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Cerebral Blood Flow and Intracranial Pressure

Lisa Hill*, Carl Gwinnutt
*Correspondence Email: lambpie10@hotmail.com

Summary

The normal adult skull can be considered as a bony box of fixed volume, containing brain, blood and cerebrospinal fluid (CSF). An understanding of how these components interact is essential in managing normal patients under anaesthesia and those with intracranial pathology. These factors will be considered in two sections - cerebral blood flow and intracranial pressure.

CEREBRAL BLOOD FLOW

The brain is unusual in that it is only able to withstand very short periods of lack of blood supply (ischaemia). This is because neurones produce energy (ATP) almost entirely by oxidative metabolism of substrates including glucose and ketone bodies, with very limited capacity for anaerobic metabolism. Without oxygen, energy-dependent processes cease, leading to irreversible cellular injury if blood flow is not re-established rapidly (3 to 8 minutes under most circumstances). Therefore, adequate cerebral blood flow must be maintained to ensure a constant delivery of oxygen and substrates, and to remove the waste products of metabolism.

Cerebral blood flow (CBF) is dependent on a number of factors that can broadly be divided into:

1. those affecting cerebral perfusion pressure

2. those affecting the radius of cerebral blood vessels

This relationship can be described by the Hagen-Poiseuille equation (see below) which describes the laminar flow of an incompressible uniformly viscous fluid (so called Newtonian fluid) through a cylindrical tube with constant circular cross-section. Although blood does not fulfill all of these criteria, it tends to flow in a laminar manner at the level of capillaries.

The Hagen-Poiseuille equation

$$\text{Cerebral Blood Flow} = \frac{\Delta P \, \pi \, R^4}{8 \, \eta \, l}$$

where: ΔP = cerebral perfusion pressure
R = radius of the blood vessels
η = viscosity of the fluid (blood)
l = length of the tube (blood vessels)
π = constant, 3.14

Some facts and figures

- CBF averages 50ml.100g^{-1}.min^{-1} (ranging from 20ml.100g^{-1}.min^{-1} in white matter to 70ml.100g^{-1}.min^{-1} in grey matter).
- The adult brain weighs 1400g or 2% of the total body weight. Therefore it can be seen that CBF is 700ml.min^{-1} or 15% of the resting cardiac output.
- This reflects the high oxygen consumption of the brain of 3.3ml.100g^{-1}.min^{-1} (50ml.min^{-1} in total) which is 20% of the total body consumption. This is often referred to as the cerebral metabolic rate for oxygen or $CMRO_2$. This is higher in the cortical grey matter and generally parallels cortical electrical activity.

CEREBRAL PERFUSION PRESSURE

Perfusion of the brain is dependent on the pressure gradient between the arteries and the veins and this is termed the cerebral perfusion pressure (CPP). This is the difference between the mean arterial blood pressure (MAP) and the mean cerebral venous pressure.

The latter is difficult to measure and approximates to the more easily measured intracranial pressure (ICP).

CPP = MAP – ICP

MAP can be estimated as equal to: diastolic blood pressure + 1/3 pulse pressure (difference between systolic and diastolic pressures) and is usually around 90mmHg. ICP is much lower and is normally less than 13mmHg.

CPP is normally about 80mmHg

Clearly, CPP will be affected by anything that changes the MAP or ICP. Blood loss causing hypotension will reduce MAP and CPP (hence the reduced level of consciousness seen in severely shocked patients), while an intracerebral haematoma will increase ICP, with the same effect (see below for more details). Clearly if both co-exist, the effect is a catastrophic fall in CPP and the risk of brain ischaemia. An increase in CPP is usually the result of an increase in MAP, the contribution made by reducing ICP is minimal, except in pathological states when ICP is very high. In a normal brain, despite the potential for changes in MAP (sleep, exercise etc), CBF remains constant over a wide range of CPPs. This is achieved by a process called autoregulation (see below).

REGULATION OF CEREBRAL ARTERIAL BLOOD VESSEL CALIBRE

This is regulated by four primary factors:

Lisa Hill
Specialist Registrar in Anaesthesia
Royal Oldham Hospital
Lancashire OL1 2JH
UK

Carl Gwinnutt
Consultant Neuroanaesthetist
Hope Hospital
Salford M6 8HD
UK

1. Cerebral metabolism
2. Carbon dioxide and oxygen levels
3. Autoregulation
4. Neurohumeral factors.

The radius of the arterial vessels is particularly important because, due to its effect on CBF, an increased radius (vasodilatation) leads to an increase in cerebral blood volume which in turn increases ICP and reduces CPP, so a balance must be reached.

Cerebral metabolism

Changes in CBF and metabolism tend to follow each other; local or global increases in metabolic demand are met rapidly by an increase in CBF and substrate delivery and vice versa (often referred to as flow-metabolism coupling, Figure 1). These changes are thought to be controlled by several vasoactive metabolic mediators including hydrogen ions, potassium, CO_2, adenosine, glycolytic intermediates, phospholipid metabolites and more recently, nitric oxide (NO).

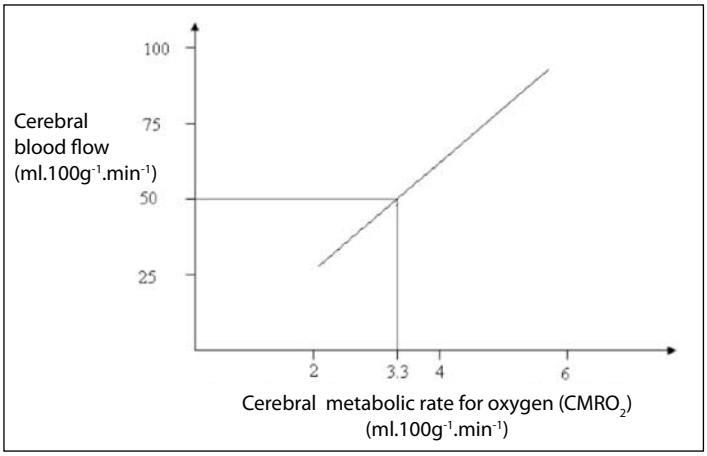

Figure 1. *Graph illustrating coupling between CBF and $CMRO_2$. Corresponding normal CBF and $CMRO_2$ values are represented by the grey line*

Carbon dioxide and oxygen levels

At normotension, the relationship between partial pressure of carbon dioxide in arterial blood ($PaCO_2$) and CBF is almost linear and at a $PaCO_2$ of 10.6kPa (80mmHg) CBF is approximately doubled. No further increase in flow is possible at this point as the arterioles are maximally dilated. Conversely at 2.7kPa (20mmHg) flow is almost halved and again cannot fall further as the arterioles are maximally vasoconstricted (Figure 2). These effects are regulated by a complex and interrelated system of mediators. The initial stimulus is a decrease in brain extracellular pH brought about by an increase in $PaCO_2$, further mediated by nitric oxide, prostanoids, cyclic nucleotides, potassium channels, and a decrease in intracellular calcium concentration as a final common mediator.

Arteriolar tone has an important influence on how $PaCO_2$ affects CBF. Moderate hypotension impairs the response of the cerebral circulation to changes in $PaCO_2$, and severe hypotension abolishes it altogether.

The response of the cerebral vessels to CO_2 can be utilised to help manage patients with raised intracranial pressure, for example after traumatic brain injury. Hyperventilation reduces the $PaCO_2$ and causes vasoconstriction of the cerebral vessels (reduces their radius) and therefore reduces cerebral blood volume and ICP. However if $PaCO_2$ is reduced too much, the resulting vasoconstriction can reduce CBF to the point of causing or worsening cerebral ischaemia. Clearly hypercapnia and the resulting vasodilatation and increase in ICP must also be avoided. $PaCO_2$ is therefore best maintained at low-normal levels to prevent raising ICP (35-40mmHg, 4.7-5.3kPa). This CO_2 reactivity may be lost in areas of the brain that are injured. Furthermore, impaired cerebral CO_2 vasoreactivity is associated with a poor outcome in patients with severe head injury. CO_2 reactivity is generally preserved during inhalation anaesthesia (up to about 1 MAC of volatile) and can therefore be utilised to help control ICP and brain swelling during surgery.

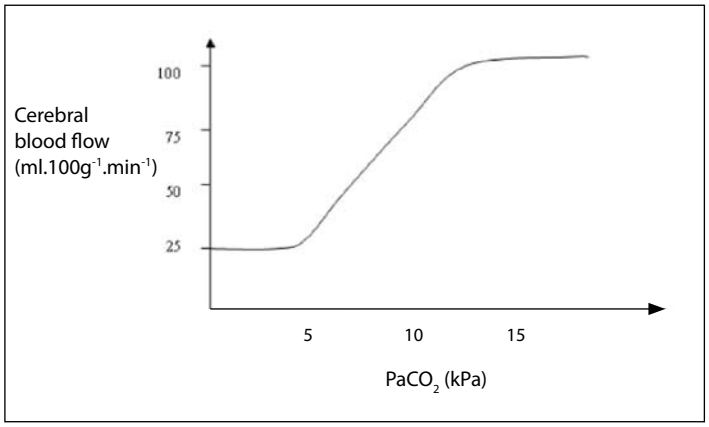

Figure 2. *Relationship between CBF and $PaCO_2$*

Oxygen has little effect on the radius of blood vessels at partial pressures used clinically (Figure 3).

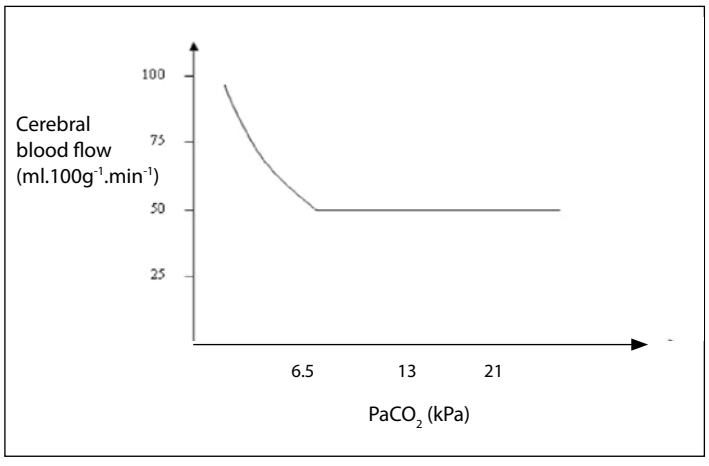

Figure 3. *Relationship between CBF and PaO_2 showing little effect on CBF in the normoxaemic range. CBF increases if PaO_2 is less than 6.6kPa*

CBF increases once PaO_2 drops below about 6.7kPa so that cerebral oxygen delivery remains constant. Hypoxia acts directly on cerebral tissue to promote the release of adenosine, and in some cases prostanoids that contribute significantly to cerebral vasodilatation. Hypoxia also acts directly on cerebrovascular smooth muscle to produce hyperpolarisation and reduce calcium uptake, both mechanisms enhancing vasodilatation.

Autoregulation

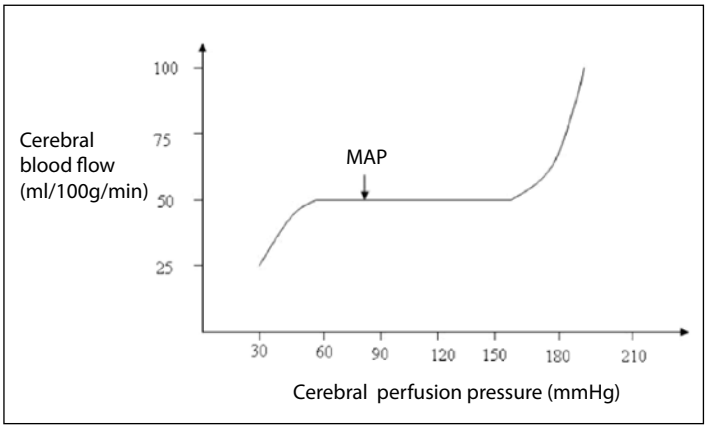

Figure 4. *Relationship between cerebral blood flow and cerebral perfusion pressure. In chronic hypertension, the curve is shifted to the right*

The brain requires a constant flow of blood over a range of pressures and this is achieved by the process of autoregulation. The stimulus to autoregulation is CPP, not MAP. In adults, under normal circumstances (ICP <10mmHg), CPP and MAP are very similar and CBF remains constant with a CPP of 60-160mmHg (Figure 4). The higher the ICP the more CPP deviates from MAP and must be calculated. The autoregulation curve is shifted to the right in chronic hypertensive patients and to the left in neonates and younger children, gradually moving to adult values as they get older.

Autoregulation is thought to be a myogenic mechanism, whereby vascular smooth muscle constricts in response to an increase in wall tension and to relax to a decrease in wall tension. At the lower limit of autoregulation, cerebral vasodilation is maximal, and below this level the vessels collapse and CBF falls passively with falls in MAP. At the upper limit, vasoconstriction is maximal and beyond this the elevated intraluminal pressure may force the vessels to dilate, leading to an increase in CBF and damage to the blood-brain-barrier. Metabolic mediators, such as adenosine, may also be involved in the low-pressure range of autoregulation. As with all the other mechanisms that affect the radius of the blood vessels, autoregulation will also change the cerebral blood volume and may affect ICP.

Pressure autoregulation can be impaired in many pathological conditions including patients with a brain tumour, subarachnoid haemorrhage, stroke, or head injury. A loss of CBF regulatory capacity can be attributed either to damage of the control system (eg. cerebral vessels) or of the feedback mechanisms involved in the brain's haemodynamic control. At this time, CBF becomes pressure-dependent and thus small changes in MAP can have profound changes on CBF and cerebral blood volume.

Neurohumeral factors

A major difference between other systemic circulations and the cerebral circulation is the relative lack of humoral and autonomic control on normal cerebrovascular tone. The main action of the sympathetic nerves is vasoconstriction that protects the brain by shifting the autoregulation curve to the right in hypertension. The parasympathetic nerves contribute to vasodilatation and may play a part in hypotension and reperfusion injury (for example after cardiac arrest).

Other factors

Blood viscosity

This is directly related to haematocrit. As viscosity falls, CBF increases (see Hagen-Poiseuille equation). However, there will also be a reduction in oxygen-carrying capacity of the blood. The optimal haematocrit is where there is a balance between flow and capacity, usually about 30%.

Temperature

$CMRO_2$ decreases by 7% for each 1°C fall in body temperature and is paralleled by a similar reduction in CBF. At 27°C, CBF is approximately 50% of normal. By 20°C, CBF is about 10% of normal. The reduction in $CMRO_2$ is the factor that allows cold patients to withstand prolonged periods of reduced CBF without ischaemic damage for example during cardiopulmonary bypass. Again, because of vasoconstriction, cerebral blood volume and ICP are reduced. Although this has been tried to help control high ICP, clinical trials have been disappointingly ineffective in showing an improved outcome.

Drugs

Cerebral metabolism can be manipulated (reduced) and consequently CBF, cerebral blood volume and ICP is reduced. Infusions of the barbiturate thiopentone have been used to help control high ICP after head injury, however there is little convincing evidence of benefit.

Anaesthetic drugs have a significant effect on cerebral blood vessels; volatile agents cause a reduction in the tension of cerebral vascular smooth muscle resulting in vasodilatation and an increase in CBF. Interestingly many of the newer drugs (isoflurane, sevoflurane) also reduce neuronal function and metabolic demands, and as a result this can lead to uncoupling of flow-metabolism. This appears to be dependent on the concentration of volatile anaesthetic given. The vasodilatation can be countered by mild hyperventilation to a $PaCO_2$ at the low end of the normal range (4.0-4.5kPa), without serious risk of cerebral ischaemia.

INTRACRANIAL PRESSURE (ICP)

Intracranial pressure is important as it affects cerebral perfusion pressure and cerebral blood flow. Normal ICP is between 5 and 13mmHg. Because it is very dependant on posture, the external auditory meatus is usually used as the zero point.

Some facts and figures

- Constituents within the skull include the brain (80%, 1400ml), blood (10%, 150ml) and cerebrospinal fluid (CSF 10%, 150ml).
- The skull is a rigid box, so if one of the three components increases in volume then there must be compensation by a decrease in the volume of one or more of the remaining components otherwise the ICP will increase (Figure 5). The term compliance is often used to describe this relationship, but it is more accurately **elastance**, the reciprocal of compliance (change in pressure for unit change in volume).
- Compensatory mechanisms include movement of CSF into the spinal sac, increased reuptake of CSF and compression of venous sinuses. These mechanisms reduce the liquid volume of the intracranial contents.

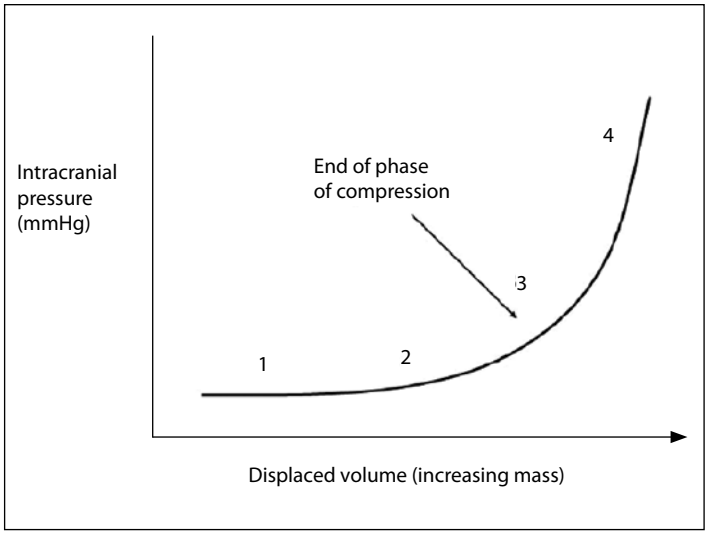

Figure 5. *ICP elastance curve (change in pressure per unit change in volume)*

Stage 1/2 *= compensation phase. As one of the intracranial constituents increases in volume, the other two constituents decrease in volume in order to keep the intracranial pressure constant.*

Stage 3/4 *= decompensated phase. When compensatory mechanisms are exhausted, small increases in the volumes of intracranial constituents cause large increases in ICP.*

The slope of the curve is dependent on which intracranial constituent is increasing. If it is blood or CSF, both of which are poorly compressible, then the slope is steeper. If it is brain tissue, such as a tumour or oedema, the curve is less steep as the tissue is compressible.

CEREBROSPINAL FLUID (CSF)

CSF is a specialised extracellular fluid in the ventricles and subarachnoid space which has a multitude of functions.

Functions of the CSF

- Mechanical protection by buoyancy. The low specific gravity of CSF (1.007) reduces the effective weight of the brain from 1.4kg to 47g (Archimede's principle). This reduction in mass reduces brain inertia and thereby protects it against deformation caused by acceleration or deceleration forces.
- CSF provides a constant chemical environment for neuronal activity.
- CSF is important for acid-base regulation for control of respiration.
- CSF provides a medium for nutrients after they are transported actively across the blood-brain-barrier.

CSF is produced at a rate of 0.3-0.4ml.min^{-1} (500ml.day^{-1}) by the choroid plexus in the lateral, third and fourth ventricles. CSF is produced by the filtration of plasma through fenestrated capillaries followed by active transport of water and dissolved substances through the epithelial cells of the blood-CSF barrier. This is distinct from the blood-brain-barrier which consists of endothelial cells linked by tight junctions whose function is to protect the brain from chemicals in the blood stream. CSF formation is dependent on the CPP and when this falls below 70mmHg, CSF production also falls because of the reduction in cerebral and choroid plexus blood flow.

Following production, CSF then circulates through the ventricular system and the subarachnoid spaces, aided by ciliary movements of the ependymal cells. Resorption takes place mostly in the arachnoid villi and granulations into the circulation: the mechanism behind the resorption is the difference between the CSF pressure and the venous pressure. An obstruction in CSF circulation, overproduction of CSF or inadequate resorption results in hydrocephalus.

PATHOLOGICAL CONDITIONS CAUSING A RISE IN VOLUME OF INTRACRANIAL CONSTITUENTS

Any of the three intracranial constituents (tissue, blood or CSF) can increase in size and volume (Table 2).

EFFECTS OF A RAISED ICP

As ICP rises, CPP falls eventually to a point when there is no cerebral blood flow, no cerebral perfusion and brain death. Prior to this, brain structures begin to herniate (protrude through an opening).

Physiological compensatory mechanisms occur to try and maintain cerebral blood flow:

- **Temporal lobe herniation** beneath the tentorium cerebelli (uncal herniation) – causes cranial nerve III palsy (dilatation of pupil on the same side as lesion (ipsilateral) followed by movement of eye down and out).

Table 1. *Comparison of the compositions of CSF and plasma*

	Plasma (mmol.l^{-1})	CSF (mmol.l^{-1})
Urea	2.5-6.5	2.0-7.0
Glucose (fasting)	3.0-5.0	2.5-4.5
Sodium	136-148	144-152
Potassium	3.8-5.0	2.0-3.0
Calcium	2.2-2.6	1.1-1.3
Chloride	95-105	123-128
Bicarbonate	24-32	24-32
Protein	60-80g.l^{-1}	200-400mg.l^{-1}

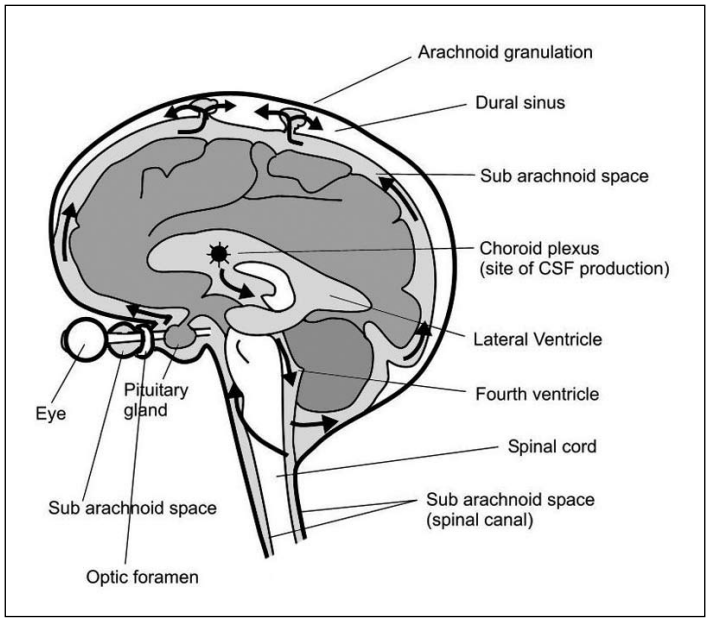

Figure 6. *Production, circulation and resorption of CSF. Production mostly takes place in the choroid plexus of the lateral ventricles. CSF circulates to the subarachnoid spaces, where resorption takes place via the arachnoid granulations and villi. When ICP is raised, the pressure is transmitted along the optic nerve causing papilloedema*

- **Herniation of cerebellar peduncles** through the foramen magnum (tonsillar herniation). Pressure on the brainstem causes the Cushing reflex – hypertension, bradycardia and Cheyne-Stokes respiration (periodic breathing).
- **Subfalcine herniation** occurs when the cingulate gyrus on the medial aspect of the frontal lobe is displaced across the midline under the free edge of the falx cerebri and may compress the anterior cerebral artery.
- **Upward or cerebellar herniation** occurs with either a large mass or increased pressure in the posterior fossa. The cerebellum is displaced in an upward direction through the tentorial opening and causes significant upper brainstem compression.

HOW CAN ICP BE INFLUENCED?

Primary brain damage occurs at the time of a head injury and is unavoidable except through preventative measures. The aim of management following this is to reduce secondary brain damage which is caused by a reduction in oxygen delivery due to hypoxaemia (low arterial PaO_2) or anaemia, a reduction in cerebral blood flow due to hypotension or reduced cardiac output, and factors which cause a raised ICP and reduced CPP.

The most important management strategy ensures A (Airway and C spine protection in trauma), B (Breathing and adequate oxygenation) and C (blood pressure and CPP). Following this, further strategies to reduce ICP and preserve cerebral perfusion are required. Techniques that can be employed to reduce ICP are aimed at reducing the volume of one or more of the contents of the skull (Table 3).

Often, blood pressure needs to be augmented with drugs that produce arterial vasoconstriction such as metaraminol or norepinephrine (which requires central venous access). Following a head injury when autoregulation is impaired, if there is a drop in MAP from drugs or blood loss, the resulting cerebral vasodilatation increases cerebral blood volume, which in turn raises ICP and further drops CPP. This starts a vicious cycle. So by raising MAP, ICP can often be reduced.

MEASURING ICP

ICP is traditionally measured by use of a ventriculostomy or external ventricular drain (EVD), which involves a catheter that is placed through a small hole in the skull (burr hole) into the lateral ventricle. ICP is then measured by transducing the pressure in a fluid column. Ventriculostomies also allow drainage of CSF, which can be effective in decreasing the ICP. More commonly ICP is now measured by placing some form of measuring device (for example a minature transducer) within the brain tissue (intraparenchymal monitor). An epidural monitor can also be used but becomes increasingly unreliable at extremes of pressure.

The normal ICP waveform is a triphasic wave, in which the first peak is the largest peak and the second and third peaks are progressively smaller. When intracranial compliance is abnormal, the second and third peaks are usually larger than the first peak. In addition, when intracranial compliance is abnormal and ICP is elevated, pathological waves may appear. Lundberg described 3 types of abnormal ICP waves in 1960, that he named A, B, and C waves. Although these can be identified, it is more common nowadays to measure the mean ICP and use this to calculate CPP.

Table 2. *Conditions causing raised ICP*

Brain Tissue	Blood	CSF
Tumours	Intracerebral, subarachnoid, subdural, extradural haematomas	Hydrocephalus
Cerebral oedema secondary to trauma, infection, infarction, hyponatraemia, hypertensive encephalopathy, acute liver failure, Reye's syndrome	Arteriolar dilatation secondary to hypoxaemia, hypercarbia, anaesthetic drugs, hyperthermia, seizures, hypotension	Meningeal diseases Choroid plexus tumour
Cerebral abcess Cerebral contusions	Venous dilatation secondary to venous obstruction from high PEEP, coughing, straining, heart failure, venous sinus thrombosis, head-down tilt, tight neck ties	

Table 3. *Strategies to reduce ICP*

Reduce brain tissue volume	Reduce blood volume	Reduce CSF volume
Tumour resection, abcess drainage	Evacuation of haematomas	Insertion of external ventricular drain or ventriculoperitoneal shunt to reduce CSF volume reduce (more long term measure)
Steroids (especially dexamethasone) to reduce cerebral oedema	Arterial: avoiding hypoxaemia, hypercarbia, hyperthermia, vasodilatory drugs, hypotension	
Mannitol/furosemide to reduce intracellular volume	Barbiturate coma to reduce $CMRO_2$ and cerebral blood volume	
Hypertonic saline to reduce intracellular volume	Venous: patient positioning with 30° head up, avoiding neck compression with ties/excessive rotation, avoiding PEEP/airway obstruction/CVP lines in neck	
Decompressive craniectomy to increase intracranial volume		

If ICP is not measured directly, we can estimate it and therefore make changes in MAP to maintain CPP:

- Patient drowsy and confused (GCS 9-13) ICP ~20mmHg
- GCS ≤ 8, ICP ~ 30mmHg

MEASURING THE ADEQUACY OF CEREBRAL PERFUSION

This is difficult as ideally adequacy of cerebral perfusion would be determined at a cellular level to determine whether neurones are receiving adequate oxygen and nutrients. Inferences about cerebral perfusion can be made by looking at a variety of measured variables. The first five techniques can be used at the bedside and are often part of multimodal monitoring of head injured patients. The latter techniques are more invasive and generally restricted to research programs.

- Measuring ICP and calculating CPP (most common method).
- Jugular venous bulb oxygen saturations ($SjvO_2$, usually 65-75%). Reflects the balance between cerebral oxygen delivery and $CMRO_2$. A low $SjvO_2$ reliably indicates cerebral hypoperfusion.
- Transcranial Doppler to measure blood velocity and estimate CBF.
- Microdialysis catheters to measure glucose, pyruvate, lactate, glycerol, glutamate (metabolic variables).
- Positron Emission Tomography – the distribution of radiolabelled water in the brain is monitored to indicate metabolic activity.
- Functional MR imaging techniques.
- Kety-Schmidt equation to determine CBF by using an inert carrier gas (using ^{133}Xe).
- Near infrared spectroscopy (NIRS) to measure oxygenation in a localised cerebral field.

FURTHER READING

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