CEREBROVASCULAR RESPONSIVENESS IN BRAIN INJURY AND OEDEMA

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DECLARATION

I declare that this thesis is my own composition, and that it is a record of original work carried out in the University Department of Neurosurgery, Institute of Neurological Sciences, and the Wellcome Surgical Research Institute, Glasgow, Scotland in 1974 and 1975. The thesis contains no material which has been accepted for the award of any other degree or diploma in any University and to the best of my knowledge and belief, it contains no material previously published or written by another person except where due reference is made in the text.

CONTENTS

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Aspects of this study have been presented at the following meetings:

The 7th International Symposium on Cerebral Blood Flow, "Blood Flow & Metabolism in the Brain".
Aviemore, Scotland.
Reilly, et al., 1975.
Rowan, et al., 1975.

The Workshop on Dynamic Aspects of Cerebral Edema,
Montreal, Canada.
Miller et al., 1976.

The 8th International Symposium on Cerebral Blood Flow, "Cerebral Function, Metabolism & Circulation".
Copenhagen, Denmark.
Reilly et al., 1977b.

In addition, part of this study has been published in the paper,

> Vascular reactivity in the primate brain after
> acute cryogenic injury.
> Reilly et al., 1977a.

The full references to these papers are given in the bibliography.

SUMMARY

Brain injuries, traumatic, ischaemic, hypoxic or inflammatory are a common cause of death or severe handicap. Clinical assessment and treatment may be hampered by difficulty in predicting and measuring the complex changes initiated by an injury and occurring within the enclosed cranium.

Clinicians seeking to increase perfusion and limit brain damage have advocated such methods as increasing arterial pressure or hypercapnia. However cerebral blood flow measurements in patients have shown that the responses of the cerebral vessels to these physiological stimuli may be quite variable. Several studies have reported constant cerebral blood flow with arterial hypertension in patients with severe brain damage, even though experimental studies have shown that physiological autoregulation may be impaired by quite minor injuries.

The present study analysed the changes in cerebral blood flow, intracranial pressure, brain tissue water and electrolyte content following an acute cryogenic injury in baboons. This model of a focal necrotic injury with oedema resembles a cerebral contusion or infarction, and the oedema is also similar to that which develops around inflammatory or neoplastic lesions. In the first series of experiments, cerebral blood flow and cerebral vascular reactivity were studied before and after cryogenic injury. Cerebral blood flow was measured by intracarotid ^{133}Xenon clearance. Following injury, arterial hypertension was accompanied by a marked increase in cerebrovascular resistance in half the animals studied. Comparison with animals which did not show this response clearly demonstrated that such an increase in cerebrovascular resistance was not physiological autoregulation, but rather indicated a severe degree of brain damage.

The second series of experiments studied changes occurring 24 hours after cryogenic injury. At this time the effects of the primary injury could be separated from those of the secondary oedema. Cerebral blood flow was measured in small areas in both cerebral hemispheres by hydrogen clearance. A methodological study established the accuracy of this technique by comparing it with the intracarotid ^{133}Xenon method.

In areas with oedema, resting cerebral blood flow was low and failed to increase with arterial hypertension, even though other parameters of cerebrovascular reactivity were impaired. In animals with injury but no oedema, cerebral blood flow increased in a pressure-passive manner indicating loss of autoregulation. Furthermore, focal injury with and without oedema produced widespread changes in resting cerebral blood flow and cerebrovascular reactivity in both hemispheres.

These experiments demonstrate that clinical studies of patients with brain damage which report intact autoregulation based on the cerebrovascular response to arterial hypertension must be interpreted with care. They also provide an explanation why apparently intact autoregulation may not correlate with the outcome from injury.

Increasing cerebrovascular resistance with arterial hypertension in areas of injury appeared to depend upon the presence of oedema. However, changes in cerebral blood flow and cerebrovascular responsiveness also occurred in grey and white matter throughout both hemispheres, and were not related to changes in tissue fluid. These widespread effects of a focal injury may underly the clinical phenomenon of diaschisis.

Clearly, the responses of the cerebral vasculature in areas of injury are quite variable. In severe injuries, particularly those associated with oedema, arterial hypertension and hypercapnia may not lead to increased tissue perfusion, but may indeed increase tissue damage.

Methods of reducing oedema and lowering cerebrovascular resistance, perhaps by reducing tissue pressure, are an essential part of any attempt to increase perfusion in areas of brain damage.

A clinical study of patients with brain lesions and oedema, measured blood flow by the inhalational ^{133}Xenon method in areas of reduced X-ray density recorded by computerized axial tomography (CAT scanning). This study showed the value of CAT scanning in detecting oedema and monitoring therapy. Cerebral blood flow was low in areas of verified oedema, and appeared to increase with steroid therapy.

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INTRODUCTION

INTRODUCTION

> "Injuries of the head affecting the brain are difficult of distinction, treacherous in their course and, for the most part, fatal in their results".
>
> George James Guthrie, 1847.

One hundred and thirty years later a clinician may be more optimistic. Nonetheless, neurological dysfunction often seems disproportionate to the apparent severity of a brain injury. Patients may show progressive impairment of function and the clinician attempting to reverse this trend must try to unravel a series of complex interrelationships between the many factors which bear on brain function. As in Guthrie's day, these problems still demand a complete solution.

The policy of active treatment of brain injury is based on the premise that acute brain damage - whether it be traumatic, ischaemic, hypoxic, or inflammatory - is compounded by secondary effects, which may be cerebral or systemic. Even though the primary injury is out of the clinicians' control, an improvement in outcome would result if the secondary effects could be prevented or reversed. To do so, it is necessary to understand the changes which occur in neural, hydrodynamic and vascular equilibria.

Several interrelated disturbances may combine to impair the function of the brain. These include changes in cerebral blood flow and its control, intracranial pressure, cerebrospinal fluid circulation, cerebral metabolism and blood-brain barrier permeability. There may develop brain oedema, brain distortion and herniation; systemic hypoxia or hypotension. These factors interact in a complex way, yet it is necessary to distinguish cause from effect in order to apply rational therapy.

The purpose of the work described in this thesis was to examine the effects of acute brain damage with oedema on intracranial pressure, cerebral blood flow, and the responses of cerebral blood flow to

physiological stimuli. It is not possible to undertake such a detailed study in man, so an animal model was used. This allowed good physiological control which is essential before valid conclusions can be drawn concerning cerebrovascular responsiveness, and allowed direct measurement of regional oedema. The literature is reviewed in sections related to the variables considered in these experiments.

LITERATURE REVIEW

INTRACRANIAL PRESSURE

Intracranial pressure (ICP) normally remains within narrow limits, but it varies with posture (Bradley, 1970). Cardiac and respiratory wave forms are transmitted from the cerebral arteries and veins (O'Connell, 1943). These pressure changes are transmitted freely throughout the open cerebrospinal (CSF) pathways (Langfitt et al., 1964a, 1964b).

Understanding of raised ICP began with the observations of Monro (1783), and Kellie (1824). Noting that the intracranial contents were contained within a rigid skull, and were themselves incompressible, they deduced that cerebral blood volume must under all circumstances remain constant. Burrows (1846) realised the importance of the CSF space and proposed that changes in the volume of one or two of the three principal intracranial components, brain, blood and CSF, could be accommodated by corresponding changes in the others. Thus an increase in CSF volume might be accommodated without pressure change, by an extracranial diversion of an equal volume of blood.

Later studies have shown that an essential requirement for volume compensation is that the cranial compartment is not completely enclosed, but communicates freely with the spinal compartment. Below a pressure of 20 mm Hg, 70 per cent of a volume addition to the CSF is accommodated by the spinal compartment and 30 per cent by the cranial compartment (Löfgren & Zwetnow, 1973). Were it not that CSF, approximately 9 per cent of total intracranial volume (Rosomoff, 1961) could be displaced rapidly to the distensible spinal subarachnoid space, a small increase in intracranial volume would cause a rise in ICP, incompatible with life (Langfitt, 1969). Slowly expanding lesions may also be accommodated by changes in the rate of formation or absorption of CSF (Ryder et al., 1953).

Cerebral blood volume (CBV), approximately 7 per cent of total intracranial volume in man, (Nylin et al., 1961) may vary rapidly by dilatation or constriction of the cerebral resistance vessels or by compression and emptying of cerebral veins to the venous sinuses. Changes in this fluid compartment may affect ICP, especially if volume compensation is already reduced. Brain tissue water is approximately 70 per cent of intracranial volume (Rosomoff, 1961). A reduction in brain tissue water may contribute to volume compensation of a slowly expanding mass but this has not been fully investigated (Langfitt, 1969).

If these compensatory mechanisms are exceeded, either in rate or degree, a further volume addition will cause a rise in ICP, the extent of which will depend upon the distensibility of the intracranial contents (Löfgren et al., 1973). The relationship between volume and pressure is therefore of fundamental importance in understanding the effects of an expanding mass. The initial stages of expansion will cause little change in ICP. However, when the capacity for volume displacement is exhausted, further expansion will lead to increasing rises in pressure. This exponential relationship is the basis of Kocher's "Four Clinical Grades in Cerebral Compression" (Langfitt et al., 1965b).

The gradient of the volume-pressure curve may be measured at any point by the increase in pressure accompanying a given increase in volume. This pressure change per unit volume change (dP/dV) measures the overall elastance or inverse of compliance, of the intracranial contents (Löfgren et al., 1973). As volume reverse diminishes, elastance increases. Used as a provocative test, the volume-pressure response (VPR) allows decompensation to be anticipated before ICP begins to rise, that is, while ICP is still on the horizontal part of the volume-pressure curve (Leech & Miller, 1974a).

Intracranial elastance may vary independently of the level of ICP,

thus altering the shape of the volume-pressure curve. When ICP has been raised by a supratentorial balloon, elastance is further increased by arterial hypertension, thus shifting the "break-point" of the curve towards the left and rendering the brain more susceptible to further rises in ICP (Löfgren, 1973a; Leech & Miller, 1974b). By contrast, steroids and mannitol reduced elastance, beyond any accompanying change in ICP (Leech & Miller, 1974c). Changes in arterial pCO_2 ($PaCO_2$) alter elastance only insofar as ICP is affected (Rowed et al., 1975).

Guillaume & Janny (1951) and Lundberg (1960) pioneered continuous isovolumetric monitoring of ICP from the lateral ventricles of patients. Lundberg described three pathological wave forms, A, B & C waves, seen in states of raised ICP. It seems likely that each of these pressure waves is due to fluctuation in CBV - the intracranial component with the greatest capacity for rapid changes. Plateau waves (A waves) which may have an amplitude up to 100 mm Hg and last for 5 to 20 minutes, are accompanied by angiographic vasodilatation, even though cerebral blood flow (CBF) falls. They may be abolished by reducing intracranial volume with hypertonic solutions or by withdrawing CSF, or else by increasing the distensibility of the cranial compartment with a bony decompression (Lundberg et al., 1968). B waves occur at about one per minute and are synchronous with the respiratory periods in Cheyne-Stokes respiration. C waves occur at about six per minute and are synchronous with the variations in systemic arterial pressure (SAP) of the Traube-Hering-Mayer type (Kjällquist et al., 1964).

Changes in CBV also underlie the influence of blood gas concentration on ICP. Hypercapnia (Harper & Glass, 1965; Reivich, 1964) and hypoxia (McDowell, 1966) cause vasodilatation and raise ICP while hypocapnia (Lundberg et al., 1959) and hyperoxia (Miller et al., 1970a) lower ICP. The effects of changes of SAP on ICP will depend on the state of cerebrovascular autoregulation (see page 9). If autoregulation is lost,

cerebral blood vessels behave in a pressure passive manner, and an increase in SAP will increase CBF, CBV, and ICP (Langfitt et al., 1965b; Harper, 1966).

In most clinical situations, raised ICP is caused by an expanding mass lesion and is accompanied by brain distortion. Failure to recognise these two components led to conflicting views on the significance of raised ICP in brain injury. Browder and Meyers (1936) used lumbar CSF pressure as an index of ICP, and found that in many patients who later died from head injuries, the lumbar CSF pressure was not raised. They presumed that ICP was not raised either. Dandy, on the other hand, observed at operations that brain swelling frequently accompanied severe injury, and concluded that early death after head injury was due almost entirely to intracranial hypertension. He made the important deduction that lumbar CSF pressure was not an accurate index of ICP, when ICP was elevated (Dandy, 1933). Description of the tentorial pressure cone by Jefferson (1938) and of brainstem displacement with supratentorial mass lesions by Johnson and Yates (1956) provided an explanation for these conflicting clinical observations.

Brain displacement is a further way of accommodating an expanding mass. Displacement of brain from one supratentorial compartment to another - such as the subfalcine and ascending or descending alar herniations - is commonly seen. But more important, because of their effects on neurological function, are the herniations of the mesial temporal lobes through the tentorial incisura, and of the cerebellar tonsils through the foramen magnum. The neurological effects of brain displacement may arise by vascular compression or distortion, for example, compression of the posterior cerebral artery by tentorial hernias; by compression and distortion of cerebral tissues - the midbrain by tentorial hernias, and the medulla by tonsillar hernias; and by blocking CSF pathways thereby setting the stage for further rises in ICP.

Langfitt et al. (1964a; 1964b), studied the transmission of raised ICP through the craniospinal axis, and demonstrated the importance of brain displacement in influencing pressure transmission. Once an expanding supratentorial mass has caused tentorial impaction, supratentorial pressure will rise independently of infratentorial and spinal pressures, which may even fall to normal levels. Before a mass lesion has caused an impaction, the addition of any other volume, such as blood volume through vasodilation induced by halothane (Fitch and McDowall, 1971) or hypercapnia (Miller, 1975a) may precipitate brain impaction. Subtraction of CSF by lumbar puncture has long been known to have the same consequences.

Once impaction has occurred, a pressure difference may clearly exist across the tentorium or foramen magnum (Kaufmann & Clark, 1970; Johnston and Rowan, 1974). Intracranial elastance measurements will be high reflecting the loss of volume reserve. In a clinical study of patients with brain displacement shown by angiography, a high elastance correlated more closely with the degree of displacement than with the absolute level of ICP. Measuring both elastance and ICP gave a better indication of volume reserve capacity than measuring ICP alone (Miller & Pickard, 1974).

Raised ICP occurs alone in the syndrome of benign intracranial hypertension in which plateau waves of up to 100 mm Hg have been recorded without evidence of neurological dysfunction (Johnston and Paterson, 1974). Conversely, brain displacement can exist without raised ICP (Johnston & Jennett, 1973). Studies in patients with head injury have not shown a simple relationship between the level of ICP and other indices of brain injury. Vapalahti & Troupp (1971) found that a ICP of greater than 60 mm Hg carried a very grave prognosis. Johnston et al. (1970), on the other hand, found no clear correlation between ICP and outcome. Not only did a high mortality occur among patients with normal pressure (less than 20 mm Hg), but half of those with high pressure (greater than

40 mm Hg) showed evidence of less severe brain injury initially, having talked at some time after injury. In fact, outcome seemed more closely related to the presence of brain displacement than to the absolute level of ICP. That many of the effects previously ascribed to raised ICP may be due to brain distortion was highlighted by the neuropathological studies of Adams & Graham (1972).

Even in normal situations, there is not a "single" ICP. There are minor hydrostatic pressure differences between different parts of the cranium (Bradley, 1970). Minor transitory pressure gradients occur within brain tissue and between brain and CSF. These are sporadic, as with coughing, and regular as with the phase differences in the arterial components of the ICP wave between the supratentorial and infratentorial compartments (Miller, 1975b). In pathological states, as well as the intercompartmental pressure gradients associated with CSF obstruction which have already been discussed, gradients may develop within brain tissue. Rapidly expanding lesions such as an area of cerebral infarction (Brock et al., 1972) or an epidural balloon (Symon et al., 1974) cause interhemispheric pressure gradients before there is any obstruction to the CSF pathways. Around such lesions, tissue pressure may be significantly higher than CSF pressure, and may decrease with distance from the lesion (Reulen & Kreysch, 1973; Brock et al., 1975). Local blood flow and oxygenation may depend more on tissue pressure than on CSF pressure (Brock, 1971). Pressure gradients may drive oedema fluid and metabolic products from the injured area (Pöll et al., 1972) affecting both the metabolic and physical characteristics of the surrounding brain.

The elastance of brain tissue, which normally differs between grey and white matter, may be affected by local vascular changes and by changes in tissue water content (Brock et al., 1975). Pressure gradients cause shearing stresses and deformation (Weinstein et al., 1968) which may affect cell membrane function directly as well as influence blood flow.

CEREBRAL BLOOD FLOW

Kety & Schmidt (1945) developed the first accurate, quantitative technique for measuring CBF. By this and by later adaptations of their method, total resting CBF in man is approximately 50 ml/min. 100G (Lassen & Ingvar, 1961; Glass & Harper, 1963; Fieschi & Bozzao, 1972). This value remains remarkably constant through a wide range of functional states, from sleep to active intellectual and physical exercise (Mangold et al., 1955; Lassen, 1959). Resting blood flow varies between different regions of the brain. Cortical blood flow is approximately 80 ml/min. 100G and white matter flow, 20 ml/min. 100G (Kety & Schmidt, 1948a; Lassen et al., 1963; Ingvar et al., 1965).

Although total CBF normally remains relatively constant, it has been recognised for many years that blood flow will increase in areas which have increased functional demand. Roy and Sherrington (1890) in their paper "On the Regulation of the Blood Supply to the Brain", were the first to postulate a metabolic control of CBF. Using changes in brain volume measured through a trephine opening as an index of changes in blood supply, they deduced that the blood supply to the brain was determined by blood pressure in the systemic arteries, and by a second mechanism - "an intrinsic one by which the blood supply of various parts of the brain can be varied locally in accordance with local requirements". A metabolic control for CBF was disputed by others (Hill, 1896), and for some time, it was generally believed that CBF depended solely on SAP.

This view was challenged in the 1920's and 1930's by two sets of observations. Fog (1937; 1939), observed directly that pial vessels were capable of active vasomotor responses. Abrupt rise in blood pressure

led to vasoconstriction; fall to vasodilatation, the change being in the direction opposing a change in blood flow. Secondly, several workers reported increases in local blood flow with increased functional activity. Fulton (1928) observed the vascularity of the human occipital lobe during visual stimulation; Gerard & Serota (1936) measured blood flow in the sensorimotor cortex during sensory stimulation, and Penfield et al., (1939) measured blood flow in the exposed brain during focal epileptic seizures. Recent studies have confirmed that blood flow will increase in functionally appropriate areas; during vigorous hand exercises (Olesen, 1971); with psychometric testing (Risberg & Ingvar, 1973; Brooks et al., 1975); and during speech (Larsen et al., 1977).

It is now clear that there are two primary mechanisms controlling CBF; local metabolic demand, particularly through changes in CO_2 and O_2 tension and secondly changes in perfusion pressure. Because the brain is enclosed in a semi-rigid container, changes in CBF induced by these mechanisms influence and are influenced by ICP.

(1) Carbon-dioxide reactivity

CBF is more sensitive to changes in $PaCO_2$ than to any other known substance. Kety and Schmidt (1948b) found that in man, inhaling 5 per cent CO_2 caused a 50 per cent increase in CBF. In experimental animals, the relationship between $PaCO_2$ and CBF has been recorded as approximately linear between 20 and 80 mm Hg (Harper & Glass, 1965) or continuously sigmoid with the steepest part at 40 mm Hg (Reivich, 1964). Studies in man show the gradient of flow through the range of maximum sensitivity, which includes the normal physiological range, to be approximately 1.5 to 2 ml/min. 100G CBF per mm Hg $PaCO_2$ or a 2.5 per cent change in CBF per mm Hg $PaCO_2$ (Reivich, 1964). Below a $PaCO_2$ of 20 mm Hg, CBF no longer decreases. Vasoconstriction of this degree may be counterbalanced by tissue hypoxia (Gibbs et al., 1942). Conversely in experimental animals,

$PaCO_2$ of greater than 80 mm Hg no longer increases CBF suggesting that maximal vasoconstriction has been reached. The upper end of the response range has not been delineated in man.

CBF will adapt if $PaCO_2$ is held constant over several hours (Agnoli, 1968; Severinghaus et al., 1964). The CO_2 response is lessened by lowering the metabolic rate (Fujishima et al., 1971), and by competition with other vasomotor stimuli. At moderate arterial hypotension, the gradient is reduced and then abolished below 40 to 50 mm Hg mean SAP (Harper & Glass, 1965). Hypercapnia increases CBF in both grey and white matter, although the absolute increase is greater in grey matter (Hansen et al., 1957). Because of its effects on CBF in normal subjects, CO_2 inhalation has been used in the treatment of states of cerebral hypoxia.

(2) Oxygen reactivity

Hypoxia increases CBF by vasodilatation which begins below a threshold of about 50 mm Hg arterial pO_2 (PaO_2) (McDowall, 1966). This effect is unrelated to any accompanying change in $PaCO_2$. Hyperoxia at normal atmospheric pressure causes only a slight vasoconstriction; 100 per cent oxygen at two atmospheres absolute results in a 20 per cent fall in CBF; higher levels of oxygenation however do not produce further vasoconstriction due perhaps to a toxic effect of extreme hyperoxia (Ledingham et al., 1966; Miller, 1973).

Hence CBF is affected by changes in both $PaCO_2$ and PaO_2. Within physiological limits, $PaCO_2$ has the most marked effect, whereas below a PaO_2 of 50 mm Hg, hypoxic vasodilatation begins to over-ride hypocapnic vasoconstriction (Reivich, 1969).

(3) Responses to blood pressure

Within a physiological range of perfusion pressure, CBF remains remarkably constant (Lassen, 1959; Rapela & Green, 1964; Harper, 1966).

This response has been interpreted as an example of autoregulation - that is, an intrinsic property of the cerebral resistance vessels. Blood flow in a vascular bed depends upon the perfusion pressure, defined as arterial pressure minus venous pressure, and on the vascular resistance. Hence,

$$CBF = \frac{\text{cerebral perfusion pressure (CPP)}}{\text{cerebrovascular resistance (CVR)}} \qquad (1)$$

Constant CBF in the face of an increasing perfusion pressure implies a change in CVR. In normal subjects, CBF remains constant to a mean SAP of 40 to 60 mm Hg. Below this level CBF falls with arterial pressure. That is, no further active reduction in CVR occurs. Conversely, the upper limit of autoregulation is reached at a mean SAP of about 120 mm Hg and beyond this CVR is constant.

CVR represents the sum of the resistances of the individual components from arteries to veins, (Rowan et al., 1972). Normally arterioles provide the major resistance, and active change in the diameter of these vessels controls the level of CBF. Capillaries, venules and veins respond passively to the balance between intramural and extramural pressure. At high ICP, bridging veins to the sagittal sinus may collapse (Wright, 1938). Similarly an expanding mass lesion may compress the venous bed (Rowan et al., 1972). Autoregulatory vasodilatation induced by the rise in ICP may then further increase ICP and venous compression to the point where total CBF falls (Löfgren, 1973b). In support of this, Zwetnow (1975) pointed to the paradoxical decrease in CBF in the presence of angiographic vasodilatation during plateau waves (Lundberg et al., 1968).

Thus, in states of raised ICP the site of major vascular resistance may shift from arterioles to veins. CBF is then directly related to ICP. Before this stage is reached, an expanding lesion may compress local veins directly. Gyral vessels may be compressed against the

calvarium while sulcal vessels are still patent. Hence there will be a local reduction in blood flow even though total CBF is maintained by autoregulation (Weinstein & Langfitt, 1967).

Autoregulation is affected by other factors which alter vasomotor tone. Hypercapnia or hypoxia, which cause vasodilatation, limit the ability of the arterioles to dilate further in the face of falling SAP. At a $PaCO_2$ of 70 to 80 mm Hg, autoregulation is abolished. Hypocapnia, by increasing vasomotor tone increases autoregulatory capacity at low perfusion pressure (Häggendal & Johansson, 1965; Harper, 1966). Conversely, hypercapnia lowers the upper limit of autoregulation (Ekström - Jodal et al., 1972).

Within the cranium, the relationship of ICP to pressure in different parts of the venous system must be considered. The major dural sinuses are enclosed within semi-rigid walls, so that venous sinus pressure is dependent more on extracranial venous pressure than on cerebral venous pressure (Rowan et al., 1972). However, before entering the dural sinuses, the cerebral veins are suspended within the subarachnoid space. To maintain forward flow, cerebral venous pressure must be at least slightly greater than ICP. In fact, cerebral venous pressure and ICP are nearly identical at all levels of ICP (Shulman, 1965; Rowan et al., 1972). CPP may therefore be defined as SAP minus ICP, and formula (1) re-written:

$$CBF = \frac{SAP - ICP}{CVR} \qquad (2)$$

In accordance with this formula, autoregulation will occur if CPP is altered by changing SAP, cerebral venous pressure (Jacobson et al., 1963) or ICP (Miller et al., 1972). Changes in ICP not only affect cerebral venous pressure, but also the transmural pressure of the arterioles,

since,

transmural pressure = SAP - ICP

In an animal with the skull opened, cerebral venous pressure may be artificially separated from ICP. Cerebral venous pressure may be elevated, yet ICP remain constant. Hence CPP will decrease while transmural pressure remains constant. In these circumstances, even when autoregulation to changes in SAP has been shown to be intact, a rise in cerebral venous pressure will cause a fall in CBF (Ekström - Jodal, 1970), suggesting that the autoregulatory reflex is initiated by changes in transmural pressure.

The mechanism of cerebrovascular autoregulation has not yet been fully explained. There are three main theories, myogenic, metabolic and neurogenic. The myogenic theory, based on studies by Bayliss (1902) of a denervated hind-limb preparation, states that autoregulation is an intrinsic response of the vascular smooth muscle. Distension is countered by contraction and vice versa. The metabolic theory states that autoregulation, as well as changes induced by $PaCO_2$ and PaO_2 occur through local changes in tissue metabolites, which react directly upon the vascular smooth muscle. Autoregulation is seen as part of an overall adjustment of flow directed by local metabolic requirements. The metabolic theory is supported by the observation that the vasomotor reaction to a change in SAP occurs after a delay of 20 to 30 seconds. This may allow build-up of tissue metabolites. However, Zwetnow (1975) noted that tissue pH, and energy metabolites remain virtually constant through the autoregulatory range. Furthermore, in certain circumstances, autoregulation and the responses to metabolic stimuli may be dissociated (Lassen & Paulson, 1969; Fieschi et al., 1969).

The neurogenic theory, is based upon a consideration of the known presence and postulated function of the nerve supply to the cerebral vessels. The extraparenchymal vessels have an extensive noradrenergic

and cholinergic nerve supply. However, there is no firm evidence that this nerve supply plays a significant role in the normal control of CBF. Indeed Fitch et al. (1975) found that sympathetic activity was not necessary for autoregulation in response to haemorrhagic hypotension. Acute sympathectomy actually increased the lower limit of autoregulation. Harper et al. (1972) suggested that the sympathetic supply to the extra-parenchymal vessels acts in concert with the autonomic nervous system elsewhere but does not affect the intraparenchymal vessels where the major component of the CVR lies.

The neurogenic theory has received impetus from recent anatomical studies suggesting that catecholaminergic nerve fibres terminate on small intraparenchymal vessels (Hartman et al., 1972; Edvinsson et al., 1973; Björklund, 1977). These fibres originate in brain stem nuclei, perhaps including the locus caeruleus, and project widely through the brain. Postulated functions of this intrinsic system include regulation of metabolic activity of the forebrain (Schwartz et al., 1976) and of regional CBF (Hartman et al., 1972). Raichle et al. (1975) produced physiological evidence of a central innervation of capillaries and suggested that this may influence capillary water exchange as well as regional CBF. Earlier studies have indeed suggested brain stem regulation of cerebral vasomotor activity (Molnár and Szántó, 1964; Shalit et al., 1967; Langfitt & Kassell, 1968). This has been recently reaffirmed by Hass et al. (1977) who found widespread reduction in metabolic rate and CBF following destructive lesions in the brain stem.

(4) Interrelationship between CBF and ICP

CBF and ICP have important interrelationships. An increase or decrease in CBF will be accompanied by a change in ICP, determined by the accompanying change in CBV and the original ICP (Ryder et al., 1952). At normal levels of ICP, moment-to-moment changes in CBF and CBV are

accommodated without large changes in pressure. However, as predicted by the volume - pressure curve, if volume compensation is reduced and intracranial elastance is increased, small changes in CBV, perhaps following an episode of hypercapnia due to respiratory insufficiency, will cause a marked rise in ICP (Miller, 1975a). Reflecting the increase in elastance, the pulsatile components of the ICP wave become larger, and plateau waves may occur. Increased CBF, in these circumstances, can increase intercompartmental pressure gradients, and by increasing elastance, shift the volume - pressure curve towards decompensation.

Conversely, changes in ICP will affect CBF in a manner dependent upon the capacity of the cerebral vessels to respond to changes in CPP. If autoregulation to changes in SAP is intact, so will be autoregulation to changes in ICP (Miller et al., 1972). Beyond the limit of autoregulation, a further rise in ICP will reduce CBF. If autoregulation is impaired, the relationship between perfusion pressure and flow will become more linear. Loss of autoregulation is not "all or none", however, and partial autoregulation is indicated by a pressure-flow curve, which is concave to the pressure axis (Rapela and Green, 1964), or by a straight line relationship between pressure and flow. Since blood vessels are distensible, total loss of autoregulation would result in a curve which is convex towards the pressure axis (Miller et al., 1972).

(5) CBF in brain damage

In states of brain damage, vasomotor responses may be lost or reduced and the relationship between CPP and CBF changed accordingly. In experimental studies even minimal injury produced by continuous or intermittent compression, can impair the autoregulatory response to changes in SAP when normotensive and normocapnic values of CBF are unchanged (Brock, 1968; Reivich et al., 1969a). Even though the

cerebrovascular response to changes in $PaCO_2$ may still be present, arterial hypertension with hypercapnia will cause pronounced swelling of the damaged area of brain due to a combination of vascular distension and extracellular oedema (Schutta et al., 1968; Marshall et al., 1969; Meinig et al., 1972). At a later stage of brain compression, when ICP has risen close to SAP and CBF has fallen, the cerebrovascular response to changes in $PaCO_2$ will finally disappear, first to hypercapnia, then to hypocapnia (Langfitt et al., 1965a; Miller et al., 1970a).

At this pre-terminal stage, the cerebral vessels are also unresponsive to changes in PaO_2 and to the volatile anaesthetic agent halothane, which under normal circumstances is a cerebral vasodilator (Miller et al., 1970a; 1970b; Fitch and Miller, unpublished observations). Langfitt et al. (1965b) proposed the term "cerebral vasomotor paralysis" for this advanced stage of cerebrovascular dysfunction, and suggested that this may be preceded by a vasomotor paresis which is more severe in some parts of the brain than in others, and in different forms of brain injury. Reduction of ICP after a period of marked intracranial hypertension is followed by a brief return to normal pressure, then a rise beyond the previous level (Langfitt et al., 1965b). CBV (Zwetnow, 1975) and CBF (Häggendal, 1970) will overshoot. This may be explained by the release of venous congestion in the presence of persistent arterial vasodilatation.

The Cushing reflex, a rise in SAP induced by ICP close to diastolic pressure, has been interpreted as a protective measure whereby CBF might be maintained in the face of rising ICP (Cushing, 1901). However, whether a rise in SAP, either reflex or induced therapeutically, will lead to an increase in CBF, will depend upon the accompanying change in ICP. In states of vasomotor paralysis with marked intracranial hypertension and a high elastance, a rise in SAP may be transmitted by

the fully dilated resistance vessels to capillaries and veins, so that ICP rises equally. If CPP does not change, CBF will remain constant. A constant CBF in the face of a change in SAP in these circumstances does not imply a change in CVR and has been termed "false autoregulation" (Lassen, 1972).

Measurement of regional CBF in patients has shown that areas of impaired autoregulation and CO_2 responsiveness may occur near cerebral tumours (Pálvölgyi, 1969), focal ischaemia (Fieschi & Bozzao, 1972; Paulson et al., 1972) and post-traumatic haemorrhage and contusion (Bruce et al., 1973; Overgaard & Tweed, 1974; Enevoldsen et al., 1976). Some studies have reported a global loss of autoregulation and CO_2 response. Pálvölgyi (1969) found that regional CBF surrounding brain tumours was quite variable, sometimes showing paradoxical flow reactions to CO_2 and to induced hypotension. In some areas the vasoconstrictor response to hypocapnia was preserved while the vasoconstrictor response to hypertension was lost (Easton & Pálvölgyi, 1968). Lassen and Paulson (1969) found this pattern of dissociation, among others, in patients with apoplexy and later suggested that it might be explained by an increase in extracellular pH sufficient to impair autoregulation. This hypothesis has been supported by the observation that hyperventilation may restore autoregulation (Paulson et al., 1972).

In patients with head injuries studied within a few hours of injury, Overgaard & Tweed (1974) found that resting CBF varied widely. Yet both ischaemic, that is less than 20 ml/min. 100G and hyperaemic flow levels might be associated with a poor clinical outcome. All patients studied within 24 hours had impaired autoregulatory responses, although this was compatible with a good recovery. Severely impaired CO_2 reactivity seemed an unfavourable prognostic factor, yet intact reactivity had no prognostic significance. In a group of comatose patients, Bruce et al. (1973) found that autoregulation to arterial hypertension was defective

in some patients who made a good recovery, yet intact in all regions studied in patients moribund at the time of the study. Furthermore, intravenous mannitol tended to produce a greater increase in CBF in patients who showed little or no decrease in ICP. Fieschi et al. (1972), found that in some patients with head injuries, CBF was reduced beyond any accompanying rise in ICP; in others, a rise in SAP resulted in a fall in CBF. Langfitt (1976) concluded that in patients with head injuries the relationship between CBF and ICP is unpredictable.

Miller et al. (1975) found that after an acute cryogenic injury in baboons, induced arterial hypertension was sometimes accompanied by an increase in CVR. They felt that this response was unlikely to represent normal physiological autoregulation, because as a result of the injury, resting CBF had decreased and ICP had increased. Furthermore, there was macroscopic damage visible on brain sections.

It is difficult to reconcile such studies of patients with brain damage and of animals with focal lesions, with experimental studies demonstrating the susceptibility of autoregulation to moderate trauma which is not accompanied by obvious structural damage. In the latter studies the pressure-flow relationship which characterises the autoregulatory response is lost, and CBF responds passively to changes in CPP induced by changes in SAP or ICP. Finding a constant CBF in patients or experimental animals with clear evidence of brain damage suggests that either normal vasomotor reactivity has been preserved, which is unlikely, or some direct effect of injury has led to an increase in CVR with increase in CPP.

It is not clear from these clinical and experimental studies whether there is an orderly progression of cerebrovascular dysfunction in different forms of brain damage. Were this so, an assessment of the extent and severity, and perhaps even aetiology of a brain lesion might be aided by measurement of regional CBF and cerebrovascular responsiveness.

Clearly, in the many types of brain damage encountered clinically, assessment of cerebrovascular function may be a complex problem. This is particularly so in areas of oedema, where CBF may be severely reduced at a time when ICP is not greatly increased. This dissociation between CBF and measured CPP implies a direct effect of oedema on CVR.

CEREBRAL OEDEMA

Brain swelling has been recognized for many years as a common response to different types of injury. Von Bergmann (1880) and Hill (1896) described swelling surrounding intracerebral haemorrhage. Courtney (1899) considered that contusion and swelling were constant features of head injury. It is well known that cerebral tumours, particularly rapidly growing metastatic tumours, may be surrounded by wide areas of swollen brain.

While brain swelling is clearly due to an increase in the volume of one of the intracerebral fluid compartments, intracellular, extracellular or vascular,its study has been confused over the years by varying terminology and by uncertainty as to the distribution of the excess fluid in different pathological states. Reichardt, (1904) attempted to distinguish "brain oedema" due to an increase in extracellular fluid from "brain swelling", due to an increase in intracellular fluid, by appearance and certain physico-chemical properties. Early electron microscope studies of samples of grey matter, revealed an extremely small extracellular space. It was concluded that pathological brain swelling must be predominately intracellular. In fact, recent morphological and physiological evidence suggests an extracellular space of 12 to 25 per cent (Katzman and Pappius, 1973). It is clear now that the increased water content of most forms of brain swelling is extracellular and occurs in white matter, which has a smaller cellular component, and a larger extracellular space. Intracellular swelling mainly affects grey matter. Brain water is the largest intracranial fluid compartment. An increase in total brain water of only 2 per cent would be sufficient to exhaust intracranial volume compensation (Rosomoff & Zugibe, 1963; Langfitt & Bruce, 1975).

Underlying any form of tissue water excess is an imbalance in normal fluid exchange across the semi-permeable membranes separating

the vascular, extracellular and intracellular compartments. Brain capillaries have certain permeability and morphological peculiarities. The observation that certain vital dyes such as Trypan Blue, injected intravenously, do not normally stain brain tissue gave rise to the concept of a blood-brain barrier. Electrolytes cross the barrier by diffusion along concentration gradients. The passage of other substances is aided by lipid solubility and specific active transport mechanisms. Fluid exchange follows the Starling model, and is based on capillary transmural pressure, determined by pre- and post-capillary pressures and interstitial fluid pressure, and on the plasma-tissue osmotic pressure gradient.

Katzman and Pappius (1973) pointed out that in most clinical situations where there is brain swelling, it is not possible to determine whether the excess fluid is intracellular or extracellular. The terms "swelling" and "oedema" with respect to brain tissue, are often used interchangeably. A defect in this convention is that one important form of brain swelling is overlooked, that is, swelling due to increased blood volume. As discussed earlier, arterial hypertension in states of vasoparalysis may cause a marked increase in CBV. Thus, vascular engorgement may cause acute brain swelling following brain injury (Langfitt & Kassell, 1966; Meinig et al., 1975).

Klatzo (1967) defined brain oedema as an abnormal accumulation of extravascular fluid, excluding CSF, associated with volumetric enlargement of brain tissue. He suggested that states of oedema should be classed as vasogenic or cytotoxic. Vasogenic oedema is caused by a gross break-down of vascular components. There is increased permeability of blood-brain barrier indicators. Plasma derived isotonic fluid leaks into the extracellular space driven by the hydrostatic pressure head. Fluid will extravasate preferentially into white matter, determined perhaps by the cyto-architecture which offers the least resistance.

The astrocyte may show some swelling (Klatzo, 1967). However, this accounts for only a small part of the increased tissue volume (Katzman & Pappius, 1973). Cytotoxic oedema arises from a defect in fluid exchange across the cell membrane. In contrast to vasogenic oedema, the extracellular space is reduced. There may be a secondary increase in fluid leaving the vascular compartment thereby causing volumetric enlargment, however there is no defect in vascular permeability.

In pathological states, both forms of oedema may co-exist. The dominant type in head injuries, tumours and inflammation is vasogenic, whereas that associated with water intoxication and certain toxins such as triethyl tin and Hexachlorophane, is cytotoxic (Klatzo, 1967).

Although oedema is a component of many forms of brain injury, there has been considerable debate as to how it affects brain function. Oedema around a brain tumour will act as a mass lesion and influence ICP and brain displacement according to the principles already outlined. If volume compensation is already compromised by the primary lesion, even a small additional volume of oedema may have serious consequences (Miller, 1974).

Oedema may exert direct effects on the involved tissue. Clinical and experimental studies have shown that in areas of oedema, CBF may be markedly reduced when ICP is not greatly increased (Meinig et al., 1973). This indicates a state of "pressure-flow dissociation", so that the pressure-flow relationship discussed earlier and based on CSF-infusion or balloon-inflation studies, may not apply. This dissociation between CBF and measured CPP implies a direct effect of oedema on CVR. Indeed CBF in areas of oedema bears an inverse relationship to tissue water content, whether increased generally in hypo-osmolar oedema (Meinig et al., 1973) or around a focal brain injury (Frei et al., 1973). Explanations for this effect of oedema on CBF include distortion and compression

of the vascular bed (Hekmatpanah, 1970; Matakas et al., 1973); focal loss of autoregulation so that a general rise in ICP reduces flow in the oedematous region in a pressure-passive manner (Brock, 1971); a rise in tissue pressure beyond measured ventricular pressure so that reduction in local flow might be explained by reduction in local transmural and perfusion pressures (Brock et al., 1972).

Support for this third concept comes from direct measurement of tissue pressure around cold injury oedema (Reulen and Kreysch, 1973; Reulen et al., 1975). Formation of brain oedema was associated with an increase in local brain tissue pressure in the white matter adjacent to the lesion. Tissue pressure nearby rose only with the advancing oedema front. Hence pressure gradients may exist between oedematous tissue and CSF and between oedematous tissue and normal brain within the same hemisphere.

Reulen et al. (1975) deduced a volume-pressure curve for the interstitial space which showed an initial steep slope indicating high tissue resistance followed by a break-point and a rapid transition to a lower tissue resistance. They concluded that once the extracellular spaces had been dilated to a certain point, a further volume increase was accommodated by a smaller pressure rise. That is, tissue elastance had fallen. Brock et al. (1975) felt that compensation for increased interstitial volume occurred mainly through compression of the vascular compartment.

Local increase in tissue pressure may well be responsible for propagation of oedema fluid (Pöll et al., 1972). Oedema fluid has been shown to spread by bulk flow rather than diffusion (Klatzo, 1967; Reulen et al., 1975). A tissue pressure 10 mm Hg above CSF pressure may be sufficient to propagate a flow of interstitial fluid (Marmarou et al., 1976). Leakage of fluid from damaged capillaries may not only increase interstitial fluid pressure and reduce CBF but also, by

increasing venous compression, lead to further capillary leakage and a further rise in interstitial pressure (Shulman et al., 1975).

In summary therefore, oedema may exert a direct effect on tissue blood flow, and capillary fluid exchange. Pressure gradients will drive oedema fluid into normal tissue thereby setting up the same process of increased interstitial pressure, tissue deformation, and reduced blood flow. By changing elastance, oedema may render tissue more easily deformed by shearing stresses.

There is however no firm evidence that oedema directly alters cellular metabolism or nerve cell excitability. Such effects could arise by changes in extracellular electrolyte concentrations, by increasing the distance for metabolite diffusion or by changes in the storage or release of transmitter substances. Increased anaerobic glycolysis has been found in human and experimental oedema, but this may be secondary to a decrease in blood flow (Reulen et al., 1969; Bartko et al., 1972).

Of greater importance to the clinician than base-line CBF is the response of the circulation in areas of brain damage and oedema to physiological stimuli. If this is known, methods of increasing CBF may be proposed. In brain oedema, the response to changes in $PaCO_2$ particularly elevation, is impaired (Wallenfang et al., 1975). The paradox of apparent preservation of autoregulation in areas of brain injury has been reported in clinical and experimental studies. It is clear that brain injuries with oedema - one of the commonest problems facing neurological clinicians - involve complex interactions between ICP and CBF, and produce changes within the tissues which may seriously affect recovery.

SUMMARY

Understanding of the physiology of cerebral circulation, cerebral metabolism and ICP is advancing rapidly, yet the changes initiated by a brain injury still pose many important questions. These include:

1. How does the ease with which autoregulation is lost in controlled animal experiments correlate with reports of intact autoregulation in patients with severe brain injuries?
2. Is there a predictable progression of cerebrovascular dysfunction in different forms of brain injury? If so, might assessment of the extent, severity or aetiology of the injury be aided by measurement of regional CBF and cerebrovascular responsiveness?
3. How does oedema after brain injuries affect function and how may these effects be prevented or reversed?

PURPOSE OF THE STUDY

The aim of the experiments reported in this thesis was to study the effects of acute brain damage associated with oedema, on regional CBF, ICP and on the responses of these parameters to physiological stresses; in particular to discover whether CBF in and around areas of acute brain damage could be increased by an increase in mean CPP; and to find out if disturbances in cerebrovascular regulation occurred only in areas of damage and oedema or were more widespread throughout the brain.

Patients with focal lesions and oedema were also studied, relating changes in regional CBF to changes in the extent of oedema indicated by computerized axial tomography and confirmed by direct measurement of tissue water content.

GENERAL METHODS

THE EXPERIMENTAL ANIMAL

Adult baboons (Papio cynocephalus and Papio anubis) were chosen for this study. Many studies in baboons have shown that the CBF and cerebrovascular responses compare closely with man. Human and baboon intracranial morphology and ICP transmission are similar (Langfitt et al., 1964a; 1964b; Kaufmann & Clark, 1970). Because of the anatomy of the carotid tree, radioactive Xenon (^{133}Xe) can be used to measure CBF in most of one hemisphere. Because of the size of the brain, H_2 electrodes can be used to measure regional CBF both in lesions and in remote areas. Finally, baboons have been used in many studies of CBF and ICP dynamics in this laboratory. They have a high stress tolerance, and provide excellent steady state conditions.

ANAESTHESIA

The anaesthesia used in these experiments has been validated in several previous studies of CBF and ICP in baboons (Rowan et al., 1970; Johnston & Rowan, 1974; Fitch et al., 1976).

Each animal was sedated in a restraint cage with Phencyclidine 12 mg I.M. and within 20 minutes could be carried to the operating room. General anaesthesia was induced with Thiopentone 7.5 mg per kg and Suxamethonium 100 mg I.V. and the animal was then intubated with a cuffed endotracheal tube.

Anaesthesia was maintained with nitrous oxide (6 L/min.), augmented every 30 minutes with intramuscular Phencyclidine 4 to 5 mg and Suxamethonium 100 mg. Respiration was controlled at a constant rate by a Starling pump (Palmer modification) in which stroke volume could be adjusted to maintain normocapnia. In most experiments, end-tidal CO_2 was monitored with a capnograph (Godart-Statham n.v.). Body temperature was monitored by an oesophageal thermocouple and kept at $37^{o}C$ by

blankets and heat lamps.

SURGERY (Fig. 1)

The head, neck and groin were shaved, and the animal placed on its left side on the operating table. Both femoral arteries were catheterized (Portex 6FG, I.D. 2.10 mm) to monitor SAP and arterial blood gases. One catheter was passed to the upper aorta for controlled withdrawal of blood and infusion of norepinephrine later in the experiment.

(1) For CBF measurement by ^{133}Xenon clearance

The right carotid bifurcation was exposed through an L-shaped neck incision. The external carotid, superior thyroid, and lingual arteries were identified and ligated. The hypoglossal nerve was often divided to gain access. A catheter (Portex 4FG, I.D. 1.34 mm) was advanced via the lingual artery to lie at the carotid bifurcation. The catheter was filled with heparinized saline. The scalp was removed from the left superior temporal line to the right zygoma, and from the supra-orbital crest to the occiput. The right temporal muscle was transected at the zygoma. Blood loss was minimized by prior ligation of the external carotid artery. In this way, contaminating extracranial flow in the scalp and extracranial to intracranial flow via the opthalmic artery were eliminated. A right lateral 12 mm burrhole was made, in preparation for the cryogenic lesion.

(2) For CBF measurement by hydrogen clearance

The whole scalp was removed and the temporalis muscles stripped laterally. The head was then fixed in the sphinx-position in a stereotaxic head-holder (Labtronics Inc.)

Bilateral ventricular catheters were inserted (Portex 3FG, I.D. 1.02 mm). Using a high speed dental drill, 3 mm drill holes were made

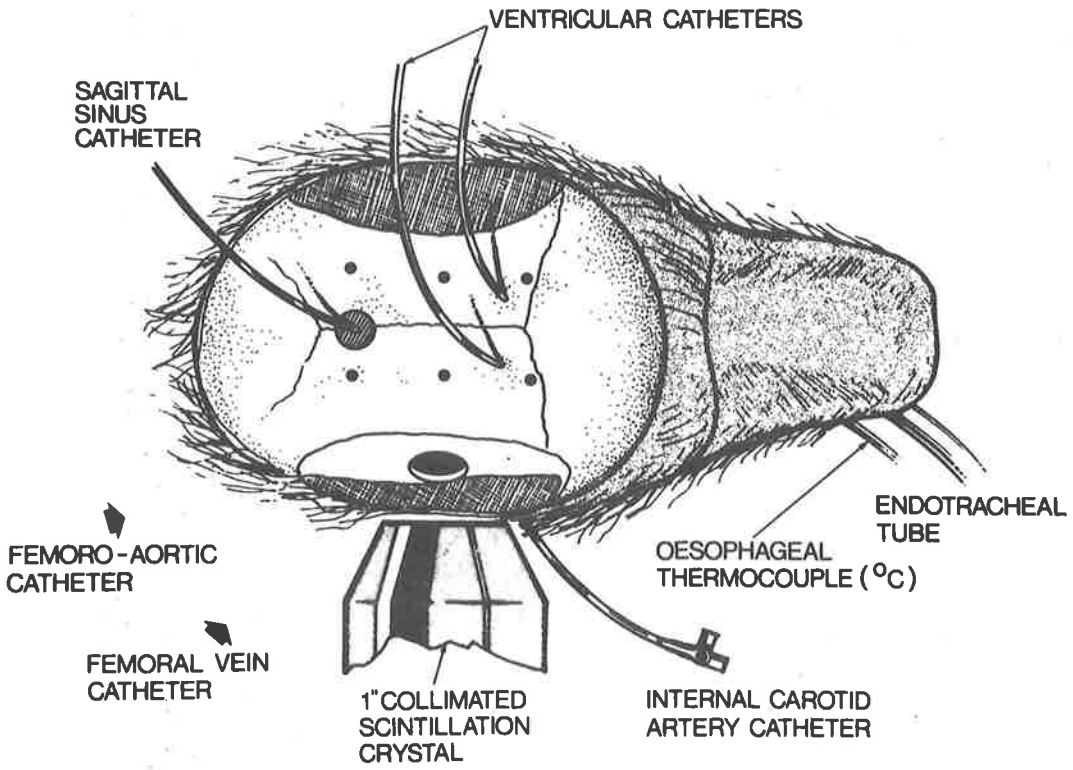


Figure 1: Standard surgical preparation.

Scintillation counter and internal carotid artery catheter are placed for measuring CBF by ^{133}Xe clearance (Series 1).

8 mm on either side of the midline, just posterior to the coronal suture. The dura was incised with fine-pointed scissor tips. A catheter filled with saline and open to the pressure transducer and chart recorder, was inserted to a depth of 2.6 cm in a strictly vertical plane. The catheter was flushed with 0.02 ml of saline and correct placement was indicated immediately by a stable, pulsatile pressure trace. The catheters were sealed in position with fast curing dental cement (Model Kryptex).

To obtain cerebral venous blood samples the sagittal sinus was catheterised through a 12 mm burrhole placed over the torcula. When possible, the catheter (Portex 3FG) was passed forward and wedged in the anterior sinus, to record sagittal sinus wedge pressure (SSP). The burrhole was sealed with dental cement.

The arterial, sagittal sinus, and ventricular catheters were connected to arterial-range pressure transducers (Bell and Howell). Three-way stop-cocks allowed the catheters to be flushed and samples to be withdrawn. The transducers were zeroed to the level of the animal's heart, and calibrated at two pressure levels against a mercury manometer. They were connected for continuous recording to Devices M2 hot-stylus chart recorders (Fig.2).

STANDARD MEASUREMENTS

(1) Blood gases

Arterial blood gas samples, drawn in capped, heparinized 2 ml syringes, were checked immediately before each CBF measurement. Midway through each flow measurement, arterial and sagittal sinus blood samples were withdrawn simultaneously. Blood gases and pH were measured by a direct reading electrode system (Corning 165 Blood Gas Analyser, or Radiometer B 175.3). The electrodes were calibrated against solutions of known pH and gases of known CO_2 and O_2 concentration. Corrections

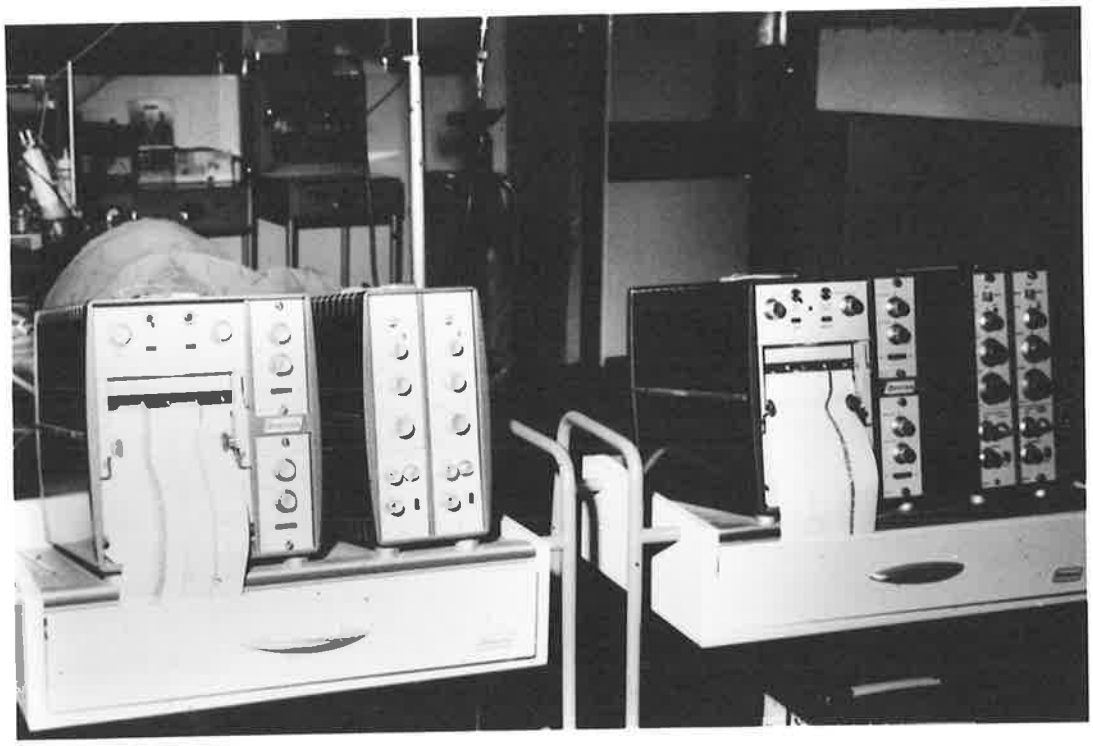


Figure 2: Chart recorders showing ventricular and arterial blood pressures.

were made for differences between oesophageal temperature and that of the electrode system exceeding 0.5°C, using the Radiometer Blood Gas Calculator. Blood O_2 saturation was derived either from PaO_2 values or by direct measurement on an O_2 saturation meter (Colorimeter - SP 1300 Series 2). Arterial haemoglobin was checked several times in each experiment by the cyanomethaemoglobin method, using a Kipp Hemoreflector M O 1.

Total O_2 content of arterial and cerebral venous blood was obtained from the formula:

$$C(O_2)\ (ml/100\ ml) = Hb \times 1.34 \times S\ (O_2)$$

where $C(O_2)$ = blood oxygen content

$S(O_2)$ = blood oxygen saturation

Arterio-venous O_2 difference $(Ca-Cv)\ O_2$, was obtained by subtraction.

Cerebral metabolic rate for O_2 ($CMRO_2$), was obtained from the formula:

$$CMRO_2 = \frac{CBF \times (Ca-Cv)\ O_2}{100}$$

(2) Blood pressure

SAP was recorded continuously from the intra-aortic catheter. Mean pressure was calculated as diastolic pressure plus one-third pulse pressure.

(3) Intracranial pressure

ICP was recorded continuously from bilateral ventricular catheters. In all experiments, a good pressure record was obtained from at least one catheter. An inadequate recording was indicated by damping of the pulsatile components and progressive falling of the recorded pressure level. Sometimes the trace could be restored by flushing the line with 0.1 ml saline or by slightly repositioning the catheter; however, if

the reliability of a trace was in doubt, that pressure recording was discarded. As with arterial pressure, mean pressure was calculated as diastolic pressure plus one-third pulse pressure.

(4) Volume-pressure response

The VPR was recorded as the immediate increase in intraventricular pressure following a bolus injection into a lateral ventricle of 0.1 ml of normal saline in 1 second (Leech & Miller, 1974a).

(5) Brain water and electrolytes

After the final measurement of CBF, when normocapnia and normotension had been resumed, the calvarium was removed as quickly as possible. The baboon was killed with intravenous sodium pentobarbitone (Euthatal, May & Baker), and the brain frozen in situ by immersion in liquid nitrogen. The brain was sectioned, and tissue samples taken, avoiding arcuate fibres in white matter. The samples were placed in sealed, pre-weighed containers, weighed, then dried in an oven at 100°C to a constant weight from which the percentage wet weight was calculated. The dried sample was placed in a pre-weighed test-tube, re-weighed then 15 times the sample weight of 0.75 N nitric acid added. This mixture was shaken for two days, centrifuged and the electrolyte concentration determined by flame spectrophotometry and converted to m Eq/100G dry weight (Selzer et al., 1972).

(6) Tests of cerebrovascular responses

(a) Hypotension

Blood was slowly withdrawn through a femoral artery catheter into a heparinized glass container standing in a water bath at 37°C. The container was sealed and pressurized by a sphygmomanometer enabling the arterial pressure to be held at a steady level through the period of CBF measurement, after which the blood was slowly reinfused.

Haemorrhagic hypotension has been used in several studies of autoregulation (Harper, 1966; Fitch et al., 1975; 1976). If severe hypotension is avoided, that is, less than 60 mm Hg mean SAP, there is no subsequent impairment of cerebrovascular reactivity.

(b) Hypertension

Hypertension was induced by an intra-aortic infusion of norepinephrine (2 mg in 200 ml of 5 per cent dextrose solution) via a slow infusion pump (Sage Instruments). SAP was raised by 40 to 50 mm Hg and held constant through the period of blood flow measurement (Miller et al., 1972; 1975).

(c) CO_2 response

Sufficient CO_2 was added to the inspired anaesthetic gases to raise the $PaCO_2$ by 15 to 20 mm Hg.

CEREBRAL BLOOD FLOW MEASUREMENT

(1) Principles

CBF was measured from the clearance of the inert, diffusable gases ^{133}Xe, and H_2. These methods are based on the Fick principle which states that if the quantity of a substance increases or decreases during passage through an organ, the blood flow through the organ may be calculated by dividing the quantity taken up or added to the blood in a given time (Qt), by the arterio-venous difference (Ca-Cv) (Fick, 1870).

That is blood flow in time t,

$$= \frac{Qt}{(Ca-Cv)}$$

Kety and Schmidt (1945) adapted this formula to measure total CBF in patients inhaling the inert diffusable gas nitrous oxide. The arterio-venous concentration difference from the beginning of inhalation to full blood saturation was obtained by repeated arterial and jugular venous blood measurements. At saturation, brain tissue concentration was assumed to equal venous concentration multiplied by λ, the blood brain partition coefficient for the inert gas,

Hence Q_t = concentration of the substance in the brain at time to full saturation, t, multiplied by brain weight,

= λ Cvt x brain weight,

where Cvt = venous concentration at full saturation.

Hence, blood flow per unit weight in time t,

$$= \frac{\lambda \text{ Cvt}}{\int_0^t (\text{Ca} - \text{Cv})\, dt}$$

This method has been modified in several ways:

(a) To allow continuous measurement of tissue clearance, either after full tissue saturation or following a bolus injection of a rapidly diffusing inert substance. This yields a mean flow over the period of measurement. Thus steady state conditions are needed.

(b) By using radioactive isotopes which permit external monitoring of tissue and blood clearance.

(c) By recording clearance from specific brain regions rather than from the whole brain.

Blood flow measurement by tissue clearance depends on the following assumptions:

(a) At the end of a bolus injection of a tracer, arterial concentration is zero and the rate of clearance is dependant upon the rate of arterial blood flow. An

ideal tracer should be eliminated rapidly by the lungs so that arterial re-circulation is mimimal.

(b) Distribution equilibrium between brain tissue and blood is reached rapidly and remains constant throughout the period of clearance.

(c) The tissue is homogeneously perfused.

(d) The indicator is neither metabolised by the tissue nor itself influences blood flow.

(2) Calculation of CBF

In these experiments CBF was derived from a clearance curve by:

(a) Compartmental analysis.

Clearance curves from brain tissue are composed of several levels of blood flow. Ingvar & Lassen (1962) proposed that for the purpose of blood flow analysis, brain tissue might be considered as consisting of a number of homogenous compartments with different flow levels arranged in parallel. They concluded that curves obtained by monitoring isotope clearance from exposed cerebral cortex fitted the sum of two exponentials. Indeed even cortical blood flow consists of several flow levels (Harper et al., 1961). However, the population of flow rates for whole brain is essentially bimodal, having a fast and slow component which under normal conditions represent flow in grey and white matter respectively (Kety, 1965; Harper, 1967; Reivich et al., 1969b).

In states of low blood flow, these two components may become inseparable so that the clearance curve is mono-exponential. Similarly, if overall flow increases, a fast component may become measurable. Such changes in the proportion of the fast and slow components have been reported in disease states (Høedt-Rasmussen & Skinhøj, 1966; Salmon & Timperman, 1971; Fieschi & Bozzao, 1972). Iliff et al. (1974) stress that the fast and slow components represent physiological rather than anatomical entities.

To calculate CBF, the clearance curve is transferred to semilog paper, and by exponential stripping, two components may be derived. $T\frac{1}{2}$, the time taken for tissue and blood concentration in the brain to fall to half its initial value is determined for each component. The partition coefficient for grey matter (λg) is used to calculate fast component flow, and the partition coefficient for white matter (λw) for slow component flow.

$$\text{Blood flow (ml/min. 100G)} = \frac{\lambda \log_e^2 \ .60 \ .100}{T\frac{1}{2}}$$

where λ = tissue : blood partition coefficient for grey or white matter.

(b) Initial Slope Index (Sveinsdottir et al., 1969).

A value for CBF may be calculated from the slope of the first two minutes of the clearance curve transferred to semilog paper. The first 15 seconds are excluded. Calculating $T\frac{1}{2}$ for this slope and using λg,

$$\text{Blood flow (ml/min. 100G)} = \frac{\lambda g \log_e^2 \ .60 \ .100}{T\frac{1}{2}}$$

This gives a value biased towards the more rapidly clearing components, but which correlates closely with stochastic flow values.

(c) Stochastic or height/area analysis (Zierler, 1965). This gives a mean CBF based on the area beneath the clearance curve.

$$\text{Blood flow (ml/min. 100G)} = \frac{\lambda_b \ (H - H_{10}) \quad .60 \quad .100}{A_{10}}$$

where, λ_b = tissue : blood partition coefficient for whole brain.

H = maximum height of the clearance curve.

H_{10} = height of clearance curve at 10 minutes.

A_{10} = area under curve at 10 minutes.

(3) ^{133}Xenon Clearance

^{133}Xe is a gamma emitter with an energy peak at 81 keV. A bolus injected into the carotid artery of humans or baboons will diffuse predominantly through the ipsilateral cerebral hemisphere and will be cleared at a rate dependent upon blood flow. The partition coefficient for white matter is 1.5 and for grey matter is 0.81 (Veall & Mallett, 1965). Assuming a grey:white volume of 60:40, the partition coefficient for whole brain is 1.1. The intra-arterial bolus is rapidly diluted by the venous pool. In addition, the blood air partition coefficient for ^{133}Xe is such that approximately 95 per cent of the initial bolus is cleared in a single passage through the lungs. Hence recirculation is insignificant (Rowan, 1972). Gamma emission attenuates by absorption in the tissues at 50 per cent per 4 cm. Energy reduction by the inverse square of the distance from the source does not apply to an extended energy source and a detector with a conical field of view (Rowan, 1972).

Method (Fig. 3)

CBF was measured by the intracarotid technique described by Rowan et al. (1970). ^{133}Xe in normal saline, warmed to 37°C was injected by hand into the internal carotid artery over 1 second. The dose was selected to give a peak count of 400 per second. Isotope clearance was measured by a heavily collimated one inch diameter sodium iodide crystal mounted directly lateral to the skull. The crystal was connected to a photo-multiplier pre-amplifier (Nuclear Enterprises) which amplified the light signals and converted them to electrical impulses. A pulse-height analyser selected counts from the peak of ^{133}Xe activity (81 KeV). A combined scaler/ratemeter (Nuclear Enterprises SR3) accumulated total counts for the 10 minute period of measurement and also relayed to a potentiometer chart recorder (Servoscribe-Venture RE 511.20) to give a clearance curve. Background activity was measured for 100 seconds before and after each 10 minute clearance period. The curve was transferred to semilog paper and CBF calculated by stochastic analysis and initial slope index.

In calculating the stochastic flow value, correction was made for background activity. Thus,

$$\text{CBF (ml/min. 100G)} = \frac{\lambda_b \, (H - H_{10}) \; .60 \;\; .100}{A_{10} \; - \; 6 \; BG}$$

where BG = background counts for 100 seconds.

A_{10} = area under the curve given by the total counts at 10 minutes.

(4) Hydrogen Clearance

H_2 clearance has been used by many workers to measure tissue blood flow since the principle was outlined by Aukland et al. (1964). The current generated by oxidation of molecular H_2 to H^+ at the surface of a platinum electrode is proportional to the H_2 partial pressure. Hence

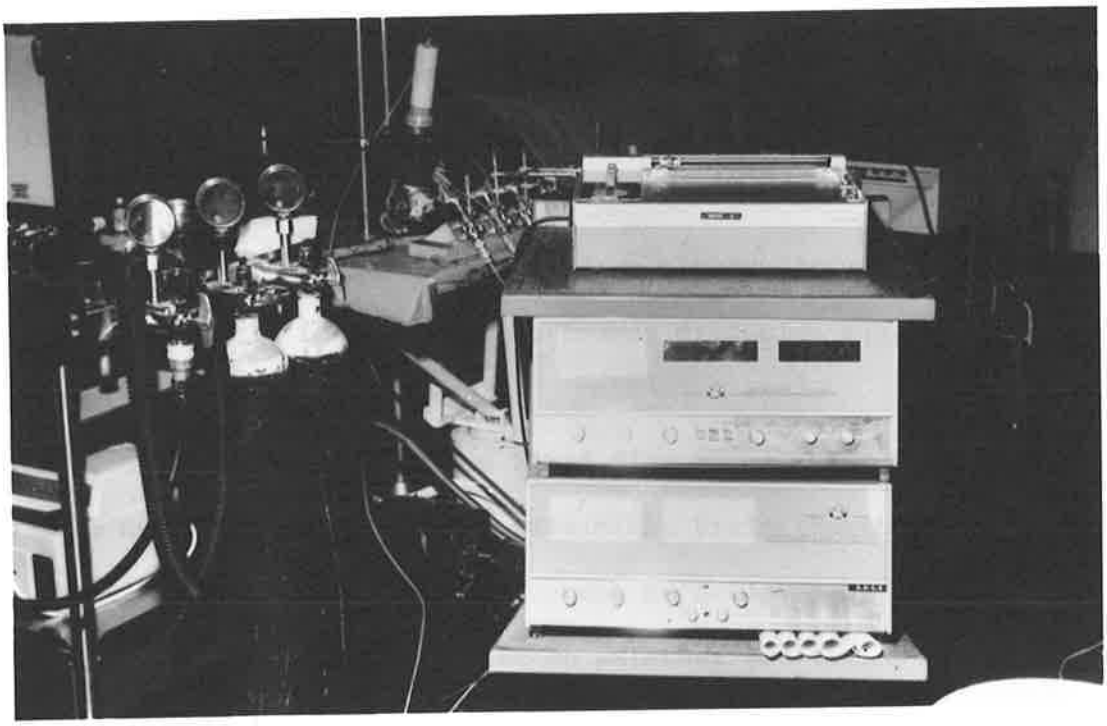


Figure 3: Measuring CBF by ^{133}Xe clearance.

Sodium iodide crystal (centre background) centres on the laterally placed burrhole and is connected to the preamplifier, scaler/ratemeter and potentiometer chart recorder.

tissue H_2 concentration may be measured continuously from small electrodes, allowing blood flow to be measured in well defined regions.

When H_2 is inhaled, arterial concentration rises rapidly and the tissues equilibrate more slowly. When inhalation ceases abruptly, approximately 90 per cent of the venous concentration is eliminated by a single passage through the lungs and arterial concentration falls to about 15 per cent in 40 seconds. Any error due to recirculation can be avoided by ignoring the first 40 seconds of the clearance curve (Pasztor et al., 1973; Griffiths et al., 1975). H_2, a highly diffusable lipid-soluble gas, is assumed to be in instantaneous diffusion equilibrium throughout the de-saturation period.

The H_2 clearance method allows blood flow to be recorded simultaneously from numerous discrete areas within the brain (Pasztor et al., 1973; Griffiths et al., 1975). This cannot be achieved by isotope clearance methods which depend either on external monitoring and cannot discriminate discrete intrahemispheric areas, or else require relatively large intracerebral probes with the risk of tissue damage. A small zone of tissue damage will be present at the tip of the H_2 electrode, however this is minimized by using a needle-pointed tip. A zone of damaged tissue will delay clearance but not alter the shape of the curve (Aukland et al., 1964). The brain:blood partition coefficient for H_2 is assumed to be 1 (Aukland et al., 1964).

Therefore, by initial slope index or compartmental analysis,

$$CBF = \frac{\lambda \log_e^2 \quad .60 \quad .100}{T^{1}/_{2}}$$

$$= \frac{4158}{T^{1}/_{2}}$$

Method (Fig. 4)

CBF was measured by H_2 clearance as described by Griffiths et al. (1975). Electrodes were prepared from 0.3 mm Grade 2 platinum wire thinly coated with Araldite. A 1 mm tip was bared and sharpened under a microscope. Before each experiment the electrode tips were cleaned and the insulation checked for current leakage by immersing the insulated section in normal saline and measuring the resistance to current flow.

The electrodes were mounted on micro-manipulators (Research Instruments Ltd.) and fitted to the stereotaxic head-holder. Coordinates were derived from the atlas of Davis & Huffman (1968). A Ag/AgCl reference electrode was placed subcutaneously in the mid-dorsal region. The output from each electrode was connected to a 6 channel amplifier system using Analog Devices amplifiers type 233K and then to potentiometer chart recorders (Servoscribe-Venture RE 520.20) so that the output from all electrodes could be recorded simultaneously. Each amplifier could be adjusted to record zero, for zero H_2. The system was allowed to stabilise for 60 minutes.

To measure CBF, H_2 was added to the inspired anaesthetic gases, N_2O was switched off and O_2 increased giving a H_2 concentration of 30 to 40 per cent. Tissue saturation, measured by the H_2 current, rose slowly to full saturation which was indicated by a steady current. This took 10 to 20 minutes. The H_2 supply was then switched off abruptly, N_2O and O_2 returned to their previous levels and tissue clearance followed for 15 minutes. The washout curve, ignoring the first 40 seconds was transferred to semilog paper and CBF calculated by initial slope index or by compartmental analysis which also allowed estimation of a weighted mean flow.

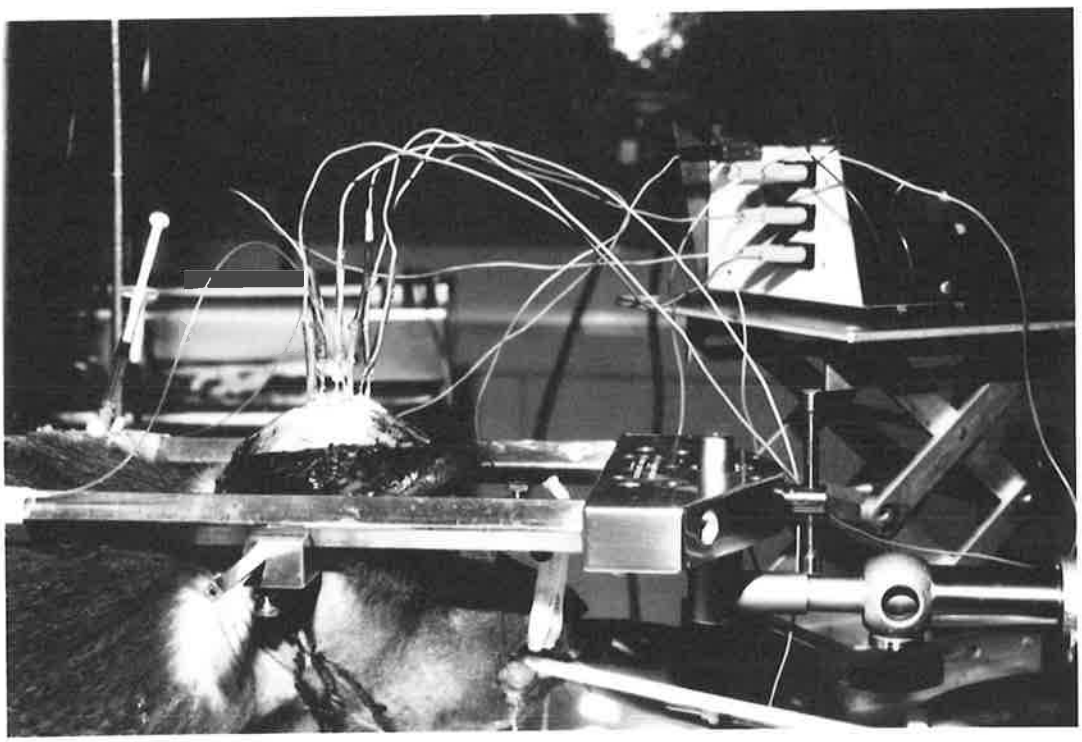


Figure 4: Measuring CBF by H_2 clearance.
Stereotaxically placed platinum electrodes are connected to the amplifier unit. There are ventricular catheters bilaterally.

CRYOGENIC INJURY

Production of a standardised brain injury by hypothermia was first described by Hass and Taylor (1948). The hypothermal instrument may be applied to the calvarium (Clasen et al., 1953), the exposed cortex (Klatzo et al., 1958), or the intact dura (Rosomoff, 1959).

The pathological changes have been described in detail by Klatzo et al. (1958) and Clasen et al. (1953). The lesion consists of a sharply defined area of haemorrhagic necrosis extending in a cone through the cortex and subjacent white matter. The sulcal cortex may be injured to a greater depth than the white matter. Surrounding the necrotic mass, oedema fluid spreads through the white matter. Blood-brain barrier markers indicate abnormal permeability of vessels within the lesion, but not within the oedematous area.

The oedema fluid includes all plasma protein components, with a marked increase in the albumin fraction (Blakemore, 1969) and has a Na and K concentration consistent with a plasma filtrate (Pappius and Gulati, 1963). Intracellular changes within the oedematous area include a rise in Na and fall in K concentrations and a corresponding rise in water content. There is a net fall in energy metabolites. 70 per cent of the total tissue water increase in cold injury oedema occurs in the extracellular space of white matter (Reulen et al., 1971).

In animals with intact skulls, ICP rises during freezing and again during thawing, haemorrhage and congestion about 10 minutes later. Even with a standardised method of production there may be great variation in lesion volume, and no direct relationship between lesion size and the level of ICP (Miller et al., 1970b).

Marked changes occur soon after injury in the vessels within the lesion. Fluorescein angiography shows perivascular leakage of dye within 10 minutes and complete arrest of the micro-circulation within 30 minutes (Yamamoto et al., 1976). Hyperaemic flows may be found around

the lesion in animals with open skulls (Heipertz, 1968) but not those with closed skulls in which ICP rises (Christ et al., 1969).

Hence a cryogenic injury has elements of ischaemia and necrosis. Vascular changes with disruption of the blood-brain barrier lead to vasogenic oedema. The primary injury resembles a focal contusion (Miller et al., 1975), and the oedema which develops resembles that associated with contusions, tumours, infarction and inflammation (Clasen et al., 1967; Klatzo et al., 1967).

Method

Under general anaesthetic a 12.0 mm right lateral burrhole was made. The closed end of a copper cylinder 1.0 cm in diameter was placed against the intact dura which was smeared with electrode jelly (Aquasonic 100) to ensure an air-tight seal. The cylinder was filled with liquid nitrogen for recorded periods at the end of which contact with the dura was broken by irrigating with saline at body temperature. The burrhole was sealed with dental cement.

Vital Staining

The extent of oedema, and the site of blood-brain barrier disruption were determined by vital staining.

Evans Blue has been used extensively as a blood-brain barrier marker. It binds to plasma protein within seconds of injection, and passes through the site of barrier breakdown with the oedema fluid (Clasen et al., 1970). Evans Blue (1 ml/kg of a 2.5 per cent solution) was injected intravenously a few minutes before the cryogenic injury so that the extent of oedema reached by the end of the experiment could be assessed visually.

Sodium fluorescein also binds to plasma protein and after intravenous injection, passes immediately through the disrupted blood-brain

barrier (Klatzo et al., 1958). Injected immediately before sacrifice, sodium fluorescein (0.5 ml/kg of a 10 per cent solution) was used to identify the site of blood-brain barrier breakdown.

DEFINITIONS

(1) Autoregulation: In this study, autoregulation was assessed by calculating the percentage change in CVR induced by a change in CPP. CVR was derived from CBF and CPP (formula 2, page 13).

$$\text{Hence, CVR} = \frac{\text{CPP}}{\text{CBF}}$$

$$= \frac{\text{SAP - ICP}}{\text{CBF}}$$

Intact autoregulation was defined as a greater than 20 per cent change in CVR accompanying an increase or decrease in CPP, any lesser change being regarded as impaired autoregulation. The relative effectiveness of autoregulation in different groups of animals was assessed by comparing this percentage change in CVR.

(2) CO_2 response: The response of CBF to a change in $PaCO_2$ was calculated as the change in CBF per unit (mm Hg) change in $PaCO_2$. Thus,

$$CO_2 \text{ response (ml/min. 100G/mm Hg } PaCO_2) = \frac{\Delta CBF}{\Delta PaCO_2}$$

NORMAL VALUES

(Note: Data from individual experiments in this and subsequent sections are given in the Appendix. Tables within the text show the reference to the appropriate Appendix table).

1. General (Table 1)

The normal values are derived from animals studied in these experiments. Values obtained for CBF are given in the tables of control values in the relevant experimental sections.

TABLE 1

NORMAL VALUES (MEDIAN & RANGE)

Blood gases:		
	Arterial (n=23)	Venous (n=11)
pO_2 (mm Hg)	104.0 (91.0-184.0)	40.7 (28.9-50.0)
pCO_2 (mm Hg)	40.5 (37.2-44.0)	46.4 (42.9-52.5)
pH	7.43 (7.33-7.49)	7.38 (7.29-7.49)
Haemoglobin (G/100G) (n=12)	10.8 (9.1-13.4)	
$CMRO_2$ (n=12)	2.2 (1.2-3.1)	
Body Temperature (^oC) (n=12)	36.7 (36.0-38.0)	
Arterial Pressure (mm Hg) (n=23)	92.0 (70.0-118.0)	
Intracranial Pressure (mm Hg) (n=23)	7.0 (3.0-21.0)	
Volume-Pressure Response (mm Hg/0.1 ml)(n=12)	1.0 (1.0-5.0)	
Sagittal Sinus Pressure (mm Hg) (n=8)	12.5 (4.0-25.0)	

(See Appendix Table 1)

2. Comparison of Cerebral Blood Flow Measured by ^{133}Xenon and Hydrogen

Before measuring CBF by H_2 clearance in these studies, the values obtained by this method were compared with those obtained by the intracarotid ^{133}Xe method (Rowan et al., 1975).

Method

In 10 anaesthetised baboons, platinum electrodes were inserted stereotaxically into the cortex, white matter (centrum semiovale) and deep grey matter (putamen) of each hemisphere. CBF was measured from each of these sites by H_2 clearance. Placement was verified at the end of each experiment by brain dissection. CBF was measured simultaneously by the intracarotid ^{133}Xe method using a scintillation counter placed over the right parietal region.

In five baboons, CBF was measured repeatedly at normal levels of $PaCO_2$ and SAP. In the remaining animals after measuring CBF at normal levels of $PaCO_2$ and SAP, $PaCO_2$ was altered by hyperventilation or by adding CO_2 to the inspired gases. Hence, the correlation between values obtained by the two methods could be studied over a wide range of flow values.

Fast and slow components of the clearance curves were derived by compartmental analysis.

Results

In 10 animals at normal levels of $PaCO_2$ and SAP, there were no significant differences between the fast flow values obtained by either method (Table 2). The slow component of ^{133}Xe clearance was significantly higher than that obtained by H_2 clearance from white matter or cortex. When CBF was varied over a wide range by changes in $PaCO_2$ in five animals, there were significant correlations between the values obtained by H_2 clearance in cortex and white matter and the fast and slow components obtained by ^{133}Xe. There was however, no apparent correlation between

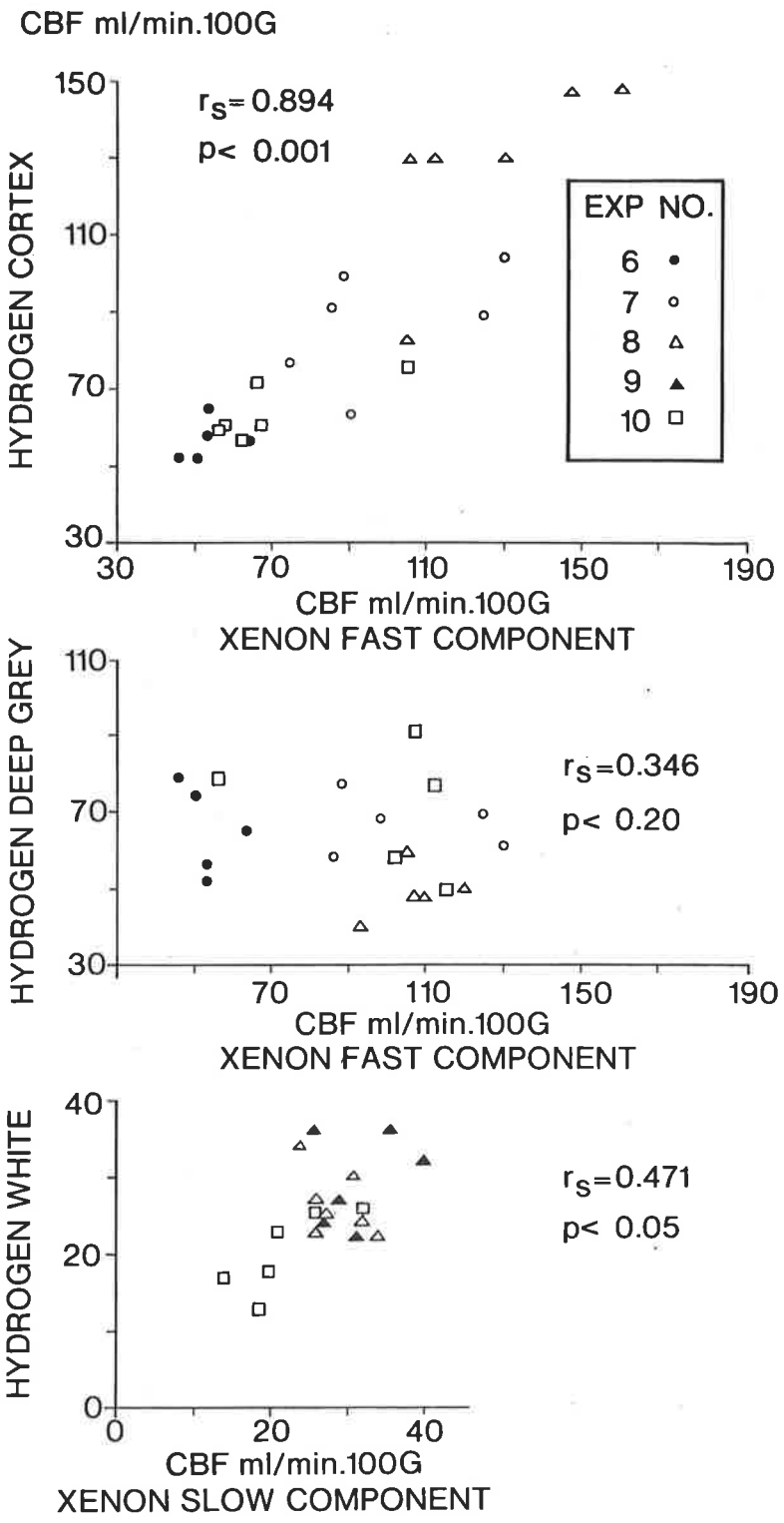


Figure 5: Comparison of CBF measured by ^{133}Xenon and Hydrogen. Correlation when $PaCO_2$ was varied from 34.5 to 76.0 mm Hg, by Spearman rank order correlation coefficient.

(See Appendix Table III)

TABLE 2

COMPARISON OF CEREBRAL BLOOD FLOW MEASURED BY ^{133}XENON AND HYDROGEN (MEDIAN & RANGE)

	Fast Component (ml/min. 100G)	Slow Component (ml/min. 100G)
Xenon (n=10)	93.8 (51.0-103.7)	26.3 (13.0-38.0)
Hydrogen (n=9)		
White		18.0 (11.5-29.0)*
Cortex	73.7 (63.0-130.0)	16.0 (12.0-26.5)†
Deep Grey	84.0 (74.2-104.5)	20.5 (12.0-32.0)

(See Appendix Table II)

*p<0.05)
†p<0.025) compared with ^{133}Xenon slow component, by Mann-Whitney U Test.

the fast flow value in deep grey matter and the fast flow value derived from ^{133}Xe clearance. As this study aimed to test the correlation between values obtained by two methods of measurement and not the relationship between blood flow and any other physiological parameter, the individual pairs of values obtained in the five animals were compared. (Fig. 5).

Conclusions

1. The correlation between fast flow values obtained by the two methods confirmed the accuracy of H_2 clearance in recording absolute flow values.

   This supports the observation by other workers that omitting the first 40 seconds of the H_2 clearance curve does not significantly affect the flow value obtained. Very fast

early components may be excluded. However their weight is likely to be low, so that the average initial flow value is not affected.

2. White matter flow and cortex slow component flow measured by H_2 clearance were significantly lower than the slow component of ^{133}Xe clearance. This might be explained by reduced accuracy of the H_2 clearance method at low flow levels. Alternatively, flow recorded from a small area of white matter is likely to contain a more restricted range of flow values than that derived from external monitoring. The slow component of externally monitored flow may include faster clearing flow values from other areas such as cortex. Recirculation of H_2 would tend to reduce the measured flow value. Without continuous measurement of arterial H_2 concentration, a true correction for recirculation cannot be made. However, as stated earlier (p.42), studies in which such measurements have been made indicate that the effect of recirculation after 40 seconds is minimal (Pasztor et al., 1973; Griffiths et al., 1975).

3. There was a close correlation between flows obtained by the two methods over a wide range of flow levels. This tended to substantiate the accuracy of H_2 clearance at low flow levels.

4. The failure of deep grey matter flow to correlate with ^{133}Xe fast flow suggested that ^{133}Xe fast flow was influenced more by cortex flow.

3. Cryogenic Injury (Fig. 6)

After each experiment, the lesion was inspected externally and in coronal section. There was a central haemorrhagic core 2.5 to 4.0 cm in diameter involving cortex and white matter and sharply demarcated from the adjacent brain. In animals in which Evans Blue had been injected immediately before injury, a band of blue-staining extended from the edge of the central core into the white matter. Fluorescein injected immediately before sacrifice stained the margin of the central core only.

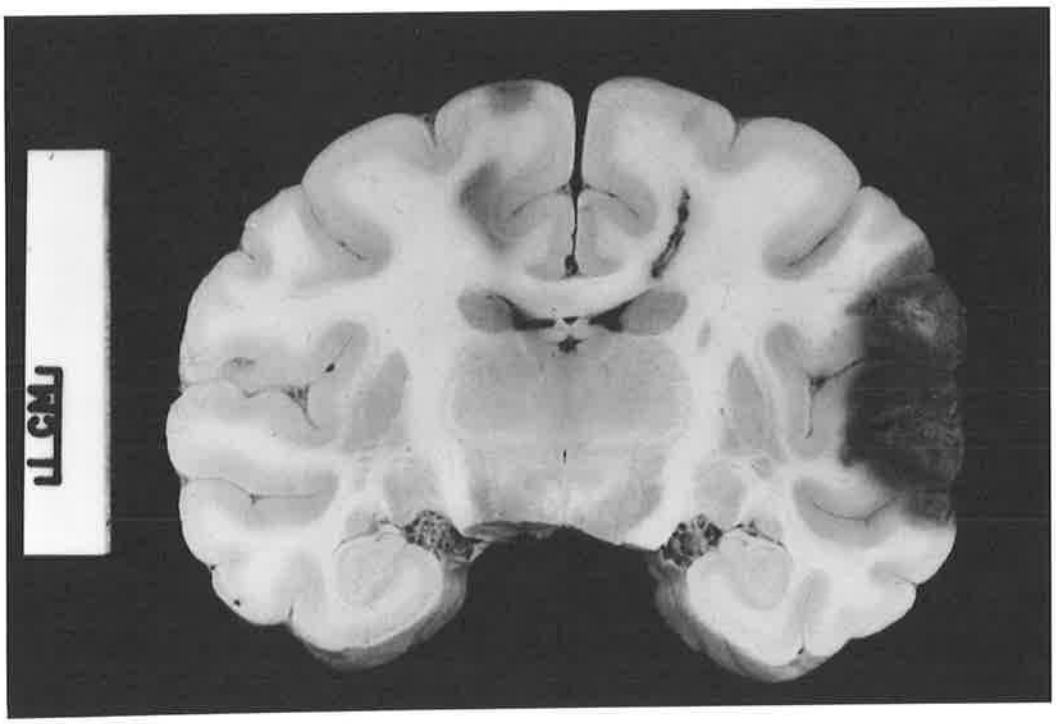


Figure 6: The cryogenic lesion at 5 hours.

There is a central zone of haemorrhagic necrosis with a thin band of Evans Blue staining the adjacent white matter. Evans Blue also stains the left ventricular catheter track.

SECTION 2

VASCULAR REACTIVITY IMMEDIATELY AFTER CRYOGENIC INJURY

PURPOSE

This series of experiments examined the immediate effects of a cryogenic injury on CBF and on the responses of CBF to physiological stimuli in and around the area of injury. Changes occurring soon after injury were compared with the vasomotor responses before injury. Concurrent changes in ICP, VPR, $CMRO_2$ and brain tissue water and electrolyte content were measured.

The questions posed were:

1. What are the early effects of injury on CBF?
2. How does the cerebral vasculature respond to physiological stimuli in the injured area?
3. Do these responses indicate how blood flow in the injured area might be increased?

PROTOCOL (Table 3, Fig. 7)

The study was conducted on 12 young adult baboons weighing 9 to 32 kg. CBF was determined by the intracarotid ^{133}Xe method. The blood flow values were derived by stochastic analysis.

Two control measurements of CBF were obtained under stable conditions of SAP, blood gases and ICP. Autoregulation was then assessed by reducing SAP by 30 mm Hg, using controlled haemorrhage. After reinfusion, and a further control CBF measurement at normal SAP, the cerebrovascular responses to hypercapnia was tested. In all tests requiring changes in the physiological state, steady conditions were maintained for several minutes before the CBF measurement.

When normocapnia had been restored, a cryogenic lesion was made in the brain underlying the blood flow detector. The freezing probe was applied for periods of 2 to 12 minutes. CBF was measured 30 to 60 minutes later, the detector being repositioned precisely over the burrhole to record the flow changes about the area of injury.

TABLE 3

PROTOCOL - SERIES 1

1.	Control	-	Normocapnia/normotension
2.	↓ SAP	-	Calculate Δ CVR
3.	Control		
4.	↑ CO_2	-	Calculate CO_2 response
	COLD LESION		
5.	CBF at 30 minutes		
6.	CBF at 60 minutes		
7.	↓ SAP (if possible)	-	Compare Δ CVR
8.	↑ SAP	-	Compare Δ CVR
9.	Control		
10.	↑ CO_2	-	Compare CO_2 response
11.	Control		
	FREEZE BRAIN IN SITU	-	Section to inspect the lesion and to take tissue samples for water and electrolyte measurement

Autoregulation was then re-tested, firstly by reducing SAP by controlled haemorrhage, then after a normotensive control, by increasing SAP using an intra-aortic infusion of norepinephrine. After a further control, CBF was measured during hypercapnia of the same degree as before. Midway through each flow measurement, blood gases, SAP, ICP and the VPR were recorded.

Finally, normocapnic and normotensive conditions were resumed and the animal was killed. Tissue samples were taken from non-haemorrhagic white matter underlying the cortical lesion and from the equivalent area in the opposite hemisphere. These samples were assayed for water and

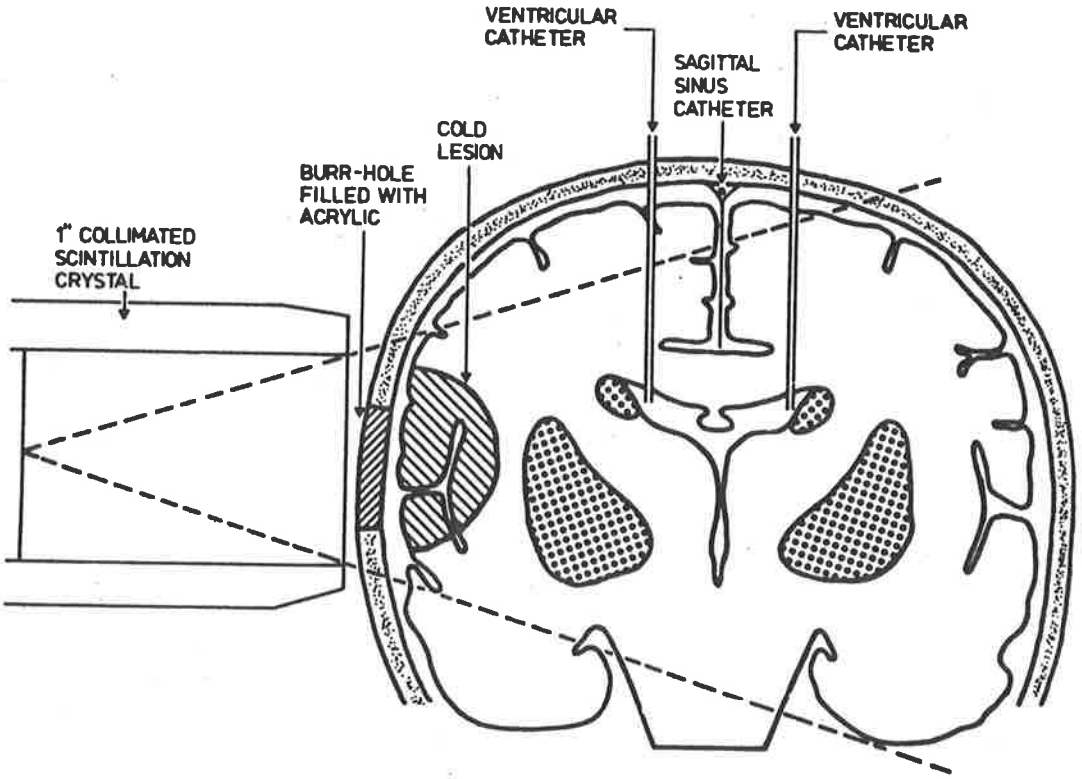


Figure 7: Measuring CBF and ICP immediately after cryogenic injury.

The scintillation counter with its conical field of view centres on the lateral burr-hole and records blood flow around the cryogenic lesion.

electrolyte content.

In six animals, Evans Blue was injected intravenously a few minutes before the cryogenic injury to assess the extent of the oedema at the time of sacrifice six to nine hours later.

RESULTS

Measurements before cryogenic injury (Table 4)

A control value for CBF of 43.5 (30.0-78.0) ml/min. 100G was obtained at normocapnia ($PaCO_2$ 40.5, 37.0-42.0 mm Hg) and normotension (SAP 92.5, 85.0-108.0 mm Hg). ICP for the whole group was 10.5 (6.0-21.0) mm Hg. Levels from 15 to 21 mm Hg occurred following preparation in four animals, three of which were found later to have haemorrhage at the site of ventricular puncture. No cause for raised pressure was found in the fourth. The VPR was 1.0 (1.0-5.0) mm Hg/0.1 ml. Significantly higher values occurred in baboons with raised ICP ($p<0.01$, $r_s = 0.814$; Appendix Table IV). There was no obvious relationship between ICP and resting CBF at this stage in the experiment. Autoregulation was tested by induced arterial hypotension in 11 animals and by hypertension in one (Fig. 8). There was only slight change in median CBF for the group as a whole, however by the definition of autoregulation used in this thesis, only seven animals were considered to have intact autoregulation. Of the 5 animals in which autoregulation was impaired, ICP was elevated in three. Median ICP in those animals with intact autoregulation was 9.0 (6.0-15.0) mm Hg, and in those with impaired autoregulation was 17.0 (9.0-21.0) mm Hg ($p<0.01$).

Hypercapnia produced an increase in CBF in all animals, a median increase in $PaCO_2$ of 12.0 (7.0-25.0) mm Hg, resulting in a 60 per cent increase in flow. Thus the CO_2 response was 2.4 ml/min. 100G per mm Hg change in $PaCO_2$, with the responses ranging from 0.5 to 3.7 in individual animals (Fig. 9). Paradoxically, the CO_2 response was higher in those

TABLE 4

MEASUREMENTS BEFORE CRYOGENIC INJURY IN BABOONS WITH INTACT AND IMPAIRED AUTOREGULATION (MEDIAN & RANGE)

	Intact (n=7)	Impaired (n=5)	Whole Group
Control			
Arterial pH	7.46 (7.39-7.49)	7.41 (7.37-7.47)	7.45 (7.37-7.49)
Arterial pCO_2 (mm Hg)	40.0 (37.0-42.0)	41.0 (38.0-41.0)	40.5 (37.0-42.0)
Arterial pressure (mm Hg)	92.0 (85.0-108.0)	93.0 (87.0-100.0)	92.5 (85.0-108.0)
Intracranial pressure (mm Hg)	9.0 (6.0-15.0)	17.0 (9.0-21.0)‡	10.5 (6.0-21.0)
Volume-pressure response (mm Hg/0.1 ml)	1.0 (1.0-3.0)	2.0 (1.0-5.0)	1.0 (1.0-5.0)
Cerebral blood flow (ml/min. 100G)	42.0 (32.0-78.0)	45.0 (30.0-53.0)	43.5 (30.0-78.0)
$CMRO_2$	2.0 (1.6-2.3)	2.3 (1.2-3.1)	2.2 (1.2-3.1)
Response to change in SAP			
Arterial pCO_2 (mm Hg)	40.0 (37.0-47.0)	41.0 (40.0-43.0)	41.0 (37.0-47.0)
Change in intracranial pressure (mm Hg)	1.0 (0-2.0)	3.0 (1.0-7.0)δ	1.5 (0-7.0)
Change in perfusion pressure (mm Hg)	18.0 (13.0-29.0)	19.0 (17.0-38.0)	19.0 (13.0-38.0)
Change in cerebral blood flow (ml/min. 100G)	1.0 (0-5.0)	14.0 (3.0-27.0)δ	4.0 (0-27.0)
% Change in cerebrovascular resistance	26.0 (20.0-43.0)	14.0 (0-18.0)§	21.5 (0-43.0)
$CMRO_2$	2.4 (1.8-3.1)	2.3 (0.9-2.8)	2.3 (0.9-3.1)
Response to hypercapnia			
Arterial pCO_2 (mm Hg)	53.0 (45.0-65.0)	52.0 (50.0-59.0)	52.5 (45.0-65.0)
Arterial pressure (mm Hg)	92.0 (80.0-122.0)	97.0 (82.0-102.0)	94.5 (80.0-122.0)
Intracranial pressure (mm Hg)	12.0 (10.0-34.0)	29.0 (11.0-38.0)	17.5 (10.0-38.0)
CO_2 response (ml/min. 100G per mm Hg $PaCO_2$)	1.0 (0.5-2.9)	3.0 (2.3-3.7)‡	2.4 (0.5-3.7)
$CMRO_2$	1.6 (1.1-3.1)	2.5 (1.2-3.6)	2.1 (1.1-3.6)

(See Appendix Tables IV & V)

‡ $p<0.01$ δ $p<0.005$ § $p<0.001$ by Mann-Whitney U test, compared with intact.

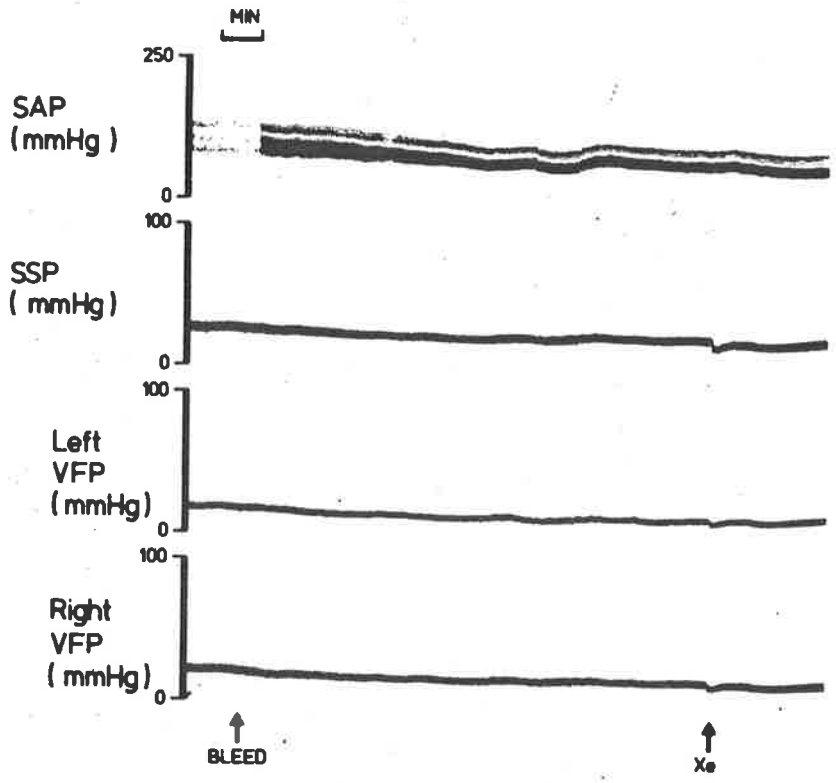


Figure 8: Arterial hypotension before cryogenic injury.

There is a slight fall in ventricular fluid pressure (VFP) and in SSP.

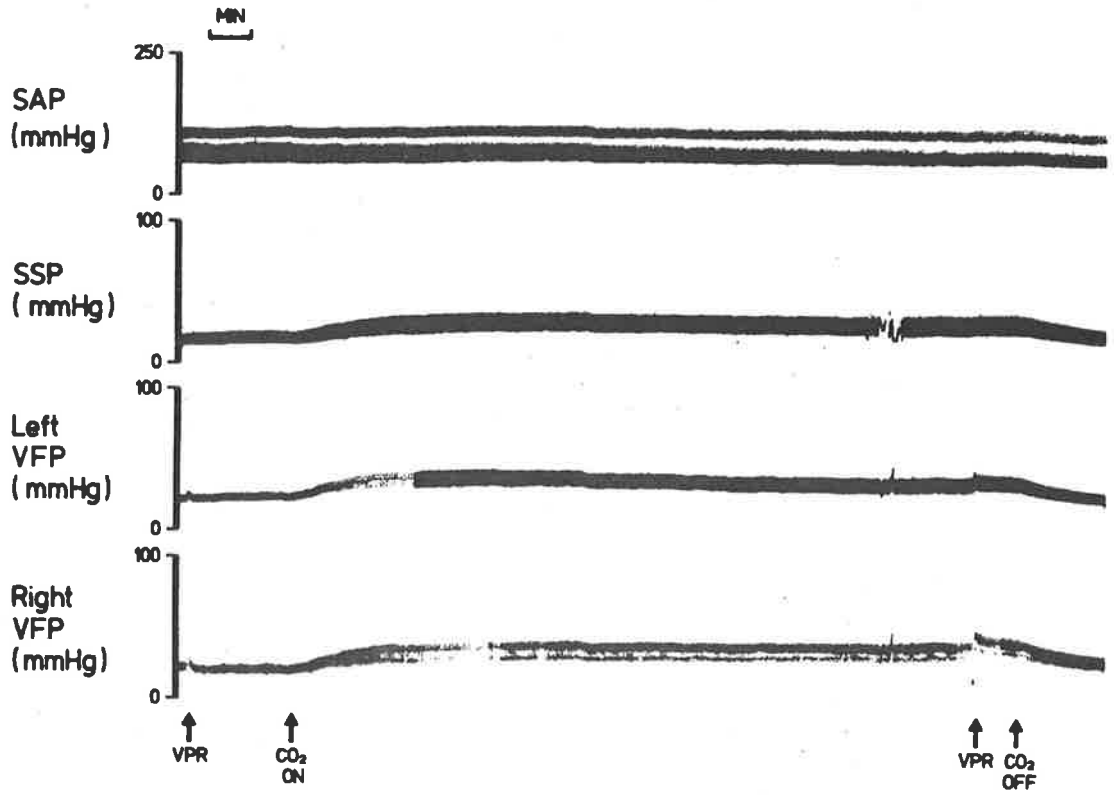


Figure 9: Hypercapnia before cryogenic injury.

There is an immediate rise in VFP and SSP and no change in SAP.

with impaired autoregulation ($p<0.01$). $CMRO_2$ was 2.1 (1.1-3.6) and did not change significantly with variation in either SAP or $PaCO_2$.

Effects of Cryogenic Injury (Table 5 and 6)

During application of the freezing probe, ICP and SAP usually fell for several minutes, then returned to normal. About 10 minutes after freezing, ICP and SAP rose above normal (Fig.10).

When measurements were made 30 and 60 minutes after freezing, SAP had returned near to control levels. ICP was still significantly elevated ($p<0.005$ and $p<0.01$) and CPP significantly reduced ($p<0.005$ and $p<0.005$). The VPR had increased with ICP at 60 minutes ($p<0.01$, $r_s = 0.982$). CBF was reduced at 30 minutes and 60 minutes ($p<0.01$ and $p<0.025$). $CMRO_2$ had fallen by 60 minutes ($p<0.005$). Groups of animals which had intact and those which had impaired autoregulation prior to injury, were analysed separately. A significant reduction in CBF at 60 minutes was found both in animals with previously impaired autoregulation ($p<0.05$) and in those with previously intact autoregulation ($p<0.01$).

Cerebrovascular Responses following Cryogenic Injury (Table 7)

It was possible to test autoregulation to a reduction in SAP in only two animals. In the remainder, the increase in ICP following injury had so reduced CPP that a further reduction large enough to provide a meaningful physiological stimulus, would have lowered CPP below the point (40 to 50 mm Hg) where autoregulation would occur even under normal circumstances. In one of these two animals, autoregulation to hypotension had been intact prior to the lesion. This was clearly impaired afterwards in both.

In 12 animals, the autoregulatory response to an increase in SAP of 40 to 50 mm Hg was then tested. A change of this magnitude was necessary, because the accompanying increase in ICP tended to diminish

TABLE 5

EFFECT OF THE CRYOGENIC INJURY (MEDIAN & RANGE)

	Whole Group (n=12)		
	Control	30 min.	60 min.
Arterial pCO_2 (mm Hg)	40.5 (37.0-42.0)	41.5 (35.0-48.0)	40.0 (37.0-45.0)
Arterial pressure (mm Hg)	91.0 (72.0-103.0)	81.5 (68.0-175.0)	77.0 (70.0-130.0)
Intracranial pressure (mm Hg)	12.0 (6.0-21.0)	22.0 (10.0-78.0)δ	21.0 (12.0-56.0)‡
Cerebral perfusion pressure (mm Hg)	80.5 (58.0-89.0)	61.5 (38.0-97.0)δ	58.0 (36.0-83.0)δ
Cerebral blood flow (ml/min. 100G)	46.5 (30.0-83.0)	37.5 (26.0-68.0)‡	34.5 (24.0-68.0)†
Cerebrovascular resistance (mm Hg/ml/min. 100G)	1.69 (0.76-2.48)	1.62 (0.78-3.34)	1.64 (0.76-2.77)
$CMRO_2$	2.0 (1.1-3.0)	2.0 (0.8-2.6)	1.6 (0.6-2.6)δ
Volume-pressure response (mm Hg/0.1 ml)	1.5 (1.0-4.0)	2.0 (1.0-5.0)	4.0 (1.0-8.0)*

(See Appendix Table VI)

* $p<0.05$ † $p<0.025$ ‡ $p<0.01$ δ $p<0.005$,

By Wilcoxon matched-pairs, signed - ranks test. Values at 30 min. and 60 min. compared with control values.

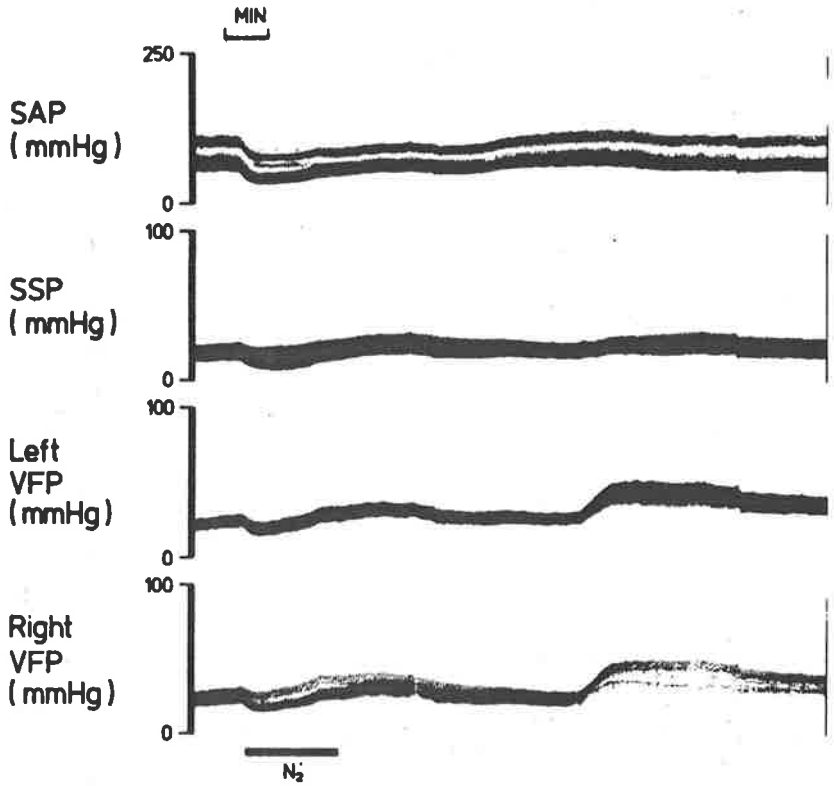


Figure10: The immediate effects of cryogenic injury.

VFP and SAP fall during freezing, and rise sharply about 10 minutes later. This rise is probably due to expansion of the lesion with thawing.

TABLE 6

EFFECT OF THE CRYOGENIC INJURY IN BABOONS WITH INTACT AND IMPAIRED AUTOREGULATION (MEDIAN & RANGE)

	Autoregulation intact (n=7)			Autoregulation impaired (n-5)		
	Control	30 min.	60 min.	Control	30 min.	60 min.
Arterial pCO_2 (mm Hg)	40.0 (37.0-42.0)	40.0 (39.0-44.0)	41.0 (37.0-45.0)	41.0 (38.0-42.0)	44.0 (35.0-48.0)	41.0 (38.0-42.0)
Arterial pressure (mm Hg)	90.0 (72.0-103.0)	78.0 (68.0-175.0)	74.5 (70.0-130.0)	95.0 (87.0-100.0)	85.0 (72.0-108.0)	85.0 (72.0-93.0)
Intracranial pressure (mm Hg)	11.0 (6.0-15.0)	24.0 (12.0-78.0)‡	27.5 (12.0-47.0)*	17.0 (9.0-21.0)	20.0 (10.0-50.0)	21.0 (13.0-56.0)
Cerebral perfusion pressure (mm Hg)	80.0 (58.0-88.0)	61.0 (48.0-97.0)*	58.0 (36.0-83.0)*	81.0 (66.0-89.0)	65.0 (38.0-83.0)**	59.0 (37.0-69.0)
Cerebral blood flow (ml/min. 100G)	51.0 (32.0-83.0)	40.0 (26.0-68.0)*	33.0 (24.0-68.0)‡	45.0 (30.0-53.0)	35.0 (29.0-49.0)	36.0 (27.0-46.0)**
Cerebrovascular resistance (mm Hg/ml/min. 100G)	1.61 (0.76-2.48)	1.53 (0.82-3.34)	1.77 (0.76-2.77)	1.80 (1.45-2.16)	1.77 (0.78-2.76)	1.64 (0.82-2.52)
$CMRO_2$	1.6 (1.3-2.5)	1.6 (0.8-2.6)	1.2 (0.6-2.1)*	2.3 (1.1-3.0)	2.0 (1.0-2.5)	2.2 (1.6-2.6)

(See Appendix Table VI)

* $p<0.05$ ‡ $p<0.01$, By Wilcoxon matched-pairs, signed-ranks test.

** $p<0.05$, By Sign test.

Values at 30 min. and 60 min. compared with control values.

TABLE 7

EFFECT OF ARTERIAL HYPERTENSION AFTER CRYOGENIC INJURY: COMPARISON OF GROUPS ACCORDING TO CHANGE IN CEREBRO-VASCULAR RESISTANCE (MEDIAN & RANGE)

	Δ CVR > 20% (n=6)		Δ CVR < 20% (n=6)	
	Control	Experimental	Control	Experimental
Arterial pCO_2 (mm Hg)	42.5 (38.0-47.0)	40.5 (38.0-45.0)	41.5 (39.0-42.0)	42.0 (39.0-43.0)
Arterial pressure (mm Hg)	78.5 (55.0-87.0)	129.5 (93.0-148.0)†	91.0 (72.0-102.0)	131.5 (95.0-145.0)†
Intracranial pressure (mm Hg)	17.0 (10.0-41.0)	27.0 (19.0-79.0)	30.5 (14.0-56.0)	51.5 (21.0-101.0)†
Cerebral perfusion pressure (mm Hg)	51.0 (42.0-70.0)	94.0 (64.0-118.0)†	59.0 (37.0-68.0)	70.5 (42.0-100.0)
Cerebral blood flow (ml/min. 100G)	40.5 (24.0-53.0)	46.5 (19.0-57.0)	37.0 (20.0-68.0)	47.0 (22.0-107.0)†
Cerebrovascular resistance (mm Hg/ml/min. 100G)	1.43 (0.96-1.88)	2.32 (1.37-3.37)†	I.60 (0.82-3.00)	1.58 (0.69-2.73)
$CMRO_2$	1.8 (0.9-2.3)	1.5 (0.8-2.6)	2.2 (1.0-2.5)	2.1 (1.7-3.6)

* $p<0.05$ † $p<0.025$, by Wilcoxon matched-pairs signed-ranks test, compared with control values.

(See Appendix Table VII)

the increase in CPP produced by arterial hypertension. Indeed, in two of the animals, one of which failed to autoregulate to induced hypotension, rises in SAP of 23 mm Hg and 50 mm Hg were accompanied by an equal rise in ICP, so that CPP remained constant (Fig. 11). The median passive increase in ICP during arterial hypertension was 13.0 mm Hg with no obvious relationship between this change in ICP and that produced by the cryogenic lesion, or the status of autoregulation prior to injury.

Overall, induced arterial hypertension with a constant $PaCO_2$ increased CBF from 40.5 (20.0-68.0) to 46.5 (19.0-107.0), ml/min. 100G, ($p<0.005$, Appendix Table VII). From this wide range of values, it is apparent that the response of CBF to the increase in SAP varied greatly. In six of the 12 animals, there was a rise in CVR of less than 20 per cent with arterial hypertension. In two of these, CPP did not increase, and CBF remained relatively constant. In four others, arterial hypertension produced an increase in CPP, and CBF increased by 18 to 67 per cent.

By contrast, in the remaining six animals, there was a rise in CVR of more than 20 per cent with arterial hypertension, and related to this, there was no significant change in CBF.

This apparent persistence of autoregulatory activity after cryogenic injury was not related to the status of autoregulation prior to injury (Fig. 12). Thus, three of the six animals which showed apparent autoregulation after injury had impaired autoregulation beforehand, and three had intact autoregulation. Of the six with impaired autoregulation after injury, it was previously intact in three and impaired in three.

The response of CBF to hypercapnia, was assessed in 11 animals and was generally reduced after injury compared with the initial response (Fig. 13 a, Appendix Table VIII). In one baboon, administration of CO_2 triggered off a massive increase in SAP and ICP associated with a

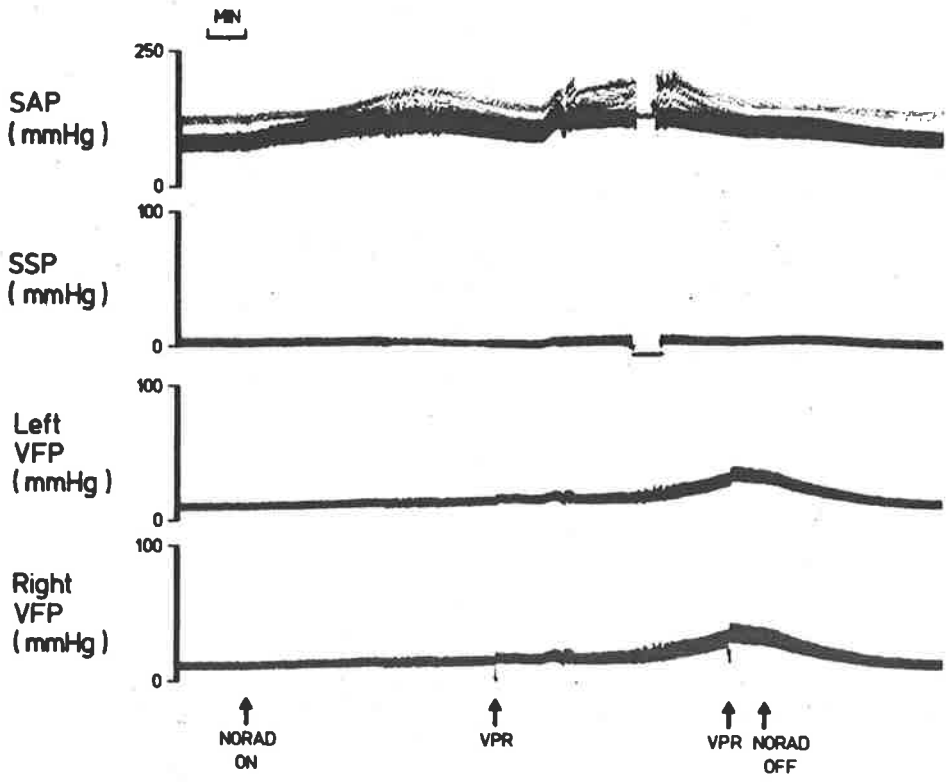


Figure 11: Arterial hypertension after cryogenic injury.

The rise in SAP is accompanied by a delayed but more sustained rise in VFP, reducing the change in CPP. SSP fails to reflect VFP in this animal.

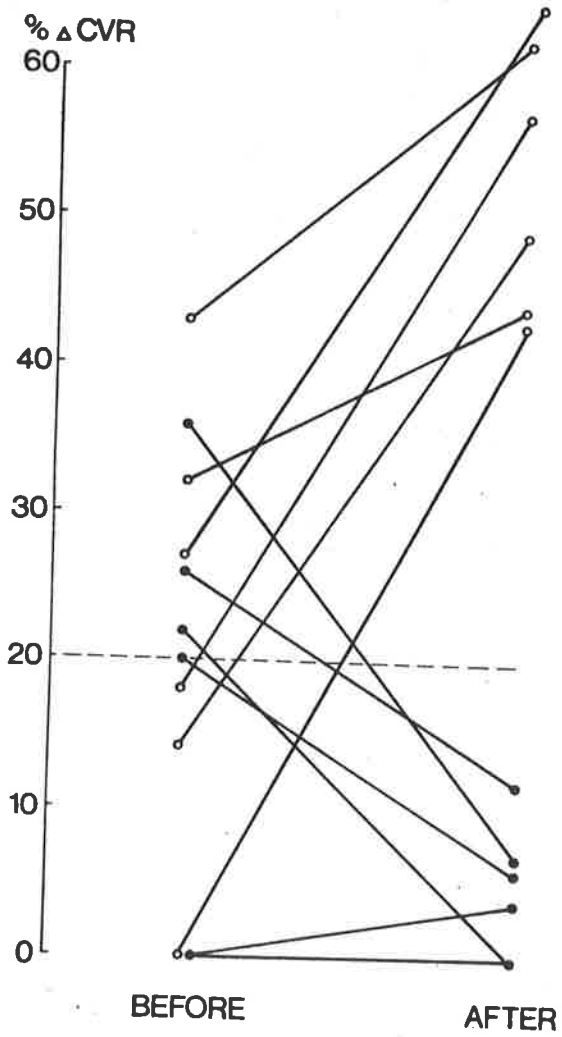


Figure 12: Response to change in blood pressure before and after cryogenic injury.

Open circles represent baboons showing a greater than 20 per cent increase in CVR with arterial hypertension after injury.

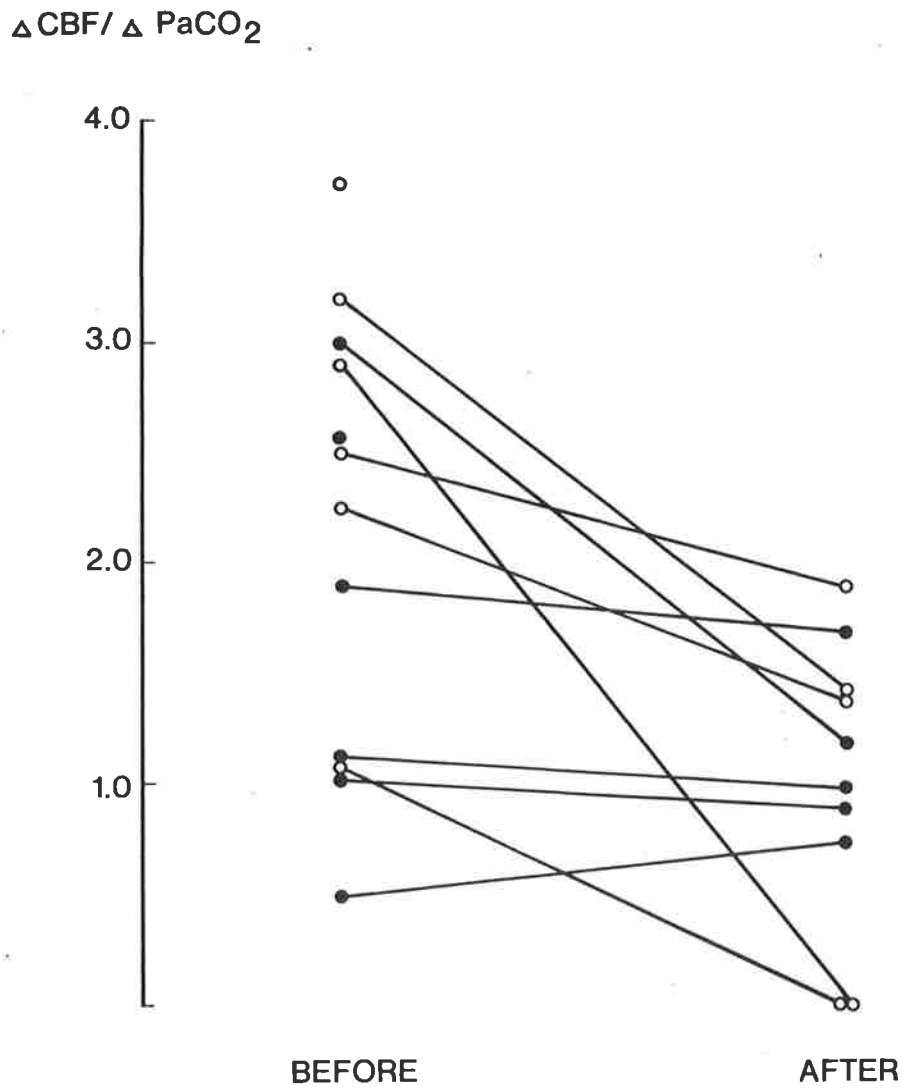


Figure 13(a): Response to hypercapnia before and after cryogenic injury.

Open circles as for Fig. 12.

Note: A CO_2 response after injury was not calculated in two animals (Appendix Table VIII).

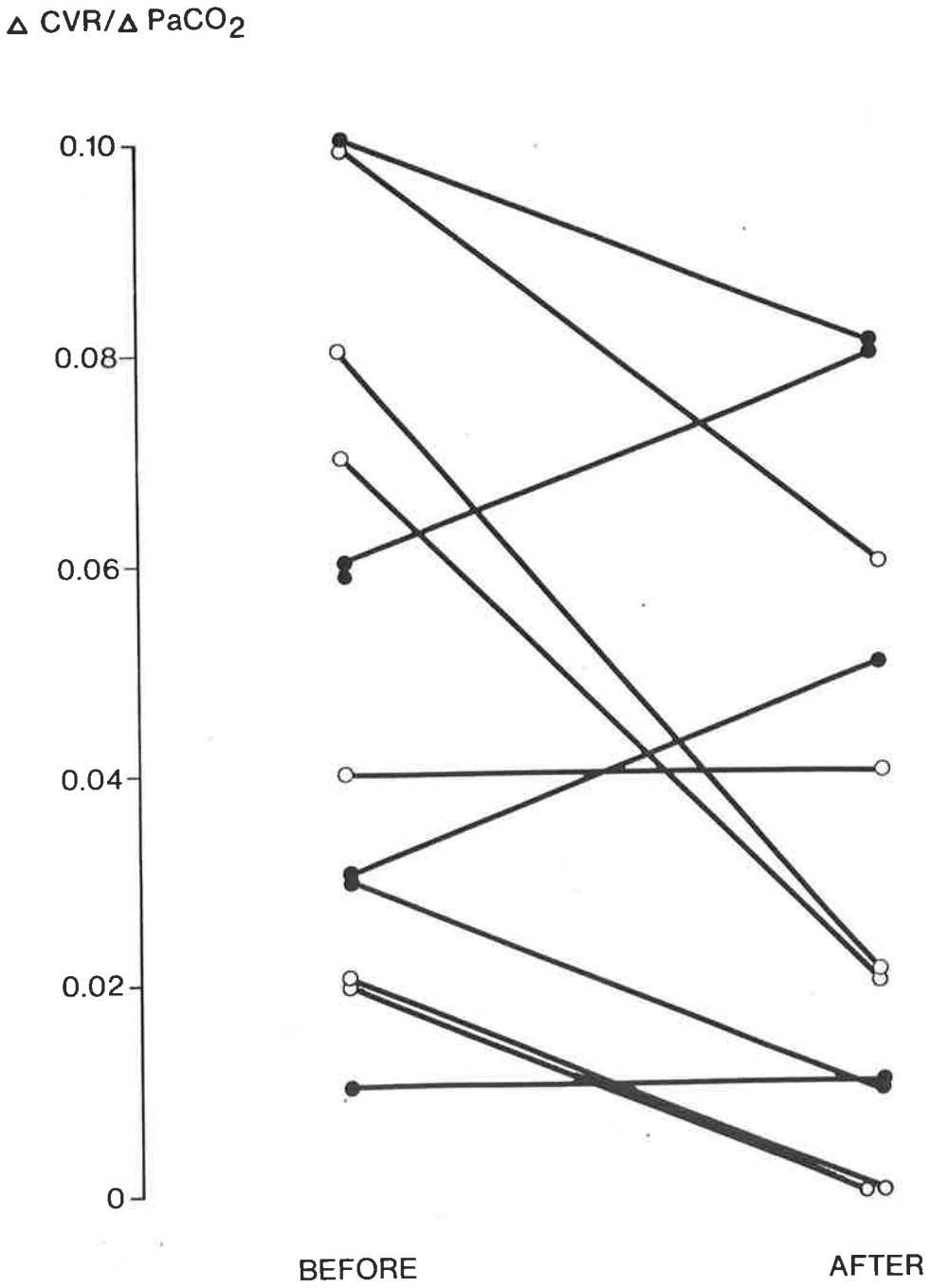


Figure 13(b): Response to hypercapnia before and after cryogenic injury calculated by ΔCVR.

Open circles as for Fig. 12.

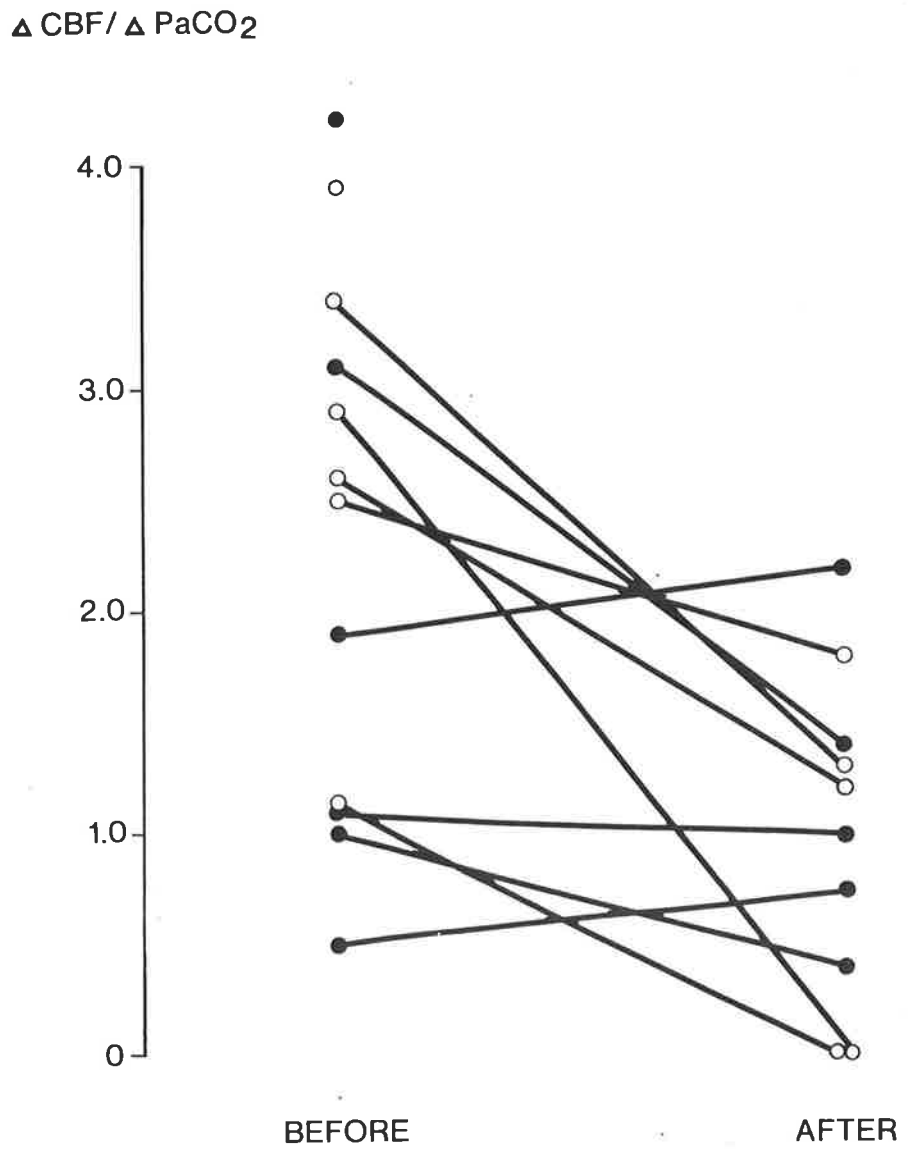


Figure 13(c): Response to hypercapnia before and after cryogenic injury.

CO_2 response calculated as in Fig. 13(a) and adjusted for change in CBF attributable to accompanying change in SAP.

Open circles as for Fig. 12.

pronounced increase in CBF. Because of the increase in SAP this could not be considered to represent a true CO_2 - induced rise in CBF, and this result has not been expressed as a CO_2 response. This baboon was one of the six which demonstrated a more than 20 per cent rise in CVR during arterial hypertension after injury. The CO_2 response was reduced in the remaining five baboons in this group, with reversal of the response in two animals, so that CBF in the affected area actually fell during hypercapnia. This was recorded as a CO_2 response of zero. In five baboons which demonstrated impaired autoregulation after injury, the CO_2 response was essentially unchanged compared with the original level in four cases, and decreased in one.

Hypercapnia was however, often associated with a marked rise in ICP, not seen before the lesion, and with a variable effect on SAP (Fig. 14). To partly compensate for the changes in CPP, the CO_2 response was also calculated as change in CVR per unit $PaCO_2$ in the 11 animals in which a hypercapnic response was tested after injury. The same pattern of altered responsiveness to hypercapnia was demonstrated. In the 6 animals which showed a greater than 20 per cent increase in CVR with arterial hypertension after injury, the CO_2 response was reduced in 5 and unchanged in 1 (Fig. 13b). Another method of partially "correcting" the CO_2 response was to subtract the change in CBF which would have occurred with an identical change in CPP at normocapnia. This was derived in each animal from the appropriate response to a change in SAP. Again the same pattern emerged (Fig. 13c).

It appeared, therefore, that apparent persistence of autoregulatory activity following brain injury was associated with a deterioration of the response to CO_2 in the injured hemisphere. A pressure passive response of CBF to an increase in CPP, on the other hand, was associated with some retention of responsiveness of the cerebral circulation to hypercapnia.

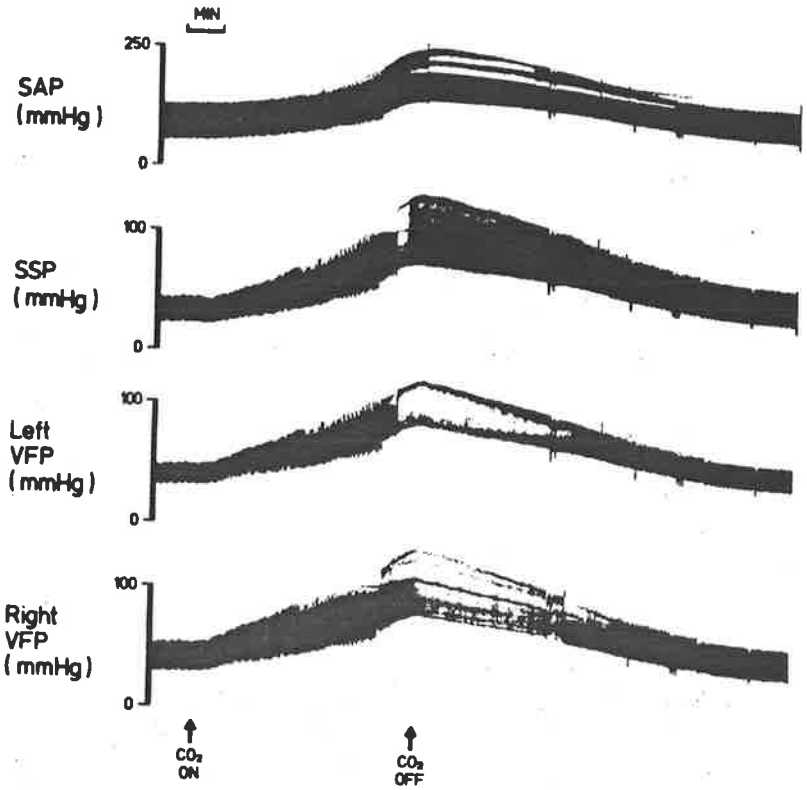


Figure 14: Hypercapnia after cryogenic injury.

In an animal with raised VFP, hypercapnia caused a marked rise in VFP and SSP, and a simultaneous rise in SAP.

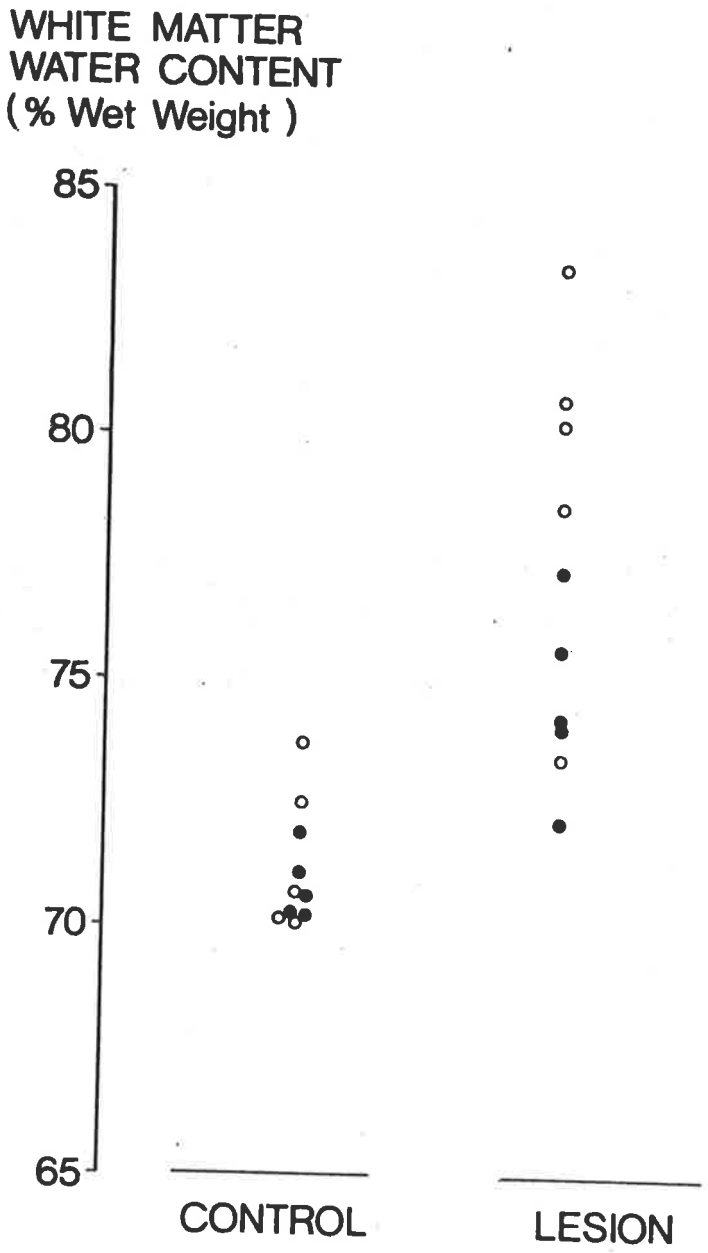


Figure 15: White matter water content deep to the cryogenic lesion compared with control values in the opposite hemisphere.

The VPR after the cryogenic injury showed an increase with arterial hypertension ($p<0.01$) but not with hypercapnia (Appendix Tables VII and VIII).

Brain Water Content and Cerebrovascular Response

White matter water content underlying the visible cortical lesion was increased in all animals with levels ranging from 72.1 to 83.4 per cent wet weight. These values can be compared with the water content of the equivalent area in the opposite hemisphere, 70.7 (70.1-73.7) per cent wet weight (Table 8, Fig. 15). There was a positive correlation between the water content of the affected white matter and the extent to which CVR rose during induced arterial hypertension. Thus, the four highest

TABLE 8

WATER CONTENT RELATED TO CEREBROVASCULAR RESPONSE TO INDUCED HYPERTENSION (MEDIAN & RANGE)

	Δ CVR < 20% (n=5)	Δ CVR < 20% (n=5)	Opp. Hemisphere (n=10)
Water (% wet weight)	74.2 (72.1-77.2)‡	81.7 (73.4-83.4)§ *	70.7 (70.1-73.7)

(See Appendix Table IX)

‡ $p<0.01$ § $p<0.001$, by Mann-Whitney U test

Values after injury compared with opposite hemisphere.

* $p<0.05$, by Mann-Whitney U test, compared with the other group after injury.

values of brain water content were found in animals which had a greater than 20 per cent increase in CVR, ($r = 0.60$; $p<0.05$), (Fig. 16). There was no correlation between tissue water content and response to hypercapnia (Fig. 17), or between tissue water content and the extent to

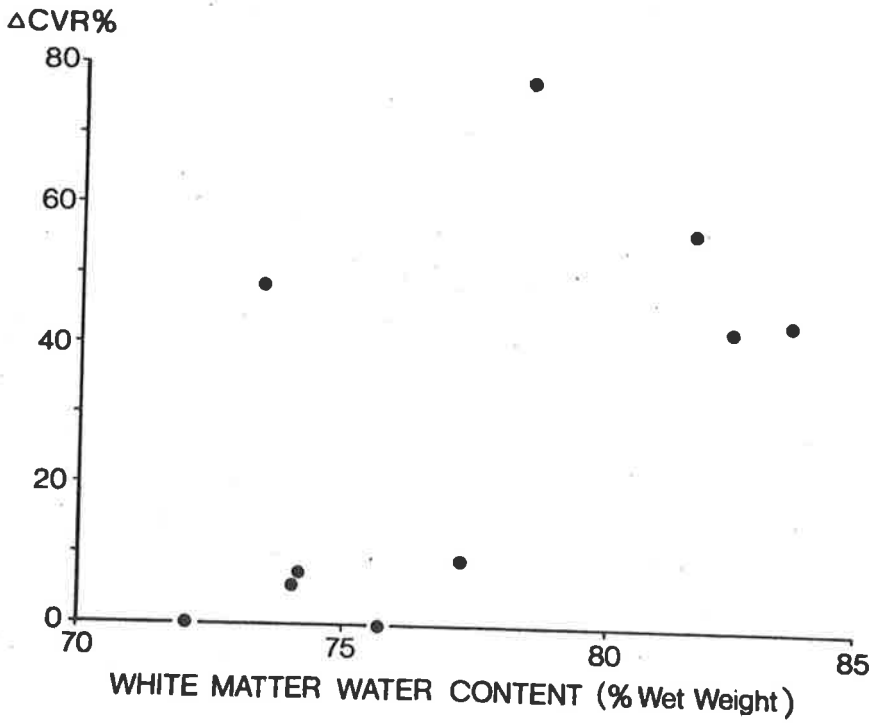


Figure 16: Relationship between white matter water content deep to the cryogenic lesion and the cerebrovascular response to induced arterial hypertension ($r = 0.60$, $p<0.05$).

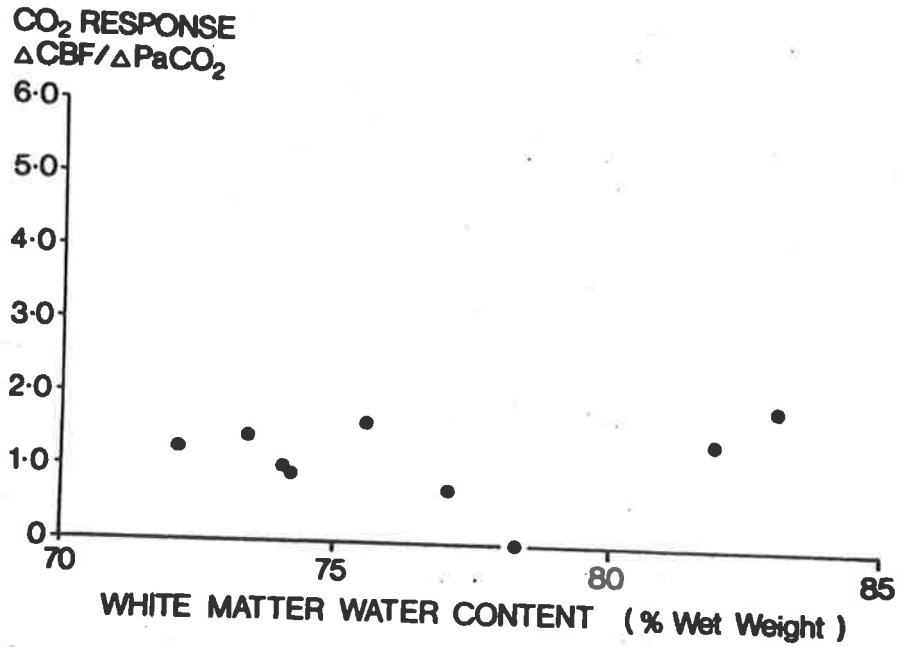


Figure 17: Relationship between white matter water content deep to the cryogenic lesion and the cerebrovascular response to hypercapnia.

which ICP and VPR increased after the lesion.

Cerebral metabolic rate and vascular responsiveness

Animals which demonstrated a large increase in CVR during induced arterial hypertension tended to have low values for $CMRO_2$. There was a wide scatter of results, however, and the overall difference in $CMRO_2$ between the groups with impaired and with apparently persisting autoregulation following injury just failed to attain statistical significance (Table 7). $CMRO_2$ showed a negative correlation with the height of ICP after injury ($r = 0.69$; $p<0.02$) but not with the level of brain water content.

CONCLUSIONS

Before the cryogenic injury, two groups of animals could be identified by the vasomotor response to induced arterial hypotension. Both groups had normal resting levels of CBF and a normal vasodilator response to hypercapnia. Arterial blood pressure, arterial gases, pH and $CMRO_2$ were similar, so that the two groups differed only in the response to arterial hypotension, and in a slightly higher ICP in the group in which this response was impaired.

Hypotension was used to test autoregulations before injury for the following reasons:

1. Break-through of autoregulation with arterial hypertension may occur at a mean SAP as low as 120 mm Hg, making subsequent tests of autoregulation invalid (Strandgaard et al., 1974).
2. Arterial hypertension was used to test autoregulation before cryogenic injury in an earlier study (Miller et al., 1975). This led to difficulties in defining autoregulation after injury. In some animals CPP may have exceeded the range of

autoregulation. In others, sudden arterial hypertension may have damaged vasomotor control, irrespective of any effects of the experimental injury which followed.

3. Hypotension above 60 mm Hg may be used repeatedly without physiological impairment (Fitch et al., 1976).

Thus induced arterial hypotension provided a clear test of autoregulation before injury.

In a study such as this, the method of defining normal vasomotor responsiveness must be clearly stated, even though such definitions are somewhat arbitrary (p.48). Perfect autoregulation, that is, constant CBF with a change in CPP, is indeed not the usual response. A review of a large number of measurements of CBF in patients and in normal experimental animals has shown that the usual response is a 3 to 5 per cent change in CBF per 10 mm Hg change in SAP (Kontos et al., 1978; Kontos, personal communication, 1979). In all but three animals, change in blood pressure before the cryogenic injury was accompanied by a change in CVR in a direction to normalize CBF. Hence these animals showed some autoregulatory response, even though by the strict definition used in this study, the response was not considered normal. Comparing this group of animals with those in which the autoregulatory response before injury was normal, helped to interpret the meaning of an increase in CVR in response to arterial hypertension after injury.

Following focal cryogenic lesions of different size, CBF was reduced to a degree which was only partly related to the previous status of autoregulation. An induced increase in SAP had a variable effect on CBF in the area of injured brain. Three types of response could be identified; an increase in CBF in proportion to the increase in CPP, with no change in CVR - a passive pressure response; secondly, little change in CBF but a parallel increase in ICP, so that CPP remained constant - "false autoregulation"; finally, little change in CBF, despite a significant rise in CPP.

The first two responses are well documented in brain injuries in which the physiological response to a change in SAP has been lost (see page 16).

The dissociation between CPP and CBF in the third group implies an increase in CVR in response to a rise in arterial pressure - such as occurs with physiological autoregulation. This response was not related to the presence of intact autoregulation before injury, indicating that the response after injury was abnormal, unless the cryogenic injury had restored physiological autoregulation in animals in which it had been impaired previously, or there was a marked dissociation between the responses to hypotension and hypertension within the same range of perfusion pressures.

Hypercapnia has a complex effect on CBF. As well as inducing cerebral vasodilatation, hypercapnia may directly increase SAP and in turn, alter ICP and CPP. It is not possible in this experimental protocol to apply a correction factor which will normalize the change in SAP with certainty. Even so, a dissociation between CPP and CBF was associated with clear evidence of brain injury and with greater impairment of the CO_2 response, higher levels of brain tissue water (that is, greater oedema), and lower levels of calculated $CMRO_2$ when compared with animals in which autoregulation was clearly impaired. The results suggest that in this group of animals, injury produced an impedence to CBF which became more severe as arterial pressure increased. Brain elastance, as measured by the VPR, also increased with arterial hypertension. It may be suggested that brain interstitial pressure also rose, or that there was a mechanical obstruction to blood flow in the area of brain injury and oedema.

SECTION 3

REGIONAL VASCULAR REACTIVITY 24 HOURS AFTER CRYOGENIC INJURY

PURPOSE

This series of experiments aimed to separate the effects of oedema from that of the focal injury. Animals were studied 24 hours after cryogenic injury. In this way animals could be studied in which measurable focal brain oedema had developed from small necrotic lesions without markedly elevated ICP. CBF was measured simultaneously in several small, precisely located areas in grey and white matter, both near to and remote from the lesion. The questions posed were:

1. What relationship do regional CBF and the cerebrovascular responses to changes in SAP and $PaCO_2$ have to the level of ICP and to regional tissue water content?
2. Does a focal lesion influence CBF in distant parts of the brain?
3. Are there differences in the responses to injury in grey and white matter, either near to or remote from the lesion?

PROTOCOL (Table 9, Fig. 18)

This study was conducted on 11 young adult baboons weighing 9 to 23 kg. CBF was determined by hydrogen clearance. The blood flow values were derived by initial slope index as this method was found to give the most reliable results.

Day 1: The baboon was checked to be neurologically normal then placed under general endotracheal anaesthesia. The scalp was shaved and a right lateral 12 mm burrhole made through a linear incision. The scalp edges were protected with gauze. The freezing probe was applied to the intact dura for periods of 30 seconds to 4 minutes. After scalp suture the baboon was extubated carefully to avoid straining and returned to its cage.

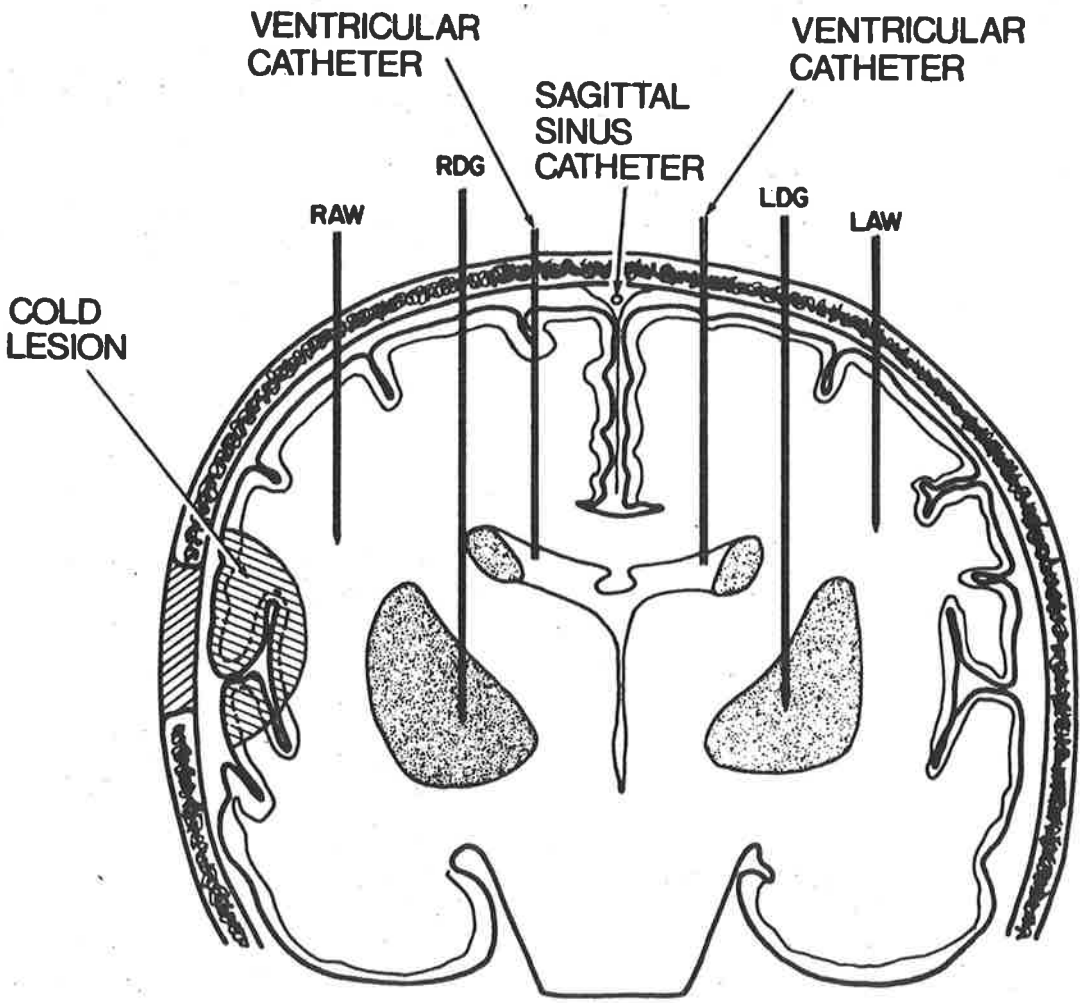


Figure 18: Measuring CBF and ICP 24 hours after cryogenic injury.

Platinum electrodes record CBF by H_2 clearance.

RAW = right anterior white

RDG = right deep grey

LAW = left anterior white

LDG = left deep grey.

TABLE 9

PROTOCOL - SERIES 2

DAY 1 -

1. Examine baboon in cage.
2. G.A. Cryogenic lesion through right lateral burrhole.

DAY 2 -

1. Examine baboon in cage.
2. G.A. Insert 3 electrodes into each hemisphere:

   1 deep grey (putamen),
   2 white matter, (anterior and posterior).

3. Measure CBF in the following order:

   (a) Control - Normocapnia, normotension

   (b) ↓ SAP Calculate Δ CVR

   (c) Control

   (d) ↑ SAP Calculate Δ CVR

   (e) Control

   (f) ↑ CO_2 Calculate CO_2 response

   (g) Control

4. FREEZE BRAIN IN SITU - section to inspect the lesion, verify electrode placement, and to take tissue samples for water and electrolyte measurement.

Day 2: 24 hours later the baboon was examined for evidence of neurological dysfunction then anaesthetised and artificially ventilated. Arterial and venous lines were inserted and blood gases checked to ensure that no period of hypercapnia or hypotension occurred during the preparation. Six 0.3 mm platinum electrodes, 3 on each side, were inserted stereotaxically using co-ordinates for anterior and posterior white matter (centrum semiovale) and for deep grey matter (putamen), (Davis & Huffman, 1968). The right anterior white electrode lay deep to the cryogenic lesion (Fig. 18). Arterial, bilateral ventricular and sagittal sinus pressures, oesophageal temperature and end-tidal CO_2 were recorded.

Two control measurements of CBF were obtained under stable conditions of SAP, blood gases and ICP. CBF was then measured during arterial hypotension of 30 to 40 mm Hg. After reinfusion and a further control at normotension, CBF was measured during arterial hypertension of 30 to 40 mm Hg. Finally, after a further control, the effect of hypercapnia was assessed by adding sufficient CO_2 to the inspired gases to raise $PaCO_2$ by 20 mm Hg.

When normocapnic and normotensive conditions had been restored, the animal was killed. The brain was frozen in situ and sectioned to identify the electrode positions visually. Tissue samples were taken adjacent to each electrode tip to measure tissue water and electrolyte content. The experiments ended 34 to 36 hours after cryogenic injury.

RESULTS

Appendix tables show values obtained from each electrode site. In some animals, electrode failure reduced the number of measurements.

Statistical tests were based upon the average of multiple values obtained in individual animals.

TABLE 10

LESION TIME AND CLINICAL STATUS

Animal	Lesion Time (minutes)	Lesion Size (cm)	Evans Blue (cm)	Clinical deficit at 24 hrs.
2	0.5	Pial congestion	0.2	Nil
3	1.0	"	Nil	Nil
*4	3.0	1.5	1.0	Left hemiplegia and hemianopia. Alert though initially drowsy.
*5	2.0	1.0	1.5	Nil
*6	2.5	0.5	1.0	Left arm weakness. Left focal seizure.
*7	2.0	1.0	1.0	Nil
8	2.5	Pial congestion	Nil	Nil
*9	3.0	1.5	1.0	Left arm weakness. Alert.
*10	3.0	1.5	1.0	Left arm weakness. Alert.
*11	4.0	1.5	0.5	Nil
12	4.0	Pial congestion	0.3	Nil

* White matter oedema verified by tissue water estimation.

TABLE 11

INITIAL AND FINAL CONTROL VALUES WITH FINAL TISSUE WATER AND ELECTROLYTES ON THE SIDE OF THE CRYOGENIC INJURY IN ANIMALS WITH AND WITHOUT A CLINICAL DEFICIT (MEDIAN & RANGE)

	Initial		Final	
	No deficit (n=7)	Deficit (n=4)	No deficit	Deficit
Arterial pCO_2 (mm Hg)	41.0 (37.0-43.0)	40.0 (38.0-42.0)	40.0 (38.0-42.0)	39.5 (38.0-40.0)
Arterial pressure (mm Hg)	98.0 (85.0-110.0)	79.5 (70.0-87.0)	82.0 (72.0-110.0)*	79.5 (57.0-113.0)
Intracranial pressure (mm Hg)	4.0 (1.0-19.0)	6.5 (2.0-14.0)	11.0 (2.0-31.0)*	21.5 (6.0-35.0)
White Matter				
Cerebral blood flow (ml/min. 100G)	19.0 (14.0-42.0)	16.5 (13.0-21.0)	18.0 (10.0-29.0)*	10.0 (5.0-23.0)
Water (% wet wt.)			69.6 (66.8-83.3)	79.3 (78.5-82.7)
Sodium (mEq/100G dry wt.)			34.5 (19.2-58.0)	42.4 (26.0-47.5)
Potassium (mEq/100G dry wt.)			25.9 (21.4-30.8)	28.5 (22.0-33.0)
Grey Matter				
Cerebral blood flow (ml/min. 100G)	43.0 (32.0-95.0)	29.0 (18.0-36.0)‡	33.5 (28.0-78.0)	22.0 (17.0-35.0)‡
Water (% wet wt.)			78.4 (77.0-80.0)	76.1 (72.0-80.1)
Sodium (mEq/100G dry wt.)			28.5 (21.0-46.5)	27.0 (25.5-43.5)
Potassium (mEq/100G dry wt.)			42.8 (33.0-45.0)	40.5 (31.5-45.0)

(See Appendix Tables X & XI)

* $p<0.05$, by Wilcoxon matched-pairs, signed-ranks test, compared with initial value.

‡ $p<0.01$, by Mann-Whitney U test, compared with animals with no deficit.

Clinical Status (Table 10 and 11)

24 hours after cryogenic injury, 4 of the 11 baboons had a neurological deficit. One animal had a complete hemiplegia and hemianopia and although initially drowsy, was alert at 24 hours. Three animals had a weakness of the left arm and were alert. Each was later shown to have white matter oedema as indicated by an increase in white matter water content. Blood flow levels in grey and white matter were lower in the animals with neurological deficits.

By the end of the experiment, normocapnic, normotensive regional white matter blood flow (r CBF w) on the side of the lesion had fallen to 10.0 (5.0-23.0) ml/min. 100G, compared with 18.0 (10.0-29.0) ml/min. 100G in the seven animals which had no neurological signs, even though three of the seven had measurable oedema. There was no difference in ICP at the beginning of the study in the two groups, although ICP had risen more by the end of the study in the four animals with neurological deficits ($p<0.025$, by Mann-Whitney U test). In these animals, freezing times ranged from 2½ to 3 minutes. In those without deficits freezing times ranged from 30 seconds to four minutes.

Water and Electrolyte Content

(a) White matter (Fig. 19)

Ten electrode sites in the right hemispheres of seven baboons were oedematous, having a brain white matter water content greater than 75 per cent wet weight. Corresponding to the increased water content, sodium but not potassium was increased. Hence three areas of white matter could be compared; those with oedema; secondly, the corresponding areas in the left hemisphere of the same seven animals where water and electrolyte content were normal; finally in the remaining four baboons where water and electrolyte content were normal at each electrode site. This constituted a third control group of animals with injury but no oedema.

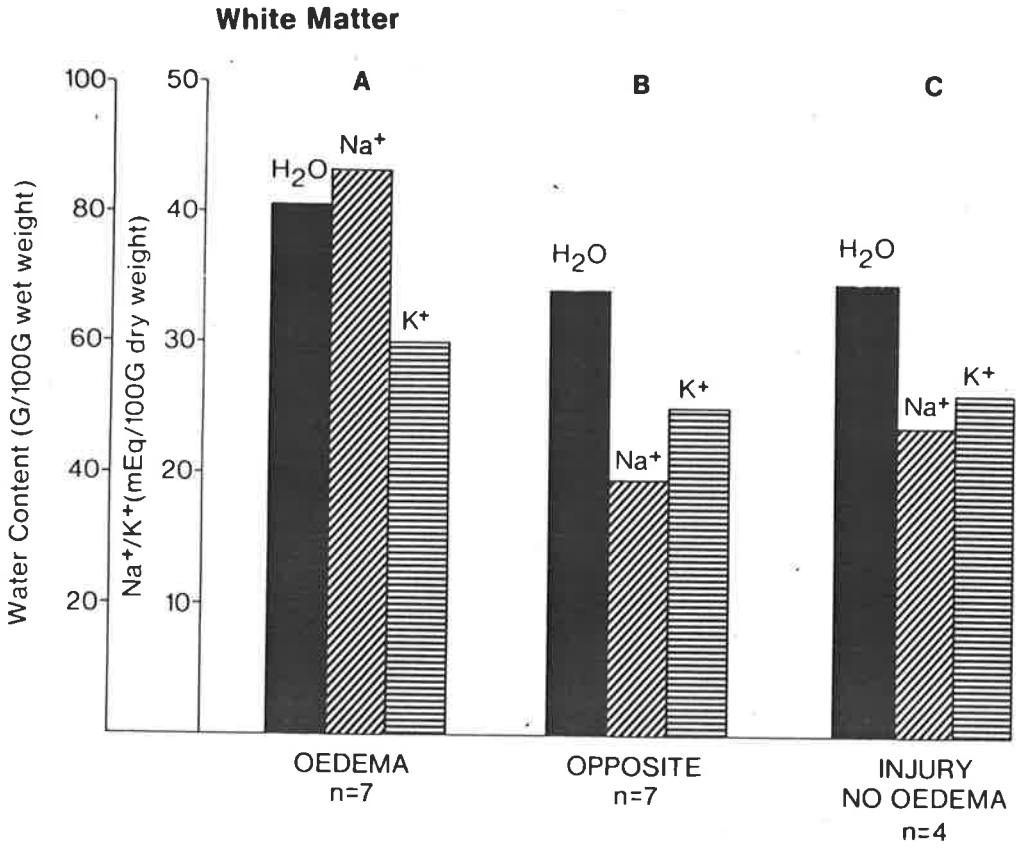


Figure 19: White matter water and electrolyte content at the sites of blood flow measurement.

A – areas of white matter oedema (H_2O > 75G/100G wet weight).

B – equivalent areas of white matter in the opposite hemisphere (normal water content).

C – white matter areas in baboons with injury but no oedema (normal water content).

‡ $p<0.01$,

δ $p<0.005$,

§ $p<0.001$, by Mann-Whitney U test, compared with A.

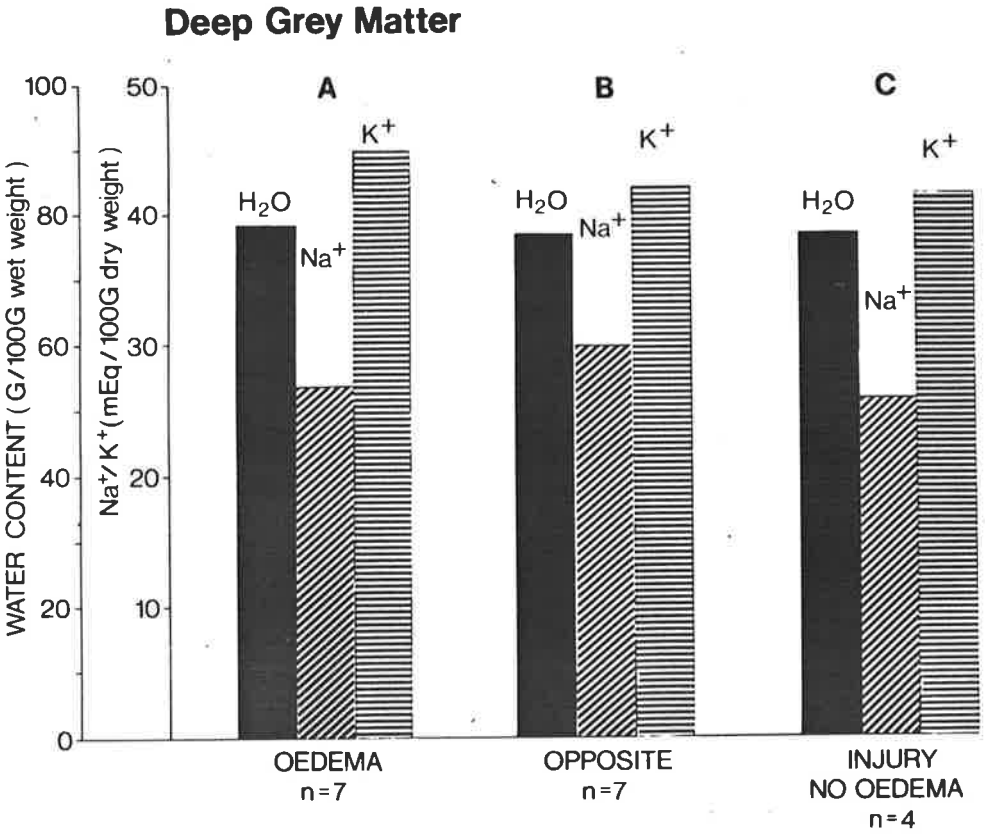


Figure 20: Grey matter water and electrolyte content at the sites of blood flow measurement.

A - in hemisphere with white matter oedema.

B - equivalent area of grey matter in opposite hemisphere.

C - in animals with injury but no oedema.

(b) Grey matter (Fig. 20)

None of the electrode sites in grey matter were oedematous (grey matter water content greater than 80 per cent wet weight). The areas of grey matter were compared according to the changes in the adjacent white matter. Hence there were three groups; adjacent to white matter oedema; secondly, in left hemisphere of the same animals; finally in animals with injury but no oedema. There were no significant differences in the water and electrolyte values of these groups.

Baseline Measurement of CBF and ICP

(a) White matter (Table 12)

Normocapnic and normotensive levels of rCBFw were compared in the three groups of electrode sites at the beginning and end of the experiment. In oedematous areas, flow was 15.0, (14.0-26.0) falling in eight of the ten electrode sites to 12.0 (5.0-23.0) ml/min. 100G by the end of the experiment. In the opposite hemisphere of these baboons, rCBFw was 18.0 (14.0-28.0) falling to 17.0 (13.0-29.0) ml/min. 100G. In those animals with injury but no oedema, initial CBF was 21.5 (18.0-33.0) and final 22.5 (11.0-25.3) ml/min. 100G, the initial and final values being higher than the corresponding values in the oedematous areas ($p=0.055$). ICP in baboons with oedema (4.0, 1.0-14.0 rising to 11.0, 2.0-35.0) mm Hg ($p<0.025$) was not significantly different from those without oedema (11.5, 3.0-19.0 rising to 14.0, 4.0-31.0) mm Hg suggesting that the process remained localised.

(b) Grey matter (Table 13)

Normocapnic, normotensive levels of rCBFg had fallen by the end of the experiment at each of the three groups of grey matter electrode sites. This was most marked in the hemisphere with oedema, where rCBFg fell from 34.0 (18.0-95.0) ml/min. 100G to 27.0 (17.0-78.0) ml/min. 100G ($p<0.025$).

TABLE 12

INITIAL AND FINAL CONTROL VALUES IN WHITE MATTER (MEDIAN & RANGE)

	Initial			Final		
	A	B	C	A	B	C
Arterial pCO_2 (mm Hg)	41.0 (38.0-42.0)		41.0 (37.0-43.0)	40.0 (38.0-42.0)		39.0 (38.0-40.0)
Arterial pressure (mm Hg)	87.0 (70.0-98.0)		105.0 (85.0-110.0)	80.0 (57.0-113.0)		84.5 (78.0-90.0)
Intracranial pressure (mm Hg)	4.0 (1.0-14.0)		11.5 (3.0-19.0)	11.0 (2.0-35.0)†		14.0 (4.0-31.0)
Cerebral blood flow (ml/min. 100G)	15.0 (14.0-26.0)	18.0 (14.0-28.0)	21.5 (18.0-33.0)	12.0 (5.0-23.0)	17.0 (13.0-29.0)	22.5 (11.0-25.3)
Water (% wet wt.)				81.1 (78.5-83.3)	68.0 (66.8-70.7)	68.9 (67.2-69.7)
Sodium (mEq/100G dry wt.)				44.3 (26.0-58.0)	19.5 (15.7-26.3)	23.5 (17.6-37.0)
Potassium (mEq/100G dry wt.)				30.0 (22.0-34.5)	25.1 (24.0-34.9)	26.0 (21.2-29.2)

A, B and C - areas of white matter as in Fig. 19. (See Appendix Table XII)

† $p<0.025$, by Wilcoxon matched-pairs signed-ranks test, compared with initial values.

TABLE 13

INITIAL AND FINAL CONTROL VALUES IN
GREY MATTER (MEDIAN & RANGE)

	Initial			Final		
	A	B	C	A	B	C
Cerebral blood flow (ml/min. 100G)	34.0 (18.0-95.0)	46.0 (33.0-87.0)	43.5 (28.0-44.0)	27.0 (17.0-78.0)†	42.0 (22.0-60.0)	28.5 (27.0-58.0)
Water (% wet wt.)	78.5 (72.0-80.1)			78.5 (72.0-80.1)	76.8 (69.9-79.5)	77.5 (77.1-79.5)
Sodium (mEq/100G dry wt.)	27.0 (25.5-43.5)			27.0 (25.5-43.5)	30.0 (21.0-54.0)	25.7 (22.9-41.3)
Potassium (mEq/100G dry wt.)				45.0 (31.5-51.0)	42.0 (21.0-51.0)	41.3 (38.3-45.0)

A, B and C - areas of grey matter as in Fig. 19 (See Appendix Table XIII)

† $p<0.025$, by Wilcoxon matched-pairs signed-ranks test, compared with initial values.

TABLE 14: RESPONSES TO ARTERIAL HYPOTENSION, HYPERTENSION AND HYPERCAPNIA IN WHITE MATTER (MEDIAN & RANGE)

	A		B		C	
	Control	Exp.	Control	Exp.	Control	Exp.
Hypotensive Response						
Arterial pressure (mm Hg)	97.0 (92.0–118.0)	72.0 (63.0–73.0)	97.0	72.0	106.5 (100.0–117.0)	82.0 (65.0–83.0)
Cerebral perfusion pressure (mm Hg)	91.0 (79.0–115.0)	64.0 (51.0–70.0)	91.0	64.0	91.5 (88.0–113.0)	68.5 (56.0–75.0)
Cerebral blood flow (ml/min. 100G)	16.0 (11.0–23.0)	13.0 (10.0–20.0)‡	17.0 (14.0–28.0)	14.0 (12.0–23.0)*	25.0 (16.0–34.0)	21.5 (10.0–33.0)
Cerebrovascular resistance (mm Hg/ml/min. 100G)	5.86 (3.84–10.45)	4.33 (2.75–7.00)	5.72 (3.36–6.50)	3.89 (3.04–5.00)	3.98 (2.59–7.06)	2.92 (2.15–7.50)
% change in cerebrovascular resistance	26.0 (11.0–49.0)		26.0 (10.0–77.0)		14.0 (0–37.0)	
Hypertensive Response						
Arterial pressure (mm Hg)	85.0 (65.0–98.0)	122.0 (92.0–129.0)	85.0	122.0	92.5 (73.0–108.0)	128.5 (117.0–155.0)
Cerebral perfusion pressure (mm Hg)	73.0 (58.0–94.0)	113.0 (82.0–122.0)	73.0	113.0	75.0 (71.0–96.0)	116.5 (91.0–138.0)
Cerebral blood flow (ml/min. 100G)	18.0 (12.0–24.0)	19.0 (15.0–22.0)	18.0 (16.0–31.0)	19.0 (15.0–22.0)	24.0 (15.0–31.0)	28.0 (20.0–40.0)
Cerebrovascular resistance (mm Hg/ml/min. 100G)	4.06 (3.33–6.27)	5.86 (4.62–10.17)	4.29 (2.58–5.22)	6.13 (3.53–7.33)	3.41 (3.10–4.73)	4.04 (3.14–5.65)
% change in cerebrovascular resistance	35.0 (9.0–111.0)		37.0 (21.0–111.0)		19.0 (11.0–23.0)‡‡	
Hypercapnic Response						
Arterial pCO_2 (mm Hg)	40.0 (38.0–42.0)	60.0 (57.0–74.0)	40.0	60.0	40.0 (38.0–41.0)	55.0 (53.0–67.0)
Intracranial pressure (mm Hg)	11.0 (2.0–35.0)	26.0 (16.0–47.0)	11.0	26.0	12.5 (4.0–31.0)	28.0 (26.0–52.0)
Cerebral blood flow (ml/min. 100G)	18.0 (5.0–23.0)	21.0 (6.0–30.0)	17.0 (13.0–32.0)	19.0 (13.0–50.0)	23.0 (14.0–28.0)	33.0 (24.0–40.0)
CO_2 response (ml/min. 100G per mm Hg $PaCO_2$)	0.17 (0–1.22)		0.19 (0–2.33)		0.78 (0.19–0.92)**	

* $p \leq 0.05$
‡ $p < 0.01$ by Wilcoxon matched-pairs, signed-ranks test, compared with initial values.

‡‡ $p < 0.01$, by Mann-Whitney U test.

** $p < 0.05$, by Mann-Whitney U test compared with B and $p = 0.055$, by Mann-Whitney U test compared with A.

(See Appendix Tables XIV, XVI, XVIII).

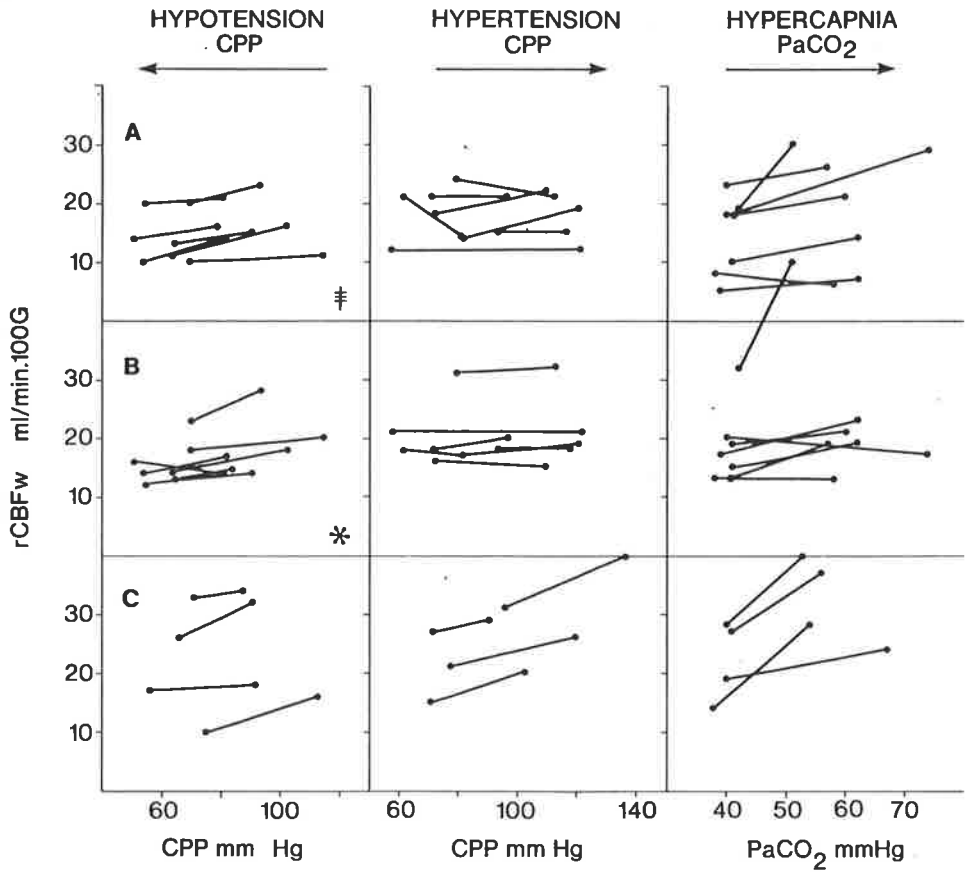


Figure 21: CBF responses in white matter. Changes in CBF in response to hypotension, hypertension and hypercapnia are compared in the three areas of white matter.

* $p<0.05$,

‡ $p<0.01$, by Wilcoxon matched-pairs, signed-ranks test, compared with initial values.

The significance of changes between groups are given in Table 14.

Cerebrovascular Response to Arterial Hypotension

(a) White matter (Table 14, Fig. 21)

SAP was reduced by 25 mm Hg. This resulted in a 19 per cent fall in rCBFw in areas of oedema ($p<0.01$) and a 18 per cent fall in rCBFw in the opposite hemisphere ($p\leq0.05$). In the 4 baboons with injury but no oedema the same reduction in SAP was associated with a similar (14%) fall in rCBFw. The changes in cerebrovascular resistance were similar in the 3 groups of areas and were consistent with some impairment of autoregulation.

(b) Grey matter (Table 15, Fig. 22)

Induced arterial hypotension resulted in no change in median rCBFg in the hemisphere with white matter oedema and a 6 per cent fall in the opposite hemisphere. In animals with injury but no oedema there was a 35 per cent fall in rCBFg corresponding to a 10 per cent change in CVR.

Cerebrovascular Response to Arterial Hypertension

(a) White matter (Table 14, Fig. 21)

SAP was increased by 35 to 40 mm Hg. Changes in ICP were small so that perfusion pressure was increased by approximately the same amount. In the areas of verified white matter oedema rCBFw did not change (18.0, 12.0-24.0 and 19.0, 15.0-22.0 ml/min. 100G) indicating a 35 per cent increase in CVR. In only one of these animals was there less than a 20 per cent increase in CVR. A similar response to the change in SAP and CPP, occurred in the opposite hemisphere where CVR increased overall by 37 per cent, all animals showing an increase of greater than 20 per cent. In the baboons with injury but no oedema the response was quite different. With the same increase in CPP, rCBFw increased from 24.0 (15.0-31.0) to 28.0 (20.0-40.0) ml/min. 100G,

TABLE 15: RESPONSES TO ARTERIAL HYPOTENSION, HYPERTENSION AND HYPERCAPNIA IN GREY MATTER (MEDIAN & RANGE)

	A		B		C	
	Control	Exp.	Control	Exp.	Control	Exp.
Hypotensive Response						
Arterial pressure (mm Hg)	97.0 (92.0-118.0)	72.0 (63.0-73.0)	97.0	72.0	106.5 (100.0-117.0)	82.0 (65.0-83.0)
Cerebral perfusion pressure (mm Hg)	91.0 (79.0-115.0)	64.0 (51.0-70.0)	91.0	64.0	91.5 (88.0-113.0)	68.5 (56.0-75.0)
Cerebral blood flow (ml/min. 100G)	30.0 (21.0-69.0)	30.0 (14.0-62.0)	47.0 (30.0-64.0)	44.0 (23.0-57.0)	33.0 (28.0-44.0)	27.5 (22.0-32.0)
Cerebrovascular resistance (mm Hg/ml/min. 100G)	3.31 (1.36-3.86)	2.16 (1.13-3.86)	1.93 (1.47-2.73)	1.41 (1.09-2.35)	3.04 (2.07-3.29)	2.33 (2.20-3.41)
% change in cerebrovascular resistance	35.0 (0-36.0)		25.0 (14.0-35.0)		10.0 (0-32.0)	
Hypertensive Response						
Arterial pressure (mm Hg)	85.0 (65.0-98.0)	122.0 (92.0-129.0)	85.0	122.0	92.5 (73.0-108.0)	128.5 (117.0-155.0)
Cerebral perfusion pressure (mm Hg)	73.0 (58.0-94.0)	113.0 (82.0-122.0)	73.0	113.0	75.0 (71.0-96.0)	116.5 (91.0-138.0)
Cerebral blood flow (ml/min. 100G)	35.0 (18.0-73.0)	29.0 (22.0-73.0)	46.0 (33.0-65.0)	45.0 (29.0-57.0)	30.0 (29.0-44.0)	36.0 (30.0-53.0)
Cerebrovascular resistance (mm Hg/ml/min. 100G)	2.18 (1.10-3.44)	3.96 (1.55-4.58)	1.49 (1.22-1.88)	2.44 (1.70-4.21)	2.43 (2.18-2.60)	2.88 (2.60-4.00)
% change in cerebrovascular resistance	55.0 (8.0-125.0)		54.0 (39.0-183.0)		24.0 (5.0-54.0)*	
Hypercapnic Response						
Arterial pCO_2 (mm Hg)	40.0 (38.0-42.0)	60.0 (57.0-74.0)	40.0	60.0	40.0 (38.0-41.0)	55.0 (53.0-67.0)
Intracranial pressure (mm Hg)	11.0 (2.0-35.0)	26.0 (16.0-47.0)	11.0	26.0	12.5 (4.0-31.0)	28.0 (26.0-52.0)
Cerebral blood flow (ml/min. 100G)	27.0 (17.0-78.0)	33.5 (16.0-88.0)	42.0 (22.0-60.0)	47.0 (25.0-77.0)	28.5 (27.0-30.0)	40.0 (27.0-48.0)
CO_2 response (ml/min. 100G per mm Hg $PaCO_2$)	0.45 (0-1.11)		0.21 (0.13-1.89)		0.72 (0-1.38)	

* $p<0.05$. by Mann-Whitney U test, compared with B

(See Appendix Tables XV, XVII, XIX)

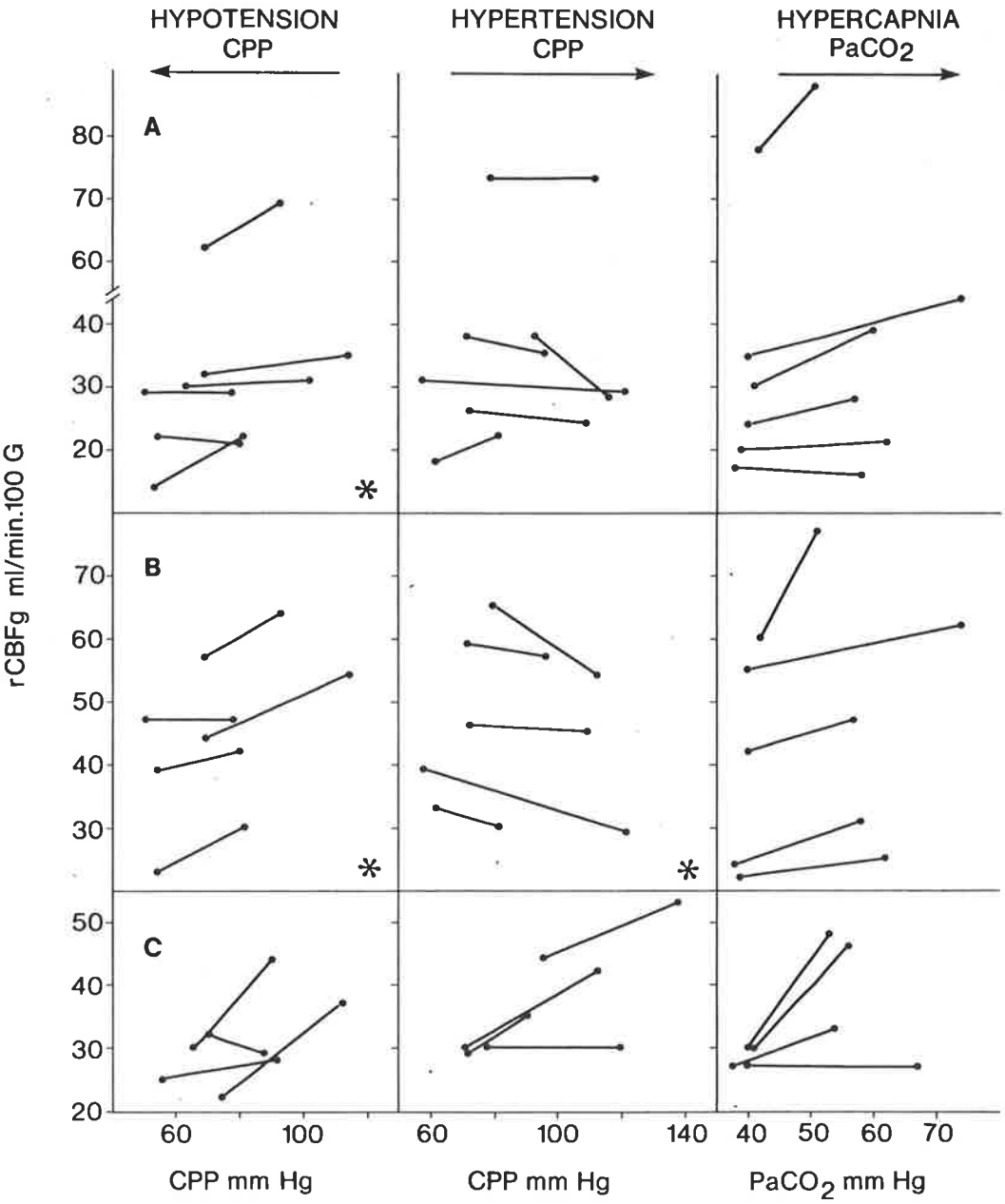


Figure 22: CBF responses in grey matter. Changes in CBF in response to hypotension, hypertension and hypercapnia are compared in the three areas of grey matter.

* $p<0.05$, by Wilcoxon matched-pairs, signed-ranks test, compared with initial values.

The significance of changes between groups are given in Table 15.

having increased in each animal in this group ($p<0.05$, by Fisher exact probability compared with the change in CBF in the other two groups). There was a smaller increase in CVR of 19 per cent ($p<0.01$) indicating a lesser degree of autoregulation with a more pressure passive response to arterial hypertension. In only one of this group of animals did the average response from all electrode sites exceed 20 per cent.

(a) Grey matter (Table 15, Fig. 22)

In all animals with white matter oedema, arterial hypertension resulted in a fall in rCBFg in both hemispheres, corresponding to an increase in CVR of 55 per cent on the side with oedema and of 54 per cent on the opposite side. In animals with injury but no oedema, the response resembled that found in white matter. rCBFg increased in each animal, and at six out of seven electrode sites, an overall increase in CVR of 24 per cent ($p<0.05$).

Cerebrovascular Response to Hypercapnia

(a) White matter (Table 14, Fig. 21)

$PaCO_2$ was raised by 20 mm Hg. In areas of brain oedema, rCBFw rose only from 18.0 (5.0-23.0) to 21.0 (6.0-30.0) ml/min. 100G, a CO_2 response of 0.17 (0-1.22) ml/min. 100G/mm Hg change in $PaCO_2$. In the opposite hemisphere of these animals the change in rCBFw was similarly attenuated, rising from 17.0 (13.0-32.0) to 19.0 (13.0-50.0) ml/min. 100G, a CO_2 response of 0.19 (0-2.33) ml/min. 100G/mm Hg change in $PaCO_2$. In two of the ten areas of oedema, there was a fall in rCBFw with hypercapnia, recorded as a CO_2 response of zero. In three of ten areas in the opposite hemisphere, where there was no oedema, hypercapnia also produced a fall in blood flow.

In the 4 baboons in which there had been an injury but no oedema, the CO_2 response was better preserved. rCBFw increased from

23.0 (14.0-28.0) to 33.0 (24.0-40.0) ml/min. 100G, a CO_2 response of 0.78 (0.19-0.92) ml/min. 100G per mm Hg change in $PaCO_2$ which was greater than that seen in the areas of oedema ($p=0.055$) and in the opposite hemispheres ($p<0.05$). The change in ICP produced by hypercapnia was similar in each group of animals.

(b) Grey matter (Table 15, Fig. 22)

The CO_2 response with hypercapnia was generally higher in grey matter than in the corresponding areas of white matter. Although there was a greater variability of individual values, the pattern of response resembled that in white matter. Thus the CO_2 response adjacent to white matter oedema was 0.45 (0-1.11) and in the opposite hemisphere 0.21 (0.13-1.89) ml/min. 100G per mm Hg $PaCO_2$. In animals with injury but no oedema, the CO_2 response was higher at 0.72 (0-1.38) ml/min. 100G per mm Hg $PaCO_2$ but these differences were not significant.

The Cryogenic Lesion at 36 hours (Table 10)

Appearance of the lesion ranged from a haemorrhagic, necrotic cone 1.0 to 1.5 cms in diameter surrounded by a zone of Evans Blue, 0.5 to 1.5 cms in width, to minimal lesions which were not associated with an increase in measurable white matter water content. Such lesions consisted of a zone of pial congestion without macroscopic tissue damage, sometimes surrounded by a thin rim of Evans Blue.

CONCLUSIONS

In oedematous white matter, normotensive, normocapnic blood flow was reduced. Arterial hypotension caused some further reduction and the vasomotor response to hypercapnia was impaired. However, an increase in CPP and SAP caused a large increase in CVR and no significant increase in CBF.

In baboons with injury but no oedema, control rCBFw and the CO_2 response in white matter were normal as compared with the values

obtained in the methodological study reported earlier and in other studies (Symon et al., 1973; Griffiths et al., 1975). However, in these animals the autoregulatory responses to both hypotension and hypertension were impaired.

In the opposite hemisphere of baboons with unilateral oedema, rCBFw was reduced to a value midway between normal values and those of the oedematous areas, even though water and sodium content were normal. The responses to hypertension and hypotension resembled those in the areas of oedema and in addition, the CO_2 response was attenuated.

These experiments confirm that in areas of brain oedema, an increase in SAP may not be accompanied by an increase in CBF even though other indices suggest impaired cerebrovascular responsiveness. This capacity to increase CVR in response to arterial hypertension is not present in brain which has been injured but which is not oedematous. Arterial hypertension and hypercapnia are known to increase the spread of vasogenic oedema. In accord with this, there was a greater reduction in rCBFw over the duration of the study in oedematous areas compared with other areas. However, changes in tissue pressure in excess of measured intraventricular pressure are unlikely to be so large or so rapid as to explain the rapid changes in CVR.

In baboons with injury but no oedema, impairment of autoregulation to hypotension and hypertension at a time when normocapnic, normotensive rCBFw was normal, resembled the response to injury described in the cat by Reivich et al. (1969a). It is probable that this represents the first stage of blood flow disturbance following brain injury.

An explanation of the changes in blood flow in the oedematous white matter must take into account the changes which occurred in the white matter of the opposite hemisphere and in the deep grey matter of baboons with unilateral white matter oedema. Although no area of grey matter was oedematous, the cerebrovascular responses following injury

resembled those in the adjacent areas of white matter. Blood flow in grey matter showed a greater variability, and this was particularly so in animals with oedema.

Evans Blue did not stain the opposite hemisphere or the deep grey matter of the animals with oedema and so these more distant effects cannot be due to changes in either tissue pressure or the blood-brain barrier. Brain stem water content was not measured, but since all animals were alert and the only focal neurological deficits were consistent with the site of cortical injury, it is unlikely that oedema extended to the brain stem. Similarly, the alert status of the animals spoke against a general metabolic depression as a cause for the reduction in flow in the opposite hemisphere and the deep grey matter.

SECTION 4

OBSERVATIONS IN PATIENTS WITH BRAIN OEDEMA

PURPOSE

This study examined the relationship between regional CBF, brain tissue water content, and tissue density measured by computerized axial tomography (CAT scanning). CAT scanning enables horizontal sections of the cranium to be "viewed" as a matrix based on the X-ray absorption of small volumes of tissue (Hounsfield, 1973). Tissue densities may be compared against an arbitrary scale on which air is -500 and water is zero. Normal brain densities range from +11 to +15 for white matter, and +16 to +22 for grey matter. Lower densities may be found in oedema, infarction, or resolving blood clots, and higher or lower densities may occur in tumour tissue and in areas of contusion and haemorrhage after head injury.

PROTOCOL

CAT units had only recently been put into general clinical use, and the time available for experimental studies was limited.

This study was conducted on five patients shown by CAT scanning to have mass lesions associated with areas of reduced tissue density consistent with oedema.

The CAT scans were performed with an EMI head scanning unit, using an 80 x 80 matrix which allowed blocks of tissue 3 mm x 3 mm x 13 mm to be viewed (Fig. 22). Results were stored on magnetic discs and later printed out by a line pointer as X-ray density figures, and displayed on an oscilloscope unit as an anatomical representation, using a black-white scale to indicate X-ray density.

Regional CBF was measured by the ^{133}Xe inhalation technique with the patient fully conscious (Wyper et al., 1975). End-tidal CO_2 was monitored continuously. Blood flow was measured in two areas in the same hemisphere, at least one of which was judged to include the area of reduced X-ray density. In one patient, CAT scanning and CBF

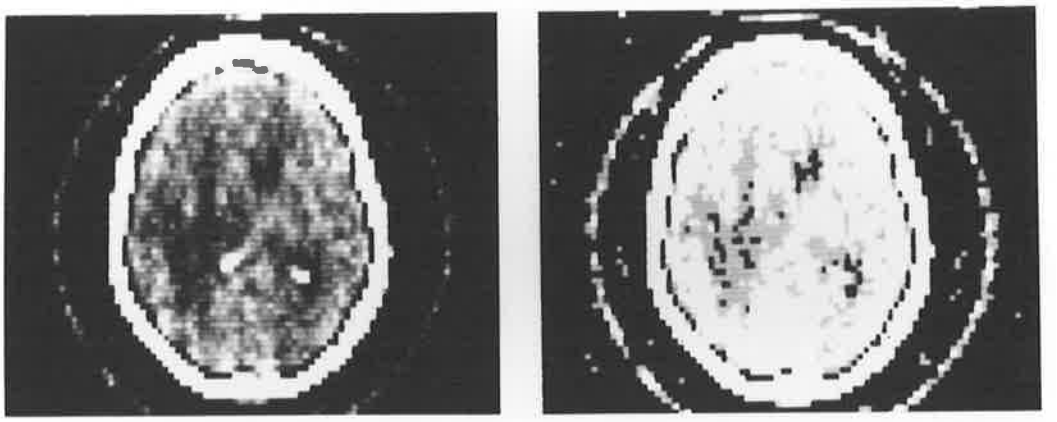


Figure 23: CAT scan of a glioma with oedema.

There is an area of reduced density in the left tempero-parietal region. This is highlighted on the right by selecting the scale range 8 to 15 X-ray density units (Patient E.H.).

measurements were repeated after 72 hours of steroid therapy (dexamethasone 4 mg six-hourly orally).

At operation, brain tissue samples were taken from areas adjacent to, but not including, macroscopic tumour. Samples were placed immediately into pre-weighed containers for wet weight/dry weight estimation of tissue water content.

RESULTS (Table 17, Fig. 23)

Tissue Water Content

Biopsies were performed in four patients. The fifth patient was diagnosed on clinical grounds as having a cerebral infarct. All four biopsies confirmed the CAT scan evidence of white matter oedema.

CBF in Oedematous Zones

In three patients, there was reduced tissue density in the CAT scan in both the frontal and parietal regions. CBF was reduced in all six regions compared with normal values obtained with this technique (Lennox et al., 1975).

In the two patients in whom reduced tissue density occurred in one region only, CBF was lower in this region compared with the region with normal density.

The Effect of Steroids

In a single patient (E.H.), treatment with dexamethasone was followed by an increase in both tissue X-ray density and CBF in the same area. Tissue water content after treatment was still above normal.

CONCLUSIONS

This small study suggests three tentative conclusions. Firstly, the area of reduced density around a tumour mass commonly shown on CAT scanning may have an increased tissue water content. The CAT

TABLE 16

CEREBRAL BLOOD FLOW AND BRAIN TISSUE WATER CONTENT IN PATIENTS WITH BRAIN LESIONS

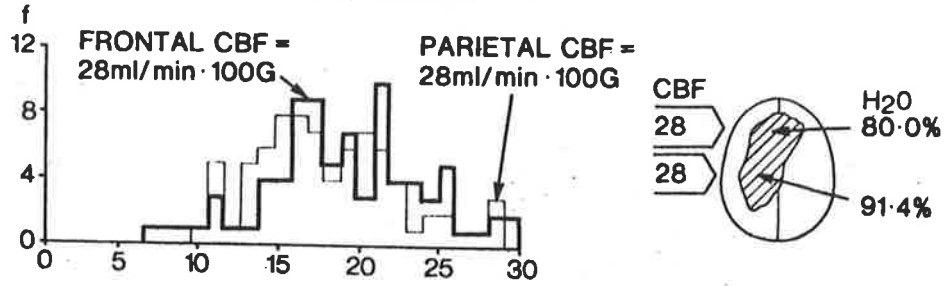
Patient	Diagnosis	Cerebral Blood Flow (ml/min. 100G) Frontal	Parietal	Tissue Water (% wet weight)
I.McT.	Rt frontal glioma	26	36	82.4
J.A.	Bifrontal glioma	28	28	80.4 91.4
K.C.	Left temporal glioma	24	23	88.0
P.M.	Left deep frontal infarct	25	45	-
E.H.	Left temporal glioma	36 44	32 41	83.4*

*After steroid therapy

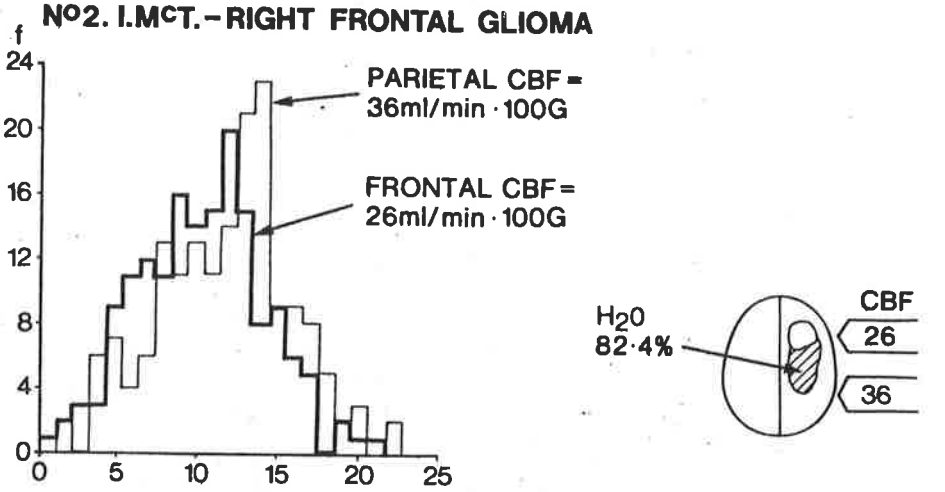
scan will therefore detect oedema and may be a guide to the effectiveness of different modes of therapy. Although several disease processes reduce tissue X-ray density, recent developments in CAT scanning, such as enhancement of tumour tissue by iodine-containing contrast media, and the use of finer matrices, may allow oedema to be distinguished more easily.

Secondly, this study confirms that regional CBF may be low in areas of verified oedema. Finally, the single case in which CBF was measured before and after treatment with dexamethasone is consistent with other evidence that one beneficial effect of steroids is to increase CBF in areas of oedema (Reulen et al., 1972). Although tissue water content could only be measured after treatment, the increase in tissue X-ray density with treatment suggests that the increase in CBF was accompanied by a reduction in tissue water content.

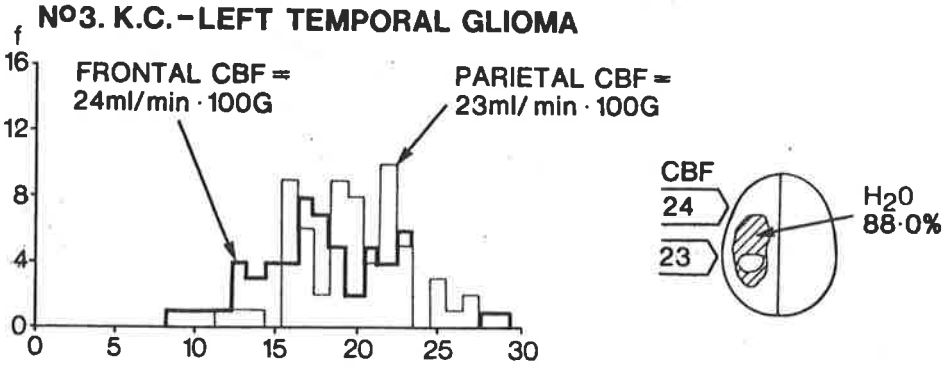
NO1. J.A. – BIFRONTAL GLIOMA



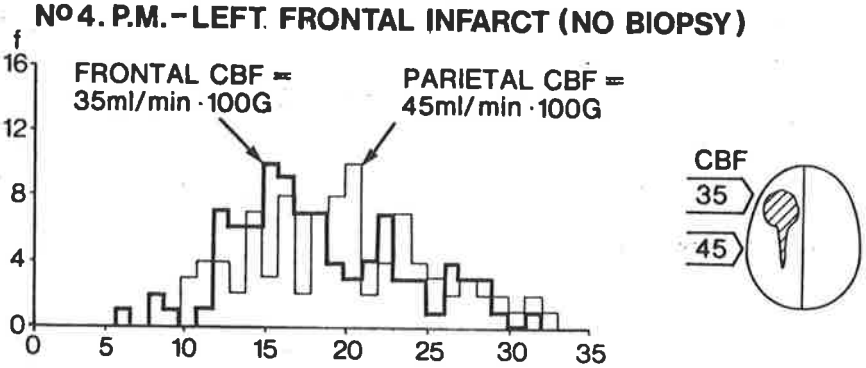
NO2. I.MCT. – RIGHT FRONTAL GLIOMA



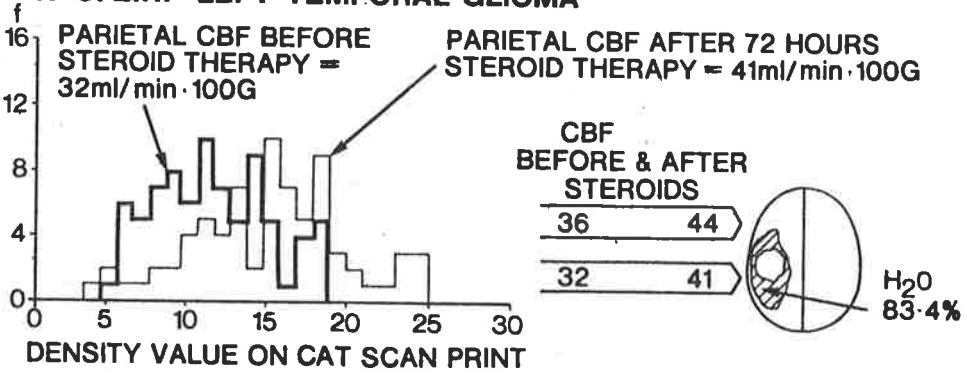
NO3. K.C. – LEFT TEMPORAL GLIOMA



NO4. P.M. – LEFT FRONTAL INFARCT (NO BIOPSY)



NO5. E.H. – LEFT TEMPORAL GLIOMA



SECTION 5

FINAL DISCUSSION

These experiments have studied the cerebral circulation after brain injury. By using a model which is associated with oedema, the influence of this common component of brain injuries has been examined. The first series of experiments showed that soon after injury, there was a reduction in CBF in the injured area. Furthermore, CBF could not always be increased either by increasing CPP or by hypercapnia. This raised important questions about autoregulation in areas of brain injury.

It is clear from many studies, that autoregulation is a characteristic of a healthy cerebral circulation and that loss of autoregulation may be an early effect of injury. Yet in this study, soon after a focal injury, three types of cerebrovascular response to arterial hypertension were identified; a pressure passive pressure-flow relationship, indicating loss of autoregulation; secondly, "false-autoregulation" in which perfusion pressure did not change - this response does not depend upon, nor provide, information on the state of vascular reactivity; thirdly, constant flow accompanying increasing perfusion pressure - "pressure-flow dissociation".

Pressure-flow dissociation after injury could not be regarded as a persistence of physiological autoregulation. It did not depend upon the presence of autoregulation before injury, and it occurred in animals with evidence of more severe tissue damage than those which did not show this response. In other words, pressure-flow dissociation after injury represented a more severe state of disordered cerebrovascular responsiveness than did a pressure passive response.

The second series of experiments analysed this problem further by separating the effects of the primary tissue injury from that of the secondary oedema. Brain injury without oedema impaired autoregulation and a pressure passive pressure-flow relationship resulted. Oedema however, was associated with pressure-flow dissociation. Resting CBF in oedematous areas was reduced in proportion to tissue water content. The decrease was not related to the level of ICP, suggesting that CBF was

influenced more by tissue pressure than ICP. Arterial hypotension reduced CBF, further evidence that physiological autoregulation was impaired and that the increase in CVR with arterial hypertension was not a normal physiological response, but rather an indication that any factor which might tend to increase CBF directly would meet with increasing CVR. Thus, both arterial hypertension and hypercapnia which have contrary effects on CVR in a normal vascular bed and will increase flow in damaged brain without oedema, were unable to increase flow in oedematous brain.

This form of flow regulation is clearly not physiological autoregulation which is lost in much less severe injuries. Reduction in resting levels of CBF with increased tissue water content may be partly due to increased tissue volume, so that CBF per unit volume is decreased. This does not explain loss of vascular reactivity. Increased tissue water content may increase tissue pressure beyond ICP. Calculation of effective perfusion pressure and transmural pressure within the oedematous tissue may therefore be based more properly upon tissue pressure, rather than ICP or cerebral venous pressure. It is well known that arterial hypertension will augment oedema formation. Perhaps by driving fluid into the extravascular compartment, increasing tissue pressure and deforming the vascular bed, arterial hypertension induces a type of passive autoregulation, analogous to that once postulated in the renal vascular bed (Hinshaw et al., 1959). In support of this, there was a greater reduction in regional CBF in areas of white matter oedema through the period of study. However, changes in tissue pressure would need to be well in excess of measured ipsilateral ventricular pressure in order to negate the increase in calculated CVR found in these studies.

Damage to the blood-brain barrier might allow vasoactive blood-borne metabolites to enter the extravascular space. It is unlikely however, that the exogenous norepinephrine used to induce arterial

hypertension would act directly on cerebral vessels in such a way as to increase CVR. Studies in which the blood-brain barrier has been deliberately opened by osmotic agents, suggest that norepinephrine increases rather than decreases CBF and metabolism (MacKenzie et al., 1975). A reduction in local metabolic rate may occur following injury. Although this may explain a reduction in resting regional blood flow, it does not explain an increase in CVR with arterial hypertension.

Changes in tissue pressure and the blood-brain barrier may contribute to the effects of oedema in the area of brain injury. However such changes cannot explain the findings in the opposite hemisphere of animals with unilateral oedema. Although tissue water and electrolyte content in these areas were normal, CBF in the white matter of the opposite hemisphere was reduced to values mid-way between normal values and those in oedematous areas. As in oedematous areas, hypotension caused a fall in CBF, yet the response to hypertension indicated pressure-flow dissociation. Furthermore, the CO_2 response was attenuated. Blood flow in the non-oedematous grey matter was more variable, particularly in animals with white matter oedema. The general pattern of cerebrovascular responses followed those of the adjacent white matter.

von Monakow (1914) postulated on clinical evidence, that a circumscribed cerebral lesion may cause a transient depression of neurological function in areas remote from the lesion. He termed this diaschisis. In an experimental study, Kempinsky (1958) found that acute unilateral cerebral injury caused bilateral depression of spontaneous and evoked cortical electrical activity. This depression was prevented by dividing the corpus callosum. Høedt-Rasmussen & Skinhøj (1964), Skinhøj (1965) and Meyer et al. (1970) reported bilateral reduction in hemisphere blood flow in patients with unilateral cerebral lesions or brain stem infarction. Meyer et al (1970) found an accompanying reduction in hemisphere metabolism. These workers suggested that the distant effects of focal lesions indicated a transneural depression of function perhaps mediated by transcallosal or brain stem pathways.

Contralateral reduction in blood flow has been reported after cryogenic injury (Bruce et al.,1972; Wallenfang et al., 1975). In a model of focal ischaemia, Reivich et al. (1977) reported a contralateral reduction of CBF and of glucose metabolism. These studies provide strong support for von Monakow's clinical concept, but the mechanism responsible for the remote effects is not yet clear.

An extension of oedema into the brain stem might explain cerebrovascular impairment in the contralateral hemisphere (Shalit et al., 1967; Fenske et al., 1975). Although brain stem water content was not measured in this study, the animals were alert and in those with neurological deficits, the deficits were strictly localised. For similar reasons, an overall metabolic depression is an unlikely explanation for a reduction of flow in the opposite hemisphere. Release of endogenous norepinephrine from the site of injury was invoked by Kogure et al.(1975). However, as already discussed, experimental evidence indicates that norepinephrine tends to increase CBF and metabolism. Furthermore, such a mechanism would not explain an increase in CVR during arterial hypertension. It is indeed interesting to speculate whether the intrinsic catecholaminergic neuronal systems which have been shown recently to arise from brain stem nuclei and to project widely through the cerebrum (see page 15) may provide the pathway for the remote effects of focal brain injuries.

The small study in patients indicated how CAT scanning may be used in clinical studies of brain disease with oedema. CBF was reduced in areas of verified oedema. Steroid therapy was associated with an increase in regional blood flow and most likely, a decrease in brain water content as indicated by the CAT scan. This clearly needs further study.

How the cerebral circulation in damaged brain responds to changes in SAP and $PaCO_2$ has considerable importance for the clinician who wishes

to increase tissue perfusion in order to reduce or prevent brain damage; who wishes to gauge the degree or extent of a brain injury, or who wishes to assess the effectiveness of treatment. It is clear that attempts to increase CBF by increasing SAP or increasing $PaCO_2$ may be quite ineffective. Both manoeuvres are known to increase vasogenic oedema. They may therefore compound the deleterious effects on regional CBF, and by increasing ICP and tissue elastance, render the brain susceptible to further increases in ICP, to brain distortion and herniation. Hypercapnia may even decrease flow in the injured area.

Clearly the ideal method of increasing tissue perfusion is to decrease CVR. To do so, one needs to know why CVR is increased. Although the exact mechanisms cannot be deduced from this study, there seems to be a close relationship with tissue water content. It may be suggested that reducing tissue water content and tissue pressure, perhaps by steroids or osmotic diuretics, are an essential part of any attempt to increase perfusion in areas of brain damage and will be more effective than attempts to increase CBF directly.

There are clearly many factors influencing CBF in areas of brain injury. Controlled experiments such as those reported in this thesis, may lead to a better understanding of the way in which brain injuries affect function, and help clinicians to determine the most effective methods of treatment.

CONCLUSIONS

1. In brain injury, the relationship between CBF and SAP is complex, but one of three general patterns may occur; impairment of autoregulation with a pressure passive pressure-flow relationship; secondly "false autoregulation" in which CPP does not change, and finally, pressure-flow dissociation in which CBF is constant despite increasing CPP.

2. This third response is related to increased tissue water content and is not present in minor brain injuries without oedema.
3. The cerebrovascular response to hypercapnia is reduced in areas of oedema.
4. Pressure-flow dissociation in damaged brain is distinct from physiological autoregulation. This may explain the paradox of clinical studies which have reported intact autoregulation in patients with severe brain injuries.
5. Changes in CBF and in cerebrovascular responses occur in areas of brain which are not oedematous and are remote from the focal injury. This adds support to the clinical concept of diaschisis.
6. In areas of injury and oedema, attempts to increase CBF by increasing SAP or $PaCO_2$ may be harmful. Reducing CVR by reducing tissue water content and tissue pressure are an essential part of any attempt to increase perfusion in areas of brain damage.
7. Regional CBF measurement may be the only way of accurately assessing the effects of different modes of therapy in specific brain injuries.

APPENDIX

TABLE 1

NORMAL VALUES

	Exp. No.	Blood Gases: Arterial pO_2 (mm Hg)	Arterial pCO_2 (mm Hg)	Arterial pH	Venous pO_2 (mm Hg)	Venous pCO_2 (mm Hg)	Venous pH	Hb (G/100G)	SAP (mm Hg)	ICP (mm Hg)	VPR (mm Hg/ 0.1 cc)	SSP (mm Hg)	$CMRO_2$	Body Temp. °C
SERIES 1	1	102.9	40.9	7.48	40.0	46.4	7.41	13.4	92	6	1	11	2.2	36.5
	2	112.0	37.7	7.49	33.5	44.5	7.42	10.9	87	11	1	6	1.7	36.5
	3	91.0	41.0	7.44	39.5	48.5	7.40	10.0	103	15	3	18	1.8	36.8
	4	94.5	39.3	7.44	40.7	50.8	7.38	11.8	97	7	1		1.2	36.5
	5	98.0	40.8	7.37	42.2	46.2	7.36	10.8	92	12	2		2.2	36.8
	6	99.0	39.5	7.41	41.0	45.0	7.35	10.8	108	7	1		1.6	37.0
	9	88.0	40.5	7.36	42.2	52.5	7.29	10.8	93	19	5	14	3.1	37.0
	11	104.0	39.5	7.40	50.0	50.5	7.36	9.2	90	7	1	25	2.0	36.5
	12	88.0	40.0					10.0	70	7	1		2.3	38.0
	13	107.5	38.8	7.46	28.9	44.5	7.38	9.1	97	6	1	9	2.3	37.0
	15	132.5	38.0	7.46	42.5	42.9	7.49	12.5	90	9	1	4	2.7	36.5
	16	102.0	39.5	7.41	35.0	49.4	7.34	12.1	87	21	2	19	2.3	36.0
SERIES 2	2	115.0	44.0	7.43					100	12				
	3	158.0	41.5	7.41					110	17				
	4	184.0	38.0	7.47					70	9				
	5	134.0	42.0	7.42					92	3				
	6	138.0	42.0	7.46					87	5				
	7	98.0	39.5	7.40					98	4				
	8	93.5	37.2	7.45					110	9				
	9	103.5	44.0	7.33					118	3				
	10	111.0	41.3	7.46					87	14				
	11	135.5	41.3	7.41					98	4				
	12	141.0	42.5	7.35					85	3				
	Median	104.0	40.5	7.43	40.7	46.4	7.38	10.8	92.0	7.0	1.0	12.5	2.2	36.7
	Range	91.0- 184.0	37.2- 44.0	7.33- 7.49	28.9- 50.0	42.9- 52.5	7.29- 7.49	9.1- 13.4	70.0- 118.0	3.0- 21.0	1.0- 5.0	4.0- 25.0	1.2- 3.1	36.0- 38.0

TABLE II

COMPARISON OF CEREBRAL BLOOD FLOW MEASURED BY ^{133}XENON & HYDROGEN

Exp. No.	$PaCO_2$ (mm Hg)	SAP (mm Hg)	CBF (ml/min. 100G)						
			Xenon		Hydrogen				
					Cortex			Deep Grey	
			Fast	Slow	Fast	Slow	White	Fast	Slow
1	39.5	88	112	29	68	17	-	87	28
	43.0	83	82	47	63	11	-	122	29
2	36.0	70	94	24	88,51,95	14	35	-	17
	38.8	68	91	27	69,58,72	19	23	-	27
3	37.0	73	99	28	130	-	20,23	-	-
	36.0	68	135	23	115	-	18,19	91	-
	43.0	70	77	39	124	-	18,25	91	-
4	41.5	77	82	21	74,87	20,15	17	99	16
	43.5	78	120	26	72,65	21,14	18	69	20
	40.0	80	112	23	90,65	27,14	21	148	15
	35.5	80	80	23	87,47	13,7	14	72	10
5	35.5	85	94	23	99	-	9	61	-
	37.5	80	91	35	97	-	16	62	-
	36.0	85	112	33	139	12	16	99	12
	38.5	83	116	34	122	-	15	82	13
	38.5	85	105	30	-	-	17	67	11
6	38.9	67	51	18	52,74	15,24	11,12	74,88	18,16
7	43.0	78	91,99	25,14	63,74	17,12	13,14	-	32
8	41.5	100	62	33	104,115	30	22,25	99	25
	41.5	108	105	31	83,92	23	24,27	59	16
9	38.0	90	-	26	-	17	24,26	52	31,35
	39.5	88	73	28	130	14	27,23	122	26
10	43.0	87	66	13	72,76	12,20	17,19	77	16,16
Median	39.5	82.0	93.8	26.3	73.7	16.0	18.0	84.0	20.5
Range	37.2-43.0	67.0-104.0	51.0-103.7	13.0-38.0	63.0-130.0	12.0-26.5	29.0-11.5	74.2-104.5	12.0-32.0

Median and range based on average of multiple values obtained in individual animals.

TABLE III

COMPARISON OF CEREBRAL BLOOD FLOW MEASURED BY ^{133}XENON & HYDROGEN: CORRELATION AT DIFFERENT LEVELS OF $PaCO_2$

Exp. No.	Run No.	$PaCO_2$ (mm Hg)	SAP (mm Hg)	CBF (ml/min. 100G) Xenon Fast	Xenon Slow	Hydrogen Cortex	Hydrogen White Matter	Hydrogen Deep Grey
6	1	38.9	67	51		52		74
	2	52.0	73	46		53		79
	3	54.0	58	54		58		56
	4	66.0	63	65		56		64
	5	69.0	73	54		65		52
7	1	43.0	78	91		63		
	2	44.5	87	89		99		
	3	48.0	98	75		77		
	4	55.0	102	86		91		
	5	58.5	98	125		89		
	6	60.9	108	130		104		
8	1	41.5	100	62	33		22	99
	2	41.5	108	105	31	83	24	59
	3	56.5	93	112	30	130	30	40
	4	64.0	107	130	25	130	27	48
	5	61.0	107	147	23	147	29	48
	6	72.0	120	160	26	148	25	50
	7	47.0	103	105	25	130	23	45
9	1	38.0	90		26		24	
	2	39.5	88	73	28		27	122
	3	45.0	75	89	30		22	110
	4	60.5	83	169	39		32	231
	5	75.0	82	94	25		36	139
	6	76.0	85	169	35		36	245
10	1	34.5	115	58	18	61	13	50
	2	45.0	112	62	19	57	18	77
	3	53.0	107	67	25	61	25	91
	4	63.5	102	105	31	76	26	58
	5	46.0	83	56	20	60	23	79
	6	43.0	87	66	13	72	17	-

TABLE IV

MEASUREMENTS BEFORE CRYOGENIC INJURY - RESPONSE TO CHANGE IN BLOOD PRESSURE

CONTROL (C) & EXPERIMENTAL (E) VALUES IN BABOONS WITH INTACT & IMPAIRED AUTOREGULATION

	Exp. No.	$PaCO_2$ (mm Hg)		SAP (mm Hg)		ICP (mm Hg)		CBF (ml/min. 100G)		%ΔCVR	$CMRO_2$		pH (Art.)	VPR (mm Hg/ 0.1 ml)	
		C	E	C	E	C	E	C	E		C	E		C	E
Auto-regulation intact	1	41	40	92	67	6	7	35	33	26	2.2	1.8	7.48	1	1
	2	38	37	87	70	11	9	32	32	20	1.7	2.6	7.49	1	1
	3	41	41	103	85	15	15	61	66	43	1.8	1.8	7.44	3	3
	6	40	44	108	83	7	7	40	(47)43*	30	1.6	1.8	7.41	1	2
	11	42	47	92	75	10	9	68	(84)69*	24	2.0	3.1	7.48	1	2
	12	38	39	85	72	9	9	78	83	22	2.3	2.6	7.39	1	1
	13	37	37	97	70	6	8	42	42	32	2.3	2.4	7.46	1	1
	Median	40.0	40.0	92.0	72.0	9.0	9.0	42.0	43.0	26.0	2.0	2.4	7.46	1.0	1.0
	Range	37.0-42.0	37.0-47.0	85.0-108.0	67.0-85.0	6.0-15.0	7.0-15.0	32.0-78.0	32.0-83.0	20.0-43.0	1.6-2.3	1.8-3.1	7.39-7.49	1.0-3.0	1.0-3.0
Auto-regulation impaired	4	41	43	100	73	11	4	41	27	0	1.2	0.9	7.47	1	1
	5	41	41	100	80	17	16	48	45	18	2.2	2.3	7.39	4	7
	9	41	41	93	73	19	16	53	36	0	3.1	2.3	7.37	5	3
	15	38	40	90	68	9	6	45	40	14	2.7	2.8	7.47	1	
	16	40	42	87	132	21	28	30	57	17	2.3	2.2	7.41	2	
	Median	41.0	41.0	93.0	73.0	17.0	16.0	45.0	40.0	14.0	2.3	2.3	7.41	2.0	
	Range	38.0-41.0	40.0-43.0	87.0-100.0	68.0-132.0	9.0-21.0	4.0-28.0	30.0-53.0	27.0-57.0	0-18.0	1.2-3.1	0.9-2.8	7.37-7.47	1.0-5.0	
	Median	40.5	41.0	92.5	73.0	10.5	9.0	43.5	42.5	21.5	2.2	2.3	7.45	1.0	1.5
	Range	37.0-42.0	37.0-47.0	85.0-108.0	67.0-132.0	6.0-21.0	4.0-28.0	30.0-78.0	27.0-83.0	0-43.0	1.2-3.1	0.9-3.1	7.37-7.49	1.0-5.0	1.0-7.0

* Since $PaCO_2$ had risen inadvertently through the period of CBF measurement, CBF values in these two runs only have been corrected, using the appropriate CO_2 gradient, to obtain the CBF at the control level of $PaCO_2$.

The measured flow values are shown in brackets.

TABLE V

MEASUREMENTS BEFORE CRYOGENIC INJURY - RESPONSE TO HYPERCAPNIA
CONTROL (C) & EXPERIMENTAL (E) VALUES IN BABOONS WITH INTACT & IMPAIRED AUTOREGULATION

	Exp. No.	$PaCO_2$ (mm Hg)		CBF (ml/min. 100G)		$\frac{\Delta CBF}{\Delta PaCO_2}$	SAP (mm Hg)		ICP (mm Hg)		CVR (mm Hg/ml/ min. 100G)		$\frac{\Delta CVR}{\Delta PaCO_2}$	$CMRO_2$		VPR mm Hg/ 0.1 ml)	
		C	E	C	E		C	E	C	E	C	E		C	E	C	E
Auto-regulation intact	1	41	53	35	41	0.5	92	98	6	12	2.46	2.09	0.03	2.2	1.1	1	1
	2	38	45	32	40	1.1	87	88	11	10	2.38	1.95	0.06	1.3	1.6	1	1
	3	41	58	61	80	1.1	103	122	15	34	1.44	1.10	0.02	1.8	1.4	3	2
	6	39	64	51	75	1.0	93	120	11	22	1.61	1.31	0.01	1.5	1.1	2	3
	11	42	49	68	88	2.9	82	92	10	11	1.06	0.92	0.02	1.3	3.1	1	1
	12	33	45	57	80	1.9	75	85	4	12	1.25	0.91	0.03	2.2	2.3		
	13	42	65	58	115	2.5	90	80	10	19	1.38	0.53	0.04	3.1	3.1	1	2
	Median	41.0	53.0	57.0	80.0	1.1	90.0	92.0	10.0	12.0	1.44	1.10	0.03	1.8	1.6	1.0	1.5
	Range	33.0-42.0	45.0-65.0	51.0-61.0	40.0-115.0	0.5-2.9	75.0-103.0	80.0-122.0	4.0-15.0	10.0-34.0	1.06-2.46	0.53-2.09	0.01-0.06	1.3-3.1	1.1-3.1	1.0-3.0	1.0-3.0
Auto-regulation impaired	4	41	53	41	68	2.3	100	102	11	16	2.17	1.26	0.08	1.1	1.2	2	2
	5	41	50	48	81	3.7	100	97	17	29	1.73	0.84	0.10	2.2	1.9	4	7
	9	42	59	53	96	2.5	95	82	18	34	1.45	0.50	0.06	3.0	2.8	3	2
	15	38	51	45	87	3.2	90	85	9	11	1.80	0.85	0.07	2.7	3.6		
	16	40	52	30	66	3.0	87	102	21	38	2.20	0.97	0.10	2.3	2.5		
	Median	41.0	52.0	45.0	81.0	3.0	95.0	97.0	17.0	29.0	1.80	0.85	0.08	2.3	2.5		
	Range	38.0-42.0	50.0-59.0	30.0-53.0	66.0-96.0	2.3-3.7	87.0-100.0	82.0-102.0	9.0-21.0	11.0-38.0	1.45-2.20	0.50-1.26	0.06-0.10	1.1-3.0	1.2-3.6		
	Median	41.0	52.5	49.0	80.0	2.4	91.0	94.5	11	17.5	1.67	0.95	0.05	2.2	2.1	2.0	2.0
	Range	33.0-42.0	45.0-65.0	30.0-61.0	40.0-115.0	0.5-3.7	75.0-103.0	80.0-122.0	4.0-21.0	10.0-38.0	1.06-2.46	0.50-2.09	0.01-0.10	1.1-3.1	1.1-3.6	1.0-4.0	1.0-7.0

TABLE VI

EFFECT OF CRYOGENIC INJURY IN BABOONS WITH INTACT AND IMPAIRED AUTOREGULATION
VALUES IMMEDIATELY BEFORE INJURY (C) & 30 & 60 MINUTES AFTER INJURY

	Exp. No.	$PaCO_2$ (mm Hg)			SAP (mm Hg)			ICP (mm Hg)			CPP (mm Hg)			CBF (ml/min. 100G)			CVR (mm Hg/ml/ min. 100G)			$CMRO_2$			VPR (mm Hg/ 0.1 ml)		
		C	30	60	C	30	60	C	30	60	C	30	60	C	30	60	C	30	60	C	30	60	C	30	60
Auto-regulation intact	1	41	40	41	92	120	130	6	46	47	86	74	83	35	26	30	2.48	2.85	2.77	2.2	1.1	1.5	1	5	8
	2	37	44	38	82	78	72	13	20	14	69	58	58	32	34	26	2.15	1.71	2.23	1.3	2.6	1.3	1	1	1
	3	41	44	45	103	175	92	15	78	41	88	97	51	61	29	24	1.43	3.34	2.12	1.8	0.8	0.9	3	5	5
	6	39	42	45	93	85		11	24		82	61		51	40	33	1.61	1.53		1.5	1.2	0.6	3	2	5
	11	40	40	43	72	73	77	14	25	41	58	48	36	44	45	65	1.64	1.07	0.76	1.3	2.0	1.1	1	2	5
	12	39	39	39	72	68	72	9	12	14	63	56	58	83	68	68	0.76	0.82	0.85	2.5	2.5	2.1	1	1	
	13	42	39	37	90	73	70	10	12	12	80	61	58	58	42	41	1.38	1.45	1.41						
	Median	40.0	40.0	41.0	90.0	78.0	74.5	11.0	24.0	27.5	80.0	61.0	58.0	51.0	40.0	33.0	1.61	1.53	1.77	1.6	1.6	1.2			
	Range	37.0-42.0	39.0-44.0	37.0-45.0	72.0-103.0	68.0-175.0	70.0-130.0	6.0-15.0	12.0-78.0	12.0-47.0	63.0-88.0	48.0-97.0	36.0-83.0	32.0-83.0	26.0-68.0	24.0-68.0	0.76-2.48	0.82-3.34	0.76-2.77	1.3-2.5	0.8-2.6	0.6-2.1			
Auto-regulation impaired	4	41	48	38	100	108	77	11	25	21	89	83	56	41	30	32	2.16	2.76	1.75	1.1	1.0	1.6	2	1	3
	5	41	44	41	100	85	85	17	15	16	83	70	69	48	49	46	1.73	1.43	1.50	2.2	1.5	2.0	4	1	3
	9	42	45	42	95	88	93	18	50	56	77	38	37	53	49	45	1.45	0.78	0.82	3.0	2.2	2.2	3	2	
	15	38	41	38	90	72	72	9	10	13	81	62	59	45	35	36	1.80	1.77	1.64	2.7	2.0	2.6	1		1
	16	40	35	41	87	85	92	21	20	24	66	65	68	30	29	27	1.83	2.24	2.52	2.3	2.5	2.5			
	Median	41.0	44.0	41.0	95.0	85.0	85.0	17.0	20.0	21.0	81.0	65.0	59.0	45.0	35.0	36.0	1.80	1.77	1.64	2.3	2.0	2.2			
	Range	38.0-42.0	35.0-48.0	38.0-42.0	87.0-100.0	72.0-108.0	72.0-93.0	9.0-21.0	10.0-50.0	13.0-56.0	66.0-89.0	38.0-83.0	37.0-69.0	30.0-53.0	29.0-49.0	27.0-46.0	1.45-2.16	0.78-2.76	0.82-2.52	1.1-3.0	1.0-2.5	1.6-2.6			
	Median	40.5	41.5	40.0	91.0	81.5	77.0	12.0	22.0	21.0	80.5	61.5	58.0	46.5	37.5	34.5	1.69	1.62	1.64	2.0	2.0	1.6	1.5	2.0	4.0
	Range	37.0-42.0	35.0-48.0	37.0-45.0	72.0-103.0	68.0-175.0	70.0-130.0	6.0-21.0	10.0-78.0	12.0-56.0	63.0-89.0	38.0-97.0	36.0-83.0	30.0-83.0	26.0-68.0	24.0-68.0	0.76-2.48	0.78-3.34	0.76-2.77	1.1-3.0	0.8-2.6	0.6-2.6	1.0-4.0	1.0-5.0	1.0-8.0

TABLE VII

MEASUREMENTS AFTER CRYOGENIC INJURY - EFFECT OF ARTERIAL HYPERTENSION
CONTROL (C) & EXPERIMENTAL (E) VALUES IN GROUPS ACCORDING TO CHANGE
IN CEREBROVASCULAR RESISTANCE

	Exp. No.	$PaCO_2$ (mm Hg)		SAP (mm Hg)		ICP (mm Hg)		CPP (mm Hg)		CBF (ml/min. 100G)		CVR (mm Hg/ml/ min. 100G)		%ΔCVR	$CMRO_2$		VPR (mm Hg 0.1 ml)	
		C	E	C	E	C	E	C	E	C	E	C	E		C	E	C	E
ΔCVR >20%	3	43	42	82	143	37	79	45	64	24	19	1.88	3.37	80	0.9	0.8	4	6
	4	38	38	77	122	21	37	56	85	32	34	1.75	2.50	43	1.6	1.4	3	5
	5	43	41	80	137	10	19	70	118	53	57	1.32	2.07	57	1.9	1.5	1	4
	11	42	40	87	148	41	35	46	113	47	48	0.98	2.35	141	1.3	1.4		
	13	47	45	55	93	13	19	42	74	44	54	0.96	1.37	44	2.3	2.3	1	2
	15	39	39	70	122	13	19	57	103	37	45	1.54	2.29	49	1.9	2.6	1	2
	Median	42.5	40.5	78.5	129.5	17.0	27.0	51.0	94.0	40.5	46.5	1.43	2.32		1.8	1.5	1.0	4.0
	Range	38.0-47.0	38.0-45.0	55.0-87.0	93.0-148.0	10.0-41.0	19.0-79.0	42.0-70.0	64.0-118.0	24.0-53.0	19.0-57.0	0.96-1.88	1.37-3.37		0.9-2.3	0.8-2.6	1.0-4.0	2.0-6.0
ΔCVR <20%	1	40	42	102	125	42	65	60	60	20	22	3.00	2.73	12	1.0	1.9	2	8
	2	42	43	82	125	15	27	67	98	29	40	2.31	2.45	6	1.9	1.7	1	2
	6	42	42	90	145	37	78	53	67	60	71	0.88	0.94	7	2.3	1.7	2	2
	9	42	42	93	143	56	101	37	42	45	49	0.82	0.85	4	2.2	2.2	2	2
	12	39	39	72	95	14	21	58	74	68	107	0.85	0.69	-19	2.1	3.6	2	2
	16	41	43	92	138	24	38	68	100	27	45	2.52	2.22	-12	2.5	3.5		
	Median	41.5	42.0	91.0	131.5	30.5	51.5	59.0	70.5	37.0	47.0	1.60	1.58		2.2	2.1	2.0	2.0
	Range	39.0-42.0	39.0-43.0	72.0-102.0	95.0-145.0	14.0-56.0	21.0-101.0	37.0-68.0	42.0-100.0	20.0-68.0	22.0-107.0	0.82-3.00	0.69-2.73		1.0-2.5	1.7-3.6	1.0-2.0	2.0-8.0
	Median	42.0	42.0	82.0	131.0	22.5	36.0	56.5	79.5	40.5	46.5	1.43	2.55		1.9	1.8	2.0	2.0
	Range	38.0-47.0	38.0-45.0	55.0-102.0	93.0-148.0	10.0-56.0	19.0-101.0	37.0-70.0	42.0-118.0	20.0-68.0	19.0-107.0	0.82-3.00	0.69-3.37		0.9-2.5	0.8-3.6	1.0-4.0	2.0-8.0

TABLE VIII

MEASUREMENTS AFTER CRYOGENIC INJURY - EFFECT OF HYPERCAPNIA
CONTROL (C) & EXPERIMENTAL (E) VALUES

Exp. No.	$PaCO_2$ (mm Hg)		CBF (ml/min. 100G		$\frac{\Delta CBF}{\Delta PaCO_2}$	SAP (mm Hg)		ICP (mm Hg)		CVR (mm Hg/ml/ min. 100G)		$\frac{\Delta CVR}{\Delta PaCO_2}$	$CMRO_2$		VPR (mm Hg/ 0.1 ml)	
	C	E	C	E		C	E	C	E	C	E		C	E	C	E
1	41	60	30	32	0.75	130	121	47	61	2.77	1.88	0.05	1.5	0.8	8	
2	38	43	26	31	1.0	72	69	14	12	2.23	1.84	0.08	1.3	2.1	1	1
3	43	55	24	21	0	82	103	37	44	1.88	2.81	0	0.9	0.9	5	4
4	38	55	32	55	1.4	77	115	21	33	1.75	1.49	0.02	1.6	1.8	2	2
6	38	55	45	60	0.9	77	103	31	47	1.02	0.93	0.01	1.6	1.6	1	2
11	42	66	47	31	0	87	80	41	25	0.98	1.77	0	1.3	1.8	5	
12	39	55	107	130	1.7	95	95	21	26	0.69	0.53	0.01	3.6	3.6	2	2
13	37	54	41	73	1.9	70	70	12	18	1.41	0.71	0.04	2.7	2.3	2	2
15	38	52	40	60	1.4	72	92	12	21	1.50	1.18	0.02	2.6	2.6	1	1
16	41	52	27	40	1.2	92	100	24	35	2.52	1.63	0.08	2.5	2.5		
Median	38.5	55.0	36.0	47.5	1.10	78.5	97.5	22.5	29.5	1.63	1.56	0.02	1.6	2.0	2.0	2.0
Range	37.0-43.0	43.0-66.0	24.0-107.0	21.0-130.0	0-1.9	70.0-130.0	70.0-121.0	12.0-47.0	18.0-61.0	0.69-2.77	0.53-2.81	0-0.08	0.9-3.6	0.8-3.6	1.0-8.0	1.0-4.0
*5	43	57	46	94		85	87	16	21	1.50	0.70	0.06	2.0	2.8	2	1

* Exp. No.5: Excluded from calculation of a CO_2 response as $\frac{\Delta CBF}{\Delta PaCO_2}$ (see p.74), but included in calculations by $\frac{\Delta CVR}{\Delta PaCO_2}$

Exp. No.9: The effect of hypercapnia after lesion was not recorded because of mechanical failure.

TABLE IX

WATER AND ELECTROLYTE CONTENT
RELATED TO CEREBROVASCULAR RESPONSE TO INDUCED HYPERTENSION

	Exp. No.	Water (% wet wt.)		Sodium (mEq/100G dry wt.)		Potassium (mEq/100G dry wt.)		Chloride (mEq/100G dry wt.)	
		Lesion	Opp	Lesion	Opp	Lesion	Opp	Lesion	Opp
ΔCVR >20%	3	78.5	73.7	28.5	13.5	14.5	22.5	19.4	8.9
	4	82.3	72.5	54.0	16.5	16.5	27.7	36.0	8.9
	5	81.7	70.7	53.9	22.5	24.0	23.2	34.5	11.9
	13	83.4	70.1						
	15	73.4	70.2	21.7	20.9	22.5	22.5	10.5	7.5
	Median	81.7	70.7						
	Range	73.4-83.4	70.1-73.7						
ΔCVR <20%	1	77.2	70.3			17.5	33.0	27.0	10.2
	2	74.1	71.1						
	6	74.2	70.2	23.2	16.5	19.5	20.2		8.9
	12	75.6	71.9	35.6	14.9				
	16	72.1	70.6	29.9	21.7	29.9	28.4		
	Median	74.2	70.6						
	Range	72.1-72.2	70.2-71.9						
	Median	76.9	70.7	29.9	16.5	19.5	23.2	27.0	8.9
	Range	72.1-83.4	70.1-75.7	21.7-54.0	13.5-22.5	14.5-29.9	20.2-33.0	10.5-36.0	7.5-11.9

TABLE X

ANIMALS WITH NO CLINICAL DEFICIT

INITIAL (I) & FINAL (F) CONTROL VALUES WITH FINAL TISSUE WATER AND ELECTROLYTE CONTENT ON THE SIDE OF THE CRYOGENIC LESION

Exp. No.	$PaCO_2$ (mm Hg)		SAP (mm Hg)		ICP (mm Hg)		$rCBF_w$ (ml/min. 100G)		H_2O (% wet wt.)	Na^+ (mEq/100G dry wt.)	K^+ (mEq/100G dry wt.)	$rCBF_g$ (ml/min. 100G)		H_2O (% wet wt.)	Na^+ (mEq/100G dry wt.)	K^+ (mEq/100G dry wt.)
	I	F	I	F	I	F	I	F				I	F			
2	40	39	108	78	12	14	23	21	69.2	34.5	25.5	44	58	77.0	29.9	33.0
							29	25	69.9							
3	42	39	110	82	19	31	56	37	66.7	21.8	23.2	56	37	77.0	21.0	37.5
							28	21	66.8	16.5	19.5					
5	42	41	92	70	1	5	17	11	83.3	66.0	27.0					
							12	9	81.1	46.5	34.5					
7	40	42	98	80	4	2	26	19	83.3	58.0	34.5	95	78	80.0	42.0	45.0
8	37	40	103	87	11	14	15	13	68.3	33.0	30.7	32	29	77.3	46.5	45.0
							18	16	69.9	30.7	21.0					
11	41	40	98	110	4	11	14	18	81.1	40.5	24.0	38	30	79.5	27.0	45.0
12	43	38	85	90	3	4	20	13	69.3	22.5	27.0	42	28	79.8	24.0	40.5
							17	7	69.0	20.2	26.2					
Median	41.0	40.0	98.0	82.0	4.0	11.0	19.0	18.0	69.6	34.5	25.9	43.0	33.5	78.4	28.5	42.8
Range	37.0-43.0	38.0-42.0	85.0-110.0	70.0-110.0	1.0-19.0	2.0-31.0	14.0-42.0	10.0-29.0	66.8-83.3	19.2-58.0	21.4-30.8	32.0-95.0	28.0-78.0	77.0-80.0	21.0-46.5	33.0-45.0

Median and range derived from the average of multiple values obtained in individual animals.

TABLE XI

ANIMALS WITH A CLINICAL DEFICIT

INITIAL (I) & FINAL (F) CONTROL VALUES WITH FINAL TISSUE WATER & ELECTROLYTE CONTENT ON THE SIDE OF THE CRYOGENIC LESION

Exp. No.	$PaCO_2$ (mm Hg) I	F	SAP (mm Hg) I	F	ICP (mm Hg) I	F	$rCBF_w$ (ml/min. 100G) I	F	H_2O_w (% wet wt.)	Na^+_w (mEq/100G dry wt.)	K^+_w	$rCBF_g$ (ml/min. 100G) I	F	H_2O_g (% wet wt.)	Na^+_g (mEq/100G dry wt.)	K^+_g
4	38	38	70	77	8	20	15	5	84.4	24.0	23.0	18	17	75.1	27.0	40.5
							27	10	75.6	28.0	21.0					
6	42	40	87	113	5	35	15	12	78.5	47.5	30.0	36	35	72.0	43.5	37.5
9	39	39	72	57	2	6	10	5	79.4	49.5	24.0	32	20	77.1	25.5	43.5
							16	4	77.6	39.0	30.0					
10	41	40	87	82	14	23	18	23	82.7	40.5	33.0	26	24	80.1	27.0	45.0
Median	40.0	39.5	79.5	79.5	6.5	21.5	16.5	10.0	79.3	42.4	28.5	29.0	22.0	76.1	27.0	40.5
Range	38.0-42.0	38.0-40.0	70.0-87.0	57.0-113.0	2.0-14.0	6.0-35.0	13.0-21.0	5.0-23.0	78.5-82.7	26.0-47.5	22.0-33.0	18.0-36.0	17.0-35.0	72.0-80.1	25.5-43.5	31.5-45.0

Median and range derived from the average of multiple values obtained in individual animals.

TABLE XII

INITIAL (I) & FINAL (F) CONTROL VALUES WITH FINAL TISSUE WATER & ELECTROLYTE CONTENT IN WHITE MATTER

Exp. No.	A $PaCO_2$ (mm Hg)		SAP (mm Hg)		ICP (mm Hg)		A $rCBF_w$ (ml/min. 100G)		H_2O (% wet wt.)	Na^+ (mEq/100G dry wt.)	K^+ (mEq/100G dry wt.)	B $rCBF_w$ (ml/min. 100G)		H_2O (% wet wt.)	Na^+ (mEq/100G dry wt.)	K^+ (mEq/100G dry wt.)
	I	F	I	F	I	F	I	F				I	F			
4	38	38	70	77	8	20	15	5	84.4	24.0	23.0	10	9	67.5	31.5	29.2
							27	10	75.6	28.0	21.0	26	17	68.5	18.0	21.0
5	42	41	92	70	1	5	17	11	83.3	66.0	27.0	14	12	69.7	24.0	33.0
							12	9	81.1	46.5	34.5	14	18	71.7	28.5	36.7
6	42	40	87	113	5	35	15	12	78.5	47.5	30.0	14	20	66.8	19.5	24.0
7	40	42	98	80	4	2	26	19	83.3	58.0	34.5	28	29	69.3	23.2	26.2
9	39	39	72	57	2	6	10	5	79.4	49.5	24.0	18	13	68.1	18.0	27.0
							16	4	77.6	39.0	30.0	27	20	67.1	16.5	24.0
10	41	40	87	82	14	23	18	23	82.7	40.5	33.0	16	13	68.9	15.7	24.0
11	41	41	98	110	4	11	14	18	81.1	40.5	24.0	18	19	67.7	18.0	24.7
Median	41.0	40.0	87.0	80.0	4.0	11.0	15.0	12.0	81.1	44.3	30.0	18.0	17.0	68.0	19.5	25.1
Range	38.0-42.0	38.0-42.0	70.0-98.0	57.0-113.0	1.0-14.0	2.0-35.0	14.0-26.0	5.0-23.0	78.5-83.3	26.0-58.0	22.0-34.5	14.0-28.0	13.0-29.0	66.8-70.7	15.7-26.3	24.0-34.9
C 2	40	39	108	78	12	14	23	21	69.2	34.5	25.5					
							29	25	69.8	46.5	38.2					
							29	25	69.9							
							16	20	69.7	29.9	24.0					
3	42	39	110	82	19	31	56	37	66.7	21.8	23.2					
							28	21	66.8	16.5	19.5					
							18	16	67.5	15.6	21.0					
							31	27	67.6	16.5	20.9					
8	37	40	103	87	11	14	15	13	68.3	33.0	30.7					
							18	16	69.9	30.7	21.0					
							20	33	68.5	19.5	24.7					
							20	25	67.8	19.5	24.7					
12	43	38	85	90	3	4	20	13	69.3	22.5	27.0					
							17	7	69.0	20.2	26.2					
							20	12	69.3	21.0	27.0					
Median	41.0	39.0	105.5	84.5	11.5	14.0	21.5	22.5	68.9	23.5	26.0					
Range	37.0-43.0	38.0-40.0	85.0-110.0	78.0-90.0	3.0-19.0	4.0-31.0	18.0-33.0	11.0-25.3	67.2-69.7	17.6-37.0	21.2-29.2					

A - areas of white matter oedema.

B - equivalent areas in opposite hemisphere, without oedema.

C - areas in baboons with injury but no oedema.

Median and range based on average of multiple values obtained in individual animals.

TABLE XIII

INITIAL (I) & FINAL (F) CONTROL VALUES WITH FINAL TISSUE WATER & ELECTROLYTE CONTENT IN GREY MATTER

(Values for ICP, SAP & $PaCO_2$ are given in Table XII)

Exp. No.	A $rCBF_g$ (ml/min. 100G) I	F	H_2O (% wet wt.)	Na^+ (mEq/100G dry wt.)	K^+	B $rCBF_g$ (ml/min. 100G) I	F	H_2O (% wet wt.)	Na^+ (mEq/100G dry wt.)	K^+
4	18	17	75.1	27.0	31.5	33	24	77.1	39.0	34.5
5			78.5	36.0	51.0			76.8	39.0	51.0
6	36	35	72.0	43.5	37.5	52	55	75.1	25.5	39.0
7	95	78	80.0	42.0	45.0	87	60	79.5	54.0	51.0
9	32	20	77.1	25.5	43.5	44	22	76.3	30.0	45.0
10	26	24	80.1	27.0	45.0	46	42	69.9	25.5	21.0
11	38	30	79.5	27.0	45.0			78.4	21.0	42.0
Median	34.0	27.0	78.5	27.0	45.0	46.0	42.0	76.8	30.0	42.0
Range	18.0-95.0	17.0-78.0	72.0-80.1	25.5-43.5	31.5-51.0	33.0-87.0	22.0-60.0	69.9-79.5	21.0-54.0	21.0-51.0

	C				
2	44	58	77.0	29.9	33.0
			77.1	26.2	43.5
3	56	37	77.0	21.0	37.5
	31	23	78.4	24.7	42.0
8	32	29	77.2	36.0	45.0
	24	25	77.3	46.5	45.0
12	42	28	79.8	22.5	45.0
	44	26	79.2	24.0	40.5
Median	43.5	28.5	77.5	25.7	41.3
Range	28.0-44.0	27.0-58.0	77.1-79.5	22.9-41.3	38.3-45.0

A - Adjacent to areas of white matter oedema.

B - Equivalent areas in opposite hemisphere but without adjacent white matter oedema.

C - Areas in baboons with injury but no oedema.

Median and range derived from the average of multiple values obtained in individual animals.

TABLE XIV

RESPONSE TO ARTERIAL HYPOTENSION IN WHITE MATTER
CONTROL (C) & EXPERIMENTAL (E) VALUES

Exp. No.	A SAP (mm Hg)		CPP (mm Hg)		$rCBF_w$ (ml/min. 100G)		CVR (mm Hg/ml/ min.100G)		%ΔCVR	B $rCBF_w$ (ml/min. 100G)		CVR (mm Hg/ml/ min.100G)		%ΔCVR
	C	E	C	E	C	E	C	E		C	E	C	E	
4	92	67	82	54	9 18	7 13	5.86	5.40	8	11 22	10 17	4.82	3.86	20
5	92	68	91	65	17 12	15 11	6.07	4.33	29	14 14	12 13	6.50	5.00	23
6	87	63	79	51	16	14	4.94	3.64	38	14	16	5.64	3.19	77
7	98	72	94	70	23	20	4.09	3.50	17	28	23	3.36	3.04	10
9	118	72	115	70	11	10	10.45	7.00	49	20	18	5.75	3.89	48
10	97	73	81	55	21	20	3.84	2.75	40	14	12	5.78	4.59	26
11	113	72	103	64	16	11	6.44	5.82	11	18	14	5.72	4.57	25
Median	97.0	72.0	91.0	64.0	16.0	13.0	5.86	4.33	26.0	17.0	14.0	5.72	3.89	26.0
Range	92.0- 118.0	63.0- 73.0	79.0- 115.0	51.0- 70.0	11.0- 23.0	10.0- 20.0	3.84- 10.45	2.75- 7.00	11.0- 49.0	14.0- 28.0	12.0- 23.0	3.36- 6.50	3.04- 5.00	10.0- 77.0
2	C 100	82	88	71	26 32 39 39	25 29 43 33	2.59	2.15	17					
3	110	83	91	66	56 28 18 25	39 20 13 30	2.84	2.54	11					
8	103	65	92	56	15 18 20 20	13 17 20 17	5.11	3.29	37					
12	117	82	113	75	18 13 18	12 7 11	7.06	7.50	6					
Median	106.5	82.0	91.5	68.5	25.0	21.5	3.98	2.92	14.0					
Range	100.0- 117.0	65.0- 83.0	88.0- 113.0	56.0- 75.0	16.0- 34.0	10.0- 33.0	2.59- 7.06	2.15- 7.50	0- 37.0					

Median and range based on average of multiple values obtained in individual animals.

TABLE XV

RESPONSE TO ARTERIAL HYPOTENSION IN GREY MATTER
CONTROL (C) & EXPERIMENTAL (E) VALUES

(Values for SAP and CPP are given in Table XIV)

Exp. No.	A rCBF$_g$ (ml/min. 100G) C	E	CVR (mm Hg/ml/ min.100G) C	E	%ΔCVR	B rCBF$_g$ (ml/min. 100G) C	E	CVR (mm Hg/ml/ min.100G) C	E	%ΔCVR
4	22	14	3.73	3.86	0	30	23	2.73	2.35	+14
6	29	29	2.72	1.76	35	47	47	1.68	1.09	+35
7	69	62	1.36	1.13	17	64	57	1.47	1.23	+16
9	35	32	3.29	2.19	33	54	44	2.13	1.59	+25
10	21	22	3.86	2.50	35	42	39	1.93	1.41	+27
11	31	30	3.32	2.13	36					
Median	30.0	30.0	3.31	2.16	35.0	47.0	44.0	1.93	1.41	25.0
Range	21.0- 69.0	14.0- 62.0	1.36- 3.86	1.13- 3.86	0- 36.0	30.0- 64.0	23.0- 57.0	1.47- 2.73	1.09- 2.35	14.0- 35.0
	C									
2	39 19	43 20	3.03	2.41	20					
3	56 31	39 20	2.07	2.20	0					
8	24 32	21 28	3.29	2.24	32					
12	37 36	21 23	3.05	3.41	12					
Median	33.0	27.5	3.04	2.33	10					
Range	28.0- 44.0	22.0 - 32.0	2.07- 3.29	2.20- 3.41	0- 32.0					

Median and range derived from the average of multiple values obtained in individual animals.

TABLE XVI

RESPONSE TO ARTERIAL HYPERTENSION IN WHITE MATTER
CONTROL (C) & EXPERIMENTAL (E) VALUES

Exp. No.	A SAP (mm Hg)		ICP (mm Hg)		CPP (mm Hg)		$rCBF_w$ (ml/min. 100G)		CVR (mm Hg/ml/ min.100G)		%ΔCVR	B $rCBF_w$ (ml/min. 100G)		CVR (mm Hg/ml/ min.100G)		%ΔCVR
	C	E	C	E	C	E	C	E	C	E		C	E	C	E	
4	70	92	8	10	62	82	15 27	9 18	2.95	5.86	99	10 26	11 22	3.44	4.82	40
5	87	126	5	5	82	121	16 12	21 17	5.86	6.37	9	14 19	15 22	4.82	6.37	32
6	85	110	13	13	72	97	21	21	3.43	4.62	35	18	20	4.00	4.85	21
7	83	115	3	2	80	113	24	21	3.33	5.38	62	31	32	2.58	3.53	37
9	65	129	7	8	58	122	10 14	12 12	4.85	10.17	111	17 25	17 24	2.76	5.81	111
10	87	128	14	18	73	110	18	22	4.06	5.00	23	16	15	4.56	7.33	61
11	98	122	4	5	94	117	15	15	6.27	7.80	24	18	18	5.22	6.50	24
Median	85.0	122.0	7.0	8.0	73.0	113.0	18.0	19.0	4.06	5.86	35.0	18.0	19.0	4.29	6.13	37.0
Range	65.0- 98.0	92.0- 129.0	3.0- 14.0	2.0- 18.0	58.0- 94.0	82.0- 122.0	12.0- 24.0	15.0- 22.0	3.33- 6.27	4.62- 10.17	9.0- 111.0	16.0- 31.0	15.0- 32.0	2.58- 5.22	3.53- 7.33	21.0- 111.0
	C															
2	108	155	12	17	96	138	23 29 44	30 38 53	3.10	3.45	11					
3	97	125	25	34	72	91	29 38 23 15	37 47 25 17	2.67	3.14	18					
8	88	132	10	12	78	120	33 16 20 25	28 16 23 35	3.75	4.62	23					
12	73	117	2	4	71	113	23 14 10 13 22	27 18 13 18 29	4.73	5.65	19					
Median	92.5	128.5	11.0	14.5	75.0	116.5	24.0	28.0	3.41	4.04	19.0					
Range	73.0- 108.0	117.0- 155.0	2.0- 25.0	4.0- 34.0	71.0- 96.0	91.0- 138.0	15.0- 31.0	20.0- 40.0	3.10- 4.73	3.14- 5.65	11.0- 23.0					

Median and range based on average of multiple values obtained in individual animals.

TABLE XVII

RESPONSE TO ARTERIAL HYPERTENSION IN GREY MATTER
CONTROL (C) & EXPERIMENTAL (E) VALUES

(Values for SAP, ICP and CPP are given in Table XVI)

Exp. No.	A $rCBF_g$ (ml/min. 100G) C	E	CVR (mm Hg/ml/ min.100G) C	E	%ΔCVR	B $rCBF_g$ (ml/min. 100G) C	E	CVR (mm Hg/ml/ min.100G) C	E	%ΔCVR
4	18	22	3.44	3.73	8	33	30	1.88	2.73	45
6	38	35	1.89	2.77	47	59	57	1.22	1.70	39
7	73	73	1.10	1.55	41	65	54	1.23	2.09	70
9	31	29	1.87	4.21	125	39	29	1.49	4.21	183
10	26	24	2.81	4.58	63	46	45	1.59	2.44	54
11	38	28	2.47	4.18	69					
Median	35.0	29.0	2.18	3.96	55.0	46.0	45.0	1.49	2.44	54.0
Range	18.0-73.0	22.0-73.0	1.10-3.44	1.55-4.58	8.0-125.0	33.0-65.0	29.0-57.0	1.22-1.88	1.70-4.21	39.0-183.0
	C									
2	44	53	2.18	2.60	19					
3	38	47	2.48	2.60	5					
	19	23								
8	33	29	2.60	4.00	54					
	27	31								
12	31	36	2.37	3.05	29					
	29	37								
Median	30.0	36.0	2.43	2.88	24.0					
Range	29.0-44.0	30.0-53.0	2.18-2.60	2.60-4.00	5.0-54.0					

Median and range derived from the average of multiple values obtained in individual animals.

TABLE XVIII

RESPONSE TO HYPERCAPNIA IN WHITE MATTER
CONTROL (C) & EXPERIMENTAL (E) VALUES

Exp. No.	A $PaCO_2$ (mm Hg)		ICP (mm Hg)		$rCBF_w$ (ml/min. 100G)		$\frac{\Delta CBF}{\Delta PaCO_2}$	B $rCBF_w$ (ml/min. 100G)		$\frac{\Delta CBF}{\Delta PaCO_2}$
	C	E	C	E	C	E		C	E	
4	38	58	20	39	5	4	0	9	11	0
					10	8		17	15	
5	41	62	5	18	11	15	0.17	12	11	0.19
					9	12		18	26	
6	40	74	35	47	18	29	0.32	20	17	0
7	42	51	2	16	19	30	1.22	32	50	2.33
9	39	62	6	26	5	7	0.09	13	18	0.26
					4	7		20	28	
10	40	57	23	28	23	26	0.18	13	19	0.35
11	41	60	11	22	18	21	0.16	19	21	0.11
Median	40.0	60.0	11.0	26.0	18.0	21.0	0.17	17.0	19.0	0.19
Range	38.0-42.0	57.0-74.0	2.0-35.0	16.0-47.0	5.0-23.0	6.0-30.0	0-1.22	13.0-32.0	13.0-50.0	0-2.33
	C									
2	40	53	11	28	21	28	0.92			
					23	33				
					40	66				
					28	31				
3	41	56	31	52	37	66	0.67			
					25	26				
					17	23				
					28	31				
8	40	67	14	26	13	13	0.19			
					17	16				
					24	33				
					23	35				
12	38	54	4	28	13	21	0.88			
					7	21				
					12	21				
					25	49				
Median	40.0	55.0	12.5	28.0	23.0	33.0	0.78			
Range	38.0-41.0	53.0-67.0	4.0-31.0	26.0-52.0	14.0-28.0	24.0-40.0	0.19-0.92			

Median and range derived from the average of multiple values obtained in individual animals.

TABLE XIX

RESPONSE TO HYPERCAPNIA IN GREY MATTER
CONTROL (C) & EXPERIMENTAL (E) VALUES

(Values for $PaCO_2$ and ICP are given in Table XVIII)

Exp. No.	A $rCBF_g$ (ml/min. 100G) C	E	$\frac{\Delta CBF}{\Delta PaCO_2}$	B $rCBF_g$ (ml/min. 100G) C	E	$\frac{\Delta CBF}{\Delta PaCO_2}$
4	17	16	0	24	32	0.40
6	35	44	0.26	55	62	0.21
7	78	88	1.11	60	77	1.89
9	20	21	0.43	22	95	0.13
10	24	28	0.11	42	47	0.14
11	30	39	0.47			
Median	27.0	33.5	0.45	42.0	47.0	0.21
Range	17.0-78.0	16.0-88.0	0-1.11	22.0-60.0	25.0-77.0	0.13-1.89
	C					
2	40 20	66 29	1.38			
3	23 37	25 66	1.06			
8	25 29	26 28	0			
12	26 28	34 32	0.38			
Median	28.5	40.0	0.72			
Range	27.0-30.0	27.0-48.0	0-1.58			

Median and range derived from the average of multiple values obtained in individual animals.

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