

# Effect of carotid ligation on cerebral blood flow in baboons<sup>1</sup>

## 1. Response to altered arterial PCO<sub>2</sub>

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**SUMMARY** Measurements of cerebral blood flow (CBF) were made in anaesthetized baboons before and after ipsilateral carotid artery ligation and also after bilateral carotid ligation. Results showed that at normocapnia (PaCO<sub>2</sub> 38-39 mmHg) there was little change in cerebral blood flow on ipsilateral carotid ligation, but when both carotid arteries were tied the blood flow to the brain fell significantly. At hypercapnia (PaCO<sub>2</sub> 58-60 mmHg) the CBF/CO<sub>2</sub> gradient fell significantly on ipsilateral carotid ligation; on bilateral carotid ligation there was only minimal rise in cerebral blood flow in response to the rise in PaCO<sub>2</sub>. At hypocapnia (PaCO<sub>2</sub> 20-21 mmHg) the gradients of fall in the CBF were similar before and after ipsilateral carotid ligation; after bilateral carotid ligation there was minimal change in the CBF in response to the fall in the PaCO<sub>2</sub>. It is suggested that, although cerebral blood flow may be normal after ipsilateral carotid ligation, the circulatory reserve of the brain is not sufficient to meet physiological challenges. This may be the reason for the development of delayed neurological complications after carotid artery ligation.

Carotid ligation in the neck is an accepted method of treating certain intracranial aneurysms. This procedure carries some risk of ischaemic brain damage; Millikan (1969) has reported focal neurological disability after carotid ligation in 43% of 188 patients, but only 4.2% of the patients developed immediate complications. In Nishioka's (1966) report on carotid ligation cerebral ischaemia was observed in 29.7% of 785 patients; 6.4% of this series had immediate ischaemic complications. Although only a minority of patients developing ischaemic complications do so immediately, the reason for the delay is not known. One possibility is the development of distal intra-arterial thrombosis, but there is no evidence of this from post-mortem findings (Nishioka, 1966), nor from the experience of neurosurgeons (Symon, 1969). It is pos-

sible that delayed ischaemia results from the reduced capacity of the cerebral circulation to adapt to physiological variations in blood gases or blood pressure.

This paper reports experiments designed to test the effects of carotid ligation on cerebral flow and on the physiological responses of the cerebral circulation to alteration of arterial PCO<sub>2</sub>.

### METHODS

Baboons (*Papio cynocephalus*) weighing approximately 10 kg were premedicated with phencyclidine (12 mg intramuscularly) and anaesthetized with intravenous sodium thiopentone (7.5 mg/kg). 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) and suxamethonium chloride (100 mg) were administered intramuscularly at 30 minute intervals in order to maintain adequate levels of anaesthesia and muscular relaxation.

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The common carotid artery and its branches were exposed on both sides, avoiding damage to the carotid sinuses. All the branches of the external carotid arteries on the right side were ligated except the linguofacial trunk, which was cannulated with a fine polyethylene catheter. The scalp and temporal muscles were excised on the same side of the head. The temperature of the animal was maintained at about 37° C using infra-red lamps. The femoral artery and vein were exposed in the left groin. A polyethylene catheter was introduced into the thoracic aorta via the femoral artery and connected to Statham strain gauges and chart recorders for con-

tinuous recording of pulsatile and mean arterial blood pressure (MABP).

End-tidal carbon dioxide was monitored by an infra-red analyser. PaCO<sub>2</sub>, arterial pH, and PaO<sub>2</sub> were measured frequently with micro-electrodes (Astrup).

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

Two sets of experiments were carried out. In one

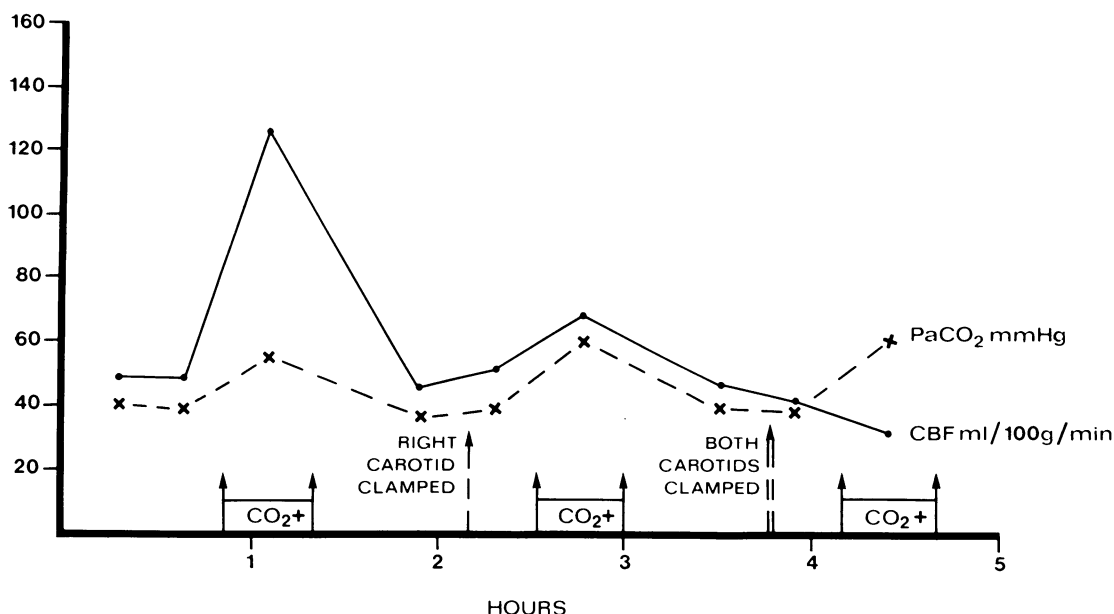


FIG. 1. The effect of hypercapnia on CBF before and after carotid ligation.

TABLE 1

EFFECT OF HYPERCAPNIA ON CBF AND BP BEFORE AND AFTER CAROTID LIGATION—MEAN RESULTS AND STANDARD DEVIATION (SEVEN BABOONS)

|                              | Normocapnia              |                |                     | Hypercapnia              |                |                     |
|------------------------------|--------------------------|----------------|---------------------|--------------------------|----------------|---------------------|
|                              | PaCO <sub>2</sub> (mmHg) | Mean BP (mmHg) | CBF (ml./100 g/min) | PaCO <sub>2</sub> (mmHg) | Mean BP (mmHg) | CBF (ml./100 g/min) |
| Control                      | 39 ± 0.5                 | 94 ± 7         | 46 ± 6.5*           | 58 ± 6                   | 94 ± 7*        | 103 ± 1*            |
| Ipsilateral carotid ligation | 38 ± 1                   | 95 ± 7         | 44 ± 9              | 58 ± 6                   | 99 ± 11        | 62 ± 12*            |
| Bilateral carotid ligation   | 39 ± 0.5                 | 102 ± 7        | 36 ± 6*             | 60 ± 3                   | 126 ± 19*      | 38 ± 12*            |

\* P < 0.01.

group CBF was measured at normocapnia and then during hypercapnia before and after ligation of the right carotid artery and then again after both carotid arteries had been tied. Hypercapnia was induced by adding 3–4% CO<sub>2</sub> to the inhaled gas mixture, resulting in a PaCO<sub>2</sub> of around 60 mmHg.

In the second group, the cerebral blood flow at normocapnia was compared with that at hypocapnia. Hypocapnia was induced by increasing the stroke volume of the respiratory pump until the PaCO<sub>2</sub> was around 20 mmHg.

## RESULTS

**HYPERCAPNIA EXPERIMENTS (SEVEN ANIMALS)** (Fig. 1, Table 1) At normocapnia there was no significant difference between the CBF values

before and after ipsilateral carotid ligation but CBF was significantly reduced after bilateral carotid ligation ( $P < 0.01$ ). The increase in flow after hypercapnia was significantly less after ipsilateral carotid ligation or after bilateral carotid ligation ( $P < 0.001$ ). Before carotid ligation the increase in CBF during hypercapnia was 123%, a gradient of change in CBF of 3.3 ml./100 g/min per 1 mmHg change in PaCO<sub>2</sub> (CBF/CO<sub>2</sub> gradient). After ipsilateral ligation the increase with hypercapnia was 41%, a CBF/CO<sub>2</sub> gradient of 0.90. After bilateral carotid ligation there was only a 6% increase with hypercapnia, a CBF/CO<sub>2</sub> gradient of 0.10.

The PaCO<sub>2</sub> values at normocapnia showed no

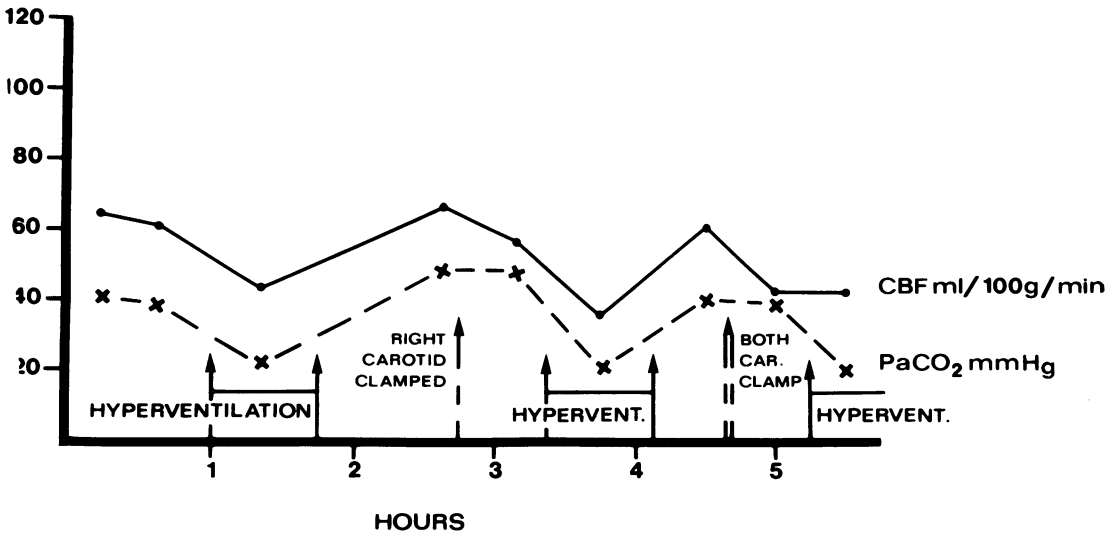


FIG. 2. The effect of hypocapnia on CBF before and after carotid ligation.

TABLE 2

EFFECT OF HYPOCAPNIA ON CBF AND BP BEFORE AND AFTER CAROTID LIGATION—  
MEAN RESULTS AND STANDARD DEVIATION (FIVE BABOONS)

|                              | Normocapnia                 |                   |                        | Hypocapnia                  |                   |                        |
|------------------------------|-----------------------------|-------------------|------------------------|-----------------------------|-------------------|------------------------|
|                              | PaCO <sub>2</sub><br>(mmHg) | Mean BP<br>(mmHg) | CBF<br>(ml./100 g/min) | PaCO <sub>2</sub><br>(mmHg) | Mean BP<br>(mmHg) | CBF<br>(ml./100 g/min) |
| Control                      | 38 ± 1                      | 97 ± 9            | 55 ± 5*                | 20.5 ± 3                    | 92 ± 5†           | 42 ± 3†                |
| Ipsilateral carotid ligation | 39 ± 2                      | 95 ± 11           | 49 ± 12                | 20 ± 1                      | 82 ± 6†           | 35 ± 4*                |
| Bilateral carotid ligation   | 39 ± 1                      | 99 ± 14           | 35 ± 7*                | 21 ± 3                      | 87 ± 9            | 31 ± 7†                |

\*  $P < 0.01$ .

†  $P < 0.05$ .

significant difference between control, after ipsilateral and after bilateral carotid ligation: nor did the PaCO<sub>2</sub> values at hypercapnia show any significant difference before and after carotid ligation. There was little change in MABP during control and after ipsilateral carotid ligation at either normocapnia or hypercapnia, but after bilateral carotid ligation the MABP did become elevated.

**HYPOCAPNIC EXPERIMENTS (Fig. 2, Table 2)** Again, at normocapnia, there was no significant difference between the CBF values before and after ipsilateral carotid ligation, but after bilateral ligation CBF was significantly reduced ( $P < 0.01$ ) as compared with CBF before carotid ligation. However, at hypocapnia, a significant difference was found between the CBF values before and after ipsilateral carotid ligation ( $P < 0.01$ ) as well as after bilateral carotid ligation ( $P < 0.05$ ). Before carotid ligation there was a 24% decrease in the CBF during hypocapnia, a CBF/CO<sub>2</sub> gradient of 0.72. On ipsilateral carotid ligation, there was a 29% decrease of CBF during hypocapnia, a CBF/CO<sub>2</sub> gradient of 0.74. After bilateral ligation, there was a 12% decrease in the CBF after hypocapnia, a CBF/CO<sub>2</sub> gradient of 0.22.

There was no significant difference in the PaCO<sub>2</sub> values during control, after ipsilateral carotid ligation, and after bilateral carotid ligation at normocapnia and also during hypocapnia.

At normocapnia, there was little change in MABP during control and after ipsilateral and bilateral carotid ligation. At hypocapnia, the MABP was reduced by 10 mm after unilateral carotid ligation.

#### DISCUSSION

The baboon was chosen as the experimental animal because of the anatomical similarity of its cerebral vasculature to that of man. The only remarkable 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 are reported to have little influence on the CBF. It has 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 taken to ensure steady state conditions in respect of those physiological variables considered of importance in the control of the cerebral circulation. Some changes in mean arterial blood pressure (MABP) in these experiments were unavoidable but they resemble those seen in similar clinical states. The MABP became elevated with ligation of the carotid artery and more markedly when both carotid arteries were tied. Again MABP became raised to some extent with hypercapnia and fell with hypocapnia. These changes were minimized to a large extent by waiting for a few minutes after carotid ligation until the MABP returned to near the control value before measuring CBF. The changes in arterial pCO<sub>2</sub> were induced gradually over 10 to 15 minutes in order to avoid large changes in the MABP.

The CBF values at normocapnia compare well with previous experience in this laboratory (Harper, Deshmukh, Rowan, and Jennett, 1972). After ipsilateral carotid ligation, at normocapnia, there was some fall in CBF of 4% in the first and 11% in the second group, a difference which is not significant by Student's *t* test.

The CBF/CO<sub>2</sub> gradient, before carotid ligation, was 3.3 in the first group, which is higher than some figures quoted in the literature (Reivich, 1964; Harper and Glass, 1965), but compares well with that reported by Harper *et al.* (1972). In each individual animal, after ipsilateral carotid ligation, the CBF/CO<sub>2</sub> gradient was reduced, although there was still a moderate increase in CBF values with hypercapnia. This is contrary to a report published by Kindt and Youmans (1968) which showed that CO<sub>2</sub> was ineffective in increasing internal carotid flow on one side (as measured by an EMF probe) in the monkey when the opposite carotid artery had been tied. We did not observe a paradoxical CBF response to elevation of PaCO<sub>2</sub> as described by Boysen *et al.* (1971) in 25% of patients with diseased arteries after carotid clamping during endarterectomy. In the report by Pistolesse *et al.* (1971) only one out of five patients with diseased

arteries had an increase in CBF with hypercapnia after carotid clamping during endarterectomy. In two patients there were no changes in CBF at hypercapnia and in the remaining two patients reduction of CBF occurred in the ipsilateral hemisphere.

In the second group of experiments, before carotid ligation, the CBF/CO<sub>2</sub> gradient of fall in CBF during hypocapnia was only 0.72. This is because of the sigmoid shape of the CO<sub>2</sub> response curve (Harper and Glass, 1965). There was no marked difference in the mean CBF/CO<sub>2</sub> gradient of fall before and after carotid ligation, probably because severe hypocapnia leads to a degree of brain tissue hypoxia which prevents a further fall in the CBF (Betz *et al.*, 1968; Granholm *et al.*, 1968; Reivich *et al.*, 1968). One animal, after ipsilateral carotid artery ligation, showed a small rise in CBF on hyperventilation.

When both carotid arteries were ligated, the CBF values at normocapnia in each group of experiments showed a significant decrease (22% and 46%) in spite of an elevation of blood pressure, and there was little change in the CBF after hypocapnia or hypercapnia.

When one carotid artery was ligated, the cerebral blood flow was maintained, presumably by dilatation of the distal arteriolar tree, consequent to the fall in the intra-arterial pressure in the brain. However, it has been shown that cerebral vessels, already dilated to compensate for moderate hypotension, are unable to respond effectively when a further dilatory stimulus such as CO<sub>2</sub> is superimposed (Harper and Glass, 1965). The vessels which are already dilated after carotid ligation respond less effectively to increase in PaCO<sub>2</sub> and the CBF/CO<sub>2</sub> gradient is therefore reduced. With both carotid arteries ligated, the dilatation of the distal cerebral arteries is greater still, in order to maintain cerebral blood flow from collateral sources, and the CO<sub>2</sub> response is even more reduced. During hypocapnia, perhaps because of the development of tissue hypoxia, there was no change in CBF/CO<sub>2</sub> gradient with one carotid ligated. When both carotid arteries were tied, hypocapnia had very little effect on the cerebral blood flow, presumably due to maximal dilatation of the distal arteries.

From these experiments it may be inferred that the CBF may appear to be approximately

normal after carotid ligation but there is a reduced reserve; this will be obvious if metabolic needs are increased, or if there is development of moderate hypotension or hypoxia which would normally cause further arterial dilatation. This is probably the state of 'carotid insufficiency' described by Denny-Brown (1960).

It is presumed that the patient who has undergone carotid ligation may have normal cerebral blood flow and no neurological deficit, but that he is at risk if the cerebral circulation is physiologically stressed by increased metabolic demands, by hypoxia or by hypotension. This state of carotid insufficiency may be an explanation for the development of delayed neurological complications after carotid ligation.

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