Cerebral physiology

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Key points

The brain is enclosed in a rigid box with a fixed volume and an increase in the volume of any of its constituents will lead to an increase in intracranial pressure (ICP).

The volume of venous blood in the cerebral vasculature is small but very important as it can provide immediate compensation for increases in ICP.

The cerebrospinal fluid provides the largest compensation for raised ICP but changes occur slowly.

Volatile anaesthetic agents increase the ratio of cerebral blood flow and cerebral metabolism.

Maintaining sufficient cerebral blood flow to meet metabolic demands after a neurological insult is important to prevent secondary (ischaemic) brain injury.

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The brain is a very complex organ which needs a continuous delivery of oxygen and nutrients. To sustain consciousness, satisfactory perfusion and adequate oxygen delivery is vital but it is equally essential to maintain a constant supply of glucose as the brain has virtually no stores of glucose. Loss of consciousness ensues within seconds of ischaemia secondary to a reduction in cerebral blood flow (CBF), with permanent brain damage occurring with 3–8 min of insufficient blood supply.[1] The brain also has a unique heterogeneous structure with areas of variable blood supply that is directly related to its function and metabolism.

Cerebral blood volume

The brain receives its blood supply from the internal carotid and vertebral arteries (Fig. 1) which drain via the cerebral veins and dural venous sinuses into the internal jugular veins. The volume of blood in the whole brain is small and contained mainly in the venous sinuses and pial veins. The grey matter is composed of the cell bodies of the neurons which are involved with the complex functions of the human body and hence requires a larger proportion of the arterial blood supply. On the other hand, the white matter is essentially composed of axons which transmit impulses in between the neurons. As it is involved with less complicated functions than the grey matter, it needs a smaller fraction of the blood supply.

Cerebral blood flow

Although the brain constitutes only 2% of body mass (1400 g), it receives a large proportion (12–15%) of the resting cardiac output in the adult.

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 calibre of cerebral vessels:

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

where π is the mathematical constant, ΔP the pressure gradient which is the CPP, r the radius/calibre of blood vessel, μ the dynamic viscosity of blood, and l the length of the blood vessel.

CBF will thus improve if the CPP increases and the cerebral vasculature is vasodilated.

Cerebral perfusion pressure

Perfusion pressure is the difference in the pressures between the arterial and venous circulation which dictates the blood flow to the organ. In the brain, the perfusion pressure or the CPP is affected by another pressure within the skull [i.e. intracranial pressure (ICP) explained below]. In pathological conditions, if the ICP is increased, the flow through the cerebral blood vessels can be restricted.

In adults,

$$\mathrm{CPP} = \mathrm{MAP} - (\mathrm{CVP} + \mathrm{ICP})$$

where MAP is the mean arterial pressure and CVP the central venous pressure.

In normal adults, the CPP is variable, usually ranging between 70 and 90 mm Hg and the CBF is constant. When the CPP decreases below 50 mm Hg, there is an increased risk of brain ischaemia affecting the electrical activity in the brain.

The cerebrovascular resistance (CVR) is essentially the hindrance to the CBF determined predominantly by the calibre of the vessels. When cerebral vasodilatation occurs, the increase in the radius of the vessels not only decreases the CVR but also augments CBF. On the other hand, vasoconstriction of the cerebral vasculature will decrease CBF by increasing the CVR.

Cerebral metabolic rate

The cerebral metabolic rate (CMR) is the rate at which the brain utilizes metabolic substrates [e.g. oxygen ($CMRO_2$), glucose (CMR_{glu}), or generates by-products, e.g. lactate (CMR_{lact})]. The brain has the highest metabolic requirements

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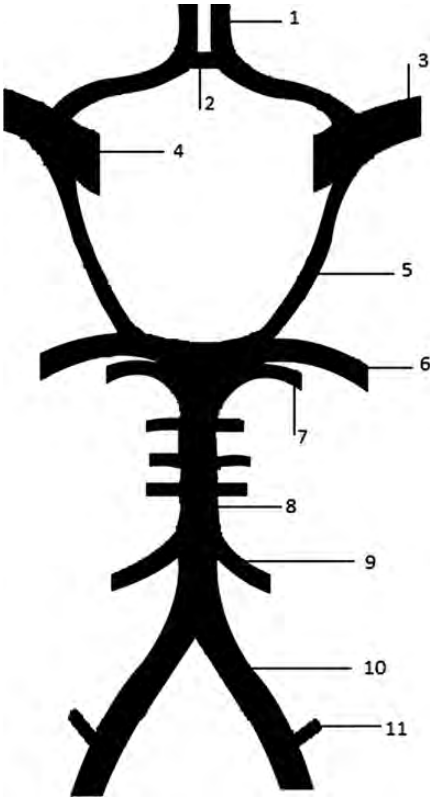

Fig 1 Arterial supply of the brain (Circle of Willis). 1: Anterior cerebral artery. 2: Anterior communicating artery. 3: Middle cerebral artery. 4: Internal carotid artery. 5: Posterior communicating artery. 6: Posterior cerebral artery. 7: Superior cerebellar artery. 8: Basilar artery. 9: Anterior inferior cerebellar artery. 10: Vertebral artery. 11: Posterior inferior cerebellar artery.

of any organ in the body which is reflected by its high blood flow. The brain oxygen consumption accounts for 20% of basal oxygen consumption (~50 ml min^{-1}) at rest and relies, almost completely, on oxygen-dependent metabolism of glucose for energy production:

$$CMRO_2 = CBF \times (A - V)O_2 \text{ content difference}$$

where A is the cerebral artery and V the cerebral veins.

Because CBF is adjusted to meet the metabolic demand, oxygen by the grey matter is approximately five times more than by the white matter.

Glucose is not only the main energy substrate for the brain but also a precursor for neurotransmitters, including γ-aminobutyric acid, glutamate, and acetylcholine, and is essential to maintain a constant CBF and therefore the substrate supply. Under aerobic conditions, oxidative phosphorylation produces 38 molecules of ATP for every molecule of glucose. Sixty per cent of the energy produced is utilized for the functioning of the neurons (i.e. their chemical and electrical activity), and the other 40% to maintain the integrity and homeostasis of the neuronal cells.[2] The brain has very 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 utilized 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. For values of cerebral blood volume, cerebral blood flow and cerebral metabolic rate of oxygen and glucose in normal adults, see Table 1.

Table 1 Average values in normal healthy individuals

	Grey matter	White matter	Average (whole brain)
CBV (ml per100 g tissue)	4–6	1.5–2.5	3.5–4.5
CBF (ml per 100 g tissue per min)	100–110	20–25	45–55
$CMRO_2$ (ml per 100 g tissue per min)	4–4.5	0.7–1.0	3–3.5
CMR_{glu} (mg per 100 g tissue per min)	6.5–8.5	1.2–2.2	4–5

Intracranial pressure

The concept of ICP can best be understood if we compare the brain to a 'closed box' or a fixed and rigid container. The Monro–Kellie hypothesis states that the volume of the brain and its constituents inside the bony cranium is fixed and cannot be compressed. To preserve a constant pressure in the box, the volume of the contents inside must be maintained.[3]

The intracranial contents can be theoretically divided into three compartments:

(i) brain volume ≈ 85%,
(ii) cerebrospinal fluid (CSF) ≈ 10% (150 ml) and
(iii) blood ≈ 5% (50–75 ml).

In adults, ICP is normally 5–15 mm Hg when supine and is posture-dependent, being lowest in the upright position. Increase in ICP above a critical level is not tolerated because it results in a decrease in the CPP of the brain and can also cause local compression of brain tissue against the tentorium, falx, and foramen magnum and ultimately herniation.

Control of ICP

There are many ways that ICP is controlled.

Volume buffering (pressure–volume relationship)

Blood and CSF provide the main protection to the brain when the intracranial volume increases. There is an initial compensation which prevents major changes in the intracranial compliance with minimal increases in ICP. In the presence of intracranial pathology, the volume of one component within the cranium increases (e.g. haematoma, brain swelling) and, when the compensatory mechanisms are exhausted, there is a marked increase in ICP with a reduction in CPP and cerebral ischaemia (Fig. 2).

Blood, despite being the smallest volume compartment within the cranium, has the most significant role in compensation for ICP changes as the cerebral venous volume can be changed very

promptly and hence ICP can be modified almost immediately. Cerebral blood volume (CBV) can be increased by increasing the amount of blood flow that enters the cranium (e.g. by venodilation, or by hindering its venous drainage, e.g. head down position, jugular vein obstruction, increase right heart or intrathoracic pressures).

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 at a rate of 0.3–0.4 ml min^{-1} (500 ml day^{-1}) and reabsorbed by the arachnoid granulations into the venous circulation. The production of CSF is constant, but if re-absorption is hampered or there is a mechanical obstruction to the CSF outflow, its volume increases causing an increase in ICP.

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. Spatial compensation occurs slowly and is significant in tumours which expand gradually but provides limited compensation for acute and sudden increase in ICP (e.g. in haematomas as it gets exhausted rapidly).

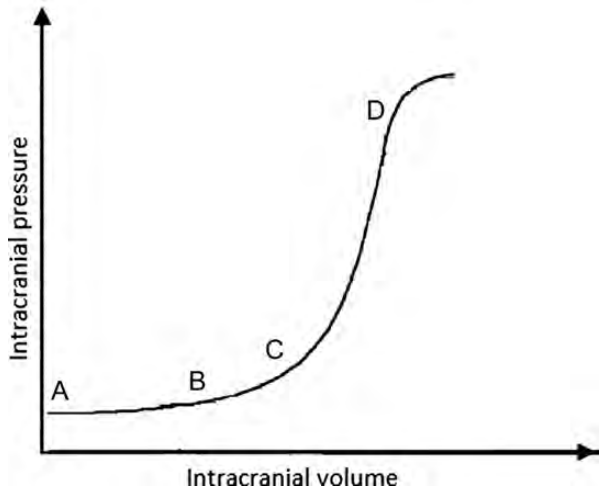

Fig 2 ICP–volume compliance curve. (A and B) Compensation phase—ICP nearly constant with increase in intracranial volume initially. (C and D) Decompensation phase—ICP increases rapidly with increasing intracranial volume as the buffers are exhausted.

Control of CBF and CBV

Various factors discussed below affect CBF and CBV which in turn control ICP (Fig. 3).

Autoregulation (myogenic, hydrostatic pressure)

Autoregulation is a physiological process which refers to the capacity of cerebral circulation to adjust its resistance to maintain a constant CBF regardless of changing systemic blood pressure/CPP:

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

In the upright position in a normal brain, ICP and CVP at the level of the head are negative and therefore not accounted for. Changes in MAP will thus largely govern the perfusion pressure and hence CPP is roughly equivalent to MAP.

Autoregulation is believed to occur via a myogenic mechanism whereby an increase in MAP increases the transmural vessel tension causing depolarization of vascular smooth muscle and constriction of the precapillary resistance vessels. The reverse happens when the MAP and transmural tension decreases. It occurs between MAP of 50–150 mm Hg, is an almost instant process (occurs within 1–10 s of change in pressure), and is mediated primarily by a endothelium-derived relaxing factor and nitric oxide (EDRF/NO).[4] Above and below the autoregulatory plateau, CBF becomes pressure-dependent and directly changes with changes in MAP. In chronic arterial hypertension, the upper and lower limits of autoregulation are both displaced to higher levels, shifting the curve to the right. In hypertensive patients, cerebral hypoperfusion

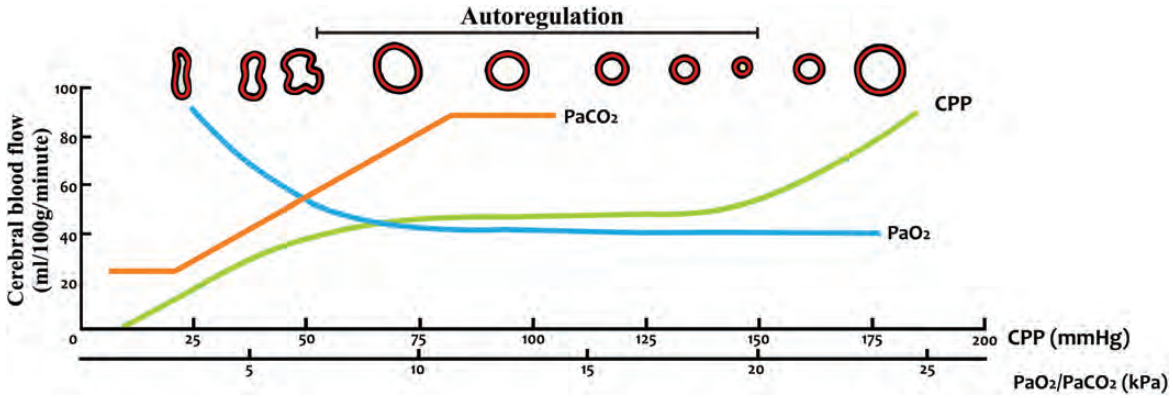

Fig 3 Effect of changes in MAP, arterial oxygen and carbon dioxide tensions, and cerebral vascular resistance on cerebral blood flow. Reproduced with permission from Shardlow and Jackson.[10] Elsevier Limited.

occurs at higher values of MAP compared with healthy individuals.

The limits of autoregulation are affected by various factors including sympathetic nerve activity, Pa_{CO_2}, and pharmacological agents.

Arterial carbon dioxide tension

The relationship between Pa_{CO_2} and CBF is typically a sigmoid curve with lower and upper plateaus. It is fairly linear between Pa_{CO_2} 2.7–10.5 kPa with CBF changing by ~11–15 ml per 100 g tissue per min for each 1 kPa change in Pa_{CO_2}. The upper plateau occurs at a Pa_{CO_2} of 10.5 kPa when the arterioles are maximally dilated. At this point, CBF is nearly doubled and cannot increase further. On the other hand, decreasing Pa_{CO_2} causes vasoconstriction with its maximum effect occurring at Pa_{CO_2} levels of 2.7 kPa, when CBF is halved and cerebral ischaemia is a possibility. Clinically, it is not recommended to decrease Pa_{CO_2} to such low levels and normocapnia should be maintained after brain injury.

These changes are more pronounced in the grey matter than in the white matter and occur because of the change in H^+ concentration in the interstitium. The blood–brain barrier (BBB) is permeable to carbon dioxide which readily diffuses across it and thereby decreases extracellular pH. This affects the vascular smooth muscles directly causing dilatation.

The response of CBV and CBF to altering levels of Pa_{CO_2} is very rapid and occurs within 1 min and plateaus at 12 min. Decreasing the Pa_{CO_2} from 5.3 to 2.7 kPa decreases the whole brain volume by 10–14 ml almost immediately. This volume, although small, is extremely important in controlling ICP highlighting the significance of hyperventilation and reducing Pa_{CO_2} in 'acute' control of ICP only, but at a risk of causing cerebral ischaemia with severe hypocapnia. Prolonged hypocapnia has failed to show a beneficial role as CBF returns to the baseline after 6–8 h because of adaptation in the brain.[5]

Arterial oxygen tension

Hypoxia increases CBF by causing cerebral vasodilatation. The response of CBF to altering levels of Pa_{CO_2} is not very significant in clinical practise provided Pa_{O_2} is maintained above 6.7 kPa. Below this level, oxygen-sensitive ion channels in the vascular smooth muscles are activated and vasoactive substances, such as nitric oxide, adenosine, prostacyclin, angiotensin, vasopressin, and opioids, released. Imbalance in these mediators is responsible for the vasodilatation and increases in CBF during hypoxaemia. Increasing oxygen will have the reverse effect and causes vasoconstriction which is not clinically significant.

Flow-metabolic coupling

CBF is very variable across the brain and largely dependent on neuronal activity. Increase in activity, either regional or general, causes an increase in the CMR which in turn results in proportional increases in blood flow. This method of matching oxygen or glucose delivery to metabolic requirements is termed as 'flow-metabolism coupling' (Fig. 4). The change occurs within seconds of increased functional cerebral activity. Although many chemical mediators, such as H^+, carbon dioxide, adenosine, glycolytic intermediates, K^+, and phospholipid metabolites, have been implicated, nitric oxide of neuronal origin seems to be the most likely cause of the metabolism-associated vasodilatation. While volatile anaesthetic agents are intrinsic vasodilators, they also decrease $CMRO_2$ in a dose-dependent manner. Therefore, in the presence of intact flow-metabolism coupling, volatiles cause a coupled decrease in both $CMRO_2$ and CBF. The decrease in CBF caused by coupling is opposed by the vasodilatory effect of these agents, ultimately resulting in either no change or small decrease in CBF at low minimum alveolar concentration (MAC). However, CBF increases with MAC after metabolic suppression is maximal. Volatile agents were previously believed to uncouple flow-metabolism coupling but in fact the CBF/CMR ratio is altered or, more strictly, increased. At the same MAC dose, $CMRO_2$ decreases much more than the decrease in CBF (Fig. 5).

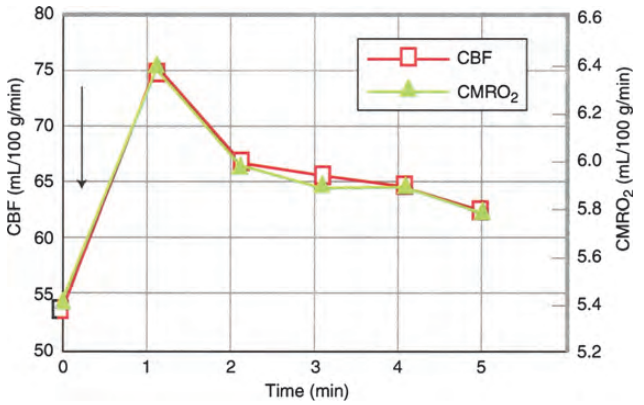

Fig 4 Flow metabolism coupling is a dynamic occurrence where CBF changes in relation to changes in the $CMRO_2$. Electrical stimulation of the femoral nerve in dogs (at the arrow) caused an increase in $CMRO_2$ which immediately caused as increase in the CBF. Reproduced with permission from Todd and colleagues.[11]

At 0.5 MAC, isoflurane, desflurane, and sevoflurane minimally delay, but preserve the cerebral autoregulation, whereas at 1.5 MAC autoregulation is considerably reduced by isoflurane and desflurane. Sevoflurane, in contrast, produces much lesser cerebral vasodilation and delays but preserves the autoregulatory response even at 1.5 MAC, making it the favoured volatile agent during neuroanaesthesia.

Neurogenic control

The cerebral vasculature receives its postganglionic sympathetic nerve supply from the superior cervical ganglion which contains norepinephrine and neuropeptide Y. Excessive sympathetic activity

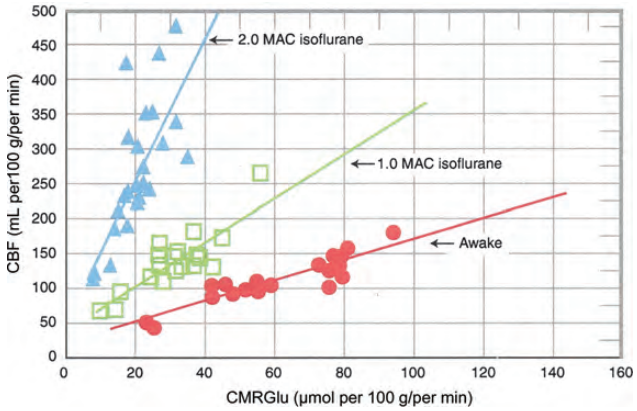

Fig 5 This figure shows the relationship between CMR_{glu} and CBF in rats and demonstrates that flow-metabolic coupling persists in the presence of inhalation anaesthetic agents. Isoflurane is a cerebral vasodilator and increasing its concentration also increases the slope of the relationship between CBF and $CMRO_2$ (i.e. flow-metabolic coupling is maintained but there is a higher CBF for a given $CMRO_2$). Reproduced with permission from Todd and colleagues.[11]

causes vasoconstriction and shifts the autoregulation curve to the right (e.g. during chronic hypertension). This response is particularly important during acute increases in blood pressure as it protects against cerebral hyperaemia disruption of the BBB especially in the brain stem. The parasympathetic innervation arises from the sphenopalatine and the otic ganglia. They contain acetylcholine and vasoactive intestinal peptide which may lead to cerebral vasodilatation which is particularly prominent in hypotensive states and during postischaemia reperfusion. A third group of sensory fibres originate from the trigeminal ganglion which express vasodilators like substance P and calcitonin gene-related peptide. Stimulation of these nerves during special situations like hypertension and seizures can cause vasodilatation and a substantial increase in CBF. Neurogenic control may be responsible for the immediate increases in CBF in response to increased metabolism, until chemical control takes over.

Temperature

Decreasing temperature decreases cerebral metabolism and the reverse occurs when temperature is increased. For every 1°C decrease in brain temperature, CMR and hence the CBF decrease by ~7%. CBF is nearly halved at a temperature of 27°C and the $CMRO_2$ 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 post-cardiac arrest patients and as a treatment of raised ICP refractory other treatment modalities. In addition to its effects on $CMRO_2$, it has multiple other potential mechanisms of action including prevention of reperfusion injury by reducing chemical-mediated mitochondrial damage and cell death.[6,7] Hyperthermia, on the other hand, increases CMR and CBF between 37 and 42°C, after which protein degradation occurs with a resultant decrease in $CMRO_2$.

Rheology

In normal healthy individuals, changes in haematocrit and blood viscosity have minimal effects on CBF. 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. However, a reduction in haematocrit also lowers the oxygen content of blood which may exacerbate an ischaemic insult. Currently, there are no guidelines with regard to a target haemoglobin level in neuroanaesthesia, but clinical experience suggests that the balance between improved blood flow and reduced oxygen delivery is probably best maintained at haematocrit of 30–34%.

Cerebral physiology in pathological states

Autoregulation may respond to changes in CVR and CPP even in pathological states but its state varies from minimal impairment to complete absence after brain injury, including head injury, stroke, ruptured intracranial aneurysms, ischaemic cerebrovascular diseases, and tumour.

In the brain-injured patients, the integrity of the BBB is often impaired and vasoactive neurotransmitters released produces 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 also varies with time after injury. The Brain Trauma Foundation recommends a target CPP of 50–70 mm Hg for traumatic brain injury.[7] Although patients with an intact pressure autoregulation can tolerate higher CPP, levels >70 mm Hg should be avoided as potential benefits do not outweigh the risk of developing acute lung injury.[8] CBF is normally reduced in the first 24 h after brain injury and normocapnia (4.5–5.3 kPa) should be maintained because hypocapnia will further decrease CBF and risk cerebral ischaemia. Hence, hyperventilation with hypocapnia should be strictly avoided. 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%, and this is especially important in patients who have return of spontaneous circulation after cardiac arrest.[9] In the presence of cerebral vasospasm, induced hypertension may help improve CBF. The brain can compensate for short periods of high metabolic demands but prolonged episodes of increased cerebral metabolism, such as during seizures, can result in permanent neurological damage and should be dealt with immediately.

Declaration of interest

None declared.

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Please see multiple choice questions 5–8.