Pharmacological and pathological modulation of cerebral physiology

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Abstract

Anaesthesia for neurosurgery aims to provide optimal surgical conditions whilst maintaining adequate cerebral blood flow in order to supply the brain with appropriate amounts of oxygen and glucose. Most anaesthetic drugs influence the normal cerebral physiology either directly or indirectly. They can cause changes in cerebral blood flow by influencing cerebral blood vessel calibre, by interfering with autoregulatory processes and by modifying cerebral metabolism. The brain's limited ability to store oxygen and glucose means that its supply must be continuous if neuronal damage is to be avoided. Ischaemic cerebral damage is the most important pathological mechanism in patients with stroke, subarachnoid haemorrhage and traumatic brain injury. Significant traumatic brain injury causes widespread derangement of cerebral physiology, including changes in cerebral blood flow, autoregulation and cerebral energy dynamics. This article outlines the effect of anaesthesia on cerebral physiology and reviews the pathophysiology of traumatic brain injury and subarachnoid haemorrhage.

Keywords Autoregulation; cerebral blood flow; cerebral ischaemia; cerebral metabolic rate; neuroanaesthesia; subarachnoid haemorrhage; traumatic brain injury

Royal College of Anaesthetists CPD Matrix: 1A01; 1A02

Learning objectives

After reading this article, you should:

- Have an understanding of the effects of anaesthetic agents on cerebral physiology
- Recognize that some anaesthetic agents are more appropriate for neuroanaesthesia than others
- Understand how cerebral ischaemia ultimately leads to cell death
- Understand how cerebral physiology is disrupted by traumatic brain injury and subarachnoid haemorrhage

In health, intrinsic controls of the cerebral blood flow ensure an appropriate supply of oxygen and glucose that is essential for neuronal activity. However, this control is affected by both pharmacological agents and cerebral disease. A thorough understanding of these modifying conditions is vital for those anaesthetizing and managing patients with cerebral pathology.

Influence of anaesthetic drugs on cerebral physiology

To provide safe operating conditions during cranial surgery, intracranial pressure (ICP) must be kept within normal limits. According to the Monro–Kellie doctrine, ICP is dependent on the contents contained within the rigid skull (i.e. brain tissue, blood and cerebrospinal fluid (CSF)). The volume of contents within the skull, if venous drainage is not impaired, is largely dependent on cerebral blood flow (CBF) and the balance between CSF production and absorption.

Anaesthetic drugs and cerebral blood flow

Anaesthetic drugs can modify cerebral blood flow in a number of ways. Drugs, such as the volatile anaesthetic agents, increase CBF by causing a dose-related cerebral vasodilatation; this, in turn, increases cerebral blood volume (CBV), which increases ICP. As long as cerebral vascular reactivity remains intact, this increase in ICP can be reduced by inducing cerebral vasoconstriction by lowering the arterial carbon dioxide tension ($PaCO_2$). In contrast, the commonly used anaesthetic induction agents, such as thiopental and propofol, cause a dose-related fall in CBF, which results in a reduction of ICP. In health, autoregulatory processes ensure that CBF remains constant, despite variations in mean arterial pressure (MAP). Some anaesthetic drugs such as the volatile anaesthetic agents can impair or abolish autoregulation, and therefore CBF (and ICP if other factors are constant) varies with MAP. Other anaesthetic drugs, in therapeutic doses, including the intravenous induction agents and the benzodiazepines, maintain autoregulation.

Anaesthetic drugs and cerebral metabolism

The commonly used anaesthetic drugs generally lower the cerebral metabolic rate (CMR) for both oxygen ($CMRO_2$) and glucose (CMRGI). In health, CBF is closely coupled with CMR and therefore a reduction in CMR will lower CBF and consequently ICP.

Anaesthetic drugs and CSF production and absorption

Some anaesthetic drugs, notably the volatile anaesthetic agents, modify the mechanics of CSF production and absorption. If production is increased with no change in absorption, the increased volume of CSF within the skull will result in an increase in ICP. Table 1 gives a summary of the effects of commonly used anaesthetic agents on the physiological variables described above.

Inhalational anaesthetic agents

All fluorinated volatile anaesthetic agents cause a dose-dependent rise in CBF, and therefore CBV and ICP. The rise in

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CBF is negated to various degrees by the lowering of the $CMRO_2$ and CMRGI caused by these agents. Therefore, the overall change in CBF (and therefore ICP) reflects the balance between these two effects. Apart from halothane, the decrease in $CMRO_2$ outweighs the increase in CBF (Figure 1).

Cerebral vascular reactivity is largely preserved in the healthy brain during anaesthesia with volatile anaesthetic agents, and therefore their vasodilatory effects can be negated by a reduction in $PaCO_2$ by moderate hyperventilation of the lungs. However, if $PaCO_2$ is allowed to rise above normal limits, more rapid increases in CBF occur (i.e. the CBF—$PaCO_2$ curve is shifted to the left). Autoregulation is gradually abolished by increasing doses of volatile anaesthetic agents (Figure 2). Thus, if hypertension occurs during anaesthesia with high doses of volatile agents, there is an increase in CBF and therefore ICP. Conversely, if hypotension exists under these conditions, it may result in critical levels of cerebral hypoperfusion.

Although now discontinued, most of the early investigations into the cerebral effects of inhalational anaesthetic agents used halothane and other, newer agents tend to be compared with this agent.

Halothane is a potent cerebral vasodilator and therefore causes a rise in CBF, CBV and ICP. This rise is exaggerated in the presence of cerebral swelling. It also causes a fall in MAP, and the combination of these effects therefore results in a marked decrease in cerebral perfusion pressure. Although halothane does produce a dose-dependent decrease in CMR, the decrease is less than with other volatile agents. Autoregulation is impaired at inspired concentrations of 1% and abolished at 2%. Cerebral vessel reactivity is maintained up to concentrations of 0.5%. Its use in neuroanaesthesia has been supplanted by other more pharmacodynamically favourable agents.

Effect of anaesthetic agents on cerebral physiology

	CBF	ICP	$CMRO_2$	Autoregulation	CO_2 reactivity	CSF production	CSF absorption
Intravenous anaesthetics							
Thiopental	↓	↓	↓	↔	↔	↔	↔
Etomidate	↓	↓	↓	↔	↔	↔	↔
Propofol	↓	↓	↓	↔	↔	↔	↔
Ketamine	↑	↑	↑	↔	↔	↔	↓
Inhalational agents							
Halothane	↑	↑	↓	Impaired	↔	↓	↓
Enflurane	↑	↑	↓	Impaired	↔	↑	↓
Isoflurane	↑/↓[a]	↑	↓	Impaired	↔	↓	↑
Sevoflurane	↑/[a]↓	↑	↓	Impaired	↔	↓	↔
Desflurane		↑	↓	Impaired	↔	↑ (prolonged delivery)	↔
Nitrous oxide	↑	↑	↓	↔	↔	↔	↔
Xenon	↑	↑	?	↔	?	?	?
Benzodiazepines	↓	↓	↓	↔	↔	↔	↔
Muscle relaxants							
Non-depolarizing	↔	↔	↔	↔	↔	↔	↔
Suxamethonium	↑	↑	↔	↔	↔		
Opioids (IPPV)							
Fentanyl	↔/↑[b]	↔/↑[c]	↔/↓[b]	↔	↔	↔	All produce small increase in CSF absorption at low doses
Alfentanil	↔	↔/↑[c]	↔	↔	↔	↔	
Remifentanil	↔/↑[b]	↔	↔/↓[b]	↔	↔	↔	
Morphine	↔	↔	↔	↔	↔	↔	
Opioids (SV)	↑	↑	↔	↔	↔	↔	
Others							
Vasodilators	↑	↑	↔	Impaired	↔	↔	↔
Mannitol	↔	↓	↔	↔	↔	↓	↔
α_2-Agonists	↓	↓	↓	↔	Impaired	↔	↔
Anticholinesterase	↔	↔	↔	↔	↔	↔	↔
Nimodipine	↑	↑	↔	↔	↔	↔	↔

CBF, cerebral blood flow; $CMRO_2$, cerebral metabolic rate of oxygen utilization; CSF, cerebrospinal fluid; ICP, intracranial pressure; IPPV, intermittent positive pressure ventilation; SV, spontaneous ventilation; ↑, increased; ↓, decreased; ↔, no effect; ?, unknown/uncertain.

[a] At lower concentrations CBF is decreased, at higher concentrations it is increased.

[b] At high doses may decrease CBF and $CMRO_2$.

[c] In large bolus doses may cause rise in ICP.

Table 1