RAISED INTRACRANIAL PRESSURE AND THE CEREBRAL CIRCULATION

BY

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FACULTY OF SCIENCE

Dear Professor Lenihan,

Professor Lindsay T.D. Symon, Institute of Neurology,
The National Hospital, Queen Square, London, WC1N 3BG

has intimated his willingness to act as Exa
Ph.D. application by John O. Rowan.

Yours sincer

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DECLARATION

This thesis has been written entirely by myself. I had overall responsibility for the scientific component of the work, the methods of measurement, and the methods of data analysis used in the experiments described. Neurosurgical collaboration was provided initially by Mr. I. H. Johnston, Neurosurgeon, Royal Alexandra Hospital for Children, Sidney, Australia (formerly Senior Registrar in the Division of Neurosurgery, Institute of Neurological Sciences, Glasgow) and latterly by Mr. Graham Teasdale, Senior Lecturer, University Department of Neurosurgery, Institute of Neurological Sciences, Glasgow.

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SUMMARY

The first five chapters of the thesis review the literature on intracranial pressure, the cerebral circulation and their inter-relation and set the scene for the experimental work which is described in chapters 6 to 11. Intracranial pressure is now measured routinely in many clinical centres but a great deal of caution is required in interpreting the results, particularly with respect to the method of measurement, the history of any raised pressure and the values of other physiological variables such as blood pressure and cerebral blood flow. The cerebral circulation itself displays a remarkable tendency to remain constant, the fundamental concept being that there exists a basic control mechanism which acts to maintain cerebral blood flow in order to meet the metabolic requirements of the brain.

The methods used to measure cerebral blood flow in the work described are metabolically inert gas clearance techniques based on the Fick principle. Hemisphere blood flow in baboons was measured by the xenon-133 intracarotid injection technique while micro-regional blood flow was measured by the hydrogen clearance technique utilising inhalation of hydrogen gas. All pressures were measured by the use of in-dwelling fluid filled catheters and strain gauge pressure transducers.

The effect of raised intracranial pressure on cerebral blood flow was examined in three animal models in which intracranial hypertension was created by different methods, viz:- general diffuse compression, focal supratentorial compression and focal infratentorial compression. These experiments confirm that the effect of raised intracranial pressure on the level of cerebral blood flow depends on the cause of the raised pressure. In each situation there are different effects on compensatory mechanisms such as blood pressure

and cerebral resistance vessel diameter.

The experiments on cerebrovascular pressures and resistances showed for the first time that intracranial pressure represents cerebral venous outflow pressure to within a few mmHg over a wide range of pressure values and also that outflow vascular resistance changes are independent of the cause of intracranial hypertension thus confirming that it is changes in prevenous cerebrovascular resistance which result in the different cerebral blood flow responses observed.

The investigations into the blood pressure response observed during intracranial hypertension have demonstrated quite clearly that neither global cerebral ischaemia nor brain stem ischaemia is the trigger mechanism for the response. The results support the hypothesis that the initiating stimulus is local pressure changes both in the brain stem and spinal cord. Considerable doubt is also cast on the assumption that the role of the blood pressure response is to maintain cerebral blood flow in the face of rising intracranial pressure.

Finally, it has been shown that an intact spinal cord is necessary for the maintenance of cerebral blood flow autoregulation to raised intracranial pressure, while autoregulation to blood pressure changes remains intact. This disassociation of the autoregulatory function has not been previously demonstrated.

INTRODUCTION

It is of the utmost importance that the brain receives an adequate supply of blood during conditions of physiological stress. The level of cerebral blood flow is determined by the pressure differential and the resistance across the cerebrovascular system. This pressure differential (cerebral perfusion pressure) is generally calculated as the difference between mean arterial pressure and mean intracranial pressure, the calculation relying on the assumption that intracranial pressure represents the effective cerebral venous outflow pressure. Cerebrovascular resistance is calculated from the ratio of cerebral perfusion pressure to cerebral blood flow.

The brain possesses the unique characteristic of being enclosed within a rigid skull. Intracranial pressure can increase in certain conditions and may in fact rise to levels approaching arterial pressure. Cerebral blood flow is maintained approximately constant as the arterial pressure is varied down to a lower limit of approximately 60 mmHg and up to a higher limit of 130 mmHg. Beyond the lower limit cerebral blood flow falls while above the higher limit it increases. The maintenance of cerebral blood flow during arterial blood pressure changes is called autoregulation. It has also been demonstrated that cerebral blood flow can be maintained at a constant level when cerebral perfusion pressure has been decreased as a result of rising intracranial pressure until an upper intracranial pressure threshold is reached. The maintenance of cerebral blood flow during raised intracranial pressure is also considered to be a form of autoregulation.

The main aims of the experimental work described in the thesis has been to examine the effects of raised intracranial pressure on the other components of the cerebral circulation, i.e. cerebral blood flow, blood pressure, cerebral perfusion pressure and cerebrovascular

resistance. Special emphasis has been placed on studying the effects of different causes of raised intracranial pressure. The outflow pressure and vascular resistance differentials were studied over a wide range of intracranial pressure levels and the mechanism and function of the blood pressure response during intracranial pressure were investigated. Differences in the pattern of cerebral blood flow autoregulation to changes in arterial pressure and to changes in intracranial pressure were examined.

The literature on these topics is reviewed in the first five chapters in order to provide the background to the experimental work which is described in the following six chapters. The final chapter summarises the discussion on all the results obtained and considers the conclusions which can be drawn from each study.

CHAPTER 1

INTRACRANIAL PRESSURE

The Monro-Kellie doctrine expounded by Monro in 1783 (1) and supported by Kellie in 1824 (2) stated that the spino-cranial compartment was rigid and could not expand. According to this concept the cranial cavity could be considered as a rigid sphere filled to capacity with brain tissue and blood, both of which were incompressible, so that if the volume of brain tissue did not change then the volume of blood within the head must also remain constant. In this early form the doctrine did not take cognisance of the presence of cerebrospinal fluid and it was later modified by Burrows in 1846 (3) who stated that an increase or decrease in the size of one or more spaces within the spino-cranial cavity results in equal and opposite changes in the size of other spaces so that the total volume remains the same.

As a result of experiments in animals Duret in 1878 (4) categorised four grades of cerebral compression resulting from an expanding intracranial lesion. During grade one compression, expansion of the lesion was compensated by absorption of cerebrospinal fluid, compression of intracranial veins and utilisation of the elastic properties of the walls of the craniospinal compartment. During cerebral compression at the grade two and grade three levels, elevation of the blood pressure with bradycardia occurred and cerebral blood flow was reduced. With grade four compression intracranial pressure exceeded arterial pressure, cerebral blood flow stopped and blood pressure fell with resultant apnoea. These ideas were later supported by Von Bergmann, 1885 (5), and Bayliss et al, 1895 (6).

Kocher, in 1901 (7), took the four stages of cerebral compression classified by Duret and expressed them in clinical terms with reference to the expansion of brain tumours. He stated that during stage one the initial increase in the volume of the brain tumour was

compensated mainly by the reduction in volume of cerebrospinal fluid and venous blood resulting therefore in neither an increase in intracranial volume nor pressure. At stage two the compensation mechanisms had become exhausted, intracranial pressure increased and the patient became drowsy and suffered headaches. When stage three was reached intracranial pressure had increased considerably, conscious level had also decreased and there were intermittent increases in blood pressure accompanied by bradycardia. Finally at stage four the patient became deeply unconscious and blood pressure began to fall and death ensued.

Cairns, in 1939 (8), suggested that there could be four causes of raised intracranial pressure resulting from an expanding lesion.

(1) Increase in tumour size.

(2) Increase in the water content of the brain surrounding the tumour, i.e. cerebral oedema.

(3) Increase in the quantity of cerebrospinal fluid in the lateral ventricles of the brain as a result of obstruction of the cerebrospinal fluid absorption pathways.

(4) Increase in intracranial blood volume due either to venous obstruction or active dilatation of blood vessels resulting from episodes of hypoxia or hypercapnia.

Intracranial Pressure Measurement

Intracranial pressure has been assessed largely by the measurement of cerebrospinal fluid pressure although some workers have used a fluid-filled tambour inserted into the subdural space while others have used implanted transducers in the subdural and epidural space (9). Ideally, measurement of CSF pressure should involve negligible movement of fluid during measurement. This situation is achieved by modern pressure transducers.

The upper limit of CSF pressure in the normal subject is often considered to be 200 mmH_2O (14.7 mmHg). Pressures above this limit

are categorised as hypertensive. This level refers to the pressure measured with the patient in the lateral recumbent position with needles in the lumbar sac, cisterna magna or lateral ventricle. Similar values have been reported in experimental animals.

The measured pressure waveform exhibits both a cardiac pulse variation and a respiratory variation. The amplitudes of these variations are of the order of 1 mmHg and 2.5 mmHg respectively, the former being at a frequency of 1 Hz while the frequency of the latter is approximately 0.05 Hz. If damping could be avoided the measured variations could be larger, e.g. 1.5 mmHg and 4.4 mmHg respectively. A rise in the CSF pressure results in an increase in amplitude of both the cardiac and respiratory variations. When the CSF pressure is high the venous pressure is also high and the pulsatile increase in diameter of the blood vessels can no longer be so easily compensated by venous collapse. The arterial pressure changes are therefore not so strongly damped and this results in a higher fluid pulse pressure.

The CSF pressure in the normal subject varies a great deal, e.g. a cough can raise the pressure from 1.8 mmHg to 14.7 mmHg and a sneeze can increase it to 20 mmHg. During a vigorous Valsalva manouevre intracranial pressure can be raised to 70 mmHg. The mean level of CSF pressure in the normal subject, however, is reproducible to within 2 to 3 mmHg from day to day.

Pressure Gradients

Pressure in an extradural mass may be many times the pressure recorded in the remainder of the intracranial space because the dura is highly elastic. The cortical surface of the brain with its dense network of blood vessels could also have significant elastic properties which would resist displacement and deformation. The rest of the brain, however, is probably more plastic than elastic so that it is easily deformed and displaced by mass lesions and sustained

pressure differences are unlikely to develop within its substance.

The existence of inter-compartmental pressure gradients in conditions of intracranial hypertension has been reported by many workers (10, 11, 12). These pressure gradients occur between supratentorial and infratentorial compartments across the tentorium cerebelli or between infratentorial and spinal compartments across the foramen magnum and develop because displaced brain tissue eliminates subarachnoid spaces. The differences in pressure can be abolished if the subarachnoid space is reconstituted (13). In this situation it is important to differentiate between cause and effect since it is displacement of brain substance which results in substantial pressure gradients and not the reverse.

The situation is more obscure, however, when one considers the possibility of intra-compartmental pressure gradients. Within recent years there have been several reports of the development of pressure differentials within the supratentorial compartment during raised ICP (14, 15). The precise characteristics of the differentials appear to depend on the sites at which pressure is measured. These pressure gradients have been measured extradurally and in some cases the size and direction has been quite variable and may only reflect the variations in transmission in pressure across the dura due to the physical characteristics of the membrane and its attachment to the cranium. Measurements of relatively low extradural pressure in patients have shown that they may not correspond completely to intra-ventricular pressures (16).

Other investigations have shown that when extradural pressures are increased by addition of fluid to the extradural space, these pressures are transmitted to the subdural space in a variable manner (13). The demonstration of intra-compartmental pressure gradients employing extradural pressure transducers cannot therefore be accepted as completely reliable evidence of the existence of such gradients.

In contrast, if the subarachnoid space is patent an increase in pressure resulting from the addition of fluid to that space should be transmitted freely. Also with a patent subarachnoid space there should be equalisation of pressure within a short time period when ICP is raised in any way so that a pressure gradient should exist only transiently. Pascall's Law dictates, that when the ventricular CSF is in communication with the subarachnoid CSF pressure will be uniform throughout the whole fluid system.

The whole question of intra-compartmental pressure gradients depends on the extent to which pressure within the subarachnoid space represents pressure within the brain substance itself and to what extent pressure within the tissue is transmitted to the rest of the brain.

It would seem likely that prior to brain shift substantial pressure gradients may exist transiently and would be dissipated by the redistribution of the intracranial contents.

Pressure Waves

For some years spontaneous fluctuations in CSF pressure have been described in some patients with intracranial pathology. Guillaume and Janny (17) studied these pressure phenomena in some considerable detail and in particular noted large paraxysmal waves which developed for no apparent reason and were sometimes seen with flushing of the face. They attributed these waves to disturbances in vasomotor control of the cerebral circulation. Lundberg (18) was the first to record intracranial pressure continuously for long periods of time in patients with space occupying intracranial pathology. He recorded intraventricular fluid pressure on a strip chart recorder for periods of days to one week in 48 pre-operative patients with intracranial tumours.

Three types of pressure waves were described, viz. A, B and C. Only the A waves were found to be of clinical significance. The A

waves can be divided into two types.

(1) Arrhythmic fluctuations in pressure occurring at 15 to 30 minute intervals.

(2) Plateau waves that can persist for much longer periods of time and are particularly prone to produce severe neurological signs.

Often there was no change in the patient's clinical status during pressure increases as high as 80 mmHg. At other times, and almost always when the pressure exceeded 80 mmHg, the patient had attacks that began as the pressure wave approached its peak and subsided rapidly as the pressure fell. The plateau waves often rose to 120 to 140 mmHg at which time the patient was in danger of dying. Evacuation of ventricular fluid was accompanied by a prompt fall in pressure and clinical improvement. The pressure waves could be aborted or sharply reduced at their peak by removal of ventricular fluid. High power ventilation was equally effective in most of Lundberg's cases. Although the pressure waves usually occurred spontaneously, they could be induced by hypoxia or hypercapnia. Induction of pressure waves by hypoxia and hypercapnia, the response to hyperventilation and their enhancement by an arterial response favour alterations in cerebral blood volume as the most likely cause. Hypoxia and hypercapnia dilate cerebral vessels and in normal man and animals cause a small increase in intracranial pressure. On the vertical portion of the volume-pressure graph, however, this small increase in blood volume can produce an enormous increase in pressure. Reversal of the vaso-dilatation by hyperventilation produces an equally large and prompt fall in pressure. Whenever most of the displaceable CSF has been eliminated from the intracranial space, from whatever cause, slight changes in cerebrovascular diameter and cerebral blood volume produce enormous changes in pressure. Thus mild respiratory insufficiency that may have no effect on brain function in normal patients, can cause severe intracranial hypertension and a critical reduction in

cerebral blood flow. The origin of pressure waves that occur in adequately ventilated patients is unknown but those who have studied the problem have attributed them to an instability of cerebral vasomotor tone.

CHAPTER 2

THE CEREBRAL CIRCULATION AND ITS CONTROL

The Cerebral Circulation

Cerebral metabolism depends on the aerobic combustion of glucose for its energy supply. Disturbances of the cerebral circulation, even of short duration, can have profound effects on neurological and mental functions since very little oxygen and glucose is stored. After complete cessation of cerebral blood flow consciousness will exist for less than 10 seconds.

The cerebral blood flow in normal man is, on the average, 54 ml/100g/min, i.e. 750 ml per minute in the adult brain. The corresponding oxygen consumption is 3.3 ml per 100g of brain tissue or 45 ml per minute for the whole brain. The brain, representing about 2% of the total body weight, receives 16% of the cardiac output and uses up about 20% of the oxygen consumption of the whole body. Flow in grey matter is about 3 to 4 times greater than flow in white matter.

The brain in man is supplied with blood via the two internal carotid arteries in the neck and by the two vertebral arteries. At the base of the cerebral hemispheres the circle of Willis with its six large branches unites these input arteries forming a distributive manifold for blood and from there branches project into the brain tissue. Generally speaking, the internal carotid arteries supply blood to the anterior and middle portions of the brain on the right and left sides, while the vertebral arteries united into the basilar artery supply blood to the occipital lobes and the posterior fossa structures. In normal situations there is little cross-over of blood between the right and left halves of the circle of Willis, probably as a result of a lack of pressure differential.

The superficial and deep cerebral veins open into the venous sinuses. These spaces are situated between the folds of the dura mater

or between the dura and bone. The openings of the larger cerebral veins into these sinuses have no valves. They are kept patent by the structure of the dura around the orifices. The most important output pathways for blood leaving the brain are the internal jugular veins. Blood may also leave by anastomoses with the orbital and pterygoid plexuses of veins, by means of emissary vessels passing through the cranium, and by channels which join the vertebral plexus of veins. There is considerable mixing of the venous blood draining from the two halves of the brain.

Elastic fibres are more numerous in cerebral arteries than in vessels in other parts of the body. The cerebral veins have extremely thin walls composed largely of connective tissue. Cerebral arteries and veins are accompanied by myelinated and unmyelinated nerve fibres. It is believed that the unmyelinated fibres carry vasomotor impulses while the myelinated fibres are thought to be sensory afferents. The internal carotid and vertebral arteries are innervated by sympathetic fibres (constrictor) while the pericarotid plexus is innervated by parasympathetic fibres (vasodilator). The degree of functional activity of these fibres in man is still uncertain.

Grey matter has a richer supply of blood vessels than does white matter which is consistent with the higher rate of metabolism in grey matter.

Control of the Cerebral Circulation

It is generally known that a change in certain physiological variables will alter cerebral blood flow but there is a great deal of uncertainty concerning the underlying mechanisms.

Effect of Blood Pressure

The cerebral perfusion pressure is defined as mean arterial blood pressure minus mean cerebral venous blood pressure. The pressure in the cerebral veins will be influenced by the intracranial pressure and vice versa. Blood flow in the normal brain is autoregulated in

response to changes in arterial blood pressure. In other words, a relatively constant blood flow is maintained in face of changing perfusion pressure. In fact, cerebral blood flow will not alter significantly until the mean arterial blood pressure has dropped below 70 mmHg. Thereafter it will fall passively with blood pressure (19). If blood pressure rises beyond 130 mmHg cerebral blood flow will increase (20) - the so called breakthrough penomenon.

By observing the pial blood vessels through a window in the skull Forbes in 1928 in the United States (21) and Fog in 1937 in Copenhagen (22) were able to demonstrate that when arterial blood pressure is reduced the pial arteries and arterioles dilate and when arterial blood pressure is increased these blood vessels constrict. The changes in vascular resistance resulting from these changes in vessel calibre maintains blood flow relatively constant during changes in blood pressure. The time taken for these changes in vessel calibre to occur after an instantaneous change in blood pressure is of the order of 30 seconds to 2 minutes.

Autoregulation is a characteristic of the normal brain in man and in animals. In the abnormal brain, however, autoregulation can be diminished or completely abolished. Ischaemic brain damage resulting from reduced cerebral perfusion pressure results in loss of autoregulation and Harper (19) has shown that autoregulation to blood pressure changes may be severely reduced in the presence of cerebral vasodilatation resulting from hypoxia or hypocapnia. In fact, the autoregulation mechanism is very sensitive and can be easily upset.

Autoregulation Mechanism

The initiating mechanism for the vasodilatation and constriction of cerebral blood vessels still remains uncertain. There are, however, three classical theories.

According to the myogenic theory, the cerebral arteries and arterioles have smooth muscle tone, inherently, such that an increase

in distension pressure will give rise to contraction while the reverse will result in dilatation. This is known as the Bayliss effect.

The protagonists of the metabolic theory, on the other hand, claim that there is a transient reduction in cerebral blood flow when blood pressure falls and this results in a fall in tissue pO_2. There will then be an increase in tissue pCO_2 and a drop in tissue pH. Since it is known that all of these changes can cause cerebral vasodilatation, it is suggested that one or all of these variables may act to control the diameter of the cerebral arterioles thus maintaining constant blood volume.

There is a great deal of evidence that there is a nerve supply to cerebral blood vessels. However, although all the main arteries supplying blood to the circle of Willis have a rich adrenergic supply this is not so pronounced in the case of the cerebral arterioles and smaller cerebral arteries. Eidelman et al (23) have claimed that autoregulation can be impaired after cervical sympathectomy while Nanda et al (24) have shown that autoregulation can be intact several weeks after cervical sympathectomy. Furthermore, it has been shown that autoregulation can be preserved in patients with idiopathic orthostatic hypotension (25).

Although early studies on the effect of sympathetic stimulation on pial artery diameter indicated slight vasoconstriction (26, 27), the generally held view until recently has been that the cerebral circulation is independent of neurogenic influences. Nevertheless, these nerve fibres which are present must have some function. It is worthy of note that the cerebral blood flow/carbon dioxide response is reduced when the sympathetic nerve in the neck is stimulated (28, 29). It has been proposed by Harper et al (30) that this could be due to constriction of the major arteries supplying the brain. These arteries have a dense adrenergic nerve supply. If they were constricted this would not normally cause a reduction in cerebral

blood flow. When there is a pre-existing vasodilatation, however, such as when pCO_2 is raised, constriction of these arteries will reduce blood flow. Nevertheless, the function of the autonomic nerve supply to the cerebral blood vessels remains uncertain.

Effect of Carbon Dioxide

Changes in the partial pressure of carbon dioxide in the arterial blood ($paCO_2$) have a pronounced influence on the cerebral circulation. Cerebral blood flow will increase and decrease as the $paCO_2$ rises and falls. Increasing $paCO_2$ from the normal value of 40 mmHg to 80 mmHg will increase cerebral blood flow by more than a factor of 2. Again, lowering $paCO_2$ to 20 mmHg from 40 mmHg will half the blood flow. Below 20 mmHg and above 80 mmHg there is very little change in flow. If the changes in $paCO_2$ occur suddenly the increases in flow can be greater such that the gradient of the CBF/$paCO_2$ graph between 20 and 80 mmHg can be 3 ml/100g/min per mmHg. When the $paCO_2$ is raised slowly the value of the gradient is of the order of 1.5 ml/100g/min per mmHg. If the $paCO_2$ level is kept high for long periods the cerebral blood flow will tend to fall back to normal values.

When blood pressure is low the cerebral blood flow/carbon dioxide response is reduced or indeed absent if the blood pressure is severely reduced. After subarachnoid haemorrhage the cerebral blood flow/carbon dioxide response can be lost in the region of the brain which is affected.

The cerebral blood flow/carbon dioxide reactivity can be considered as being under the control of three possible mechanisms.

Carbon dioxide can cause relaxation of isolated vascular smooth muscle and it is possible therefore that it could act directly on the smooth muscle of the blood vessels in the brain. It has also been suggested that carbon dioxide can act by changing the pH of the extracellular fluid of the brain or, indeed, of the vascular smooth

muscle itself. The basic idea is that carbon dioxide can collect locally in areas of increased cerebral metabolism or during hypercapnia or can diffuse rapidly across the capillaries and enter the extracellular fluid causing an increase in the hydrogen ion concentration surrounding the cerebral arterioles thus causing vasodilatation. The third suggestion is that carbon dioxide reactivity is under neurogenic control. However, present evidence favours a local metabolic control mechanism.

It should be noted that there can be situations where carbon dioxide reactivity is present while autoregulation to cerebral perfusion pressure changes has been lost.

Effect of Oxygen

A fall in the partial pressure of oxygen in the arterial blood (paO_2) can result in an increase in cerebral blood flow and vice versa. However, it is only at a paO_2 below 50 mmHg that these effects are demonstrated. When the paO_2 falls to 30 mmHg the flow is approximately doubled. Raising the paO_2 above 50 mmHg changes the cerebral blood flow only very slightly.

Again in this situation the mechanism is uncertain. It has been demonstrated that oxygen can act directly on isolated perfused vessels. When the perfusate had a low pO_2 dilatation was observed. Furthermore, it has been observed that when cerebral blood flow is increased when the paO_2 is below the threshold level of 50 mmHg, there is a decrease in pH on the cortical surface. It would appear, therefore, that there is a possibility that hypoxia can increase the hydrogen ion concentration in the cerebral extracellular fluid resulting in vasodilatation of the cerebral arterioles.

Effect of Intravascular Hydrogen Ion Concentration

Provided $paCO_2$ does not change, variations in intravascular pH do not affect cerebral blood flow (31). During metabolic acidosis and alkalosis only slight changes in extracellular fluid pH have been

demonstrated and flow has remained constant. There is no doubt, however, that extracellular fluid pH changes can have an effect on the diameter of cerebral arterioles with low pH solutions causing dilatation and high pH solutions constriction.

Functional Changes in the Brain

There is mounting evidence that alterations in cerebral function can be accompanied by cerebral blood flow changes, e.g. it has been demonstrated that light stimulation can result in the increase in flow in the occipital lobe of the brain of the cat. Use of analeptic drugs can result in increases in cerebral blood flow and cerebral oxygen uptake. Mental stimulation can cause changes in the pattern of regional cerebral blood flow (32, 33).

It has been assumed that when a particular region of the brain is functioning at a higher rate than normal, that there is a higher regional utilisation of oxygen which would be necessary for the increased metabolic requirements. An increase in the carbon dioxide output would then result with consequent regional cerebral vaso-dilatation due to extracellular fluid pH changes. Regional cerebral blood flow would then be maintained at an adequate level.

Effect of Haemotcrit and Viscosity

Severe anaemia can result in increased cerebral blood flow but it is not clear whether this is due to the anaemia itself or to the effect of reduced arterial pO_2.

Infusion of packed red cells or high molecular weight dextran increases blood viscosity and causes a reduction in the carbon dioxide reactivity of the cerebral vessels.

Effect of Temperature

It has been reported that a decrease in cerebral blood flow of the order of 7% will occur for $1^{o}C$ fall in oesophageal temperature. (34).

Summary

The cerebral circulation displays a remarkable tendency to remain

constant. Hypercapnia, hypoxia and extreme levels of arterial blood pressure and intracranial pressure, however, have profound effects. The fundamental concept is that there is a basic control mechanism for maintaining blood flow to meet the metabolic requirements of the brain. The most generally accepted hypothesis, at present, is that, in the main, control is exercised through the pH of the cerebral extra-cellular fluid.

CHAPTER 3

THE MEASUREMENT OF CEREBRAL BLOOD FLOW

Although the first attempt to measure cerebral blood flow in man was made by Ferris in 1941 (35) - by observing the displacement of spinal fluid caused by compression of the two jugular veins - it was not until Kety developed the inert gas method for the measurement of cerebral blood flow in 1945 (36) that blood flow in human and animal brains was studied intensively. This technique is based on the Fick Principle and from it are derived many of the techniques which are used today.

This chapter will concentrate mainly on these derived techniques which employ diffusible indicators.

Fick Principle

This principle states that the quantity, Q, of a substance taken up by an organ at a specific time, t, is the product of the blood flow, F, and the arterio-venous difference for that substance at that time, $C_{at} - C_{vt}$.

$$\text{i.e.} \quad Q_t = F(C_{at} - C_{vt}) \tag{3.1}$$

$$F = \frac{Q_t}{C_{at} - C_{vt}} \tag{3.2}$$

The flow in a period, T, can be found by integration.

$$\text{i.e.} \quad F = \frac{\int_o^T Q_t.dt}{\int_o^T (C_{at} - C_{vt})dt} \tag{3.3}$$

If C_{Bt} is the concentration of the substance in brain tissue at time, t, and W_B is the weight of brain tissue then

$$Q_t = C_{Bt}.W_B \tag{3.4}$$

If equilibrium is reached within the time, T, the concentration of the substance in the brain tissue will be equal to the final venous concentration C_vT multiplied by a constant, λ, the partition

coefficient (which expresses the ratio of the solubility of substance in brain tissue and blood).

$$\text{Hence } F = \frac{C_vT.W_B.\lambda}{\int_o^T (C_{at} - C_{vt})dt} \qquad (3.5)$$

(The brain concentration will be exactly equal to the final venous concentration only where the solubility of the tracer in brain tissue and in blood are equal, i.e. when $\lambda = 1$.)

$$\frac{F}{W_B} = \frac{C_{vt}.\lambda}{\int_o^T (C_{at} - C_{vt})dt} \qquad (3.6)$$

It has become the custom to express cerebral blood flow measurements in ml/100g weight of tissue/min.

The Kety and Schmidt Nitrous Oxide Technique

Kety realised that the brain absorbs, by physical solution, an inert gas, such as nitrous oxide, which reaches it via the arterial blood. His subjects inhaled a low concentration of nitrous oxide over a period of 10 minutes. During this time a series of blood samples were taken from an artery and from the internal jugular vein. These were analysed for nitrous oxide content. At the end of the 10 minute inhalation period the arterial blood, brain tissue and cerebral venous blood were in equilibrium containing approximately equal amounts of nitrous oxide. Flow could then be calculated using equation (3.6).

There have been a number of modifications to the original method, e.g.

(1) Continuous withdrawal of blood samples during the inhalation period to give integrated arterial and venous concentrations of the indicator (37).

(2) Use of radioactive Krypton-85 instead of nitrous oxide (38). The main advantage here was that the concentration of Krypton-85 in the blood samples could be measured by the detection of beta

radiation employing Geiger-Müller tubes. This avoids the tedious measurement of nitrous oxide.

(3) Use of the desaturation curve instead of the saturation curve (39,40). This modification eliminates the need for precise control of indicator concentration during inhalation and reduces the effect of extracerebral contamination of the jugular bulb samples.

Disadvantages and Advantages of the Kety-Schmidt Technique

The method gives an average blood flow over the 10-15 minutes saturation or desaturation period. If the blood flow is low, equilibrium between brain and blood will probably not occur in this period of time and as a result blood flow will be over estimated. This inaccuracy can be reduced somewhat by employing indicators of lower blood solubility, e.g. Krypton-85 instead of nitrous oxide. Lassen and Munck introduced a correction factor to extrapolate the arterio-venous difference to infinity (38).

Furthermore, the method also depends on whether internal jugular bulb blood samples are representative of cerebral venous drainage. It has been calculated that, except on rare occasions, only 3% of the blood from the internal jugular bulb comes from extracranial sources (41).

Lassen and Klee (40) concluded that subjects should inhale Krypton-85 for at least 15 minutes if flow was expected to be normal but this might have to be extended to 30 minutes if blood flow was severely reduced. Multiple arterial and jugular venous blood samples should be taken and the resultant arterio-venous difference extrapolated to infinity. They suggested that alternatively, following a 30 minute saturation period, McHenry's desaturation technique should be used; the arterio—venous difference also being extrapolated to infinity. These suggestions would result in considerable beta-radiation doses to the lungs and today it would be much more satisfactory to use xenon-133.

One great advantage of the Kety-Schmidt technique is that it allows investigation of cerebral metabolism from measurements of cerebral arterio-venous differences of oxygen, glucose and other metabolites.

Measurement of Regional Cerebral Blood Flow By Analysis of the Clearance Rates of Inert Gases following Carotid Artery Injection

The Kety-Schmidt method gives an average measurement of cerebral blood flow expressed as total blood flow per unit weight of brain tissue. In 1961 Lassen and Ingvar reported a method for the determination of local cerebral blood flow (42). The method involved the measurement of rate of clearance of beta-radiation from the exposed cerebral cortex using a Geiger-Müller tube after Krypton-85 dissolved in saline had been injected into the carotid artery. This method was later adapted by Glass and Harper (43) so that regional cerebral blood flow in man could be measured by externally monitoring the clearance of gamma ray activity after injection of xenon-133.

Theory of Inert Gas Clearance Method

The tracer employed should be metabolically inert and should be able to diffuse rapidly between blood and tissue. The radioisotopes commonly used are:-

(a)	Krypton-85:	Half life	- 10.6 years
		Main emissions	- 670 KeV, beta-radiation
			510 KeV, gamma radiation
(b)	Xenon-133:	Half life	- 5.27 days
		Main emission	- 81 KeV, gamma radiation

The beta rays from Krypton-85 have a maximum range in tissue of only 2.6 mm. Beta counting techniques are therefore limited to the measurement of flow in the exposed brain cortex.

Only 0.4% of the total Krypton-85 disintegrations result in the emission of 510 KeV gamma radiation, giving rise to low count rates and the requirement for considerable amounts of lead for collimation

to define the filed of view at this energy. As a consequence xenon-133 has been more widely used in recent years.

Since, after injection has ceased, the arterial blood contains no tracer, the Fick equation for the clearance technique can be written as:-

$$dQ = -F.C_v.dt \qquad (3.7)$$

where dQ = the change of quantity of tracer in the tissue in time dt.

F = blood flow.

C_v = the venous concentration of the tracer.

$$Q = C_B.W_B$$

where C_B is the concentration of the tracer in tissue and W_B is the weight of brain tissue.

Therefore $$dC_B = \frac{-F.C_v}{W_B}.dt \qquad (3.8)$$

$$C_v = \frac{C_B}{\lambda}$$ where λ is the partition coefficient.

$$\frac{dC_B}{C_B} = \frac{-F}{W_B.\lambda}.dt \qquad (3.9)$$

The solution of this differential equation is

$$C_B = C_{BO}.e^{-\frac{F}{W_B.\lambda}.t} \qquad (3.10)$$

where C_{BO} is the concentration at time 0.

(3.10) is an equation of an exponential decay and will result in a straight line when points are plotted on semi-log paper. In fact, two exponential components can be extracted from the clearance curve obtained from a normal brain after intracarotid injection. These are taken to represent the distribution of flows in grey and white matter of the brain. The exponential stripping process can be carried out manually by plotting the clearance curve on semi-log paper and fitting a straight line to the latter part of the curve. This defines the slow

component and by subtraction from the initial part of the curve the fast component can be found. This, of course, can be done more accurately and more quickly using a computer (44).

The slopes of the two components can be expressed as half times ($T_{\frac{1}{2}}$), (the time taken for any point on the graph to decrease to another of half its value). From these $T_{\frac{1}{2}}$ values, flow values can be calculated for grey and white matter using the following equations.

$$\text{Flow (grey matter) (ml/100g/min)} = \frac{\lambda_g . \log_e 2.100.60}{T_{\frac{1}{2}} \text{ (fast component)}} = \frac{3370}{T_{\frac{1}{2}} \text{ (fast component)}} \qquad (3.11)$$

$$\text{Flow (white matter) (ml/100g/min)} = \frac{\lambda_w . \log_e 2.100.60}{T_{\frac{1}{2}} \text{ (slow component)}} = \frac{6237}{T_{\frac{1}{2}} \text{ (slow component)}} \qquad (3.12)$$

where $T_{\frac{1}{2}}$ = half time in seconds.

λ_g = the partition coefficient for grey matter = 0.81 for xenon-133.

λ_w = the partition coefficient for white matter = 1.5 for xenon-133.

The mean cerebral blood flow through the whole region of the brain under study can be calculated from the peak count rate obtained and the area under the clearance curve using the formula:-

$$\text{Mean flow } (F_H) \text{ (ml/100g/min)} = \frac{H_{max} . \lambda_B . 100.60}{A_\infty} \qquad (3.13)$$

where H_{max} = the peak count rate of the clearance curve.

A_∞ = the area under the clearance curve extrapolated to infinity.

λ_B = the partition coefficient for whole brain.

This relation was basically formulated by Zierler (45), but it can be also proved using the more general Occupancy principle enunciated by Orr and Gillespie (46).

Where computer facilities are not available a 10 minute measurement period can be used and the height/area formula modified to:-

$$\text{Mean flow } (F_H) \text{ (ml/100g/min)} = \frac{(H_{max} - H_{10})\,\lambda_B.100.60}{A_{10}} \qquad (3.14)$$

where H_{10} = the count rate 10 minutes after injection.

A_{10} = the area under the clearance curve, i.e. the total number of counts recorded in 10 minutes.

For some time now an "initial slope" flow index has been used (47, 48, 49). The fundamental assumption here is that during the first one to two minutes the slope of the clearance curve is proportional to cerebral blood flow, i.e. for the short time interval the curve is assumed to be mono-exponential, thus:-

$$\text{Mean flow } (F_I) \text{ (ml/100g/min)} = \frac{\text{Empirical Constant}}{T_{\frac{1}{2}} \text{ (initial slope)}} \qquad (3.15)$$

Highly significant correlations ($r = 0.94$; $p < 0.001$) have been obtained between F_I and F_H over a wide range in flow values. However, with very high flows greater than 100 ml/100g/min this method tends to reflect blood flow more and more in the faster brain compartment.

Method

When xenon-133, dissolved in saline, is injected as a bolus into the internal carotid artery the tracer is carried to the cerebral tissue, and equilibration between blood and tissue occurs rapidly. Furthermore, since the inert gas is highly soluble in air, about 95% of the tracer reaching the lungs is excreted so that there is no significant recirculation. On completion of the injection the fresh arterial blood containing no radioisotope clears the tracer from the tissue, and the rate of this clearance depends on the blood flow.

Detection and Data Processing Systems

A number of collimated scintillation detectors can be mounted around the head. The number and size of the detectors and the degree of collimation are chosen to define the regions of the brain to be studied. The output pulses from each detector are fed to pulse height analysers and the selected pulses can be processed as follows.

(1) The pulses can be fed to a multi-track magnetic tape recorder with a "down stream monitoring" head, such that any chosen channel can be monitored by a ratemeter and scaler to allow immediate data analysis (if desired all channels could be monitored in this way). A paper chart recording of the ratemeter output will give the shape of the clearance curve, while the scaler will display the total number of curves recorded (i.e. the area under the clearance curve).

This is the simplest method of storing data so that various types of analysis can be carried out on all channels "off-line". However, the tape recording system can impose definite dead time limitations on the acceptable count rate and if these limits are exceeded serious loss of counts will result.

(2) The pulses can be fed through a multi-plexing system to a multi-channel analyser operating in "multi-scaler mode" and the data stored in the instruments ferrite core memory in the form of time histograms with selectable time intervals. This is an improvement, although, depending on the multi-plexing system, this method may also be dead time limited. In general these systems have to write out the stored data so that analysis can be carried out.

(3) The pulses can be fed on-line to a laboratory digital computer where again data can be collected in the form of time histograms. Analysis can then be carried out by the computer and the results for every regional channel can be obtained in a very short time.

Sources of Error

Eagerness to measure cerebral blood flow in smaller and smaller regions of the brain can be accompanied by the temptation to use systems which are unable to provide the necessary spatial resolution.

The regions of the brain defined by some systems have been assessed using point sources. The response of a scintillation detector to a point source of radiation depends on:-

(a) The inverse square of the distance of the source to the detector.

(b) The area of the crystal exposed to radiation.

(c) The attenuation produced by the intervening tissue.

In the situation where cerebral blood flow is being measured, the source of radioactivity is not a point and the use of this type of assessment is misleading, since due to the inverse square law effect it tends to suggest that the effective volume from which gamma radiation is being detected is confined to a localised region close to the scintillation detector. However, if thin infinite uniform sources perpendicular to the axis of the detector are considered, then the detector response to such a source is independent of the source to detector distance. This results from the fact that the detector response to any point source within the extended source varies inversely with the square of the source to detector distance, whereas the area of the extended source viewed is directly proportional to the square of the source to detector distance and the two squared distance factors cancel. However, in the practical situation, the detector response will fall off with distance from the detector due to absorption within the intervening tissue, but this reduction in response is not as severe as that predicted by point source measurement. Thus in a multi-detector system, designed using a point source assessment method, there will be considerable overlap in the adjacent detector fields of view and the idea of well defined regions of measurement using such a system is questionable.

This situation is aggravated by Compton scatter of the 81 KeV gamma rays of xenon-133 within the brain tissue. If large pulse height analyser window widths are used a significant percentage of the detected photons in fact originate outwith the collimated detector field of view again limiting the regionality of the measurement. With xenon-133 the optimum setting of the lower threshold on the analyser is of the order of 75 KeV eliminating all first order scatter greater than 60°. Naturally this reduces the counting sensitivity and as the

detector size is reduced more and more in the attempt to measure cerebral blood flow in smaller regions of the brain, the effect on counting sensitivity can be considerable. Furthermore, if the comparison of cerebral blood flow measurements from different small regions of the brain are to be meaningful then not only must all the nucleonic channels be set up accurately in the same way, each gamma ray energy response must be the same, otherwise each detector will be viewing regions of different size.

The accuracy of cerebral blood flow measurement using tracer clearance techniques also depends on the uniformity of partial pressure of xenon within the tissue. This becomes a problem where the region under consideration is small and consists of inhomogenous tissue. At microscopic levels in a situation where flow is high the xenon partial pressure will decrease more rapidly than where flow is low and as a result partial pressure gradients can be set up around different tissue boundaries. The inert gas will then diffuse from areas of high mean partial pressure to areas of low mean partial pressure altering the mean rate of tracer clearance. This further imposes a lower limit on the size of the region from which meaningful cerebral blood flow measurements can be made.

Xenon Inhalation Technique

The most clinically attractive technique for the measurement of cerebral blood flow is the xenon-133 inhalation technique first introduced by Mallet and Veal in 1963 (50) and further developed by Obrist (51) and Wyper, Lennox and Rowan (52, 53). In this method xenon-133 is inhaled by the patient for times ranging from one to five minutes and the resulting brain tissue clearance curve is monitored by external detectors for times ranging from two to 50 minutes. This technique is completely atraumatic since no arterial punctures or blood samples are necessary. However, there are two major disadvantages. During inhalation, all the body tissues take up xenon and as a

consequence there is appreciable recirculation which distorts the clearance curve. A correction is applied by measuring the xenon activity in the end-expired air which reflects the arterial concentration. The brain clearance curves are also distorted by the addition of a slow third component due to isotope in the extra-cranial tissues. If the clearance curve is monitored for a sufficiently long time (30 to 50 minutes) then this third component can be measured and defined. This requires a physiological stability which is rarely achieved in practice. In the two minute slope technique of Wyper et al the patient inhales xenon for two minutes and after a delay of 30 seconds the clearance curve is monitored for a further two minutes. Under these conditions there is little loading of the third component and this changes only slowly over the two minute monitoring period and does not affect the result significantly. The use of such a brief investigation time allows the patient to maintain reasonable steady state conditions and the technique has been used in normal volunteers and with a wide spectrum of patients. Xenon-133 dissolved in saline can also be given by intravenous injection for the measurement of cerebral blood flow. The analysis of the clearance curves is carried out in a similar fashion to that described for the inhalation method but greater amounts of radioactivity must be given to obtain reasonable counting statistics.

Hydrogen Clearance Technique

Hydrogen gas has been used to measure cerebral blood flow in animals. In 1964 Aukland, Bower and Berliner (54) described the theoretical basis of the method in which the partial pressure of hydrogen in cerebral tissue is measured by polarised platinum electrodes. After administration of hydrogen the tissue desaturation process can be monitored and washout curves similar to those obtained by the xenon clearance technique can be recorded. The hydrogen can be given by inhalation (55, 56, 57, 58) or by injection (59, 60). The major

advantage of the method is that blood flow can be measured in small regions of the brain with very little damage to the surrounding tissue because of the small diameter of the electrodes (0.05 - 0.2 mm) which are used.

The platinum tissue electrodes are insulated with teflon and a 1 mm length at the end is scraped bare. A silver/silver chloride EEG electrode can be used as a reference electrode and is normally placed subcutaneously in the animal's back and a polarising voltage of the order of 700 mV is employed. The small electric currents (less than 10^{-6} Amps) obtained from the tissue electrodes can be monitored using a multichannel DC amplifier having low drift characteristics and recorded on a multi-pen Servo chart recorder.

In general mono-exponential clearance curves are obtained although bi-exponential curves can be recorded when the electrodes are inserted close to tissue boundaries.

Non-Diffusible Tracer Techniques

A number of attempts have been made to find alternatives to the tissue clearance techniques of measuring cerebral blood flow.

A method suggested by Oldendorf in 1962 (61) measured the circulation time of a non-diffusible isotope after a bolus injection was given intravenously. The method has been applied to patients with various types of intracranial pathology.

Basically the method consists of injecting a bolus of non-diffusible isotope intravenously (0.5 mCi Iodine-131 labelled hippuran and 1.5 mCi Technetium-99m in the form of sodium pertechnetate has been used) and monitoring the passage of radioactivity through the brain by means of externally mounted detectors. After amplification and pulse height analysis the output pulses are fed to a ratemeter the output of which is filtered and electronically differentiated to give a recording of the rate of change of radioactivity with respect to time. The peaks of the resultant bi-polar wave form indicate the

maximum rate of entry and the maximum rate of exit into and from the field of view of the detectors. The time interval between these peaks is the mode circulation time.

The relative simplicity of this method makes it attractive but the information concerning the cerebral circulation acquired in this way is limited because the method in fact provides an index of velocity and not a measure of blood flow (62). Under conditions of changing radius flow through tubes will change more markedly than velocity and investigations in baboons have shown that circulation time is not a reliable index of cerebral blood flow. In addition, in a series of 200 patients studied in the Institute of Neurological Sciences in Glasgow, many patients with gross intracranial pathology showed no abnormal cerebral circulation times. However, the average mode circulation time for groups of patients with ischaemia, subarachnoid haemorrhage and haematoma were increased (63). This result is of limited practical value since when faced with a particular patient the investigator will probably be confronted with a mode circulation time result which will lie within the expected range for normal patients. This is due to the rather large range of mode circulation times found in normal subjects.

The conclusion is, therefore, that the assumption that changes in flow will be reflected in changes in velocity is valid in such restricted circumstances that it would appear to be unwise to base clinical decisions on such measurements.

Electro-Magnetic Flow Meter Measurements

Again the fundamental parameter measured by electro-magnetic flow meters is velocity. However, these devices are normally used with relatively large blood vessels under conditions where it can be assumed that there is little or no change in vessel diameter and hence velocity can be related to flow.

The electro-magnetic flow probe is placed around the blood vessel

under investigation. In cerebral blood flow determinations this is normally the carotid artery. An electro-magnet within the probe is excited by means of a square wave or sinusoidal electric signal and the resulting magnetic field is set up at right angles to the direction of flow. Blood flowing through the vessel cuts the magnetic lines of force and an electric field is induced mutually perpendicular to the direction of blood flow and the magnetic field. The induced electric field is detected by electrodes placed diametrically opposite on the blood vessel. The detected signal is amplified and demodulated and displayed on a chart recorder. Calibration is carried out by passing a known amount of blood through the vessel. To allow good correlation between velocity and flow, the probe must produce a homogenous magnetic field and for this reason a "cuff" type is normally used. The main advantage of this method of flow measurement is that it permits continuous monitoring of flow in intact blood vessels. The disadvantages are that the blood vessels have to be exposed and in the case of cerebral blood flow investigations only total blood flow in and out of the brain can be measured.

Other Methods of Cerebral Blood Flow Determination

(a) Heat Clearance Technique

With this method a bolus of hot or cold saline is given intra-arterially and the step function change in temperature and subsequent clearance is monitored by thermistors placed in brain (64). The assumption is that the rate of clearance of heat from the area of brain under study will be proportional to regional cerebral blood flow. The main criticism of the method is that heat is not a physiologically inert tracer and any changes in body temperature will affect the result.

(b) Electrical Impedance Methods

When a high frequency signal is passed through the body it is modulated due to changes in the electrical impedance between the

electrodes. One of the factors producing these changes is the pulsating blood flow (65). An attempt is made in this method to correlate the measured impedance changes with cerebral blood flow. The impedance curves obtained are analysed by measuring amplitude and rise and fall times. Unfortunately it can be shown that a significant proportion of the recorded waveform results from extracranial blood flow and changes in cerebrospinal fluid.

(c) Ultrasonic Doppler Technique

When ultrasonic waves impinge on the blood stream the frequency of the detected waves reflected from the moving particles of blood, is altered due to the Doppler effect (65). The beat frequency is proportional to the velocity of the moving particles.

In this method, a probe which acts as both a transmitter and receiver is held against the neck at an acute angle to the direction of flow in the carotid artery and the Doppler beat frequency is detected. It is assumed that the diameter of the carotid artery does not change significantly and the blood velocity will vary in proportion to flow. If this assumption is not made determinations of carotid artery diameter must be made by angiographic techniques (67) or by pulsed ultrasound (68).

The basic advantages of the method are that it is atraumatic and that instantaneous changes in carotid artery velocity patterns can be detected instantaneously. However, a great deal of controversy still exists concerning the design of probes necessary to give consistent results when used by different investigators.

Summary

The most precise techniques for the measurement of cerebral blood flow are the inert gas clearance techniques which are based on the Fick Principle. The xenon-133 intracarotid injection technique is the method against which all others are judged and although regional cerebral blood flow can be measured with this method the regions

involved are relatively large. Micro regional cerebral blood flow can be measured by the hydrogen clearance technique where the hydrogen tracer can be given either by carotid artery injection or by inhalation. The most successful atraumatic methods for the determination of cerebral blood flow in man are the xenon-133 inhalation and intravenous techniques.

CHAPTER 4

EFFECTS OF RAISED INTRACRANIAL PRESSURE ON CEREBRAL BLOOD FLOW

Raised intracranial pressure may have an adverse effect on the function of the brain in a number of ways, one of the more important being reduction of cerebral blood flow. Brain tissue depends on a continuous supply of oxygen and metabolites and reduction of cerebral blood flow therefore has particular significance. The resultant effects range from transient reversible neuronal disfunction to irreversible ischaemic brain damage (69, 70, 71).

The increasing use of continuous monitoring of intracranial pressure in neurosurgical patients (18, 72) has highlighted the requirement for more precise quantitative information on the relationship between intracranial pressure and cerebral blood flow. The major factors controlling cerebral blood flow in these situations are the pressure differential or cerebral perfusion pressure and the resistance across the cerebral vascular bed. In these situations it is customary to measure cerebral perfusion pressure as the difference between mean arterial pressure and mean intracranial pressure since it is assumed that intracranial pressure and cerebral venous pressure are approximately equal. Because of the factors involved it would seem unlikely that intracranial pressure would have a direct relationship to cerebral blood flow. Furthermore, cerebral perfusion pressure will only have a direct relationship to cerebral blood flow when the cerebral vascular resistance remains constant. This assumption will only be justified in certain situations such as the state of vasomotor paralysis (73).

Clinical and experimental work has shown that intracranial hypertension does indeed reduce cerebral blood flow but a clear relationship between cerebral blood flow and either intracranial pressure or cerebral perfusion pressure has not emerged from these studies (70, 74, 75, 76). The level of intracranial pressure at which cerebral blood flow is

reduced has varied considerably in these studies and would appear to depend on the rate of development and method of production of the intracranial hypertension. The significance of both these factors may lie in the variability of the compensatory mechanisms which act to preserve cerebral blood flow in the face of rising intracranial pressure. These mechanisms include systemic hypertension, which may maintain cerebral perfusion pressure (77, 78), and also alterations in vascular resistance (79, 80). The underlying mechanisms behind both these responses are still not clearly understood.

In 1929 Wolff and Blumgart (81) found that increased intracranial pressure prolonged cerebral circulation time in cats. They stated that the increased cerebral circulation time and assumed decrease in cerebral blood flow were due to cerebral venous stasis. Williams and Lennox in 1939 (82) measured cerebral blood flow in patients with increased intracranial pressure and found little or no change. Courtice in 1940 (83) reported similar findings in patients with supratentorial tumours. However, in several patients with posterior fossa tumours, cerebral blood flow was significantly reduced. In both these investigations, the method used for the estimation of cerebral blood flow was the arterial and venous difference methods for oxygen and carbon dioxide. Kety, Shenkin, and Schmidt in 1948 (74) measured cerebral blood flow in patients using the nitrous oxide technique and found low values of cerebral blood flow only when the intracranial pressure exceeded 450 mm CSF (33 mmHg).

The relation between intracranial pressure and cerebral blood flow has been studied extensively in experimental animals and has found to be complex. In 1965 in an experiment using electromagnetic flow meters Langfitt, Kassell and Weinstein (76) found that cerebral blood flow varied inversely with intracranial pressure. During acute expansion of an extracerebral balloon, blood flow began to fall as the intracranial pressure rose. Clearly these observations are at variance

with those of Kety et al noted above and were attributed to the rate of increase of intracranial pressure and to the fact that the monkeys were under moderately deep barbiturate anaesthesia. Zwetnow in 1968 (84), slowly infused artificial CSF into the cisterna magna of dogs and demonstrated that cerebral blood flow, as measured with the xenon-133 clearance method, did not fall until cerebral perfusion pressure reached a level of 40-50 mmHg. Thus it was shown that the cerebral circulation was capable of compensating within limits for rising intracranial pressure. However, the situation in human intracranial pathology is even more complex. This is demonstrated by some early observations by Shenkin, Novack and Goluboff in 1952 (85). They found that cerebral blood flow was reduced in several patients with brain tumours and increased intracranial pressure. However, blood flow did not significantly improve after the intracranial pressure had been reduced by ventricular drainage. Cronqvist and Lundberg (86) reported that spontaneous fluctuations in intraventricular pressure in brain tumour patients were accompanied by reciprocal changes in cerebral blood flow. On the other hand, in several patients with prolonged sustained intracranial hypertension, reduction of intracranial pressure with hypertonic Mannitol had the opposite effect, i.e. cerebral blood flow fell with the intracranial pressure.

Changes in cerebral blood flow also have an effect on intracranial pressure. If cerebral blood flow increases due to dilatation of one portion or more of the cerebral vascular bed, this will result in an increase in cerebral blood volume and the intracranial pressure will increase (87, 88). In the normal situation the effect on intracranial pressure has little significance because the changes in cerebral blood volume produced by even a considerable arterial constriction or dilatation are small and these alterations in cerebral blood volume are compensated by increases or decreases in CSF volume. However, on the steep portion on the volume-pressure curve, when most

of the CSF has been displaced, small changes in vascular diameter and intravascular blood volume have a considerable effect on intracranial pressure.

What are the mechanisms responsible for the maintenance of cerebral blood flow during raised intracranial pressure, and for the decrease in cerebral blood flow that occurs when intracranial pressure exceeds certain limits?

In 1928 Wolff and Forbes (79) observed the cortical surface through a cranial window during induced changes in intracranial pressure and noted dilatation of the pial vessels. When pressure is uniformly increased by injection of fluid into the spinal canal or cisterna magna, the cortical vascular dilatation is also diffuse. Weinstein and Langfitt in 1967 (89), demonstrated this in monkeys in which the bone over a large portion of both cerebral hemispheres was replaced by a transparent, water-tight calvarium. This would therefore appear to be the principal mechanism responsible for maintenance of cerebral blood flow in the face of rising intracranial pressure and represents a form of cerebral autoregulation. These observations are applicable to diffuse intracranial hypertension where it is assumed that the pressure is distributed uniformly throughout the intracranial space and all vessels are subjected to the same physical forces. On the other hand a space-occupying mass produces vascular compression in the space surrounding the mass. Probably in the early stages these vessels are capable of dilating and maintaining local cerebral blood flow but ultimately the autoregulatory capacity of the vessels is overcome by the forces generated within the mass. In his observations through the transparent calvarium Weinstein demonstrated that this vascular collapse spread circumferentially from a gradually expanding subdural balloon. Simultaneously cortical vessels remote from the balloon dilate as diffuse intracranial pressure rises. Langfitt's group has suggested that, if cerebral blood flow

was measured with the nitrous oxide technique (total cerebral blood flow) it might be shown to be normal at a time when regional cerebral blood flow in the vicinity of the mass had virtually ceased (90). Clearly, local cerebral ischaemia produces local neurological signs appropriate to the region involved and these signs will be superimposed on those produced by the diffused intracranial hypertension. The collapse of vessels in the cortex surrounding the subdural balloon is not due to the balloon itself but rather to compression of the vessels against the overlying calvarium. The collapse begins on the surface of gyri, and involves arteries and veins alike. When these superficial vessels have been obliterated throughout most of the ipsilateral hemisphere, other vessels in the deep sulci are still patent. These observations were made in acute experiments and simulate fairly closely acute subdural and extra-dural haematomas but they do not necessarily apply to chronic space-occupying lesions. In this situation there is more time for the cerebral vessels to compensate and the degree of vascular compression is probably less for a mass of the same size. This may help to explain the absence of local neurological signs in so many patients with large chronic subdural haematomas and meningiomas.

What is the cause of the decrease in cerebral blood flow that ultimately occurs throughout the brain as intracranial pressure rises? Wright, in 1938 (91), reported that bridging cerebral veins, observed through a cranial window, remain patent until rising intracranial pressure exceeded the blood pressure. When collapse occurred, blood was forced proximally, indicating that the outflow resistance exceeded the resistance in the proximal vascular bed. He suggested that intracranial hypertension caused constriction of the cerebral veins at their junction with the dural sinuses, and this explanation has been supported by the experiments of Hedges et al (92), and Greenfield and Tindall (75).

Langfitt's group investigated the problem in monkeys and measured intracranial and dural sinus pressures during expansion of an extracerebral balloon and during the development of an experimental brain swelling (90, 93). They claimed that the relationship of sagittal sinus pressure to intracranial pressure in these experimental conditions seemed to be best explained by the combination of compression of the cerebral veins proximal to the sinus and compression of the sinus itself distal to the recording catheter. Severe brain swelling was produced in a number of monkeys by repeated expansion and deflation of the balloon. When intracranial pressure had risen to the level of the diastolic blood pressure the animals were sacrificed and their heads immersed in liquid nitrogen. The frozen heads were then sectioned in coronal planes. Many of the cortical veins were obliterated by compression between the expanded brain and the inner table of the skull, and both the sagittal and straight sinuses had collapsed. The sagittal sinus was narrow throughout much of its course, and complete obliteration of the lumen was found only in the region of the coronal suture. This occurred because the sinus is partially encased in bone throughout much of its length and is least so at the coronal suture. The transverse sinus, which is surrounded by bone on three sides, was only slightly affected. Arteries as well as veins were compressed. In one animal the large, single anterior cerebral artery of the rhesus monkey was nearly collapsed throughout much of its course over the corpus callosum.

Summary

Cerebral blood flow is maintained at normal levels during increased intracranial pressure by dilatation of resistance vessels in the brain. When blood flow does eventually decrease it is due primarily to compression of the venous outflow tract. The cause of the intracranial hypertension is as important as the height of the pressure in determining the level of cerebral blood flow. It is

believed by some authors that a mass lesion may produce severe reduction of regional cerebral blood flow at a time when total cerebral blood flow is normal. If the process responsible for the increase in pressure is diffused brain swelling, the subarachnoid space over the cerebral hemispheres is obliterated and cortical vessels are compressed between the expanding brain and calvarium. In these circumstances, blood flow can be as much a function of the volume of the brain as it is of the intracranial pressure. In patients with sustained brain swelling there may be considerable collapse of cortical vessels with only moderate intracranial hypertension.

CHAPTER 5

EFFECTS OF RAISED INTRACRANIAL PRESSURE ON SYSTEMIC ARTERIAL PRESSURE

It has been confirmed in many experimental studies that acute systemic hypertension will result if intracranial pressure is raised to a sufficiently high level (77, 94, 95). Furthermore, there has been a tendency, ever since Cushing's descriptions of the blood pressure response in man (78), for some workers to regard systemic hypertension as a reliable clinical sign of increased intracranial pressure. Nevertheless, many important aspects of this blood pressure response have to be clarified. For example, just how reliable is a rise in blood pressure as an index of rising intracranial pressure in patients and what is the correlation between the two measured pressures? What is the mechanism responsible for the increased blood pressure and what is the function of the response?

Results from patient studies in Glasgow where continuous monitoring of both arterial and intracranial pressures were carried out, suggest that the blood pressure response to acute, and substantial increases in intracranial pressure is quite unpredictable (72). This observation has also been reported by other workers (18, 96).

At the beginning of the 20th century, experimental work on the blood pressure responses to direct stimulation of the brain, and the demonstration of the vasomotor centre in the medulla gave credence to the opinion that a blood pressure regulating mechanism was present in the brain. However, this hypothesis of a vasomotor centre for the regulation of blood pressure was rejected when the striking effects of carotid sinus stimulation were demonstrated. It was then felt that the intracranial mechanisms had a subsidiary role as the final common pathway for regulatory impulses originating outside the cranium.

A number of experiments using raised intracranial pressure and based on Cushing's studies were carried out. For example in 1933

Guernsey and his colleagues (97) reported that denervation of the carotid sinus and aortic depressor nerves resulted in a greater response to intracranial compression than that which occurred in the intact animal. Yesinick and Sellhorn (98) demonstrated that after a buffer nerve section the breathing of nitrogen caused a fall in blood pressure while tracheal occlusion produced a rise suggesting that the blood pressure response to raised intracranial pressure was due to asphyxia rather than hypoxia.

In 1902 Cushing (99) demonstrated that injection of cocaine into the cisterna magna resulted in a transient inhibition of the blood pressure response while section of the spinal cord caused a permanent blockage of the effect. Freemen et al in 1940 (100) found that the blood pressure response depended on the integrity of the sympathetic chain particularly the thoracic segment. Forster (101) demonstrated that this intracranial mechanism did not depend on the cerebral cortex, the hypothalamus or the vagosupraoptic pathways. Therefore, while much of the early data supported the hypothesis that a blood pressure response was elicited as a result of anaemia, ischaemia, hypoxia or asphyxia, there were still a number of unresolved problems.

Rodbard and Saiki (94) claimed that the blood pressure response to raised intracranial pressure exhibits different characteristics from that due to hypoxia. The response to intracranial compression is rapid and quite marked while that due to hypoxia or asphyxia usually occurs more slowly and is of a lesser degree. They found in dogs that hypoxia produced by nitrogen breathing and asphyxia following tracheal occlusion produced only a limited increase in blood pressure. They showed that during the blood pressure response resulting from asphyxia an increase in intracranial pressure produced a further and much greater increase in blood pressure. They also demonstrated that the production of a negative intracranial pressure usually resulted in a fall in blood pressure. They interpreted their data as lending

support to the concept of an intracranial baroreceptor mechanism similar to that of the carotid sinus. They suggested that because of its position it would act as a differential manometer registering the difference between intravascular and intracranial pressures.

Thompson and Malina (102) claimed that the mechanism responsible for the cardiorespiratory changes in increased intracranial pressure is "an acute dynamic axial distortion of the brain stem affecting the conductivity of the ponto-medullary centres for respiration and cardiovascular activity". In experiments with dogs their results indicated that intracranial pressure by itself was not the factor responsible for the cardiorespiratory changes but what was important was the magnitude of the pressure difference between the supratentorial and infratentorial spaces. They postulated therefore that this pressure difference caused movement of the brain stem towards the lower pressure area. In another series of experiments in which the roof of the posterior fossa was removed and the dura opened widely to eliminate any direct pressure effect on the medulla or its blood vessels, they raised the pressure in the supratentorial space and found that the cardiorespiratory changes occurred simultaneously with axial distortion of the brain stem.

Thompson and Malina also claimed that ischaemia of the medulla could be ruled out since there was no direct pressure effect on the blood vessels in the posterior fossa in their experiments. They also demonstrated that with an intact neuraxis and in the absence of raised intracranial pressure, mechanical stimulation of the medulla produced cardiorespiratory changes which were similar to those produced by increased intracranial pressure. Finally, by placing a small metallic foreign body into various parts of the neuraxis and using x-rays for localisation they showed that distortion of the brain stem could be visualised when the cardiorespiratory changes associated with raised intracranial pressure occurred.

The concept advanced by Thompson and Malina was that dynamic distortion of the brain stem produces stress patterns along the neuronal pathways and alters the neuronal electrical conductivity. The direction and magnitude of the force exerted by these stress patterns determines the cardiorespiratory changes thus accounting for the variability of the responses elicited by various pathological changes in different patients and experimental animals. They claimed as secondary effects, tension exerted on the cranial nerves and mechanical stress caused by pull on the blood vessels as the brain stem distorts.

Evans (103), on the other hand, disputed the philosophy of Rodbard and Saiki. In experiments with dogs, in which all the arteries supplying the brain were ligated except the left common carotid artery which was occluded in a controlled fashion, he demonstrated that reduction of the blood supply to the brain resulted in an increase in systemic arterial pressure. He claimed that in these circumstances the blood pressure increase, the respiratory response and EEG changes resulting from partial or complete occlusion of cerebral blood flow were in essence the same as those produced by a rising intracranial pressure. He therefore supported the concept that an increase in intracranial pressure results in ischaemia of the brain stem and that this is the trigger mechanism for the blood pressure response.

Evans was also able to demonstrate in dogs with spinal cord section at C-2, that a blood pressure response could be elicited when the cord was compressed by the infusion of fluid. He believed that these results, since they demonstrated that the blood pressure response to increased intracranial pressure was not limited to the brain stem alone, were indicative of the fact that the response was a general one involving stimulation of sympathetic neurons. He felt that these results clearly did not substantiate the theory of the presence of a baroreceptor mechanism in the brain stem. He concluded that the

blood pressure response to increased intracranial pressure was a phenomenon of the entire nervous system and that ischaemia of the involved neurons is a major factor in the response.

In 1970 Hoff and Reiss (104) concluded from their experiments that the Cushing response was due to stimulation of highly localised structures in the medulla and spinal cord. They claimed the significant stimulus was pressure and/or stretching of neural tissue. Their experiments were carried out in cats and they found that the blood pressure response to raised intracranial pressure persisted after transection of cranial nerves v to xi following cerebellectomy and after decerebration of the pontomesencephalic border, thus indicating that the blood pressure response is initiated from structures lying within the CNS below the mid-brain. Spinal cord transection at C-1 abolished the blood pressure response to increased intracranial pressure but not to spinal cord compression. This was indicative of the presence of pressure sensitive regions in the spinal cord distinct from those in the lower brain stem. They delineated these pressure sensitive regions by graded local pressure using a 1.5 mm probe.

Summary

Unanswered questions still remain concerning the mechanism and function of the blood pressure response to increased intracranial pressure. Possible mechanisms which have been suggested are:

(a) ischaemia or hypoxia of medullary centres (Cushing, 1901) (78).

(b) action of intracranial baroreceptors sensitive to changes in cerebral perfusion pressure (Rodbard and Saiki, 1952) (94).

(c) brain stem distortion (Thompson and Malina, 1959) (102).

(d) cerebral ischaemia (Evans, 1967) (103).

CHAPTER 6

CISTERNA MAGNA INFUSION

The question posed in Chapter 4 was:-

What are the mechanisms responsible for the maintenance of cerebral blood flow during rising intracranial pressure, and for the decrease in cerebral blood flow that occurs when intracranial pressure exceeds certain limits?

A series of experiments were designed with a view to elucidating the relationship between raised intracranial pressure and cerebral blood flow. A further aim of the study was to investigate if a quantitative relationship did exist between these two physiological variables and to evaluate the significance of the compensatory mechanisms which act to preserve cerebral blood flow in conditions of raised intracranial pressure.

Methods

Adult baboons weighing approximately 10 kg were anaesthetised with phencylidine hydrochloride (10 mg) and sodium thiopentone (60 mg) and maintained with a combination of phencylidine hydrochloride, suxamenthonium and a nitrous oxide/oxygen mixture. Ventilation was controlled using a Starling pump, delivering a tidal volume adjusted to produce the required arterial pO_2 and pCO_2 levels.

The undernoted pressures were monitored continuously by means of indwelling polyethylene catheters connected to strain gauge transducers (Bell and Howell type 4-327-L221). The systems were calibrated against a mercury column and the pressure wave forms were written out on heat sensitive chart recorders (Devices Limited).

1. Ventricular Fluid Pressure: from the frontal horn of the right lateral ventricle.
2. Cisterna Magna Pressure
3. Arterial Pressure: from the left femoral artery.

Cerebral blood flow was measured using both the xenon-133 intracarotid injection method and an electromagnetic flow meter placed on the carotid artery on the neck.

The right external carotid artery was ligated immediately beyond the carotid bifurcation and a polyethylene catheter was inserted into the right internal carotid artery via the right lingual artery which was ligated distal to the point of entry of the catheter. A bolus injection of 0.5 mCi of xenon-133, dissolved in 0.45 to 0.55 ml saline at constant temperature was given via this catheter. The rate of clearance of radioactivity was monitored using a 1" sodium iodide scintillation detector placed over the right parietal region. Cerebral blood flow was calculated from the initial slope and by the height/area technique employing the 10 minute correction.

An electromagnetic flow probe (Nycotron) was placed on the right common carotid artery after the external carotid artery had been ligated.

At the beginning of each cerebral blood flow measurement arterial pO_2, pCO_2, pH, jugular venous pO_2, pH, venous haemoglobin and PCV values were estimated. End-tidal CO_2 was continuously monitored using an infra red analyser. An electrocardiograph tracing was obtained at intervals.

Three series of experiments were performed.

Group 1

In eight animals intracarotid pressure was raised by infusion of "mock" cerebrospinal fluid at constant temperature into the cisterna magna (mock CSF formula in m.equiv./litre: Na 145.0, K 3.5, Cl 101.5, H_2PO_4 2.0, HCO_3 25.0). An aneroid barometer and sphygmomanometer bulb were used to keep the infusion pressure constant and the resultant cisterna magna and ventricular fluid pressures were monitored continuously. Control conditions were established and the pressure was raised in increments of five to 20 mmHg approximately every 30 minutes.

After each pressure increase equilibrium was established before cerebral blood flow was measured by xenon clearance. Intracranial pressure was increased in this manner until there was a substantial reduction in cerebral blood flow.

Group 2

Before proceeding as noted above, in four animals the cervical cord was sectioned at the C3/C4 segment in order to abolish the systemic hypertension which developed in the first group of animals as intracranial pressure was raised.

Group 3

In a further four animals when the intracranial pressure had reached the level at which systemic hypertension and increased cerebral blood flow developed, i.e. approximately 60 mmHg, blood pressure was reduced progressively by intermittent withdrawal of blood from a catheter placed in the right femoral artery. After blood pressure was reduced, it was raised again by intravenous infusion or pressor drugs.

At the end of each experiment the animal was sacrificed using intravenous sodium pentobarbitone. In the first group of animals the brain was removed for histological examination.

Results

Group 1

Cerebral Blood Flow

The eight animals maintained control values of cerebral blood flow up to intracranial pressures in the region of 50 mmHg. There was a tendency for the flow to increase slightly although one animal with a high resting flow did exhibit a slight fall. When intracranial pressure rose to between 50 and 96 mmHg, a significant increase in flow developed in all animals. This increase ranged from 28% to 75% above control levels. In six of the animals there was also a substantial increase in mean arterial pressure during this phase. With

the other animals there was a moderate increase in blood pressure in one and no change in the other. In no animal had the cerebral perfusion pressure dropped below 50 mmHg at the time of maximum hyperaemia. In seven of the eight animals there had been a marked reduction in cerebrovascular resistance (see Table 6.1).

When the hyperaemia had been established, the cerebral blood flow remained high during further small increases in intracranial pressure. When intracranial pressure approached levels in the range of 60 to 116 mmHg cerebral blood flow fell below control values and continued falling as intracranial pressure increased further. Cerebral blood flow had virtually ceased when intracranial pressure was increased to levels ranging from 95 to 153 mmHg. Figure 6.1 describes the sequence of events in each experiment.

Systemic Arterial Pressure

In all eight animals the mean arterial pressure rose with increasing intracranial pressure (Table 6.2). The systolic pressure rose more than diastolic pressure thus increasing the pulse pressure. In one animal the blood pressure response occurred abruptly while in the other seven it developed gradually.

Maximum systemic hypertension occurred during an intracranial pressure range of 67 to 146 mmHg. In all but one experiment this intracranial pressure level was less than the control mean arterial pressure. Immediately before the development of the maximum blood pressure response cerebral perfusion pressure ranged from 14 to 70 mmHg and cerebral blood flow from 22 to 100 ml/100g/min. Therefore, reduction in neither of these variables was a prerequisite for the occurrence of the blood pressure response. In none of these experiments did a significant pressure difference occur between the pressure measured in the lateral ventricles and the infusion pressure measured from the cisterna magna. Table 6.3 shows the values of the measured parameters immediately before maximum system hypertension occurred.

	CBF (ml/100g/min)	MAP (mmHg)	ICP (mmHg)	CPP (mmHg)	CVR
Experiment 1.a	56	115	10	105	1.88
b	98	203	80	123	1.26
c	44	155	116	39	0.89
Experiment 2.a	47	117	25	92	1.96
b	77	177	75	102	1.32
c	46	148	107	41	0.89
Experiment 3.a	74	88	1	87	1.18
b	95	137	71	66	0.69
c	63	122	75	47	0.75
Experiment 4.a	58	107	11	96	1.66
b	75	182	96	86	1.18
c	0	114	112	2	-
Experiment 5.a	45	125	7	118	2.62
b	68	143	68	75	1.10
c	46	151	93	58	1.26
Experiment 6.a	87	93	20	73	0.84
b	126	178	67	111	0.88
c	47	122	86	36	0.77
Experiment 7.a	42	116	6	110	2.62
b	54	120	50	70	1.29
c	44	127	60	67	1.52
Experiment 8.a	28	105	24	81	2.89
b	49	170	85	85	1.73
c	0	117	112	5	-

CBF: cerebral blood flow, MAP: mean arterial blood pressure, ICP: intracranial pressure, CPP: cerebral perfusion pressure, CVR: cerebrovascular resistance.

(a) (c) control values, (b) values at maximum cerebral blood flow, values when cerebral blood flow had returned to control values or below.

TABLE 6.1

GROUP 1 - DATA SUMMARY

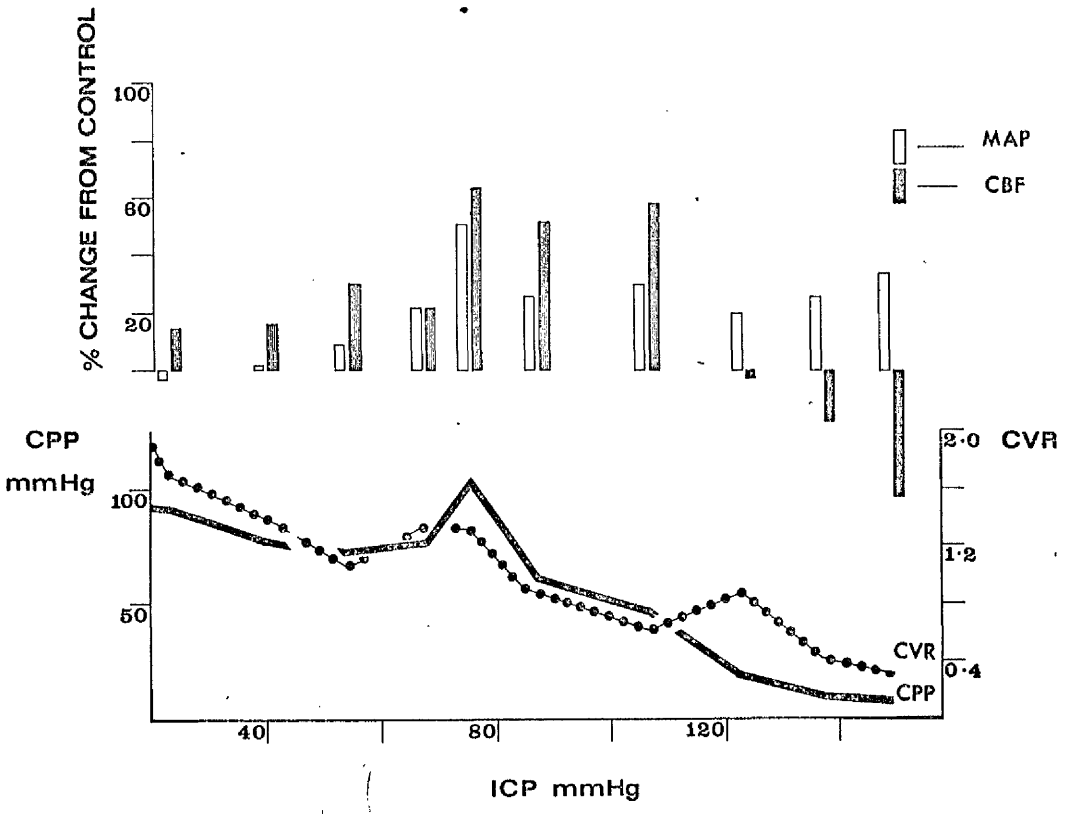


Fig. 6.1. Cerebral blood flow (CBF), mean arterial blood pressure (MAP), cerebral perfusion pressure (CPP) and cerebrovascular resistance (CVR) changes with progressive increases in intracranial pressure (ICP). Data taken from one experiment.

EXPERIMENT	CONTROL MAP (mmHg)	MAXIMUM MAP (mmHg)
1	115	203
2	117	177
3	88	137
4	107	182
5	125	205
6	93	178
7	116	148
8	105	170

TABLE 6.2

GROUP 1 - RANGE OF INCREASE IN MEAN ARTERIAL PRESSURE

EXPERIMENT	ICP (mmHg)	CPP (mmHg)	CBF (ml/100g/min)
1	80	70	62
2	75	68	57
3	71	51	86
4	96	61	67
5	146	14	22
6	67	63	100
7	112	33	28
8	85	30	49

TABLE 6.3

GROUP 1 - VALUES IMMEDIATELY BEFORE MAXIMUM ARTERIAL PRESSURE

Maximum values of cerebral blood flow and blood pressure occurred at the same level of intracranial pressure in six animals which suggests that there is some connection between the two responses. In the other two animals high blood flow levels preceded the development of a significant blood pressure response and in this case they were associated with a substantial reduction in cerebrovascular resistance.

Cerebrovascular Resistance

In seven animals the cerebrovascular resistance fell until the hyperaemia developed. In four of the seven cases cerebrovascular resistance was then maintained at this reduced level during, and even beyond, the hyperaemia phase. In the other three cases the reduction in resistance continued until flow began to fall off after which it remained constant.

Cerebral Perfusion Pressure

Figure 6.2 shows that during these experiments a variable relationship existed between cerebral perfusion pressure and cerebral blood flow. It can be seen that a reduction in either cerebral blood flow or cerebral perfusion pressure to values which could be expected to be critical were associated with a wide range of values of the other parameter. For example, if one were to regard 40 ml/100g/min and below as critical cerebral blood flow levels, it is clearly shown that associated cerebral perfusion levels varied from 0 to 80 mmHg. At the same time cerebral blood flow values varied between 0 and 70 ml/100g/min at cerebral perfusion pressure levels below 40 mmHg.

Figure 6.3 illustrates the three distinct phases in the cerebral blood flow/cerebral perfusion pressure relationship.

Stage 1 - Normal autoregulation was seen (points 1 to 6).

Stage 2 - Further increases in pressure resulted in higher flows but at cerebral perfusion pressure levels at approximately control values (points 7 and 8). During this phase cerebral blood flow remained high despite a fall in

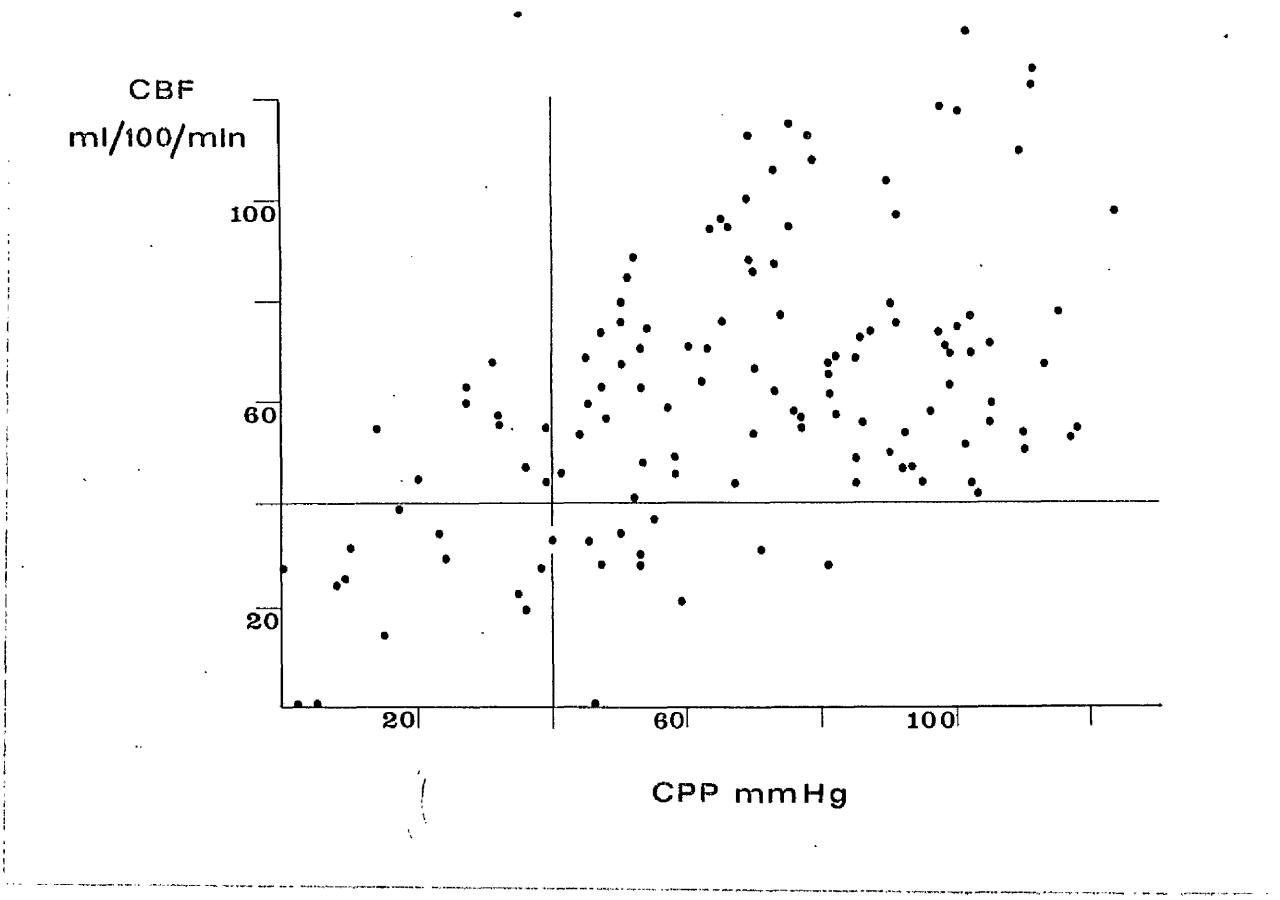


Fig. 6.2. Composite plot of cerebral blood flow (CBF) against cerebral perfusion pressure (CPP).
Data from all Group 1 experiments.

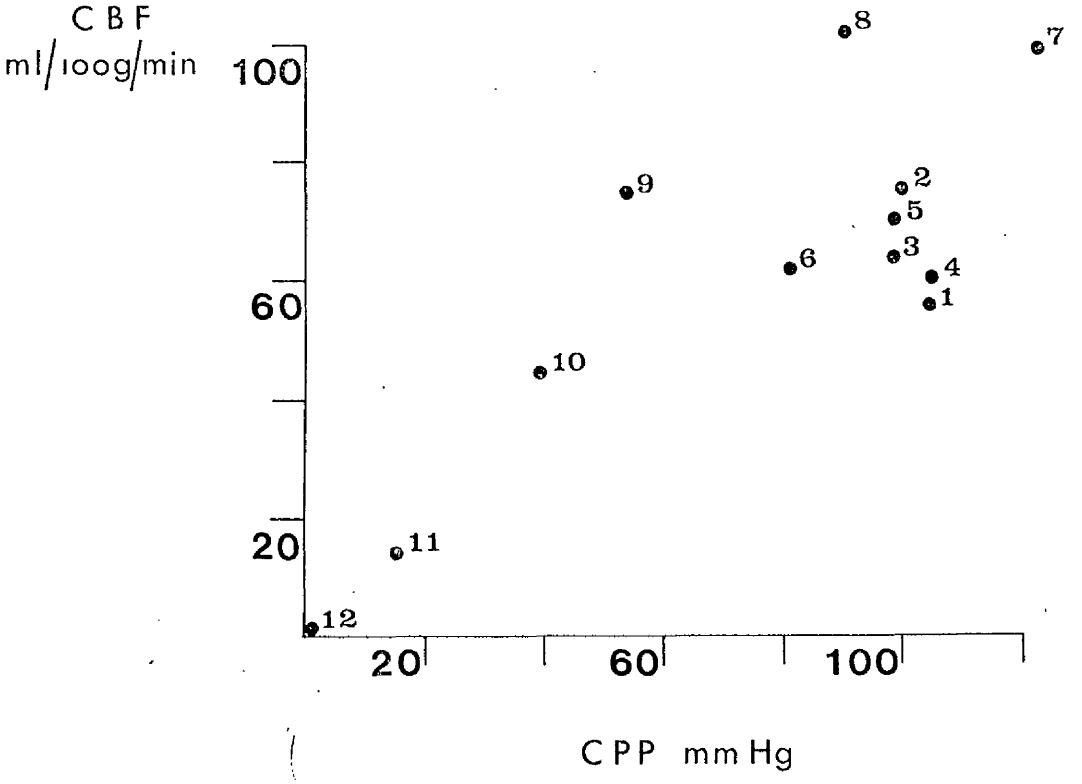


Fig. 6.3. Plot of cerebral blood flow (CBF) against cerebral perfusion pressure.
Data from one experiment.
(The numbers indicate the sequence of the xenon clearance measurements).

cerebral perfusion pressure over a narrow range.

Stage 3 - Finally after maximum hyperaemia had occurred cerebral blood flow fell progressively in a linear fashion with decreasing cerebral perfusion pressure. Autoregulation was clearly absent during this phase.

Group 2

Cerebral Blood Flow

The four animals studied all showed a progressive fall in cerebral blood flow as intracranial pressure was increased. No sustained hyperaemia was observed with this group of animals and flow had virtually ceased when intracranial pressure had reached levels ranging from 27 to 52 mmHg. However, transient increases in flow associated with rhythmic variations of mean blood pressure were seen in two animals.

In two animals after a "no flow" situation had been established, release of intracranial pressure resulted in a return to control flow levels in one animal and no return of flow in the other, i.e. post compression hyperaemia did not occur in either animal.

Systemic Arterial Pressure

After cervical cord section a sustained blood pressure increase did not occur. Blood pressure remained at control levels throughout the range of intracranial pressure increase in two animals while the other two animals displayed marked variations of mean blood pressure in association with pulse rate variations at intracranial pressure levels of 42 and 52 mmHg. There was no clear reason for these variations.

Cerebrovascular Resistance

The cerebrovascular resistance increased when intracranial pressure was increased in two animals. In one animal it remained more or less constant while in the fourth it fell. Generally speaking, no substantial changes in cerebrovascular resistance occurred and there

was no evidence of significant vasodilatation with increasing intracranial pressure.

Cerebral Perfusion Pressure

With this group of animals, apart from transient increases during the time of fluctuations in mean blood pressure levels described before, cerebral perfusion pressure fell progressively as intracranial pressure was increased. Graphs of cerebral blood flow plotted against cerebral perfusion pressure exhibited a linear relationship as indicated in Figure 6.4.

Group 3

The aim in this group of experiments was to study autoregulation of cerebral blood flow to changes in mean arterial pressure during and after the hyperaemic phase described in the Group 1 experimental results. Changes in arterial pressure levels were achieved either by withdrawing blood or by infusing fluid intravenously.

During Hyperaemic Phase

Hyperaemia was maintained or increased slightly during reduction of cerebral perfusion pressure resulting from reduction in blood pressure levels in three of the four animals. Furthermore, there was a fall in cerebrovascular resistance which suggested that increasing vascular dilatation was the means whereby these high flow rates were being maintained.

The cerebral perfusion pressure range over which the hyperaemia was maintained was, however, quite narrow, being between 10 and 32 mmHg.

Post Hyperaemic Phase

Further reduction of cerebral perfusion pressure by bleeding produced a progressive fall in cerebral blood flow in all four animals. After reduction of mean arterial blood pressure attempts were made to restore blood pressure levels in three of the four animals by intravenous infusion. In two animals cerebral blood flow increased when mean arterial pressure rose with infusion of 0.9% saline and fell

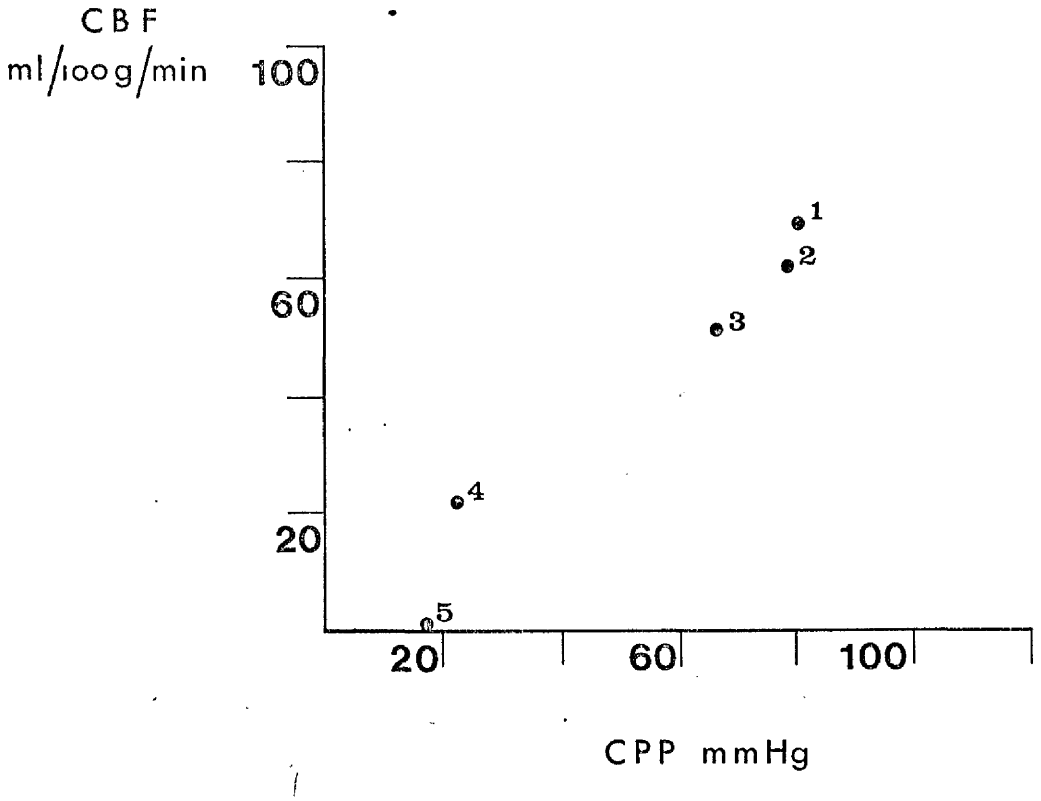


Fig. 6.4. Plot of cerebral blood flow (CBF) and cerebral perfusion pressure (CPP) after cervical cord section.
Data from one experiment.
(The numbers indicate the sequence of the xenon clearance measurements).

again when blood pressure was subsequently reduced. With the third animal it was necessary to add dextran and noradrenaline to the saline in order to raise mean arterial pressure and in this case cerebral blood flow remained unchanged despite increases in cerebral perfusion pressure from 9 to 50 mmHg.

Summary of Results

Group 1

During increases in intracranial pressure to levels below 50 mmHg cerebral blood flow remained at control levels despite a tendency for the mean arterial pressure to rise and cerebral perfusion pressure to fall.

At intracranial pressure levels between 50 and 96 mmHg cerebral blood flow increased and this higher level of blood flow was maintained over a narrow range of increased intracranial pressure. This hyperaemia appeared to depend on the combination of a substantial increase in blood pressure levels and the reduction in cerebrovascular resistance.

Once maximum hyperaemia had developed cerebral blood flow fell progressively as intracranial pressure was increased indicating failure of the cerebral vessels to autoregulate to cerebral perfusion pressure changes (Figure 6.1).

Group 2

After cervical cord section sustained systemic hypertension was not observed as intracranial pressure was increased and hyperaemia did not occur in any animal.

Graphs of cerebral blood flow values plotted against cerebral perfusion pressure values exhibited an approximately linear relationship throughout indicative of absence of autoregulation.

Group 3

Autoregulation appeared to be preserved or at worst only slightly impaired during the period of hyperaemia and systemic hypertension. After maximum hyperaemia autoregulation was lost and cerebral blood flow changed linearly with cerebral perfusion pressure.

Discussion

These results show that cerebral blood flow may be reduced by raised intracranial pressure. However, as intracranial pressure increases progressively as a result of infusion of mock cerebrospinal fluid into the cisterna magna important differences exist with regard to the sequence of cerebral blood flow changes and also in the nature of the compensatory mechanisms which function in an attempt to preserve flow. Clearly cerebral vessels do autoregulate to changes in cerebral perfusion pressure up to a limit as intracranial pressure is increased. However, what is the clinical relevance of these findings?

Results from previous experimental studies (see Chapter 4) have fallen into two patterns.

(i) Cerebral blood flow has been maintained until intracranial pressure has reached a particular level and then has fallen progressively. This has been found in both infusion and balloon expansion experiments.

(ii) Rapid expansion of supratentorially placed balloons led to progressive reductions in cerebral blood flow starting immediately with the initial increments in intracranial pressure.

Early clinical studies, on the other hand, using differences in arterial and venous oxygen tensions as an index of cerebral blood flow, did not show flow reductions as intracranial pressure was increased as a result of supratentorial lesions. Cerebral blood flow reductions were reported in patients with posterior fossa tumours (see Chapter 4).

An interpretation of the literature would suggest that the most likely situation is that cerebral blood flow is initially maintained at a constant level as intracranial pressure is increased up to a particular limit. Then the situation changes and cerebral blood flow falls progressively as intracranial pressure rises further.

This study, however, suggests a more complex situation. During

the initial phase of infusion, cerebral blood flow is maintained constant. Then as intracranial pressure rises to levels lying within the range 50 to 96 mmHg a marked increase in cerebral blood flow can occur in association with a substantial increase in arterial blood pressure or with a combination of increased blood pressure and reduced cerebrovascular resistance. This high blood flow level may be maintained as intracranial pressure is increased further over a narrow range. Further increases in intracranial pressure cause cerebral blood flow to fall progressively and blood flow ceases at levels of intracranial pressure within the range 96 to 150 mmHg.

The differences in results reported from both experimental and clinical investigations can most probably be attributed to the following.

(a) The different mechanisms causing the increase in intracranial pressure.

(b) The differences in the volumes of brain tissue from which flow has been measured, i.e. the differences in behaviour between local flow and total brain flow.

(c) The development of inter-compartmental pressure differences which could alter compensatory mechanisms.

(d) The infusion of fluid could alter the chemical status of the cerebrospinal fluid and therefore effect vascular reactivity.

(e) Differences in the time course of the raised pressure could result in different actions and reactions.

(f) Differences in the method used to measure cerebral blood flow (Chapter 3 discusses the various methods used and their inaccuracies).

(g) Differences in the anaesthesia regime and the surgical procedures employed.

(h) The age and health of the experimental animal and whether or not autoregulation was present from the start of the experiment.

These differences could all act to affect compensatory mechanisms

such as systemic blood pressure and the diameter of resistance vessels.

Systemic hypertension may act to preserve cerebral perfusion pressure and hence cerebral blood flow. This action has been accepted as the well known Cushing Response (see Chapter 5). Other characteristics of this phenomenon which have been reported are low heart rate and alterations in respiratory rhythm. Strictly speaking, to conform to the definition of this response, intracranial pressure should reach diastolic blood pressure levels before marked systemic hypertension occurs. However, many workers, particularly in the clinical realm, have queried the reliability of systemic hypertension as an index of raised intracranial pressure (72, 75, 105, 106, 107, 108). Continuous intracranial pressure monitoring with patients has shown a great deal of variability in the relationship between blood pressure and intracranial pressure.

This present study shows substantial rises in blood pressure with only moderate increases in intracranial pressure and not preceded by low levels of cerebral blood flow. These increases in intracranial pressure are at levels found in clinical practice. Furthermore, extreme levels of cerebral perfusion pressure had not been reached nor had inter-compartmental pressure differences developed before the response was initiated. One therefore has to query the suggestions that the trigger mechanisms for this blood pressure response are high intracranial pressure and cerebral ischaemia and hypoxia. In any case, one would have to cast serious doubt on the efficacy of a mechanism which is brought into action at such extreme conditions as have been suggested.

Cerebrovascular resistance changes may play an important role in the development of the hyperaemia since calculation shows that vasodilatation does occur. However, the mechanism and site for these changes are still not clear. Raised pressure on the neuraxis may directly excite sympathetic effector neurons and the intense

sympathetic activity produce marked systemic hypertension. It has been shown that 40% of the cerebrovascular resistance can be attributed to the extra parenchymal arterial system (109, 110). Furthermore, it has been postulated in a paper by Harper, Deshmukh, Rowan and Jennett (30) that the cerebral circulation behaves as two resistances in series, each under a different control system, viz., the intraparenchymal resistance (IPR) controlled by the products of cerebral cellular metabolism and by changes in the level of blood gases and the extra parenchymal resistance (EPR) under a degree of autonomic control. It would appear therefore that at the onset of the blood pressure response that the pattern of vascular resistance and blood pressure differences across the cerebrovascular system becomes re-arranged such that autoregulation becomes established at a different level of flow than before.

Beyond a certain intracranial pressure limit (66-116 mmHg in the animals in Group 1) the cerebrovascular system loses the power to autoregulate to changes in cerebral perfusion pressure. This loss of autoregulation takes place during the hyperaemic phase and furthermore the systemic hypertension is not maintained and mean blood pressure begins to fall. This results in a falling cerebral perfusion pressure and a progressive reduction in cerebral blood flow.

A great deal of caution is required in applying these results to the clinical situation since this model is not directly analogous to the condition of an expanding lesion in either the mechanism or time course of the raised intracranial pressure. Nevertheless, it is clear that a knowledge of intracranial pressure alone or even of cerebral perfusion pressure is not sufficient to define the level of cerebral blood flow. The response of cerebral blood flow to changes in intracranial pressure and cerebral perfusion pressure depends on the state of autoregulation at the time and therefore on the previous sequence of events. Clearly, if it could be established that autoregulation

had been abolished, a knowledge of cerebral perfusion pressure could be useful in predicting cerebral blood flow changes.

CHAPTER 7

EXPANDING SUPRATENTORIAL AND INFRATNETORIAL MASS LESIONS

In Chapter 6 the changes in cerebral blood flow resulting from raised intracranial pressure due to cisterna magna infusion were discussed. These observations, rather than effecting any unifying hypothesis, added to the large amount of varying results already reported on this matter from clinical and experimental investigations. These results as a whole do not provide a secure reference for the clinician who wishes to make quantitative estimates of cerebral blood flow from measurements of intracranial pressure in patients. Changes in cerebral blood flow depend on changes in cerebral perfusion pressure and cerebrovascular resistance which, in turn, depend on the mechanism and time course of the raised intracranial pressure. It should be seen clearly, therefore, that it is not possible to define a single quantitative relationship between either intracranial pressure or cerebral perfusion pressure and cerebral blood flow. What would appear to be more relevant would be to study the different patterns of cerebral blood flow response which are evoked by raised intracranial pressure caused by different mechanisms.

The aim of the study which is to be described in this chapter was to investigate the cerebral blood flow changes which occur with raised intracranial pressure resulting from focal mass lesions in either the supratentorial or infratentorial subdural space.

Methods

Baboons weighing between 9.5 and 12.5 kg were used and anaesthesia was induced and maintained as described in Chapter 6. Controlled ventilation was achieved by means of a Starling pump so that arterial pCO_2 was maintained at approximately 40 mmHg.

The following physiological variables were measured.

(i) Intracranial Pressure

This was recorded continuously from a polyethylene cannula

inserted into the right lateral ventricle. In addition cerebrospinal fluid pressure was also monitored continuously from either the cisterna magna or the lumbar subarachnoid space by means of another polyethylene cannula. Bell and Howell strain gauge transducers Type 4-327-L221 were again used and the pressure waveforms written out on Devices heat sensitive chart recorders.

(ii) Cerebral Blood Flow

This was again measured by the xenon-133 clearance technique and also by means of an electromagnetic flow probe as described in Chapter 6.

(iii) Blood Pressure

Systemic arterial pressure was measured by means of a polyethylene catheter placed in the abdominal aorta via the left femoral artery. Superior sagittal sinus and jugular venous pressures were also measured using indwelling polyethylene catheters. Similar recording apparatus to that used for the measurement of intracranial pressure was employed.

(iv) Other Variables

Before each cerebral blood flow run measurements were made of arterial pCO_2, pO_2 and pH. End tidal CO_2 was continuously monitored using an infra red analyser (Capnograph). Estimations were made at intervals throughout the experiment of arterial packed cell volume (PCV) and haemoglobin levels.

Intracranial pressure was raised approximately every 30 minutes by adding small quantities of fluid to a latex balloon so that each increase in pressure was of the order of 10-20 mmHg. When cerebral blood flow eventually became too low to be measured with any accuracy the experiment was terminated.

Two different series of experiments were carried out.

(i) Supratentorial Series

In five animals the balloon was placed over the parietal region of the left cerebral hemisphere via a parietal burrhole.

(ii) Infratentorial Series

In another five animals the balloon was placed over the lateral aspect of the right cerebellar hemisphere through a laterally placed suboccipital burrhole.

After the balloon had been correctly sited the cranial defects were sealed with dental cement. A post mortem examination was carried out at the end of each experiment in order to ensure that the balloon had not been in direct contact with any major blood vessel or had caused a cerebral haemorrhage.

Results

Supratentorial Series

Cerebral Blood Flow/Intracranial Pressure

During expansion of the supratentorial balloon a uniform relation between cerebral blood flow and intracranial pressure was observed in all animals (Figure 7.1). Cerebral blood flow remained constant during the initial phase of raised intracranial pressure. Beyond a certain intracranial pressure level, however, it fell progressively as intracranial pressure was increased further. In the case of four of the animals, the level of intracranial pressure at which a greater than 10% reduction in flow occurred, was in the range 41-68 mmHg. The fifth animal showed exceptional preservation of cerebral blood flow until an intracranial pressure level of 131 mmHg was reached. The intracranial pressure levels at which cerebral blood flow had fallen to negligible levels in successive experiments were 55, 131, 75, 79 and 32 mmHg. The last value of 32 mmHg occurred in one experiment in which the mean arterial blood pressure dropped sharply to around 40 mmHg and intracranial pressure dropped from 41 to 32 mmHg at the time of a marked reduction in cerebral blood flow.

Cerebral Blood Flow/Cerebral Perfusion Pressure

The relation between cerebral blood flow and cerebral perfusion pressure was also observed to be uniform in this series of animals

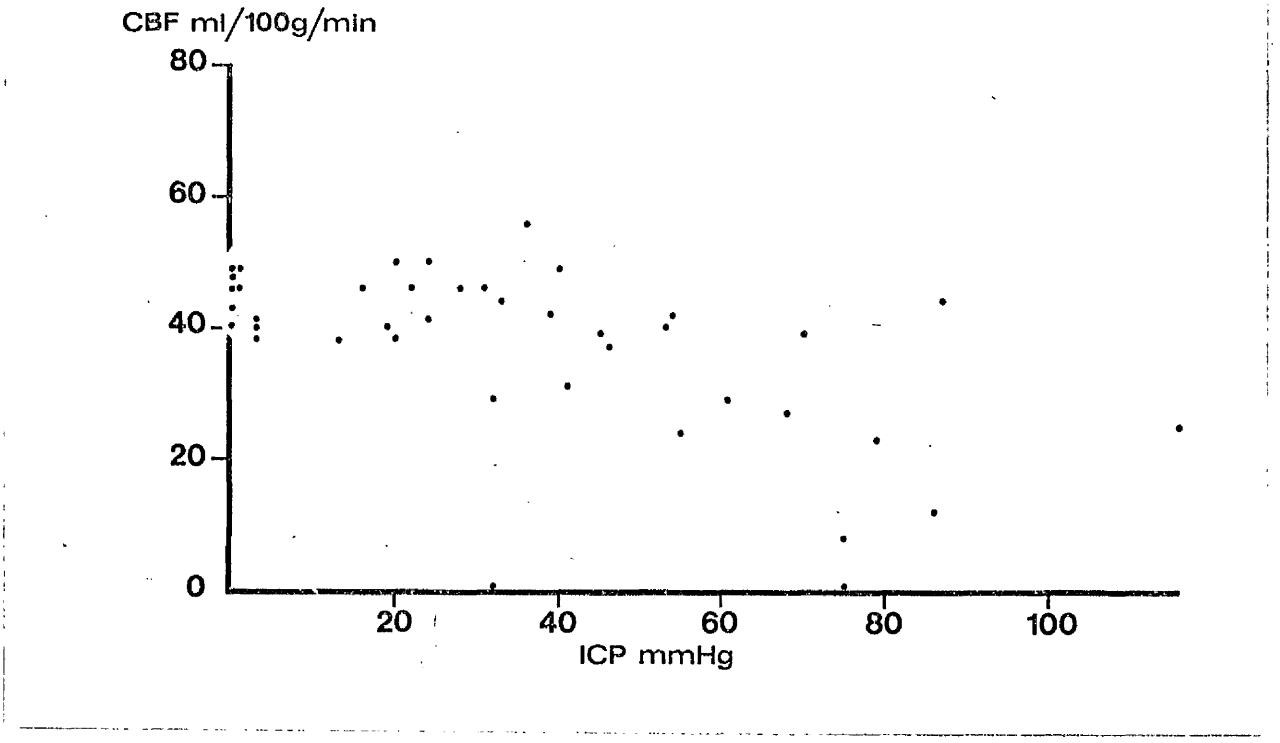


Fig. 7.1. Relation between cerebral blood flow (CBF) and intracranial pressure (ICP) during supratentorial balloon expansion.
Data from five animals.

(Figure 7.2). Cerebral blood flow remained within 90% of control values over a cerebral perfusion pressure range of 32-108 mmHg. The cerebral perfusion pressure levels beyond which cerebral blood fell below 30 ml/100g/min were 32, 36, 45, 54 and 64 mmHg in each of the five experiments. Furthermore, initially during the transient changes in cerebral perfusion pressure resulting from the transient hypertensive episodes at the time of each balloon inflation, cerebral blood flow as determined by the electromagnetic flow probe on the common carotid artery remained constant apart from a 30 second fall before autoregulation became effective. However, during the latter stages of the experiments when cerebral blood flow had fallen significantly from control levels, transient cerebral perfusion pressure changes were reflected in corresponding changes in cerebral blood flow.

Cerebrovascular Resistance

In general, cerebrovascular resistance fell progressively as intracranial pressure rose to approximately 60 mmHg (Figure 7.3). This reduction in cerebrovascular resistance was associated with relatively constant values of cerebral blood flow. Beyond this range of intracranial pressure cerebrovascular resistance remained constant or rose slightly in three animals while in the remaining animals cerebrovascular resistance continued to fall.

Autoregulation

Effective autoregulation was maintained until the supratentorial balloon expansion resulted in an intracranial pressure level of approximately 60 mmHg (Figure 7.1). This corresponded to a cerebral perfusion pressure level of approximately 40 mmHg. Furthermore, during the transient changes in intracranial pressure and blood pressure, which occurred in association with each balloon inflation, effective autoregulation was also observed. Below a cerebral perfusion pressure of 40 mmHg autoregulation was progressively lost and cerebral blood flow eventually fell in a linear fashion with

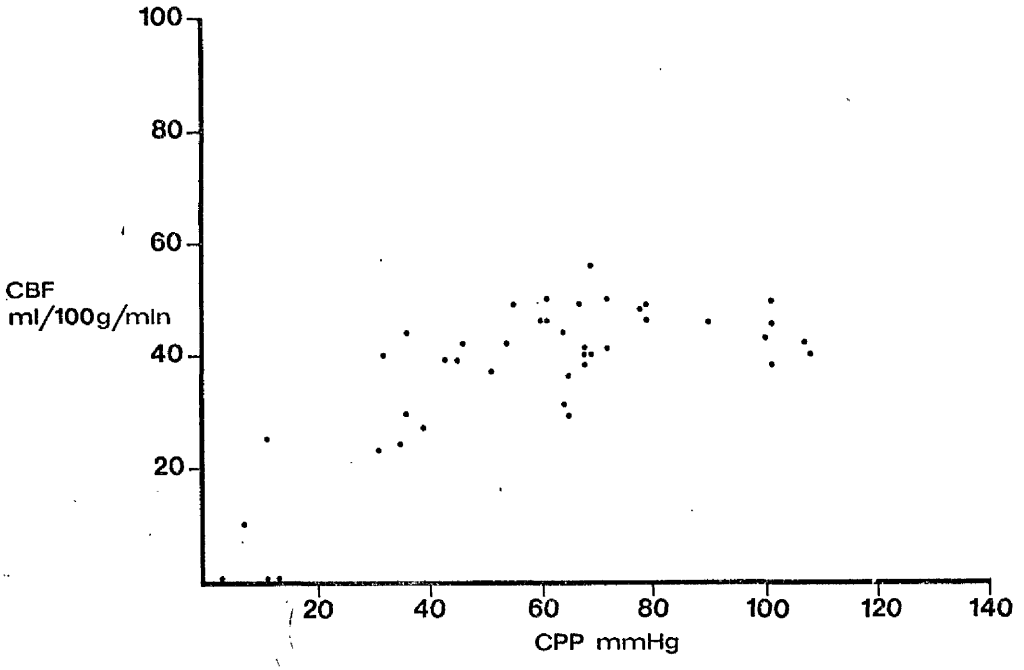


Fig. 7.2. Relation between cerebral blood flow (CBF) and cerebral perfusion pressure (CPP) during supratentorial balloon expansion.
Data from five animals.

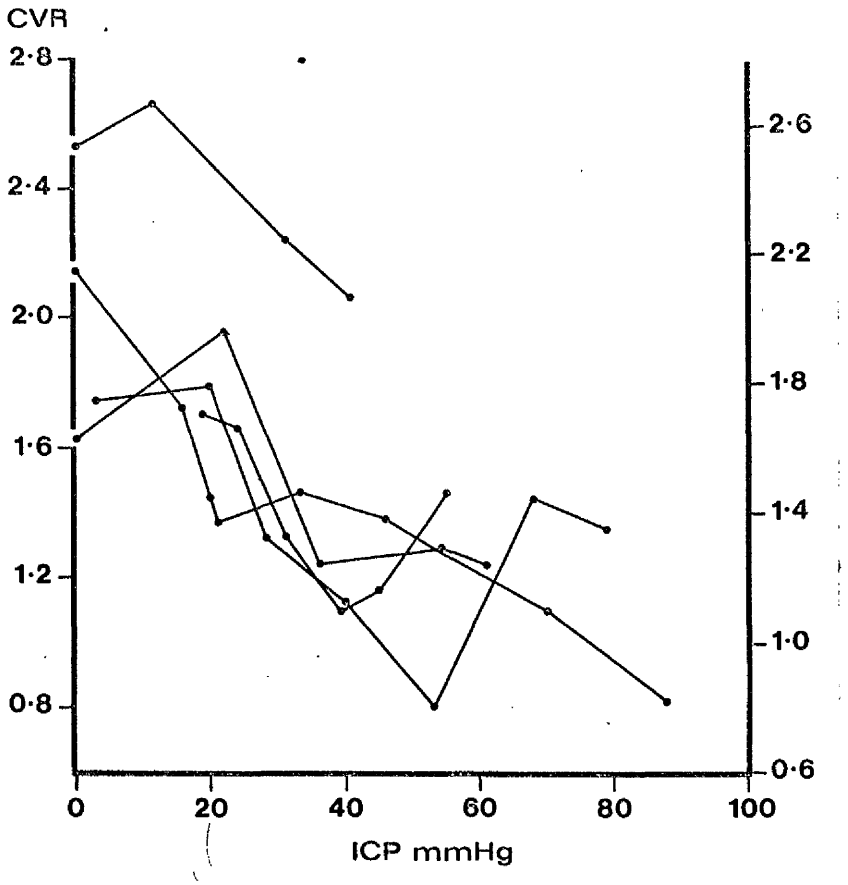


Fig. 7.3. Cerebrovascular resistance (CVR) changes in each experiment during supratentorial balloon expansion.

cerebral perfusion pressure.

Infratentorial Series

Cerebral Blood Flow/Intracranial Pressure

No clear relation between cerebral blood flow and intracranial pressure was observed in the animals in this series. Figure 7.4, which is a plot of cerebral blood flow measurements against the corresponding intracranial pressure values, displays the lack of any consistent relation between these two variables. At relatively low values of intracranial pressure a wide range of cerebral blood flow values were obtained and critical reductions in blood flow were observed over a wide range of intracranial pressure. For example, flow reductions to values below 30 ml/100g/min were associated with intracranial pressure levels ranging from 7 to 77 mmHg. Furthermore, it was very striking with this series that cerebral blood flow consistently fell to negligible levels or ceased altogether at relatively low values of intracranial pressure. The levels of intracranial pressure at which this occurred in the five animals were 35, 35, 42, 47 and 77 mmHg respectively.

Cerebral Blood Flow/Cerebral Perfusion Pressure

In contrast to the cerebral blood flow/intracranial pressure relationship the cerebral blood flow/cerebral perfusion pressure relationship was observed to be uniform (Figure 7.5). When cerebral blood flow values from all five experiments were plotted against the corresponding cerebral perfusion pressure values a linear relationship was obtained (correlation coefficient:- 0.90, $p << 0.001$). This relationship was exemplified during the transient increases in blood pressure which occurred with each balloon inflation when cerebral blood flow, as measured by the electromagnetic flow meter, varied pari passu with blood pressure and cerebral perfusion pressure (Figure 7.6). The marked blood pressure changes which occurred in the animals in this series together with the direct linear relation between cerebral blood

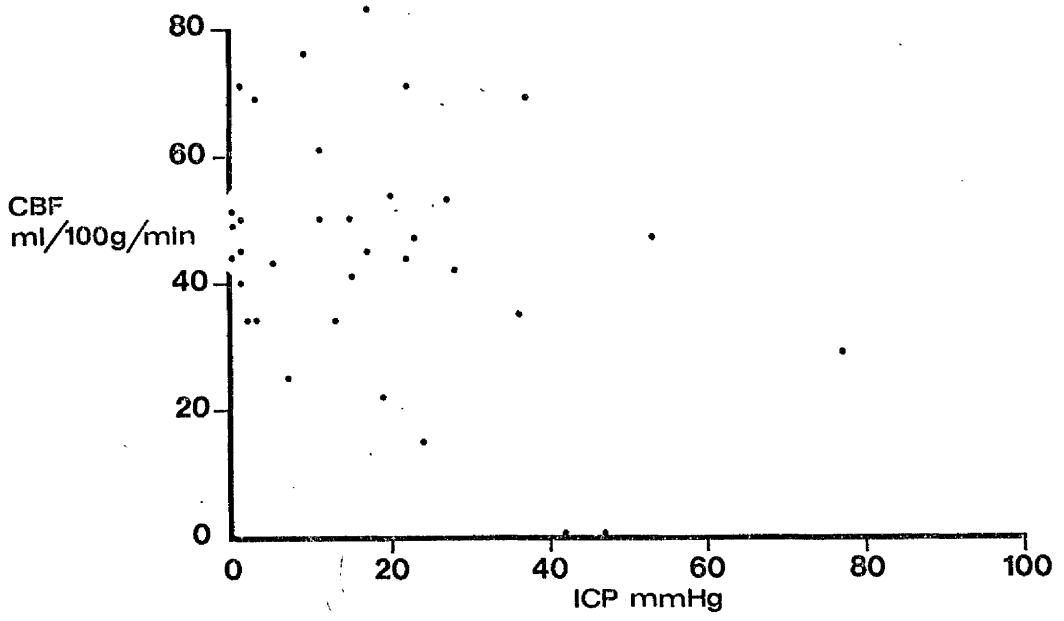


Figure 7.4. Relation between cerebral blood flow (CBF) and intracranial pressure (ICP) during infratentorial balloon expansion.
Data from five animals.

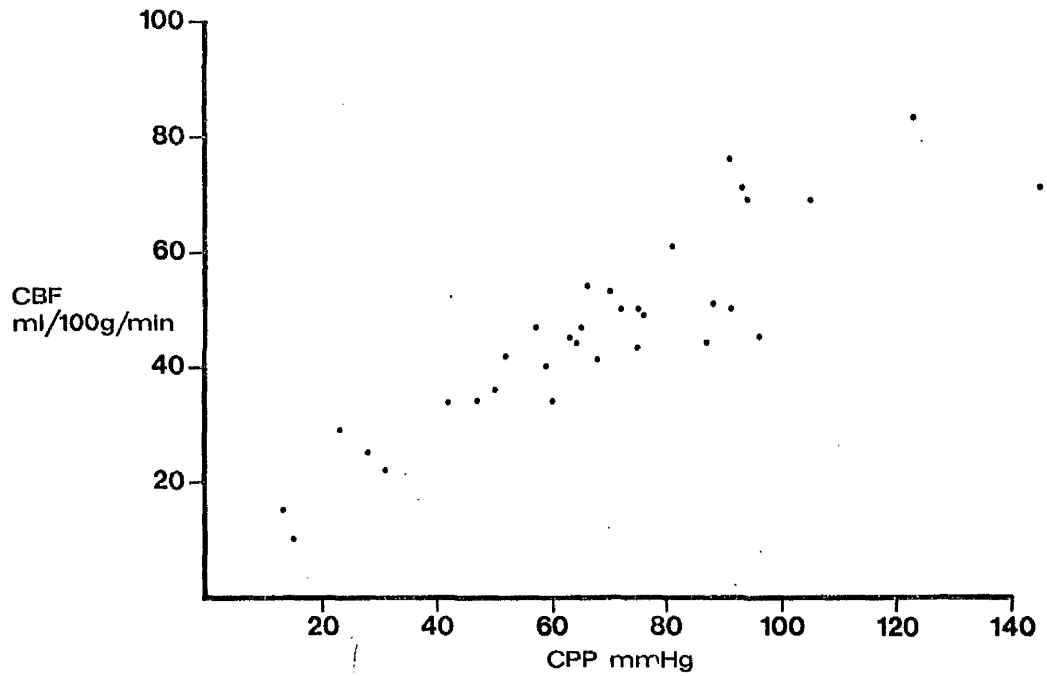


Fig. 7.5. Relation between cerebral blood flow (CBF) and cerebral perfusion pressure (CPP) during infratentorial balloon expansion.
Data from five animals.

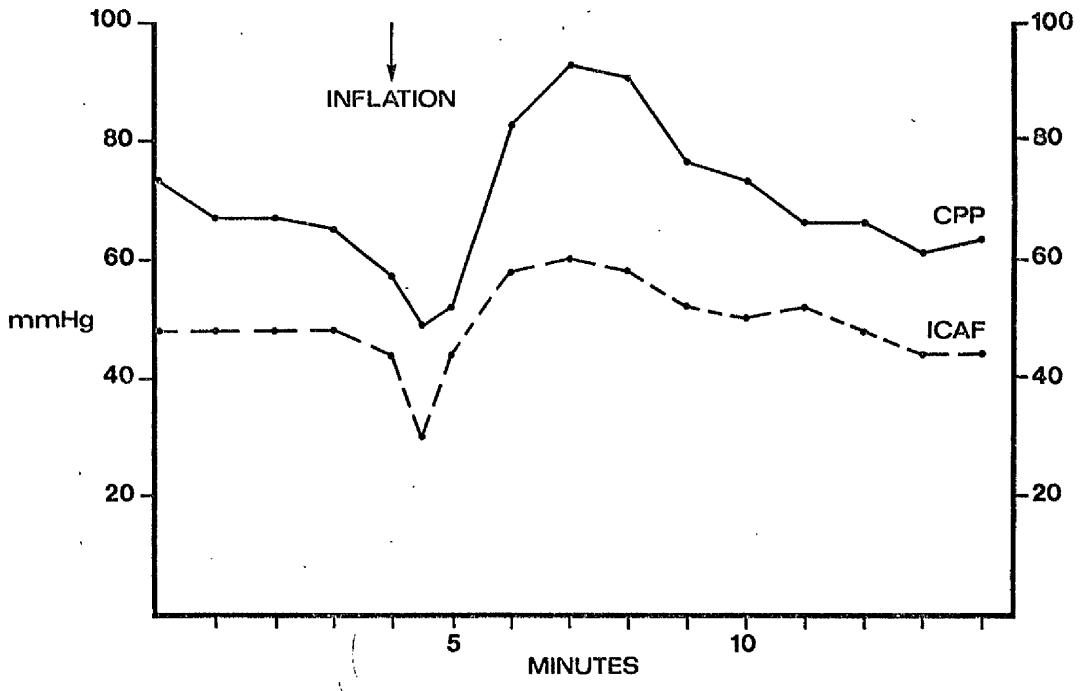


Fig. 7.6. Typical transient changes in cerebral perfusion pressure (CPP) and internal carotid artery flow (ICAF) during infratentorial balloon expansion.

flow and cerebral perfusion pressure go a long way to explain the lack of a consistent relationship between cerebral blood flow and intracranial pressure.

Cerebrovascular Resistance

With this group of animals cerebrovascular resistance tended to remain constant within the intracranial pressure range 10-60 mmHg (Figure 7.7). In two animals the initial increase in intracranial pressure resulted in an increase in cerebrovascular resistance which later fell sharply to a steady level as intracranial pressure rose further. Another two animals displayed a sharp fall in cerebrovascular resistance before reaching a steady level. The remaining animal exhibited a constant level of cerebrovascular resistance before finally falling at the terminal stages of the experiment. The general pattern consisted therefore of initial changes in cerebrovascular resistance followed by the maintenance of a constant level between an intracranial pressure range from 10-60 mmHg.

Autoregulation

It is clear from the plot of cerebral blood flow against cerebral perfusion pressure (Figure 7.5) that in all five animals autoregulation was absent from the first injection of fluid into the infratentorial balloon. As with the composite plot for all five experiments, the plot of cerebral blood flow against cerebral perfusion pressure for each animal was also linear (correlation coefficients:- 0.97, 0.89, 0.96, 0.93, 0.94 respectively with $p << 0.001$). Furthermore, the close correspondence between the transient changes in blood pressure, cerebral perfusion pressure and cerebral blood flow which was observed between each balloon inflation is also clearly indicative of the absence of autoregulation.

Discussion

Starting from similar control levels of cerebral blood flow, intracranial pressure and arterial blood pressure, the level of intracranial pressure reached before there was a marked reduction in cerebral blood

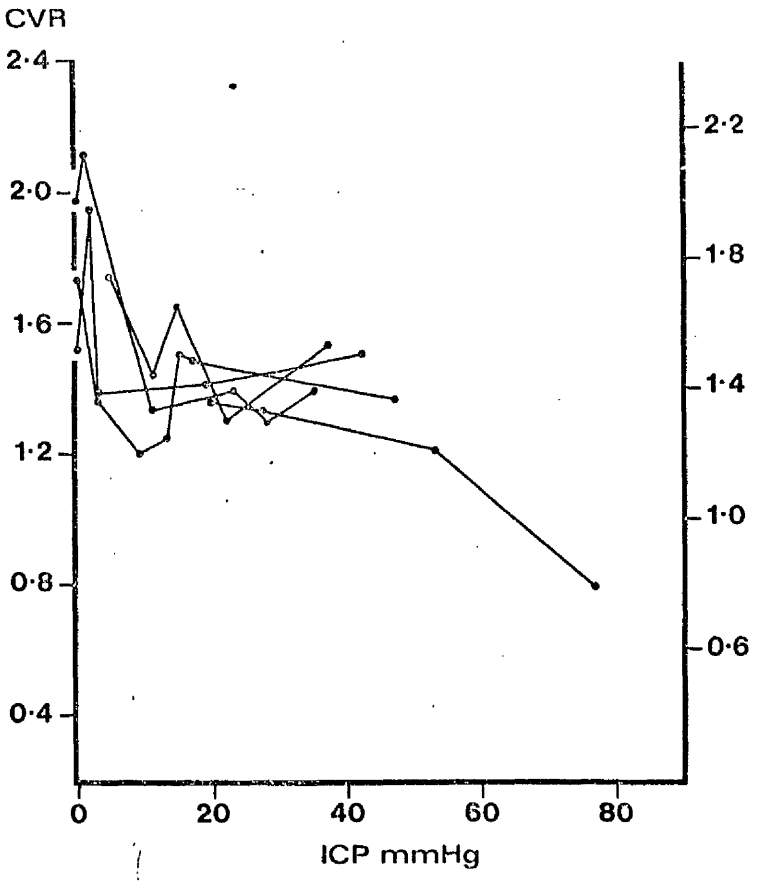


Fig. 7.7. Cerebrovascular resistance changes in each experiment during infratentorial balloon expansion.

flow, depended on the site of the balloon. With inflation of a supratentorial balloon cerebral blood flow fell at intracranial pressure levels in the range 42-131 mmHg while with infratentorial balloon inflation cerebral blood flow fell at relatively low levels of intracranial pressure (38-77 mmHg). Less fluid had to be added to the infratentorial balloon (5 ml) than to the supratentorial balloon (14-22 ml) in order to reach these critical blood flow levels. At the time the fluid was added to the balloon, both groups of animals displayed a marked transient blood pressure response with each fluid addition to the balloon.

The results of these experiments together with the results outlined in Chapter 6 confirm that cerebral blood flow changes in response to raised intracranial pressure depend on the mechanism of the intracranial pressure increase. With infusion of fluid into the subarachnoid space (Chapter 6), three response phases were seen.

(i) With intracranial pressure in the range 0-50 mmHg cerebral blood flow remained constant.

(ii) With intracranial pressure within the range 50-85 mmHg hyperaemic levels were observed.

(iii) At greater levels of intracranial pressure cerebral blood flow fell progressively.

Expansion of a supratentorial balloon resulted in cerebral blood flow being maintained constant through a wide range of intracranial pressure (0-60 mmHg) and cerebral perfusion pressure (100-40 mmHg). Beyond these pressure levels cerebral blood flow again fell progressively. With infratentorial balloon expansion no clear relationship between cerebral blood flow and intracranial pressure was observed. Both high and low cerebral blood flow levels were recorded over a wide range of intracranial pressure. However, a highly significant linear correlation was found between cerebral blood flow and cerebral perfusion pressure with these animals. These observations of the response of cerebral

blood flow to different methods of raising intracranial pressure were carried out under the same basic experimental conditions and over very similar periods of time. They therefore suggest a possible explanation of the variability which is characteristic of previously reported experimental and clinical findings with regard to the relation between cerebral blood flow and intracranial pressure (70, 74, 75, 76, 111 and 112). It would appear that the mechanisms which control cerebral blood flow act differently according to the cause of the raised intracranial pressure.

Cerebral perfusion pressure, defined as the difference between mean arterial blood pressure and mean intracranial pressure (84) and cerebrovascular resistance defined as the ratio of cerebral perfusion pressure to cerebral blood flow, are the major factors which control cerebral blood flow. Cerebral perfusion pressure and cerebrovascular resistance can be influenced by a number of factors and the definitions given above are based on assumptions which can still be subjects of controversy. The level of cerebral perfusion pressure at a particular level of intracranial pressure depends on the blood pressure level. The magnitude and the time course of the blood pressure response differed according to the method used to raise intracranial pressure such that, at any given intracranial pressure, cerebral perfusion pressure differed in each group of animals. The definition of cerebral perfusion pressure used depends on two main assumptions.

(i) The mean arterial pressure represents the effective in-flow pressure.

(ii) Intracranial pressure represents effective venous out-flow pressure.

The magnitude of the arterial pressure drop between extra and intracranial vessels may vary with changes in arterial pressure and intracranial pressure (109). The approximation of intracranial pressure to the effective out-flow venous pressure has to be confirmed

over a wide range of intracranial pressure values. Shulman has shown a close correlation between intracranial pressure and cortical subarachnoid vein pressure at low levels of intracranial pressure (113, 114). At extreme levels of intracranial pressure marked morphological changes which could have a significant bearing on the venous out-flow pressure have been observed in the major dural venous sinuses (91, 93, 115, 116). Furthermore, a number of workers have proposed that within the same intracranial compartment pressure does not remain uniform as intracranial pressure rises (14, 117). A great deal of controversy still surrounds this proposition.

Calculated values of cerebrovascular resistance have also exhibited a different pattern depending on the method used to raise intracranial pressure. With cisterna magna infusion (Chapter 6) cerebrovascular resistance fell during the initial intracranial pressure increase and fell more gradually during the hyperaemic phase. Supratentorial balloon expansion resulted in a steady fall in cerebrovascular resistance whereas infratentorial balloon expansion gave rise to sharp initial changes followed by a constant cerebrovascular resistance level. These differing patterns of cerebrovascular resistance changes reflect the different influence of the factors which control cerebral vessel resistance and capacitance during different forms of raised intracranial pressure. Raised pressure due to infusion of fluid into the subarachnoid space may result in changes in blood vessel environment which in turn may alter the response of vessels to metabolic stimuli. A focal, supratentorial mass may cause brain shift and hence cause distortion and mechanical obstruction of the superficial cortical veins. An infratentorial mass may locally stimulate the brain stem and thereby influence sympathetic activity and cause cerebral blood flow changes as a result of altering the diameter of both the extraparenchymal intracranial vessels and the large vessels in the neck (30).

Autoregulation of cerebral blood flow is achieved as a result of

cerebrovascular resistance changes which act to preserve cerebral blood flow in the face of a changing cerebral perfusion pressure. With the cisterna magna experiments described in Chapter 6 autoregulation of cerebral blood flow was present over a range of 0-50 mmHg. At higher levels of intracranial pressure autoregulation still appeared to be effective although at a higher setting of blood flow. After the hyperaemic phase autoregulation was no longer effective and cerebral blood flow became directly proportional to cerebral perfusion pressure. In the experiments described in this chapter, as a supratentorial balloon was expanded autoregulation was present down to a cerebral perfusion pressure of approximately 40 mmHg and then was lost. Infratentorial balloon expansion resulted in loss of autoregulation from the time of the initial expansion. Therefore, three distinctly different patterns of autoregulation were seen in the three different sets of experiments. These observations suggest that there is probably no single autoregulation mechanism but indeed that there must be a number of complex inter-related compensatory mechanisms which are brought into action to preserve cerebral blood flow in stress situations when the blood supply to the brain is compromised. The actual format of the total compensatory response will depend on the initiating mechanism which results in the increase in intracranial pressure.

It is clear from the results of the experiments described so far that it is not possible to define an overall quantitative relationship between intracranial pressure, cerebral perfusion pressure and cerebral blood flow. Therefore, any clinician who attempts to forecast cerebral blood flow values from measurements of intracranial pressure or cerebral perfusion pressure has no secure basis for his forecast. Clearly, increasing intracranial pressure will eventually lead to a reduction in cerebral blood flow but there is no real basis for drawing quantitative conclusions concerning cerebral blood flow from intra-

cranial pressure and cerebral perfusion pressure measurements made in the hospital ward. A number of unanswered questions still remain concerning the mechanism of autoregulation and the assumptions concerning the concepts associated with cerebral perfusion pressure and cerebrovascular resistance.

CHAPTER 8

CEREBRAL PERFUSION PRESSURE AND CEREBROVASCULAR RESISTANCES IN INTRACRANIAL HYPERTENSION

The major factors determining cerebral blood flow are the pressure difference and the sum of the resistances across the cerebrovascular system. This pressure difference, or as it is often called, cerebral perfusion pressure, can be altered by a change in in-flow pressure (carotid artery blood pressure) or by a change in out-flow pressure (cortical venous pressure, also referred to as cerebral subarachnoid venous pressure). The accepted convention of defining cerebral perfusion pressure as the difference between mean carotid artery blood pressure and mean intracranial pressure assumes an equation between intracranial pressure and the vascular out-flow pressure. It has been shown in previous chapters that raised intracranial pressure may substantially reduce cerebral blood flow although no consistent quantitative relationship can be derived. This failure to define a direct quantitative relationship between cerebral blood flow and cerebral perfusion pressure could result from the limitations of the definition of cerebral perfusion pressure or from the correspondence between the type of cerebrovascular resistance changes and different types of raised intracranial pressure. Cerebrovascular resistance changes could alter cerebral blood flow levels without any change in cerebral perfusion pressure. These resistance changes could result from changes in transmural pressures and also from changes in neural, chemical or metabolic factors.

The study which will be described was initiated with the aim of measuring directly the pressure changes which occur in different segments of the venous out-flow tract from the brain when intracranial pressure is raised experimentally in a number of ways. In this way it would be possible to determine whether or not intracranial pressure did represent the effective venous out-flow pressure over a wide range of

intracranial pressure in widely different circumstances. Thus the validity of the concept of cerebral perfusion pressure as mean arterial blood pressure minus mean intracranial pressure could be properly examined. Furthermore, it would be possible to study the nature of the cerebrovascular resistance changes which occur and relate them to the different types of cerebral blood flow changes which result from the various types of raised intracranial pressure.

Methods

Thirteen adult baboons weighing between 8 and 13 kg were used and anaesthesia was induced and maintained in the standard fashion. Ventilation was again controlled throughout using a Starling pump with the tidal volume adjusted to maintain normal arterial blood gas levels. Cerebral blood flow was measured at intervals using the xenon-133 clearance technique in the manner described previously, while an electromagnetic flow meter was used to obtain continuous measurements of carotid artery blood flow.

Using strain gauge transducers (Bell and Howell, type 4-327-L221) pressures were continuously monitored by means of indwelling catheters in:-

(i) The carotid artery (carotid artery blood pressure - CABP).

(ii) The frontal horn of the right lateral ventricle (ventricular fluid pressure - VFP).

(iii) Large cortical vein in the area of entry into the superior sagittal sinus (cortical vein pressure - C_0VP or cerebral subarachnoid venous pressure - CSAVP).

(iv) Posterior end of the superior sagittal sinus (sagittal sinus pressure - SSP).

(v) Jugular bulb (jugular venous pressure - JVP).

The resultant pressure wave forms were written out on heat sensitive chart recorders (Devices M2 and M4).

All cranial defects were sealed using dental cement.

End-tidal CO_2 was monitored continuously by means of an infra-red analyser (Capnograph) and arterial pO_2, pCO_2 and pH, sagittal sinus pO_2 and Hb were estimated at frequent intervals.

Intracranial pressure was increased in one of the three ways described in the previous chapters, i.e.

(1) By infusion of mock cerebrospinal fluid, at constant temperature, into the cisterna magna (six animals).

(2) By expansion of a supratentorial balloon placed subdurally in the right parietal region (six animals).

(3) By expansion of an infratentorial balloon placed subdurally in the right cerebello-pontine angle (one animal).

In all experiments the ventricular fluid pressure was raised in increments of 10-20 mmHg approximately every 30 minutes.

Results

Pressure Changes

Table 8.1 shows the mean control pressure values for each of the three experimental groups.

(1) Cortical Vein Pressure

With cisterna magna infusion, cortical vein pressure increased steadily as intracranial pressure was raised up to extreme levels. Figure 8.1 is a plot of values of cortical venous pressure against corresponding values of ventricular fluid pressure obtained during cisterna magna infusion. A highly statistically significant linear correlation coefficient of 0.98 was obtained and the regression line is closely parallel to the line of identity $y = x$. A positive intercept on the cortical venous pressure axis of 2.8 mmHg was obtained and this exhibits the tendency of the pressure within the cortical veins to remain slightly higher than the intracranial pressure. The dotted lines are boundary lines signifying two standard errors of estimate.

Similar highly significant correlations were obtained between cortical venous pressure and ventricular fluid pressure when the

	BP (mmHg)	VFP (mmHg)	C_0VP (mmHg)	SSP (mmHg)	JVP (mmHg)	CPP (mmHg)	CBF (ml/100g/min)
Cisterna Magna Infusion							
Control	91	9	11	5	4	82	42
At Maximum ICP	130	114	113	44	6	16	12
Supratentorial Balloon							
Control	71	6	9	8	5	65	49
At Maximum ICP	91	74	78	11	4	17	15
Infratentorial Balloon							
Control	75	12	17	-	-	63	39
At Maximum ICP	133	47	51	-	-	86	66

TABLE 8.1

MEAN OF CONTROL VALUES AND VALUES AT MAXIMUM INTRACRANIAL PRESSURE IN EACH OF THE THREE GROUPS

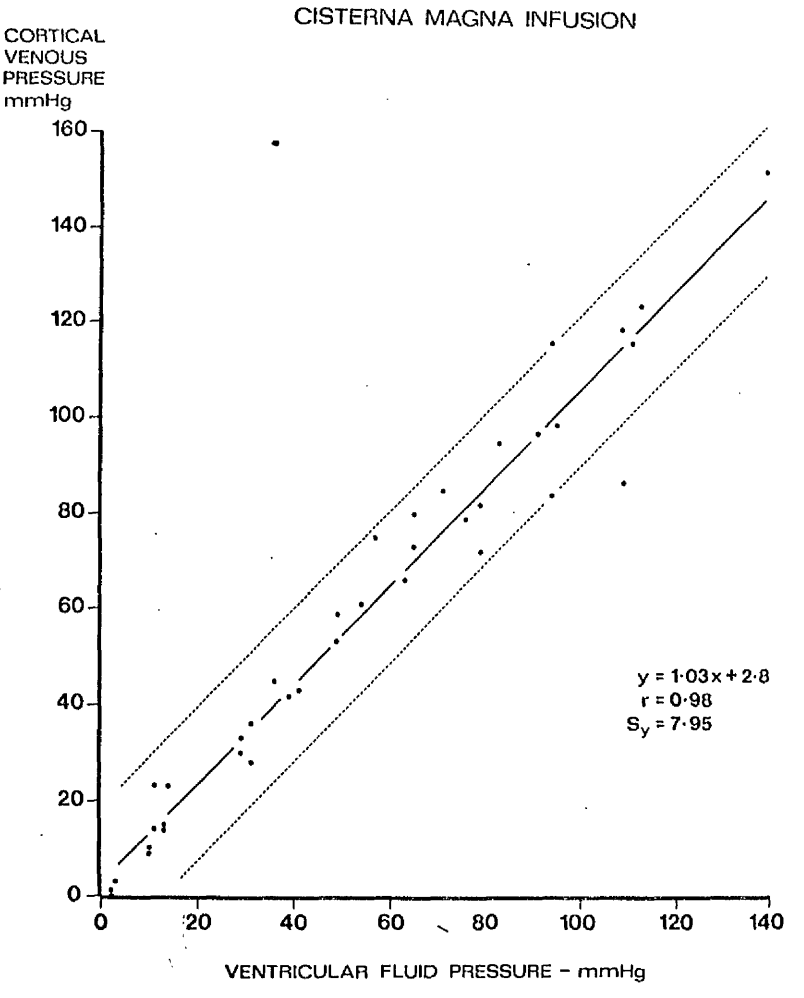


Fig. 8.1. Relation between cortical venous pressure and ventricular fluid pressure during cisterna magna infusion.
Data from six animals.

latter was increased as a result of supratentorial and infratentorial balloon inflation (Figures 8.2 and 8.3).

Table 8.2 summarises the results of the statistical analysis carried out on data from the three groups of experiments while Figure 8.4 is a composite plot of cortical venous pressure values and ventricular fluid pressure values from all experiments. The regression equation for each group of experiments exhibits similar characteristics of a gradient close to unity together with a small positive intercept on the cortical vein pressure axis.

Transient induced changes in intracranial pressure were also closely reflected in similar cortical vein pressure changes.

Under control conditions there was a positive pressure difference between cortical vein pressure and sagittal sinus pressure. Generally, with all methods of raising intracranial pressure this difference increased progressively. However, in the case of three animals in the cisterna magna infusion group, a progressive rise in sagittal sinus pressure also occurred and as a result the cortical vein pressure/sagittal sinus pressure difference did not increase as much as it did in the other experiments. Furthermore, in one of these three animals sagittal sinus pressure increased to the level of cortical vein pressure for a short period of time towards the later stages of the experiment.

(2) Sagittal Sinus Pressure

In the cisterna magna infusion group of animals sagittal sinus pressure remained at jugular venous pressure levels in three animals; it rose to intermediate pressure levels in two animals and eventually reached intracranial pressure levels in one animal. In all experiments in this group carotid artery blood pressure, cortical venous pressure, ventricular fluid pressure and jugular venous pressure behaved in a similar fashion.

Figures 8.5a, 8.5b and 8.5c show graphs of carotid artery blood

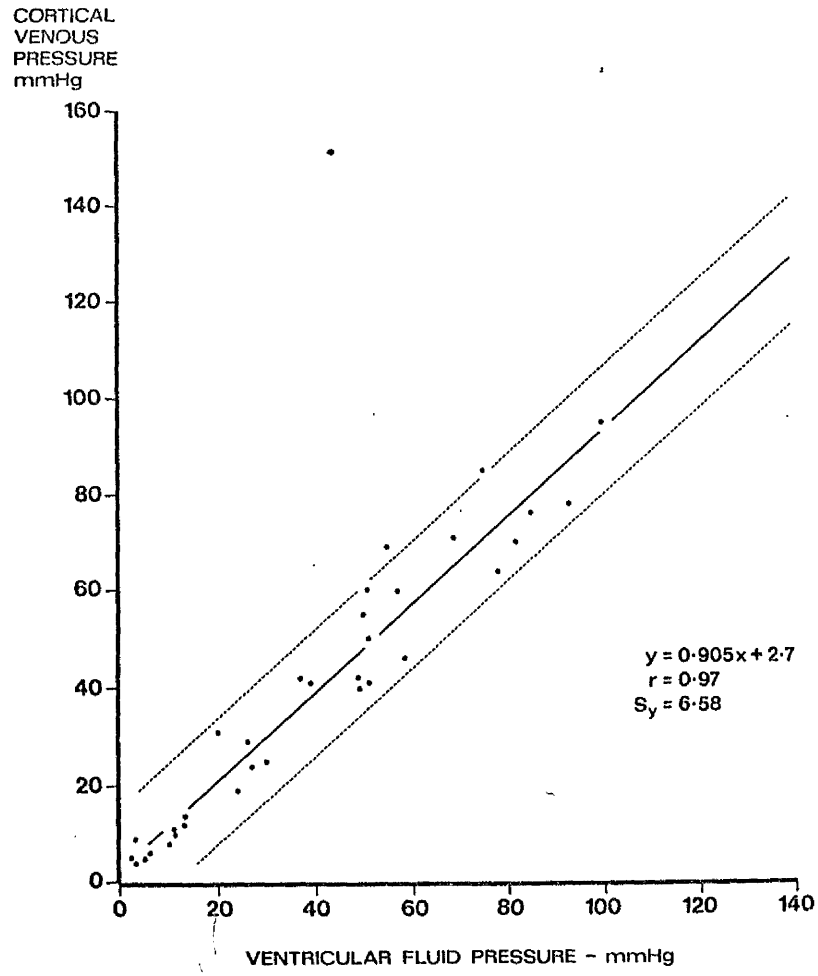


Fig. 8.2. Relation between cortical venous pressure and ventricular fluid pressure during supratentorial balloon expansion.
Data from six animals.

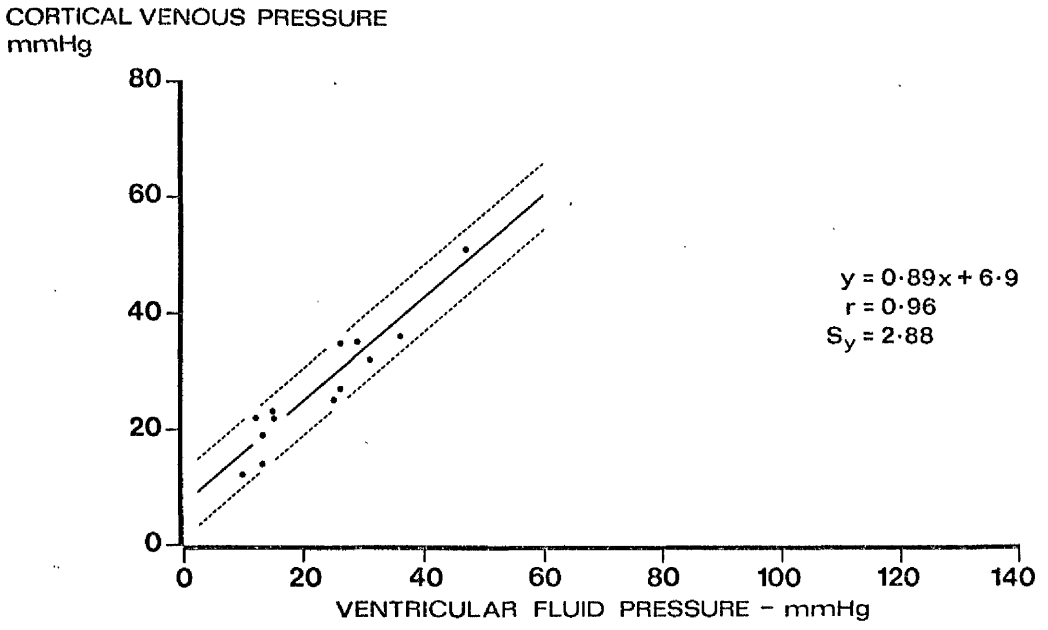


Fig. 8.3. Relation between cortical venous pressure and ventricular fluid pressure during infratentorial balloon expansion. Data from one animal.

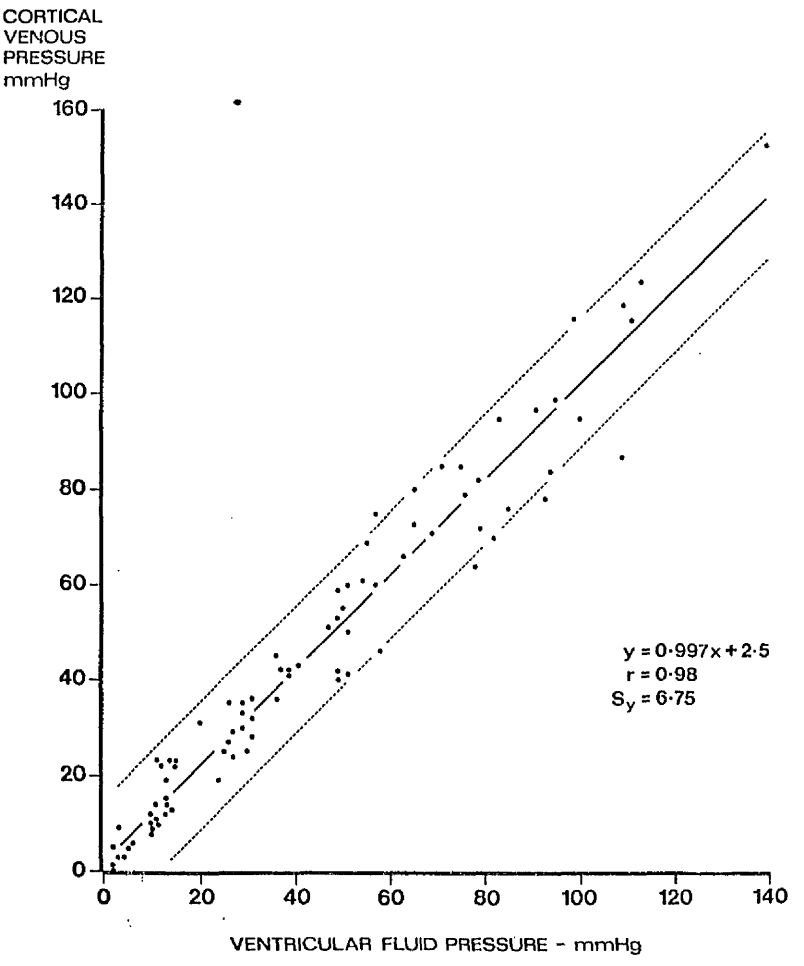


Fig. 8.4. Composite plot of cortical venous pressure values and ventricular fluid pressure values from all experiments.

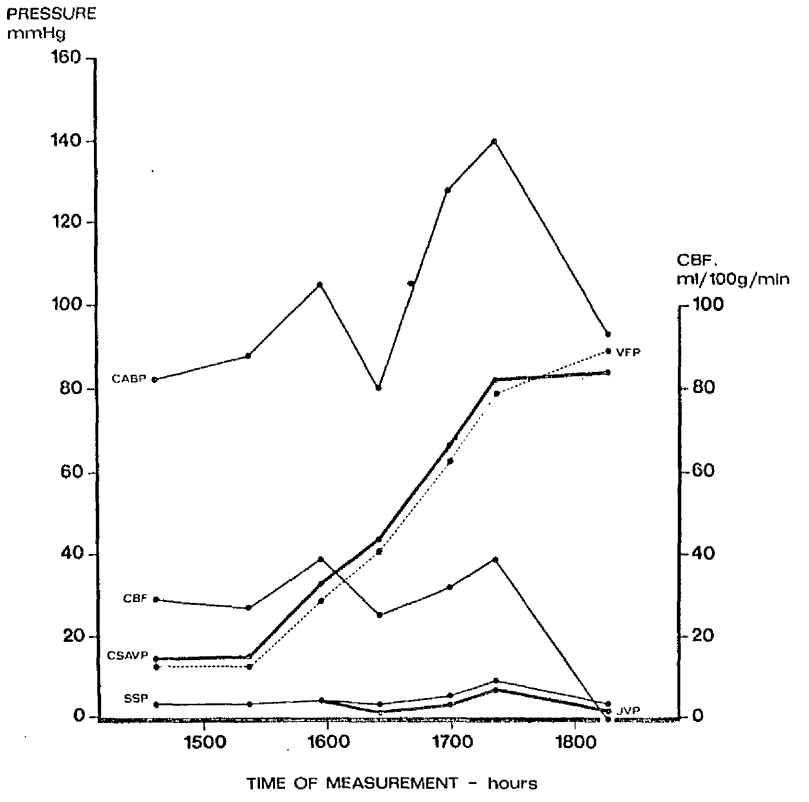


Fig. 8.5(a) Low sagittal sinus pressure.

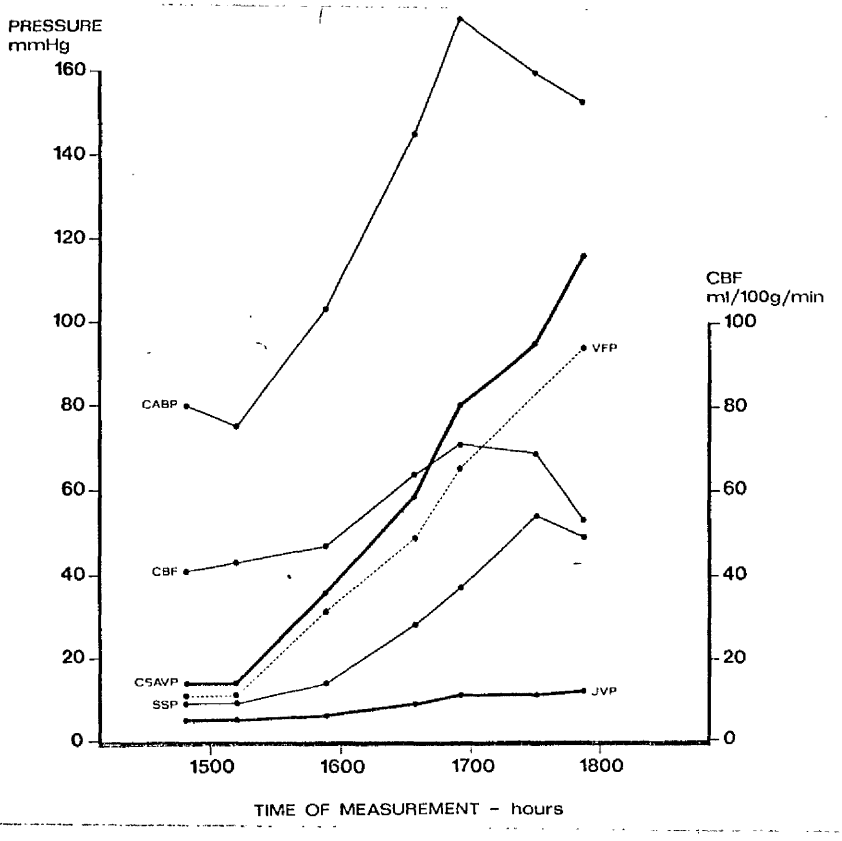


Fig. 8.5(b) Increased sagittal sinus pressure.

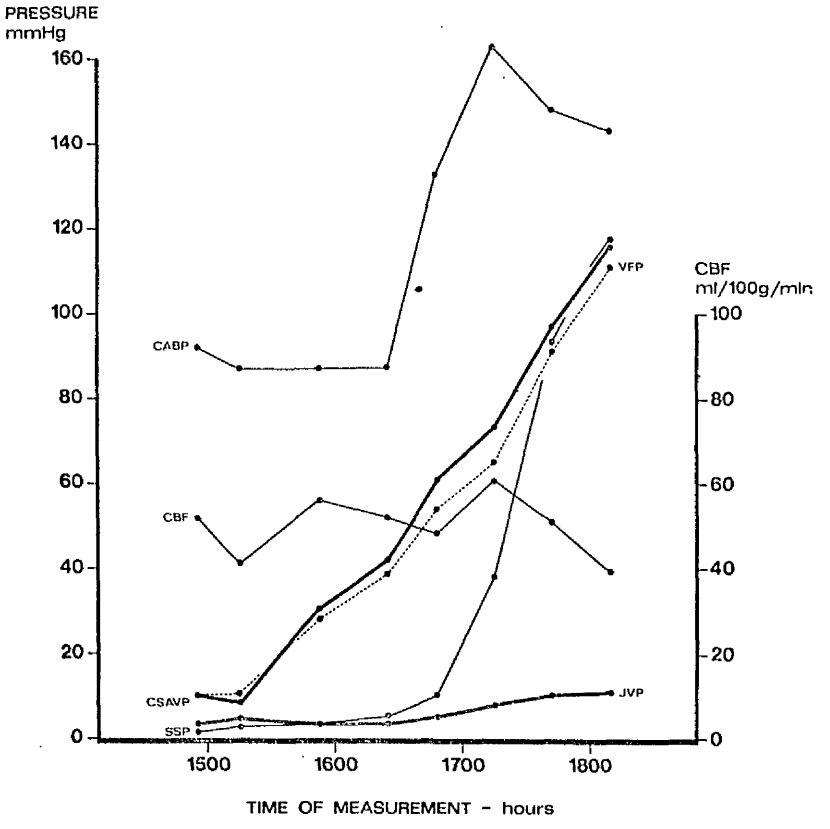


Fig. 8.5(c) High sagittal sinus pressure.

Figs. 8.5(a), (b) and (c).

Plots of carotid artery blood pressure (CABP), cerebral subarachnoid venous pressure (CSAVP), ventricular fluid pressure (VFP), sagittal sinus pressure (SSP), jugular venous pressure (JVP) and cerebral blood flow (CBF) against times of measurement in three different cisterna magna infusion experiments.

METHOD OF RAISING ICP	REGRESSION EQUATION	CORRELATION COEFFICIENT r	STUDENTS t	PROBABILITY p	STANDARD ERROR OF ESTIMATE of y	NUMBER OF PAIRED OBSERVATIONS n
Cisterna Magna Infusion	$y = 1.03x + 2.8$	0.98	32	$<< 0.001$	7.95	39
Supratentorial Balloon	$y = 0.91x + 2.7$	0.97	22	$<< 0.001$	6.58	33
Infratentorial Balloon	$y = 0.89x + 6.9$	0.96	10	$<< 0.001$	2.88	14
All three methods	$y = 0.997x + 2.5$	0.98	41	$<< 0.001$	6.75	86

TABLE 8.2

SUMMARY OF RESULTS OF STATISTICAL ANALYSIS CARRIED OUT ON CORTICAL VENOUS PRESSURE AND INTRACRANIAL PRESSURE DATA FOR EACH METHOD OF RAISING INTRACRANIAL PRESSURE

pressure (CABP), cerebral subarachnoid venous pressure (CSAVP), ventricular fluid pressure (VFP), sagittal sinus pressure (SSP), jugular venous pressure (JVP) and cerebral blood flow (CBF) plotted against the times of measurement in three different cisterna magna infusion experiments.

In Figure 8.5a sagittal sinus pressure remained at jugular venous pressure levels (2-10 mmHg) throughout the time course of the experiment. Cerebral blood flow remained within control limits until perfusion pressure fell below the autoregulatory level while blood pressure exhibited the characteristic response. The CSAVP and VFP curves followed each other extremely closely, the maximum difference being 5 mmHg.

In Figure 8.5b sagittal sinus pressure rose progressively to an intermediate pressure level of 54 mmHg. A hyperaemic phase, in which cerebral blood flow rose to 71 mm/100g/min, was initiated as well as a blood pressure response.

In Figure 8.5c sagittal sinus pressure began to rise at a ventricular fluid pressure of the order of 54 mmHg and continued to rise with successive intracranial pressure increases until there was no significant difference between VFP, CSAVP and SSP. JVP did not rise above 11 mmHg and CBF remained between 41 and 61 ml/100g/min throughout the experiment.

In the three animals in which sagittal sinus pressure remained low there was a slight increase at extreme levels of intracranial pressure. However, the pressure always remained below 20 mmHg. Any small fluctuations that were seen were the result of changes in cerebral blood flow as monitored by the electromagnetic flow meter on the carotid artery. In the other three animals in this group sagittal sinus pressure began to rise when intracranial pressure approached 40 mmHg and continued to rise to reach pressures of 59, 79 and 117 mmHg at corresponding intracranial pressure levels of 95, 113 and

111 mmHg. Furthermore, during the final stages of these three experiments, transient changes in sagittal sinus pressure were observed (Figure 8.6). These changes were of considerable magnitude and appeared to be independent of changes in any of the other measured physiological variables. Sagittal sinus pressure remained low throughout the experiments involving supratentorial and infratentorial balloon expansion. Furthermore, no transient changes in sagittal sinus pressure of the type described above were observed.

In those animals in which the sagittal sinus pressure exhibited an increase during extreme levels of intracranial pressure a substantial difference between sagittal sinus pressure and jugular venous pressure was therefore observed.

(3) Jugular Venous Pressure

In the cisterna magna infusion experiments there was a slight increase in jugular venous pressure as the experiment progressed. However, jugular venous pressure did tend to fall when blood pressure and cerebral blood flow fell in the final stages of the experiment. In the supratentorial and infratentorial balloon experiments little change in jugular venous pressure was observed.

(4) Cerebral Perfusion Pressure

In the experiments involving cisterna magna infusion blood pressure behaved as described previously. During the initial stages of the experiments a marked blood pressure response was observed and eventually maximum blood pressure was reached at intracranial pressure levels in the range 40-90 mmHg. With further increases in intracranial pressure blood pressure tended to fall. Again with the balloon inflation experiments, transient blood pressure responses were observed with each addition of fluid to the balloon. A progressive blood pressure increase did occur in these animals over the time course of the experiment.

The resultant perfusion pressure changes caused by these blood pressure and intracranial pressure changes were calculated from the

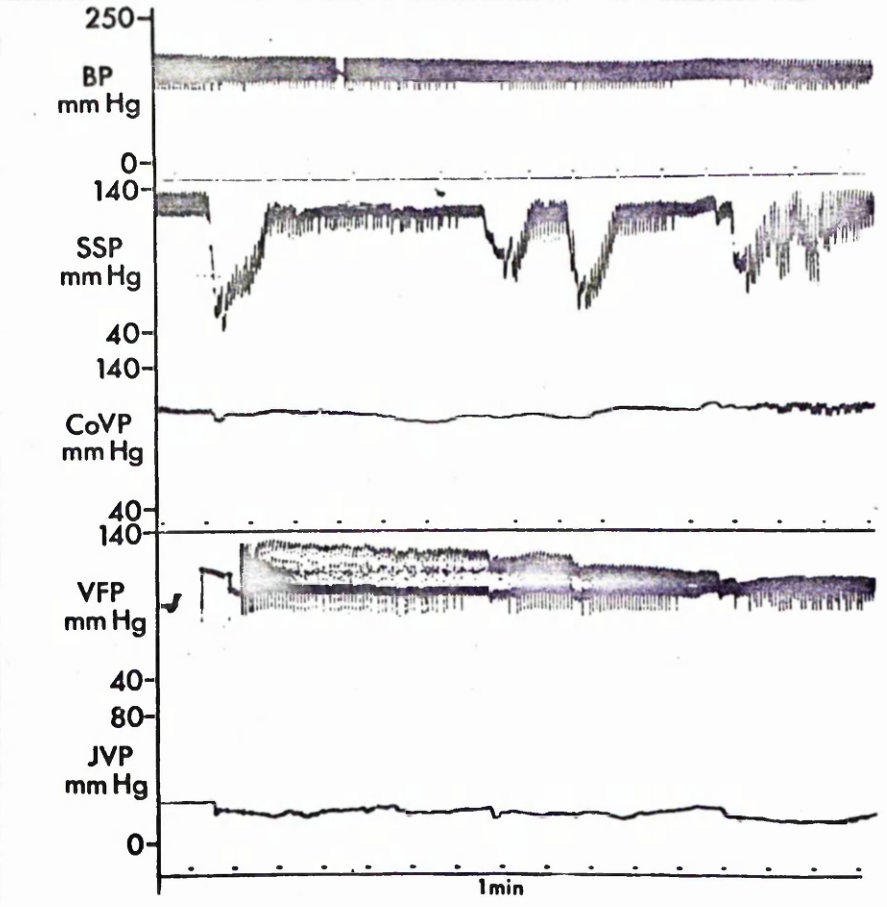


Fig. 8.6. Typical changes in monitored pressures during the final stages of cisterna magna infusion experiments.

difference between carotid artery blood pressure and cortical vein pressure. These changes were dependent, in the main, on the magnitude and timing of the blood pressure response.

With three animals in the cisterna magna infusion group cerebral perfusion pressure rose steadily reaching a maximum at intracranial pressure levels of 36, 49 and 65 mmHg respectively and then fell as intracranial pressure was increased further. In the other three animals in this group, cerebral perfusion pressure decreased at intracranial pressure levels of 25, 39 and 41 mmHg and then increased to control levels as intracranial pressure was increased further. In all the cisterna magna infusion experiments cerebral perfusion pressure and cerebral blood flow fell progressively at extreme levels of intracranial pressure.

As before cerebral perfusion pressure/intracranial pressure changes were more uniform with supratentorial balloon inflation. In different animals cerebral perfusion pressure remained at control levels within the intracranial pressure range 38-93 mmHg and then fell with further increases in intracranial pressure. Cerebral perfusion pressure was never observed to be greater than control values in any of the supratentorial balloon experiments.

With infratentorial balloon inflation cerebral perfusion pressure rose initially and then fell progressively as intracranial pressure was increased.

Vascular Resistance Changes

Cerebrovascular resistance (or pre-venous resistance) as calculated from the ratio of perfusion pressure (CABP - CSAVP) to cerebral blood flow varied considerably in the cisterna magna infusion group of animals. In three animals it fell progressively with rising intracranial pressure while in the others the level varied considerably. In one animal in which there was a very marked blood pressure response (87-133 mmHg) at an intracranial pressure of 61 mmHg (Figure 8.7c) the

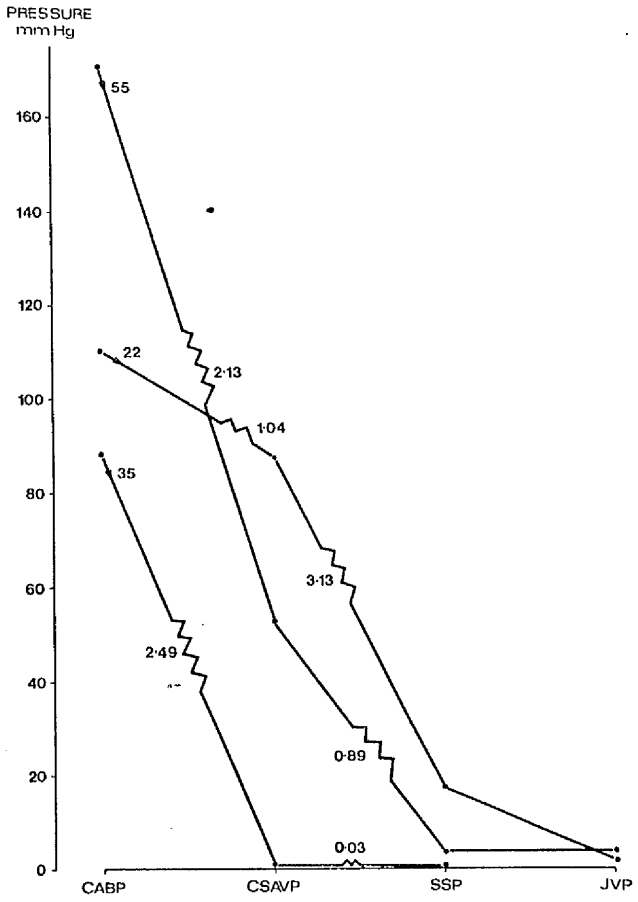
pre-venous resistance which, up until that time, had been progressively decreasing (1.88 - 0.85) appeared to be reset to control levels and then started to decrease again as intracranial pressure was increased further.

In the supratentorial balloon group of animals the changes in pre-venous resistance were more consistent. In five animals there was a slight progressive fall over the time course of the experiment while in the sixth animal the pre-venous resistance rose slightly towards the end of the experiment.

However, when segmental venous out-flow resistances were considered (Figures 8.7a, 8.7b, 8.7c and 8.8) it was noted that the sum of the venous outflow resistances increased steadily as intracranial pressure was increased. In three of the six cisterna magna infusion experiments where sagittal sinus pressure remained low the major locus of resistance stayed between cortical vein and sagittal sinus (typified by Figure 8.7a). In the two animals in which sagittal sinus pressure rose to intermediate values the venous resistance eventually became almost equally divided between cortical vein/sagittal sinus and sagittal sinus/jugular vein (typified by Figure 8.7b). In the one animal in which sagittal sinus pressure rose to cortical vein pressure levels the outflow resistance became concentrated between sagittal sinus and jugular vein (typified by Figure 8.7c).

With expansion of a supratentorial balloon the major locus of resistance remained between the cortical veins and the sagittal sinus (Figure 8.8).

The major difference between the cisterna magna infusion and supratentorial balloon experiments was that the pre-venous resistance showed less tendency over all to fall when intracranial pressure was raised by supratentorial balloon expansion (Figures 8.9a and 8.9b). Furthermore, whereas at control levels the major vascular resistance is concentrated between the carotid artery and cortical veins



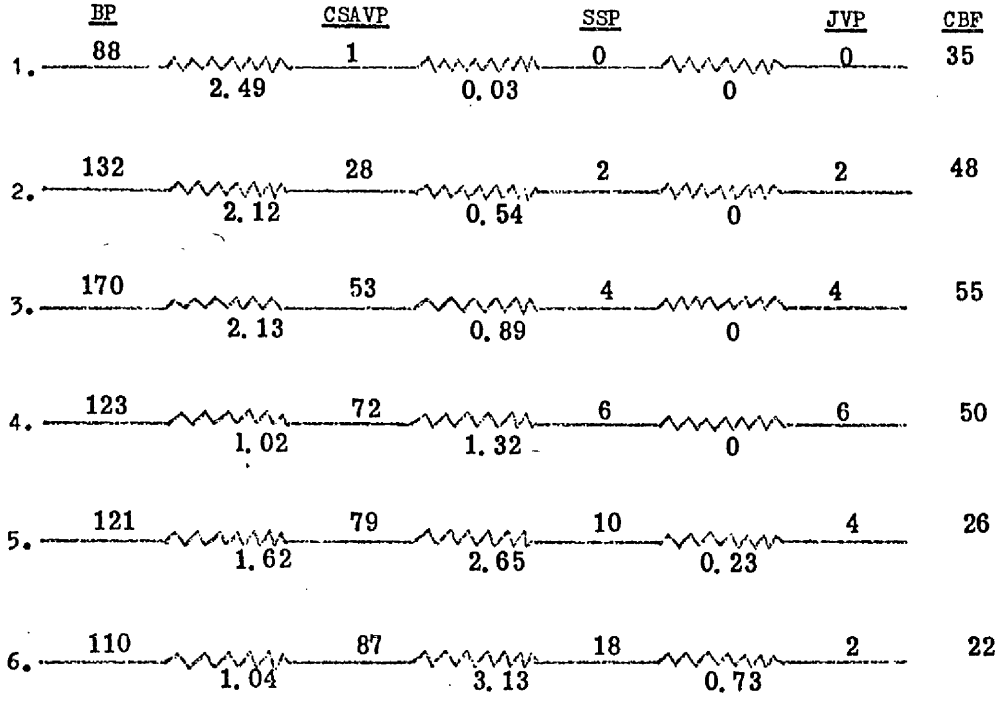
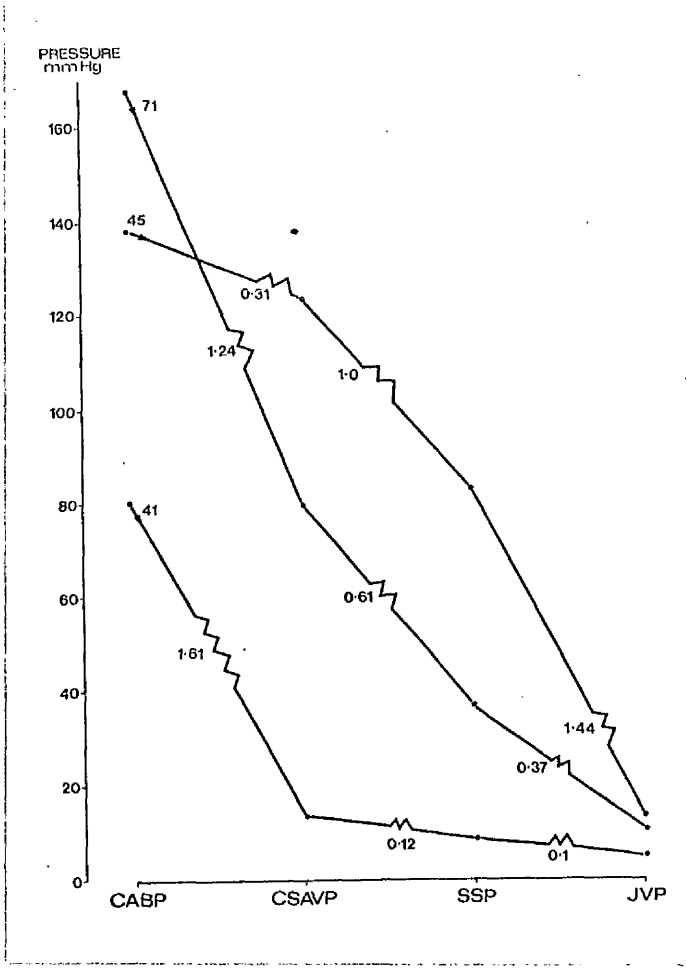
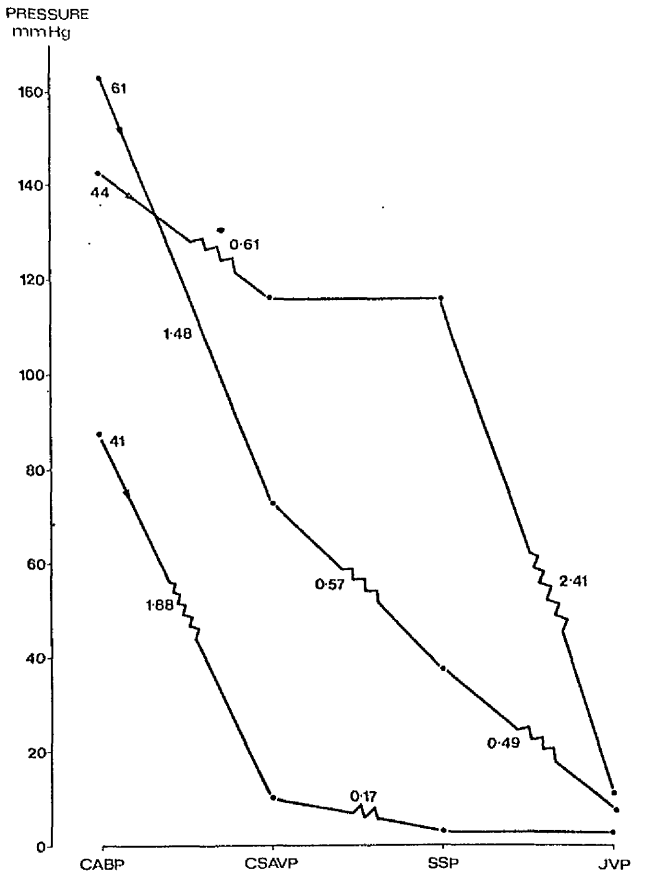


Fig. 8.7a. Cerebrovascular pressure differences and resistances during cisterna magna infusion - low sagittal sinus pressure.



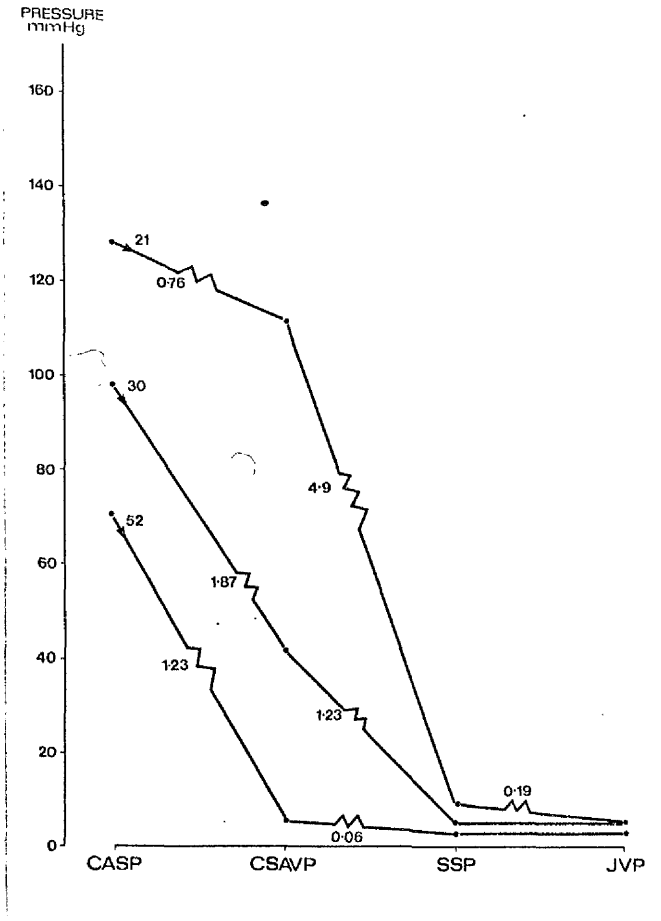
	BP		CSAVP		SSP		JVP	CBF
1.	80	1.61	14	0.12	9	0.1	5	41
2.	103	1.43	36	0.47	14	0.17	6	47
3.	145	1.34	59	0.48	28	0.3	9	64
4.	168	1.24	80	0.61	37	0.37	11	71
5.	160	0.94	95	0.59	54	0.62	11	69
6.	153	0.7	116	1.26	49	0.7	12	53
7.	138	0.31	124	1.00	79	1.44	14	45

Fig. 8.7b. Cerebrovascular pressure differences and resistances during cisterna magna infusion - increased sagittal sinus pressure.



	BP		CSAVP		SSP		JVP	CBF
1.	87	1.88	10	0.17	3	0	3	41
2.	87	1.02	30	0.48	3	0	3	56
3.	87	0.85	42	0.70	5	0	5	53
4.	133	1.50	61	1.06	10	0.10	5	48
5.	163	1.48	73	0.57	38	0.49	8	61
6.	148	1.00	97	0.08	93	1.62	10	51
7.	143	0.61	116	0	116	2.41	11	44

Fig. 8.7c. Cerebrovascular pressure differences and resistances during cisterna magna infusion - high sagittal sinus pressure.



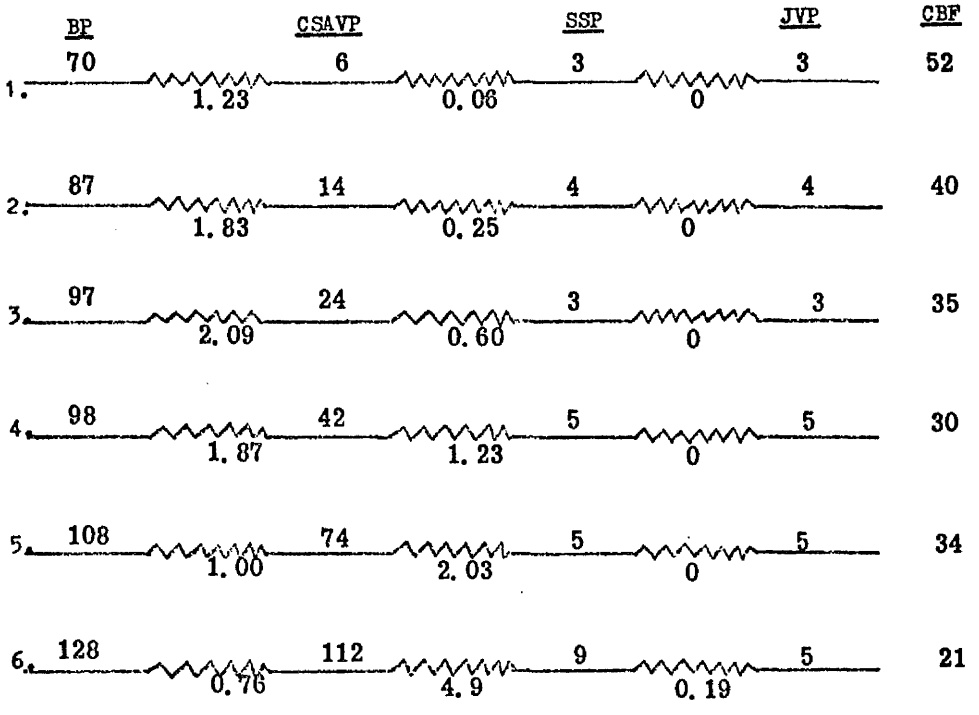
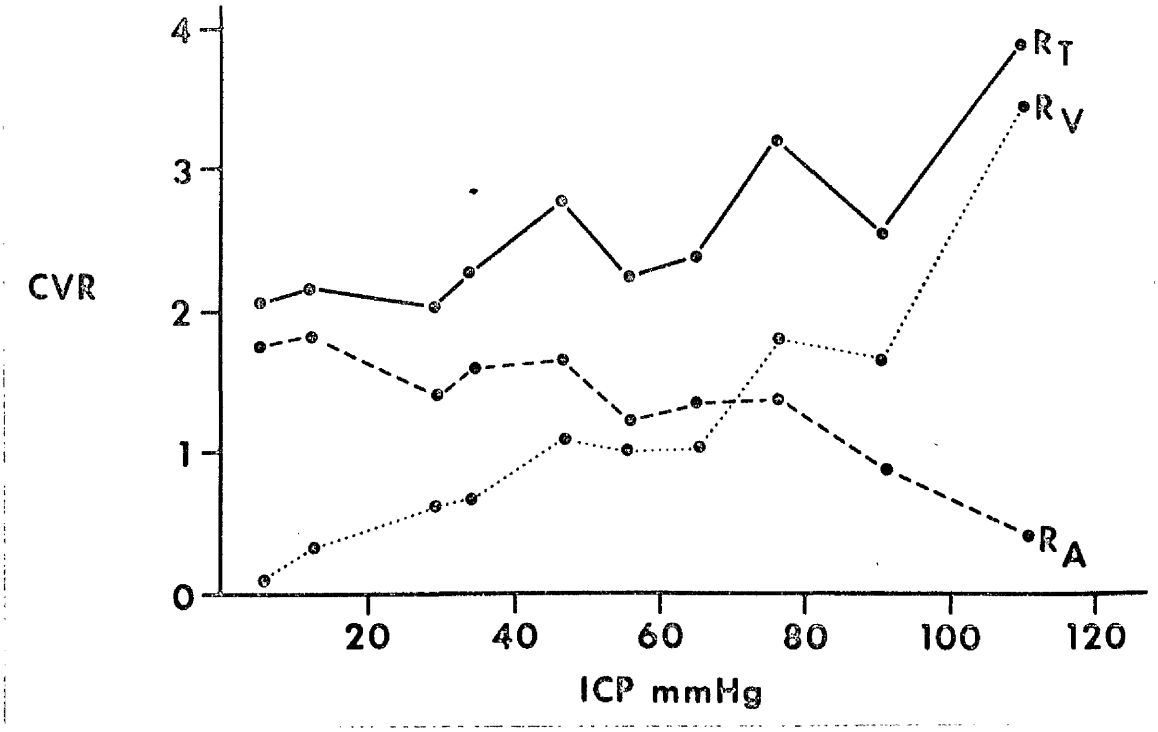
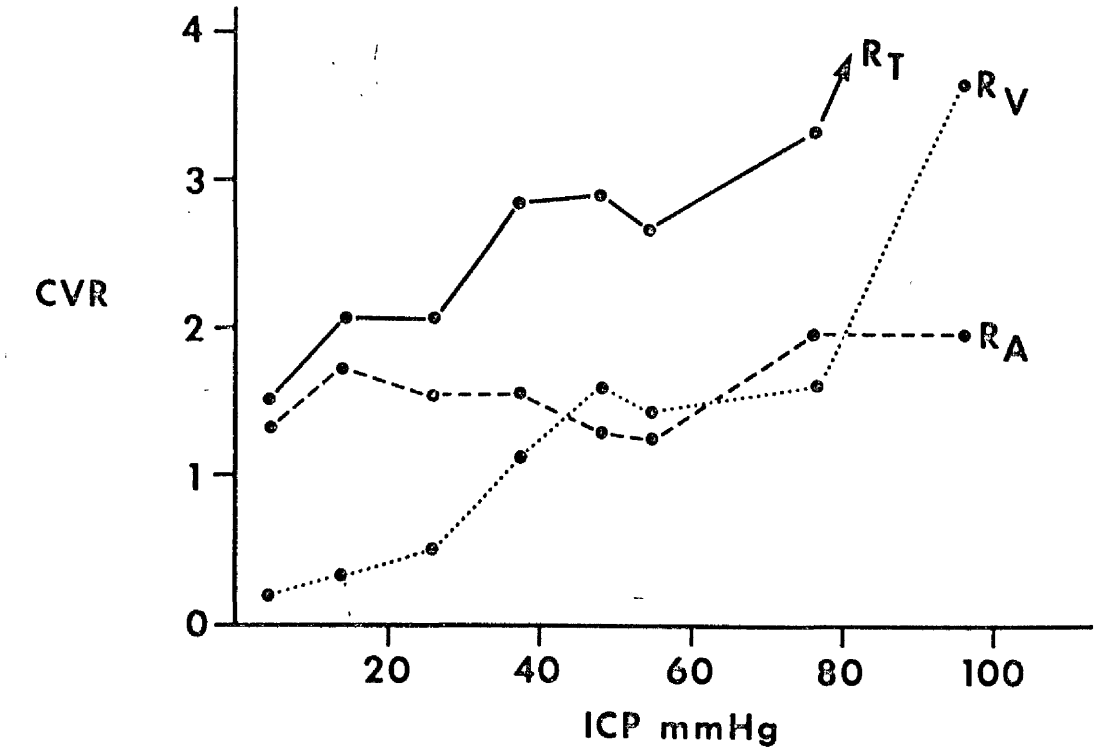


Fig. 8.8. Cerebrovascular pressure differences and resistances during supratentorial balloon expansion.



(a) During cisterna magna infusion.



(b) During supratentorial balloon expansion.

Fig. 8.9. Changes in prevenous resistance (R_A), venous resistance (R_V) and total cerebrovascular resistance (R_T) with progressive increases in intracranial pressure. Mean values from each experimental group.

(pre-venous resistance) as intracranial pressure is increased the sum of the venous outflow resistance increases until, at extreme levels of intracranial pressure, the major vascular resistance is the outflow resistance (Figures 8.7a, 8.7b, 8.7c and 8.8).

Cerebral Blood Flow Changes

Control values of cerebral blood flow are shown in Table 8.1.

The observed response patterns with respect to intracranial pressure and cerebral perfusion pressure were basically similar to those described in Chapters 6 and 7. Three out of the six animals in the cisterna magna infusion group exhibited a hyperaemic phase associated with an increase in perfusion pressure. In these three animals the pre-venous resistance decreased by a relatively small amount. In the case of the other three animals there was a substantial decrease in pre-venous resistance at the time of maximum blood flow while cerebral perfusion pressure remained at control levels (Table 8.3).

Discussion

It has been shown that if intracranial pressure is increased in different ways then different cerebral blood flow responses and different blood flow/cerebral perfusion pressure relationships result. This could be due to the definition of cerebral perfusion pressure (the difference between mean blood pressure and mean intracranial pressure) being invalid or to the different types of cerebrovascular resistance changes which occur as a result of the different methods used to produce intracranial hypertension.

Previous to this study, cortical venous pressure had only been measured over a small range of intracranial pressure values and the results obtained from measurements of sagittal sinus pressure had not been consistent. The results from this series of experiments show clearly that pressure in the large cortical veins increases linearly with increases in intracranial pressure agreeing with the results from

EXPERIMENT	CBF (ml/100g/min)	Ra	Rv	R_T	CPP (mmHg)	CBF (ml/100g/min)	Ra	Rv	R_T	CPP (mmHg)
1	27	2.70	0.44	3.14	73	39	1.85	0.74	2.59	72
2	41	1.88	0.17	2.05	77	61	1.48	1.06	2.54	90
3	43	1.42	0.21	1.63	61	71	1.24	0.98	2.22	88
4	53	1.55	0.32	1.87	90	83	0.96	0.40	1.36	80
5	35	2.49	0.03	2.52	87	55	2.13	0.89	3.02	117
6	40	2.38	0.03	2.41	95	110	0.74	0.26	1.00	81
MEAN	40.7	2.07	0.20	2.27	80.5	69.8	1.40	0.72	2.12	88.0
S.D.	10.3	0.53	0.16	0.54	12.6	24.6	0.53	0.32	0.78	15.6

TABLE 8.3

VALUES OF CEREBRAL BLOOD FLOW (CBF), PREVENOUS RESISTANCE (Ra), VENOUS OUTFLOW RESISTANCE (Rv), TOTAL VASCULAR RESISTANCE (R_T) AND CEREBRAL PERFUSION PRESSURE (CPP) AT CONTROL AND AT MAXIMUM CEREBRAL BLOOD FLOW FOR EACH EXPERIMENT IN THE CISTERNA MAGNA INFUSION GROUP

the studies undertaken by Shulman (113) and Shulman and Verdier (114) in which cortical vein pressure was measured at relatively low levels of intracranial pressure. A small positive pressure difference between cortical veins and the cerebrospinal fluid compartment was observed maintaining the patency of the veins.

Sagittal sinus pressure exhibited a less uniform response as intracranial pressure gradually increased. With cisterna magna infusion there was a substantial increase in sagittal sinus pressure in some animals. This pressure increase was initiated at intracranial pressure levels of the order of 40 mmHg and proceeded as intracranial pressure was progressively raised. This sagittal sinus pressure increase was not observed in other animals in the cisterna magna infusion group nor in animals in the supratentorial or infratentorial balloon groups. When there was a significant rise in sagittal sinus pressure large transient pressure fluctuations were noted. These fluctuations were not related in any way with the other measured variables. It is possible that they indicate intermittent opening and closing of the lumen of the sinus in the stress field set up by the raised intracranial pressure.

If one considers these observations of sagittal sinus pressure in the light of previous results reported in the literature it is difficult to construct a completely unifying hypothesis. Under control conditions pressure within the sinus is expected to be, and is in fact, found to be lower than intracranial pressure. It should relate largely to right atrial pressure (118). In addition to the present study this has been confirmed in many other reported investigations (119, 120, 121, 122). In contrast, reported results on measurements of sagittal sinus pressure during intracranial hypertension have been quite variable. Wright (91) and Bedford (121) reported very little change in sagittal sinus pressure while Dixon and Haliburton (123) and Langfitt et al (90) reported significant increases in sagittal sinus pressure when

intracranial pressure was raised. Furthermore, Shulman et al (122), Kinal (115) and Osterholm (116) reported that, in acute and chronic intracranial hypertension, sagittal sinus pressure may increase with increasing intracranial pressure. Pressure in the sagittal sinus will be under the influence of many factors, such as the compressibility characteristics of the sinus itself, the level of blood flow in the sinus, and central venous pressure. The relative magnitude of the influence exerted by each factor will depend on the site of measurement, the species of experimental animal, and the method used to raise intracranial pressure.

In the series of experiments described no significant variation in jugular venous pressure was detected no matter how intracranial pressure was raised. This is in agreement with the reports of jugular bulb and torcular pressures made by Bedford (121) and Langfitt et al (90). Jugular venous pressure changes should be secondary effects resulting from central venous pressure changes or changes in cardiovascular function resulting from the raised intracranial pressure (124). In earlier studies a number of workers attempted to quantify the relation between cerebral blood flow and intracranial pressure (74, 125). Later cerebral perfusion pressure was proposed as an index for the level of cerebral blood flow (70, 84, 126). A direct relationship between the level of cerebral blood flow and the level of intracranial pressure or cerebral perfusion pressure would be an immense advantage to clinicians. Unfortunately, experiments described in earlier chapters, and also investigations carried out by Miller et al (127) have clearly shown that no such direct relationship exists. But why is this so? Is it because of an incorrect definition of perfusion pressure? Or is it the result of varying cerebrovascular resistant patterns changing according to the cause or the history of the intracranial hypertension?

The results of the present set of experiments clearly demonstrate

the close correlation between cortical venous pressure and intracranial pressure and confirm the underlying assumption that intracranial pressure is a very reliable and consistent index of the effective cerebral venous outflow pressure. Therefore, provided there is no significant change in the size of the pressure drop between the major extracranial and intracranial arteries (109) then the definition of cerebral perfusion pressure as the difference between mean blood pressure and mean intracranial pressure is satisfactory.

It is therefore to the changes in cerebrovascular resistance response to which we must direct our attention in the attempt to explain the variability of the cerebral blood flow response during intracranial hypertension.

Taking into account the measurements of pressure at a series of points in the cerebrovascular system and assuming uniform blood flow through each segment, calculation can be made of the segmental resistances associated with the blood vessels supplying and draining the brain. From these calculations it can be shown that a progressive increase in venous (or outflow) resistance takes place as intracranial pressure increases with the major locus existing between the cortical veins and sagittal sinus. It follows, therefore, that, since the uniformity in direction of the venous resistance changes are independent of the method used to increase intracranial pressure, it must be differences in the pre-venous resistance which result in the variable cerebral blood flow response. This hypothesis is supported by calculated values of pre-venous resistance. When intracranial pressure is increased by cisterna magna infusion there is a marked fall in pre-venous resistance whereas with supratentorial balloon inflation pre-venous resistance remains relatively high. It is not at all certain what initiates these changes in pre-venous vessel behaviour. This, of course, has a direct bearing on the mechanism of cerebral blood flow autoregulation. As explained earlier, there are a number

of theories which postulate metabolic, myogenic, neurogenic and tissue pressure control. The matter remains largely unresolved although current thinking favours metabolic control of the intraparenchymal vessels supported by neurogenic control of the extraparenchymal vessels. The conclusion that can be drawn from this series of experiments is that while changes in venous resistance depend directly on the level of intracranial pressure, changes in pre-venous resistance depend on the way in which intracranial pressure is raised.

In summary, it has been demonstrated quite clearly that a progressive rise in intracranial pressure results in a corresponding increase in cortical vein pressure. The vein pressures remain slightly higher than intracranial pressure and in this way vein patency is preserved.

In most situations sagittal sinus pressure and jugular venous pressure do not vary significantly although it is possible for sagittal sinus pressure to increase substantially during cisterna magna infusion.

It can be stated that the currently used definition of cerebral perfusion pressure is valid provided that the size of the pressure drop between extracranial and intracranial arteries does not change substantially as intracranial pressure is raised. With increases in intracranial pressure there is a progressive increase in venous resistance which is independent of the way intracranial pressure is increased. Differences in cerebral blood flow response observed with different types of intracranial pressure increase depend on the variations in pre-venous resistance response.

These observations establish the validity of the definition of cerebral perfusion pressure and demonstrate once again that clinical measurements of cerebral perfusion pressure alone do not allow conclusions to be drawn about cerebral blood flow levels in individual patients.

CHAPTER 9

THE BLOOD PRESSURE RESPONSE DURING RAISED INTRACRANIAL PRESSURE

As stated in Chapter 5 it has been confirmed consistently in experimental investigations that systemic hypertension can occur if intracranial pressure is raised to a sufficiently high level. However, controversy still surrounds the mechanism and function of this blood pressure response during intracranial hypertension although ever since Cushing's descriptions (78) there has been a tendency to consider systemic hypertension as a reliable clinical indication of raised intracranial pressure and to regard the function of the blood pressure response to be the preservation of cerebral blood flow during raised intracranial pressure. Nevertheless a number of questions remain to be answered, e.g.

(i) How reliable is a rise in blood pressure as an index of rising intracranial pressure and is there any quantitative relationship between the two pressures?

(ii) What is the mechanism responsible for the response?

(iii) What is the function of the response?

A number of mechanisms have been suggested by previous workers, viz:-

(i) Ischaemia or hypoxia of medullary centres (Cushing, 1901) (78).

(ii) Action of intracranial baroreceptors sensitive to changes in cerebral perfusion pressure (Rodbard and Saiki, 1952) (94).

(iii) Brain stem distortion (Thompson and Malina, 1959) (102).

(iv) Cerebral ischaemia (Evans, 1967) (103).

(v) Pressure on localised areas in the brain stem and spinal cord (Hoff and Reis, 1970) (104).

The purpose of the investigations to be described was to study the mechanism and function of the blood pressure response recorded experimentally.

Methods

Anaesthetised baboons weighing approximately 10 kg were used. In all experiments anaesthesia was induced with phencyclidine hydrochloride and sodium thiopentone and maintained with phencyclidine hydrochloride, suxamethonium and a nitrous oxide/oxygen mixture. A Starling pump was used to control ventilation with the tidal volume adjusted to maintain normal pO_2 and pCO_2 levels.

Intracranial and spinal CSF pressures were measured continuously using strain gauge transducers and indwelling polyethylene canullae placed in the lateral ventricle, cisterna magna and lumbar subarachnoid space. Arterial pressure was measured in a similar manner from the femoral artery.

Cerebral blood flow was measured at intervals using the xenon-133 clearance technique and also continuously by means of an electromagnetic flow probe placed on the exposed right common carotid artery, the external carotid artery having been ligated above the bifurcation.

Repeated estimations were made of arterial pO_2, pCO_2, pH, venous haemoglobin, pCV, end tidal CO_2 and heart rate.

Different experimental groups of animals were studied according to the method used to increase CSF pressure, viz:-

(1) Diffuse compression.

(a) Cisterna magna infusion - spinal cord intact.

(b) Cisterna magna infusion - spinal cord sectioned in the mid-cervical region.

(c) Lumbar infusion - spinal cord intact.

(d) Lumbar infusion - spinal cord sectioned in the mid cervical region.

(2) Focal supratentorial compression by means of a subdural balloon placed in the right parietal region.

(3) Focal infratentorial compression by means of a subdural balloon placed over the right cerebellar hemisphere.

(4) Focal spinal cord compression by means of a subdural balloon placed over the dorsal aspect of the mid-thoracic spinal cord.

Results

Group 1a - cisterna magna infusion (eight animals)

All eight animals displayed a progressive and sustained increase in mean systemic arterial pressure as intracranial pressure was raised. The maximum arterial pressures reached ranged from 148 to 205 mmHg. The increase to maximum levels developed gradually in seven animals while in the remaining animal there was an abrupt rise. In all animals the increase in arterial pressure was sustained and persisted until the extreme stages of intracranial hypertension (Figure 9.1).

In seven of the animals the level of intracranial pressure at which maximum blood pressure occurred was less than the control mean blood pressure while in four animals it was less than the mean diastolic pressure. The mean maximum blood pressure level reached in the eight animals was 162.7 mmHg corresponding to a mean intracranial pressure of 78.2 mmHg. A significant pressure gradient between supratentorial and infratentorial compartments was not observed in any animal prior to the development of the hypertensive response nor was there any consistent fall in cerebral perfusion pressure or cerebral blood flow (Table 9.1). In the majority of animals there was a substantial increase in cerebral blood flow as the blood pressure response developed (Figure 9.2).

Group 1b - cisterna magna infusion - spinal cord sectioned (four animals)

A sustained increase in blood pressure did not occur with this experimental group despite increases in intracranial pressure up to 52 mmHg (Figure 9.1). The relatively low maximum intracranial pressure attained indicates both the absence of a blood pressure response and the relatively low initial blood pressure after cord transection which together ensured that there was a rapid fall in cerebral perfusion pressure and hence a fall in cerebral blood flow. Blood pressure

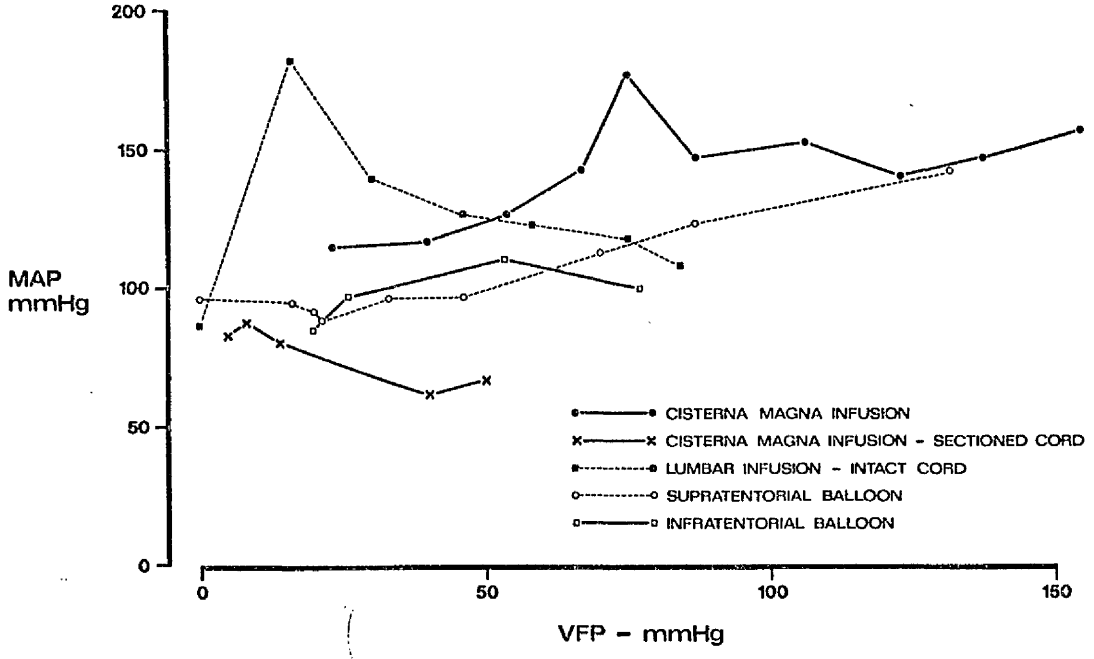


Fig. 9.1. Relation between mean arterial blood pressure (MAP) and ventricular fluid pressure (VFP).
Data taken from one experiment in each group.

ANIMAL		MAP (mmHg)	ICP (mmHg)	CPP (mmHg)	CBF (ml/100g/min)
1	(a)	115	10	105	56
	(b)	133	28	105	60
	(c)	135	36	99	70
2	(a)	117	25	92	47
	(b)	127	54	73	62
	(c)	143	67	76	57
3	(a)	88	1	87	74
	(b)	122	52	70	86
	(c)	137	71	66	95
4	(a)	107	11	96	58
	(b)	133	16	117	53
	(c)	143	30	113	68
5	(a)	125	7	118	45
	(b)	125	23	102	44
	(c)	147	37	110	54
6	(a)	93	20	73	87
	(b)	130	61	69	100
	(c)	178	67	111	126
7	(a)	116	6	110	42
	(b)	112	79	33	28
	(c)	148	90	58	30
8	(a)	105	24	81	28
	(b)	115	77	38	27
	(c)	170	85	85	49

MAP: Mean Arterial Pressure, ICP: Intracranial Pressure,
CPP: Cerebral Perfusion Pressure, CBF: Cerebral Blood Flow.

(a) Control values.
(b) Values immediately before first significant blood pressure increase.
(c) Values at the time of measurement of first significant blood pressure increase

(MEAN CONTROL BLOOD PRESSURE: 108 mmHg; S.D: 12.6)

TABLE 9.1

Comparison of cerebral blood flow and cerebral perfusion pressure at control levels, immediately before first significant increase in blood pressure ($\geq$133 mmHg), and at the time of measurement of the first significant increase in blood pressure for animals in Group 1a.

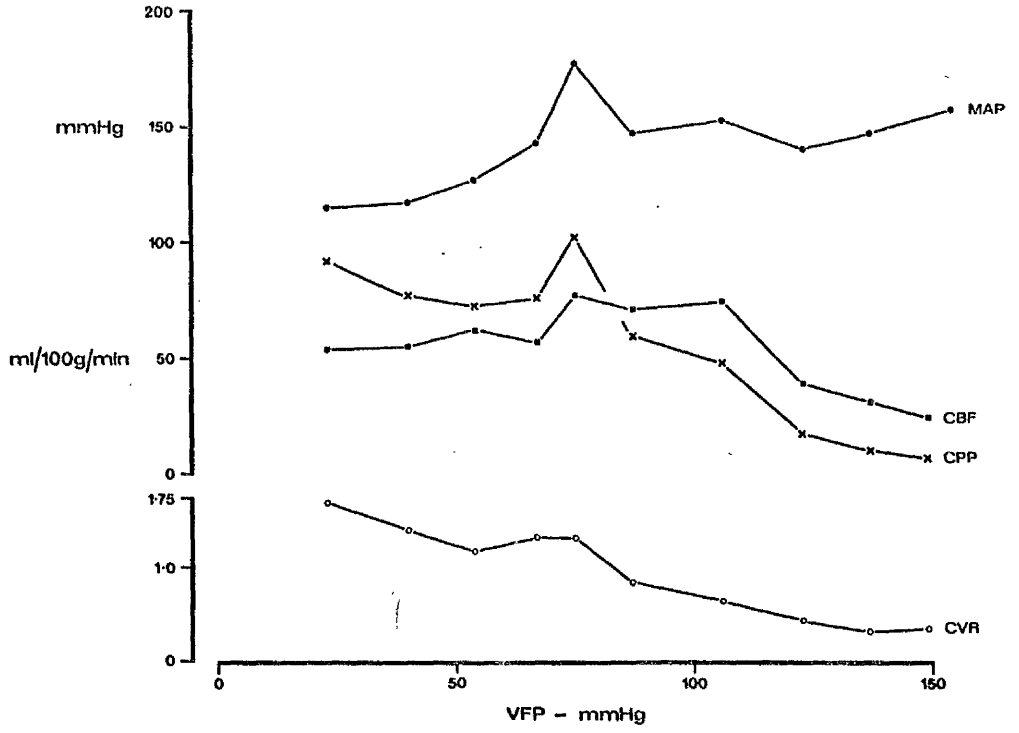


Fig. 9.2. Relation between mean arterial blood pressure (MAP), cerebral perfusion pressure (CPP), cerebral blood flow (CBF), cerebrovascular resistance (CVR) and ventricular fluid pressure (VFP) during cisterna magna infusion. Data from one animal.

remained at control levels in two of the four animals while the other two animals displayed transient rhythmic fluctuations in blood pressure. The steady level of cerebrovascular resistance values with changing cerebral blood flow values indicated loss of autoregulation (Figure 9.3).

Group 1c - lumbar infusion - spinal cord intact (five animals)

Marked systemic hypertension did develop in this group of animals as intracranial pressure was raised (Figure 9.1). The maximum arterial pressures reached corresponded to those in group 1a although in this case four of the five animals displayed an abrupt rise from control blood pressure levels to values approaching the maximum levels. The maximum mean arterial pressure reached tended to occur at lower levels of intracranial pressure compared to group 1a and whereas the blood pressure response was sustained in group 1a there was a tendency for the levels of arterial pressure to drop in this group after the initial marked systemic hypertension. Nevertheless, blood pressure levels remained considerably higher than the control levels (Figures 9.1 and 9.4).

As with group 1a there was no preceding intercompartmental pressure gradients or prior reductions in cerebral perfusion pressure or cerebral blood flow although, as with cisterna magna infusion, cerebral hyperaemia did develop with a blood pressure increase in four of the five animals (Figure 9.5).

Group 1d - lumbar infusion - cord sectioned (four animals)

Three out of the four animals in this group showed a marked increase in blood pressure from control levels as soon as infusion began. With the fourth animal blood pressure increased gradually as intracranial pressure was increased. In two of the animals blood pressure tended to decrease after the initial increase although the levels always remained above control values. In the other two animals the increase in blood pressure was sustained (Figure 9.2). All animals in this group displayed a significant rise in cerebral blood flow (Figure 9.6).

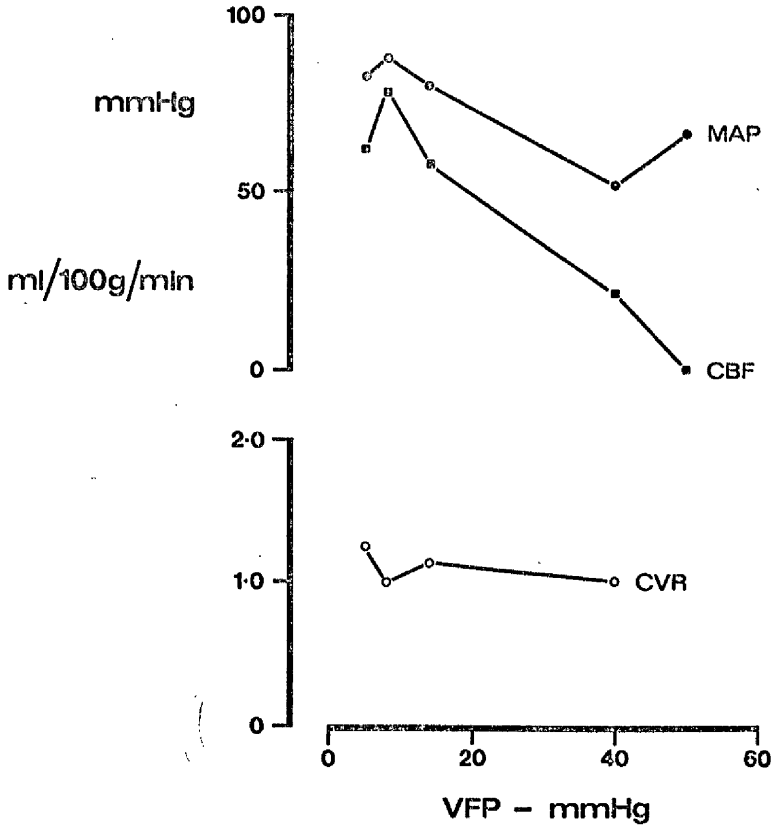


Fig. 9.3. Relation between mean arterial pressure (MAP), cerebral blood flow (CBF), cerebrovascular resistance (CVR) and ventricular fluid pressure (VFP) during cisterna magna infusion in an animal with a sectioned spinal cord.

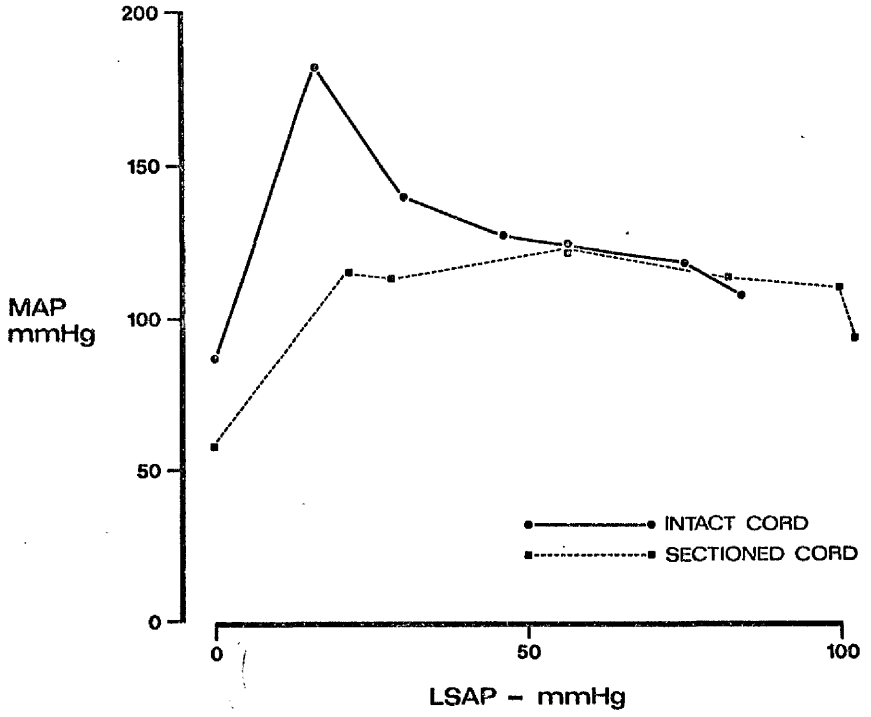


Fig. 9.4. Comparison of the relations between mean arterial pressure (MAP) and lumbar subarachnoid pressure (LSAP) during lumbar infusion when the spinal cord is intact and when it is sectioned.
Data from one animal in each group.

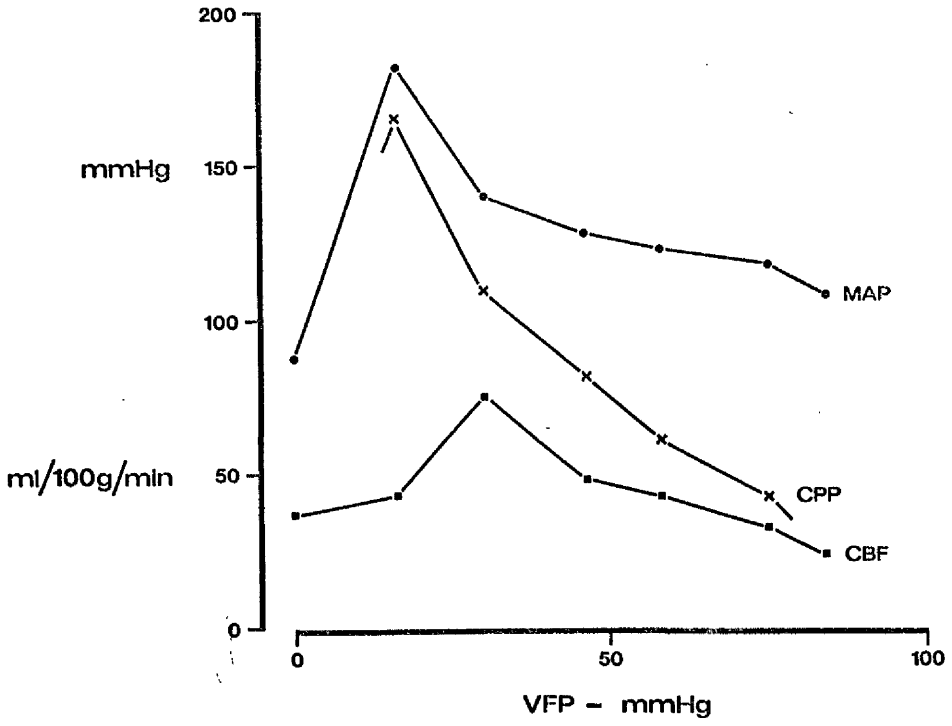


Fig. 9.5. Relation between mean arterial pressure (MAP), cerebral perfusion pressure (CPP), cerebral blood flow (CBF) and ventricular fluid pressure (VFP) during lumbar infusion in an animal with an intact spinal cord.

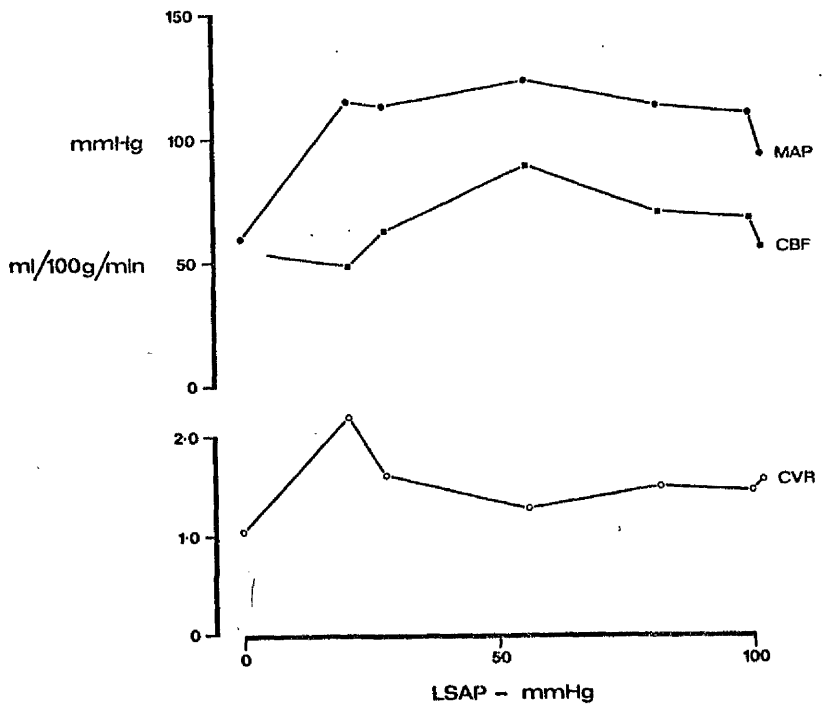


Fig. 9.6. Relation between mean arterial pressure (MAP), cerebral blood flow (CBF), cerebrovascular resistance (CVR) and lumbar subarachnoid pressure (LSAP) during lumbar infusion in an animal with a section cord.

Intracranial pressure remained virtually unchanged during each experiment and again no change in either cerebral perfusion pressure or cerebral blood flow preceded the hypertensive response. A number of animals did display a hyperaemia together with the blood pressure response similar to that seen in groups 1a and 1c.

Group 2 - focal supratentorial compression

A transient increase in blood pressure occurred with each addition of fluid to the balloon. There was a time lag of approximately 60 seconds after infusion before the blood pressure began to rise. Peak blood pressure levels were reached within two to three minutes and a return to control levels occurred at eight to twelve minutes. The blood pressure response was in general of considerable magnitude and was associated with varying changes in cardiac rate and rhythm. There was no sustained hypertensive response although blood pressure tended to rise gradually at high intracranial pressure levels (Figure 9.7), and towards the later stages of the experiment the magnitude of the transient response became less marked. The initial addition of fluid to the balloon when intracranial pressure changes were slight produced the response. The response did not depend on the development of transtentorial pressure gradients nor a prior reduction of cerebral perfusion pressure or cerebral blood flow. In fact, cerebral blood flow in general remained relatively constant up to intracranial pressure levels of around 50 mmHg apart from the slight transient changes with each intracranial pressure increase. These changes lasted approximately 30 seconds and were presumably due to the time taken for the autoregulation mechanism to become effective.

In contrast to groups 1a, 1c and 1d, there was no sustained increase in blood pressure (Figure 9.1).

Group 3 - focal infratentorial compression

All animals in this group again showed marked transient increases in blood pressure with each addition of fluid to the balloon and the

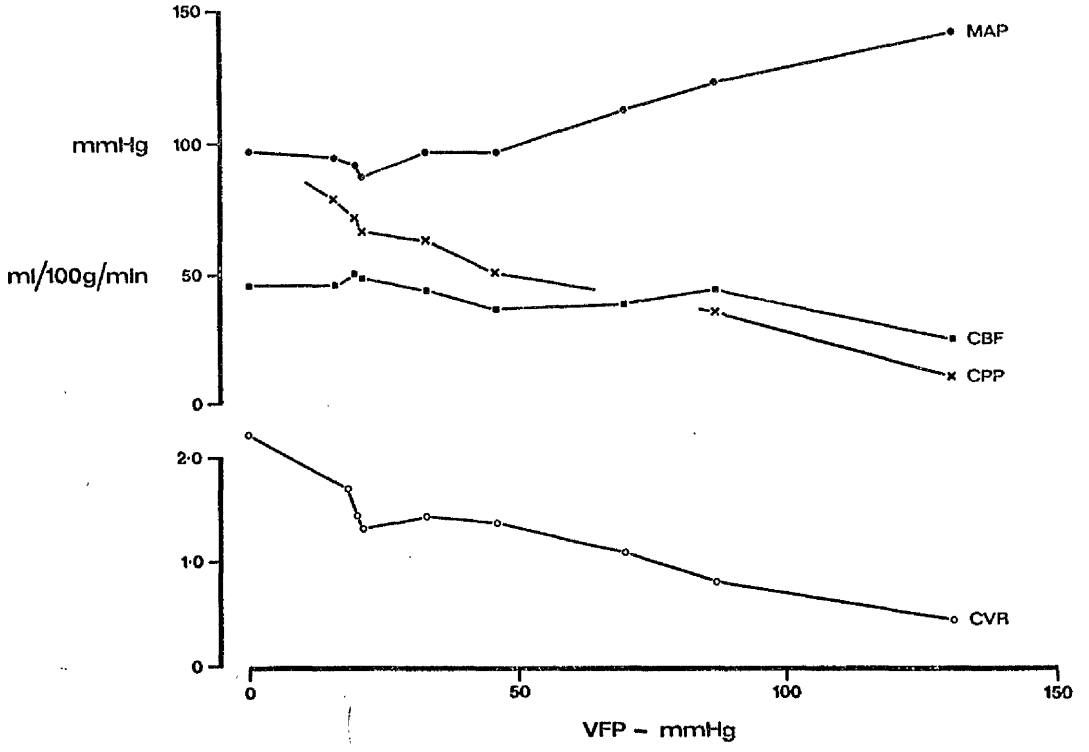


Fig. 9.7. Relation between mean arterial pressure (MAP), cerebral perfusion pressure (CPP), cerebral blood flow (CBF), cerebrovascular resistance (CVR) and ventricular fluid pressure (VFP) during supratentorial balloon expansion. Data from one animal.

timing of the response was similar to that seen with supratentorial compression. In general, however, the response was of greater magnitude and after a variable number of additions of fluid to the balloon the response seemed to become exhausted. The overall blood pressure level tended to fall at relatively low levels of intracranial pressure.

Similar to group 2, the development of transtentorial pressure gradients and reductions in cerebral perfusion pressure or cerebral blood flow were not prerequisites for the response.

In this group of animals, however, there was no evidence of effective autoregulation and changes in cerebral blood flow were directly related to changes in cerebral perfusion pressure (Figure 9.8).

Group 4 - focal spinal cord compression

Again there was a marked transient increase in blood pressure with each expansion of the balloon similar to that seen with focal supratentorial and infratentorial compression. However, the response was more rapid with spinal cord compression with no lag period and an earlier peak. The overall duration tended to be longer (greater than 10 minutes) and the magnitude of the response was variable. Between the transient blood pressure increases the blood pressure tended to fall below control levels and in no case was there a sustained increase in blood pressure. Again the blood pressure response did not depend on prior changes in cerebral perfusion pressure or cerebral blood flow. It was, however, associated with secondary increases in cerebrospinal fluid pressure and internal carotid artery flow tended to parallel the blood pressure response suggesting defective autoregulation.

Discussion

In this study diffuse compression of the intact neuraxis resulted in a marked sustained increase in blood pressure at intracranial pressure levels well below the resting diastolic pressure. A similar response was observed with diffuse compression of the isolated spinal

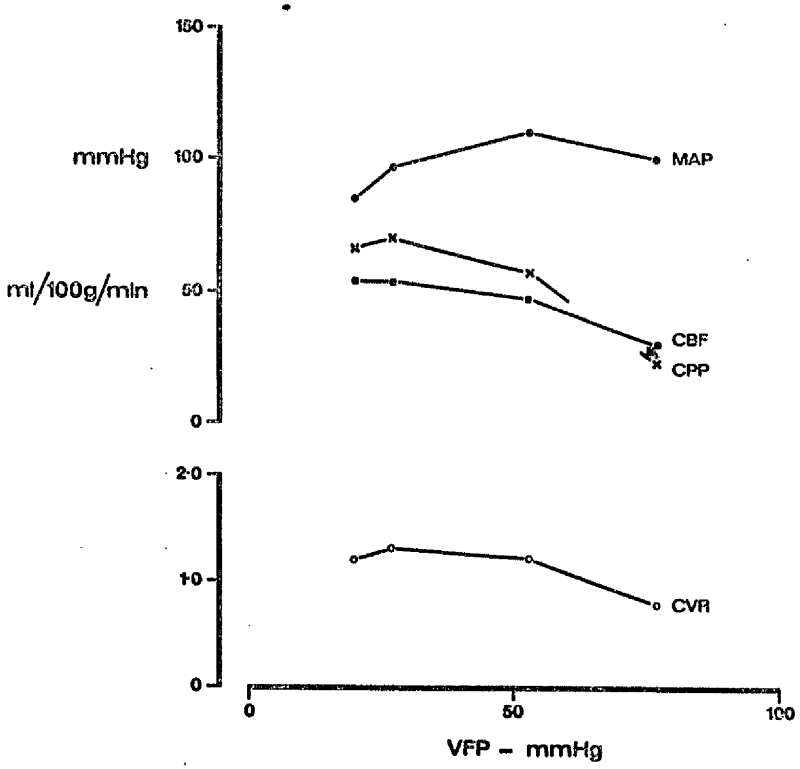


Fig. 9.8. Relation between mean arterial pressure (MAP), cerebral perfusion pressure (CPP), cerebral blood flow (CBF), cerebrovascular resistance (CVR) and ventricular fluid pressure (VFP) during infratentorial balloon expansion. Data from one animal.

cord after mid-cervical section whereas there was no response to intracranial compression alone after section of the spinal cord in the same region. Focal compression of the intact neuraxis with expansion of a subdural balloon placed in the left parietal region, right cerebellar region and the mid-thoracic region of the spinal cord provided a different response resulting in transient acute increases in blood pressure but with no sustained systemic hypertension. There were differencies according to balloon site but these were limited to a lower threshold and greater magnitude of the response with posterior fossa and spinal cord compression and a shorter latency with expansion of the spinal cord balloon.

The basic mechanism of the response has therefore seemed to be established. It would appear that it is mediated through central sympathetic neurons within the lower brain stem, which act via descending pathways on sympathetic neurons in the spinal cord. The precise site of the central neurons still remain a matter of conjecture although the work of Hoff and Reis (104), would indicate that they are localised within a narrow strip along the floor of the fourth ventricle. Their results suggest that the required stimulus is local changes in pressure which may be small in magnitude. Other postulated trigger mechanisms such as brain stem ischaemia, marked brain stem distortion, general cerebral ischaemia and transtentorial and transforaminal pressure gradients would appear to be ruled out by the findings of this study although it should be remembered that it was hemisphere blood flow which was measured in these investigations and in order to exclude fully the possibility of an ischaemic trigger, brain stem blood flow itself would have to be monitored.

Discharge of the central sympathetic neurons in the medulla would activate the sympathetic outflow neurons within the thoracic spinal cord, which could also be directly sensitive to local pressure changes. Clearly the magnitude of the sympathetic response would depend on both

the degree of stimulation of these central mechanisms and the relative influence of rostral or local inhibitory or excitatory mechanisms. The resultant effect would be a change in cardiovascular function including both neurogenic vasoconstriction and direct effects on cardiac output.

The unpredictability of the blood pressure response in clinical intracranial hypertension could be due to threshold changes within the primary receptor neurons in states of increased intracranial pressure and also as a result of failure of transmission of episodic increases in supratentorial pressure if there is transtentorial herniation.

The low threshold of the blood pressure response shown in this and in other studies (104) and the lack of a response to marked variations in intracranial pressure in clinical situations also casts doubt on the assumed role of the response of maintaining cerebral blood flow in situations of raised intracranial pressure. Unless auto-regulation is imparied an increase in blood pressure alone will not alter cerebral blood flow. It could be possible, of course, that the same stimulus which resulted in a blood pressure response could also effect cerebrovascular resistance.

In summary, the results of this study would support the hypothesis that the blood pressure response to raised intracranial pressure is mediated primarily by receptor neurons situated within a relatively restricted area of the lower brain stem which act, via descending pathways, on thoracic sympathetic outflow neurons causing changes in cardiac muscle function.

The results which are similar to the results of Hoff and Reis obtained in anaesthetised cats support the hypothesis that blood pressure response to raised intracranial pressure is due to local stimulation either by the direct application of pressure or due to distorting forces which act on the central sympathetic neurons in the brain stem or spinal cord leading to an increase in blood pressure by

a neurally mediated effect on cardiac function. This effector system is subject to rostral and local inhibitory systems, the importance of which may depend on the species being studied, the presence and type of anaesthesia and the cause and time course of the increase in intracranial pressure. The results cast considerable doubt on the clinical reliability of systemic hypertension as a sign of raised intracranial pressure and on the functional importance of the response as a means of preserving cerebral perfusion in states of intracranial hypertension.

CHAPTER 10

BRAIN STEM BLOOD FLOW AND THE BLOOD PRESSURE RESPONSE DURING RAISED INTRACRANIAL PRESSURE

PART I

COMPARISON OF THE HYDROGEN AND XENON-133 CLEARANCE TECHNIQUES USED TO MEASURE CEREBRAL BLOOD FLOW

In the previous chapter it was clearly shown that global cerebral ischaemia was not a prerequisite for the blood pressure response during raised intracranial pressure. However, brain stem ischaemia has been postulated as a trigger mechanism and the results shown previously cannot completely rule this out. The xenon clearance method of measuring cerebral blood flow is unable to provide the localisation necessary to measure brain stem blood flow and so another method of blood flow measurement had to be developed. The most promising method appeared to be the hydrogen clearance technique described in principle in chapter 3. It was hoped that by using platinum electrodes 0.1 mm in diameter placed stereotactically in the brain stem of baboons, local blood flow in the brain stem could be measured.

However, the hydrogen clearance technique, although used by a number of workers had not been assessed in depth with reference to the standard xenon clearance technique and it was decided therefore before proceeding to measure brain stem blood flow, comparative studies of the two techniques should be carried out.

The first study attempted to answer two questions. Firstly, are there any significant differences between the fast and slow component values obtained by the xenon method and the local flow measurements obtained in the cerebral cortex, white matter and deep grey matter using the hydrogen method? Secondly, do the flow results obtained by both methods correlate significantly over a wide range of flow values?

Methods

Ten baboons, anaesthetised as described in previous chapters were

used. Teflon coated platinum wire 0.1 mm in diameter, with an exposed 1 mm tip, was inserted into cortex, white matter and deep grey matter on the right and left side of the brain. A silver/silver chloride electrode was placed subcutaneously in the backs of the animals and used as the reference electrode. A polarising voltage of 700 mV was used.

The electrode currents were amplified using a six channel system employing Analog Devices amplifiers type 233K which have a low input bias current drift of less than 1 pA/^{o}C. The current amplifying system is shown schematically in Figure 10.1a and details of the amplifier circuit are shown in Figure 10.1b. A six channel Watanabe servo-recorder was used to display the output from each amplifier channel. Each amplifier channel had an input balance control in order that the output to each recorder channel could be set to zero to correspond with zero hydrogen concentration in tissue. The gain of each amplifier was set to give an output of 1 volt for an input of 1 μAmp. Each recorder channel had an independent variable gain control so that the hydrogen concentration equilibrium plateau level could be set to full scale deflection without affecting the original zero concentration setting. The amplifier band width was restricted to zero to 1 Hz to limit the effect of high frequency noise.

Hydrogen gas was introduced into the anaesthetic circuit before the respiratory pump. During hydrogen inhalation the nitrous oxide level was reduced and the level of oxygen increased to prevent critical reductions in paO_2 levels. Dependent on the type of tissue and the state of tissue perfusion, concentration equilibrium was obtained in three to six minutes. The hydrogen was then turned off, nitrous oxide and oxygen returned to their former levels and the hydrogen clearance curves recorded. Semi-logarithmic plots of the data were made and the half times ($T_{\frac{1}{2}}$) were measured in seconds. Where the curves were bi-exponential, the two components were extracted by

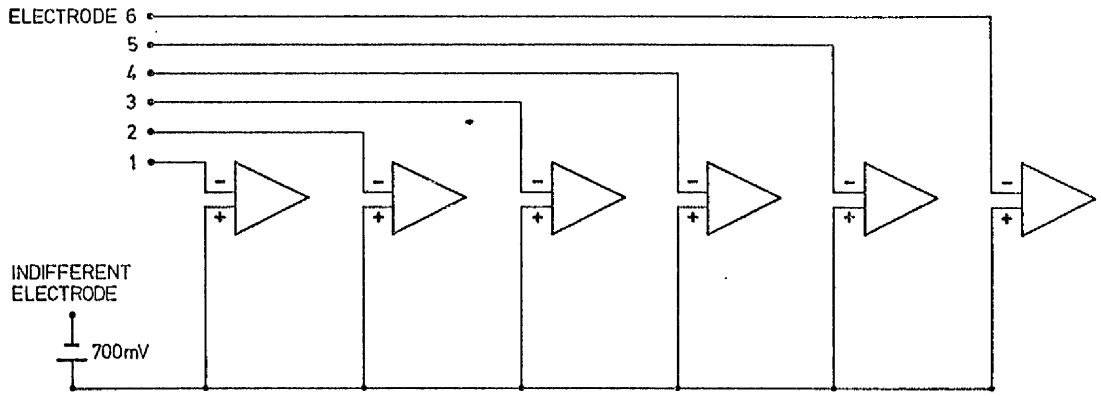


Fig. 10.1a. Schematic of six channel amplifying system.

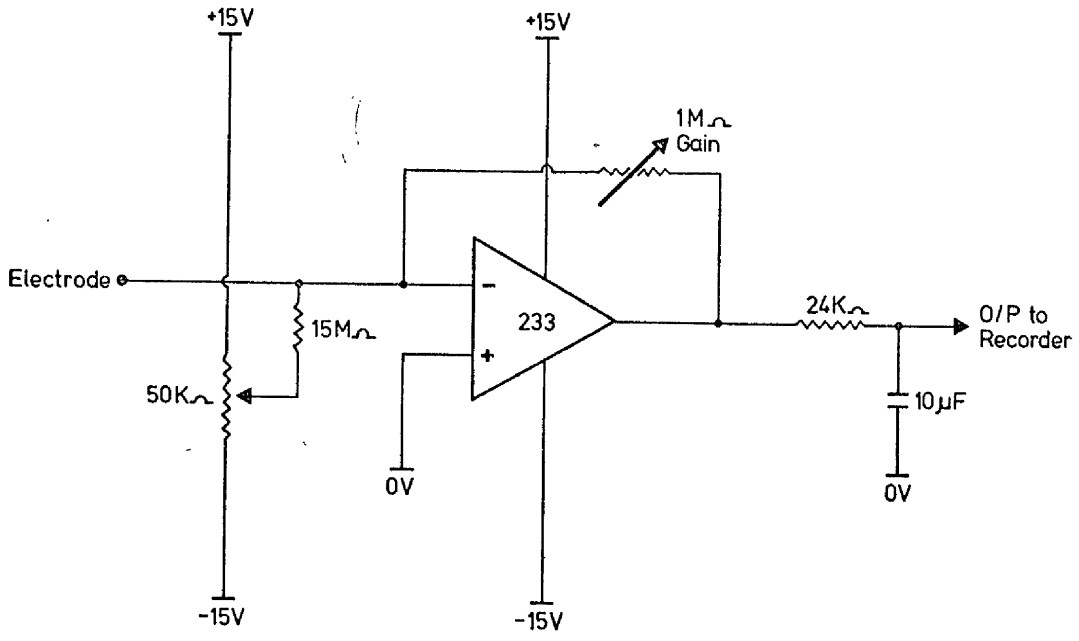


Fig. 10.1b. Electronic circuit of D.C. amplifier.

Fig. 10.1. Details of amplifying system used to measure the rate of hydrogen clearance from tissue.

stripping procedures and the fast and slow component half times measured. Cerebral blood flow was calculated using the formula:-

$$CBF = \frac{\lambda \times \log_e 2 \times 60 \times 100}{T_{\frac{1}{2}}} \text{ ml/100g/min}$$

(λ - tissue/blood partition coefficient. Taken as unity (54)).

Cerebral blood flow was also measured by the xenon-133 method using a collimated 1" scintillation detector placed over the right parietal region.

Arterial blood pressure and intraventricular pressure were monitored continuously and measurements were made of $paCO_2$, paO_2, pH, S_aO_2, S_vO_2 and haemoglobin.

The flow values obtained by both the hydrogen and xenon methods at control values of $paCO_2$ (38.7 mmHg. S.D: 2.7) and blood pressure (78.3 mmHg. S.D: 6.6) were compared in five baboons. In the other five baboons, correlations between results obtained using both methods were investigated over a wide range of flow values when $paCO_2$ was changed in the range 34.5 - 86 mmHg. All flow values were expressed in ml/100g/min.

Results

	n	MEAN	S.D.	S.E.	t	p	DIFFERENCE
XENON	16	100	16.6	4.2			
CORTEX	23	85.9	25.9	5.4	1.9	>0.05	NOT SIGNIFICANT
DEEP GREY	13	88.5	25.0	6.9	1.4	>0.1	NOT SIGNIFICANT

TABLE 10.1

COMPARISON OF FAST COMPONENT FLOW VALUES OBTAINED USING HYDROGEN AND XENON-133 AT CONTROL VALUES OF $paCO_2$ AND BP

	n	MEAN	S.D.	S.E.	t	p	DIFFERENCE
XENON	16	29.1	7.1	1.7			
WHITE MATTER	17	19.1	5.5	1.35	4.5	< 0.01	SIGNIFICANT
CORTEX	13	15.7	5.1	1.4	5.4	< 0.01	SIGNIFICANT
DEEP GREY	11	18.0	7.0	2.1	4.6	< 0.01	SIGNIFICANT

TABLE 10.2

COMPARISON OF SLOW COMPONENT FLOW VALUES OBTAINED USING HYDROGEN AND XENON-133 AT CONTROL VALUES OF $paCO_2$ AND BP

The results given in Tables 10.1 and 10.2 show that, at control levels, although there were no significant differences in the mean fast flows as measured by both the hydrogen and xenon techniques there were, in fact, significant differences in the slow flow values obtained using the two methods, weighting factors affecting component resolution.

	REGRESSION EQUATION	CORRELATION COEFFICIENT	p
R. CORTEX	$y = 0.81x + 11.8$	0.9	$<< 0.001$
R. WHITE MATTER	$y = 0.59x + 9.7$	0.63	< 0.01

TABLE 10.3

RELATIONSHIPS BETWEEN CBF MEASUREMENTS OBTAINED USING HYDROGEN AND XENON-133 WHEN $paCO_2$ LEVELS WERE VARIED

The results obtained in Table 10.3 show that highly statistically significant correlations exist between blood flow values obtained from cortex and white matter using hydrogen fast and slow component values. No significant correlations were found between flows measured with hydrogen in deep grey matter and the xenon results.

Summary

Although statistically significant differences may exist between flow values measured in white matter using hydrogen and xenon-133 slow components, flow measurements in the cortex and white matter correlate highly with corresponding xenon flow values over a wide range.

PART II

MEAN CEREBRAL BLOOD FLOW INDICES

Any analysis of local cerebral blood flow data which involves bi-exponential stripping of tracer clearance curves can suffer from two major disadvantages.

(1) As flow is varied over a wide range the ability to resolve the two components can vary such that when flow becomes extremely slow it may be possible to define only one component while in contrast when flow becomes extremely fast it is sometimes possible for more than two components to be extracted.

(2) If two different tissue compartments lie adjacent to the electrode (or other detector) position or if the tissue is heterogeneous, diffusion of tracer between slow and fast compartments may be significant and can result in inaccuracies in flow component resolution.

In these situations, consideration has to be given to the measurement of an index of mean flow. In the experiments to be described, comparisons are made of mean flow indices calculated from hydrogen and xenon-133 clearance curves.

Methods

In a total of five anaesthetised baboons platinum electrodes were inserted into the cerebral cortex close to cortex/white matter boundaries and local cerebral blood flow measurements were obtained using the hydrogen technique. Cerebral blood flow was also measured by the xenon-133 clearance technique using a collimated 1" sodium iodide scintillation detector placed over the right parietal region.

As before, systemic arterial blood pressure was monitored continuously and measurements were made of $paCO_2$, paO_2, pH, S_aO_2 and haemoglobin.

Cerebral blood flow was then again varied over the range 35-86 mmHg and comparisons of the initial slope flow index (F_{IS}) and the weighted mean flow index ($\overline{F}$) were obtained using the hydrogen technique. These indices were also compared with similar indices calculated from xenon clearance curves obtained during the same experiments. Their relationships to the xenon height/area flow index ($F_{H/A}$) were also obtained.

Results

RESULTS	r	p	REGRESSION EQUATION	STANDARD ERROR OF ESTIMATE
$F_{IS}(H_2) \sim \overline{F}(H_2)$	0.96	$<< 0.001$	$y = 0.7x + 1.4$	7.1
$F_{IS}(H_2) \sim F_{IS}(Xe)$	0.86	$<< 0.001$	$y = 0.81x + 1.5$	13.9
$F_{IS}(H_2) \sim F_{H/A}(Xe)$	0.92	$<< 0.001$	$y = 0.88x + 3.6$	11.0
$\overline{F}(H_2) \sim \overline{F}(Xe)$	0.93	$<< 0.001$	$y = 1.08x + 4.5$	11.9
$\overline{F}(H_2) \sim F_{H/A}(Xe)$	0.94	$<< 0.001$	$y = 1.04x + 2.0$	11.1

TABLE 10.4

RELATIONSHIPS BETWEEN MEAN CBF INDICES

Summary

The results in Table 10.4 and Figures 10.2, 10.3 and 10.4 show that when cerebral blood flow is changed as a result of variation in $paCO_2$ levels, highly significant correlations exist between the initial slope flow indices, the more fundamental weighted mean flow indices and the standard height/area index calculated from hydrogen and xenon-133 clearance curves. The usefulness and the reliability of the quickly calculated initial slope flow index when measuring wide variations in local flow or flow in heterogeneous tissue is therefore established.

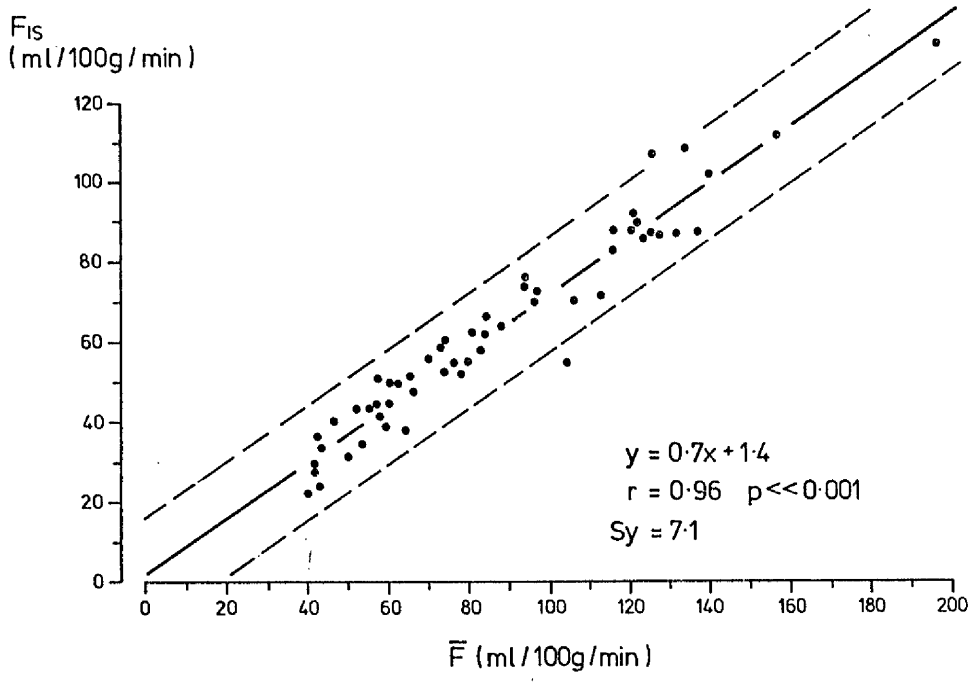


Fig. 10.2. Comparison of initial slope flow and weighted mean flow in the cortex as measured by the hydrogen clearance technique.

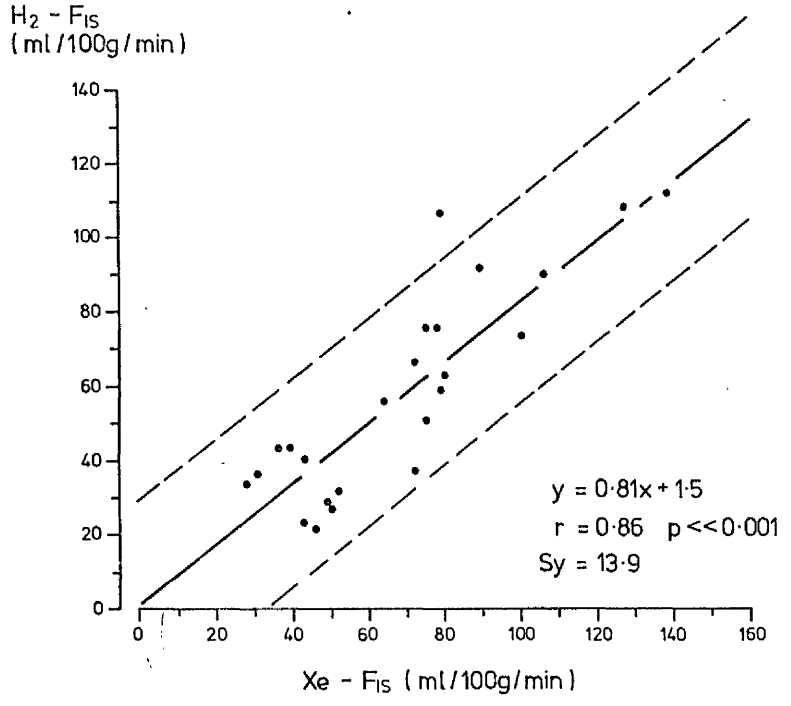


Fig. 10.3. Comparison of cortical initial slope flow measured by hydrogen clearance and initial slope flow measured by xenon-133 clearance.

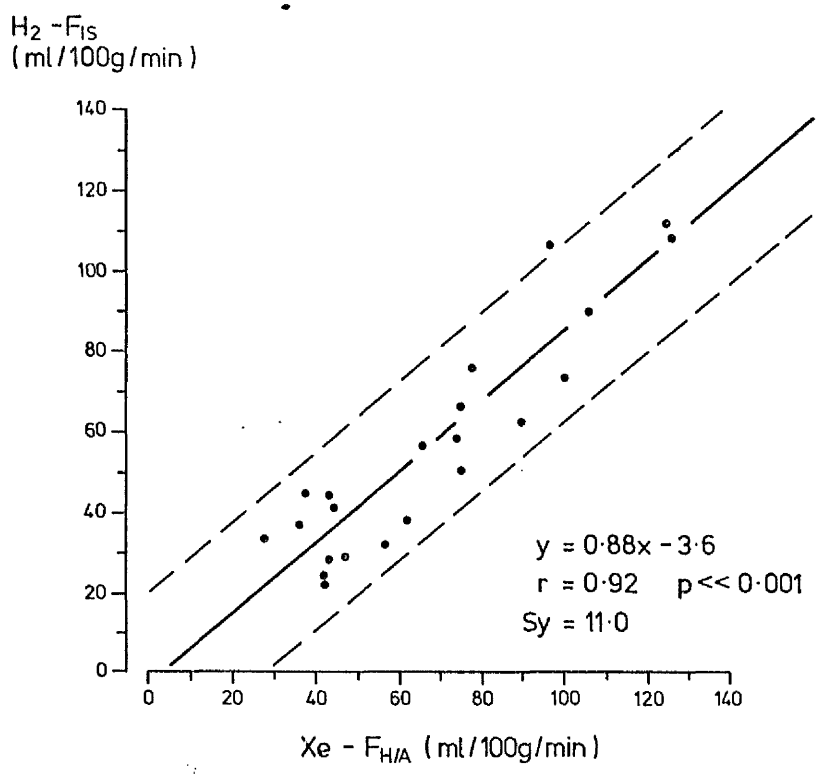


Fig. 10.4. Comparison of cortical initial slope flow measured by hydrogen clearance and height/area flow measured by xenon-133 clearance.

PART III

BRAIN STEM BLOOD FLOW

As a result of being able to develop a reliable hydrogen clearance technique it now became possible to study the behaviour of brain stem blood flow before and during the blood pressure response which can occur during raised intracranial pressure.

Methods

Platinum electrodes 0.1 mm in diameter were placed stereotactically in the brain stem of six anaesthetised baboons. These electrodes were placed as close as possible to the sensitive areas described by Hoff and Reis (104). Brain stem blood flow was measured by the hydrogen clearance technique, using initial slope flow indices, before and after serial increases in intracranial pressure produced by cisterna magna infusion. Two electrodes were placed in the cerebral hemispheres for reference and the positions of the electrodes were confirmed at post mortem. Arterial, intraventricular and cisterna magna pressures were monitored continuously by means of polyethylene cannulae in the femoral artery, frontal horn of the lateral ventricle and cisterna magna. The animals were ventilated to maintain normal $paCO_2$ and paO_2 levels.

Results

The mean control brain stem blood flow in the six animals was found to be 34 ml/100g/min (S.D: 8). In general the brain stem blood flow did not fall until intracranial pressure was greater than 90 mmHg and cerebral perfusion pressure was less than 40 mmHg.

Blood pressure rose significantly in all animals but at different levels of intracranial pressure. At no time was a reduction in brain stem blood flow recorded before the development of the blood pressure response. A substantial increase in flow after the response had occurred was recorded in two animals (Figure 10.5). Flow remained approximately

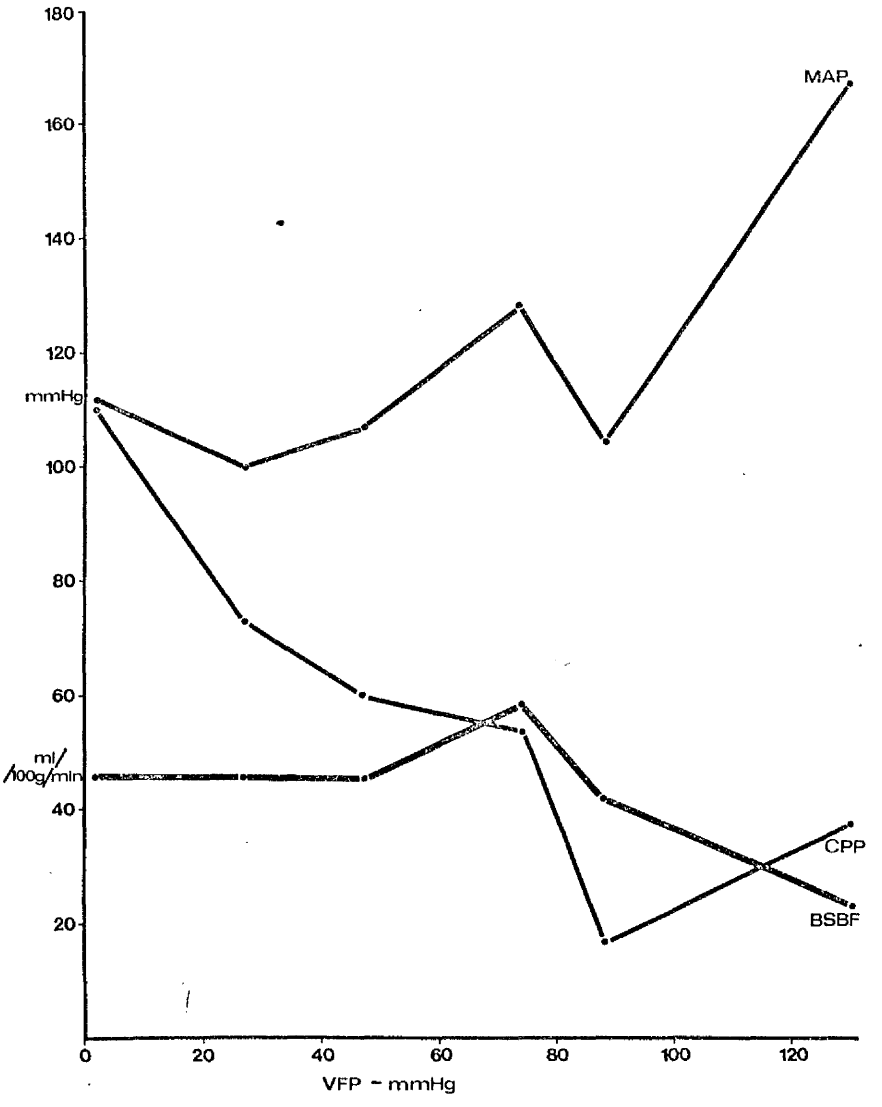


Fig. 10.5. Relation between mean arterial pressure (MAP), cerebral perfusion pressure (CPP) and brain stem blood flow (BSBF) during cisterna magna infusion - animal 2.

constant in the other four animals (Figure 10.6). Supratentorial blood flow measurements exhibited similar relationships to blood pressure and cerebral perfusion pressure as those previously described.

ANIMAL	CONTROL		FIRST SIGNIFICANT BP INCREASE	
	BP (mmHg)	BRAIN STEM BLOOD FLOW (ml/100g/min)	BP (mmHg)	BRAIN STEM BLOOD FLOW (ml/100g/min)
1	93	27	157 (+69%)	43 (+60%)
2	112	46	128 (+14%)	59 (+28%)
3	92	30	142 (+45%)	30 (+ 0%)
4	97	42	122 (+26%)	44 (+ 5%)
5	84	26	128 (+52%)	26 (+ 0%)
6	90	34	120 (+33%	35 (+ 3%)

TABLE 10.5

COMPARISON OF BRAIN STEM BLOOD FLOW AT CONTROL LEVELS AND AT THE TIME OF THE FIRST SIGNIFICANT INCREASE IN BLOOD PRESSURE ($\geq$114 mmHg) (MEAN CONTROL BLOOD PRESSURE 95 mmHg, S.D: 9.5)

Conclusions

The hydrogen clearance method is clearly a useful technique for measuring flow in local tissue areas and results compare favourably with those obtained from the standard xenon-133 clearance method. The initial slope flow index calculated from hydrogen clearance curves is a reliable index of mean flow over a wide range of flow values.

These results further emphasise that a prior reduction in blood flow whether in the brain stem or cerebral hemispheres is not a pre-requisite for the blood pressure response observed during raised intracranial pressure. There must be considerable doubt, therefore, with regard to the concept of the response as a means of preserving cerebral perfusion in conditions of intracranial hypertension. The results add

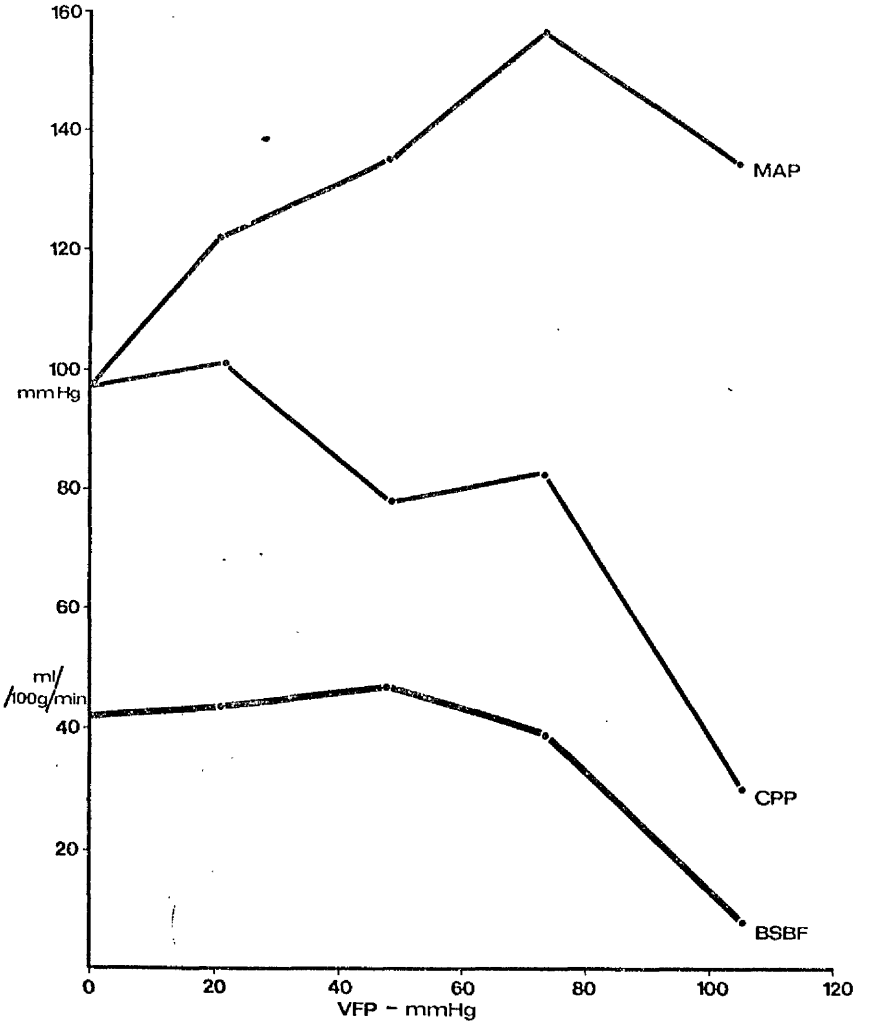


Fig. 10.6. Relation between mean arterial pressure (MAP), cerebral perfusion pressure (CPP) and brain stem blood flow (BSBF) during cisterna magna infusion - animal 4.

further support to the concept that the blood pressure response results from local stimulation of central sympathetic neurons in the brain stem or spinal cord by means of direct application of pressure or as a result of distorting forces.

CHAPTER 11

AUTOREGULATION OF CEREBRAL BLOOD FLOW IN STATES OF INTRACRANIAL HYPERTENSION

As shown from the results of experiments described in previous chapters the ability of the cerebral circulation to autoregulate to cerebral perfusion pressure changes depends on the method of increasing intracranial pressure. This could be merely a reflection of the different types of blood pressure response which occur when intracranial pressure is raised in different ways.

A series of investigations was designed to investigate autoregulation of cerebral blood flow to changes in blood pressure at control levels and in conditions of raised intracranial pressure.

Methods

Adult baboons, anaesthetised in the standard fashion with phencyclydine hydrochloride, suxamethonium and a nitrous oxide/oxygen mixture, were used. A Starling pump was again used to control ventilation and maintain normal $paCO_2$ and paO_2 levels.

Pressures were measured continuously by means of strain gauge transducers and in-dwelling catheters in the femoral artery, lateral ventricle, sagittal sinus and jugular vein.

Cerebral blood flow was measured using the xenon-133 clearance technique.

Three groups of experiments were performed.

(1) Expansion of a balloon placed infratentorially (five animals).

(2) Cisterna magna infusion of mock CSF after cord section at the C3/C4 level (four animals).

(3) Expansion of a subdural balloon over the dorsal aspect of the mid-thoracic region (four animals).

Autoregulation of cerebral blood flow to systemic arterial pressure changes was investigated before and after compression of the neuraxis.

Results

Group 1

Expansion of an infratentorial balloon reversibly abolished autoregulation (Figure 11.1). In the five animals autoregulation to hypotension (bleeding) and to hypertension (iv. angiotensin) was confirmed before balloon inflation. Over a cerebral perfusion pressure range of 64 to 130 mmHg, cerebral blood flow did not vary by more than $\pm$ 10 ml/100g/min from control values. When cerebral perfusion pressure was changed by expanding the balloon autoregulation was defective and a linear cerebral blood flow/cerebral perfusion pressure graph was obtained (Figure 11.2). The regression equation describing this linear relation between percentage change in cerebral blood flow and percentage change in cerebral perfusion pressure from control for results within the range 43% to 196% was calculated to be $y = 0.67x + 44.3$. The correlation coefficient was 0.78 with $p < 0.001$.

Only one baboon displayed defective autoregulation to blood pressure after balloon pressure was released. Reactive hyperaemia was observed for a short period in another animal after deflation of the balloon. However, cerebral blood flow then fell and remained at control levels in spite of increases in cerebral perfusion pressure up to 113 mmHg. In the remaining animals cerebral blood flow did not change by more than 8 ml/100g/min when cerebral perfusion pressure was varied between 67 and 127 mmHg by altering blood pressure.

Group 2

After section of the cervical cord, autoregulation to cerebral perfusion pressure changes caused by cisterna magna induced increases in intracranial pressure was abolished while autoregulation to cerebral perfusion pressure changes produced by hypotension (bleeding) and hypertension (iv. angiotensin) remained intact (Figure 11.3).

Group 3

In contrast to groups 1 and 2 focal compression at the mid-thoracic region of the intact cord produced little change in the state of auto-

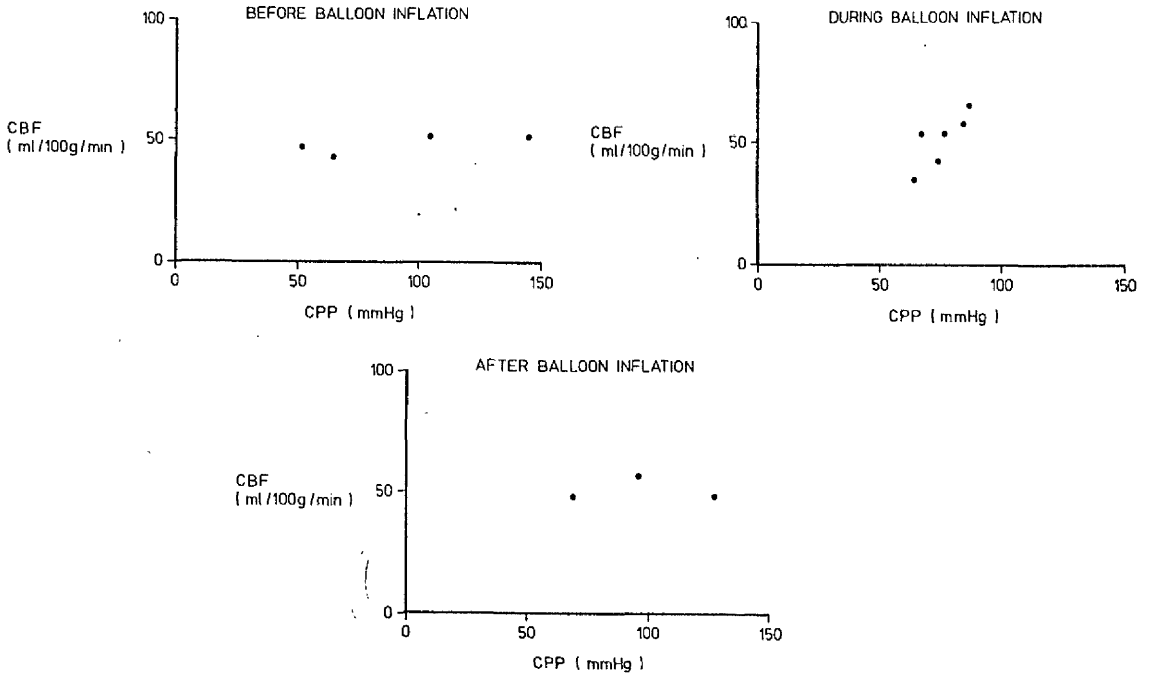


Fig. 11.1. Comparison of the state of cerebral blood flow autoregulation before, during and after infratentorial balloon expansion.
Data from one animal.

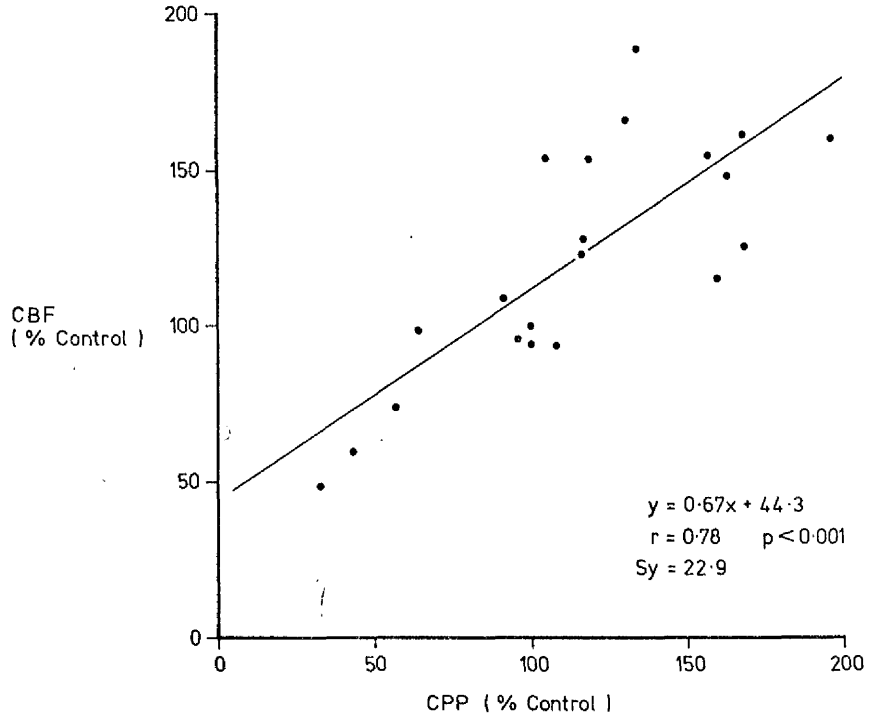


Fig. 11.2. Relation between cerebral blood flow (CBF) and cerebral perfusion pressure (CPP) during infratentorial balloon inflation - values percentage of control.
Data from 5 animals.
(High cerebral perfusion pressure values obtained during blood pressure increases immediately following balloon inflation.)

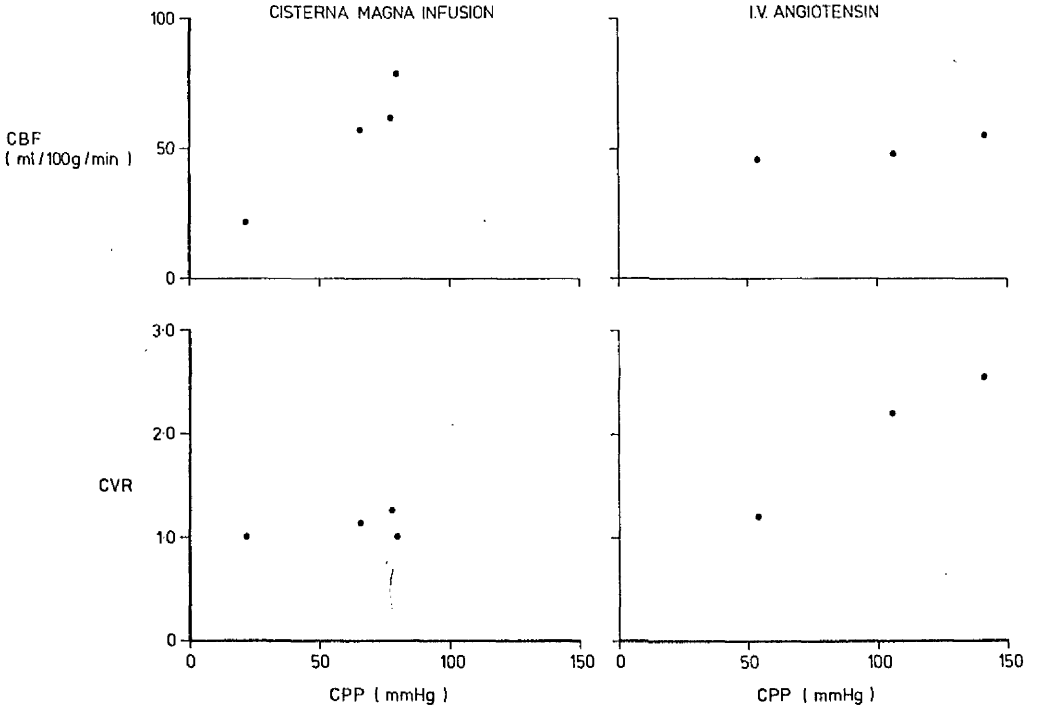


Fig. 11.3. Comparison of the cerebral blood flow autoregulation response to intracranial pressure changes and to blood pressure changes in an animal with a sectioned spinal cord.

regulation in five out of six animals. Nevertheless, once the balloon was deflated autoregulation to blood pressure changes was inpaired in all animals to varying degrees (Figure 11.4).

Conclusions

These experiments have shown that the mechanism of autoregulation which maintains cerebral blood flow in the face of rising intracranial pressure becomes impaired if destruction of brain stem - spinal cord pathways occurs while cerebral blood flow autoregulation to changes in blood pressure may remain intact. Focal compression of the mid-thoracic region of the intact cord may interfere with this latter mechanism.

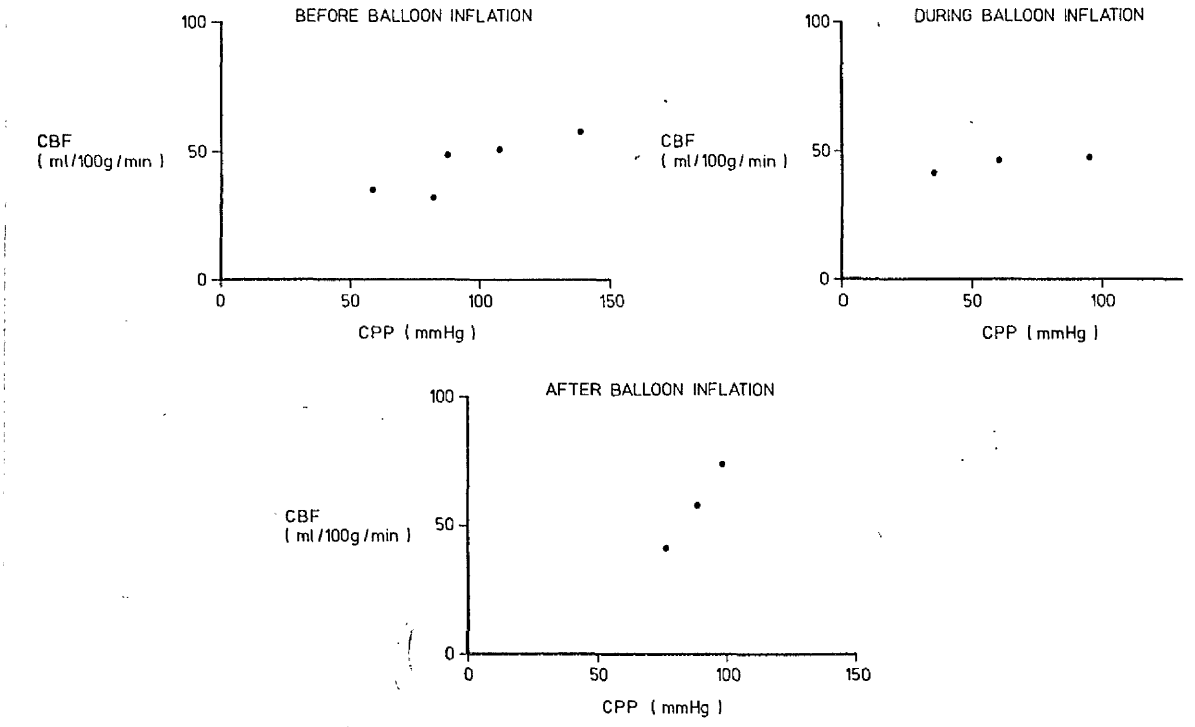


Fig. 11.4. Comparison of the state of cerebral blood flow autoregulation before, during and after focal compression of the spinal cord.
Data from one animal.

CHAPTER 12

DISCUSSION SUMMARY

Raised Intracranial Pressure and Cerebral Blood Flow

During raised intracranial pressure cerebral blood flow is maintained by dilatation of resistance vessels until an upper intracranial pressure limit is reached. This boundary condition varies from animal to animal. When cerebral blood flow is eventually reduced it is due primarily to compression of the venous outflow tract. In determining the level of cerebral blood flow, the cause of the intracranial hypertension and its time course play just as important a role as the height of the intracranial pressure. With gradual general diffuse compression and focal supratentorial compression cerebral blood flow is in general maintained up to an intracranial pressure level of approximately 50 mmHg and down to cerebral perfusion pressures in the region of 40 mmHg. However, in the case of cisterna magna infusion the sequence of events before these limits are reached are more complex than with supratentorial balloon expansion with hyperaemic values often being reached at the time of the blood pressure response. However, it should always be remembered that cisterna magna infusion is in no way analogous to the expanding lesion situation and considerable care has to be taken when considering the cisterna magna infusion results in a clinical context. In the case of infratentorial balloon inflation cerebral blood flow fell when intracranial pressure rose and autoregulation to changes of cerebral perfusion pressure was absent. These results are in accord with the clinical studies carried out in 1940 by Courtice who found no cerebral blood flow reduction in patients with supratentorial tumours, but did observe flows lower than normal in patients with posterior fossa tumours. Langfitt has shown that with rapid supratentorial balloon expansion in monkeys cerebral blood flow fell progressively as intracranial pressure rose.

The different causes of raised intracranial pressure can result in different effects on compensatory mechanisms such as blood pressure and resistance vessel diameter. Intracranial hypertension produced by infusion of fluid into the subarachnoid space could cause a change in environment surrounding the blood vessels which could lead to a change in the blood vessel response to metabolic stimuli. On the other hand, a localised supratentorial mass may result in brain shift causing distortion and obstruction of superficial cortical veins. An infratentorial mass may cause stimulation of the brain stem and as a result have an influence on sympathetic activity leading to cerebral blood flow changes due to alterations in the diameter of both extraparenchymal intracranial vessels and the large vessels in the neck. The results from the experiments described suggest that there is no single autoregulation response but there exists a number of complex inter-related compensatory mechanisms which can be brought into action whenever the blood supply to the brain is threatened. The actual pattern of the integrated compensatory response depends on the initiating mechanism for the intracranial hypertension. It is impossible, therefore, to define fully quantitative relationships between intracranial pressure and cerebral blood flow and between cerebral perfusion pressure and cerebral blood flow. Any clinician who attempts to estimate cerebral blood flow values from measurements of intracranial pressure and cerebral perfusion pressure alone has no secure basis for his calculations.

Raised Intracranial Pressure and Cerebral Perfusion Pressure

The definition of cerebral perfusion pressure as the difference between mean systemic arterial pressure and mean intracranial pressure relies heavily on the assumption that intracranial pressure represents the effective venous outflow pressure over a wide range of pressure values. The results from the experiments described in chapter 8 show that this is indeed true. Pressure in the cortical veins does increase

linearly with intracranial pressure with a slightly higher pressure in these veins allowing them to remain patent. The definition of cerebral perfusion pressure is therefore valid provided no significant changes occur in the pressure drop across the major extracranial and intracranial arteries.

At control levels sagittal sinus pressure is lower than intracranial pressure and depends on the right atrial pressure. During intracranial hypertension pressure in the sagittal sinus will be subject to different influences. These include the elastic properties of the sinus itself, the level of blood flow in the sinus and central venous pressure. The relevance of each of these factors depends on the site of measurement, the species of experimental animal and the method used to increase intracranial pressure.

No significant changes in jugular venous pressure occur as intracranial pressure rises. Any small changes that do occur are related to central venous pressure changes and changes in cardiac function.

Raised Intracranial Pressure and Cerebrovascular Resistance

No matter how intracranial pressure is raised a progressive increase in venous or outflow resistance occurs with the greatest resistance existing between the cortical veins and the sagittal sinus. Since these outflow resistance changes are independent of the cause of the intracranial hypertension one is inevitably led to the conclusion that it is changes in the prevenous resistance which lead to the different cerebral blood flow responses observed. It is still not certain what the initiating mechanism is for these changes in diameter of prevenous vessels. This has a direct bearing on the mechanism of cerebral blood flow autoregulation. Cerebral blood flow autoregulation can be defined as the capacity of the brain to maintain constant flow in the face of changing cerebral perfusion pressure. A number of theories postulate metabolic, myogenic, neurogenic and tissue pressure control. Although it would seem unlikely that tissue pressure could

effectively control autoregulation at high intracranial pressure levels the relative influence of the other factors could depend on the type of insult threatening the cerebral circulation and as a result, as is found in practice, the changes in prevenous resistance depend on the cause of the raised intracranial pressure. Furthermore, although the autoregulation mechanism which maintains cerebral blood flow in the face of rising intracranial pressure is impaired if brain stem/spinal cord pathways are destroyed, cerebral blood flow autoregulation to changes in blood pressure can remain intact in these circumstances.

Raised Intracranial Pressure and Systemic Arterial Pressure

Previous theories concerning the blood pressure response during raised intracranial pressure have postulated various trigger mechanisms. These include cerebral ischaemia, ischaemia or hypoxia of medullary centres, action of baroreceptors sensitive to changes in cerebral perfusion pressure and sever brain stem distortion. In addition it has been thought that systemic hypertension may act to preserve cerebral perfusion pressure and hence cerebral blood flow - the well known Cushing response. This response is also characterised by low heart rate and irregular respiratory rhythm. Strictly speaking, to conform to the definition of the Cushing response, the intracranial pressure should reach diastolic blood pressure levels before marked systemic hypertension occurs. However, during continuous monitoring of intracranial pressure in clinical practice a very variable relationship between blood pressure and intracranial pressure has been observed.

The experimental studies described in this thesis have shown consistently that substantial rises in systemic arterial pressure can occur with quite moderate increases in intracranial pressure and at levels commonly found in clinical practice. Furthermore, before the blood pressure response had developed low levels of cerebral blood flow and cerebral perfusion pressure had not been reached nor had

intercompartmental pressure differences developed. Diffuse compression of the intact neuraxis led to sustained increase in blood pressure at intracranial pressure levels considerably below the resting diastolic blood pressure level. A similar blood pressure response was obtained with diffuse compression of the isolated spinal cord after mid-cervical section. There was no blood pressure response to intracranial hypertension after spinal cord section. Focal compression of the intact neuraxis resulting from expansion of a subdural balloon placed in the left parietal region, right cerebellar region or mid-thoracic region of the spinal cord gave rise to transient increases in blood pressure but no sustained hypertension.

The basic mechanism therefore seems to be that the blood pressure response during raised intracranial pressure is mediated through central sympathetic neurons within the lower brain stem which act by way of descending pathways on sympathetic neurons in the spinal cord which may also be sensitive to local pressure changes. The precise location of the central neurons remains a matter for discussion but they would appear to be situated within a narrow strip along the floor of the fourth ventricle. The iniating stimulus is local changes in pressure both in the brain stem and spinal cord. These changes in pressure may be quite small. The resultant effect is a change in cardiovascular function including both neurogenic constriction and direct effects on cardiac output. Measurements of blood flow in the cerebral hemispheres and brain stem rule out cerebral and brain stem ischaemia as trigger mechanisms for this response. Other postulated mechanisms such as severe brain stem distortion and transtentorial and transforaminal pressure gradients also appear to be ruled out.

The unpredictability of the blood pressure response in clinical practice could be due to threshold changes within the receptor neurons in prolonged states of raised intracranial pressure and also because of a breakdown in the transmission of periodic increases in

supratentorial pressure as a result of transtentorial herniation. The low threshold of the blood pressure response and the lack of response to marked variations in intracranial pressure in patients cast considerable doubt on the assumption that the role of the response is to maintain cerebral blood flow in states of intracranial pressure. In any case, in these circumstances, unless autoregulation is impaired an increase in blood pressure alone will not alter cerebral blood flow.

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