Delayed effects of subarachnoid haemorrhage on cerebral metabolism and the cerebrovascular response to hypercapnia in the primate

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SUMMARY A technique is described for the production of subarachnoid haemorrhage in baboons and their subsequent recovery for chronic study of cerebrovascular reactivity. The baboons make complete neurological recoveries but the response of their cerebral circulation to hypercapnia is impaired one week later. Baseline values of cerebral blood flow and of cerebral oxygen consumption are unaffected at this time. There is no evidence of hypoxic brain damage.

The aetiology of cerebral ischaemia associated with subarachnoid haemorrhage remains poorly defined. Cerebral ischaemia occurs naturally after subarachnoid haemorrhage but often appears to be aggravated by surgical intervention, particularly when this is carried out during the first week after rupture of the aneurysm. While angiographic "vasospasm" and neurological deficit often develop simultaneously, there can be marked discrepancies between the clinical state and the angiographic appearances (Millikan, 1975; Fisher *et al.*, 1977; Adams *et al.*, 1978). It is very difficult to determine in the individual patient whether there has been a sufficient reduction in local blood flow, at some stage after subarachnoid haemorrhage, to produce a partial or total arterial territory infarction. On the basis of our previous work with acute subarachnoid haemorrhage in monkeys in Edmonton (Petruk *et al.*, 1973, 1974; Boisvert *et al.*, 1978), and on experimental spasm and proximal vessel occlusion in baboons in Glasgow (Harper *et al.*, 1972; Jennett *et al.*, 1976), we have developed a baboon preparation with which to study the more chronic effects of subarachnoid haemorrhage on the reactivity of the cerebral circulation and the associated neuropathological sequelae. Previous experimental studies of subarachnoid haemorrhage in animals

have been limited to the acute effects, extending beyond 48 hours after the induction of haemorrhage only for angiographic studies or baseline measurements of cerebral blood flow. In such acute studies it has not been possible to dissociate the changes in cerebrovascular reactivity from changes in intracranial pressure, cerebral metabolism and CSF acid-base balance (Löfgren and Zwetnow, 1972; Hashi *et al.*, 1972a).

Methods

STAGE 1

Young adult baboons (10-20 kg), tranquillised with phencyclidine (12 mg im) were anaesthetised with thiopentone (7.5 mg/kg iv) and halothane 0.5% in nitrous oxide 70% and oxygen. Endotracheal intubation was performed and ventilation was controlled. The suprachiasmatic cistern was punctured with a needle (22G spinal needle) passed percutaneously through the optic foramen without enucleation of the orbit. A similar technique has been described in the dog (McQueen and Jeanes, 1962). Free flow of CSF was obtained. One operator (JDP) always performed this technique to minimise the failure rate. A small incision over one femoral artery was made, and 0.75 ml/kg arterial blood withdrawn and injected manually into the suprachiasmatic cistern over 30 seconds. Hypoxic brain damage caused by a transient respiratory arrest was avoided by artificial positive pressure ventilation. Anaesthesia was

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discontinued and the animals were returned to their cage. This injection technique was found to be more convenient in the baboon than the transfrontal method developed for the rhesus monkey in Edmonton (Boisvert *et al.*, 1978).

Boisvert *et al.* (1977, 1978) have found in separate experiments that injection of mock cerebrospinal fluid into the suprachiasmatic cistern produces the same pattern of immediate rise in intracranial pressure as does the injection of blood but that there is no effect on intracranial arterial diameter, baseline cerebral blood flow or the autoregulatory response to changing blood pressure. At no point on its path to the suprachiasmatic cistern does the needle for the transorbital injection of blood touch the internal carotid artery, and at no time was arterial blood obtained on withdrawal of the stylet.

STAGE 2

One week later the animals were sedated with phencyclidine (12 mg, im), and anaesthesia was then induced with sodium thiopentone (7.5 mg/kg, iv). After endotracheal intubation, anaesthesia was maintained by half-hourly injections of phencyclidine (2–4 mg, im) and with 70% N₂O–30% O₂ delivered by an intermittent positive pressure respiratory pump in open circuit. Muscular relaxation was provided with suxamethonium chloride (50 mg, im) administered at half hourly intervals. End-tidal CO₂ was monitored continuously with an infrared analyser and controlled either by altering the stroke volume of the pump or by adding CO₂ to the inspired gas mixture. The PaO₂ was always maintained above 80 mmHg. A catheter was inserted into the abdominal aorta, via a femoral artery, for the measurement of arterial blood pressure and for the withdrawal of blood samples for the measurement of PCO₂, pH, PO₂, oxygen content, and haemoglobin concentration. A slow saline drip was given via a femoral vein catheter. Body temperature was maintained close to 37°C by the use of a heating blanket and infrared lamps.

Cerebral blood flow was measured from the parietal area of the brain with a collimated one inch sodium iodide scintillation crystal and calculated by the height/area method (Høedt-Rasmussen *et al.*, 1966) after the intracarotid injection of xenon-133 via a catheter in the right linguofacial trunk. The remaining branches of the right external carotid artery were ligated, and the scalp and temporalis muscle on the same side removed in order to eliminate errors caused by isotope clearance from any extracranial tissues. A thin catheter was inserted into the superior

sagittal sinus in order to measure sagittal sinus pressure and oxygen content. Cerebral oxygen consumption (CMRO₂) was calculated from the product of cerebral blood flow (CBF) and the arteriovenous oxygen content difference. Intracranial pressure was recorded either from a cisternal needle or from a sagittal sinus catheter. Samples of CSF (1 ml) were withdrawn at the first and second stages for acid base and lactate analyses.

Angiography was performed in the first seven animals only, because of anxiety over effects on cerebrovascular reactivity (Grubb *et al.*, 1974; Herrschaft *et al.*, 1974). At least 30 minutes were allowed to elapse after each angiogram (maximum of three per animal) before any measurements of CBF were made. The contrast medium used was 2 ml meglumine iothalamate (Conray 280), warmed beforehand to 37°C. After stable baseline measurements of CBF had been achieved the response to hypercapnia was assessed by adding carbon dioxide to the inspiratory gases to raise PaCO₂ to approximately 55 mmHg. The response to changing blood pressure will be reported in a separate paper.

At the end of the procedure 10 of the 11 animals were placed supine before perfusion-fixation (Brierley *et al.*, 1969; Fitch *et al.*, 1978a). After heparinisation (1000 IU/kg), a thoracotomy was performed and a cannula secured in the proximal part of the arch of the aorta. After incising the right atrium and clamping the descending aorta, physiological saline was infused briefly at the mean arterial blood pressure. Perfusion was continued at the same pressure with five litres of FAM fixative (40% formaldehyde; glacial acetic acid; absolute methanol 1:1:8). After perfusion the animals were decapitated and the head stored in the same fixative for 12–24 hours. The brain was then removed and immersion fixed in FAM for a further 24 hours. The hind-brain was then detached by a cut through the midbrain and cerebral hemispheres were cut into slices 8 mm thick. The brainstem was cut at right angles to its long axis into slices 6 mm thick and the cerebellum into two slices perpendicular to the folia of the dorsal surface of each hemisphere. Large representative bilateral blocks of brain were embedded in paraffin wax and celloidin. The paraffin sections were stained with haemalum and eosin and by a method combining cresyl violet and Luxol fast blue, and the celloidin sections by cresyl violet. The major cerebral arteries and their branches were prepared by the method of Beesley and Daniel (1956) and stained with haemalum and eosin, van Gieson and Miller's

method for elastica, and by the methods of Martius scarlet blue and phosphotungstic acid haematoxylin for fibrin.

Results

NEUROLOGICAL CONDITION

Thirteen animals were injected by the transoptic foramen route: two were discarded. In one animal an orbital haematoma developed. There have been two deaths in the series, both from intracerebral haematomata. This was presumed to be the result of pushing the needle in too far, despite the free return of CSF. Apart from the two deaths the other animals recovered well from the procedure and had no neurological or overt behavioural deficit. Their feeding patterns were unaltered. None developed clinically evident meningitis or wound infections.

HAEMODYNAMIC DATA (TABLE)

Mean arterial blood pressure in the 11 animals studied one week after subarachnoid haemorrhage was 96 ± 13 SD mmHg (12.8 ± 1.7 kPa). The mean intracranial pressure was 11 ± 7 mmHg but four animals had an intracranial pressure in the range 15–20 mmHg at normocapnia (PaCO_2 in the range 38–42 mmHg).

Baseline CBF (by the height over area method) was 46 ± 11 ml/100 g/min with a range of 32–65 ml/100 g/min. This value is the same as in normal baboons previously studied in Glasgow with this anaesthetic technique.

Cerebral oxygen consumption was 3.20 ± 0.60 ml O_2 /100 g/min with a range of 2.28–4.29 ml/ O_2 /100 g/min. Again, this value is the same as for normal baboons anaesthetised by this technique. The cisternal CSF lactate and bicarbonate con-

centrations were not significantly changed one week after subarachnoid haemorrhage compared to pre-haemorrhage values (before subarachnoid haemorrhage: lactate 2.21 ± 0.36 SD mmol/l; bicarbonate 25.3 ± 4.2 mmol/l; one week after haemorrhage: lactate 2.66 ± 0.71 mmol/l; bicarbonate 24.3 ± 5.4 mmol/l).

RESPONSE OF CEREBRAL CIRCULATION TO HYPERCAPNIA

The overall response to hypercapnia was significantly impaired one week after subarachnoid haemorrhage in the 11 baboons examined (Table). However, there was considerable variation between animals so that not all animals had an impaired response to hypercapnia. The response to hypercapnia in 30 control baboons was 3.27 ± 1.11 SD ml/100 g min^{-1} mmHg $^{-1}$ (Pickard and MacKenzie, 1973; MacKenzie *et al.*, 1976; Pickard *et al.*, 1977, 1979; and unpublished observations). One week after a subarachnoid haemorrhage, the response was 1.60 ± 1.07 SD ml 100 g $^{-1}$ mmHg $^{-1}$ (Student's *t* test = 4.308; $P < 0.001$). There was no inverse correlation between intracranial pressure and CO_2 response.

ANGIOGRAPHY

In seven baboons in whom angiography was performed in stage 2 none showed any evidence of segmental vasospasm. More quantitative data were not possible because we had deliberately avoided angiography in stage 1.

NEUROPATHOLOGY

As judged by the uniform hardening of the specimens and by the absence of blood in the vessels, perfusion-fixation appeared to be good in all animals. There was no evidence of brain swelling or of internal herniation.

Table Response of the cerebral circulation to hypercapnia, one week after subarachnoid haemorrhage in 11 baboons

Animal no.	Baseline CBF (ml. 100g $^{-1}$. min $^{-1}$)	Baseline BP (mmHg)	ICP (mmHg)	Response to CO_2 (ml. 100g $^{-1}$. min $^{-1}$. mmHg $^{-1}$)
2	46	93	20	1.59
3	57	99	7	0.84
4	65	104	8	0.82
5	46	92	20	4.27
6	55	94	17	0.56
7	47	77	4	0.44
8	50	116	10	1.56
10	34	91	0	2.00
11	44	103	7	2.16
12	32	112	12	1.43
13	32	74	16	1.95
Mean	46	96	11	1.60*
SD	11	13	7	1.07

* $P < 0.001$ when compared to control data by Student's *t* test (see text)
ICP = intracranial pressure.

Microscopy of the brain showed that the cytological artefacts, "the dark cell" and "hydropic cell", were minimal (Cammeyer, 1961). Apart from a single small focus of selective neuronal necrosis in the cortex of the posterior temporal region of one animal, the brains were normal. There was no evidence of raised intracranial pressure (Adams and Graham, 1976).

No significant abnormalities were seen in the intracranial vessels, and in particular there was no evidence of thrombus formation or of necrosis of the walls of arteries and veins.

Small amounts of blood were present in the subarachnoid space and the meninges also contained a mild infiltrate of polymorphonuclear leucocytes and monocytes.

Discussion

METHODS

Before assessing the results obtained in this investigation it is necessary to consider the possible influence of the anaesthetic agents used, the validity of the measurements of cerebral blood flow, and any consequence of the subarachnoid injection of blood on the preparation.

The anaesthetic agents used were those which are thought to influence minimally both cerebral blood flow and cerebral metabolism. There is some divergence of opinion as to the effects of nitrous oxide on cerebral blood flow and cerebral metabolism (Wollman *et al.*, 1965; Laitinen *et al.*, 1967; Theye and Michenfelder, 1968; Sakabe *et al.*, 1978). However, in the present investigation the animals were receiving a constant inspired concentration of nitrous oxide (70%). As a result, we felt that any influence nitrous oxide might exert on the cerebral blood flow would not affect the results materially. Indeed, the baseline values for cerebral blood flow (Table) compare closely with those obtained in normal unanaesthetised man (Kety and Schmidt, 1948) and are virtually identical to values obtained in previous groups of animals without intracranial pathology anaesthetised similarly (Fitch *et al.*, 1978b) and subjected to drug-induced hypotension with halothane (Fitch *et al.*, 1976).

The xenon-133 technique for the measurement of cerebral blood flow depends on the tracer being distributed to, and detected from, the brain alone and not being influenced by blood flow through extracranial tissues. To ensure this, the significant anastomotic channels present in the baboon between the circle of Willis and the extracranial tissues were obliterated during the procedure of scalp resection. In addition, it is felt

unlikely that the production of the artificial subarachnoid haemorrhage would, in any way, influence the determination of cerebral blood flow. During the actual injection of blood into the suprachiasmatic cistern any tendency to respiratory arrest in the animals was counteracted by the use of controlled ventilation, and once the animals were returned to their cages, apart from the two with intracerebral haematoma, they appeared intact neurologically and remained so until the definitive investigations took place. This was reflected both by the normal baseline values for CBF and cerebral oxygen consumption and the paucity of neuropathological damage. It will be appreciated that presence of the subarachnoid haemorrhage had influenced minimally the systemic circulation.

This preparation is an incomplete replica of the human disease as many patients have evidence of pre-existing arterial disease such as atheroma and hypertension. However, the model allows examination of certain physiological factors without the complicating effects of atheroma or of direct vessel trauma.

PATHOLOGICAL CHANGES AND THE CBF CO₂ RESPONSE

Experimental "vasospasm" has been produced in diverse laboratory animals by various methods that include arterial injury and subarachnoid haemorrhage (Heros *et al.*, 1976 for review). Experimental subarachnoid haemorrhage frequently produces angiographic narrowing lasting only one to three days and such "vasospasm" has been demonstrated in the baboon after cisternal injections of blood (Du Boulay *et al.*, 1972). Our limited angiographic studies revealed no segmental vasospasm after one week. Nevertheless, the ultrastructural changes of myonecrosis can be identified in the major cerebral arteries after subarachnoid haemorrhage (Alksne and Greenhoot, 1974; Fein *et al.*, 1974; Tanabe *et al.*, 1978; Tani *et al.*, 1978). Structural changes have also been described in the cerebral vessels of patients dying after subarachnoid haemorrhage (Conway and McDonald, 1972; Hughes and Schianchi, 1978). Hughes and Schianchi (1978) carried out a systematic light microscopic examination of the larger arteries known formerly to have been in vasospasm, and found in the short surviving cases that there was slight swelling of the intima, necrosis of the tunica media, and irregularities of the tunica elastica. These "acute" changes in the vessel wall could be related to the time interval between subarachnoid haemorrhage and death. After some three weeks they were

replaced by the "late" changes of medial and subendothelial fibrosis. The animals in this study were killed seven days after the induction of subarachnoid haemorrhage, and so it is not surprising that light microscopy of the cerebral vessels failed to identify any significant changes. This does not preclude the possibility of ultrastructural damage, and indeed the experience of other workers in this field strongly suggests that, had electron microscopy been carried out, evidence of myonecrosis might have been found. Work is in progress to explore the possibility that the reduced CBF CO_2 response in our animals is related to ultrastructural change in the intracranial vessels.

While injection of mock CSF alone to mimic the acute rise in intracranial pressure had no persisting effect on the CBF, its CO_2 or autoregulatory responses, a reduced response to CO_2 was noted acutely after subarachnoid haemorrhage in the rhesus monkey, accompanied by a CSF lactic acidosis (Hashi *et al.*, 1972a, b; Shannon *et al.*, 1972; Petruk *et al.*, 1974; Sugi *et al.*, 1975). In the present study, the cisternal CSF lactate concentration was slightly higher one week after subarachnoid haemorrhage compared to before it, but not significantly so. Bulk cisternal CSF acid-base parameters are notoriously difficult to relate to local cerebral tissue values, and our data cannot be used to confirm or refute the notion that impairment of the CBF CO_2 response or of autoregulation (see Pickard *et al.*, 1979) is related to a cerebral perivascular acidosis (Paulson, 1971; Symon *et al.*, 1973), particularly as the source of the lactate in haemorrhagic CSF is probably from red cell metabolism rather than from ischaemic brain (Froman and Crampton-Smith, 1966; Shannon *et al.*, 1972; Sugi *et al.*, 1975).

The normal level of cerebral oxygen consumption contradicts the possibility that the reduction in CBF CO_2 response is secondary to changes in cerebral oxygen consumption (Fujishima *et al.*, 1971; Fein, 1975). Intracranial pressure was not raised: hence the reduction in CBF CO_2 response cannot be explained on the basis of reduced levels of cerebral perfusion pressure, particularly as there was no change of baseline CBF.

The reduced response to hypercapnia indicates that the cerebrovascular response to local tissue acidosis will also be impaired after subarachnoid haemorrhage. This may be one of the factors responsible for the poor results associated with early surgical intervention, even in the absence of cerebral vasospasm on angiography.

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