Autoregulation of cerebral blood flow during controlled hypotension in baboons

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Synopsis

The effect of graded, progressive hypotension on the autoregulation of cerebral blood flow was studied in anaesthetised baboons. Progressive hypotension was produced over a period of four to five hours, either by graded haemorrhage or by the administration of increasing concentrations of hypotensive drugs. During haemorrhagic hypotension autoregulation was maintained until the mean arterial pressure had decreased to 65% of its baseline value, below which cerebral blood flow was pressure passive. In those animals subjected to drug-induced hypotension, autoregulation persisted to lower levels of mean arterial pressure (35–40% of baseline). It is postulated that under conditions of haemorrhagic hypotension, constriction of the extraparenchymal cerebral vessels in response to sympathetic stimulation decreases the possible range of autoregulation in the anaesthetised baboon.

Since its introduction into anaesthetic and surgical practice (Gardner, 1946), controlled hypotension has been used extensively to reduce bleeding and to facilitate surgery. However, despite the widespread use of the technique, the indications for induced hypotension have not been defined clearly and considerable disagreement exists regarding its safety (Davison, 1958; Enderby, 1958; 1972; Mayrhofer, 1971). The primary objections stem from uncertainties regarding the adequacy of cerebral tissue perfusion during the period of lowered arterial pressure (Briery and Cooper, 1962; Adams et al., 1966).

The present investigations were undertaken to measure the effect of a graded and progressive decrease in systemic arterial pressure on the cerebral blood flow of anaesthetised baboons and to compare the effects of haemorrhagic and pharmacologically-induced hypotension.

Methods

Young adult baboons (9–14 kg) were tranquillised with phencyclidine (12 mg intramuscularly) and then anaesthetised with thiopentone (7.5 mg/kg intravenously), nitrous oxide and oxygen (70%:30%). In addition, half-hourly doses of phencyclidine (2 mg intramuscularly) and suxamethonium (100 mg intramuscularly) were administered to prevent awareness and to produce muscular relaxation. The trachea was intubated and ventilation was controlled throughout each investigation (Starling respiratory pump), the minute volume and the inspired oxygen concentration being adjusted to produce normocapnia and normoxia. The end-tidal carbon dioxide concentration was monitored continuously by an infra-red analyser (URAS 4: Hartmann and Braun). During each determination of cerebral blood flow, the arterial pH and blood-gas tensions were measured using appropriate, suitably calibrated electrodes (Radiometer). Body temperature was maintained within normal limits (36°C–38°C) by means of heating lamps. Correction was made, where necessary, for any temperature difference existing between the animal and the electrode system (Severinghaus, 1966).

Cerebral blood flow was determined by external scintillation counting over the right parietal area after

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the intracarotid injection of $^{133}$Xenon. Mean cerebral blood flow was calculated from the height/area equation (Høedt-Rasmussen et al., 1966). The scalp and temporal muscle were removed from the right side of the cranium and the right common carotid artery and its branches were exposed in the neck. All the branches of the right external carotid artery except the lingual branch were ligated distally. The lingual branch was cannulated with a fine polyethylene catheter placed at its junction with the carotid artery.

For each measurement of cerebral blood flow 0.4–0.8 mCi $^{133}$Xenon, dissolved in approximately 0.5 ml saline, was injected into the internal carotid artery by the catheter in the lingual branch. A heavily collimated 2.5 cm scintillation crystal was placed directly over the exposed skull and angled in such a way that there was no possibility of counting radioactivity from the surrounding tissues of the face and neck. The scintillation crystal was connected to a ratemeter, a scaler, and a direct writing recorder. The pulse height analyser was set at 81 keV with a gate of $\pm 10\%$—that is, with a lower limit of 74 keV—thus effectively preventing any recording of Compton scatter. On each occasion, the recording of the decay of $^{133}$Xenon was followed for 10 minutes.

Systemic arterial pressure was measured electronically (Bell and Howell transducer) from the abdominal aorta through a catheter inserted via the left femoral artery. Other catheters were inserted similarly into the inferior vena cava by the left femoral vein and into the right femoral artery and vein. Intravenous infusions were administered through the venous catheter and blood was withdrawn for the measurement of arterial blood-gas tensions and for the production of haemorrhagically-induced hypotension through the arterial catheter.

The response of the cerebral circulation to changes in the systemic arterial pressure was studied under the following conditions:

**HAEMORRAGHIC HYPOTENSION (10 animals)**

Step-wise reductions in mean arterial pressure were obtained by the intermittent withdrawal of blood. Sufficient blood was withdrawn on each occasion to decrease mean arterial pressure by approximately 1.3 kPa. The blood was withdrawn into a reservoir which was heparinised and kept at 37°C. The reservoir was connected to a sphygmomanometer and could thus be held at any desired pressure. The animals were heparinised during the investigation. Cerebral blood flow was measured at each step-reduction in pressure. In each animal, mean arterial pressure was decreased from baseline values to approximately 3.3–4.0 kPa.

**DRUG-INDUCED HYPOTENSION (15 animals)**

Hypotension was induced pharmacologically by the intravenous infusion or the inhalation of increasing concentrations of the following drugs: halothane plus trimetaphan camphorsulphonate (Arfonad: 0.1%), halothane plus sodium nitroprusside (0.01% solution), and halothane alone. There were five animals in each group.

The maximum inspired halothane concentration was 0.5% except in the group of animals given halothane alone. In this particular group, inspired concentrations of up to 3.5% halothane were used to induce the required degree of hypotension. In each animal, sufficient of the drug under study was administered to decrease mean arterial pressure in steps of approximately 1.3 kPa. In each animal mean arterial pressure was decreased step-wise from baseline values to approximately 4.0 kPa. Cerebral blood flow was measured at each decrement in pressure.

In all four groups of animals, each step-reduction in mean arterial pressures took approximately 15 minutes to complete. Mean arterial pressure was then held steady for at least five minutes before the start of each cerebral blood flow determination and for the 10 minutes required to complete the measurement.

**TREATMENT OF RESULTS**

In the presentation of the results of this investigation, mean arterial pressure has been calculated as the diastolic pressure plus $\frac{1}{3}$ pulse pressure. Where applicable, significant differences between groups have been assessed using Student’s $t$ test for unpaired data and are indicated by the appropriate $p$ value.

Each animal’s resting or baseline cerebral blood flow and baseline mean arterial pressure has been used as its own control and expressed as 100%. Changes in mean arterial pressure and in cerebral blood flow in each animal have been expressed as a percentage of its own baseline value. In addition, for ease of analysis the blood flow results in each group of animals have been meaned at 10% intervals of the baseline mean arterial pressure—for instance, 79%–70%, 69%–60% of baseline mean arterial pressure.

**RESULTS**

Before the induction of hypotension, baseline values for mean arterial pressure, mean cerebral blood flow (CBF), arterial carbon dioxide tension (PaCO$_2$) and arterial pH were noted to be comparable in each of the groups studied (Table). The mean control values for CBF ranged from 48 to 52 ml/100g min$^{-1}$ (average 50 ml/100g min$^{-1}$) in each group. These values are similar to values obtained in other studies.
utilising the same method of CBF measurement and studied under similar conditions of anaesthesia (Harper et al., 1972; Strandgaard et al., 1974). The mean arterial pressures of the groups of animals ranged from 11.3 to 12.6 kPa (average 12.0 kPa). PaCO₂ was held consistently at 5.32 kPa with a maximum standard deviation of 0.29 kPa. In each group of animals there was a decrease in arterial pH as a result of the hypotension. The decreases in pH ranged from 0.19 unit in the animals subjected to haemorrhagic hypotension to 0.10 unit in those given halothane alone. The degree of systemic acidosis was significantly greater (p < 0.02) in the haemorrhagic hypotension group when compared with each of the drug-induced hypotension groups.

HAEMORRHAGIC HYPOTENSION

The results from the 10 animals subjected to haemorrhagic hypotension are presented in Fig. 1. Before the induction of hypotension, baseline values for mean arterial pressure ranged from 10.2 to 13.7 kPa (mean ± SD = 12.2 kPa ± 0.93) in the individual animals. At normal PaCO₂ values, mean CBF ranged from 40 to 70 ml/100g min⁻¹ (mean ± SD = 52 ml/100g min⁻¹ ± 11).

After the induction of hypotension there was, in each animal, a period during which the CBF remained relatively constant despite the decreases in mean arterial pressure. As the mean arterial pressure was decreased further, this period of relative stability of CBF was succeeded by a phase during which CBF was observed to decrease with the decreasing arterial pressure (Fig. 1). In this group of animals, mean arterial pressure could be decreased to approximately 60–65% of its initial value before there was any decrease in CBF. At mean arterial pressures below this value, CBF was pressure dependent.

DRUG-INDUCED HYPOTENSION

Halothane plus trimetaphan

Before the induction of hypotension in this group of animals, pressure ranged from 11.7 to 14.0 kPa (mean ± SD = 12.6 kPa ± 0.81) and the baseline values for mean CBF varied between 35 and 72 ml/100g min⁻¹ (mean ± SD = 47.8 ml/100g min⁻¹ ± 11.8) at a mean PaCO₂ of 5.29 kPa.

As mean arterial pressure was decreased progressively by the intravenous infusion of increasing amounts of trimetaphan, the changes in mean CBF followed the pattern depicted in Fig. 2. Once again there was a period of relatively stable CBF at moderately decreased levels of mean arterial pressure which was followed, at lower mean arterial pressures, by the second phase during which cerebral blood flow decreased concomitantly with the decreasing arterial pressure. However, it was observed that, in this group, the pressure/flow plateau was present to a lower level of mean arterial pressure (40% of initial value) than had been found in those animals subjected to haemorrhagic hypotension alone (Fig. 2). It was found also
Halothane alone

been (P<0.01) plus trimetaphan (--- PaCO₂ values, sodium of pressure and persisted compared as kPa ± hypotension. In

that at mean arterial pressures of approximately 45% and 35% of baseline value, mean CBF was significantly greater (p<0.005 and p<0.05 respectively) in those animals subjected to drug-induced hypotension as compared with those animals subjected to haemorrhagic hypotension alone.

Halothane plus sodium nitroprusside

In this group of five animals baseline values for mean CBF ranged from 38 to 60 ml/100g min⁻¹ (mean ± SD = 49.9 ml/100g min⁻¹ ± 5.9) and mean arterial pressure ranged from 9.6 to 13.3 kPa (mean ± SD = 11.3 kPa ± 1.17).

With the induction of hypotension it was found that, as in the two previous groups of animals subjected to drug-induced hypotension, the pressure/flow plateau was present and persisted to levels of mean arterial pressure significantly lower (p<0.001) than was found in those animals subjected to haemorrhagic hypotension. In these animals mean CBF remained relatively unchanged despite the progressive changes in mean arterial pressure, until a mean arterial pressure of approximately 40% of the baseline value had been reached (Fig. 4). In addition, when mean arterial pressure was 45% of baseline, mean CBF was significantly greater (p<0.01) in this group than in those animals subjected to haemorrhagic hypotension.

It is interesting to note that, during the administration of a low concentration of halothane (mean arterial pressure 75% of baseline) mean CBF was slightly, although not significantly, lower when compared with the results obtained at the same mean arterial pressure in the animals given trimetaphan and nitroprusside. At a mean arterial pressure of 45% of resting value the opposite was true, mean CBF being greater, although again not significantly so, when compared with the other two groups of animals subjected to drug-induced hypotension (Fig. 5).
FIG. 4 Effect of decreasing mean arterial pressure on mean cerebral blood flow in baboons subjected to haemorrhagic hypotension (●—●) and those subjected to drug-induced hypotension with halothane (○—○). Values shown are means ± SE. **p < 0.01.

FIG. 5 Comparison of the effect of decreasing mean arterial pressure on mean cerebral blood flow in baboons subjected to drug-induced hypotension: halothane plus trimetaphan (□), halothane plus sodium nitroprusside (×), and halothane alone (○). Values shown are means.

DISCUSSION

METHODS

Before assessing the results obtained in this series of investigations, it is necessary to discuss the possible effects of the anaesthetic agents used and the validity of the measurements of cerebral blood flow.

The anaesthetic agents used were those which are thought to have a minimal influence on CBF and cerebral metabolism. The baseline values for CBF (Table) compare closely with those obtained in normal unanaesthetised man (Kety and Schmidt, 1948). Wilkinson and Browne (1970) showed that patients anaesthetised with nitrous oxide, oxygen, and phenoperidine had CBF values similar to those obtained in conscious patients. Although there is some divergence of opinion as to the effects of nitrous oxide on CBF and cerebral metabolism (Laitinen et al., 1967; Wollman et al., 1965), most studies support the view that its influence is minimal (Wollman et al., 1965; Theye and Michenfelder, 1968). In the present investigation, the effects of both haemorrhagic and drug-induced hypotension were studied, both at baseline values and during hypotension, while the animals were receiving a constant inspired concentration of nitrous oxide (70%) during and for two to three hours before the experiment. As a result, it is felt that any influence nitrous oxide might exert on the CBF would not affect the results materially.

The $^{133}$Xenon technique for the measurement of CBF depends on the tracer being distributed to, and detected from, the brain alone and not being influenced by blood flow through extracranial tissues. To this end, the scalp and temporal muscle on the ipsilateral side of the skull were resected and the branches of the external carotid artery, with the exception of the linguofacial trunk, ligated. The significant anastomotic channels in the baboon between the circle of Willis and the extracranial tissues, the supratrochlear and supraorbital branches of the ophthalmic artery and the occipital diploic vessels, were obliterated during the procedure of scalp resection.

HAEMORRHAGIC HYPOTENSION

The maintenance of a relatively normal CBF in face of moderate systemic hypotension is accepted widely (Lassen, 1959; Harper, 1969). Previous investigations in animals subjected to graded haemorrhage Håggedal and Johansson, 1965; Harper, 1966; James et al., 1969; Eklöf et al., 1971) have shown that the CBF remained relatively unchanged until the mean arterial pressure had been decreased to 55–65% of baseline values. Comparable findings have been observed in man (Lassen, 1964; Olesen, 1973). In the present study, autoregulation was evident to mean arterial pressures of 60–65% of the baseline values in those animals subjected to haemorrhagic hypotension.

DRUG-INDUCED HYPOTENSION

In the animals subjected to drug-induced hypotension, not only was autoregulation present, but it was found
to persist to significantly lower levels of mean arterial pressure (35-45% of baseline values). Similar findings were obtained with each of the drugs studied. The effects of drug-induced hypotension on cerebral blood flow have been studied in animals by several groups of workers (Carter and Atkinson, 1973; Keaney et al., 1973; McDowall et al., 1974). However, in these studies hypotension was induced acutely (over a few minutes) and observation of any change in autoregulation was not possible. In contrast with the findings of the present study, Stoyka and Schutz (1975) found in dogs that, whereas the administration of nitroprusside did not affect cerebral autoregulation, animals given trimetaphan showed no evidence of autoregulation, CBF decreasing pari passu with the decreases in mean arterial pressure. The picture is confused further by the findings of Crockard et al. (1976) who demonstrated a loss of autoregulation after the infusion of nitroprusside in rhesus monkeys, whereas autoregulation was unaffected by the administration of trimetaphan. It is true, however, that the full range of autoregulation was not studied in this latter investigation, mean arterial pressure being decreased to a maximum of 35-40% from baseline. Previously, Bessman et al. (1952) had shown that, in animals subjected to ganglionic blockade with tetraethylammonium chloride, autoregulation was present to a mean arterial pressure of 6.5 kPa, and Waltz (1968) used several agents including nitroprusside to decrease arterial pressure in cats and found no change in CBF in the non-ischaemic hemisphere. It is difficult to define reasons for such variability in the response to trimetaphan and nitroprusside. It is true that these drugs produce hypotension by different mechanisms, nitroprusside acting directly on the vessel wall, whereas trimetaphan acts via ganglionic blockade. In addition, it is possible that the halothane administered concurrently (albeit in low concentrations) in the present study may have influenced the results in those animals given trimetaphan and nitroprusside. Nevertheless, one would have expected the effect of the halothane to be similar in both groups of animals.

No single study appears to have examined the effects of a graded decrease in mean arterial pressure, to levels of around 4.0 kPa, on the CBF in man. However, several studies on conscious volunteers (Stone et al., 1955) and awake patients (Finnerty et al., 1954; Moyer and Morris, 1954; Parrish et al., 1957) examined the effects of acute decreases in arterial pressure. Marked changes in CBF were not found despite decreases in mean arterial pressure of approximately 40%. Several studies in anaesthetised patients support the contention that CBF is altered minimally during drug-induced hypotension to mean arterial pressures of between 5.3 and 8.0 kPa. Hypotension was produced by the administration of hexamethonium (Slack and Walther, 1964), hexamethonium, pentolinium, trimetaphan and/or guanethidine (Eckenhoff et al., 1963), sodium nitroprusside (Griffiths et al., 1974), or veratum during nitrous oxide anaesthesia (Smith et al., 1970). Smith and colleagues (1970) did find a decrease in CBF in patients in whom hypotension was induced with veratum during deep cyclopropane anaesthesia, CBF decreasing from an elevated value (most probably due to the effects of cyclopropane) of 67.5 ml/100g min⁻¹ to a more normal value of 46 ml/100g min⁻¹ when cerebral perfusion pressure equalled 5.6 kPa.

It is interesting to note that in serial angiographic studies of the cerebral circulation in dogs, Lin (1974) demonstrated that, during profound systemic hypotension induced either by the infusion of trimetaphan or by haemorrhage, there was prolongation of the arterial phase. This prolongation of the arterial phase occurred at a mean arterial pressure of 4 kPa in those animals given trimetaphan and at 6.7 kPa after haemorrhage.

The observations in the present study that autoregulation persisted to lower levels of mean arterial pressure under conditions of drug-induced hypotension can be explained best by the 'dual effects' hypothesis advanced by Harper and his colleagues (1972). From their studies they suggested that the cerebral circulation could be described as consisting of two resistances in series: the extraparenchymal vessels being influenced by the autonomic nervous system, while the intraparenchymal vessels are regulated by intrinsic metabolic or myogenic mechanisms. This theory has been supported by a number of more recent investigations (Olesen, 1972; Gotoh et al., 1973; Stoica et al., 1973). Before maximal vasodilatation of the intraparenchymal vessels it might be expected that any vasoconstriction of the large arteries at the base of the brain (mediated through the autonomic nervous system) would be met by a compensatory vasodilatation of the intraparenchymal arteries, thus maintaining CBF constant. Once the lower limit of autoregulation has been exceeded and the intraparenchymal vessels were dilated already, then any influences on the larger, extraparenchymal vessels would tend to reduce flow further through these vessels and compromise CBF. Additional evidence for this hypothesis comes from angiographic studies which have demonstrated, in the baboon, that in haemorrhagic shock there is vasoconstriction (not autoregulatory dilatation) of the arteries supplying the brain and at the base of the brain, the vasoconstriction being proportional to the degree of
hypotension (du Boulay et al., 1972). In addition, carotid artery flow had been shown to be significantly reduced under conditions of acute oligoergic hypotension (Rittman and Smith, 1966; Yashon et al., 1971). In the context of the present study it is suggested that the increased sympathetic discharge present during haemorrhagic hypotension would cause vasoconstriction of the extraparenchymal arteries and a reduction in the possible range of autoregulation. It is postulated that, under the condition of normovolemic drug-induced hypotension, this effect occurs at lower levels of mean arterial pressure or is, in some way, 'blocked' by the action of the drugs used in the study. Further investigations on the effects of chemical and surgical sympathectomy on the pattern of autoregulation would tend to confirm this postulate (Fitch et al., 1975).

CLINICAL SIGNIFICANCE
The animals used in this study were young adult baboons with normal intracranial circulations. Thus it would seem reasonable to extrapolate the findings of this study to the use of induced hypotension in young adult patients with normal intracranial circulations and with intact autoregulation. In these circumstances, drug-induced hypotension to levels of mean arterial pressure approximately 35–40% of the patients' baseline values would not be expected to produce any significant effect on CBF. The successful use, in the clinical situation, of a technique of hypotensive anaesthesia similar to that used in this study (Aitken and Drake, 1974) would tend to support this contention. Although autoregulation of cerebral blood flow was impaired or lost at the levels of mean arterial pressure noted in this study, mean CBF was still within the accepted normal range. It was not until mean arterial pressures of less than 4.0 kPa had been attained that the mean CBF decreased to values of less than 30 ml/100g min⁻¹ in the animals subjected to drug-induced hypotension.

Although in this study no significant difference was observed between the effects of the three techniques of drug-induced hypotension on mean CBF, it may be that the known cerebral vasodilator actions of halothane (Wollman et al., 1964; McDowall, 1967) would be of marginal benefit to the cerebral circulation during hypotension, although the additional actions of halothane on the myocardium (Prys-Roberts et al., 1974) would have to be considered in any hypotensive technique.

It is more difficult to extrapolate the results of this study to patients undergoing neurosurgical operations. In all probability the results would be valid in patients subjected for surgery but with intact autoregulation. However, the present study does not indicate what might happen to CBF when hypotension is induced in patients in whom autoregulation is impaired or lost either globally or in localised areas of the brain. Further studies would be required to elucidate this point.

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