Effect of carotid ligation on cerebral blood flow in baboons

2. Response to hypoxia and haemorrhagic hypertension

D. SENGUPTA, MURRAY HARPER¹, AND BRYAN JENNETT

From the M.R.C. Cerebral Circulation Research Group at the Wellcome Surgical Research Institute and the Institute of Neurological Sciences, The University of Glasgow

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 PaO₂, 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 CO₂ reactivity of the cerebral vessels on that side diminishes. After bilateral carotid ligation the cerebral blood flow falls more markedly and the CO₂ 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.

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 pCO₂, pH, pO₂, 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-

¹ Address for reprints: Murray Harper, Wellcome Surgical Research Institute, Garscube Estate, Bearsden Road, Glasgow G61 1QH, Scotland.

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 PaCO₂ values at normal PaO₂ before and after carotid ligation but during hypoxia PaCO₂ was slightly higher (2 mmHg) after carotid ligation. In the control CBF estimations at normal PaCO₂, there was little difference in the PaO₂ before and after ipsilateral carotid ligation. During hypoxia, PaO₂ 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 PaO₂. At hypoxia, there was about 12% increase in the MABP both before and after carotid ligation.

The differences in the PaCO₂, PaO₂, and MABP values before and following ipsilateral carotid ligation were found to be not significant by paired *t* tests.

HAEMORRHAGIC HYPOTENSION EXPERIMENTS (FIVE 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 PaCO₂ 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

	<i>n</i>	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 <i>et al.</i> (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. ($y = 32.248 + 0.714x$; $r = 0.824$; $n = 71$; $P < 0.001$.)

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 $y = 32.248 + 0.714X$; $r = 0.824$; $n = 71$; $P < 0.001$.

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.

This work was supported by the Medical Research Council. We are grateful for technical, nursing, and secretarial assistance from staff of Wellcome Surgical Research Institute, University of Glasgow. The figures were prepared by the department of Medical Illustrations, Southern General Hospital, Glasgow.

REFERENCES

- Fitch, W., Ferguson, G. G., Sengupta, D., and Garibi, J. (1974). Autoregulation of cerebral blood flow during controlled hypotension, *Proceedings of the 6th International CBF Symposium Philadelphia* 1974. Springer-Verlag (in press).
- Häggendal, E., and Johansson, B. (1965). Effects of arterial carbon dioxide tension and oxygen saturation on cerebral blood flow autoregulation in dogs. *Acta Physiologica Scandinavica*, **66** Suppl. 258), 27–53.
- Harper, A. M. (1966). Autoregulation of cerebral blood flow: influence of the arterial blood pressure on the blood flow through the cerebral cortex. *Journal of Neurology, Neurosurgery, and Psychiatry*, **29**, 398–403.
- Harper, A. M., Deshmukh, V. D., Rowan, J. O., and Jennett, W. B. (1972). The influence of sympathetic nervous activity on cerebral blood flow. *Archives of Neurology*, **27**, 1–6.
- Høedt-Rasmussen, K., Sveinsdottir, E., and Lassen, N. A. (1966). Regional cerebral blood flow in man determined by intra-arterial injection of radioactive inert gas. *Circulation Research*, **18**, 237–247.
- Kindt, G. W., Youmans, J. R., and Albrand, O. (1967). Factors influencing the autoregulation of the cerebral blood flow during hypotension and hypertension. *Journal of Neurosurgery*, **26**, 299–305.
- Kogure, K., Scheinberg, P., Reinmuth, O. M., Fujishima, M., and Busto, R. (1970a). Mechanisms of cerebral vasodilatation in hypoxia. *Journal of Applied Physiology*, **29**, 223–229.
- Kogure, K., Scheinberg, P., Fujishima, M., Busto, R., and Reinmuth, O. M. (1970b). Effects of hypoxia on cerebral autoregulation. *American Journal of Physiology*, **219**, 1393–1396.
- Lassen, N. A. (1959). Cerebral blood flow and oxygen consumption in man. *Physiological Reviews*, **39**, 183–238.
- McDowall, D. G. (1966). Interrelationships between blood oxygen tensions and cerebral blood flow. In *A Symposium on Oxygen Measurements in Blood and Tissues*, pp. 205–219. Edited by J. P. Payne and D. W. Hill. Churchill: London.
- Millikan, C. H. (1969). Cerebral circulation: clinical concepts as affected by vascular anatomy, pathology, and pathophysiology. *Clinical Neurosurgery*, **16**, 419–435.
- Nishioka, H. (1966). Results of the treatment of intracranial aneurysms by occlusion of the carotid artery in the neck. Report on the cooperative study of intracranial aneurysms and subarachnoid hemorrhage. Section 8, Part 1. *Journal of Neurosurgery*, **25**, 660–682.
- Rapela, C. E., and Green, H. D. (1964). Autoregulation of canine cerebral blood flow. *Circulation Research*, **15**, Suppl. 1, 205–211.
- Sengupta, D., Harper, A. M., Deshmukh, V. D., Rowan, J., and Jennett, W. B. (1972). Effect of carotid artery ligation on the CO_2 response in the baboon. *European Neurology*, **6**, 369–372.

- Sengupta, D., Harper, M., and Jennett, B. (1973). Effect of carotid ligation on cerebral blood flow in baboons. I. Response to altered arterial $p\text{CO}_2$. *Journal of Neurology, Neurosurgery, and Psychiatry*, **36**, 736–741.
- Sengupta, D., and Harper, A. M. The response of the cerebral blood flow to hypercapnia and hypotension following chronic carotid ligation in the baboon. (To be published.)
- Strandgaard, S., Sengupta, D., MacKenzie, E. T., Rowan, J. O., Lassen, N. A., and Harper, A. M. (1974). The upper limit for autoregulation of cerebral blood flow in the baboon. *Circulation Research* (in press).
- Symon, L., and Ross Russell, R. W. (1971). The development of cerebral collateral circulation following occlusion of vessels in the neck. An experimental study in baboons. *Journal of the Neurological Sciences*, **13**, 197–208.
- Wilkinson, I. M. S., and Browne, D. R. G. (1970). The influence of anaesthesia and of arterial hypocapnia on regional blood flow in the normal human cerebral hemisphere. *British Journal of Anaesthesia*, **42**, 472–482.

Book review

MONOGRAPHIEN AUS DEM GESAMTGEBIETE DER PSYCHIATRIE *Psychiatry Series: THE MANAGEMENT OF THE INSANE* By M. Schrenk. (Pp. 194; illustrated; DM 98.) Springer: Berlin. 1973.

It is often assumed that today's liberal and humanitarian attitude towards the insane had its immediate origin in the 'geste de Pinel' when Philippe Pinel ordered that the chains and fetters be struck off some 30 unfortunate lunatics in the Bicetre Institution. The date, 1793, may do to fix in one's mind the passing of the old and the beginning of the new, but Pinel's 'moral management' of the insane—that is, without undue violence or restraint—had been practised some 50 years earlier by other enlightened men, like Francis Willis in this country; it may even have been practised in very much earlier times in Arab institutions for the insane. It took more than half a century for it to become generally adopted.

Professor Schrenk in this excellent monograph deals mainly with developments in psychiatric practice in the first 50 years of the 19th century and concentrates on events in Germany where Pinel's moral treatment became the psychic cure-method. Professor Schrenk particularly acknowledges the debt due to the English and Scottish schools.

Even at the origin of modern psychiatry there were modes of treatment—the rotation machine, for example—which impressed by their very violence and which were as little understood as are the effects of ECT today. The 'moral management' aimed at the whole patient, his surroundings, his diet, and his social and mental stimulation. So the author of this monograph makes excursions into the architecture and the planning of new mental hospitals. One German psychiatrist in his enthusiasm for wholesome recreation made his male and female charges exercise with wooden mock-rifles to the bellowing orders of a sergeant.

The book gives a fascinating and very thorough account of psychiatry in that exciting period in history when romanticism gave violent birth to the age of reason. Yet it may be as well to remember that nearly 200 years after Pinel, political dissidents are sent to 'special' lunatic asylums in the Soviet Union where they are treated as criminals and that during the Hitler period in Germany those thought to be incurably mentally disturbed were killed.

J. SCHORSTEIN

THE OCULOMOTOR SYSTEM + BRAIN FUNCTIONS Edited by V. Zikmund. (Pp. 524; illustrated; £7.50.) Butterworth's: London. 1973.

This is a difficult book to review comprehensively, since its subject matter ranges widely from studies in the vestibular control of eye movement to observations on sleep and dreaming in relation to ocular movements. Unfortunately, some of the English is very poor and difficult or impossible to understand. Spelling errors are frequent. It is perhaps especially unfortunate that the editor's thanks to the publishers acknowledges their careful help and 'expertise' (*sic*). This language difficulty makes some of the contributions which appear to be of considerable interest hard to understand and impossible to assess. For example, the interesting paper by Gabersek and Ghiloni is marred by this sort of statement: 'Observation No 653 (Fig. 6) is a case of neuroma of the right ear affecting the tonsils.'

The symposium of which this is an account took place in 1970 in Smolenice in Czechoslovakia. As with any such collection, the quality of the contributions is uneven. The emphasis is on physiology rather than on pathology. The book is divided into six sections each covering different aspects of the general subject of eye movement. The first two are devoted to the physiology of eye movement and its control, the third to the relationship between eye movement and visual perception. The fourth deals with aspects of optokinetic nystagmus, and the sixth with the oculomotor system and postural mechanisms. The fifth section is the most unusual, and concerns itself (in eight papers) with problems of ocular movements as they relate to visual imagery sleep and dreams.

C. J. EARL

CORRECTION

In the May 1974 issue of the Journal the title of the article by D. Sengupta, Murray Harper, and Bryan Jennett should read 'Effect of carotid ligation on cerebral blood flow in baboons. 2. Response to hypoxia and haemorrhagic hypotension' (Vol. 37, No. 5, pp. 578–584).