

Cerebral physiology

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Introduction

The brain is a very interesting and complex organ. To sustain consciousness, satisfactory perfusion and adequate oxygen delivery are vital.¹ As the brain has relatively little capacity for energy storage, a continuous supply of oxygen and nutrients must be delivered by uninterrupted cerebral blood flow (CBF).²

Cerebral metabolic rate (CMR)

The brain has the highest metabolic requirements of any organ in the body, as reflected by its high blood flow rate.³ The CMR is the rate at which the brain utilises metabolic substrates, e.g. oxygen (CMRO₂), glucose (CMRglu), or generates by-products, e.g. lactate (CMRlact).⁴ The brain's oxygen consumption accounts for 20% of basal oxygen consumption (50 ml min⁻¹) at rest and relies almost completely on the oxygen-dependent metabolism of glucose for energy production. Because CBF is adjusted to meet the metabolic demand, oxygen in the grey matter is approximately five times more than in the white matter. Normal values for CBF, CMR, and other physiological variables are provided in Table I.

Table I: Cortical (mostly grey matter), sub-cortical (mostly white matter), and other physiological values⁵

Normal cerebral physiological values	
Global	44–55 ml/100 g/min
Cortical	75–80 ml/100 g/min
Sub-cortical	20 ml/100 g/min
CMR of oxygen	3–3.5 ml/100 g/min
Cerebral vascular resistance (CVR)	1.5–2.1 ml/100 g/min
Cerebral venous oxygen	3 244 mmHg
Cerebral venous oxygen saturation	55–70%
Intracranial pressure (ICP)	8–12 mmHg

Glucose is not only the main energy substrate for the brain, but also a precursor for neurotransmitters, including gamma-aminobutyric acid (GABA), glutamate, and acetylcholine, and is essential to maintain a constant CBF and therefore the substrate supply.⁶ Under aerobic conditions, oxidative phosphorylation produces 38 molecules of adenosine triphosphate (ATP) for every molecule of glucose. Of the energy produced, 60% is utilised for the electrophysiological functioning of the neurons (i.e. their

chemical and electrical activity). The other 40% is to maintain the integrity and homeostasis of the neuronal cells.^{3,7}

The brain has a limited capacity for anaerobic metabolism, and under these conditions, one molecule of glucose undergoes glycolysis to produce only two molecules of ATP. The lactate produced anaerobically is utilised to carry out the fundamental processes essential to maintain the cell structure. Aerobic metabolism is restored if perfusion is re-established immediately, otherwise, permanent cell death follows.⁸

The CMR decreases during sleep and increases during sensory stimulation, mental tasks, or arousal of any kind. During epileptic activity, increases in the CMR may be extreme, whereas regionally, after brain injury and globally with coma, the CMR may be substantially reduced. In general, anaesthetic drugs suppress the CMR, apart from ketamine and nitrous oxide (N₂O). The electrophysiological function is the component on which the CMR acts.

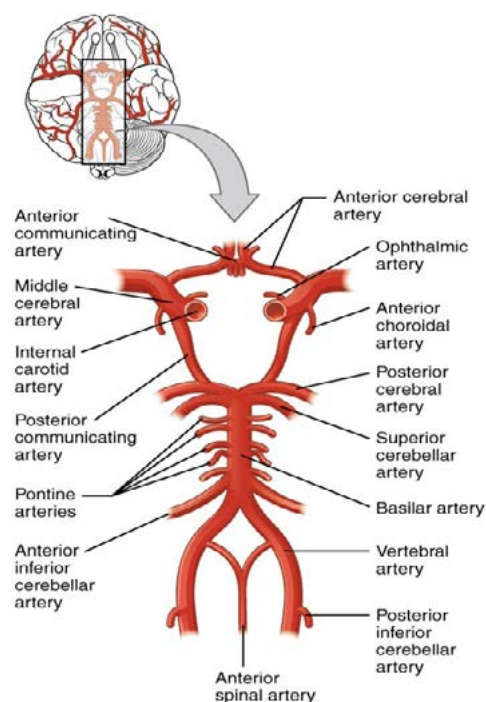


Figure 1: The cerebral arterial system¹⁰

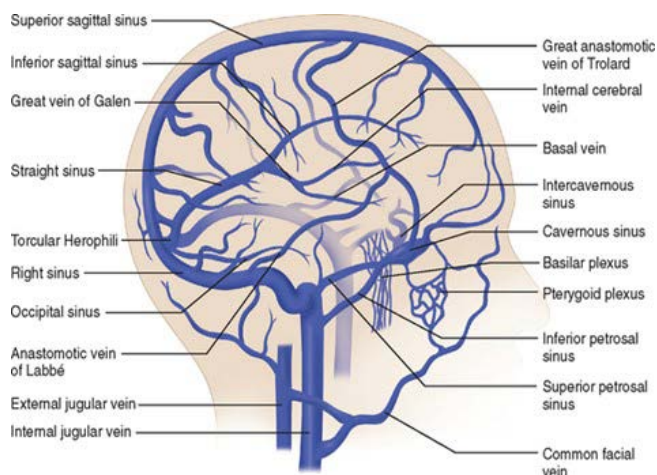


Figure 2: The brain venous system¹¹

The cerebral circulation

The arterial blood supply to the brain is composed of paired right and left internal carotid arteries, which give rise to the anterior circulation, and paired right and left vertebral arteries, which give rise to the posterior circulation. The connection of the two vertebral arteries forms the basilar artery. The internal carotid arteries and the basilar artery connect to form a vascular loop, called the circle of Willis, at the base of the brain. This permits collateral circulation between both the right and left and the anterior and posterior perfusing arteries. Three paired arteries that originate from the circle of Willis perfuse the brain, i.e. anterior, middle, and posterior cerebral arteries. The posterior communicating arteries and the anterior communicating artery complete the loop. The anterior and the posterior circulations contribute equally to the circle of Willis (Figure 1).^{3,9}

Three sets of veins drain blood from the brain. The superficial cortical veins are within the pia mater on the brain's surface. Deep cortical veins drain the deeper structures of the brain. These veins drain into dural sinuses, of which the superior and inferior sagittal sinuses and the straight, transverse, and sigmoid sinuses are the major dural sinuses. These ultimately drain into the right and left internal jugular veins (Figure 2).³

Cerebral blood flow (CBF)

The adult human brain weighs approximately 1 350 g and therefore represents approximately 2% of total body weight; however, it receives 12–15% of cardiac output. The CBF is best described by the Hagen-Poiseuille equation for laminar flow, which demonstrates a direct relationship between flow, cerebral perfusion pressure (CPP), and the calibre of cerebral vessels:

$$CBF = \frac{\pi \Delta P r^4}{8 \mu l}$$

Where π is the mathematical constant, ΔP is the pressure gradient (which is the CPP), r is the radius/calibre of the blood vessel, μ is the dynamic viscosity of blood, and l is the length of the blood vessel. CBF will thus improve if the CPP increases, and the cerebral vasculature is vasodilated.¹

Under conditions of normothermia and normoxia, CBF must remain at 50–60 ml/100 g/min to meet the metabolic demands of the functioning brain.^{2,12} Loss of consciousness ensues within seconds of ischaemia secondary to a reduction in CBF, with permanent brain damage occurring within 3–8 minutes of insufficient blood supply.^{6,8} Reserve blood flow exists to a point, but ischemic injury generally occurs once CBF drops below 22 ml/100 g/min, although concurrent pathologies such as traumatic brain injury (TBI) or hypothermia can change this threshold.

Indirect measures are often used to estimate the adequacy of CBF and brain tissue oxygen delivery in clinical settings. These methods include transcranial Doppler, near-infrared spectrometry, brain tissue oximetry, and intracerebral microdialysis.⁶

Perfusion pressure: CPP is the difference between the mean arterial pressure (MAP) and the ICP or central venous pressure (CVP) if it is greater than ICP. Because ICP is not usually measured in normal subjects, changes in MAP will thus largely govern the perfusion pressure and hence CPP is primarily dependent on MAP.⁶

$$CPP = MAP - ICP \text{ (or CVP)}$$

Patients with CPP < 50 mmHg show slowing on the electroencephalogram (EEG), and those < 25 mmHg typically have a flat EEG.^{3,6} The regulatory mechanisms that preserve CBF can broadly be categorised into cerebral autoregulation (CA), neurovascular coupling (NVC), and vasomotor reactivity (VMR).

Cerebral autoregulation (CA)

Autoregulation of blood flow exists to ensure that perfusion of vital organs remains intact and stable across the dynamic range of pressures to which the vascular bed is exposed. CA can broadly be defined as a proportional change in CVR in response to changes in perfusion pressure to maintain a constant blood flow.²

$$CBF = \frac{CPP}{CVR}$$

Autoregulation is believed to occur via a myogenic mechanism whereby an increase in MAP increases the transmural vessel tension causing depolarisation of vascular smooth muscle and constriction of the precapillary resistance vessels. The reverse happens when the MAP and transmural tension decrease.¹ The range of MAP the CA mechanism can respond to was first described in humans by Lassen in 1959. From this work, the autoregulation curve was generated, which depicts a plateau region wherein CBF is stable across a MAP range of 50–150 mmHg. It is an almost instant process that occurs within 1–10 seconds of a change in pressure (Figure 3).²

Below the lower limit of autoregulation, approximately 50 mmHg in humans, and above the upper limit, approximately 150 mmHg, the cerebral circulation is pressure passive and CBF decreases or increases, respectively, with corresponding changes in MAP. In chronic arterial hypertension, the upper

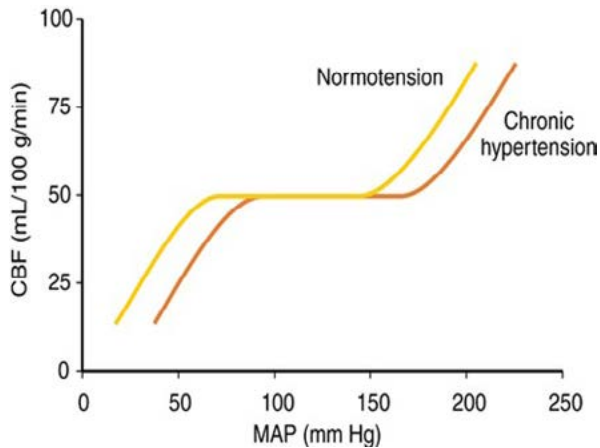


Figure 3: Autoregulation curve¹³

and lower limits of autoregulation are both displaced to higher levels, shifting the curve to the right (Figure 3), and cerebral hypoperfusion occurs at higher values of MAP compared with healthy individuals. Flow becomes more pressure-dependent at low “normal” arterial pressures in return for cerebral protection at higher arterial pressures.^{1,6} Cerebral vasculature is known to be highly innervated by the autonomic nervous system (ANS), and postsynaptic adrenergic receptors are present on vascular smooth muscle. Denervation does not alter resting CBF and only modestly reduces the upper limit of the autoregulatory curve.²

The vascular smooth muscle, endothelium, and neighbouring neurons and astrocytes, collectively referred to as the neurovascular unit, play direct and modulatory roles in establishing myogenic tone. Mechano-sensitive transient receptor potential (TRP) channel family members, present throughout the cerebral vasculature, have recently been identified as a component of the pressure detection mechanism of the neurovascular unit. These channels respond to stretch and/or shear forces, resulting in cation conductance ultimately leading to vasoconstriction.²

The density of innervation declines with vessel size, and the greatest neurogenic influence appears to be exerted on larger cerebral arteries. This innervation includes cholinergic (parasympathetic and non-parasympathetic), adrenergic (sympathetic and non-sympathetic), serotonergic, and VIPergic systems of extra-axial and intra-axial origin.

Factors affecting autoregulation include arterial carbon dioxide tension (PaCO_2), arterial oxygen tension (PaO_2), neurogenic control, temperature, and rheology.

Neurovascular coupling (NVC)

Increased neuronal activity results in increased local brain metabolism. This increase in the CMR is associated with a proportional change in CBF referred to as NVC. It is a positive feedback mechanism wherein increased neuronal activity results in energy demand; this demand is met by an increase in CBF.³ This process occurs at the level of the cerebral microvasculature of pial arterioles outside the pia mater and penetrating parenchymal arterioles (Figure 5, pink inlay). The mechanism by

which the tone of these vessels is matched to the needs of the surrounding neurons is complex and involves all members of the neurovascular unit.

In response to excitatory glutamatergic inputs, active neurons release nitric oxide that diffuses to nearby vascular smooth muscle and promotes dilation. Adenosine produced from the extracellular conversion of neuron- and astrocyte-derived ATP diffuses to vascular smooth muscle and induces changes in vascular tone. Neuron-derived prostaglandins also influence vascular tone. Prostaglandin E2 is produced by active pyramidal neurons and acts on EP2 and EP4 receptors present in cerebral vascular smooth muscle resulting in vasodilation.

Additionally, GABAergic interneurons release numerous vasoactive mediators directly onto vascular smooth muscle.² Metabolically active astrocytes that envelope the parenchymal arterioles also mediate the tone of the vascular smooth muscle. Glia also plays an important role in NVC. Their processes contact neurons, and these processes may serve as conduits for the coupling of increased neuronal activity to increases in blood flow.³ Finally, in response to neuronal activity, the endothelium itself propagates vasodilatory signals throughout the vasculature of active cortical regions. Collectively, these mechanisms allow for the modulation of CBF that is temporally and spatially correlated with neuronal activity.

Vasomotor reactivity (VMR)

PCO_2

The cerebral vasculature tone is influenced by changes in arterial blood CO_2 and, to a lesser extent, O_2 tension through a process referred to here as VMR (Figure 5, green inlay). VMR to CO_2 is stronger in the brain compared to other organs. Both pial arterioles and large calibre cerebral vessels respond. Alteration of cerebral vascular tone in response to changes in PaCO_2 is an intrinsic property of the vasculature and occurs independent of adrenergic activity, despite extensive innervation by the sympathetic nervous system. This mechanism establishes a roughly linear relationship between CBF and acute PaCO_2 changes, with a 1–2 ml/100 g/min for each 1 mmHg change in PaCO_2 across a range of 20–80 mmHg (Figure 4).⁶ Adaptation to chronic alteration of PaCO_2 occurs and CBF will tend to normalise over a 6–8 hour period.^{2,6} This response is attenuated at a PaCO_2 less than 25 mmHg (Figure 4, blue).

The magnitude of the reduction in CBF caused by hypocapnia is more intense when resting CBF is increased (as might occur during anaesthesia with volatile agents). Conversely, when resting CBF is reduced, the magnitude of the hypocapnia-induced reduction in CBF is decreased slightly. Accordingly, anaesthetic drugs that alter resting CBF cause changes in the response of the cerebral circulation to CO_2 . The level of PaCO_2 also modulates CA. With hypercarbia, CA response to hypertension is attenuated. In contrast, with the induction of hypocapnia, CBF is autoregulated over a wider MAP range.³

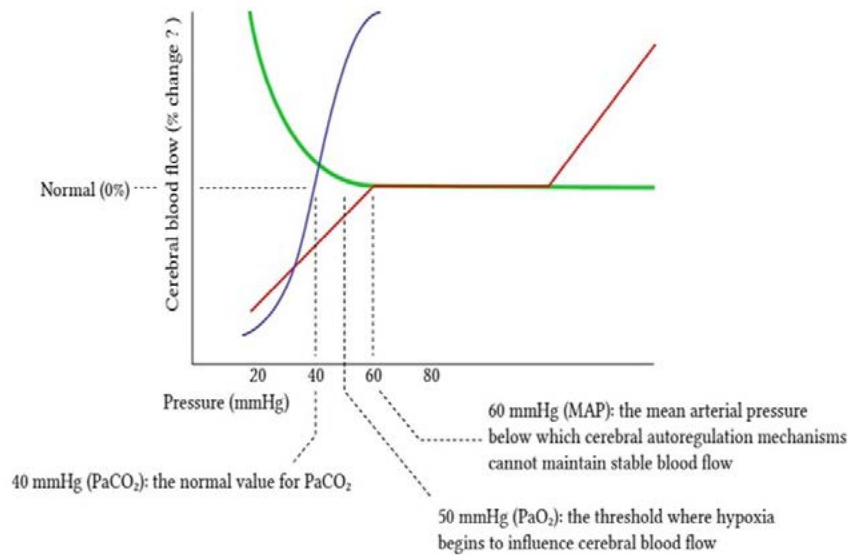


Figure 4: Factors affecting CBF, PaO₂, and PaCO₂¹⁴

PaO₂

Changes in PaO₂ from 60 to more than 300 mmHg have little influence on CBF. A reduction in PaO₂ below 60 mmHg rapidly increases CBF. Below a PaO₂ of 60 mmHg, there is a rapid reduction in oxyhaemoglobin saturation (Figure 4). Below this level, oxygen-sensitive ion channels in the smooth vascular muscles are activated and vasoactive substances, such as nitric oxide, adenosine, prostacyclin, angiotensin, vasopressin, and opioids, are released. An imbalance in these mediators is responsible for the vasodilatation and increases in CBF during hypoxaemia.¹

The relationship between oxyhaemoglobin saturation, as evaluated by pulse oximetry, and CBF is inversely linear.³ Vasodilation occurs independent of peripheral chemoreceptors and may be accompanied by a small increase in the CMR of oxygen (CMRO₂). Under hypoxic conditions, the hypocapnic cerebral vasoconstriction activity is attenuated. This prevents ischemic injury from arising due to hyperventilation-induced hypocapnia associated with hypoxic ventilatory drive.² Increasing oxygen will have the opposite effect and cause vasoconstriction, which is not clinically significant.

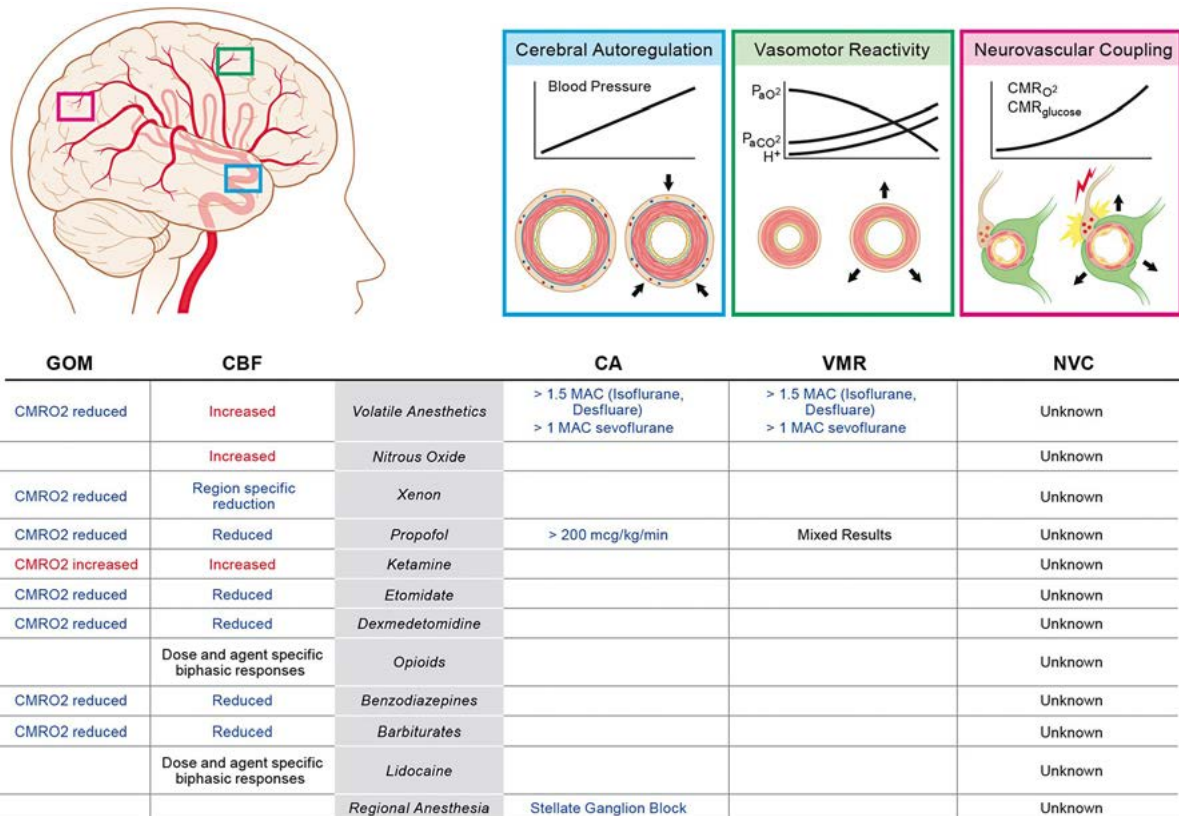


Figure 5: Summary of the effects of anaesthetic agents on global oxidative metabolism (GOM) and CBF, as well as the endogenous regulatory mechanisms such as CA, VMR, and NVC^{2,15}

Temperature

Decreasing temperature decreases cerebral metabolism, and the reverse occurs when temperature is increased. For every 1 °C decrease in brain temperature, the CMR and hence the CBF decrease by 7%.⁶ CBF is nearly halved at a temperature of 27 °C and the CMRO₂ is as low as 10% of normal at 18 °C, allowing preservation of brain function during episodes of deep hypothermic circulatory arrest. Mild hypothermia causes vasoconstriction, which decreases CBF and ICP but has failed to improve outcomes in patients with traumatic head injury.

Cooling to 32–34 °C is recommended in postcardiac arrest patients and as a treatment of raised ICP refractory above other treatment modalities.¹ Hypothermia decreases the rate of energy utilisation associated with both the electrophysiological function and the basal component related to the maintenance of cellular integrity. Mild hypothermia preferentially suppresses the basal component of the CMR.³

Hyperthermia has the opposite influence on cerebral physiological function. Between 37 °C and 42 °C, CBF and CMR increase, after which protein degradation occurs with a resultant decrease in CMRO₂. However, above 42 °C, a dramatic reduction in cerebral oxygen consumption occurs, an indication of a threshold for a toxic effect of hyperthermia that may occur because of protein (enzyme) denaturation.

Rheology

Blood viscosity can influence CBF. Hematocrit is the single most important determinant of blood viscosity. In healthy humans, variation of the haematocrit within the normal range (33–45%) probably results in only modest alterations in CBF. Beyond this range, changes are more substantial. In anaemia, CVR is reduced and CBF increases. However, this may result not only from a reduction in viscosity but also as a compensatory response to reduced oxygen delivery.³ Under ischaemic conditions, low CPP causes a low flow state resulting in compensatory vasodilation

and, during these circumstances, decreasing the viscosity of blood may improve CBF. Despite this, a reduction in haematocrit also lowers the oxygen content of blood, which may exacerbate an ischaemic insult.¹

Intracranial pressure (ICP)

The intracranial contents consist of 80% brain volume, 10% cerebrospinal fluid (CSF), and 10% blood. The concept of ICP can best be understood if we compare the brain to a closed box or a fixed and rigid structure. The Monro-Kellie hypothesis states that the volume of the brain and its constituents inside the bony cranium is fixed and cannot be compressed. Any increase in one component must be offset by an equivalent decrease in another to prevent a rise in ICP.^{1,9}

In adults, ICP is normally 8–12 mmHg when supine and is posture-dependent, being lowest in the upright position. There is an initial compensation that prevents major changes in intracranial compliance with minimal increases in ICP. A critical point is reached when further volume increases produce precipitous rises in ICP, with a reduction in CPP and cause cerebral ischaemia (Figure 6), ultimately causing local compression and herniation of brain tissue against the:

- cingulate gyrus under the falx cerebri;
- the uncinate gyrus through the tentorium cerebelli;
- cerebellar tonsil through the foramen magnum; or
- transcalvarial.^{3,6}

Blood and CSF provide the main protection to the brain when the intracranial volume increases. Blood, has the most significant role in compensation for ICP changes as the cerebral venous volume can be changed promptly and hence ICP can be modified almost immediately. CSF plays an important role in compensating for increases in ICP by spatial compensation, whereby an increase in the volume of an intracranial constituent will cause a decrease in intracranial CSF volume by displacing CSF into the spinal canal.



Figure 6: Pressure volume curve for ICP¹⁶

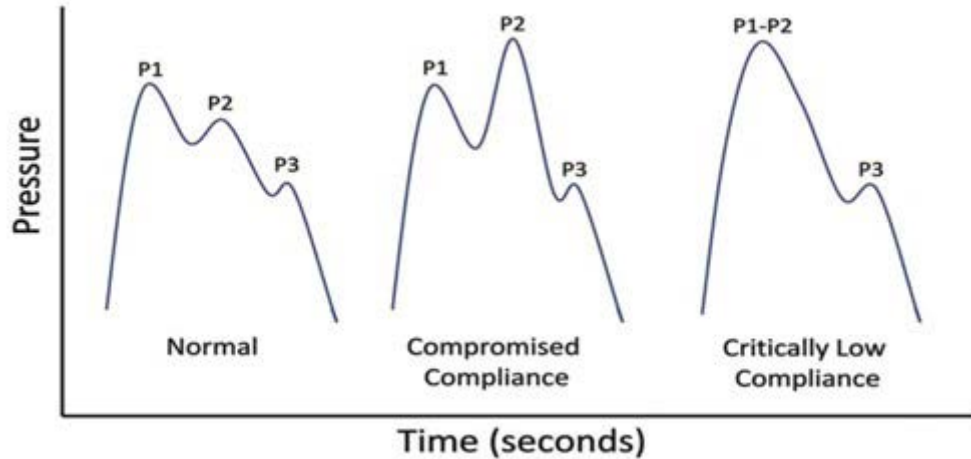


Figure 7: Intracranial waveforms¹⁷

P1 – pulsation of arterial vessels, percussion wave; P2 – brain compliance, tidal wave; P3 – closure of aortic valve, diastolic wave

Spatial compensation occurs slowly and is significant in tumours that expand gradually but provides limited compensation for acute and sudden increases in ICP.² Major compensatory mechanisms include:

- an initial displacement of CSF from the cranial to the spinal compartment;
- an increase in CSF absorption;
- a decrease in CSF production; and
- a decrease in total cerebral blood volume (CBV, primarily venous).⁶

Intracranial elastance is determined by measuring the change in ICP in response to a change in intracranial volume. Figure 7 depicts ICP waveforms with compromised brain compliance. Normal waveform shows P1 exceeds P2, which exceeds P3. With compromised intracranial compliance P2 exceeds P1. With critically low compliance, P1 and P2 merge.

Cerebrospinal fluid (CSF) formation and circulation

CSF is the fluid present extracellularly between the arachnoid and pia mater and in the ventricles, providing buoyancy to the brain. It is produced mainly by the choroid plexus in the lateral, third, and fourth ventricles at a rate of 0.3–0.4 ml/min⁻¹ (500 ml day⁻¹) with a total volume of 150 ml. There are small contributions from ventricles' ependymal cell linings, and even smaller quantities from fluid leaking into the perivascular spaces (blood-brain barrier [BBB] leakage).^{1,6}

CSF production is also under the influence of the circadian rhythm, with the peak production of CSF occurring during sleep. CSF reabsorption occurs primarily via the arachnoid granulations present in the dural sinuses into the venous circulation. A smaller proportion of CSF gains access to the cerebral venous system by transependymal flow and is absorbed in nerve root sleeves via lymphatics.^{3,9}

The blood-brain barrier (BBB)

A term commonly used to describe a barrier of tight junctions between capillary endothelial cells in the brain and epithelial

cells in the choroid plexus, effectively preventing the movement of ionised substances and those with higher molecular weights.⁹ It allows free passage of lipid-soluble molecules (most anaesthetics), oxygen, and carbon dioxide, whereas most ions, proteins, and large substances (like mannitol) penetrate poorly. Water moves freely across the BBB due to bulk flow. Acute plasma hypertonicity results in a net movement of water out of the brain, whereas acute hypotonicity causes a net movement of water into the brain. Severe hypertension, tumours, trauma, strokes, infection, and marked hypercapnia can disrupt the BBB.⁶

Pathological states and neuroprotection

The concept of neuroprotective intervention encompasses therapies that favourably shift the balance of cerebral oxygen supply and utilisation, as well as those that prolong survival in ischemic states. In addition to impacting the delivery of oxygen and nutrients to metabolically active neurons, alteration of cerebral vessel dynamics by anaesthetic agents can influence the tissue composition encountered during neurosurgical intervention.³

Ischaemic brain injury is classified as global (complete) or focal (incomplete). Global ischaemia includes total circulatory arrest, e.g. cardiac arrest, as well as global hypoxia, e.g. severe respiratory failure, drowning, and asphyxia. Focal ischaemia includes embolic, haemorrhagic, and atherosclerotic strokes, as well as blunt, penetrating, and surgical trauma.⁶

In brain-injured patients, the integrity of the BBB is often impaired, and the vasoactive neurotransmitters released produce marked changes in CBF and ICP. In these patients, autoregulation is impaired and CBF depends on CPP for adequate supply. However, the CPP in an injured brain is variable within different regions of the brain and varies with time after injury. The Brain Trauma Foundation recommends a target CPP of 50–70 mmHg for TBI.¹ With focal ischaemia, the brain tissue surrounding a severely damaged area may suffer marked functional impairment but remain viable, this area is known as the ischaemic penumbra. If further injury is limited, and normal flow is rapidly restored, these areas may recover completely.

Table II: Comparative effects of anaesthetic agents on cerebral physiology¹⁹

Agent	CMR	CBF	CSF Production	CSF Absorption	CBV	ICP
Halothane	↓↓	↑↑↑	↓	↓	↑↑	↑↑
Isoflurane	↓↓↓	↑	±	↑	↑↑	↑
Desflurane	↓↓↓	↑	↑	↓	↑	↑
Sevoflurane	↓↓↓	↑	?	?	↑	↑
Nitrous oxide	↓	↑	±	±	±	↑
Barbiturates	↓↓↓↓	↓↓↓	±	↑	↓↓	↓↓↓
Etomidate	↓↓↓	↓↓	±	↑	↓↓	↓↓
Propofol	↓↓↓	↓↓↓↓	?	?	↓↓	↓↓
Benzodiazepines	↓↓	↓	±	↑	↓	↓
Ketamine	±	↑↑	±	↓	↑↑	↑↑
Opioids	±	±	±	↑	±	±
Lidocaine	↓↓	↓↓	?	?	↓↓	↓↓

¹↑, increase; ↓, decrease; ±, little or no change; ?, unknown; CMR, cerebral metabolic rate; CBF, cerebral blood flow; CSF, cerebrospinal fluid; CBV, cerebral blood volume; ICP, intracranial pressure.

The aims to prevent or limit neuronal tissue damage are the same for both focal and global ischaemia. Clinical goals are to optimise CPP, decrease metabolic requirements (basal and electrical), possibly block mediators of cellular injury, and restore perfusion and oxygenation. CBF is normally reduced in the first 24 hours after brain injury and normocapnia (33–40 mmHg) should be maintained because hypocapnia will further decrease CBF and risk cerebral ischaemia. Therefore, hyperventilation with hypocapnia should be strictly avoided.³ Hyperoxia can be detrimental and worsen neurological injury by releasing oxygen-free radicals, and brain-injured patients have the best outcome when systemic normoxia is maintained. Oxygen delivery should be titrated to generate an arterial oxygen saturation of 94–96%. In the presence of cerebral vasospasm, induced hypertension may help improve CBF. Prolonged episodes of increased cerebral metabolism, such as during seizures, can result in permanent neurological damage and should be dealt with immediately.⁵

Hypothermia is an effective way of protecting the brain during focal and global ischaemia. It decreases both basal and metabolic requirements throughout the brain. Additionally, hypothermia reduces free radicals and other mediators of ischaemic injury. Induced hypothermia is beneficial following cardiac arrest.^{3,6}

Nimodipine plays a role in the treatment of vasospasm associated with subarachnoid haemorrhage. A dihydropyridine-type calcium-channel blocker is thought to reduce vasospasm by blocking calcium influx into ischaemic cells, preventing apoptosis of those cells. There was evidence of improved functional outcome but no angiographic vasospasm as Nimodipine was found to lower the incidence of adverse reactions and improve the prognosis of patients.^{3,6}

Effect of anaesthetics on cerebral blood flow (CBF) and metabolic rate

Anaesthetic drugs cause dose-related and reversible alterations in many aspects of cerebral physiology, including CBF, CMR, and electrophysiological function (EEG, evoked responses) (Table II). The delivery of energy substrates is dependent on CBF, and modest alterations in CBF can influence the neuronal outcome substantially in the setting of ischemia. Control and manipulation of CBF are central to the management of ICP because as CBF varies in response to vasoconstrictor-vasodilator influences, and CBV varies with it. Conversely, the effects of general anaesthesia on CBF and CMR can be altered to improve both the surgical course and the clinical outcome of patients with neurological disorders.^{3,18}

Several anaesthetics, including barbiturates, isoflurane, sevoflurane, desflurane, propofol, and etomidate, increase plasma concentrations causing progressive suppression of EEG activity and a concomitant reduction in the CMR. However, increasing the plasma level beyond what is required to first achieve suppression of the EEG results in no further depression of the CMR. The component of the CMR required for the maintenance of cellular integrity, the “housekeeping” component, is unaltered by anaesthetic drugs.¹⁸

Conclusion

Cerebral physiology encompasses many complex, yet understandable concepts, and every physician needs to have a good grasp of these concepts. Furthermore, it forms the basis for the management of patients undergoing intracranial surgery or who need neurocritical care.

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