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Effect of carotid ligation on cerebral blood flow in baboons

2. Response to hypoxia and haemorrhagic hypertension

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SYNOPSIS Cerebral blood flow (CBF) measurements were carried out in two groups of anaesthetized normocapnic baboons. In the first group of five animals the effect of hypoxia on the CBF before and after ipsilateral carotid artery ligation was studied. The results showed that, although after ipsilateral carotid ligation there was little change in the CBF at normal PaO_2, at hypoxia there was only 20% rise in the CBF as compared with an 80% rise before the carotid ligation. In the second group of 10 animals, effects of haemorrhagic hypotension on the CBF after ipsilateral carotid artery ligation were estimated. The results indicated impairment of autoregulatory response of the cerebral circulation.

After carotid ligation in the neck, there is an appreciable risk of ischaemia of the ipsilateral hemisphere (Nishioka, 1966; Millikan, 1969). Clinical signs of cerebral ischaemia may develop immediately but more often this complication is delayed for a period ranging from a few hours to a few days. The reason for this is not known.

In an endeavour to discover what factors might account for delayed ischaemia, we have explored the reactivity of the cerebral circulation after carotid ligation in the baboon.

In a previous paper (Sengupta *et al.*, 1973) we have shown that, although after carotid ligation there is little fall in the blood flow to the ipsilateral hemisphere, the CO_2 reactivity of the cerebral vessels on that side diminishes. After bilateral carotid ligation the cerebral blood flow falls more markedly and the CO_2 reactivity is virtually abolished.

In this paper we present the results of experiments designed to show the state of reactivity of the cerebral vessels in the baboon to hypoxia and haemorrhagic hypotension before and after carotid ligation.

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METHODS

Baboons (*Papio cynocephalus*) weighing approximately 10 kg were premedicated with phencyclidine (12 mg intramuscularly) and anaesthetized with sodium thiopentone (7·5 mg/kg intravenously). The animals were intubated and connected to an intermittent positive pressure respiratory pump (Starling) delivering a mixture of 75% nitrous oxide and 25% oxygen in open circuit. Phencyclidine (2 mg intramuscularly) and suxamethonium (100 mg intramuscularly) were administered at 30 minute intervals in order to maintain adequate levels of anaesthesia and muscular relaxation.

The femoral artery and vein were exposed in the left groin. A catheter was introduced into the thoracic aorta via the femoral artery and connected to a Statham strain gauge and recorder for continuous recording of mean arterial blood pressure (MABP). The femoral vein was cannulated for administration of intravenous fluids. Arterial pCO_2, pH, pO_2, packed cell volume, and haematocrit were measured frequently. The animals were kept normocapnic throughout the experiments by adjusting the respiratory pump. Temperature was maintained at 37° C with the help of heating lamps. The common carotid artery and its branches were exposed on the right side of the neck. The branches of the right external carotid artery were ligated except for the linguo-facial trunk, which was cannulated centri-

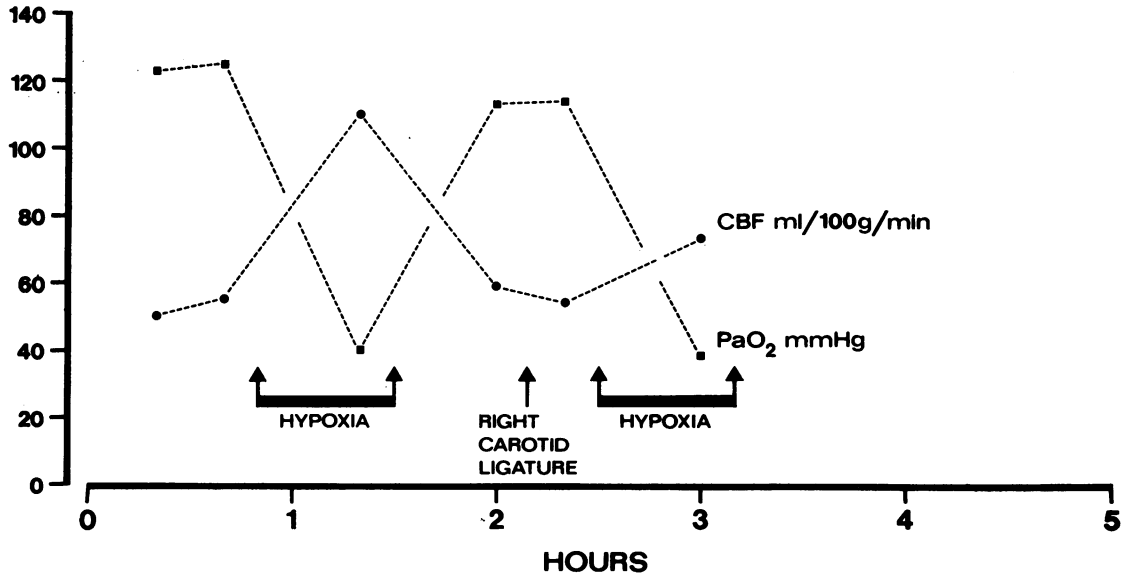

FIG. 1. *The effect of hypoxia on the cerebral blood flow before and after ipsilateral carotid artery ligation. (Illustration of one experiment.)*

petally with a fine catheter. The scalp and temporal muscles were excised from the right side of the scalp.

Cerebral blood flow (CBF) was measured by the height/area technique over periods of 10 minutes after bolus injections of ^{133}Xe via the right linguofacial trunk, using a scintillation detector placed over the right frontoparietal region (Høedt-Rasmussen *et al.*, 1966).

The effect of hypoxia and carotid ligation on the CBF was tested on five animals. In these experiments, after initial control CBF estimations, hypoxia was induced by reducing the oxygen in the gas inhalation mixture. After CBF measurement at hypoxia, the oxygen in the gas inhalation mixture was restored and CBF measured at normal PaO_2. Then the right common carotid artery was ligated and CBF measured at normal PaO_2 and then at hypoxia.

In another 10 animals, after initial control CBF measurements, the right common carotid arteries were tied. Then the animals were rendered progressively hypotensive by controlled withdrawal of blood via a catheter in the right femoral artery. CBF was measured after each step-reduction in blood pressure. The blood pressure was held steady for at least five minutes before the study and during the 10 minute period of CBF estimations. A similar protocol was used in another series of experiments in this laboratory in which the effect of controlled haemor-

TABLE 1

EFFECT OF HYPOXIA ON CEREBRAL BLOOD FLOW BEFORE AND AFTER IPSILATERAL CAROTID ARTERY LIGATION

	Normoxia				*Hypoxia*			
	PaO_2 (mmHg)	*MABP (mmHg)*	*$PaCO_2$ (mmHg)*	*CBF (H/A) (ml/100 g/min)*	*PaO_2 (mmHg)*	*MABP (mmHg)*	*$PaCO_2$ (mmHg)*	*CBF (H/A) (ml/100 g/min)*
Control (n = 5)	113 ± 14·8	81 ±9	40 ± 1·7	59‡ ± 13	38·5 ±9	94 ± 15·8	39 ± 1·2	107†‡ ± 22·9
Ipsilateral carotid ligation (n = 5)	105 ± 17	84 ± 14·9	40 ± 1·7	59* 13·4	34 ± 8·2	97 ±9	41 ± 2·9	71*† ± 18·8

Mean results and standard deviations from five baboons.
* P < 0·05. † P < 0·01. ‡ P < 0·001.

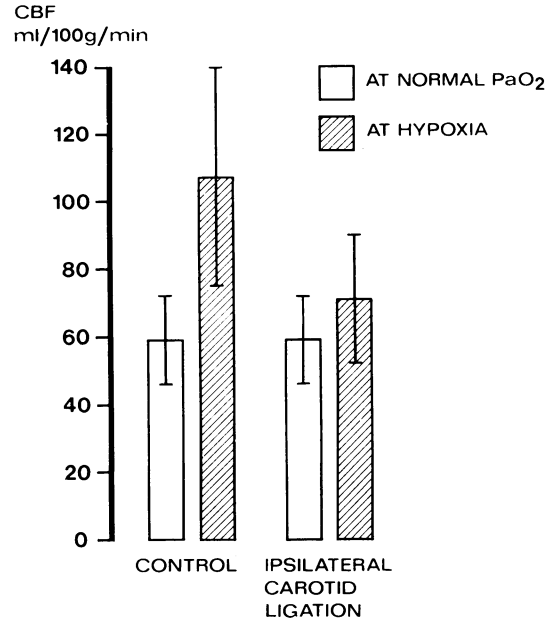

FIG. 2. *The effect of hypoxia on the cerebral blood flow before and after ipsilateral carotid artery ligation. Mean results from five baboons. The bars indicate one standard deviation.*

rhagic hypotension on the cerebral blood flow was measured in 10 baboons with intact carotid arteries (Fitch *et al.*, 1974). These last experiments have been used as controls for the present series.

RESULTS

HYPOXIA EXPERIMENTS (FIVE ANIMALS) There was no significant difference in the CBF values before and after ipsilateral carotid ligation under conditions of normoxia, but the increase in flow after hypoxia was significantly less after ipsilateral carotid ligation. Before carotid ligation, hypoxia produced an 81% increase in the CBF but after ipsilateral carotid ligation hypoxia increased the CBF by only 20% (Figs 1 and 2, Table 1).

The animals were kept at normocapnia throughout these experiments. There was no difference in the $PaCO_2$ values at normal PaO_2 before and after carotid ligation but during hypoxia $PaCO_2$ was slightly higher (2 mmHg) after carotid ligation. In the control CBF estimations at normal $PaCO_2$, there was little difference in the PaO_2 before and after ipsilateral carotid ligation. During hypoxia, PaO_2 was 4 mmHg lower after carotid ligation (38 mmHg and 34 mmHg respectively).

There was little change in the MABP, before and after carotid ligation at normal PaO_2. At hypoxia, there was about 12% increase in the MABP both before and after carotid ligation.

The differences in the $PaCO_2$, PaO_2, and MABP values before and following ipsilateral carotid ligation were found to be not significant by paired *t* tests.

HAEMORRHAGIC HYPOTENSION EXPERIMENTS (10 ANIMALS) The control values before carotid ligation in these experiments are comparable with those obtained by Fitch *et al.* (1974) (Table 2). Although in our experiments the MABP was about 10% higher, there was no significant difference in the $PaCO_2$ and CBF values as found by Student's *t* tests.

The mean CBF and MABP values in each animal after ipsilateral carotid ligation, but before withdrawal of blood, were taken as control values. Percentage changes from the control

TABLE 2

CONTROL VALUES (MEAN AND STANDARD DEVIATION) FOR HAEMORRHAGIC HYPOTENSION EXPERIMENTS ON BABOONS WITH INTACT CAROTID ARTERIES (10 BABOONS—FITCH *et al.*, 1974) AND PRESENT SERIES (10 BABOONS) WITH IPSILATERAL CAROTID ARTERY LIGATED

	n	*MABP* (*mmHg*)	*$PaCO_2$* (*mmHg*)	*CBF (H/A)* (*ml/100 g/min*)	*CBF (G)* (*ml/100 g/min*)	*CBF (W)* (*ml/100 g/min*)	*weight grey*
Fitch *et al.* (1973)	10	91·7 ± 7·4	39·8 ± 1·8	51·6 ± 11·0	74·1 ± 16·7	28·1 ± 5·3	49·8 ± 6·78
Present series	10	100·5 ± 9·9	39·5 ± 1·5	53·7 ± 10	74·2 ± 12·6	26 ± 4	52 ± 5

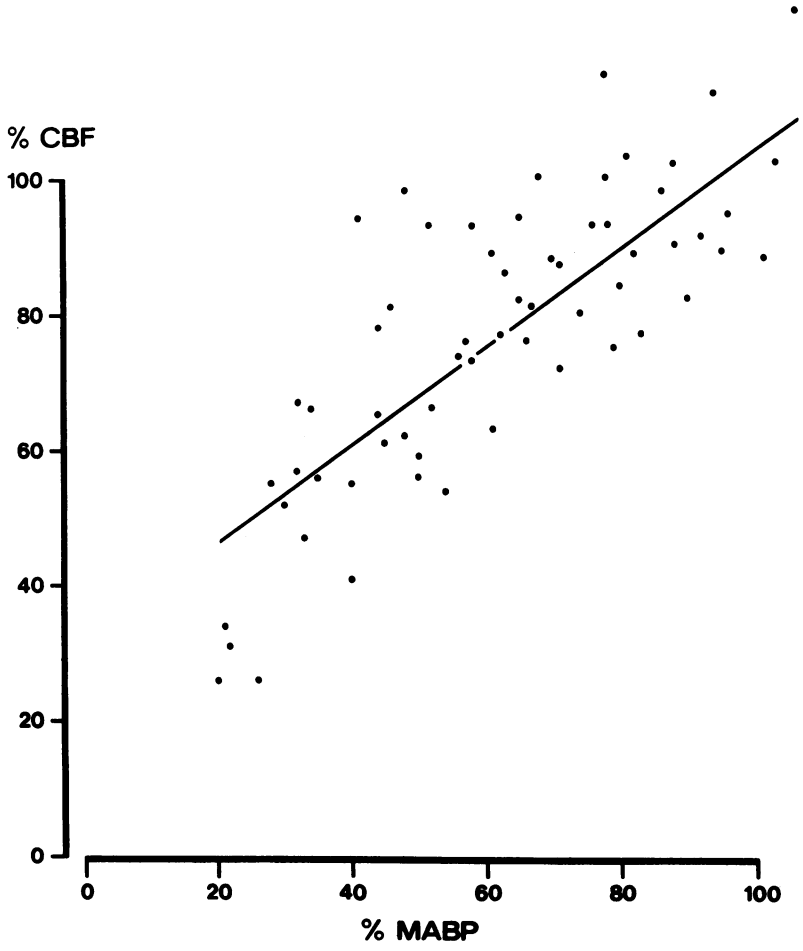

FIG. 3. *Effect of haemorrhagic hypotension on the cerebral blood flow after ipsilateral carotid artery ligation, expressed as percentage of initial values. Calculated linear regression line drawn from the pooled results in 10 baboons.* ($y = 32{\cdot}248 + 0{\cdot}714;x$ $r = 0{\cdot}824$; $n = 71$; $P < 0{\cdot}001$.)

values were calculated for the MABP and CBF values obtained, before haemorrhage and during each step-reduction in the systemic blood pressure.

Percentage changes from the control of the MABP and CBF values obtained for all the animals are plotted in Fig. 3. After ipsilateral carotid ligation, the CBF fell *pari passu* with the fall in the mean arterial blood pressure. The calculated regression line was $y = 32{\cdot}248 + 0{\cdot}714X$; $r = 0{\cdot}824$; $n = 71$; $P < 0{\cdot}001$.

Figure 4 shows the autoregulation found with intact carotid arteries by Fitch *et al.* (1974) in this laboratory as compared with the impaired autoregulation observed after ipsilateral carotid ligation in the present series.

DISCUSSION

The baboon is a suitable animal for cerebral blood flow experiments because of anatomical and physiological similarities to man. The only marked difference is the absence of an anterior communicating artery, the two anterior cerebral arteries uniting to form a single pericallosal artery (Symon and Ross Russell, 1971).

Anaesthetic agents were chosen which have little influence on the CBF, it having been shown that CBF values in patients having nitrous oxide and oxygen, supplemented by neuroleptanalgesia, compare well with a matched group of conscious patients (Wilkinson and Browne, 1970). Throughout these experiments steps were

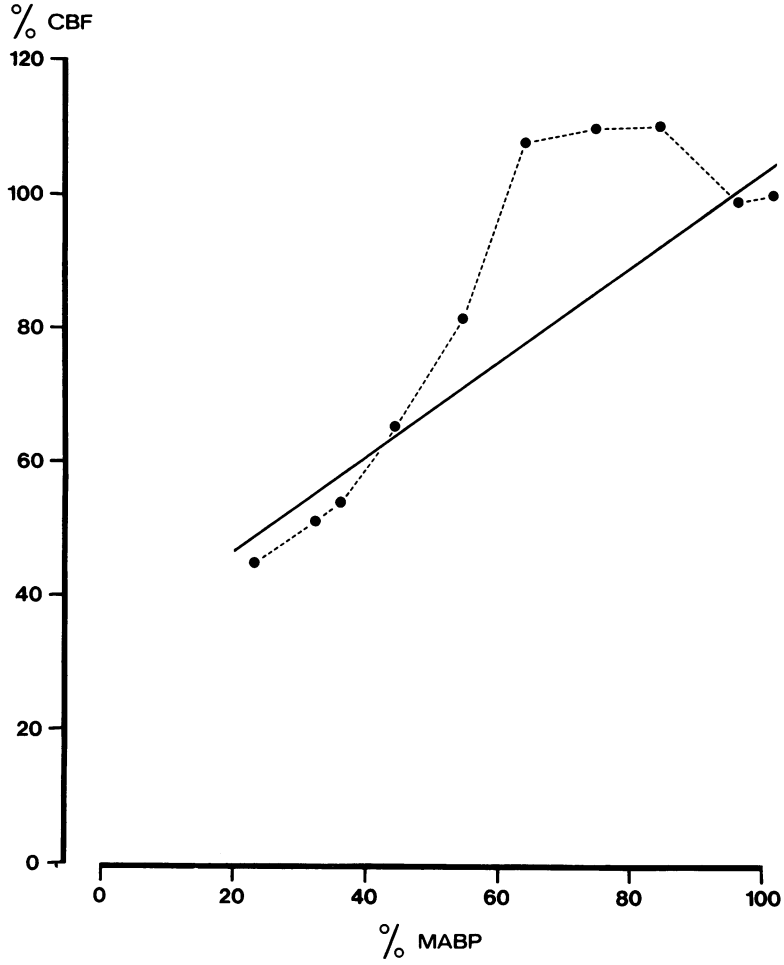

FIG. 4. *Comparison of pressure/flow relationship with intact carotid arteries (Fitch* et al., *1974) and with ipsilateral carotid ligation (regression line taken from Fig. 3).*

taken to ensure steady state conditions in respect to those physiological variables considered of importance in the control of the cerebral circulation; in particular, normocapnia was maintained, and what small changes there were in the $PaCO_2$ were insignificant.

During hypoxia, autoregulation of the cerebral blood flow in the face of alteration of systemic arterial pressure is impaired, and with severe hypoxia there is a passive pressure-flow relationship (Häggendal and Johansson, 1965). This has been disputed by Kogure *et al.* (1970b) who suggest that impairment of autoregulation may occur only at extreme hypoxia. In the present series of experiments, at normal PaO_2, there was little difficulty in keeping the MABP values steady during successive ligations but during hypoxia there was unavoidable fall in the MABP values (17% and 12% respectively) before and after ipsilateral carotid artery ligation, as compared with pre-ligation level: these changes are not significant.

The CBF values at normal PaO_2 compare well with previous experiments in this laboratory (Harper *et al.*, 1972; Sengupta *et al.*, 1972; Fitch *et al.*, 1974; Strandgaard *et al.*, 1974). In accord with our previous experience, there was no alteration in the mean CBF values after ipsilateral carotid artery ligation.

The relationship between CBF and PaO_2 has been shown by McDowall (1966). At hypoxia, when the arterial pO_2 falls below 50 mmHg,

there is a marked rise in the cerebral blood flow due to cerebral vasodilatation in order to maintain the total oxygen available to the brain. Kogure *et al.* (1970a) have shown that cerebral vascular response to hypoxia is a threshold phenomenon beginning at a PaO_2 of about 50 mmHg, and that it correlates with the development of cerebral cortical acidosis. Hypoxia (mean PaO_2 38 mmHg), before carotid artery ligation, produced an 81% rise in the mean CBF values (paired *t* test, $P < 0.01$). After ipsilateral carotid artery ligation, hypoxia (mean PaO_2 34 mmHg) increased the CBF by only 20% (paired *t* test, $P < 0.05$). Ipsilateral carotid ligation thus impairs the response of the cerebral vessels to hypoxia.

The maintenance of the CBF in the face of arterial hypotension is well accepted (Lassen, 1959; Rapela and Green, 1964; Harper, 1966), and is believed to be maintained by dilatation of the arterioles of the brain. In the series of experiments by Fitch *et al.* (1974) in this laboratory, the CBF remained at or above the initial values until the MABP was reduced to below 70% of the original value. In the present study, with the ipsilateral carotid artery ligated, autoregulation of CBF to hypotension was found to be impaired. These results agree with the findings of Kindt *et al.* (1967) who, using EMF probes to estimate the CBF in goats, demonstrated impairment of autoregulation, at hyper- and hypotension, after carotid artery occlusion.

When one carotid artery is ligated, the blood flow to the ipsilateral cerebral hemisphere is presumably maintained by dilatation of the distal arterioles because of the fall in the intra-arteriolar pressure, blood being supplied from the contralateral carotid and the vertebral arteries. The present study suggests that because these vessels are already dilated they cannot then respond effectively to the further dilatory stimulus of hypoxia or haemorrhagic hypotension; we have already shown that responsiveness to changing $PaCO_2$ is also impaired. It seems possible that this impaired reactivity of the cerebral circulation, which in a further series of experiments we have shown to persist for at least one week (Sengupta and Harper—to be published), may account for delayed ischaemia after clinical carotid ligation. This hypothesis would require some change, or combination of changes, in $PaCO_2$, PaO_2, or MABP, to which the cerebral circulation is vulnerable.

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