cervical sympathetic, or the sinus and aortic nerves.

It appears probable, therefore, that autoregulation is effected by some local intrinsic mechanism and not by nervous control from the sympathetic or parasympathetic nervous systems.

Lassen (1959) has suggested two possible mechanisms which could effect autoregulation of cerebral blood flow in response to changes in aterial blood pressure.

1 The myogenic theory Studies of segments of isolated arteries by Bayliss in 1902, suggested that alteration of intravascular pressure will produce an automatic response from the smooth muscle in the vessel wall, namely, contraction in response to a rise in pressure and relaxation in response to a drop in pressure. As this property is seen in segments of vessel perfused *in vitro*, it appears to be independent of nervous mechanisms.

2 The metabolic theory Lassen suggested that alterations in diameter of vessels following changes in blood pressure could be mediated through alterations in the tissue and blood tensions of oxygen and carbon dioxide.

One factor which might point against the myogenic theory is the speed of response of the cerebral blood vessels to changes in blood pressure. Fog (1938) demonstrated that there was vasodilatation of the pial blood vessels following a gradual reduction in the arterial blood pressure. However, he pointed out that following a sudden reduction in blood pressure, no vasodilatation was apparent for one or two minutes. Similarly, Schneider (1963) quotes Hirsch as demonstrating in the experimental animal that a sudden decrease in systemic blood pressure from 200 to 100 mm.Hg caused a marked reduction in cerebral blood flow. More than two minutes later, however, the blood flow had almost returned to the control level. Also Rapela and Green (1964) have reported a similar marked decrease in flow following a sudden drop in blood pressure, returning to control values, however, in only 30 seconds.

If the response of the cerebral blood vessels to a change in blood pressure was caused by a local myogenic reflex in the smooth muscle of the vessel wall, one might expect this to occur rapidly and the response would be unlikely to have a time lag of some 30 seconds to two minutes.

On the other hand, a time lag might easily occur if a metabolic factor were involved. A reasonable explanation of the phenomenon of autoregulation could be as follows. A decrease in blood pressure is followed by a reduction in blood flow. Thereafter, the tension of oxygen in the tissues will fall progressively and the tension of carbon dioxide will rise. Both the low PO_2 and high PCO_2 will tend to cause cerebral vasodilatation with the eventual return of the blood flow to its initial value. Such a sequence of events could account for a slight time lag before the onset of autoregulation.

Unfortunately, there is little direct evidence to support such a theory and this must await measurement of the tensions of O_2 and CO_2 in cerebral tissue during alterations in systemic blood pressure. However, studies by Carrier, Walker, and Guyton (1964) have shown that there is a twofold increase in conductance in isolated strips of artery (0·5-1 mm. in diameter) perfused with blood, when the PO_2 of the perfusate was lowered from 100 to 30 mm.Hg, this response being relatively greater in the smaller than in the larger vessels. Similarly, it has been shown by experiments *in vitro* that CO_2 dissolved in Ringer solution dilates isolated strips of artery (Cow, 1911).

If, then, one assumes that any decrease in blood flow which follows a sudden fall in pressure will result in a rise in tissue tension of CO_2 and a fall in tissue tension of O_2, and that this can have a local vasodilatory effect on cerebral arteries and arterioles,

the metabolic theory of autoregulation becomes tenable and teleogically appropriate.

The absence of autoregulation in circumstances where there is pre-existing cerebral vasodilatation—during hypercapnia or hypoxia—does not negate this theory, but probably indicates that under these circumstances the vessels have reached their mechanical limit of dilatation and can respond no further to a reduction in blood pressure, resulting in a passive pressure/flow relationship.

AUTOREGULATION IN MAN Extensive studies in man on the response of the cerebral blood flow to changes in blood pressure have not been carried out due to ethical considerations and methodological difficulties. However, some studies on the effect of hypertension and drug-induced hypotension have been reported in man. Lassen (1959) presented a graph of the pressure/flow relationship in man compiled from seven different sources in the literature. This study showed that neither essential nor drug-induced hypertension (Moyer, Miller, Tashnek, Snyder, and Bonman, 1953; Moyer and Morris, 1954; Hafkenschiel, Friedland, and Zintel, 1954; Moyer, Morris, Snyder, and Smith, 1954) nor hypertensive toxaemia of pregnancy caused any significant difference in blood flow when compared with results in control groups of normal young men and normal pregnant women (Kety and Schmidt, 1948; McCall, 1953). Similarly, moderate drug-induced hypotension was not associated with any significant change in blood flow (McCall, 1953).

Lassen suggests that within a wide pressure range (approximately 60 to 170 mm.Hg) the calibre of the cerebral blood vessels can alter to compensate for changes in blood pressure. It is only in severe hypotension, that is to approximately one-third of the normal level (Finnerty, Witkin, and Fazekas, 1954), that cerebral vasodilatation is insufficient to compensate for the low arterial blood pressure, signs of cerebral ischaemia becoming apparent.

Additional studies in which measurements of cerebral blood flow were made before and after the administration of hypotensive drugs, adrenalectomy, or spinal sympathetic block, have been reported, mainly in patients with pre-existing hypertension. These can be summarized as follows:

Series	*Blood Pressure (mm.Hg)*	*Cerebral Blood Flow*
Hafkenschiel *et al.* (1954)	Lowered from 170 to 118	No significant change
Bessman, Alman, and Fazekas (1952)	Lowered from 133 to 87	No significant change
Kleh and Fazekas (1956)	Lowered from 158 to 98	No significant change
Moyer *et al.* (1953)	Lowered from 173 to 108	No significant change
Stone, Mackrell, and Wechsler (1955)	Lowered from 117 to 62	No significant change

However, contradictory findings were reported by:

Series	*Blood Pressure (mm.Hg)*	*Cerebral Blood Flow*
Crumpton, Rowe, Capps, Whitmore, and Murphy (1965)	Lowered from 181 to 111	Fall of 14%
Morris, Moyer, Snyder, and Haynes (1953)	Lowered from 104 to 62	Fall of 30%
Kety, King, Horvath, Jeffers, and Hafkenschiel (1950)	Lowered from 155 to 106	Fall of 12%

In the last study the $PaCO_2$ fell by 5 mm.Hg, which could well account for the observed decrease in cerebral blood flow.

However, with the exception of the conflicting studies of Crumpton *et al.* (1955) and Morris *et al.* (1953), the weight of evidence seems to favour the existence of autoregulation in man. It appears that the mean arterial blood pressure can fall by at least one-third without affecting cerebral blood flow, and indeed can probably fall by more than this before affecting cerebral function and causing clinical signs of cerebral ischaemia.

But before one assumes that the administration of hypotensive drugs or the use of hypotensive anaesthesia will not imperil cerebral blood flow, one important point must be considered. The animal experiments reported in this paper demonstrate that although the systemic blood pressure can be altered over a fairly wide range without affecting the cortical blood flow in normocapnic animals, there is a passive pressure/flow relationship in hypercapnic animals. Consider now a patient who has relative ischaemia of a local area of brain. Within the local ischaemic area, the blood vessels will probably be dilated under the influence of elevation of cerebral tissue PCO_2 and reduction of tissue PO_2. This dilatation may well be sufficient to maintain a normal blood flow and the ischaemia will be 'compensated'. But if the pressure of the blood perfusing this area is now reduced, there will be a parallel reduction in blood flow (there will be no autoregulation because of pre-existing vasodilatation) with the net result of an 'uncompensated' ischaemia. I think that this is an important point which is worthy of consideration when the administration of hypotensive drugs is contemplated.

SUMMARY

Measurements of blood flow through the cerebral cortex were made in lightly anaesthetized dogs using the 85 Krypton clearance method. The systemic blood pressure was gradually reduced by bleeding. In normocapnic animals ($PaCO_2$ 30–40 mm.Hg) autoregulation of blood flow in response to changes

in arterial blood pressure was observed over the range 90 to 180 mm.Hg. However, in hypercapnic animals ($PaCO_2$ 70–90 mm.Hg) where there was pre-existing cerebral vasodilatation a passive pressure/flow relationship was observed. It was suggested that this finding may explain the failure of some previous workers to demonstrate autoregulation of cerebral blood flow in response to changes in arterial blood pressure.

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