Effects of hypotension induced with sodium nitroprusside on the cerebral circulation before, and one week after, the subarachnoid injection of blood

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SUMMARY Cerebral blood flow (CBF) and mean arterial pressure (MAP) were monitored in six normal baboons and six further animals in which an artificial subarachnoid haemorrhage (SAH) had been induced one week previously. MAP was reduced by the infusion of sodium nitroprusside. In the normal animals with administration of sodium nitroprusside, CBF increased initially but started to decrease as MAP was reduced below 65 mm Hg and fell below its baseline value when MAP was less than 50 mm Hg. In the SAH group, there was no initial hyperaemic response and CBF fell below baseline values when MAP was reduced below 50 mm Hg. When, during the infusion of the sodium nitroprusside, MAP was returned to normal using angiotensin, CBF increased above its baseline value. These results suggest that the cerebrovascular effects of sodium nitroprusside are the net result of competition between direct cerebral vasodilatation, falling arterial blood pressure and the degree of impairment of the “autoregulatory” mechanism. Evidence of ischaemic brain damage was found in the arterial boundary zones of both groups of animals.

In view of the widespread clinical use of sodium nitroprusside (SNP) both generally (management of episodes of acute systemic hypertension,^{1,2} induction of intraoperative hypotension^{3,4}) and in neurosurgery⁵ we wished to determine its effects on cerebral blood flow and cerebral oxygen consumption at different degrees of induced hypotension. There is some conflict in the literature over the cerebrovascular effects of SNP partly because previous studies have not examined the whole “autoregulatory” curve. We have examined the following questions: Does SNP have direct effects on the cerebral blood vessels and on cerebral metabolism and how are these modified one week after the subarachnoid instillation of blood? Does SNP predis-

pose to ischaemic brain damage in the boundary zones?

Methods

The effects of progressive graded decreases in systemic arterial pressure, induced by SNP, on the pressure/flow relationship of the cerebral circulation were investigated in six anaesthetised intact baboons, and in six similar animals one week after the induction of an artificial subarachnoid haemorrhage. This preparation has been described in detail.^{6,7} In brief, twelve young adult baboons were sedated with phencyclidine, anaesthesia was induced with thiopentone, the trachea intubated and anaesthesia maintained with phencyclidine and nitrous oxide in oxygen. Neuromuscular blockade was produced with suxamethonium and intermittent positive pressure ventilation used. One week previously, six of these animals were anaesthetized with thiopentone and halothane in 70% nitrous oxide and oxygen. Tracheal intubation was performed and ventilation was controlled. The suprachiasmatic cistern was punctured with a needle passed percutaneously through the optic foramen without enucleation of the orbit. Once a free flow of cerebrospinal fluid had been obtained, 0.75 ml/kg of the animal's own arterial blood was injected into the subarachnoid space over 30 seconds. After the production of the artificial subarachnoid haemorrhage anaesthesia was discontinued and the animals

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were returned to their cages. No animal developed any neurological deficits and all returned to normal feeding within 24 hours of the procedure.

Hypotensive technique

Progressive decreases in mean arterial pressure were produced in steps of approximately 10 mm Hg by the infusion intravenously (IVAC 531) of increasing amounts of sodium nitroprusside (0.01% solution in 5% dextrose) and, if required, by increases in the concentration infused. Cerebral blood flow (height/area analysis) was measured by external scintillation counting over the right parietal area after the intracarotid injection of 133 Xenon at each step decrease in arterial pressure. Each decrement in pressure took approximately 10–15 minutes to complete and once achieved, MAP was maintained at its new value for at least 5 minutes before the start of each determination of CBF and for the 10 minutes required to complete the measurement. Arterial blood gas tensions and haematocrit were measured during each CBF estimation. The oxygen contents of samples of arterial and cerebral venous blood (sagittal sinus catheter) were measured with a Lex-O₂-Con oxygen content analyser (Albury Instruments Ltd). Cerebral oxygen consumption was calculated from the product of CBF and the arteriovenous oxygen content difference. *Acute increases in systemic arterial pressure* were used to assess the physiological integrity of the cerebral circulation, and were produced by the infusion intravenously of angiotensin II amide (Hypertensin, Ciba). Prior to the start of the infusion of SNP, an acute increase in MAP (approximately 30 mm Hg) was induced and a similar acute increase in MAP was produced during the administration of the sodium nitroprusside once MAP had been decreased to around 60 mm Hg. Any change in CBF associated with the alteration in MAP was determined.

Neuropathology

At the conclusion of each investigation, the animals were perfusion-fixed and a complete neuropathological examination undertaken.^{6,7}

Statistical analysis

In the presentation of the results, mean arterial pressure has been calculated as the diastolic arterial pressure plus one third of the pulse pressure, and the values of CBF have been meaned in arterial pressure bins of 10 mm Hg; for instance, 79–70 mm Hg, 69–60 mm Hg. One-way analysis of variance was used to determine whether a significant difference existed between the two groups. Unpaired *t* tests with the Bonferroni correction were performed to examine the difference between the groups in each bin. Paired *t* tests were used to compare any increase in CBF with its baseline value.

Results

Baseline values obtained before the administration of sodium nitroprusside (or angiotensin) were comparable in both groups (table 1), and were similar to values for these indices obtained in previous studies undertaken in baboons using similar techniques of anaesthesia.^{6–8}

(A) Induced hypotension

(1) *Intact*: Before the commencement of the infusion of sodium nitroprusside MAP ranged from 87 to 113 mm Hg (mean, SD = 96 mm Hg, 7) and the control values of CBF varied between 44 and 73 ml/100 g min⁻¹ (mean, SD = 59 ml/100 min, ⁻¹ 12) at physiological carbon dioxide tensions.

As MAP was decreased progressively by the intravenous infusion of increasing amount of sodium nitroprusside, mean CBF was observed to follow the pattern depicted in fig 1. It is evident that the administration of sodium nitroprusside induced a degree of cerebral vasodilation: cerebral blood flow increasing progressively until a MAP of approximately 65 mm Hg had been achieved, at which point mean CBF was significantly (*p* < 0.005) greater than its baseline value. At lower values of MAP there was a linear pressure/flow relationship with CBF decreasing *pari passu* with the decreasing arterial pressure. CBF decreased below its baseline value when MAP decreased below about 50 mm Hg. The lowest values of CBF ranged from 26–33 ml/100 g min⁻¹ (mean, [SD] = 29 ml/100 g min⁻¹ [3]) at an average MAP of 25 mm Hg (2). The changes in CVR are illustrated in fig 1b.

(2) *Subarachnoid haemorrhage*: In this group, baseline values of mean CBF ranged from 47–70 ml/100 g min⁻¹ (mean ± SD = 56 ml/100 g min⁻¹ [± 6]) at a mean PaCO₂ of 41 mm Hg. Baseline values of mean arterial pressure varied between 83 and 122 mm Hg (mean ± SD = 104 mm Hg [± 12]).

Despite the administration of similar amounts of sodium nitroprusside, the initial hyperaemic response was virtually non-existent and the small increase in CBF did not differ significantly from the baseline value. As MAP was decreased below 50 mm Hg, CBF decreased below its baseline value (fig 1). The lowest

Table 1 Baseline values (mean ± SD) of mean arterial pressure, cerebral blood flow, cerebral metabolic rate for oxygen and arterial carbon dioxide tension

	Mean arterial pressure (mmHg)	CBF (H/A) (ml min ⁻¹ /100 g)	CMRO ₂ (ml/102 min/100 g)	PaCO ₂ (mmHg)
Intact animals (n = 6)	96 ± 7	59 ± 12	3.60 ± 1.2	40.3 ± 1.0
SAH animals (n = 6)	104 ± 12	56 ± 6	3.08 ± 0.7	41.0 ± 1.0

Fig 1 (a) Effects of the administration of sodium nitroprusside on mean arterial pressure and cerebral blood flow. Results (mean $\pm$ SEM) from 6 animals in each group. Significant differences between intact and subarachnoid (SAH) animals. * $p < 0.0125$, ** $p < 0.005$. (b) Effects of the administration of sodium nitroprusside on Mean Arterial Blood Pressure and cerebrovascular resistance (mmHg/ml 100g⁻¹ min⁻¹). Results (mean $\pm$ SEM) from 6 animals in each group. Two way analysis of variance shows that these two curves are significantly different ($p < 0.01$).

values of CBF ranged from 15–43 ml/100 g min⁻¹ (mean $\pm$ SD = 29 ml/100 g min⁻¹ [$\pm$ 9]). The changes in CVR are illustrated in fig 1(b); examination of the changes in CVR do not help to identify separate “inflection” points in the control and SAH groups.

(B) Induced hypertension

(1) *Intact*: The administration of angiotensin, at baseline values of MAP and CBF (and before the commencement of the nitroprusside infusion) increased MAP acutely by 26 mm Hg ($\pm$ 4). CBF did not change significantly from baseline in any animal (mean change = +3 ml/100 g min⁻¹ [$\pm$ 5]) (fig 2).

The infusion of angiotensin during the continued administration of sodium nitroprusside restored MAP from 57 mm Hg ($\pm$ 3) to 92 mm Hg $\pm$ 6 (99% of baseline), and this was associated with a mean increase ($\pm$ SD) in CBF of 31 ml/100 g min⁻¹ ($\pm$ 9) ($p < 0.001$) (fig 2).

(2) *Subarachnoid haemorrhage*: The administration of angiotensin, before the onset of systemic arterial hypotension, induced an acute increase ($\pm$ SD) in MAP of 31 mm Hg ($\pm$ 5). At this value of MAP mean CBF was 71 ml/100 g min⁻¹ ($\pm$ 5) – an increase of 15 ml/100 g min⁻¹ ($\pm$ 6) ($p < 0.05$) from its baseline value (fig 2).

During the continuing administration of sodium nitroprusside, and at a MAP ($\pm$ SD) of 56 mm Hg ($\pm$ 6), the infusion of angiotensin increased MAP

acutely to 112 mm Hg ($\pm$ 5). Concomitantly, CBF increased by a mean ($\pm$ SD) of 38 ml/100 g min⁻¹ ($\pm$ 15) ($p < 0.001$) (fig 2).

(C) Neuropathology

There was evidence of selective neuronal necrosis of

Fig 2 Changes in cerebral blood flow induced by acute increases in mean arterial pressure. Acute increases in mean arterial pressure were induced in both groups of animals before the administration of sodium nitroprusside and during the administration of sodium nitroprusside once mean arterial pressure had been decreased to around 60 mmHg.

the type seen in 40% formaldehyde, glacial acetic acid, absolute methanol 1:1:8 material fixed in five of both the intact and subarachnoid haemorrhage groups of six animals. No lesions were identified in one animal from each group. The ischaemic cell process was restricted mainly to the arterial boundary zones with lesions mainly between the distributions of the anterior and middle cerebral arteries (figs 3 & 4). In addition, in the intact group, one animal had lesions in the striatum and another had lesions in the thalamus. One subarachnoid haemorrhage animal had small foci of necrosis in the Sommer sector of each Ammon's Horn. In the subarachnoid haemorrhage group, some residual blood was observed in the subarachnoid space, and small amounts of haemosiderin were seen in phagocytes.

(D) Cerebral metabolic rate for oxygen

There was no substantial changes in the cerebral metabolic rate for oxygen in either group (table 2). The only changes observed were related to the final two measurements of CBF, and hence, to the two lowest values of MAP by which point $CMRO_2$ had decreased by approximately 20% and 18% from baseline in the intact and subarachnoid haemorrhage groups, respectively.

Discussion

In the normal animals, care was taken to demonstrate that the cerebral circulation had normal "autoregulatory capacity"; as confirmed by maintenance of normal CBF with moderate elevations in arterial blood pressure with angiotensin II prior to administration of sodium nitroprusside. Furthermore we have examined the complete autoregulatory curve. Our results confirmed that in the normal baboon, SNP produces an initial hyperaemia despite a moderate decrease in MAP, and that this hyperaemia was not due to metabolic stimulation as there is no change in cerebral oxygen consumption (our study is unusual in the literature for reporting values for $CMRO_2$ in such experiments). There has been some controversy in the literature as to whether such a hyperaemia exists^{9 10} or not.¹⁵⁻¹⁸ Certainly, both experimentally¹¹ and in man¹²⁻¹⁴ intracranial pressure increases with small doses of SNP. In man, there was no significant change in CBF at 50 mm Hg compared with baseline value but the intermediate steps were not examined.¹⁹

SNP would appear to impair "autoregulation", that is, the ability of the cerebral circulation to main-

Coronal sections of monkey brain

Fig 3 Intact animal: diagrammatic representation of coronal sections of brain. Hatched areas depict those with morphological evidence of ischaemic cell change.

Coronal sections of monkey brain

Fig 4 Subarachnoid animal: diagrammatic representation of coronal sections of brain. Hatched areas depict those with morphological evidence of ischaemic cell change.

Table 2 Values of cerebral oxygen consumption (mean $\pm$ SD) at different levels of mean arterial blood pressure induced by sodium nitroprusside both in intact animals and one week following subarachnoid haemorrhage

Mean arterial pressure range (mmHg)	Cerebral oxygen consumption (ml O ₂ 100g ⁻¹ /min)	
	Intact (n = 6)	Post-SAH (n = 6)
100-109	3.54 $\pm$ 1.06	2.95 $\pm$ 0.58
90- 99	3.89 $\pm$ 1.42	3.58 $\pm$ 0.67
80- 89	3.37 $\pm$ 1.24	3.29 $\pm$ 0.41
70- 79	3.90 $\pm$ 1.44	3.08 $\pm$ 0.50
60- 69	3.99 $\pm$ 1.37	2.97 $\pm$ 0.31
50- 59	3.83 $\pm$ 1.20	3.03 $\pm$ 0.61
40- 49	2.99 $\pm$ 1.03	3.03 $\pm$ 0.61
30- 39	2.98 $\pm$ 0.88	2.75 $\pm$ 0.62
20- 29	2.51 $\pm$ 0.86	2.19 $\pm$ 0.59

tain constant flow with changing perfusion pressure. Return of MAP to normal from 60 mmHg using angiotensin II during constant SNP infusions, results in a considerable increase in CBF. If SNP was not a direct vasodilator and had no effect on the autoregulatory mechanism, then return of MAP to normal would not produce any increase in CBF. This "pressor test" was originally reported by Ivankovich in 1976.⁹ Although the direct perivascular injection of angiotensin II induces significant vasoconstriction of pial arterioles, systemic administration had no effect on global CBF.²⁰ However, the systemic administration of angiotensin II may have a vasoconstrictor effect in parts of the cerebral circulation not insulated by the normal blood brain barrier. As angiotensin II has either no effect or contracts cerebrovascular smooth muscle in vivo, the increase in CBF with angiotensin in this study cannot be ascribed to its direct vascular effects. It might be argued that these effects were the result of the accumulation of toxic metabolic products of sodium nitroprusside. The fall in CMRO₂ at the lowest levels of arterial pressure might reflect cyanide toxicity. In total, a number of animals received more than the accepted maximum dose of SNP (0.5 mg/kg/hour). However, most of the administered dose was utilised to obtain, and then sustain, the lowest value of MAP. The amounts of sodium nitroprusside required to produce MAPs of around 60 mmHg were approximately 0.2 mg/kg/hour, and 0.17 mg/kg/hour in the intact and subarachnoid haemorrhage groups, respectively. We conclude that sodium nitroprusside is not only a cerebral vasodilator but that it impairs the ability of the normal cerebral circulation to respond physiologically to increases or decreases in MAP. A similar conclusion was reached by Ivankovich *et al* in the goat.⁹ Under these circumstances, the term "autoregulation" is a misnomer: CBF is determined by the interplay between the induced alterations in perfusion pressure, the direct cerebral vasodilatory actions of

the drug and the degree of impairment of the autoregulatory mechanism. The direct effects of sodium nitroprusside on the contractile mechanism of vascular smooth muscle may alter the intrinsic reactivity of the cerebral blood vessels. It is not possible to validate the presence or impairment of "autoregulation" by altering mean arterial pressure with drugs which have direct effects of vascular smooth muscle. Furthermore, the precise pattern of the pressure flow relationship differs depending on the drug employed to decrease MAP. In the intact cerebral circulation, CBF is maintained at or above the baseline value until MAP is reduced below 50 mmHg with SNP. In a previous study from this laboratory, hypotension induced by the combination of halothane (0.5%) and SNP did not increase CBF at MAP higher than 45 mmHg. However, halothane not only reduces the dose of SNP required to produce any level of hypotension but also attenuates the direct cerebral vasodilator effects of SNP.⁹

As documented fully in the earlier papers^{6,7} these animals are neurologically intact one week after the subarachnoid injection of blood, have normal intracranial pressure with no ischaemic cell change or ultra-structural damage to the cerebral arteries. Despite this rather mild insult compared with that seen in many patients, both the ability of the cerebral circulation to maintain CBF constant with moderate halothane-induced hypotension or angiotensin-induced hypertension and the reactivity to hypercapnia and hypoxia are impaired one week after a subarachnoid haemorrhage.

Autoregulation to halothane-induced hypotension during surgery for aneurysmal subarachnoid haemorrhage is impaired in about 25% of patients who had a normal conscious level and no neurological signs pre-operatively.²² These present studies confirm that, following subarachnoid haemorrhage, CBF does not remain constant but increases with moderate hypertension induced with angiotensin II prior to administration of sodium nitroprusside. There is no initial hyperaemia with SNP in the subarachnoid haemorrhage group, but CBF does not start to decrease significantly until MAP decreases below around 50 mmHg. The risk of development of delayed cerebral ischaemia after clipping of the aneurysm is greatly increased in those patients whose CBF decreases with moderate hypotension induced by halothane or trimetaphan. In a small series of patients the prognosis post-operatively was worse in those in whom CBF did not increase with SNP-induced hypotension but either remained constant or decreased.²³ Our experimental results confirm that it is abnormal for cerebral blood flow not to increase with moderate hypotension induced with sodium nitroprusside.

In contrast to our previous studies⁷ with halothane-induced hypotension where no ischaemic cell change was found using a similar experimental protocol (lowest MAP value: 26 mmHg in the intact group and 32 mmHg in the subarachnoid haemorrhage group), ischaemic cell damage was found both in the intact and subarachnoid haemorrhage groups after SNP (lowest MAP: 25 mmHg intact; 24 mmHg subarachnoid haemorrhage), despite global CBF remaining at or above 25 ml/100 gms/min. The detection of ischaemic cell change avoids the sampling errors inherent in techniques such as the determination of micro-regional CBF and the measurement of changes in the brain concentrations of extracellular ions. The pattern of ischaemic cell change noted in the present study mirrors that of the changes to the blood brain barrier demonstrated recently by Ishikawa and colleagues.²⁴ In addition, regional variation in the cerebrovascular response to SNP was found in the goat.²⁵

The net effects of SNP on global cerebral blood flow are the results of a complex interaction and the apparent maintenance of CBF above a MAP of 50 mmHg should not be taken to imply that physiological reactivity is normal. Whilst the ischaemic threshold of the brain may not be altered, the anaesthetist cannot depend on the physiological integrity of the cerebral circulation to protect the brain from the effects of inadvertent or uncontrolled decreases in arterial pressure. We do not know how long the cerebrovascular effects of SNP take to reverse after it is stopped.

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