CEREBRAL CIRCULATION

Anatomic Considerations

▪ *Vessels*

• the principal arterial inflow is via 4 arteries, - 2 internal carotids
- 2 vertebrals
• the vertebral arteries unite to form the ***basilar artery***
• the basilar artery and the internal carotids unite to form the ***circle of Willis***, which gives rise to the 6 main arteries supplying the cerebral cortex
• in humans only a small fraction of the total arterial flow is carried by the vertebrals
• each carotid essentially supplies only that side of the cortex
• flow through anastomotic channels is minimal due to their small diameter and equal pressures on each side
• there are also precapillary anastomoses between arterioles, however these also carry little flow and are insufficient to prevent infarction
• venous drainage via the deep veins and ***dural sinuses*** enters principally the internal jugular veins
• in the ***choroid plexuses*** there are gaps between the endothelial cells of the capillary wall, however the choroid epithelial cells are densely intermeshed and interlocking
• the capillaries in the brain substance resemble ***nonfenestrated*** capillaries in muscle and other parts of the body
• however there are ***tight junctions*** between the cells which prevent the passage of substances
• also, there are relatively few vesicles in the endothelial cytoplasm and little vesicular transport
• the cerebral capillaries are surrounded by the end-feet of ***astrocytes***, which are closely applied to the basement lamina of the capillary, these form gaps ~ 20 nm wide

▪ *Innervation*

• three systems of nerves supply the cerebral vessels,

1. postganglionic sympathetic from the ***superior cervical ganglion***

   → NA and neuropeptide-Y

2. cholinergic neurones from the ***sphenopalatine ganglion***

   → ACh, VIP, and PHM?

3. sensory nerves with cell bodies in the ***trigeminal ganglion***

   → substance P

NB: the actions of these neurotransmitters are,

i. vasodilators- substance P, VIP, PHM, CGRP
ii. vasoconstrictors - NA, neuropeptide Y

Cerebrospinal Fluid

Formation & Absorption

• there is ~ 150 ml of CSF in the adult, ½ within the cranium
• about 50% of the CSF is formed by the ***choroid plexuses***, the remaining 50% by the cerebral vessels lining the ***ventricular walls***
• in humans the CSF turns over ~ 4 times/day
• the composition depends on filtration and diffusion from the cerebral vessels, plus facilitated diffusion and active transport, predominantly from the choroid plexus
• the composition is essentially the same as brain ECF, and there appears to be free communication between the brain extracellular space, the ventricles and the subarachnoid space
• CSF flows out through the foramina of ***Magendie*** and ***Luschka*** and is absorbed through the ***arachnoid villi*** into the cerebral venous sinuses
• in addition, there is facilitated diffusion of glucose, and active transport of cations and organic acids out of the CSF
• bulk flow via the villi is **~ 500 ml/d**

i. ***formation*** is ***independent*** of ventricular pressure
ii. absorption, being largely by bulk flow, is proportional to ventricular pressure

• at ***normal pressure*** **~ 7.0-18.0 cmH_2O** (mean ~ 11), filtration = absorption
• when pressure falls below ~ 7 cmH_2O absorption ceases
• brain extracellular space normally occupies ~ 15% of brain volume

CSF	Secretion	Absorption	Volume
Halothane	-	-	**0**
Enflurane	+	-	++
Isoflurane	**0**	+	-
Fentanyl	**0**	+	-
N_2O	**0**	**0**	**0**
Ketamine	**0**	-	+

NB: the time course of these effects is ***slow***, and their significance in the setting of raised ICP is lesser in comparison to other factors

Protective Function

• the ***dura*** is firmly attached to bone and there is normally no "subdural space", the ***arachnoid*** being held to the dura by the surface tension of a thin layer of fluid between the two membranes
• the brain is supported by the attachments of blood vessels and nerves, and by multiple fine ***arachnoid trabeculae***
• the dry weight of the brain is ~ 1400g
• bathed in CSF the net weight reduces to ~ 50g
• this is the origin of the pain caused by decreased CSF $\rightarrow$ traction

The Blood-Brain Barrier

• the only substances entering the CNS with ease are **water, CO_2, & O_2**
• the exchange of all other substances is slow

▪ *Penetration of Substances into the Brain*

• there is a $[H^+]$ gradient between blood and brain ECF → ***pH* ~ 7.33**
• the rate of entry of substances into the brain is inversely related to their molecular size and proportional to their lipid solubility
• ***no*** substance is completely denied access to the brain, the consideration is the ***rate*** of transfer
• eg., the amines dopamine and serotonin have limited penetration, c.f. their corresponding acids, L-dopa and 5-hydroxytryptophan, which enter with relative ease

▪ *Development of the Blood Brain Barrier*

• cerebral capillaries are far more permeable at birth than in the adult and the BBB effectively develops in the first few years

a. staining of the infant brain with bile pigments → ***kernicterus***
b. increased sensitivity of the neonate to ***morphine***

▪ *Circumventricular Organs*

• 4 small areas in or near the brainstem lie outside the BBB, these are the,

1. posterior pituitary & ventral median eminence
2. area postrema (CTZ)
3. organum vasculosum of the lamina terminalis (OVLT)
4. subfornical organ (SFO)

• these are referred to collectively as the ***circumventricular organs***
• all have ***fenestrated*** capillaries and are highly permeable
• the median eminence and posterior pituitary are ***neurohemal*** organs, areas where neurones secrete substances directly into the circulation
• the ***area postrema*** acts as the ***chemoreceptor trigger zone***, initiating vomiting in response to chemical changes in plasma
• ***angiotensin II*** acts on the SFO ± the OVLT to increase water intake

NB: the pineal and ***anterior pituitary*** have fenestrated capillaries and are outside the BBB, however they are endocrine glands, not part of the brain

- ***Function of the Blood-Brain Barrier***

• essentially to maintain the constancy of the CNS environment
• CNS neurones are extremely sensitive to changes in Mg^{++}, K^{+}, Ca^{++}, H^{+} and other ions
• also functions to protect the brain from endogenous and exogenous toxic substances; when these are lipid insoluble
• the effectiveness of the BBB is greatly reduced by irradiation, infections, and tumours
• can also be temporarily disrupted by sudden marked increases in BP, or the injection of hypotonic IV fluids

Cerebral Blood Flow

Normal Values			
CBF	• Global • Cortical • Subcortical • 1400g brain	~ 45-55 ~ 75-80 ~ 20 ~ 700 ~ 12-15% CO	ml/100g/min ml/100g/min ml/100g/min ml/min
$CMRO_2$		~ 3-3.5 ~ 50 ~ 20%	ml/100g/min ml/min basal MRO_2
Cerebral P_{vO2}		~ 35-40	mmHg
ICP (supine)		~ 8-12 ~ 10-16	mmHg cmH_2O

NB: a large proportion of the brains energy consumption (~ 60%) is used to support electrophysiological function & the maintenance of ***ion gradients***

local CBF & $CMRO_2$ are heterogeneous throughout the brain,
both are ~ 4x greater in ***grey matter***

Regulation of Cerebral Circulation

- the determinants of total cerebral blood flow are,
    1. the arterial pressure at brain level
    2. the venous pressure at brain level
    3. the intracranial pressure
    4. the viscosity of blood
    5. the tone of the cerebral arterioles

- factors which influence these, and therefore determine CBF include,
    a. chemical / metabolic / humoral factors
        i. $CMRO_2$ - arousal, seizures
        - temperature
        - anaesthetic agents
        ii. $PaCO_2$
        iii. PaO_2
        iv. drugs - vasodilators/vasopressors
        - anaesthetic agents
    b. myogenic mechanisms - ***autoregulation*** & MAP
    c. rheologic factors - blood viscosity
        - temperature
    d. neurogenic mechanisms - extracranial sympathetic pathways
        - intracranial pathways

- although other intrinsic factors play a role, the most ***important factors*** are,
    1. $CMRO_2$/CBF coupling
    2. $PaCO_2$
    3. autoregulation
    4. neurogenic regulation

Coupling of $CMRO_2$ & CBF

• in the normal state there is tight coupling between *l*-$CMRO_2$ and *l*-CBF
• while it is clear that local metabolic factors play a role, the precise mechanism of flow/metabolism coupling is uncertain
• factors proported, but not proven, to contribute to this include,

a. H^+
b. extracellular K^+ and/or Ca^{++}
c. thromboxane & prostaglandins
d. adenosine

• $CMRO_2$ is influenced by a number of factors during neurosurgery,

a. functional state
   - sleep versus arousal
   - sensory stimuli
   - epileptiform activity
b. anaesthetic agents
c. temperature

• this is the mechanism of ***barbiturate*** & etomidate induced vasoconstriction
• studies in vitro devoid of metabolic influences show a direct vasodilatory effect, which is outweighed in vivo by the metabolic influences
• once the EEG is ***isoelectric***, there is no further reduction in $CMRO_2$, none of the anaesthetic agents appears to influence the basal "housekeeping" O_2 requirement

• ***lignocaine*** may be a possible exception to this, data suggesting that large doses (160 mg/kg in dogs) further reduces the $CMRO_2$, probably by its membrane stabilising effects
• this would predict that once the EEG is isoelectric, further doses of barbiturate would result in direct vasodilatation
• this ***has not*** been observed clinically
• further, the inference that isoelectricity represents a single physiological state does not hold true
• SSEP's can still be recorded at barbiturate levels far greater than those required for isoelectricity, whereas they are difficult to elicit following burst suppression doses of isoflurane
• there is a progressive decrease in CBF and $CMRO_2$ with ***age***
• this reduction in flow is probably not due to atherosclerotic vascular disease, but to the progressive neuronal loss with ageing

• temperature reduction decreases $CMRO_2$ ~ 6-7% per °C
• the EEG becomes ***isoelectric* ~ 20°C**, however, in contrast to anaesthetic agents, further reduction in temperature ***does*** result in further reduction in $CMRO_2$
• at 18°C the $CMRO_2$ ~ 10% of the basal rate and accounts for the profound protective effect during hypothermic arrest

• hyperthermia has the opposite effect, with marked increases in $CMRO_2$ up to 42°C, beyond which there is a reduction in $CMRO_2$, possibly due to inhibition of enzymatic function

■ ***Carbon Dioxide***

• CBF is ***linearly*** related to $PaCO_2$ over the range **~ 18-80 mmHg**
• for each 1 mmHg change in $PaCO_2$, CBF changes ~ 1-2 ml/100g/min
• these changes are so predictable that reactivity to $PaCO_2$ is often used for validation of methods of measurement of CBF
• under normal circumstances, CO_2 sensitivity appears positively correlated with basal $CMRO_2$
• accordingly, agents which alter basal $CMRO_2$, also alter ***slope*** of the $\delta CBF/\delta PaCO_2$ curve

• reduction of CBF & CBV by hyperventilation is useful for both ***brain decompression*** and ***brain relaxation***
• the brain actively compensates for this respiratory alkalosis and CBF gradually returns to baseline
• loss of **$PaCO_2$** ***reactivity*** is a good predictor of ***outcome*** after severe head injury
• H^+ ions also have a vasodilator effect, changes in local and CSF pH being the mechanism of action of $PaCO_2$
• the action of H^+ appears to be direct on blood vessels
• however, due to the impermeability of the BBB, metabolic acidosis has little immediate effect upon CBF, in contrast to respiratory acidosis
• the effects of $PaCO_2$ occur rapidly but are not sustained, CBF returning to normal over **~ 6-8 hrs**
• the act of causing cerebral vasoconstriction by hyperventilation may actually decrease CBF to marginally perfused areas and augment ischaemia
• studies looking at global O_2 extraction show cases exist where hyperventilation results in an increased $A\text{-}VO_2$ difference
• this is probably a better guide to the ideal minute ventilation than measurement of ICP
• in normal subjects, ischaemia will not occur at a **$PaCO_2$ ³ 20 mmHg**
• this appears to apply even during induced hypotension and there is little to be gained in terms of CBF reduction below this level
• therefore, it is generally recommended to limit hypocarbia to 20-25 mmHg in previously normocarbic individuals
• the patient who has chronically adapted to a high $PaCO_2$ requires different consideration
• CSF bicarbonate adaptation occurs with a $T_{½}$ ~ 6 hours and CSF pH gradually returns to normal despite the sustained alteration of arterial pH
• thereafter, acute normalisation of arterial pH will result in significant CSF acidosis and induced "hypocapnia" may carry a theoretical risk of ischaemia

■ ***Oxygen***

• changes in PaO_2 also affect cerebral vessels
• hyperoxia causes minimal vasoconstriction, from the range 60-300 mmHg CBF remains approximately constant and at 1 atm, CBF is decreased ~ 15%
• at a $PaO_2 < 60$ mmHg CBF begins to increase rapidly
• the mechanisms mediating this vasodilatation are not fully understood

▪ ***Autoregulation***

• maintenance of a near constant CBF over a range of **MAP ~ 50-150 mmHg**
• beyond these limits, perfusion is pressure passive
• this assures a constant metabolic supply in states of hypotension and prevents hyperaemia (which changes BBB permeability & elevates ICP) with hypertension
• there are a number of points relevant to anaesthesia,

1. hypertensive patients may have a ***right shift*** of the lower limit of autoregulation, and thus be less tolerant of hypotension
2. autoregulation is not an instantaneous process, ie. there are ***dynamic*** changes in CBF with changes in MAP ~ 3-4 minutes
3. induced hypotension should be achieved over a period of several minutes
4. volatile anaesthetics obtund autoregulation in a dose dependent manner

NB: therefore the use of high dose volatile should be avoided if autoregulation is being relied upon to maintain CBF during induced hypotension

• the precise mechanism is uncertain but appears to be ***myogenic*** in origin
• in subjects having AVM surgery, ablation of the shunt diverts flow to the adjacent brain and at a point there may be an acute breakthrough in autoregulation with massive brain swelling
• thus many centres partially obliterate the shunt embolically prior to definitive surgery

▪ ***Neurogenic Regulation***

• there is extensive innervation, the density of which declines with decreasing vessel size
• there are three types of nervous supply to cerebral vessels,

1. cholinergic
2. adrenergic - sympathetic and non-sympathetic
3. serotonergic

→ extracranial and intracranial origins

• the role of these in regulation of CBF is debated
• the effects are generally mild and not believed to be of significance in normal regulation of CBF
• animals definitely have an extracranial sympathetic influence via the superior cervical ganglion
• the clearest evidence of functional significance comes from work with autoregulation, alterations in sympathetic tone altering the limits of the autoregulatory curve
• the increase in ICP associated with the administration of succinylcholine is thought to be due to a direct neurogenic mechanism, rather than an uncoupling of $CBF/CMRO_2$

Viscosity

• ***haematocrit*** is the single most important determinant of blood viscosity
• variations within the range 33-45%, result in ***clinically insignificant*** alterations of CBF
• in polycythaemia vera, raised viscosity may reduce CBF to ½ normal values
• in anaemia, CVR decreases and CBF increases, though this may represent a response to the decreased CaO_2 and O_2 delivery
• the effects of viscosity are more obvious during focal ischaemia, when vasodilatation is already maximal, where a reduction in Hct. results in an increase in flow to the ischaemic territory
• pooled data for DO_2 in the setting of ***focal ischaemia*** suggests the ***optimal Hct. ~ 30-34%***

Vasoactive Agents

1. ***systemic vasodilators***
   - the majority of agents (SNP, GTN, hydrallazine, adenosine, CEB's) also cause cerebral vasodilatation
   - therefore, CBF is maintained at lower MAPs during induced hypotension than during hypotension 2° to,

   i. haemorrhage/hypovolaemia
   ii. a non-cerebral vasodilator - trimethaphan

   - the ICP effects of vasodilators are less when hypotension is induced ***slowly***

2. ***catecholamine agonists & antagonists***
   - the data regarding the effects of these agents is unclear, in part due to,

   i. species differences
   ii. differences in receptor populations in different vessels
   - intraparenchymal vs. extraparenchymal
   iii. experimental model differences
   iv. the degree of MAP change which occurs with each agent
   v. the status of autoregulatory mechanisms - anaesthetic effects
   - damage during preparation
   vi. the integrity of the BBB

   - many studies assess the effects on CVR, however these changes may reflect either intrinsic vessel effects or 2° effects to altered MAP
   - the following results from Miller are predominantly human *in vivo* & higher primate

Agonist	CBF	$CMRO_2$
α_1-adrenergic	-	0
α_2-adrenergic	--	0
β	0	0
β (BBB open)	+++	+++
DA	++	-
DA (high dose)	?-	?0
Noradrenaline	-	0
NA (BBB open)	++	++
Adrenaline	-	0
AD (BBB open)	+++	+++

1. the effects of adrenaline & noradrenaline where the BBB has been damaged are 2° to β-induced increases in $CMRO_2$
2. the effects of high dose dopamine are α mediated, and occur at concentrations producing significant peripheral α-agonist activity

• there has been recent interest in α_2-agonists, due to their sedative analgesic effects
• ***dexmedetomidine*** causes decreased CBF with no decrease in $CMRO_2$ (dogs)
• the α_2-antagonist ***yohimbine*** maintains CBF at lower MAPs in cats during haemorrhagic hypotension

• studies with ***clonidine*** have shown decreased CBF in humans and decreased SCBF with intrathecal injection in animal models
• these results are opposite to what might be expected from the reduction in noradrenaline release mediated by presynaptic α_2 receptors
• possible causes include activation of postsynaptic α_2-receptors or a central action (? locus ceruleus) mediating neurogenic vasoconstriction

Effects of Anaesthetics on CBF

a. delivery of energy substrate is dependent upon CBF, and in the setting of ischaemia, modest alterations of CBF can influence neuronal outcome

b. the control and manipulation of CBF is central to the management of ICP due to its effect upon CBV,

δ**CBV** ~ 0.04 ml/100g per $\delta PaCO_2$ = 1 mmHg (20-80 mmHg)
~ 17 ml $\delta PaCO_2$ = 25-55 mmHg

▪ ***Barbiturates***

• dose dependent reduction in $CMRO_2$ and CBF ~ 30% with the induction of anaesthesia
• larger doses result in an isoelectric EEG and $CMRO_2$ & CBF ~ 50%
• further dose increases have little effect
• tolerance to these effects appears to develop quickly, and increasing doses are required following 24 hours of therapy
• during deep pentobarbital anaesthesia, ***autoregulation*** is preserved to pressures ~ 60 mmHg, and CO_2 responsiveness is also maintained

▪ ***Benzodiazepines***

• result in parallel reductions in CBF/$CMRO_2$ in both humans and monkeys
• the reduction appears intermediate between the opioids and the barbiturates
• the effect is probably metabolically coupled and CO_2 responsiveness is maintained
• they are therefore safe in the presence of raised ICP, providing the dose is not sufficient increase the $PaCO_2$

• ***flumazenil*** causes no effect when given to unanaesthetised human volunteers
• following midazolam induced depression, it results in reversal to baseline
• however, this follows a brief period of "***overshoot***" in CBF (45-56%) and ICP (180-217%)
• $CMRO_2$ does not rise, indicating the effect is ***not*** metabolically mediated
• pending further studies, flumazenil should be used with caution in patients with potentially raised ICP

▪ ***Ketamine***

• results in a marked increase in $CMRO_2$ and CBF, both 2° to the metabolic effects and due to direct vasodilatation
• the changes in $CMRO_2$ are regionally variable, with predominant activation of the thalamic and limbic structures
• autoregulation during ketamine anaesthesia has not been directly tested
• CO_2 responsiveness is preserved, as hyperventilation reduces the elevation of ICP following ketamine administration

Propofol

• reduces both CBF and $CMRO_2$, up to 51% and 36% respectively
• it may however may result in a precipitous fall in ***CPP*** in patients with raised ICP (~ 50%)

Opioids

• the available data is contradictory, but it is likely opioids have little effect upon CBF & $CMRO_2$ in the normal, unstimulated animal
• generally they produce mild decreases in both variables, with autoregulation remaining intact
• only 1 study has administered morphine (1 mg/kg) alone to humans, Moyer observed no change in global CBF but a 41% decrease in $CMRO_2$
• other studies, using N_2O in addition to morphine have shown a small decrease
• fentanyl will likewise cause a moderate reduction in $CMRO_2$/CBF in the quiescent brain but much larger decreases during arousal
• there is minimal data available for alfentanyl and the studies of sufentanyl suggest similar changes in CBF/$CMRO_2$ cf. fentanyl
• however, Marx (1989) looked at CPP (MAP - lumbar CSFP) following administration of these three opioids $\rightarrow$ all three caused a reduction in MAP and the net changes in CPP were,

1. fentanyl - 14 ± 3%
2. sufentanyl - 25 ± 5%
3. alfentanyl - 37 ± 3%

• the increases in l-CSFP observed were readily overcome by hyperventilation
• due to the possible confounding effect of hypotension (2° vasodilatation), they repeated the study maintaining MAP with phenylephrine
• they observed substantial increases in CSFP with both sufentanyl and alfentanyl, but no significant change following fentanyl
• subsequent work with animals has supported a possible ***direct vasodilatory effect*** with sufentanyl and possibly alfentanyl
• there have, however, been a number of blinded clinical studies of these three agents with no discernible clinical differences being found
• they should not therefore be contraindicated but used in conjunction with hypocapnia

Lignocaine

• produces a dose related decrease in $CMRO_2$ and CBF
• doses **~ 1.5 mg/kg** are as effective as boluses of thiopentone 3 mg/kg in blunting the ICP rises associated with painful stimuli during neurosurgery
• lignocaine is associated with a smaller fall in MAP and, therefore, is recommended as an adjuvant prior to known stimuli
• although lignocaine can produce seizure activity, this has not been documented during anaesthesia within the recommended dose range (1.5-2 mg/kg)

Volatile Anaesthetics

• the order of vasodilatory effect of the commonly used volatiles is,

halothane >> enflurane > isoflurane

• there is less available data for desflurane and sevoflurane, however they appear to be similar in potency to isoflurane
• all of these agents cause a dose related decrease in $CMRO_2$ but in contrast to the IV agents an increase in CBF, ie. they "***uncouple***" $CBF/CMRO_2$
• however, there is evidence that metabolic coupling persists with the volatile agents
• the best evidence occurs during hypocapnia induced seizure activity with enflurane in dogs
• also, nociceptive stimuli during stable halothane anaesthesia increases both $CMRO_2$ & CBF

NB: it is therefore more accurate to say that the $CBF/CMRO_2$ ratio is ***reset***

• at 1.0 MAC the reduction in $CMRO_2$ in cats is ~ 25% with halothane and ~ 50% with enflurane and isoflurane
• however, with ***isoflurane*** maximal suppression of $CMRO_2$ is achieved simultaneously with the onset of isoelectricity, and this occurs at clinically relevant concentrations in humans (≤ 2.0 MAC)
• higher concentrations (≤ 6 MAC in dogs) produce no further reduction in $CMRO_2$
• halothane contrasts this, requiring ≥ 4 MAC to produce isoelectricity, and further doses result in additional decreases in $CMRO_2$
• this later effect is presumed to relate to reversible interference with oxidative phosphorylation

• the effects on CBF represent the sum of metabolic induced vasoconstriction and a direct vasodilatory effect by their action on smooth muscle
• as isoflurane suppresses $CMRO_2$ earlier, further doses may produce predominantly vasodilatation and there is some animal evidence to support this

• the ***regional CBF*** effects of these agents differs considerably
• halothane produces almost uniform changes in CBF throughout the brain
• with isoflurane, CBF increases more in the subcortical structures and hindbrain than in the neocortex
• these differences account for the variable finding of numerous studies in the literature, dependent upon the method of CBF measurement used (see later)
• the sum of these studies suggests that while isoflurane produces little vasodilatation in the cortex, it is however a global cerebral vasodilator and this needs to be considered when intracranial compliance (elastance) is low

NB: at equi-MAC levels isoflurane does produce a ***lesser increase*** in CBF and is therefore probably the agent of choice

• the effects of the volatile agents are ***time dependent***, after the initial increase CBF falls markedly
• recovery to ***preanaesthetic*** levels of CBF occurs at 2.5-5 hours post introduction of volatile
• the mechanism is uncertain and the time lag is proportional to the initial magnitude of CBF rise

• CBF influences ICP due to the positive correlation between CBF and CBV
• CBV has been shown to increase in humans with the administration of both isoflurane and N_2O
• studies looking at lumbar CSFP during administration of the volatile agents, and fentanyl, show acute rises in l-CSFP which parallel changes in CBV

> ***NB:*** however, although CBV changes last up to 3 hours with all of these agents, l-CSFP normalises after **~ 20 *minutes*** with isoflurane

• this led to the concept of differential effects on ***CSF dynamics***, in addition to the effects 2° to CBV
• the magnitude of these effects has not been classified, but is thought to be minor in comparison to the CBV effects, due to,

1. the time course of change
2. the fact that the CSF space is usually open by the time any significant change is likely to have occurred

• **CO_2-*responsiveness*** is well preserved with all of the volatile agents
• in contrast ***autoregulation*** is impaired in a dose and anaesthetic related manner

• enflurane is unique amongst these agents due to its ***epileptogenic*** activity
• of particular note is the augmentation of this effect by ***hyperventilation***
• enflurane induced seizure activity is associated with substantial increases in $CMRO_2$ and CBF
• amitriptyline and ketamine have been reported to reduce the seizure threshold for enflurane
• this property has been used in cortical EEG mapping of seizure foci during surgery for resection
• isoflurane has been shown to produce EEG spike activity and myoclonus, but has not been associated with frank seizure activity

• ***sevoflurane*** is a relatively insoluble halogenated ether (B:G ~ 0.6)
• moderate F^- ion is released in vivo and it is unstable in the presence of soda lime
• the toxicity of the subsequent metabolites is still being established
• it is indistinguishable from isoflurane in its cerebral effects

• ***desflurane*** is also an insoluble halogenated ether (B:G ~ 0.42)
• it is a gas at room temperature (T_{crit} ~ 17°C) and therefore requires pressurised delivery systems
• there is limited available data, but it also appears to be similar to isoflurane
• a single study has shown an increase in ICP, ***not responsive*** to hyperventilation, and use of desflurane for neurosurgery should be limited until this is confirmed

Nitrous Oxide

• the available data show that N_2O can unequivocally ***increase*** CBF & ICP
• the most dramatic effects are seen in studies which use little or no background anaesthesia, and probably reflect 2nd stage arousal phenomena
• when administered with other agents these effects are considerably lessened
• pretreatment, or the concomitant administration of ***thiopentone*** or the benzodiazepines reproducibly prevents the increases in ICP seen with administration of 70% N_2O
• the opioids also appear to blunt this effect

• the interaction with the volatile agents is different
• data suggests that addition of N_2O to established volatile anaesthesia will result in increases in CBF/ICP
• there is vastly divergent data on the effects of N_2O on $CMRO_2$
• the "cleanest" work has been done in awake goats, showing a marked increase,

1. in $CMRO_2$ ~ 70%, and
2. in CBF ~ 43%

• the following statement is from Miller,

NB: "it appears that N_2O induced cerebral vasodilatation can be considerably blunted by the simultaneous administration of fixed anaesthetics....N_2O has been widely used in neurosurgery and banishing it is inconsistent with the accumulated experience. Nonetheless, in circumstances in which ICP is persistently elevated or the surgical field is persistently tight, N_2O should be viewed as a potentiating factor."

Muscle Relaxants

• the only effect of nondepolarising muscle relaxants on CBF occurs via the release of ***histamine***
• vasodilatation results in a reduction in CPP by a simultaneous,

1. decrease in MAP and
2. increase in ICP

• whether the decrease in CVR (BBB intact) is a direct effect of histamine, or an autoregulatory response to the reduction in MAP is uncertain
• **dTC** is the most potent releaser, with smaller amounts being released by metocurine, atracurium and mivacurium
• the clinical effects for the later two are not significant
• pancuronium, via changes in MAP, may increase ICP when changes are abrupt or autoregulation is impaired by disease processes
• all agents of this class effectively reduce ICP by the prevention of coughing, straining and the reduction in mean intra-abdominal/intrathoracic pressure
• ***laudanosine*** a metabolite of atracurium is potentially epileptogenic, though, this is not significant clinically

• ***succinylcholin***e results in an elevation of ICP in lightly anaesthetised patients
• Minton studied patients with tumours and noted mean ICP changes from 15-20 mmHg, lasting 2-3 minutes and returning to baseline after 8-10 minutes
• the effects appear to be the result of ***cerebral activation***, by activation of the muscle spindle apparatus
• however, there is poor correlation between fasciculations & EEG activation
• consistent with the hypothesis of arousal is the observation that deep anaesthesia prevents this increase in ICP, as does prior paralysis with nondepolarising agents, or the use of "defasciculating" doses (metocurine)
• therefore, it is not contraindicated in the presence of raised ICP but due attention should be given the depth of anaesthesia and the prior use of "defasciculation"

Measurement of CBF

▪ ***Washin-Washout Methods***

• according to the ***Fick principal***, the blood flow to any organ is equal to the amount of a substance added to, or removed from the circulation, divided by the arterio-venous concentration difference, per unit time

$$CBF = \frac{Q_X}{[A_X]-[V_X]}$$

• the Kety method uses subanaesthetic amounts of N_2O
• as the blood:brain partition coefficient is ~ 1.0, and the equilibrium time is 9-11 minutes, viz.

$$CBF = \frac{100 \,.\, V_t \,.\, S}{\int_0^t [A-V].\delta t}$$

where, S = the blood:brain partition coefficient
V = the venous concentration at time t
t = time until equilibrium
A = the arterial concentration (see Ganong 32-6)

• this measures the ***average flow*** and gives no information about regional differences
• this method will not detect the decrease in flow produced by complete ***occlusion*** of a cerebral artery, as it measures ***flow/unit*** mass and the non-perfused area takes up no N_2O
• the original method described by Kety-Schmidt in 1945 has undergone numerous modifications
• measurements can be made of either the *time to equilibrium* or the *rate of washout*
• tracers used in a washout technique include,

i. H_2 - with a platinum electrode inserted in the brain substance
$\rightarrow 2H^+ + 2e^-$, clearance $\propto$ current
ii. ^{133}Xe
iii. N_2O
iv. heat
v. Xe - nonradioactive tracer

• the ^{133}Xe method is relatively noninvasive, is easily used in humans, the apparatus is reasonably portable and provides information on ***regional flow***
• however, it gives information only with respect to cortical flow

- ***Embolic Techniques***

• largely limited to ***radioactive microspheres***, usually **~ 15 µm** with gamma emitting isotopes
• these become trapped at a capillary level proportional to flow
• blood is continuously drawn into an artificial organ during the distribution phase
• tissue from the sample organs is then weighted and the radioactivity counted
• using different isotopes repeat measurements can be made allowing assessment of pharmacological interventions
• the technique is however,

a. a radiation hazard
b. expensive
c. not useful for recovery models, where CBF and outcome could be correlated

- ***Autoradiographic Techniques***

• these also employ the washin principle
• radioactive tracer is infused IV over a given time and an arterial concentration time curve constructed to establish tracer availability to the brain
• cerebral circulation is then interrupted, the brain is fast frozen and thinly sectioned
• the sections are then placed on radiographic media and images developed
• the method is moderately expensive, limited primarily to small animals and gives only one determination per animal
• evaluation of ***regional perfusion*** is however unparalleled

- ***PET Scanning***

• involves IV injection of short-lived isotopes (^{15}O, ^{11}C, ^{18}F) which decay emitting ***positrons***
• nuclear decay by positron emission emits 2 high energy annihilation gamma photons at 180°
• therefore, arrays of paired detectors, which register only coincident events, allow precise determination of the plane of origin of the decay
• this reduces radiation scatter, which decreases resolution with other radiographic techniques
• also, the high energy of the photons minimises tissue attenuation
• 2D and 3D images can be constructed using triangulation, cf. CAT scanning
• this allows determination of information from deeper structures, including,

i. CBF
ii. $CMRO_2$
iii. CBV

• the principal disadvantages are the extreme cost and the requirement for a cyclotron to generate the short-lived positron emitting radionuclides
• although, due to their short-lived nature, repeated measurements may be made

■ ***Transcranial Doppler***

• relies on the principals of ultrasound and ***doppler shift*** caused by moving red blood cells
• the probe is placed over a "cranial window" which is usually the ***temporal bone*** immediately above the zygomatic arch
• the probe emits a 2 mHz signal which allows visualisation of various vessels, but the MCA is most readily used
• actually measures ***RBC velocity***, with the mean velocity being calculated from systolic and diastolic flows, mean velocity being a reflection of CBF
• the ***pulsatile index*** is calculated as,

$$PI = \frac{\text{(systolic velocity - diastolic velocity)}}{\text{mean velocity}}$$

• this may be a reflection of cerebrovascular ***resistance***
• the advantages include,

a. relatively cheap
b. non-invasive
c. portable

• disadvantages include,

a. difficulty in finding a strong signal ~ 10%
b. patient movement disrupts the signal
c. only ***trends*** can be determined, not absolute values

■ ***Measurements of Regional Flow***

• usually determined by either ^{133}**Xe** uptake, or by the ***2-deoxyglucose*** method, combined with positron emission tomography (PET) scanning
• blood flow to the grey matter is **~ 6x** that of the white matter
• largest blood flow per gram tissue is the ***inferior colliculus***
• there are marked fluctuations in regional flow with activity in the respective regions of the brain
• flow remaining proportionate to metabolic activity

- ***Measurement Of CBF***

• the type of CBF technique used depends upon,

a. human versus laboratory animal

b. cost constraints

c. global versus regional information

• further, the type of measurement will affect the results obtained
• numerous studies have shown that CBF is greater with halothane cf. isoflurane at equi-MAC concentrations
• other studies, using global CBF techniques, have shown no significant difference
• the studies showing higher CBF with halothane are those in which predominantly cortical CBF was determined
• in reality the two agents produce different flow distribution patterns within the brain,

a. ***global*** changes for the 2 agents are similar

b. cortical flows are greater with halothane

c. subcortical flows are greater with isoflurane

• with respect to raised ICP the global effects would seem most appropriate
• the best assay for predicting effects on ICP is actually ***cerebral blood volume***
• the assumption that CBV will parallel changes in CBF does not always occur
• if vasodilatation is predominantly venous there will be little increase in CBF, but CBV and ICP will both rise

Measurement of Cerebral Metabolism

a. **arteriovenous content difference**
   i. glucose
   ii. oxygen
      - usually venous sampling from the jugular bulb
      - lack of any regional information
      - combined with CBF measurements give $CMRO_2$

b. **2-deoxyglucose**
   i. autoradiographic
   ii. PET scanning
      - 2-DG passes the 1st phosphorylation step only
      - thus it is metabolically & intracelularly trapped
      - partial consumption of 2-DG is proportional to MRO_2
      - only 1-2 measurements / patient
      - invalid in many disease states, eg. ischaemia, glucose is readily metabolised by anaerobic glycolysis
      - thus the marginal zones around an infarct light up, despite decreased perfusion & metabolism

- as for measurements of CBF, the effects of volatile agents on $CMRO_2$ depend upon the measurement used
- global measurement shows that the volatile agents uncouple $CMRO_2$ & CBF
- however, regional measurements show that the linear relationship is maintained, only the slope of the curve is altered
- the alteration of the ratio appears to be both dose & anaesthetic dependent

Oxygen Consumption

• the cerebral rate of O_2 usage ($CMRO_2$) ~ 49 ml/min for a 1400g brain
• this equates to ~ 20% of the total body O_2 consumption
• the brain is extremely sensitive to hypoxia, occlusion of the blood supply resulting in unconsciousness in **< 10 secs**
• the vegetative structures in the brainstem are more resistant to hypoxia than the cortex
• the ***basal ganglia*** also use O_2 at a rapid rate and hypoxia, therefore, frequently results in intellectual dysfunction and Parkinsonian symptoms

■ ***Energy Sources***

• glucose is the major ultimate energy source under normal conditions
• the normal respiratory quotient for cerebral tissue is ~ 0.95 to 0.99
• during prolonged starvation appreciable utilisation of other substances occurs
• even under normal conditions, as much as 30% of glucose taken up by the brain is converted to amino acids and lipids
• ***insulin*** is not required for the cerebral uptake of glucose
• uptake is increased in active neurones, as is that of 2-deoxyglucose,
• however the later is not metabolised and uptake of radioactive labelled tracer is used to map cerebral activity
• there is an average decrease of 30% uptake of all areas during slow wave sleep

■ ***Hypoglycaemia***

• the symptoms of hypoglycaemia include,

1. mental changes, confusion
2. ataxia, convulsions
3. sweating
4. coma

• the available glucose and glycogen is exhausted within ***2 minutes*** of cessation of arterial flow
• thus the brain can withstand hypoglycaemia for longer periods than hypoxia
• as for oxygen, the cortical areas are more sensitive to sublethal exposures to hypoglycaemia
• diabetic patients exposed to chronic hyperglycaemia exhibit a reduced transport of glucose across the BBB and, therefore, may exhibit symptoms of hypoglycaemia at a "normal" BSL

■ ***Glutamate & Ammonia Removal***

• the brain uptake of ***glutamate*** is ~ equal to its output of ***glutamine***, thereby clearing the CNS of ammonia; the reverse process to the clearance of ammonia by the kidney
• ammonia is very toxic to nerve cells and this process is necessary for normal CNS function, eg. the CNS effects of hepatic coma

CEREBRAL ISCHAEMIA

Def'n: has come to encompass: *"any diminution of flow sufficient to cause symptoms"*

NB: this may result from reduction in O_2 and substrate delivery, and/or insufficient removal of toxic metabolites,

a. ***global ischaemia*** - cardiac arrest

b. ***global hypoxaemia*** - drowning, suffocation
- other causes of respiratory failure
- initially associated with *hyperaemia*

- in all cases, except ***intentional cardiac arrest***, brain protection is limited to reducing the period of the insult and resuscitation measures

c. ***focal ischaemia***

i. stroke - thrombotic, embolic, haemorrhagic
- atherosclerosis, remote/local
- valvular heart disease

ii. aneurysms, AVM's

iii. tumours

iv. surgical - SAH, CEA

- ***focal ischaemia***, is far more likely to occur during anaesthesia
- the frequency of perioperative stroke varies,

a. carotid endarterectomy ~ 1-20%

b. CABG surgery - at least 1%
- most authors ~ 5%

NB: given the finding that CEA is superior to medical treatment with ***symptomatic stenosis*** **> 70%**, the frequency is not likely to decrease

- accordingly, as with intentional circulatory arrest, cerebral protective measures should include,

1. prophylactic pharmacology
2. procedural intervention during detected ischaemia
3. initiation of resuscitative measures prior to irreversible neuronal death

Normal Cellular Events

- the brain uses **~ 20%** of total body MRO_2 (~ 50 ml/min),
    a. preservation of ***cellular integrity*** **~ 40%**
    b. transmission of ***neuronal impulses*** **~ 60%**

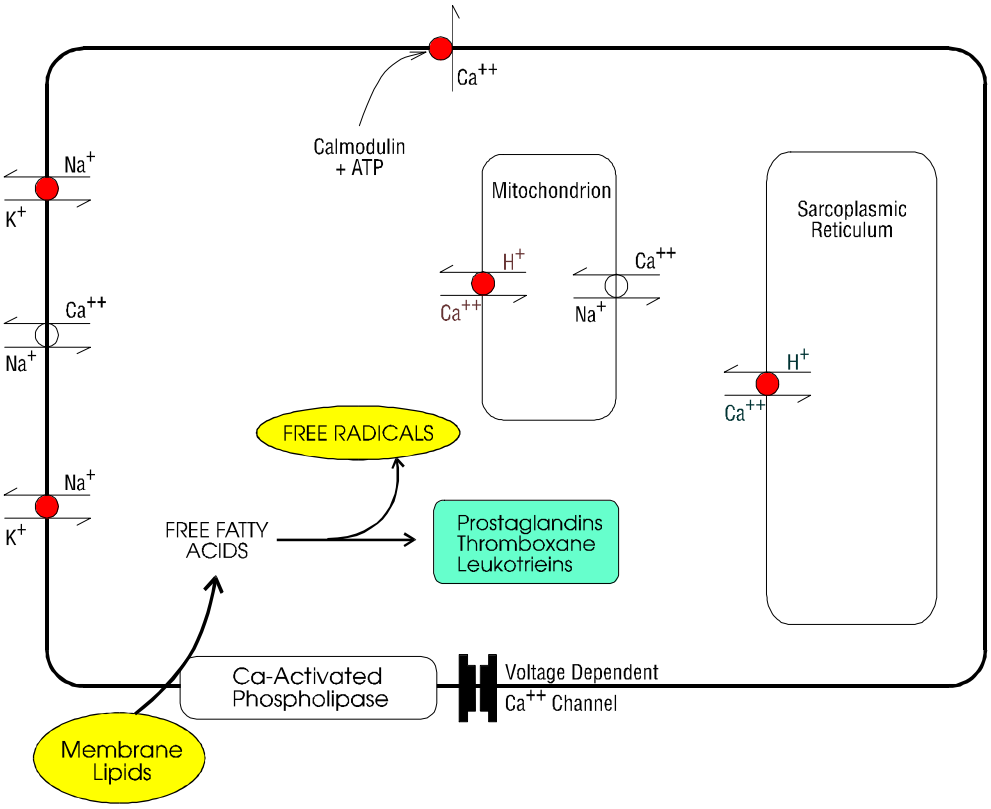
- when O_2 is abundant, glucose is metabolised to pyruvate, generating ATP from ADP & Pi and NADH from NAD
- in the mitochondria, conversion of NADH → NAD is coupled (albeit indirectly) to the production of ATP from ADP & Pi
    a. the energy from 1 NADH yielding 3 ATP molecules
    b. on balance this results in the generation of **38 ATP** per glucose molecule

- the brain contains low concentrations of ATP & stores minimal glucose as glycogen
- therefore it requires a near constant energy supply
- glucose is transported into the CNS by facilitated diffusion, ***independent*** of the action of ***insulin***

- failure of the Na^+/K^+-ATP'ase leads to an elevation of intracellular Na^+, which in turn,
    1. depolarises the membrane, activating ***voltage dependent*** Ca^{++} channels
    2. reduces the clearance of intracellular Ca^{++}

    NB: reduction of intracellular Ca^{++} is an energy dependent process, accumulation is passive

- ***calcium*** plays an integral role in intracellular function,
    a. inhibition of certain enzyme systems - hexokinase
    b. stimulation of enzyme systems - Ca^{++}-ATP'ase
        - adenylate cyclase
        - ***phospholipases A & C***
    c. regulation of actin-myosin interaction - MLCK (smooth muscle)
    d. Ca^{++}-dependent neurotransmitter release



The Ischaemic Penumbra

- in the face of declining O_2 supply neuronal function deteriorates progressively rather than in an "all or none" fashion
- the ***ischaemic thresholds*** for CBF have been well established,

a.	normal CBF	~ 45-55	ml/100g/min	
b.	EEG evidence of ***ischaemia***	~ 22	ml/100g/min	~ 50%
c.	EEG becomes ***isoelectric***	~ 15-18	ml/100g/min	~ 30%
d.	irreversible ***neuronal death***	~ 6-10	ml/100g/min	~ 15%

- as CBF falls below ~ 15 ml/100g/min the decrease in energy supply is ***progressive*** and neuronal damage occurs, but over a time course of hours rather than minutes
- this region will display EEG evidence of ischaemia but may the recovery some time later if flow is restored

Pathophysiology During Ischaemia

a. ***ATP depletion***

- in the absence of O_2, the mitochondria neither generate ATP nor regenerate NAD from NADH
- in order to allow glycolysis to proceed, pyruvate is metabolised to ***lactate***, regenerating the NAD required for the conversion of phosphoglyceraldehyde to 3-phosphoglycerate
- the regeneration of NAD releases $\mathbf{H^+}$ which lowers the intracellular pH
- on balance this results in the generation of **2 ATP** per glucose molecule
- after ~ 20 sec of complete ischaemia synaptic transmission is no longer possible and the EEG becomes ***isoelectric***
- creatine phosphokinase approaches zero at 1 min and ATP at 5-7 minutes

b. ***Ionic failure***

- the later process is insufficient to sustain homeostatic cellular function
- initially there is a failure of the Na^+/K^+-ATP'ase, with an efflux of K^+ and an influx of Na^+ and Cl^-
- membrane depolarisation and opening of ***voltage dependent*** Ca^{++} channels adds to the ICF Ca^{++} load
- membrane bound Ca^{++} pumps fail, in part due to the reduction in ATP, but also due to the increased load of Ca^{++} & the raised intracellular Na^+
- these ion exchange failures become unabated within 2-4 minutes

c. ***Calcium accumulation***

- raised ICF Ca^{++} leads to activation of ***phospholipases A & C***, with subsequent hydrolysis of membrane lipids and accumulation of ***arachidonic acid***
- FFA's have been shown to increase throughout the ischaemic period
  $\rightarrow$ membrane damaging effects & organelle dysfunction
- during incomplete ischaemia, as in ***reperfusion***, arachidonic acid is further metabolised to ***prostaglandins, thromboxanes & leukotrienes***
- oxidation also produces ***free radicals*** which lead to lipid and protein damage

d. ***Excitatory neurotransmitter release***

- depolarisation leads to the release of excessive ***glutamate***, an excitatory neurotransmitter acting at NMDA & AMPA receptors
- this receptor is predominantly found in those areas most vulnerable to ischaemia
- it is associated with an ***ionophore*** which has an extremely high Ca^{++} conductance
- activity is prevalent during periods of neuronal hyperactivity, as is seen following ischaemia
- activation induces "burst-firing" which may be responsible for ***ischaemic seizures***
- unlike other excitatory receptors, there is no down-regulation during ischaemia

e. ***Lactic acidosis***

- animal studies using MCA occlusion show almost a 4-fold rise in lactate within 30 minutes, with levels rising to ~ 17 mmol/kg by 3 hours
- levels in the region 16-20 mmol/kg are considered the threshold above which tissue damage occurs

i. necrosis of endothelial cells & rupture of astrocytes
   → reduced collateral flow

ii. denaturation & inactivation of cellular proteins

iii. suppression of the generation of NAD^+ from NADH

iv. production of O_2 free radicals

- other authors claim lactate itself is fairly ***innocuous*** and that it is the associated pH change which results in cellular damage

f. ***Glucose potentiation of ischaemic damage***

- supported by primate models of focal and global ischaemia, and by retrospective outcome studies of global ischaemia in humans
- during complete ischaemia, high brain levels of glucose allow continued anaerobic glycolysis, with the production of H^+ and lactate
- IV administration of glucose during or prior to an ischaemic event may worsen neurological outcome and should perhaps be avoided in high risk situations, ie. cardiac surgery and carotid endarterectomy

g. ***Free radical generation***

- a free radical is a chemical species with an ***unpaired electron***
- ***superoxide*** (O_2^-) appears to be one of the important species
- ischaemia increases levels of reducing species (NADH, lactate, H^+, xanthine)
- xanthine dehydrogenase is converted to ***xanthine oxidase***, ? due to Ca^{++}
- this enzyme is the major source of O_2^- during ***reperfusion*** of ischaemic tissue
- other species produced include lipid peroxide (ROO^-), lipid hydroperoxide ($RHOO^-$) and hydrogen peroxide (HO^-)
- mechanisms of damage include,

i. increased phospholipase activity & arachidonic acid formation

ii. increased membrane permeability & Ca^{++} influx

iii. protein cross-linking and strand scission

iv. release of enzymes from liposomes

v. mitochondrial disruption and decreased ATP formation

- ***superoxide dismutase*** catalyses the conversion of O_2^- to H_2O_2, which is then converted to water and oxygen
- there is no physiological defence system against HO^- radicals (? catalase)

h. ***Reperfusion injury***

- during ischaemia ***autoregulation*** is non-functional and perfusion is dependent upon CPP and vessel calibre
- upon re-establishment of flow there is a 5-10 minute period of ***hyperaemia***
- this is followed by a prolonged period of ***hypoperfusion***, which is usually heterogeneous
- ***endothelial*** cell damage results in an imbalance of the production of PGI_2 & TXA_2
- free radicals react with membrane phospholipids to produce ***lipid peroxides***, which selectively inhibit the formation of prostacycline
- upon reoxygenation the large pool of arachidonic acid is then converted predominantly to ***thromboxane*** $\rightarrow$ vasoconstriction
  platelet aggregation
  microvascular occlusion

- other factors contributing to the decrease in CBF include,

i. raised Ca^{++} in vascular smooth muscle & ***vasoconstriction***

ii. decreased RBC deformability during ischaemia & increased blood ***viscosity***

iii. ischaemic ***cytotoxic oedema*** & increased extravascular resistance

iv. ***vasogenic oedema*** (hours-days) & increased extravascular resistance

Cerebral Protection

Def'n: physical or pharmacological actions aimed at mimising ***neuronal death*** secondary to an ischaemic event, including neuronal ***salvage*** following such an event

- ***Strategies for Protection***

1. increasing regional ***blood flow*** and $\mathbf{DO_2}$
2. decreasing ***metabolism***
3. preventing loss of normal cellular ***ion gradients***
4. blocking production of ***toxic metabolites***
5. ***scavenging*** those metabolites which are produced

- ***Methods of Protection***

1. ***physiological***
   - i. maintenance of - MAP, CPP, DO_2
   - ii. prevention of - hypoxia, hypercarbia, acidosis
     * ***hyperglycaemia***
     - hyponatraemia, hypoosmolality
2. ***physical***
   - i. deep hypothermic arrest
   - ii. mild hypothermia
   - iii. haemodilution
   - iv. hypertension
3. ***pharmacological***
   - i. depression of $CMRO_2$ - barbiturates, propofol, etomidate, benzodiazepines
     - volatile GA's
   - ii. Na^+-channel blockade - lignocaine, QX-314, QX-222
   - iii. Ca^{++}-channel blockade - nimodipine, nicardipine, flunarizine, Mg^{++}
   - iv. glutamate receptor blockade
     - NMDA - ***dizocipline*** (MK-801), dexmedetomidine, dextromethorphan
     - AMPA - NBQX
   - v. membrane stabilisation
     - steroids - methylprednisolone
   - vi. free radical scavenging
     - vitamin E, steroids, dihydrolipoate

NB: some agents, eg. STP, may act via ***multiple effects***

■ ***Hypothermia***

• remains the most effective means of reducing $CMRO_2$,

a. $CMRO_2$ ~ 50% at a core temperature of 27°C

b. $CMRO_2$ ~ 8% at a core temperature of 17°C

NB: the need for formal testing is obviated by the observation that human brains often recovery after an hour of intentional circulatory arrest at 12-15°C

• although hypothermia to 28°C is routinely used during non-circulatory arrest bypass surgery, its efficacy has not been ***prospectively*** established
• Wong *et al.* (Lancet 1992) compared warm CPB (34.7°C) with hypothermic CPB (27.8°C)

a. all seven neuropsychological tests were "better" in the "warm" group, however, only one test difference achieving statistical significance

b. this would support that ***mild hypothermia*** is equally "protective", though, this is a preliminary study and numbers are too small to draw statistical significance

• recent laboratory work suggests that the principal protective effects of hypothermia are due to reduced ***glutamate & dopamine*** release
• numerous studies have shown mild hypothermia (31-34°C) improves neurologic outcome even when established ***subsequent*** to an ischaemic insult (animal studies)
• unfortunately, the deleterious membrane effects of hypothermia are quantitatively similar to those of ischaemia, but simply take longer to develop
• hypothermia is not nearly as deleterious as normothermic hypoxia
• accordingly, patients subjected to deep hypothermia & circulatory arrest can usually re-establish ion gradients if perfusion is restored
• this is a reasonable prospect during bypass but is unlikely if the heart is relied upon for circulation, as the adverse membrane effects impair cardiac function
• also, ***induced hypertension*** is gaining support for the management of focal deficits
• unfortunately it carries the risks of raised ICP and rebleed from haemorrhagic events

■ ***Mild Hypothermia***

• in distinction to deep hypothermia, the beneficial effects of ***mild hypothermia*** are likely to outweigh the manageable adverse effects (NB: Sano *et al.* Anesth., 1992)
• effects of intraoperative mild hypothermia are atributed to,

1. reduction of ***glutamate*** and ***dopamine*** release
2. recovery of ***ubiquitin*** synthesis

NB: however, probably relates to diminution of ***all*** of the adverse effects of ischaemia

• Berntman *et al.* (Anesth.1981) found that 1°C of hypothermia maintained ATP levels during a hypoxic insult which resulted in 50% depletion at 37°C
• hypothermia to 34°C more than doubles preservation of PCr
• 4 recent studies have shown improved CNS ***outcome*** even when hypothermia was induced ***subsequent*** to the injury

Induced Hypertension

• gaining some evidence for reduction of deficits
• however, associated risks of elevating ICP, rebleeding/ICH, or aggravating oedema

Anaesthetic & Adjuvant Drugs

• reducing $CMRO_2$ is the mainstay of pharmacological management of ischaemia
• ***barbiturate*** administration is the only such intervention which has proven useful in humans, and then only during ***focal ischaemia***, where they have been shown in numerous studies to reduce infarct volume
• in addition to lowering $CMRO_2$, pentobarbital often reduces ICP refractory to mannitol & hyperventilation
• some experimental work in animals suggests that a part of the protective effect of the barbiturates is due to vasoconstriction in healthy brain with shunting of CBF to the injured area
• however, other workers have argued against this effect, "***reverse steal***" (GOK)
• other effects include,

i. reducing the influx of Ca^{++}
ii. inhibiting free radical formation
iii. potentiation of GABA'ergic activity
iv. reduction of cerebral oedema
v. ability to block Na^{+} channels *may be 1° mechanism of ↓ $CMRO_2$

• the ability of the barbiturates to be protective after ***global ischaemia*** remains controversial
• the one large randomised study (NEJM study group) found only a statistically ***insignificant*** trend in favour of barbiturate therapy following cardiac arrest

• ***propofol*** reduces CBF, $CMRO_2$ and ICP similar to STP, but wuth a faster recovery
• may cause dramatic falls in CPP 2° to reductions in MAP >> reductions in ICP
• has been shown to be protective of hippocampal neurones following ~ 7 minutes of anoxia
• protective effects have been disputed by more recent studies
• ***midazolam*** reduces $CMRO_2$ in humans and animals and has shown some protective effects for hippocampal neurones following anoxic damage, by maintaining ATP and reducing Ca^{++} efflux
• ***etomidate*** also reduces $CMRO_2$, but it is limited by its tendency to produce vasoconstriction prior to the reduction in $CMRO_2$

• specific ion channel blockers may have a role
• early studies with ***nimodipine*** showed benefit, however even the benefit following acute ***subarachnoid haemorrhage*** has now been seriously challenged (Mercier *et al.*, Neurosurg'94)
• initial enthusiasm for use following ischaemic stroke and head injury has diminished
• the National Stroke Association (USA) still recommends nimodipine 60 mg qid for grade 1,2 & 3 patients, preferrably starting with 6 hours of haemorrhage

• ***nicardipine*** is another agent with cerebrovascular relaxant properties, similar to nimodipine, but is easier to administer IV
• recent multicentre trial in SAH patients showed similar results to nimodipine,

a. angiographic and CBF measurements showed a reduction in vasospasm
b. "no improvement in outcome at 3 months when compared to standard management"

• however, this study essentially compared the nicardipine group to a hypertensive/hypervolaemic group in ICU, monitored with PA and radial artery catheters, with the nicardipine group requiring significantly fewer days ICU
• other **Ca^{++}** ***channel blockers***, particularly ***flunarizine*** have shown potential for direct neuronal protection in laboratory work
• **Mg^{++}** is a potent inhibitor of Ca^{++} entry and has shown protective action *in vitro* and has recently been shown to be beneficial *in vivo*

• **Na^{+}** ***channel blockers*** should contribute to the stabilisation of neuronal membranes
• both lignocaine and phenytoin have shown some promise in laboratory work
• quaternary LA derivatives QX-314 and QX-222 have been shown to be more protective than either lignocaine or procaine, with less conduction blockade

• there has been a lot of recent research into the ***excitotoxic hypothesis*** of cerebral damage
• ischaemia results in the excessive release of the excitatory neurotransmitter ***glutamine***
• both NMDA and non-NMDA glutamate receptor blockers may prove beneficial,

1. **MK-801** → ***dizocipline***, a non-competitive NMDA receptor antagonist
   - protective in a variety of laboratory models
   - effective both with and without hypothermia
   - in conjunction with nimodipine, nicardipine and the σ-agonist SKF-10,047
   - results from less sensitive models disappointing
2. **NBQX** → an AMPA glutamate receptor antagonist (non-NMDA)
   - results may prove better than dizocipline
   - beneficial in a laboratory model of global ischaemia
3. CGS-19755competitive NMDA blocker
   - beneficial in a laboratory model of global ischaemia
4. ketamine & ***dexmedetomidine*** → NMDA receptor antagonism
   - both may show some protective effects due to catecholamine reduction
5. ***dextromethorphan*** → non-competitive NMDA antagonist
   - protective effects in focal ischaemic models
   - undergoing phase I trials in humans

- ***free radical scavengers*** should theoretically be beneficial
- large studies of ***glucocorticoids*** following cardiac arrest have shown ***no benefit*** in outcome
- conversely, a large randomised controlled trial has shown that the administration of ***methylprednisolone*** administered within 8 hours of injury reduces spinal cord deficit
- ***vitamin E*** has proven protective *in vitro* with some supportive evidence *in vivo*
- enthusiam for 21 amino-steroids has wained with a series of negative results with U74006F

- ***superoxide dismutase*** has recently been shown to be of benefit during reperfusion
- the hydroxyl scavenger dimethylthiourea has been shown to reduce the infarct size and brain oedema following MCA occlusion in rats, without affecting CBF

NB: the principal problem with scavenging is the production of free radicals occurs after ischaemia has run its course & other methods of protection are likely to be required in conjunction, ie.

i. reduction in $CMRO_2$
ii. tolerance of ischaemia without loss of membrane ionic gradients

■ ***Agents & Techniques to Avoid***

• ***hyperglycaemia*** has long been known to worsen the outcome following cerebral ischaemia
• laboratory evidence indicates that even a ***mildly*** elevated plasma glucose may be deleterious
• the assumption is that an increased supply of glucose leads to increased anaerobic metabolism and lactate production
• however, recent *in vitro* work suggests that an elevation of lactate per se ***does not*** lead to neuronal damage and may actually ameliorate some of the effects of ischaemia
• ***insulin*** has been shown to have a protective effect partially independent of a reduction in plasma glucose, however, ***hypoglycaemia*** is equally as detrimental

> ***NB:*** until the controversy regarding this is settled, glucose containing fluids are best avoided and ***normoglycaemia*** should be maintained

• all 3 of the commonly used volatiles increase CBF and ICP
• although ***isoflurane*** is considered safe for neuroanaesthesia, early enthusiasm for its protective effects ***have not*** been substantiated

• the association between $CMRO_2$ reduction and protection has been challenged upon these grounds, see argument by Todd & Hanson to follow
• others argue that all methods of CMR reduction also have deleterious effects, and the net result is a combination of these superimposed upon the protective effect of CMR reduction (Cottrell)
• ie., the benefit of CMR reduction remains constant, but the cost of achieving this varies with the method used, ranging from mild hypothermia to irreversible neurotoxins

• ***sevoflurane*** is similar in most respects to isoflurane, but may produce substantially smaller rises in ICP and has shown some protective effect *in vitro* cf. fentanyl/N_2O
• ***desflurane*** substantially ***increases ICP*** in neurosurgical patients cf. isoflurane, despite hyperventilation to a P_{aCO2} ~ 24-28 mmHg
• from one isolated paper and requires validation, however in the interim desflurane is best avoided
• ***nitrous oxide*** has been shown to,

i. ***elevate ICP*** in humans
ii. aggravate the potential for ***gas embolism***
iii. negate the protective effects of the barbiturates in laboratory studies
iv. attenuate the beneficial effects of isoflurane relative to N_2O alone
v. reduce recovery subsequent to anoxia in the hippocampal slice model

• recent work has shown that the effects of N_2O on ICP and metabolic stimulation are markedly attenuated by the prior administration of thiopentone, or in the isoelectric brain

■ ***Retractor Pressure***

• excessive or prolonged retractor pressure aggravates ischaemia

→ periodic release during long procedures or during profound hypotension

$CMRO_2$ & Cerebral Protection

• Todd and Hansen comment that we have long taken an approach to cerebral protection similar to that used for cardiac physiology, ie. control of ***supply and demand***
• the value of increasing supply is unarguable, however, that agents reducing $CMRO_2$ are also "protective" is open to debate

• Sano *et al*. compared three groups of rats anaesthetised with either 1.3MAC halothane or isoflurane, or halothane plus ***mild hypothermia*** (35°C)
• both normothermic groups showed histological evidence of severe damage, cf. the hypothermic/halothane group where damage was dramatically reduced
• at the levels used in this study, isoflurane

a. reduces the CMR for glucose by 30-50% more than halothane
b. produces burst suppression on the EEG
c. produces a far greater reduction in $CMRO_2$ compared with hypothermia to 35°C

NB: therefore, the degree of neuropathological injury in the 3 groups ***did not*** correlate with the magnitude of ***metabolic depression***

• in 1978 Michenfelder argued that the barbiturates acted by reducing the fraction of $CMRO_2$ that is linked to synaptic activity
• he concluded that barbiturates would offer little protection if the brain were already isoelectric
• he also carefully avoided the conclusion that protection is directly related to CMR *per se*
• most subsequent studies have interpreted his work as saying " *metabolic depression protects*"
• this idea requires modification for two major reasons,

1. the protective efficacy of the various anaesthetic agents ***does not*** parallel their ability to depress the EEG or $CMRO_2$
2. the protective efficacy of ***hypothermia*** is not proportional to depression of $CMRO_2$, nor is it clearly related to the accumulation of metabolic by-products

Anaesthetic Agents

• ***barbiturate*** administration is the only such intervention which has proven useful in humans, and then only during ***focal ischaemia***, where they have been shown in numerous studies to reduce infarct volume
• ***isoflurane*** produces similar EEG and $CMRO_2$ changes and can retard the accumulation of lactate and depletion of ATP during mild ischaemia
• numerous workers have shown that the "***critical CBF***" at which EEG changes indicative of ischaemia occur, is lower with isoflurane cf. halothane or enflurane
• further, the time to terminal membrane depolarisation following cardiac arrest is significantly prolonged by 0.75MAC isoflurane
• however, repeated studies of neurologic or histopathologic ***outcome*** after global or focal ischaemia have ***failed*** to demonstrate any protective effect for isoflurane
• the often purported reason for this is an adverse distribution of CBF, with vasodilatation in non-ischaemic areas "stealing" blood flow from ischaemic areas
• however, Warner *et al* in work with rats have shown that this is unlikely to occur clinically

• two anaesthetic agents, ***dizocipline*** and ***dexmedetomidine*** have shown protective efficacy *in vitro*, but neither has any significant effect upon $CMRO_2$
• ***propofol*** has been shown to reduce both $CMRO_2$ and EEG activity, but has been shown to have little protective effect, at least against focal ischaemia

Hypothermia

• a number of studies have shown that changes in brain temperature of as little as 2-4°C are associated with substantial effects on the degree of histological damage
• it has long been assumed that the protective effects of hypothermia are metabolically mediated
• however,

1. CMR decreases in a ***log-linear*** manner with temperature
2. animal studies show a ***sigmoid*** relationship between temperature and protection

• Busto *et al*. showed that the number of dead neurones in the striatum was reduced by 25% with a reduction in brain temperature from 39-36°C; a further reduction to 34°C resulted in almost 100% protection
• similar findings were obtained by Sano *et al*.
• Busto *et al*. subjected rats to 20 minutes of forebrain ischaemia at 36, 33 and 30°C
• while there was a significant protective effect at 33°C, as shown by histology, there was ***no difference*** in cellular energy charge, ATP levels and lactate concentrations, as compared with those animals at 36°C
• in 1989, Natale and D'Alecy subjected dogs to 10 minutes of VF at either 37-39°C or 33-34°C,

a. hypothermic animals all survived for 24 hours,
cf. the normothermic group, where all died
b. the brain tissue lactate concentrations, both during and after ischaemia, were not statistically different

Alternative Approaches

- ischaemic injury can be temporally divided into three phases,

1. ***diminished energy reserve***
   - if ischaemia is mild, then anaesthetic agents and hypothermia can reduce $CMRO_2$ and "buy time"
   - with severe ischaemia this target period is short, less than 1-2 min, and probably of little clinical significance
   - once membrane depolarisation has occurred other means of protection are required

2. ***complete energy failure***
   - signalled by membrane depolarisation, marked Ca^{++} influx, triggering of metabolic pathways, excessive release of certain neurotransmitters
   - there are two basic mechanisms of protection during this phase,
   i. prevention of synthesis or release of these compounds
   ii. blockade at their site of action
   - it is well known that ***mild hypothermia*** can block the release of ***glutamate***, however, the effects of the anaesthetic agents is largely unknown
   - drugs such as ***dizocipline*** and NBQX block the action of glutamate at two of its receptors, NMDA and AMPA (quisqualate)
   - other agents, such as dexmedetomidine may act by augmenting inhibitory transmission

3. ***reperfusion injury***
   - the liberation of ***free radicals*** upon the reintroduction of oxygen
   - most anaesthetic agents are relatively poor free radical scavengers
   - in the absence of seizures, post-ischaemic hypermetabolism ***does not*** occur
   - therefore agents directed at $CMRO_2$ are unlikely to have a profound influence

Recent Developments

1. ***nimodipine*** has been shown to benefit,
   i. acute ischaemic stroke - now refuted
   ii. poor grade aneurysm patients
   iii. delayed resuscitation post ventricular fibrillation
   iv. combined therapies, eg with NMDA-receptor blocker (MK-801)
2. ***methylprednisolone*** has been shown to improve outcome following spinal cord injury in humans
3. ***free radical scavengers*** have demonstrated protective effects in animals
4. work with ***glutamate receptor*** antagonists has highlighted the "excitatory hypothesis"
5. ***platelet activating factor*** antagonism is protective in post-ischaemic rodent models
6. laboratory success with,
   i. neuronal implants
   ii. neuronal regeneration
   iii. continuous culture of a human cortical neuronal cell line

INTRACRANIAL PRESSURE

• the normal contents of the cranium are;

1. brain - neural tissue & interstitial fluid ~ 1400g
2. blood ~ 75 ml
3. CSF ~ 75 ml (+75 ml spinal cord)
4. ICP ~ 7-18 cmH_2O

NB: because each of these three components is relatively ***incompressible***, the combined volume at any one time must be constant → the ***Monro-Kellie doctrine***

• this is not entirely accurate, as some change in CNS volume is possible without noticeable change on ICP
• most discussions are based upon an ***intact cranium***, which exists only at the beginning of an elective craniotomy and may not be applicable at all to the head injured patient with skull damage
• more importantly, the cerebral vessels are compressed whenever the ICP is raised, and ICP is directly proportional to ***venous pressure***
• thus, a rise in venous pressure decreases CBF by two mechanisms; one, by reducing the perfusion pressure and two, by compressing cerebral vessels
• this dual action helps to compensate for the effects of $\pm g_X$ on cerebral perfusion
• when ICP increases above ~ 33 mmHg (45 cmH_2O) over a short period of time, CBF is significantly reduced
• this causes relative ischaemia and stimulation of,

a. the vasomotor regions increasing BP, ***Cushing reflex***, and
b. the cardioinhibitory centre, slowing HR and respiration

• eventually, as ICP rises further, all regions are depressed

Measurement of Raised ICP

• continuous measurement was introduced into clinical practice ~ 1960 by ***Lundberg***
• ***indications*** for perioperative ICP monitoring include,

1. neurotrauma / head injury
2. hydrocephalus
3. large brain tumours
4. ruptured aneurysms
5. postoperative cerebral oedema / swelling
6. metabolic encephalopathy, Reye's syndrome
7. large CVA - ICH > infarction
8. proposed therapy to maximise CPP

- ***Methods of Measurement***

a. ***intraventricular catheter*** - ventriculostomy
- represents the "gold standard" for pressure measurement
- also allows therapeutic ***CSF drainage***
- difficult with large tumours & compressed ventricles
- requires ***destruction*** of brain tissue
- creates a pathway for ***infection***
- potential for ***accidental venting*** of CSF & possible subdural haemorrhage or upward brain herniation
- Camino Laboratories OLM uses a fibreoptic device within the ventricular catheter

b. ***subdural bolt***
- inserted through a burr hole & an opening in the dura
- a "Richmond Screw" or "Leeds device" connects via a fluid couple to a transducer
- less invasive than (a) and does not require penetration of brain tissue
- doesn't allow CSF drainage or study of cerebral compliance
- may underestimate high ICP and damping is a problem

c. ***subdural catheter***
- prone to signal damping and calibration drift
- Gaelic Model ICT, Camino Laboratories OLM
- potential risk of infection
- does not allow CSF drainage
- doesn't require penetration of brain tissue

d. ***epidural transducer***
- a small area of dura is freed from the cranium & the devices may have percutaneous wires or be fully implanted
- largely unsuccessful, due to problems with ***calibration*** and system stability over time
- more recent systems have improved accuracy, allowing placement in ICU
- potential risk of ***infection***
- does not allow CSF drainage
- doesn't require penetration of brain tissue

- the incidence of ***infection*** **~ 2-7%** with monitoring ≥ 5 days, and the risks are slightly greater with dural penetration
- ***intracranial haemorrhage*** may be associated with coagulopathy or difficulty during insertion
- with all methods, the zero reference point of the transducer is usually taken as the external auditory meatus
- hydrostatic potential differences between the heart and the brain need to be evaluated when calculating CPP

Intracranial Hypertension

Def'n: ***sustained*** pressure with the subarachnoid space ³ **20 mmHg***

variable definitions & lack of agreement*
Cucchiara (ASA) states a figure of ≥ 40 mmHg
other authors use upper limits of 15-25 mmHg

• this definition is somewhat arbitrary, as there are patients who tolerate levels higher without difficulty and those who demonstrate decompensation at lower pressures

▪ ***Compensatory Mechanisms***

a. ***CSF displacement*** to the spinal SA space

b. ***CSF reabsorption***
   i. by the arachnoid villi - pressure dependent up to ~ 30 mmHg ICP
   ii. intraventricular transependymal CSF reabsorption

c. reduction in CBV via compression of the ***venous sinuses***
   • results in collapse of the bridging veins entering the saggital sinus and back-pressure to the capillary bed with further elevation of ICP

d. obliteration of cisternal and convexity CSF spaces →
   i. distortion of CSF reabsorptive pathways & vicious cycle
   ii. ***craniospinal disparity*** → ICP ≠ LP pressure

• cerebral compensation is described in terms of ***compliance***, however the true relationship is $\delta P/\delta V$, or ***elastance*** (Miller 54-9 p1751)
• tissue expansion leads to pressure gradients within the cranium and localised pressure on certain areas of brain tissue
• thus, ***focal ischaemia*** is usually evident prior to ***global ischaemia***
• the brain initially attempts to compensate for this by decreased CVR and increased CBF, however, this is self limiting due to the accompanying increase in ICP
• ICP ***A waves***, or Lunberg's plateau, lasting 10-15 minutes ± neurological deterioration, may be due to this effect
• ***cerebrovasomotor paralysis*** occurs as the areas of ischaemic tissue increase and global autoregulation fails
• this is often heralded by the development of ***Cushing's triad***,

1. intracranial hypertension
2. arterial hypertension
3. reflex bradycardia

• under these circumstances the normal compensatory mechanisms become counterproductive and central to the generation of ***global ischaemia***

ICP Wave Types	
A waves:	• Lunberg's plateau • large waves, 5-20 min duration £ **50-100 mmHg** • associated with a ***baseline ICP*** > **20 mmHg** • exhaustion of intracranial spatial compensation • associated with increased CBV & decreased CBF • ? due to a variable CPP with intact autoregulation **** pathological ****
B waves:	• rhythmic (1/min) oscillations £ **50 mmHg** • partly related to depression of consciousness • often associated with periodic breathing • usually disappear with mechanical ventilation
C waves:	• rhythmic (4-8/min) oscillations £ **20 mmHg** • associated with Traube-Herring-Mayer BP waves

- ***Aetiology of Intracranial Hypertension T.Oh***

a. ***intracranial***
   i. head injury
   ii. tumours
   iii. subarachnoid haemorrhage
   iv. intracranial haemorrhage
   v. hydrocephalus
   vi. pseudotumour cerebri
   vii. post ischaemia ?? oedema omitted
   viii. infective

b. ***extracranial***
   i. hypertension - strokes
      - encephalopathy
   ii. impaired venous drainage
   iii. infection - SIRS
   iv. metabolic encepalopathy
   v. Reye's syndrome
   vi. osmolar imbalance
   vii. dialysis related
   viii. hypoxia & hypercarbia

■ *Intracranial Hypertension T.Oh*

• these produce raised ICP by 1, or a combination of 4 mechanisms,

1. intracranial ***mass effect***
2. ***CSF*** retention
3. increased cerebral ***blood volume***
4. cerebral ***oedema***

NB: management is then directed at these 4 mechanisms

Management of Raised ICP		
Cerebral Oedema	• fluid restriction	
	• diuretics	- osmolar - tubular
	• control of osmolality	
	• control of MAP	
	• hyperventilation	
	• steroids	
	• increase CVR	- barbiturates
	• surgical decompression	
	• hypothermia	
Increased CBV	• positioning	- venous drainage
	• control of MAP	≡ autoregulation - sedation/analgesia - muscle relaxants - normovolaemia ? vasodilators/pressors ? β-blockers ? inotropes
	• hyperventilation	
	• increase CVR	- barbiturates
CSF retention	• shunting procedure	
	• diuretics	- osmolar - tubular - acetazolamide
Mass effect	• surgical decompression	

■ *Aetiology of Intracranial Hypertension* *Cucchiara ASA*

• another method for grouping patients is,

a. disordered CSF regulation - hydrocephalus
- posterior fossa lesions

b. tumours - neoplastic
- haematoma

c. head trauma

d. mixed - bleeding cerebral aneurysm
- haemorrhage within a tumour or AVM
- metabolic encephalopathies
- hypertensive encephalopathy

• problems related to ***CSF regulation*** generally share a number of features,

1. the onset of symptoms & decompensation is rapid
2. relief of the pressure by drain or shunt is relatively simple
3. upon relief of obstruction recovery is usually rapid

NB: this group tolerate anaesthesia reasonably well irrespective of the approach, as compensatory mechanisms are rarely exhausted and surgery is short with complete correction of ICP

• those associated with ***neoplastic lesions*** are,

1. slower in onset and represent impending loss of compensatory mechanisms
2. are associated with more complex surgical procedures
3. are complicated by the tendency of the brain to extrude through the open craniotomy
4. recovery is usually slower, despite the return of a "normal" ICP

NB: anaesthetic technique is important, compensation may be exhausted and the time frame from induction to alleviation of ICP may be sufficient for irreversible damage

• ***head trauma*** cases tend to be,

1. rapid in onset
2. associated with limited in efficacy of surgical procedures
   - these may be limited to placement of monitoring devices
3. often in need of other surgery

NB: little is known about the impact of anaesthetic technique, with head injury, in respect to neurological outcome

Symptoms & Signs of Raised ICP	
Raised ICP	• headache • vomiting • papilloedema
Brain deformation	• headache, vomiting, drowsiness • decerebrate rigidity • 3rd nerve palsy • bradycardia, hypertension • abnormal respiration • impaired brainstem reflexes • ie. focal CNS signs
Brain ischaemia	• unconsciousness • fixed, dilated pupils • arterial hypertension • apnoea • absent brainstem reflexes

Cerebral Oedema

Def'n: an increase in the water content of the brain tissue

1. ***vasogenic cerebral oedema***
   i. mechanical trauma
   ii. inflammatory diseases
   iii. brain tumours
   iv. hypertensive encephalopathy
   v. late stages of brain infarction

   - most common variety & is due to a breakdown in the integrity of the ***BBB***
   - oedema fluid thus contains serum proteins and spreads throughout brain tissue along fibre tracts (white > grey matter)

2. ***cytotoxic cerebral oedema***
   i. metabolic encephalopathy
   ii. early stroke or hypoxia
   iii. cardiac arrest
   iv. pseudotumour cerebri
   v. chemical toxins - hexachlorophene
   vi. water intoxication - correction of hyperosmolar states

   - these essentially are the result of decreased function of the ***ion pumps*** which normally maintain neuronal integrity

c. ***interstitial cerebral oedema***
   - this results from overdistension with obstructive hydrocephalus and permeation of the brain substance with CSF
   - this is differentiated from vasogenic oedema in that the penetrating fluid contains almost ***no protein***
   - ie. it is a "transudate" of brain ECF, not of plasma

Management of Raised ICP

- ***Cerebral Oedema***

a. **fluid restriction** ~ 1.5-2.0 l/day
- avoid hyponatraemia, hyperglycaemia & water overload
- augments the action of diuretics and reduces rebound on their cessation

b. **diuretics**

i. ***osmolar*** - *mannitol ~ 0.25-0.5 g/kg q6h
- initial effect upon ICP occurs at ~ 10-15 mins and is ***independent*** of diuresis
- hyperosmolality can produce ***transient vasodilatation*** with a rise in ICP and fall in MAP (infuse slowly)
- may be useful for protection in ***focal ischaemia*** in the absence of raised ICP
- transient ***hypervolaemia*** may produce pulmonary oedema & CCF
- hypovolaemia with prolonged use may decrease MAP and CPP
- should be used cautiously in patients with vascular lesions and in elderly patients with atrophy, as rapid decompression may precipitate ICH
- plasma osmolality should be maintained £ **320 mosm/l**
- *preferable to urea as it produces less rebound oedema

ii. ***loop diuretics*** - frusemide ~ 0.5-1.0 mg/kg
- these agents produce systemic dehydration via 3 mechanisms
  1. diuresis mediated brain (& body) dehydration
  2. decreased CSF formation
  3. improved cellular H_2O transport
- slow onset of effect ~ 30-45 min, cf. ~ 15 min for osmotic agents
- frusemide is the agent of choice in the presence of CCF
- potentiation with dexamethasone in oedema is reported
- also acts synergistically with mannitol, to prolong the osmotic gradient established by the later

c. **steroids** - dexamethasone 4-8 mg q6h
- action via several mechanisms,

i. BBB repair

ii. stabilisation of membranes & lysosomal activity

iii. increased water and electrolyte excretion

iv. changes in cerebral metabolism
- efficacy with oedema associated with ***tumour*** is well established
- the clinical efficacy following head injuries or ischaemia is not established
- note complications with long term therapy
- dexamethasone used due to lack of mineralocorticoid effect

d. **hyperventilation** - P_{aCO2} ~ 25-30 mmHg
- $t_{½}$ ~ 6 hours

e. **blood pressure control** - see below

f. **barbiturates**
- various studies with conflicting results
- not indicated in global hypoxic oedema, but may be of benefit with focal ischaemia
- necessitate the use of invasive intravascular volume and IABP monitoring
- large doses are required to produce electrical silence

~ 12	mg/kg	first hour
~ 6	mg/kg	6 hrs
~ 3	mg/kg	> 7 hrs

g. **surgical decompression**
- rarely used as a last resort in intractable oedema
- may result in adverse tissue shifts
- some favourable reports when used early in Reye's syndrome

■ ***Increased CBV***

a. ***positioning*** - slight head-up position (? no real benefit on CPP)
- avoid excessive neck rotation

b. ***blood pressure control***
- vascular mechanisms are the predominant factor in acute severe head injuries
- aim for a MAP within the "normal" autoregulatory limits
- the use of high levels of PEEP should be avoided
- avoid sudden increases in intrathoracic/venous pressure
- adequate ***sedation ± paralysis*** for procedures
- maintain ***normovolaemia***
- diuresis and volume replacement with colloid has been shown to augment ICP reduction in animal models
- b-***blockade*** may be more appropriate for hyperdynamic states than vasodilators, due to their effects upon CBV
- ***esmolol*** now available in Australia
- ***inotropes*** may be required for intractable hypotension

c. ***hyperventilation*** - P_{aCO2} ~ 25-30 mmHg

d. ***cerebral vasoconstriction***
- barbiturates, benzodiazepines, lignocaine, etomidate
- most are useful at induction of anaesthesia
- lignocaine may be better than STP with hypovolaemia, as it is less of a myocardial depressant

- ***CSF Retention***

  a. ***shunt procedure*** = intraventricular drain or Omaya reservoir
     - extensive CSF drainage of the ventricles is useful for pituitary lesions, aneurysms, AVM's, repair of skull defects and operations on cranial nerves

  b. ***diuretics*** * generally less useful in hydrocephalus
     i. frusemide - decreases formation ∝ Cl^- transport
     ii. acetazolamide - carbonic anhydrase inhibition

- ***Mass Effect***

  NB: = surgical decompression

ANAESTHETIC MANAGEMENT

Patient Positioning

- ***Supine***

• usually with the head rotated to one side for temporal, parietal or occipital incisions
• bifrontal craniotomy and transphenoidal approaches usually leave the head neutral
• this may also be used for the anterior approach to the spinal cord
• extremes of head rotation may result in ***jugular venous obstruction***

- ***Prone***

• usually used for spinal cord and posterior fossa surgery
• ***circulatory stability*** must be ensured prior to prone positioning from supine, as must be the fixation of IV access and the ETT
• maintenance of CVS monitoring during the positioning period is one of the major problems associated with the prone position
• other problems relate to support of the head, either by a horseshoe harness or 3-pin head brace
• a severe complication is ***retinal ischaemia*** and subsequent blindness from excessive ocular pressure combined with a low MAP
• other potential pressure points are the axillae, breasts, iliac crests, groin vessels, knees and penis
• adequate support of the chest and pelvis to allow free movement of the abdomen & diaphragm is imperative
• obstruction leads to increased intra-abdominal, intrathoracic and intracerebral pressures
• elevation of the head during approaches to the posterior fossa increase the risk of ***air embolism***

- ***Lateral "Park Bench"***

• suitable for spinal cord and lateral posterior fossa surgery
• this is a reasonable alternative to the sitting position for a number of surgical procedures
• care is required to ensure the patient does not move after head fixation as this may lead to considerable stress in the cervical spine

■ ***Sitting***

• used principally for posterior fossa and cervical spine procedures
• the use is generally declining due to the potential risk of,

i. VAE and paradoxical VAE
ii. circulatory instability
iii. pneumocephalus
iv. subdural haematoma
v. compressive peripheral neuropathy
vi. quadriplegia
vii. skin pressure lesions

• despite these risks, it may still be used as it provide,

i. better access to midline lesions
ii. improved cerebral venous decompression & CSF drainage
iii. lower ICP

• Black (1988) performed a retrospective study of ~ 600 posterior fossa craniotomies, in the sitting and various horizontal positions, and found ***no evidence*** of increased morbidity or mortality for either group

1. ***VAE* ~ 3x** more prevalent in the ***sitting group***, however, there was no associated increase in clinical sequelae
2. patients in the sitting group lost less blood and required fewer transfusions

• there are various modifications of the sitting position to allow lowering of the head without removal of the head holder, permitting appropriate management should VAE occur
• excessive flexion of the head should be avoided to prevent extra or intraoral pressure ischaemia
• also, extreme flexion of the neck is associated with downward movement of the ETT, with the potential for endobronchial intubation

■ ***Circulatory Instability***

• assumption of the sitting position is associated with mild ***transient hypotension*** in **~ 30%** of cases (δMAP ~ -20 to -30 mmHg)
• ***severe hypotension*** (δMAP ~ -50 mmHg) requiring active treatment occurs in only **~ 2-5%**
• measures to avoid this hypotension include,

a. adequate volume loading prior to positioning
b. compressive leg stockings
c. gradual assumption of the desired position
d. small bolus doses of vasopressor (ephedrine)

• brainstem compression from extreme neck flexion can cause severe bradycardia and hypotension
• abrupt hypertension may occur upon application of the head pins

Venous Air Embolism VAE

• the conditions promoting venous air entrainment are,

1. an open vein
2. a subatmospheric IV pressure
3. a low CVP
4. poor surgical technique
5. highly vascular lesions

• these occur commonly in neurosurgery as the head is elevated above the heart to encourage venous drainage to reduce ICP
• Albin (1978) found the following incidences of VAE, using ***CVC aspiration*** as the method of detection,

a. ***sitting*** **~ 25%**
b. lateral ~ 18%
c. supine ~ 15%
d. prone ~ 10%

NB: current studies, report incidences using ***precordial doppler*** **~ 25-50%**

• older studies, using δBP, oesophageal stethoscope etc., reported incidences of 8-15%
• the use of more sensitive modalities of detection has resulted in an increase in the reported incidence but a decrease in clinical sequelae
• VAE may occur at any stage during a sitting craniectomy, but ***peak incidences*** are found with,

a. skin & muscle incision
b. exposure of the bony venous sinusoids

• VAE may occur remote from the operative site, ie. head pins, burr holes and connections in catheter systems
• once VAE has occurred the factors determining the clinical significance include,

1. the ***volume*** of air entrained
2. the ***rate*** of entrainment
3. the presence of $\mathbf{N_2O}$
4. the presence of a ***patient foramen ovale*** & elevated right heart pressure
5. the patients preanaesthetic ***cardiopulmonary reserve***
6. anaesthetic induced myocardial depression

• rapid injection of large volumes of air produces "foaming" within the chambers of the heart and effective ***EMD*** due to impedance mismatch
• small bubbles introduced slowly are trapped by the lung with a consequent rise in PA pressure
• as the rate on entrainment increases the mean PAP rises further and eventually results in CVS decompensation ± circulatory failure
• bubble trapping increases ***alveolar dead space*** → ↓ **$ETCO_2$**
↑ $PaCO_2$ - $ETCO_2$ gradient

• ***hypoxaemia*** is a late occurrence, and is 2° to a massive increase in pulmonary ***shunt fraction***
• this results from local mediator release & inhibition of hypoxic pulmonary vasoconstriction
• chronic microembolisation with air results in a postoperative increase in vascular permeability which may manifest as an ARDS picture

• ***paradoxical VAE*** may occur via a patent foramen ovale in the presence of raise right heart pressures
• the incidence of a probe ***patent foramen ovale ~ 5-10%*** (Muir ~ 25%)
• monitoring of PAOP & CVP will reveal when right sided pressures are greater and the risk of paradoxical embolism highest
• manoeuvres to increase LAP, ie. volume loading or lowering the head have been advocated
• transpulmonary passage of air is less well documented and controversial
• ***nitrous oxide*** being 34x more soluble than nitrogen will augment the effect of any air entrained into the circulation,

a. 70% N_2O/O_2 → 4x ↑ bubble volume
b. 50% N_2O/O_2 → 2x ↑ bubble volume
c. 30% N_2O/O_2 → 1x ↑ bubble volume

NB: laboratory data has shown that 70% N_2O reduces the LD_{50} of a standard IV dose of air by **~ 3.4x** when compared to a halothane anaesthetic

• guidelines for the use of N_2O during at risk procedures include,

1. the use of sensitive gas emboli detection techniques
2. restriction of the [N_2O] to 50%
3. use of 100% O_2 upon the immediate suspicion of emboli

• some workers argue that the use of N_2O actually enhances the detection of emboli
• however, the inability to effect gas exchange and removal of N_2O following massive embolisation argues against this premise

- ***Management VAE***

1. ventilation with 100% O_2
2. packing of the wound, or flooding with saline
3. lowering of the head
4. unilateral or bilateral jugular venous compression
5. aspiration of air from the right heart if a catheter is present
6. circulatory support - volume loading
   - vasopressors / inotropes

• failure to respond to these manoeuvres requires supine positioning and institution of ***CPR***
• some advocate the ***left lateral position*** as being most likely to result in breaking up of the air lock, however, this has not been established in humans and prevents effective CPR

- ***Pneumocephalus***

• loss of CSF and replacement with air occurs whenever the head is significantly above the heart
• factors which increase this effect include,

i. surgical decompression
ii. diuretics
iii. hyperventilation
iv. the sitting position
v. incorrect connection of CSF shunts

• after closure of the dura, enclosed air may act as a ***mass lesion***
• retention of some intracranial air occurs in,

i. all posterior fossa craniotomies
ii. parkbench ~ 27%
iii. prone ~ 57%

• ***intraventricular pneumocephalus*** occurs in ~ 78% of sitting cases, this being ~ 3-4x more common than in the other two positions
• symptoms are usually mild, with headache, visual disturbance, confusion and lethargy, and require no active treatment
• occasionally high pressures may build up with a ***tension pneumocephalus***
• some believe this is more likely with the use of N_2O, however, others have shown that the cessation of N_2O following closure of the dura in actually associated with a decrease in ICP
• however, when a pneumocephalus is present ***prior to surgery*** N_2O is clearly contraindicated
• tension should be suspected when there is rapid deterioration following posterior fossa surgery, or failure to awaken
• immediate treatment with ~ 100% O_2 may aid in reabsorption, but definitive treatment is ***surgical decompression***

- ***Quadriplegia***

• there are number of reports associated, but not confined to, the ***sitting position***
• the mechanism is uncertain, but may relate to cervical spinal cord compression and SCBF
• avoidance of extreme ***neck flexion***, especially in patients with symptoms referable to the cervical cord, is advisable

- ***Airway Swelling***

• marked swelling of the head and tongue, probably due to obstructed venous return has also been reported

Routine Aspects

1. preoperative assessment
2. premedication
3. drug selection
4. induction
5. maintenance
6. emergence / recovery

- ***Management Goals***

1. prevent acute elevations of ICP
2. maximise cerebral perfusion pressure & O_2 balance
3. provision of a "slack" brain
   i. surgical access
   ii. retractor ischaemia
4. cerebral protection
   i. focal ischaemia
   ii. retractor ischaemia

- ***Preoperative Assessment***

• ***neurological examination*** including documentation of,

a. the patients ***level of consciousness***

b. the presence, or symptoms of ***raised ICP***

c. the existence/extent of any ***focal deficits***

d. ***neuroradiological findings*** - space occupying lesion
   - midline shift
   - extent of oedema

e. muscle wasting, UMN lesions - ***SCh hyperkalaemia***

f. these patients are frequently dehydrated and may have ***electrolyte abnormalities***

g. plus the usual history & examination looking for other ***system diseases***

■ ***Premedication***

• the use of sedative / opioid premedicants is generally avoided in the presence of raised ICP
• lesions such as pituitary or low brainstem tumours, occlusive cerebrovascular disease, or seizure disorders are frequently uncomplicated and the use of premedication justified
• patients with ruptured aneurysms are usually already sedated and this should be continued
• when sedation ± amnesia is required, a small dose of ***benzodiazepine*** will usually not result in CO_2 retention

Monitoring

■ ***Cardiovascular Instability***

• frequently repeated NIBP, or preferably continuous IABP measurement is required during positioning of the patient
• in relatively fit, younger patients frequent NIBP will often suffice
• indications for ***IABP*** are relative and include,

a. advancing age
b. pre-existing cardiovascular disease
c. risk of air embolism
d. possibility of cervical cord or brainstem compression
e. vascular lesions
f. raised ICP $\rightarrow$ CPP = MAP - ICP
g. requirement for deliberate hypotension

• for NIBP taken with a brachial cuff, CPP should be calculated subtracting 10 mmHg per 13 cm the head is above the heart
• when using IABP the transducer should be calibrated to zero at the highest point of the skull

■ ***Venous Air Embolism***

• positioning a CVP catheter tip just proximal to the ***cavo-atrial junction*** allows assessment of intravascular volume status, in addition to diagnosis and treatment of VAE
• any standard CVC approach may be employed, though, in tight patients use of the internal jugular veins should be avoided due to the need for head rotation during insertion and the possible need for vein compression intraoperatively
• there is some debate as to the best location for the catheter tip, and the effectiveness of the technique in removal of air
• clearly the effectiveness depends upon the nature of the embolus, large emboli almost certainly being improved by aspiration
• ***multiorificed catheters*** have been developed in an attempt to improve air removal, and these have been shown to reduce mortality in animal models of VAE
• a number of techniques have been devised to ensure a peripherally introduced catheter is accurately positioned within the heart,

a. CXR - problems with interpretation
   - subsequent movement during positioning
b. pressure waveform monitoring (cf. PA catheters)
c. IV-ECG - potential for microshock
   - use ***biphasic P-wave*** as marker
   ~ 65% migrate from original position (CXR)

• ***precordial doppler*** is the most sensitive, generally applied technique for VAE detection
• under ideal conditions as little as ***0.5 ml*** of air traversing the right heart can be detected
• in only ~ 50% of cases where doppler indicates VAE will air be able to be aspirated from a right heart catheter
• commercially available systems operate at ~ 2-2.5 MHz
• earlier systems suffered with interference from radiofrequency generators within theatre, but later models incorporate suppression circuitry
• the standard position is between the 3rd-6th interspaces at the ***right sternal edge***
• however, there are large patient variations and positioning to the left is frequently required
• this may delay early detection of small bubbles in the SVC, therefore, coincident use of another technique is suggested in these cases
• problems related to movement of the probe during positioning can be obviated by application after attaining the sitting position
• verification of the probe position can be accomplished by injection of 0.5 ml of CO_2

• ***transoesophageal echocardiography*** (TOE, TEE) is ~ 5-10x more sensitive than doppler
• further, due to the visual basis, this method can localise VAE and detect paradoxical VAE
• the disadvantages include,

a. lack of specificity - also detects fat & blood microemboli
b. high cost
c. technically more difficult
d. questionable clinical significance of solitary small emboli

• ***PA catheter*** changes occur prior to changes in MAP or CO with moderate entrainment
• following an embolic episode, the return of pulmonary pressures to normal may be used as a guide to treatment/recovery

• ***$ETCO_2$*** changes tend to parallel those of the PAC in their time course and sensitivity
• changes occur due to a progressive increase in ***physiological dead space***
• as with PAP pressure, this provides a semiquantitative estimate of the volume load of entrained gas within the pulmonary circulation, and may give a guide to the effectiveness of management and physiological recovery
• a reduction in $ETCO_2$ is only a valid indication of VAE when the MAP and CO remain constant

> ***NB:*** ***hypovolaemia & hypotension*** alone, when severe, may similarly cause an increase in physiological dead space, and the P_{aCO2} - $ETCO_2$ gradient

• analysis of ***end tidal nitrogen*** by mass spectrographic analysis has also been used for the detection of VAE
• depending upon the entrainment rate, several studies have found ETN_2 to be slightly more sensitive than $ETCO_2$ in the detection of VAE
• with small emboli, there is little difference between the two
• other methods used to monitor for VAE are largely too insensitive to be used as a primary method, but may act as an adjuvant,

a. oesophageal stethoscope - "mill-wheel" murmur
b. mean arterial pressure
c. central venous pressure
d. ECG changes → these provide little advance warning of CVS collapse

Venous Air Embolism

Monitoring Method	**Sensitivity**[1]
Oesophageal stethoscope	• 1.8 ml/kg/min
Systemic hypotension	• 0.7 ml/kg/min
ECG / tachyarrhythmias	• 0.6 ml/kg/min
End Tidal CO_2	• 0.42 ml/kg/min
PA pressure rise	• 0.42 ml/kg/min
Continuous CVP	• 0.4 ml/kg/min
Doppler precordial stethoscope	• **0.02 ml/kg/min**
Transoesophageal echocardiography	• ?

[1] **≥ 0.5 ml/kg/min** has been shown to result in ***symptoms***

Choice of Anaesthetic

- factors considered important include,
    i. effects upon - CBF, ICP, CPP, $CMRO_2$
    ii. promptness of return of consciousness
    iii. related protection from cerebral oedema/ischaemia
    iv. compatibility with neurophysiological monitoring

- the majority of neuroanaesthesia is accomplished by,
    i. induction with thiopentone
    ii. intubation following nondepolarising muscle relaxation
    iii. maintenance with N_2O/O_2/isoflurane/fentanyl ± Air versus N_2O
    ± propofol by infusion
    iv. mild hyperventilation to a P_{aCO2} ~ 28-33 mmHg

- the vast majority of neuroanaesthesia is achieved with ***artificial ventilation*** and mild hypocapnia
- high respiratory frequencies with limited expiration times may lead to an increased mean intrathoracic pressure and elevation of ICP
- high levels of PEEP can have similar effects
- hypocapnia does not appear to have clinically significant effects upon CSF dynamics
- besides reducing CBF, ***extreme alkalosis*** may have the following effects,
    i. reduces the dissociation of HbO_2
    ii. increases total body MRO_2, which may be problematic in the presence of pulmonary disease and a high shunt flow
    iii. may reduce coronary blood flow
    iv. may lower cardiac sympathetic outflow

- some recommend ***spontaneous ventilation*** for operations on the posterior fossa to identify brainstem compression
- however, most would argue that observation of HR and rhythm, MAP and ECG provides adequate warning, due to the proximity of the cardiac and respiratory centres, ie. ***selective compression*** is highly unlikely
- there have, however, been several case reports of selective depression in microscopic tumour removal from the floor of the 4 th ventricle

• ***all*** of the ***volatile agents*** will increase ICP if used to obtain deeper levels of anaesthesia in the presence of normocarbia
• this is seldom the case, and ~ 1-1.5 MAC are used in association with mild hyperventilation avoiding significant rises in ICP
• the greatest reduction in CVR and increase in ICP is afforded by ***halothane***
• this effect is blunted, or eliminated by the prior establishment of hyperventilation
• ***isoflurane*** similarly increases ICP but this effect may be avoided by simultaneous, ie. not prior, establishment of hypocarbia in tumour patients
• in patients with severely decreased $CMRO_2$, due to disease or following barbiturate administration, the vasodilating properties of halothane and isoflurane are ***similar***
• there is some date to suggest that patients with midline shift on CT are more likely to suffer raised ICP with isoflurane anaesthesia (not striking)
• nonetheless, the safety of isoflurane cannot be assured under all conditions

• ***nitrous oxide*** results in dose-dependent elevations of CBF and CBV when administered under normocarbic conditions to established volatile anaesthesia
• the CBF/CBV effect of N_2O is ablated by the administration of,

i. hypocapnia & isoflurane * not halothane
ii. barbiturates or benzodiazepines

NB: the effects of N_2O on CBF are ***less*** than any of the volatile agents, are more ***easily titrated***, and are more effectively ***blunted*** by concomitant drug administration; therefore, when used appropriately, N_2O remains a useful agent

• with the exception of ketamine, the ***intravenous agents*** (thiopentone, propofol, fentanyl) all decrease CBF and $CMRO_2$, provided ventilation and P_{aCO2} are controlled
• thiopentone safely produces a balanced decrease in both to ~ ½ baseline
• this is associated with a marked reduction in ICP
• the effectiveness of thiopentone as a cerebral protective agent should probably be limited to the experimental conditions for which protection is most solidly demonstrated, ie.

cerebral ischaemia by vascular occlusion techniques

• protection by lowering ICP for cerebral tumour patients is a distinctly different proposal
• ***etomidate*** reduces $CMRO_2$ and CBF to a lesser degree
• its advantage is its haemodynamic stability, though, it is known to produce myoclonus and possible seizure activity
• ***propofol*** reduces both CBF and $CMRO_2$, however may result in a precipitous fall in CPP in patients with raised ICP (~ 50%)
• ***lignocaine*** is also useful for short-term reduction in ICP due to coupled $CMRO_2$/CBF effects
• this is in addition to its ?direct/?indirect effects in blunting cerebral arousal and the cardiovascular response to intubation
• of the short-acting opioids, ***fentanyl*** has been studied most completely
• it results in a fall in CBF slightly ***greater*** than the fall in $CMRO_2$
• although this can theoretically contribute to cerebral ischaemia, it is of little significance clinically
• fentanyl remains a useful agent as it does reduce ICP and is effective in blunting the haemodynamic responses to intubation & head-pin application
• sufentanyl and alfentanyl both potentially increase CBF & ICP, though, comparison between these agents in tumour patients showed no significant difference in outcome

■ ***Choice of Muscle Relaxant***

• succinylcholine is unequalled in achieving rapid total paralysis for rapid sequence intubation
• however, there is still controversy over the potential increase in ICP
• this is probably ***clinically insignificant*** except in the most extreme cases of intracranial hypertension
• one study showed a mean increase from 15 to 20 mmHg with suxamethonium
• this has been attributed to CNS arousal from ***muscle spindle efferent*** input, and is therefore significantly decreased by a "priming" dose of nondepolarising agent
• as complete flaccid paralysis is desirable prior to intubation, ***monitoring*** of peripheral nerve TOF is desirable
• the "priming principle", and/or high doses can be used for relatively rapid airway control
• the shorter acting agents, atracurium and vecuronium are well suited to paralysis for intubation with raised ICP
• both have little effect on either ICP or cardiovascular stability
• pancuronium used alone may produce a tachycardia and elevation of MAP

NB: when there is conflict regarding transient elevation of ICP and the requirement for prompt airway control, the later takes precedence as hypoxia and hypercarbia are more harmful than the transient rise in ICP produced by SCh

• ***rocuronium*** may become a useful agent for rapid establishment of paralysis when available

• ***hemiplegia*** from cerebral ischaemia is associated with differing responses to nondepolarising relaxants on the 2 sides of the body
• muscles on the affected side are relatively ***resistant*** to blockade
• as the side contralateral to the tumour is usually adjacent the anaesthetist and more amenable to monitoring, there are 2 possible consequences,

1. a ***relative overdose*** may be administered, making timely reversal difficult
2. this ensures movement during the procedure is unlikely, as the most resistant muscles are monitored

• the use of succinylcholine in such patients is associated with the risk of ***hyperkalaemia***
• the time course of such sensitivity is not well defined, with case reports from,

a. 1 week to 6 months following the onset of hemiplegia
b. 3 days following SCI
c. 3 days following burns

Control of ICP During Induction

1.	thiopentone		~ 2-3 mg/kg
2.	fentanyl		~ 3-5 µg/kg
3.	nondepolarising relaxants		- PNS → TOF = 0
4.	hyperventilation		- hypocarbia, hyperoxia
5.	intubation		
	i.	deepen anaesthetic	- supplemental STP, propofol - ***lignocaine*** **~ 1.5 mg/kg**
	ii.	β-blocker	- ***esmolol*** **~ 1.5 mg/kg**
	iii.	technique	- prompt, minimise stimulation

NB: the ***timing*** of events is equally as important as the method

- some authors advocate voluntary ***hyperventilation*** prior to induction
- others have shown that application of the face mask to an awake patient may be associated with a transient elevation of ICP
- ***thiopentone*** is the mainstay of management due to its effects in reducing ICP and ease of use
- however, it is a short acting agent and if used prior to nondepolarising relaxants, which may take up to 3 minutes for complete loss of train of four, may have redistributed sufficiently from brain for CBF to have returned to near baseline values
- a supplementary dose of thiopentone ~ 30-45 seconds prior to intubation will blunt this response
- other supplementary agents (β-blockers, lignocaine) blunt the hypertensive, and hence CPP, responses to intubation
- increased anaesthetic depth with volatile agents should be accomplished by increasing the ***exposure time***, rather than by the use of ***overpressure***, as the CBV effects of the volatile are dose-dependent
- some authors are concerned about increases in CBF, $CMRO_2$ and ICP in response to $\mathbf{N_2O}$
- although these effects are supported by animal studies, they are readily avoided by concomitant use of thiopentone and/or hyperventilation

- ***suxamethonium*** can result in an elevation of ICP by raised intra-abdominal/intrathoracic pressure and via a complex mechanism involving muscle spindles
- these effects are similarly eliminated by use of thiopentone and suxamethonium is therefore only ***relatively contraindicated***
- where airway protection is required rapidly this is still the agent of choice
- nondepolarising agents are generally preferred as they do not increase ICP
- control of ***mean arterial pressure*** is important, as in areas of diseased brain there may be loss of autoregulation and an exacerbated response to alterations of perfusion pressure
- blunting of the haemodynamic response may be achieved with additional thiopentone, propofol, fentanyl, lignocaine, esmolol, or nitroprusside
- a multicentre trial in the states using an infusion of esmolol from 5 minutes preinduction for a total of 12 minutes resulted in excellent control of HR and MAP

Intraoperative Management of the "Tight" Brain

1.	position	- eliminate venous obstruction - maintain slight head-up
2.	ventilation	- hypocarbia and hyperoxia - check with **AGA's**
3.	anaesthetic agents	- eliminate volatile ± N_2O - supplemental thiopentone / fentanyl ± propofol infusion
4.	muscle relaxation	- check TOF, or PTC
5.	diuretics	- osmotic - loop agents
6.	spinal fluid drainage	
7.	steroids	
8.	pneumocephalus	

NB: when the dura is bulging through the craniotomy, anaesthetic manoeuvres are ***unlikely*** to alter the situation, however, correctable factors above should be remedied

• the usual cause of profound intracranial hypertension is the ***tumour mass*** itself, or surrounding oedema
• piecemeal removal may allow enlargement of the dural opening and adequate exposure
• an ominous cause is ***occult haemorrhage*** into the tumour, this may be accompanied by,

a. development of sudden ***hypertension***, without obvious cause
b. hypertension ***resistant*** to increases in anaesthetic depth
c. initial tachycardia, followed by ***bradycardia***

• these changes are usually masked by the polypharmacy of general anaesthesia
• because of the effects upon CPP, reduction of MAP in the face of possible haemorrhage may be unwise prior to decompression of the surrounding brain
• despite the overall safety of the volatile anaesthetics, it may be prudent to avoid their use in extreme situations
• there may be no causal connection between the use of a volatile and brain size, however, avoidance of their use eliminates any such possibility
• similarly, N_2O is unlikely to be causally related, however should be avoided when the brain is particularly tight
• acute administration of a "sleep" dose of thiopentone can be expected to reduce ICP and a lack of any visible response to STP suggests a serious situation
• patients receiving anti-epileptic agents may show an increased clearance of nondepolarising relaxants
• return of abdominal and thoracic muscle tone may increase central venous and therefore ICP

- the effects of ***mannitol*** depend upon the integrity of autoregulation,

a.	intact autoregulation	- no change in CBF ~ 27% decrease in ICP @ 25 min
b.	impaired autoregulation	~ 5% increase in CBF ~ 18% decrease in ICP @ 25 min

- ***frusemide*** in fairly large doses (≥ 80 mg) also reduces ICP, but the exact mechanism is unclear
- ***CSF drainage*** is a rapid and effective mechanism of directly reducing intracranial bulk
- this can be achieved with either a needle or catheter technique
- rarely since the advent of MRI, pneumocephalus may have been present from prior examination and exacerbated by the use of N_2O

■ ***Specific Monitoring for Supratentorial Brain Tumours***

1.	direct arterial blood pressure	
2.	capnography	± arterial gas analysis
3.	central venous pressure	± placement in the right atrium
4.	monitoring for VAE	= precordial doppler
5.	? ICP	

Effects of Anaesthetic Agents on ICP			
Anaesthetic	**Hydrocephalus**	**Neoplasm**[1]	**Head Trauma**
IV Agents			
• STP	**-**	**--**	**-**
• Opioids	**0,-**	**0,-**	**0,-**
• Etomidate	**?,-**	**-**	**-**
• Ketamine	**++**	**+++**	**+++**
• Propofol	**?,0,-**	**-,0**	**?,-**
Volatile Agents[2]			
• Isoflurane	**?,0**	**?,+,-**	**?,0,+**
• Halothane	**0,+**	**0,++,-**	**?,+**
• Enflurane	**?**	**0,++,-**	**?,+**
Nitrous Oxide			
• alone	**?**	**+**	**?,0,++**
• supplement		**0**	**?**

[1] ? = little data, 0 = no change, (+) = increase, (-) = decrease

[2] hypocapnia and low concentration

FLUID MANAGEMENT IN NEUROSURGICAL PATIENTS

• important with regard to,

a. cerebral perfusion - maintenance of MAP, CPP
± effects on blood rheology

b. oedema formation

c. plasma glucose concentration

d. correction/prevention of abnormalities of Na^+/H_2O

Oedema Formation

• there are 3 relevant pressure gradients,

1. ***hydrostatic***
2. colloid ***oncotic*** pressure - relatively weak
~ 50% δCOP ≡ᵗ ~ 1 mosm/l
3. ***osmotic*** pressure

• the effective capillary pore size outside the CNS ~ 65 Å
• this allows free passage of small ions but inhibits the movement of proteins
• the effective capillary pore size within the CNS ~ 7-8 Å
• this is small enough to prevent the free movement of Na^+, only H_2O moves freely
• in other tissues the ECF space is relatively compliant and changes in COP can result in significant fluid shifts
• in normal brain, ECF is relatively ***noncompliant*** and changes in COP ***do not*** usually result in oedema formation
• investigations of manipulation of osmotic & oncotic pressure show that,

a. reducing ***plasma osmotic pressure*** by the administration of free water results in the formation of oedema in ***all tissues***, including brain (D_5W, ½N.saline)

b. reduction of ***colloid oncotic pressure*** with the maintenance of serum osmolality is associated with the formation of oedema in most tissues, but ***not*** in normal brain

c. in the setting of ***brain injury***,
   i. reduction of serum osmolality increases oedema formation & ICP
   ii. most of these changes are attributable to effects in areas of normal brain ie., areas where the BBB remains intact

d. investigations with reduction of COP with careful maintenance of serum osmolality ***do not*** demonstrate an increase in oedema in injured brain

• however, there are numerous studies which do show that there is an increase in oedema formation with reduction of COP
• Drummond (ASA 1991) states these ***do not*** establish cause/effect between COP changes and the formation of oedema

• several of these studies have used ***Hartmann's solution*** as the diluting medium, and this is not an isotonic solution (osmolality ~ 273)
• many of the studies have been confined to the first 24 hours and there are suggestions that the effects of crystalloid resuscitation may not be evident until 48 $^{+}$ hours following resuscitation
• many neurosurgeons & traumatologists have anecdotally reported the sudden appearance of oedema ~ 48 hours post-crystalloid resuscitation
• the occurrence of this phenomenon has not been demonstrated in a controlled experiment
• it has been hypothesised that areas adjacent to injured brain may have altered capillary permeability, similar to that of non-brain tissues
• 2 studies looking at ***cryogenic injury*** and lowered oncotic pressure failed to show any alteration of capillary permeability from the centre of the lesion to normal brain
• although the model of cryogenic injury is widely accepted as being representative of CHI, this is not proven

NB: because of these uncertainties, pending definitive proof that lowered COP alone is not deleterious, regimens that ***substantially*** reduce COP should be avoided

1. ***colloid solutions***
   - i. albumin - satisfactory but expensive
   - ii. dextran - impairs platelet function
   - iii. hetastarch - decreases FVIII activity
     ≤ 20 ml/kg/day in head injury patient
2. ***hypertonic solutions*** - 3% NaCl
   - laboratory data suggest these are effective for resuscitation and result in less cerebral oedema & elevation of ICP
   - this is consistent with the impermeablility of cerebral capillaries to Na $^{+}$
   - experimental at present due to the uncertainty about the effects of the very high plasma [Na^{+}] which follow its use
3. ***mannitol*** ~ 0.25-1.0 g/kg
   - causes a transient *increase* in cerebral blood volume
   - ? transient increase in ICP, but no clinical support
   - increases intravascular volume & may precipitate ***CCF*** in an unstable patient
   - some support for the use of large doses ≤ 2 g/kg,
   - increases CBF by an unknown mechanism, ??
     - i. a ***rheological*** effect on rbc's
     - ii. ***haemodilution*** from increased vascular volume
     - iii. dehydration of brain ECF decreasing ***extravascular resistance***
   - common practice to maintain serum ***osmolality ≤ 325 mosm/l***
   - there is little direct evidence for this limit and it stems from concerns about tissue effects of high osmolality, especially renal tubules & neurones
   - administration may lead to depletion of the intravascular volume 2° to ***diuresis***
   - also, concerns regarding accumulation in damaged areas of brain (? no evidence)

Maintenance of Cerebral Perfusion

• normally protected by ***autoregulation***, the acutely damaged brain is susceptible to minor, or ***secondary insults*** such as hypotension or hypoxia
• this has been demonstrated in the laboratory following both mechanical and ischaemic insults
• this concern has altered the management of acute aneurysm patients
• as these are being operated on earlier, when autoregulation may be markedly impaired, the past practice of induced hypotension has been abandoned by many institutions
• alternatively the degree and duration has been limited in others
• despite the recent evidence of the effectiveness of ***nimodipine*** in vasospasm, the mainstay of therapy remains - "triple-H therapy",

1. ***hypervolaemia***
2. ***hypertension***
3. ***haemodilution***

• of these it is likely that ***hypertension*** is the most important component
• haemodilution / hypervolaemia probably works on the basis of ***rheological*** changes
• some groups use DDAVP to sustain the effects of acute volume administration

• ***haemodilution*** has been shown to improve CBF and other measures of outcome in experimental focal cerebral ischaemia
• however, clinical trials to date have shown little benefit
• this may reflect a delay in institution of therapy or inadequate haematocrit reduction
• theoretically a ***haematocrit ~ 30-33%*** gives the optimal DO_2 and viscosity profile
• in 1 study a subgroup of patients who were treated within 12 hours showed some benefit

■ ***Plasma Glucose***

• the observation that an elevated plasma glucose prior to an ischaemic event can adversely affect neurological ***outcome*** has been made in numerous animal experiments
• supposedly this relates to increased lactate formation and a lower intracellular pH
• it has been shown that intra-ischaemic pH deterioration correlates well with the pre-ischaemic plasma glucose level
• however, it has ***not*** been shown that ***lactate*** is the mediator of this effect
• there have not been convincing studies of the relevance of pre-ischaemic plasma glucose in man
• one study looked at plasma glucose at the time of hospital admission for cardiac arrest victims
• though a high glucose correlated with poor outcome, this may have in fact reflected ***prolonged resuscitation***, which is known to correlate with an adverse outcome
• despite these questions it is standard practice to withhold glucose containing solutions except where specifically indicated, ie. hypoglycaemia

■ ***Sodium & Water Homeostasis***

• ***diabetes insipidus*** occurs most commonly following ***pituitary surgery***, but is also seen with other cerebral pathology, notably ***head injury***
• the onset is usually ~ 4-6 hours postop. with the production of large volumes of dilute urine
• diagnosis is by simultaneous urine and plasma osmolarities
• urine ***specific gravity*** is less precise but a useful and more rapid bedside test

→ SG < 1.002 in true DI

• appropriate management includes either,

a. replacement of ~ 3/4 of the hourly urine output
plus, normal maintenance fluids, or

b. (U/output - 50 ml) plus normal maintenance

NB: replacement of the entire U/output has the potential for ***progressive hypervolaemia***

• the choice of fluid replacement will be governed by serum biochemistry
• use of large volumes of D_5W has the potential to produce hyperglycaemia, which may exacerbate the polyuria
• if the U/output is > 300 ml/hr for two consecutive hours it is standard practice to administer either aqueous vasopressin q4h or ***DDAVP***

• ***SIADH*** occurs most often in association with ***head injury***,

a. iso-hypervolaemic hyponatraemia
b. continued urinary Na^+ losses - $[Na^+]_{urine}$ > 20 mmol/l
c. severe hyponatraemia < 110-115 mmol/l
- hypertonic saline ± frusemide
d. ***central pontine myelinolysis*** - too rapid correction
e. aggressive correction in the presence of seizures,
should be slowed once these are controlled to ≤ 2 mmol/l/hr

• the existence of a ***cerebral salt wasting syndrome*** is argued by some authors
• it is thought to be seen most often in association with SAH, and is characterised by,

1. hyponatraemia
2. ***hypovolaemia***
3. high $[Na^+]_{urine}$ > 50 mmol/l

• the aetiology is unknown, though, there is increased secretion of ***ANF***
• the distinction from SIADH is important, the later being characterised by isovolaemia/mild hypervolaemia and is managed by fluid restriction
• management is by administration of isotonic salt solutions to maintain normovolaemia

NB: fluid restriction is the presence of hypovolaemia may be especially deleterious in the setting of SAH & vasospasm, where the syndrome is most often seen

- with the exception of SIADH, the old teaching to "run 'em dry" post neurosurgery is incorrect
- this stems from a time when resuscitation fluids were hypotonic and administration of large volumes could produce cerebral oedema
- the aim of therapy should be to maintain ***isovolaemia*** and avoid any reduction in serum osmolarity ± oncotic pressure
- except in the case of SAH and vasospasm when hypervolaemia is desirable

Summary

1. ***hypoosmolality*** causes cerebral oedema (ie. free water)
2. effects of ***colloid osmotic pressure*** are far less important, however, a dramatic reduction of COP should be avoided
3. any brain injury predisposes the brain to ***secondary insult***
4. ***glucose*** should be withheld in the absence of hypoglycaemia
5. management of ***diabetes insipidus*** should protect against,
   i. hypovolaemia
   ii. forced fluid overload
   iii. progressive hyponatraemia / hypo-osmolality
6. ***hyponatraemia*** may reflect either SIADH or cerebral salt wasting, distinction between the two is important in subsequent management

CEREBRAL FUNCTION MONITORING

• the techniques most commonly available in operating room include,

1. electroencephalogram (EEG)
2. evoked potentials
3. electromyogram

• by pattern recognition, an experienced encephalographer can readily distinguish between consciousness, unconsciousness, epilepsy, sleep and coma
• correlation between the EEG pattern and the depth of anaesthesia is less clear
• this may be due to the wide variety of anaesthetic agents used, or that each electrode only records the activity of the adjacent cortex and the anaesthetic agents have varied effects on different regions of the brain

• evoked potentials are exceedingly small and repeated sampling and electronic summation and averaging techniques are required to extract the EP from the background EEG
• practically all of these are evaluating ***sensory pathways***, and there are three basic types,

1. SSEP - somatosensory evoked potentials
2. BAEP - brainstem auditory evoked potentials
3. VEP - visual evoked potentials

The Standard EEG

• the recording electrode (silver) impedance ~ 5 k Ω to permit clear EEG signals **~ 10-50 µV**
• as the electrode impedance increases the signal to noise ratio decreases
• the standard montage is the **"10-20" *system***, a symmetrical array of scalp electrodes,

a. 10% of the circumferential distance above the inion & external auditory meatus, and
b. 20% of the circumferential distance apart
c. 20 electrodes, several outside the recording field
d. ***16 channel*** recording, 3 basic parameters,
   i. amplitude - µV
   ii. frequency - Hz
   iii. time - real (standard)
   - epoch (processed)

NB: the conventional scalp EEG records from the surface of the brain & is referred to as the ***electrocorticogram***

■ ***Normal EEG***

• the usual base frequency in the awake state ~ β-range (> 13Hz)
• this high frequency signal is usually low amplitude in the attentive brain
• closure of the eyes immediately adds signals from the α-range (8-13 Hz), which are of slightly higher amplitude
• this range is usually used as the reference signal during anaesthesia
• events which lead to ***higher*** frequency patterns → ***activation***
• events which lead to ***lower*** frequency patterns → ***depression***,

a. β-waves > 13 Hz
b. α-waves ~ 8-13 Hz "BATD"
c. θ-waves ~ 4-7 Hz
d. δ-waves < 4 Hz

• ***all*** of these waveforms may be present in the sleep EEG, with slower frequencies and " ***sleep spindles***" in the deeper planes
• during ***REM sleep*** the EEG becomes activated, and the ***eye muscle EMG*** appears on the EEG
• general characteristics include,

a. symmetrical
b. patterns are predictable
c. spike waveforms are ***absent***
d. cannot be used to predict normal brain function

■ ***Abnormal EEG***

• general characteristics include,

a. ***asymmetry***
   i. tumour
   ii. epilepsy
   iii. infarction
   iv. infection
b. patterns of amplitude & frequency that are ***unpredictable***
c. ***spike waveforms*** *epilepsy

• ***global*** distortions of the EEG are not asymmetrical, thus there is no "normal" side with which to compare
• the clinical setting is important in assessment of these situations, eg. epilepsy, hypoxia, anaesthetic agent effects

Processed EEG

- only recently available due to the increased microprocessor power
- there are 5 general assumptions when using a processed tracing,

1. changes will be in ***amplitude***, ***frequency*** or both, and any display system which preferentially emphasises either will miss changes in the other
2. as the signal becomes more electronically remote, a point is reached where it become almost impossible to relate knowledge of the raw data to the processed signal
3. the standard 16 channel recording provides more information than can consistently be utilised in the processed EEG, and more than is needed for intraoperative use
4. since the processed EEG is derived from raw data, it cannot contain more information than is in the original recording
5. some of the diagnostic changes will be unilateral and some bilateral, thus recording of both hemispheres is necessary

NB: the "***gold standard***" remains a chart recorded, 16-20 channel EEG, analysed by an experienced encephalographer

▪ *EEG Processing*

- there appear to be certain ***key frequencies*** for analysis of EEG data
- thus, one of the simplest forms of data processing involves,

a. filtering - frequencies > 20 Hz & < 4 Hz

b. amplification - frequencies **~ 4-10 Hz** (? MCQ)

c. the ***power***, (= amplitude^2), can be displayed for each hemisphere,

4. ***cerebral function monitor*** CFM

5. ***power spectrum analysis*** PSA-1

- PSA involves ***Fourier conversion*** of the irregular EEG waveform to the corresponding sinewave components, of definite frequency and amplitude
- the 3 dimensional display may show time and amplitude, as ***power***, on one axis and ***frequencies*** on the other → ***compressed spectral array*** (Neurotrac, RDM 35-3, p1188)

- the same data can be represented in 2 dimensions by increasing the density of dots at various frequencies → ***density modulated spectral array DSA***

- another technique for processing EEG data is ***aperiodic analysis***
- each waveform is analysed without an averaging technique
- the signal is broken into 4 component frequencies (β to δ-waves), with the amplitudes at each frequency in each hemisphere
- a commercial algorithm which emphasises the amplitude is used in the "Lifescan" brain monitor
- this uses power emphasis to "map" brain areas in the "Cerebral Tracer"

- ***Data Acquisition Period***

• cf. the standard EEG which runs in ***real time***, most of the processing units divide the data into ***epochs***, which they then analyse and display
• there is a good correlation between the epoch interval and the resolution of the information supplied,

a. if the epoch is infinite, then the waveform can be describe precisely
b. if a small interval is chosen, 3 factors decrease resolution,
   i. the sample may not be representative
   ii. the nature of the data window
   iii. too few data points for Fourier transformation

• a longer epoch will reduce the epoch to epoch variability and allow more precise description of frequency and power
• however, this will increase the time delay for updating of the information, and reduce the ability to assess intraoperative changes
• in studying epochs from 2-32 seconds, Levy concluded that a ***2 second*** epoch was appropriate for intraoperative monitoring
• however, the presence of ***burst-suppression*** is an exception, as sampling during either period will produce biased information
• this is not considered to be a major problem as this pattern is readily recognised on the raw EEG

Anaesthetic Changes in the EEG

• factors which affect the EEG in relation to anaesthesia include,

a. anaesthetic agents
b. surgery
   - cardiopulmonary bypass
   - carotid endarterectomy
c. pathophysiology
   - epilepsy
   - hypoxia
   - hypotension
   - hypothermia
   - hypo/hypercarbia
   - CVA's
   - brain death

• all anaesthetics do not produce the same changes, thus making correlation between anaesthetic depth and EEG analysis virtually impossible

Barbiturates

• all of the agents used clinically appear to have a similar effect
• they produce an ***initial rapid sequence*** of fast waves ~ 20-30 Hz, which starts in the frontal regions and spreads to the occiput
• this is followed by the superimposition of ***barbiturate spindles*** ~ 5-12 Hz
• these then decline as dosage is increased and large polymorphic waves ~ 1-3 Hz develop
• if the drug is injected rapidly, the tracing proceeds almost immediately to the ***slow wave*** pattern, which corresponds with the onset of ***surgical anaesthesia***
• as the dose is increased further, periods of ***suppression*** begin to appear, each followed by ***bursts*** of renewed activity which contain high frequency components
• these bursts of activity start in the 8 Hz range & decline to 2-6 Hz
• the length of the suppression periods increases as the total dose increases until total ***electrical silence*** ensues

Opioids

• the effects produced by high dose fentanyl (30-70 μg/kg) are fairly consistent
• after ~ 1 minute the α-rhythm becomes slower and broader
• within 3 minutes diffuse θ-waves (4-8 Hz) are seen with some δ-activity (< 4 Hz)
• this is followed by irregular, diffuse slow δ-waves, which can become more synchronous producing a monomorphic EEG picture
• at the lower doses (30 μg/kg) the EEG activity is faster
• there can be isolated sharp-wave activity, especially in the fronto-temporal region
• the frequency of this occurrence increases with increasing dose (20%-80%)

Ketamine

• EEG changes appear to represent activation of the thalamic and limbic structures, producing hypersynchronous δ-waves
• there is no information regarding EEG and emergence reactions

Benzodiazepines

• midazolam produces an initial increase in amplitude, predominantly θ-wave
• increasing doses produce high amplitude activity < 8Hz
• burst/suppression ***does not*** occur, neither does electrical silence

■ ***Volatile Anaesthetics***

• subanaesthetic concentrations of ***isoflurane*** yield 15-30 Hz activity, predominantly frontal areas
• at 1 MAC, 4-8 Hz waves dominate
• at 1.5 MAC, the amplitude increases and the frequency falls to 1-4 Hz
• suppressions first appear at 1.5 MAC and ***electrical silence*** **~ 2-2.5 MAC**
• there are on occasions isolated spike-waves with suppression at 1.5-2.0 MAC

• ***enflurane*** similarly produces fast-wave activity at subanaesthetic levels
• most patients loose consciousness while this activity is still dominant
• at 1 MAC large 7-12 Hz waves appear
• at 1.5 MAC spikes and ***spike-waves*** appear, followed by ***burst suppression***
• at 2-3 MAC the EEG consists of groups of 2-3, 400-800 µV spike and wave discharges, separated by 5-15 seconds of electrical silence
• EEG seizure activity can be seen with **3%** ***enflurane*** and ***hypocapnia***
• lowered $PaCO_2$ increases the length of burst suppression and decreases the duration of bursts, but increases their amplitude and main frequency component
• the effects on $CMRO_2$ in dogs are similar to ***pentylenetetrazol***, a known convulsant agent

• subanaesthetic concentrations of ***halothane*** yield fast sinusoidal, 10-20 Hz activity, which persists until consciousness is lost
• at 1 MAC and normocarbia, the dominant frequencies are 10-15 Hz
• at 2-2.5 MAC the dominant frequency has slowed to 7.5 & 6 Hz
• this continues until at **~ 4 MAC** most activity is ~ 0.5 Hz
• with halothane, and to a lesser extent the other agents, it is important to separate the direct cortical depressant effects from the decrease in cerebral perfusion 2° to CVS depression

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NB: ***electrical silence*** occurs with lower MAC values, within the clinically useful range, for ***isoflurane*** but not halothane

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Cardiopulmonary Bypass

• the effects are complex due to the alteration of anaesthetic depth, P_{aCO2}, hypothermia and haemodilution which occurs
• assessment of anaesthetic level during opioid based anaesthesia suggests a shift to lower frequencies

Carotid Endarterectomy

• the best processed EEG data is found when specific events occur unilaterally, as during CEA
• the primary reason for monitoring hemispheric function during CEA is to obtain data for use as a basis for therapeutic intervention, ie. placement of a ***shunt***
• processed EEG changes are likely to occur when,

a. the shunt becomes kinked or displaced
b. when cerebral emboli occur 2° to plaque dissection
c. during hypotension
d. following repair 2° to other CVA (ICH)

NB: these are rare & the primary concern is the decision for placement of a shunt

• the requirement for shunt placement is not agreed upon by all surgeons
• some never shunt & claim no increase in morbidity or mortality
• Cucchiara studied 55 patients undergoing CEA,

a. 11/55 had changes on standard EEG
b. 9 had changes on CFM
c. in all 11 the CBF was < 18 ml/100g/min, below the critical CBF level for halothane

• they did another study on 50 patients using the Lifescan, which is a more sophisticated device using aperiodic analysis
• the predictive value of an anaesthetist being correct in interpreting the trace as being unchanged after clamping is ~ 91-98%
• thus, it may be used by relatively novice users with a fair degree of accuracy

Surgery for Epileptic Foci

• localisation is usually achieved by ***provocation*** with electrodes placed on, or within brain
• the anaesthetic depth is lightened and provocation with hypoventilation, small dose barbiturates or the addition of enflurane employed
• if cortical depression is too great, provocation of the focus and localisation are not possible

Pathophysiological Changes in the EEG

1. ***hypoxia***
   - nonspecific ***global slowing*** eventually replaced by electrical silence

2. ***hypotension***
   - generally needs to be severe
   - earliest signs are "flicker fusion", confusion and inability to concentrate
   - EEG changes are minimal at these levels
   - ? ability of pEEG to determine hypotension as the cause of an ischaemic event
   - sudden changes 2° to arrhythmia are easier to read than gradual changes
   - * conversely, pEEG changes with hypotension do represent significant ischaemia

3. ***hypothermia***
   - changes in spectral edge data in peak power & peak power frequency in the high frequency band correlate well with temperature

4. **$PaCO_2$**
   - ***hypocarbia*** is known to evoke ***seizure activity***
   - hypercarbia has subtle effects similar to increasing the MAC of volatile agent

5. ***CNS events***
   - assumption that if detected early may be amenable to treatment
   - most untoward events not already mentioned are peripheral nerve injuries
   - on balance unlikely to be of benefit

6. ***brain death***
   - EEG silence in the absence of confounding drugs, metabolic encephalopathy, or very young age is ***supportive*** (not diagnostic) of the diagnosis

Sensory Evoked Potentials

• used principally to monitor the integrity of the ***sensory pathways*** during anaesthesia, when these pathways are at particular risk
• these are electrical manifestations of the CNS response to ***external stimuli***
• they are of ***low amplitude* ~ 0.1 to 20 µV** and thus are difficult to distinguish from background EEG activity
• therefore, EEG activity following both a repetitive evoked and spontaneous sensory stimulus is averaged
• the signal is then extracted by summation & subtraction electronically
• generally they are of two types, depending upon the placement of the recording electrodes to the neural generation,

1. ***near field potentials*** - within 3-4 cm
2. ***far field potentials*** - greater distances
   - less localization

• as the distance increases then SEP becomes smaller and slower
• thus, more signals have to be averaged to record far field potentials
• SEP's are also defined as ***cortical*** or ***subcortical***, depending upon the origin of the activity
• thus with the standard EEG electrodes,

i. cortical SSEP's are ***near field***, and
ii. BAEP's are ***far field*** potentials

• intraoperative changes in SEP's, indicative of surgical trespass / ischaemia include,

a. increased ***latency***
b. decreased ***amplitude***
c. complete loss

• anaesthetic management is directed at maximising DO_2 and tissue perfusion
• tolerance limits for the degree of change in SEP's, or the duration of such changes are unknown
• stimulation is via skin or needle electrodes, with a 1-2 Hz square wave of 0.2 to 2 msec duration
• nerves commonly used include the median at the wrist, common peroneal and posterior tibial
• SSEP's may be either short or long-latency, the former being better suited to intraoperative study
• the ***pathways*** involved are,

1. large fibre sensory to ***dorsal root ganglia***
2. ipsilateral posterior column to the ***dorsal column nuclei*** at the cervico-medullary junction (1^{st} order)
3. ***contralateral thalamus*** (2^{nd} order) via the medial lemniscus to the frontoparietal sensori-motor cortex (3^{rd} order)

• SSEP monitoring is also used to asses the integrity of adjacent structures, such as motor tracts, which are more difficult to monitor directly

- ***Intraoperative Uses***

a. scoliosis surgery & Harrington rod placement
b. spinal cord decompression and stabilisation after acute SCI
c. spinal fusion
d. brachial plexus exploration following acute injury
e. resection of spinal cord tumours, cysts & vascular anomalies
f. correction of cervical spondylosis
g. resection of 4th ventricular cysts
h. release of tethered spinal cord
i. resection of acoustic neuroma
j. resection of intracranial lesions involving the sensory cortex
k. resection of thalamic tumours
l. abdominal and thoracic aneurysm repair

• intraoperative changes in SSEP's have been noted in between 2.5-65% of patients undergoing procedures on the spinal cord
• both false negatives & false positives are reported
• overall the sensitivity & specificity make it a valuable form of monitoring in ***high risk*** cases
• as the sensory pathways are supplied predominantly from the ***posterior spinal artery*** & the motor tracts from the anterior, a significant motor deficit can develop without significant change in SSEP's
• this is particularly likely to occur after thoracic aneurysm surgery, with one series reporting intact posterior column function and paralysis in 32% of patients with neurologic deficit
• technically difficult, or inadequate recordings are reported in 0-41% of patients monitored

■ ***Brainstem Auditory Evoked Potentials***

• recorded by delivering repetitive "clicks" to one ear,

a. 60-70 dB above the patients hearing threshold

b. 100 µsec at 10 Hz

c. variable polarity
- rarefraction/condensation
- different waveforms/latencies
± alternating to reduce noise

d. far field potentials
- recorded from the scalp
- require 500 to 2000 repetitions

• these have been used intraoperatively during,

a. procedures in or near the auditory pathway (neuroma)

b. posterior fossa & brainstem surgery
- basilar artery aneurysm clipping
- tumours & vascular lesions

c. microvascular decompression of the cranial nerves

d. section of CVIII for intractable tinnitus

• during microvascular decompression of the ***facial nerve*** for spasms, hearing loss has been reported in up to 15%
• this can be decreased dramatically with BAEP monitoring
• BAEP's are considered the easiest of the SEP's to monitor intraoperatively, and are the ***least sensitive*** to changes in perioperative variables
• ability to record adequate tracing ~ 90-100%

■ ***Visual Evoked Potentials***

• intraoperative stimulation is via flash stimulation, with altering luminance
• this is provided by a LED in a goggle over a closed eyelid
• these goggles interfere with the operative field in some instances & LEDs are available in contact lenses for these situations
• use has been described in virtually any lesion close to the optic pathways
• satisfactory intraoperative recording can be obtained in 88-100% of patients
• however, intraoperative changes not related to neurological changes may occur in up to 68-81%
• in one series there was a high incidence of both false positives & negatives
• also, the means of stimulus delivery needs improvement

Pharmacological Factors Affecting SEP's

- in general VEP's are the most sensitive and BAEP's the most resistant to drug effects
- early waveforms (brainstem) are less affected than late (cortical)

- the ***volatile agents*** have similar effects in differing degrees,
    a. dose dependent increase in ***latency***
    b. decreased ***amplitude*** - SSEP & VEP
       - not BAEP

- ≤ 0.5-1.0 MAC in the presence of N_2O/O_2 is usually adequate for SEP monitoring
- slightly higher concentrations are suitable for BAEP's
- excessive concentrations need to be avoided but more importantly, the concentration must be held ***constant*** during the "at risk" part of surgery for meaningful assessment of altered function

- **N_2O** also results in differing effects depending upon the sensory system being monitored
- in general it results in decreases in amplitude ***without*** changes in latency
- its addition during monitoring of BAEP's under volatile anaesthesia causes little change

- the ***barbiturates*** produce dose dependent changes similar to the volatiles, ie.
    a. BAEP's show only an increase in ***latency***, with no alteration of amplitude
    b. whereas other SEP's show changes in both ***latency & amplitude***

- at doses causing ***EEG electrical silence,*** SSEP's are still seen and SSEP's can be monitored in severely head injured patients during barbiturate coma

- the ***opioids*** also cause decreases in amplitude and increases in latency
- even with high dose techniques, SSEP's are still recordable
- however, bolus administration proximal to "at risk" periods should be avoided
- ***BAEP's*** are relatively ***resistant*** to opioids, with no change in latency or amplitude up to 50 µg/kg of fentanyl

Physiological Influences on SEP's

a. mean arterial pressure
b. temperature
c. arterial blood gas tensions - O_2 & CO_2

Monitoring of Motor Tracts

• intraoperative electromyographic monitoring of motor nerve function can include evaluation of three types of motor nerve & muscle activity,

1. ***neurotonic discharges***
   - recorded from fine wires placed in muscles
   - spontaneous discharges recorded 2° to operative stimulation
   - density & frequency of discharges correlate with postoperative nerve dysfunction

2. ***compound muscle action potentials*** CMAP's
   - either fine wires within the muscle or surface electrodes
   - recorded data from direct stimulation of the supplying nerve by the surgeon with a small stimulator
   - stimulation proximal to a lesion indicates neural integrity

3. ***nerve action potentials*** NAP's
   - stimulation of the nerve within or outside the operative field
   - recording of the summated AP's of axons within the operative field
   - allows localisation of slowing or conduction block within the operative field

4. ***wake-up test***
   - scoliosis or other major surgery upon the spinal column
   - tests all pathways of the motor system
   - good correlation with postoperative function

• most of the experience has been with ***facial nerve*** monitoring during resections of acoustic neuromas, or during parotid resection
• increased preservation of facial nerve function has been demonstrated, especially with medium to large sized tumours
• autoexcitation and the lateral spread response are seen in patients with hemifacial spasms, both disappearing with adequate decompression of the nerve
• other nerves which may be monitored include the motor branch of the trigeminal, the spinal accessory nerve and the hypoglossal nerve
• anaesthetic management for these patients is unremarkable, except that ***muscle relaxants*** should be avoided for the period of monitoring
• a newer technique involves transcortical stimulation of the motor tracts, allowing assessment of the descending tracts in the spinal cord
• this has potential due to the differing blood supplies of the posterior sensory and anterior motor tracts

ANAESTHESIA FOR HEAD INJURY

- leading cause of ***death*** between the ages of ***15-24 years***
- incidence ~ 25-28:100,000 in Australia (1977) ***~ 1:4,000***
- hospital admission rates for head injury are ~ 200-300:100,000
- motor vehicle accidents accounting for ~ 60% of deaths 2° to head injuries
- ***severe*** ("malignant", **GCS < 7**) head injuries form **~ 9-11%** of the total group
- incidence depends upon definition of "severe", (GCS < 9, 7, or 5!)

NB: aggressive management / ICU therapy has been shown to ***improve outcome***, ***without*** increasing the number of vegetative or severely disabled survivors (T.Oh)

Anaesthetic Management

- this is primarily directed at preventing ***secondary injury***, which may result from,

1. hypoxia, hypercarbia, acidosis
2. hypotension & hypoperfusion
3. expanding intracranial lesions
   - focal masses
   - generalised oedema

- all patients GCS < 9 (?7) require immediate ***intubation***, hyperventilation and increased FiO_2
- this may require manual, in-line axial head traction if ***cervical pathology*** has not been excluded (~ 10% of head injuries)
- nasal intubation should be avoided and a modified RSI technique used with cricoid pressure applied during preoxygenation due to the risk of ***aspiration***
- choice of anaesthetic agents is influenced by the presence of ***hypotension***, with multiple injuries being present in up to 40% of severe cases
- correction of ***hypovolaemia*** 2° to blood loss takes precedence over either,

1. CT scanning
2. definitive neurosurgical intervention

Extradural Haematoma

- has a high ***mortality ≤ 30%*** in some series
- this relates to already comatose patients undergoing surgical evacuation
- mortality is significantly higher in those,

1. requiring operative evacuation within 12 hours of admission
2. with an ICP ≥ 35 mmHg

- administration of ***barbiturates*** is usually effective in reducing refractory intracranial hypertension

Subdural Haematoma

- collections presenting **≤ 72 hours** of head injury are termed ***acute***
- high ***mortality ~ 42-63%***, and tends to be worse when there is underlying brain contusion or laceration
- following haematoma evacuation, acute ***cerebral oedema*** may complicate surgical closure
- these patients frequently require intensive pharmacological control of ICP and delayed extubation is justified

- chronic subdural haematomas develop slowly and liquefaction has frequently already commenced
- therefore they can frequently be managed by ***burr hole*** drainage
- outcome in this group largely relates to the ***preoperative state***

Neurological Sequelae

a. rebleeding
b. acute cerebral oedema
c. malignant intracranial hypertension
d. brain herniation syndromes
   i. nerve palsies - 3rd nerve palsy
      - 6th nerve palsy
   ii. cingulate gyrus
   iii. uncal gyrus
   iv. brainstem
e. epileptic seizure activity
f. posterior pituitary - SIADH, central salt wasting syndrome
   - central DI
g. focal neurological defecits
h. vegetative survival
i. brain death

- ***Systemic Sequelae***

a. ***cardiopulmonary***

i. resuscitation
- airway obstruction
- hypoxia, hypercapnia, acidosis
- hypovolaemic shock

ii. ARDS
- aspiration pneumonitis
- pulmonary trauma

iii. neurogenic pulmonary oedema (NPE)

iv. ECG changes

b. ***haematological***
- DIC
- anaemia in children

c. ***endocrinological***

i. ant. pituitary * rarely

ii. central salt wasting syndrome

iii. nonketotic hyperglycaemic coma
- unrecognised diabetics
- prolonged steroid therapy
- mannitol, water restriction
- NG enteral feeding
- phenytoin

d. ***gastrointestinal***
- stress ulceration ± haemorrhage
- steroid therapy

• a number of these complications can occur in ***nontraumatic*** neurological disease
• persistent hypoxaemia requiring raised FiO_2 or PEEP occurs in ~ 25%
• abrupt onset acute neurogenic pulmonary oedema can accompany severe head injury in young patients ***without*** a history of CVS disease
• this frequently proves refractory to conventional therapy and only resolves with reduction of ICP
• NPE is associated with intense ***sympathetic discharge***, with systemic ± pulmonary vasoconstriction
• thus, management aimed at blocking sympathetic activity may be useful

• ***tachyarrhythmias*** and ST segment changes may accompany SAH and severe head injury
• the sympathetic overactivity associated with these changes may actually result in punctate areas of myocardial necrosis
• bradycardias requiring treatment with atropine are also seen with raised ICP

• clotting abnormalities have been described following trauma and also manipulation of brain tissue during tumour resection
• this is thought to relate to the release of ***brain thromboplastin*** into the circulation
• ***mortality*** increases markedly when DIC complicates acute head injury
• the DIC is usually self-limiting and resolves with management of the primary problem
• blood component therapy is rarely required

SUBARACHNOID HAEMORRHAGE

a. ***aetiology***
   i. saccular aneurysm* ~ 6-8% of all strokes
      ~ 90-95% - ***anterior*** circle of Willis
      ~ 5-10% - vertebrobasilar
   ii. atherosclerotic
   iii. mycotic
   iv. traumatic
   v. arteriovenous malformations

b. ***incidence*** (USA)* ~ 11:100,000

c. ***mortality**** **~ 40-50%** overall
   ~ 10% in the first week
   ~ ½ the remainder within 3 months
   ~ ½ the long-term survivors have ***major disability***

• outcome is related to,
   i. the amount of subarachnoid blood, and
   ii. the neurological condition at presentation

• the major causes of death are,
   i. neurological injury from the ***initial haemorrhage***
   ii. ***rebleeding***
   iii. ischaemia from ***vasospasm***

• ***saccular aneurysms*** were originally thought to be congenital
• recent evidence is that they are ***acquired***, due to degeneration of the internal elastic membrane at the apex of bifurcations, secondary to ***haemodynamic stress***
• ***hypertension*** and turbulent flow lead to further degeneration & saccular enlargement
   → increased risk of rupture **~ 5-15 mm**

■ ***Clinical Presentation***

1. ***prodromal*** symptoms - headache, dizziness, orbital pain
   - often vague & not diagnosed
2. sudden onset of ***severe headache***
3. ***meningism*** - photophobia, neck stiffness, vomiting
   - Kernig's sign
4. transient ***neurological deficits*** - depend upon site & size of aneurysm
   - extent of intracerebral haematoma
5. ***loss of consciousness***

Clinical Neurological Classification of SAH	
Grade I	• conscious patient ± meningism
Grade II	• drowsy patient ± neurological deficit
Grade III	• drowsy patient with a neurological deficit • probably intracerebral haematoma
Grade IV	• deteriorating patient + major neurological deficit • large intracerebral haematoma
Grade V	• moribund patient, extensor rigidity & failing vital centres

• the World Federation of Neurological Surgeons has suggested another classification scheme, incorporating the GCS and the presence of absence of motor deficit (grades I-V)

NB: severe SAH with loss of consciousness and persistently raised ICP has been termed ***haemorrhagic compression***

• this is managed identically to acute head injury
• in ***noncompressive SAH*** the mass effect is minimal, and the ICP usually normalises 10-15 minutes following the bleed

■ ***Complications: Cerebral***

1. ***rebleeding*** **~ 19%** (16-25%) within the first 2 weeks
   ~ 4% within the first 24 hours
   - peak incidence at days 4-9
   - decreased by 30-50% with antifibrinolytics
   * mortality remains unchanged
   ~ 40% *mortality* from a 2nd haemorrhage
   ~ 3% per year late rebleed with 67% mortality
2. ***vasospasm*** **~ 70%** of all SAH proven by ***angiography***
   ~ 40% demonstrate ***clinical vasospasm***
   - maximal at days 6-7 post-SAH
   * major cause of morbidity / mortality
   - requires exclusion of other causes of neurological deficit
   - assessment by MCA flow velocities & CT scan

   DDx: rebleeding, ICH, oedema, hydrocephalus
   hypoxia, hypercarbia, acidosis, hyponatraemia
3. ***hydrocephalus*** - acute obstructive, with raised ICP
4. ***seizures***

- ***Complications: General***

1. ECG changes - ST segment depression, T-wave inversion
   - U-waves, prolonged Q-T
   - arrhythmias
2. sympathetic hyperactivity
3. acute neurogenic pulmonary oedema
4. hyponatraemia - SIADH / cerebral salt wasting syndrome
5. reduced total blood volume & RBC mass

- ***Preoperative Management***

a. bed rest - sedation & analgesia

b. general supportive care

c. control of ***hypertension*** - but avoid hypotension
   - sedation & analgesia
   - antihypertensives
   - β-blockers, α-methyldopa, CEB's
   - * avoid cerebral vasodilators

d. control of ***vasospasm***
   - * CEB's, ***nimodipine***
   - most consistent results are obtained with ***hypertension & hypervolaemia***
   - may require the use of antidiuretics
   - generally requires ***early surgery***

e. control of ***seizures***

f. control of ***cerebral oedema*** & raised ICP

g. control of ***hydrocephalus***

h. ***antifibrinolytics***
   - epsilon aminocaproic acid (EACA) & tranexamic acid
   - inhibit clot lysis & reduce rebleeding
   - * problems of cerebral ischaemia, hydrocephalus and thrombosis
   - no change in ***mortality***, therefore trend to decreasing use

i. prevention of ***gastric erosion / ulceration***

j. maintenance of ***fluid & electrolyte*** balance

- ***Anaesthetic Management***

1. preoperative assessment
   i. evidence of raised ICP
   ii. presence & extent of CNS deficit
   iii. volume status
   iv. biochemical derangements
   v. ECG changes ± CE's
   vi. other system diseases
2. monitoring
   i. IABP & CVP ± PAOP
   ii. ECG + V_5
   iii. * FiO_2, SpO_2, $ETCO_2$, V_E/f, PNS, CUD, T_C
   iv. ? EEG if vascular occlusion is planned
3. ***management goals***
   i. prevention of aneurysmal ***rebleed***
      - intraoperative rupture $\rightarrow$ > 60% mortality
      - avoid rapid reduction of ICP precraniotomy §
      - avoid rapid increases in ***MAP*** precraniotomy §
   ii. avoidance of ischaemia 2° to ***vasospasm***
   iii. brain ***decompression*** - surgical access
      - retractor ischaemia
   iv. ***controlled hypotension*** when required

NB: §the risk of rebleeding is determined by the vessel wall gradient, MAP - ICP
changes in MAP are of ***far greater*** significance cf. reductions in ICP

- following craniotomy, hyperventilation and osmotherapy may be used to facilitate a slack brain
- in addition to surgical access this will reduce the extent of ***retractor ischaemia***, which is enhanced by a swollen brain, application duration and pressure, and a lowered MAP
- hyperventilation may be theoretically contraindicated in the presence of symptomatic vasospasm, as it may reduce collateral flow
- ***controlled hypertension*** may be required pre/intraoperatively for patients who become symptomatic prior to surgery

- aneurysms may be treated by,

1. direct clipping
2. encasement with various materials
3. occlusion of the feeding vessel
4. stereotaxic thrombosis

■ ***Controlled Hypotension***

• may be required for,

1. reducing the risk of intraoperative bleeding
2. facilitating surgical access
3. manipulation of the aneurysm prior to clipping
4. giant aneurysms, or those near the basilar artery
   ± induced hypothermia
   ± cardiac or cerebral circulatory arrest
   ± barbiturate protection

• the benefits must be weighted against the risks of ischaemia to the brain and other organs
• under normal conditions, the brain is considered the most sensitive organ to ischaemia
• based on CBF autoregulatory thresholds and clinical data, a ***MAP* ≥ 50 mmHg** is considered safe in otherwise healthy patients
• ***autoregulation*** / compensation is not instantaneous, and ***gradual induction*** will be less likely to result in significant ischaemia
• factors which increase the risks of induced hypotension include,

1. ***intracranial***
   i. vasospasm
   ii. occlusive cerebrovascular disease
   iii. chronic arterial hypertension
      • in the absence of EEG/CBF monitoring,
        MAP should not be decreased > 50 mmHg from "normal"
   iv. excessive retractor pressure
   v. generalised cerebral oedema
   vi. the presence of an intracerebral haematoma
2. ***extracranial***
   i. fever & hypermetabolic states
   ii. anaemia
   iii. hypovolaemia
   iv. recent coronary infarction (≤ 6 months)
      • IHD is a relative risk only,
        most asymptomatic patients tolerate hypotension well
   v. pulmonary, hepatic and renal dysfunction
      • cf. IHD, these are relative, unless severe
   vi. chronic arterial hypertension

• important factors to consider with induced hypotension include,

1. patient position - venous pooling
2. choice of anaesthetic agents
3. adjuvant and cardiovascular drugs
4. ventilation
5. patient monitoring - reference points for transducers

• ***resistance*** to BP reduction can be expected,

i. in younger persons
ii. under light anaesthesia
iii. in the presence of hypervolaemia

• anaesthetic agents which reduce MAP, ie. ***volatiles***, should be used to aid vasodilator therapy
• tachyphylaxis to ***trimethaphan*** tends to develop early and higher doses may result in fixed, dilated pupils which may hinder postoperative assessment
• progressive increases in the requirement for ***nitroprusside*** may indicate evolving cyanide toxicity, with tissue ***hypoxia,*** increased ***sympathetic discharge***, increased $Pv'O_2$ and metabolic acidosis,

i. acute (2-3 hrs) **< 1.5 mg/kg**
ii. infusion **< 0.5 mg/kg/hr** (< 8 µg/kg/min)

• correction of cyanide toxicity may be enhanced by ***sodium thiosulphate*** ~ 150 mg/kg
• rapid withdrawal of SNP may lead to ***rebound hypertension***, due to reflex increased PRA
• ***captopril*** both reduces the requirement for SNP and the degree of post-SNP hypertension

• the significance of ***hypocarbia*** in the presence of induced hypotension is controversial, and is probably disease and agent specific
• in the presence of preoperative ***vasospasm*** it is best avoided
• with isoflurane, the lower limit of autoregulation does not appear to be altered by the introduction of hypocapnia, in the absence of cerebrovascular disease
• therefore, providing the lower limit of autoregulation is not traversed, mild hyperventilation may be used during isoflurane anaesthesia
• however, because retractor and vasospastic ischaemia are not estimated during the hypotensive period, ***normocapnia*** is preferable unless there is a specific indication to lower the $PaCO_2$

• ***cerebral protection*** may be required if focal circulatory arrest is necessary during surgery
• monitoring for adequate collateral flow is difficult but may be attempted by scalp/brain surface EEG, isotope CBF methods or direct microscopic observation of the brain surface
• occasionally induced hypertension may provide sufficient collateral flow
• there is some data to suggest prior extracranial-intracranial bypass may significantly reduce the deficit following prolonged clamping times
• there is reasonable laboratory evidence that high dose ***barbiturates*** offer protection during periods of focal ischaemia
• the risks of barbiturate administration to already anaesthetised patients is small providing cardiac filling pressures are maintained

■ ***Postoperative Management***

a. general supportive care

b. adequate analgesia & sedation

c. ICP measurement

d. medical complications
- seizures
- SIADH, CSWS, hyponatraemia
- cardiac arrhythmias, AMI, CCF
- pneumonia, PTE
- UTI's

e. surgical complications
- vasospasm
- rebleeding
- cerebral oedema
- subdural/extradural haematoma
- hydrocephalus
- intracranial hypertension
- persistent neurological deficit

f. vasospasm
- ***hypervolaemia & haemodilution***
- CVP ~ 8-12 mmHg / PAOP ~ 10-12 mmHg
± PAOP ~ 16-20 mmHg if no improvement
- Hct ~ 30-35%
± antidiuretics
- digoxin/inotropes with CCF

NB: patients with oedema and vasospasm may require mannitol, cautious volume loading with colloid, and IPPV

• ***hypervolaemia*** is reported to produce transient improvement in 80-90%, and permanent improvement in 60% of cases
• ***complications*** of this therapy include,

a. pulmonary oedema

b. cerebral oedema

c. haemorrhagic cerebral infarction

d. biochemical derangement

e. complications from insertion of invasive monitoring

■ ***Summary***

• only ~ 30% of SAH patients ever have surgery
• of patients who reach hospital, a favourable outcome is reported in ~ 43% of surgical cases
• of Grade I & II SAH patients ~ 60% will have a favourable outcome
• in patients without a preoperative neurological deficit, an operative mortality ≤ 5% is possible

Arteriovenous Malformation

- congenital malformations, associated with high shunt flows & low CVR
- usually increase with age and may present by,

a.	headache	
b.	epilepsy	
c.	mass effect	
d.	SAH / ICH	~ 3% per year - ***uncommon*** as a presenting symptom
e.	high output cardiac failure	- infants - adults with CVS disease
f.	cortical bruit	
g.	cerebral "steal" & ischaemic symptoms	

- surgery is the treatment of choice, if technically possible
- unless completely removed they have a propensity to re-establish growth
- procedures will typically be preceded by angiography and attempted ***embolisation*** of the lesion and are carried out in stages
- anaesthetic problems in management include,

1. intracranial mass effect
2. risk of rupture & massive blood loss

- large lesions may require hypothermia, hypotension ± other cerebroprotective measures
- following/during resection, redirection of blood flow may result in ***perfusion pressure breakthrough***,

a. malignant cerebral oedema
b. haemorrhage
c. ± death

- protection against this phenomenon consists of prior embolisation and staging of the resection (ie. limiting resection to ≤ 12 hours)
- treatment includes all of the standard measures to reduce CBF/ICP

Pituitary Tumours

• represent ~ 10% of intracranial tumours
• they are rarely metastatic, and present due to either ***mass effect*** or ***hormone secretion***, the former resulting in,

a. bifrontal headache
b. bifrontal hemianopia
c. hydrocephalus
d. panhypopituitarism ± pituitary apoplexy 2° haemorrhage
e. intracranial hypertension

Features of Pituitary Hormone Secretion

Location	Hormone	Features
Anterior[1]	PRL	• galactorrhoea, hypogonadism • amenorrhoea, infertility
	ACTH	• Cushing's syndrome
	GH	• acromegaly, giantism • glucose intolerance • airway difficulties
	None	• mass effect, hypopituitarism
Posterior	ADH	• frequently large • ↓ADH → polyuria, polydipsia • postoperative DI
Extrinsic	None	• mass effect, hypopituitarism

[1] hypersecretion of TSH or FSH/LH are exceedingly rare

• ***nonsecretory*** pituitary tumours account for ~ 20-50% and are usually ***chromophobe adenomas***
• symptoms resulting from ***compression*** generally follow the order,

gonadal function > ***growth*** > ***adrenocortical function***

• ***parastella lesions*** which may encroach on the pituitary include,

a. craniopharyngiomas
b. meningiomas
c. aneurysms
d. metastatic tumours *breast, lung
e. granulomas

■ ***Surgical Approach***

• the ***transphenoidal*** approach has regained popularity with the advent of,

1. antibiotic therapy
2. the operating microscope

• ***advantages*** including,

a. elimination of frontal lobe retraction
b. removal of ***microadenomata***, preserving normal tissue
c. reduced need for blood transfusion
d. shorter hospital stays

• appropriate for lesions confined to the ***sella turcica***, or those with minimal suprastella extension
• ***fluoroscopy*** may be required intraoperatively for localisation

■ ***Anaesthetic Factors***

a. coordination of 2 surgical teams - ENT & neurosurgery
b. sharing of the airway with the surgeons
   i. ETT fixation ? armoured ETT
   ii. dissection through the ***nasal septum*** → ***throat pack***
c. ***may*** have raised ICP if obstructive hydrocephalus, frequently not
d. operation through a contaminated field - antibiotic cover
e. large amounts of local anaesthetic with ***adrenaline***
f. microscopic dissection
   i. long & tedious procedure * all considerations for ***prolonged*** surgery
   ii. requirement for a ***stable field*** - head restraint
   - muscle paralysis
g. intra/postoperative ***complications***
   i. haemorrhage - control may be difficult
      • cavernous sinus
      • anterior venous sinusoid
   ii. cranial nerve dysfunction
   iii. air embolism

CAROTID ARTERY SURGERY

• CEA is the most commonly performed noncardiac vascular procedure in the USA
• in May 1991, a large multicentre trial comparing medical and surgical management of ***symptomatic*** patients with ***critical carotid stenosis*** (≥ 70% luminal narrowing), clearly had a better outcome with ***surgery***
• this trial is continuing and patients with severe stenosis are no longer randomised to medical therapy

■ ***Preoperative CNS Considerations***

• patients presenting for CEA will likely do so for either,

a. recurrent embolic TIA's or RIND's not manageable by anticoagulant therapy, or

b. TIA or RIND accompanied by critical luminal narrowing of one, or both carotids

• thus, there are two pathophysiological mechanisms of presentation,

→ ***haemodynamic insufficiency*** or ***embolic disease***

a. ipsilateral monocular vision loss, plus contralateral muscle weakness
→ usually 2° ICA insufficiency, ***not*** embolism

b. ***embolism***, cf. low flow, actually causes most cases of TIA/stroke from carotid disease

• either of these presentations may be accompanied by a history of ***stroke***
• the former may have global neurological manifestations as well
• collateral circulation from the circle of Willis is, in these cases, inadequate
• distal cerebral vasodilatation cannot compensate since maximal dilatation has already occurred
• further, embolic and haemodynamic mechanisms may occur simultaneously
• the nature of the lesion has a definite impact upon anaesthetic management
• symptomatic patients ***without*** critical narrowing are likely to be experiencing embolic events, and as such are able to tolerate much lower levels of intraoperative hypotension
• conversely, those with critical narrowing may be subject to hypotensive reductions in CBF
• in these patients even transient falls in MAP should be treated
• however, such treatment may increase the risk of myocardial ischaemia & MI
• therefore, it is beneficial to identify these patients preoperatively
• these patients attempt to maintain CBF by 2 mechanisms,

1. collateral flow
   i. circle of Willis
   ii. anastomoses between the external & internal carotids
      • ophthalmic artery via the orbit
      • facial & maxillary arteries
      • superficial temporal artery - small & questionable significance
   iii. distal branches of the anterior and middle cerebral arteries
   iv. ascending cervical & occipital arteries, and the distal vertebral artery
2. distal vascular vasodilatation

• ***collateral flow*** may be assessed at the preoperative ***angiogram***
• ***vasodilatory reserve*** may be assessed by inhalation of radiopaque 60% ***xenon***, pre & post use of a vasodilator (CO_2)
• areas of low uptake indicate marginal perfusion and the absence of increased uptake following vasodilatation represents exhausted reserve
• uptake to the marginally perfused area may decrease due to "steal" to normal areas of brain
• similar studies have been reported with ***transcranial doppler***
• other characteristics associated with an increased risk of ***perioperative ischaemia*** include,

1. recent stroke / stroke in evolution
2. intracranial luminal narrowing
3. significant contralateral or vertebral vessel narrowing
4. contralateral occlusion & a history of stroke

• in addition to the vascular lesion, the preoperative CNS examination is beneficial in assessment of any perioperative functional abnormality
• if at the end of surgery the patient has a ***new*** neurological deficit, the carotid artery may be re-explored at that time
• patients with prior stroke who undergo GA may experience a brief exacerbation of their neurological deficit
• the origin of this effect, the "normal" extent, duration and expected course has not been quantified in the literature
• "***anaesthesia-induced decrement of neurological deficit***" should therefore be a diagnosis of exclusion
• the presence of a prior neurological deficit increases the risk of SCh induced ***hyperkalaemia***

■ ***Preoperative CVS Considerations***

• in patients with severe carotid artery disease, the incidence of significant CVS disease (IHD & hypertension) ranges from ***50-70%***
• studies have shown the risk of perioperative MI is ***greater*** than the risk of perioperative CVA
• incidence of MI during vascular surgery is **~ 4%** (some < 25%)
• ***postoperative hypertension*** is associated with a higher incidence of CVA
• most patients who are hypertensive postoperatively are hypertensive ***preoperatively***

NB: thus, perioperative control of hypertension may lower the incidence of stroke, however, there has been ***no*** controlled random trial to establish this

• the nature of any "routine" CVS screening test is controversial,

a. stress thallium scan, or dipyridamole-thallium scan
   - high sensitivity and specificity

b. continuous ambulatory holter monitor
   - less invasive & a good predictor of perioperative cardiac ischaemic complications

• patients screening positive for these could then be assessed by ***angiography***

■ ***Intraoperative Monitoring***

• this is directed principally at the CNS and CVS
• CEA itself involves little CVS risk with regard to fluid shifts or bleeding, however considerable changes in HR & BP may accompany manipulation of the ***carotid baroreceptor***
• depending upon the patients preoperative status, they may require monitoring of ventricular function, myocardial MRO_2 balance, or both
• monitors which achieve this include,

a. ECG with continuous ST-segment analysis

b. Swan-Ganz catheter

c. transoesophageal echocardiography

NB: there are no clear-cut ***outcome studies*** documenting the efficacy of these modalities in detecting or preventing myocardial complications

• CNS monitoring is directed at O_2 supply-demand and may include,

a.	***awake patient***	- easy to apply, no special training - continuous - easy to interpret
b.	***EEG***	- requires technician ± training - continuous - requires training to interpret
c.	***processed EEG***	- requires training to use & interpret - continuous
d.	***SSEP's***	- requires technician - continuous - requires training to interpret
e.	***transcranial doppler***	- some training, no technician - continuous - requires training to interpret * data may be ***misleading***
f.	***cerebral blood flow***	- requires training ± technician - intermittent - easy to interpret
g.	***carotid stump pressure***	- easy to apply, no special training - intermittent - easy to interpret * data may be ***misleading***
h.	***jugular venous PO_2***	- reflects ***global CBF*** not regional - unreliable as a monitor of rCBF

• an ***awake patient*** allows assessment of multiple levels of CNS function
• there is no equipment cost and interpretation seems superficially simple
• however, unless the surgeon is quick and gentle, the patient may not tolerate the procedure without significant ***sedation***
• if this is required, alterations of consciousness may be due to the drug, ischaemia or both
• also, if the awake patient does suffer an ischaemic event, this may not be immediately reversible and the subsequent deterioration of conscious level may in fact worsen the ischaemia
• optimisation of ventilation and oxygenation is much easier if the airway is already secured

• ***cortical EEG***, recording of spontaneous electrical activity from the cortex has been shown conclusively to reflect cerebral O_2 balance
• the EEG becomes isoelectric ***before*** irreversible damage occurs
• the most extensive data has been collected at the Mayo Clinic with 16 channel chart recording
• this requires a technician both to set up the monitor and to analyse the large amounts of data
• processed EEG recordings using 2-4 channels ***can*** provide data which is easier to follow & interpret over time, with little loss of the sensitivity for ischaemia
• when the number of channels is limited, they may be placed in the vascular distribution of the anterior and middle cerebral arteries
• methods for display include,

1. compressed spectral array
2. density spectral array
3. pie graphs
4. others

• ***all*** processed EEG devices will display noise in addition to physiological data, and as such must have the ability to display the ***raw data*** to allow differentiation is marginal cases
• assessment of the presented data does not require extensive training, however,

a. changes in anaesthetic technique/depth may produce EEG changes indistinguishable from global ischaemia
b. the anaesthetist must spend adequate time learning to assess the raw EEG data, in order to be able to distinguish noise from real data, and to recognise the changes associated with changes in anaesthetic depth

• ***SSEP's*** differ in that the data is not spontaneous and the signal levels are lower to the extent that signal recording and computer averaging is required to assess the data
• monitoring is technically more demanding and best performed by a technician
• further, the data is ***not as sensitive*** for detection of ischaemia

• ***transcranial doppler*** uses doppler shift from RBC's to estimate flow velocity in a major intracerebral artery, usually the MCA
• the primary assumption is that flow velocity in large vessels reflects cortical CBF
• this could only be true if,

1. the vessel diameter is held constant
2. the doppler signal angle is held constant

• this has not been evaluated in a large series against either of the established monitors of CBF (EEG or direct CBF measurement)
• further, measurements with TCD have only been described during the cross-clamping period, and most CVA's occur at times other than this period
• little data is available about the degree of change in TCD allowable during the remainder of the operation
• in TCD studies on patients ***without*** cerebrovascular disease, there appears to be large variations in flow velocity
• technically satisfactory recordings cannot be obtained in some individuals, particularly elderly females
• the advantages are the ease of application and continuous nature

• ***regional CBF*** may be measured directly with either IV or intra-carotid injection of radioactive tracer (^{133}Xe), washout reflecting regional CBF
• probably the most accurate measure of focal ischaemia during GA ($\equiv^{\tau}$ RA + awake patient)
• although the measure may be repeated it is ***not continuous*** and cumbersome
• this may be used as a supplement but not a replacement of continuous monitoring

• ICA ***stump pressure*** is defined as the pressure remaining in the ICA distal to the cross-clamp
• a pressure ≥ ***50 mmHg*** has been hypothesised to represent adequate collateral flow through the circle of Willis, or external carotid circulation
• stump pressure ***does not correlate*** with,

1. measured regional CBF
2. EEG changes
3. neurological assessment of the awake patient

NB: has therefore been abandoned by most centres

Anaesthetic Techniques

• ***premedication*** prior to CEA may be useful for prevention of preinduction hypertension, tachycardia, and potential myocardial ischaemia associated with anxiety
• conversely, this may be associated with excessive postoperative somnolescence
• all regularly scheduled CVS drugs should be given

▪ *Regional Anaesthesia*

a. deep and superficial cervical plexus block
   • Melbourne suggest superficial alone as ***supplementation rate*** is identical ~ 20%
b. a single injection high (C_4) in the interscalene groove
c. cervical epidural

• the ***haemodynamic stability*** which accompanies RA is associated with a ***low*** incidence of MI
• having the patient awake allows continuous assessment of the ***neurological status***
• the disadvantages include,

a. patient discomfort during long or difficult procedures
b. confusion regarding CNS status if sedation is required
c. difficulty controlling ventilation / oxygenation adequately during ischaemic events

▪ *General Anaesthesia*

• considerations include,

a. the anaesthetic technique used
b. control of haemodynamics
c. control of CO_2 and plasma glucose

• there is ***no advantage***, based on outcome studies, which favours any one anaesthetic technique
• there is controversy regarding the possible cerebroprotective effects of isoflurane, and therefore its advantage in CEA surgery
• data from the Mayo Clinic looking at EEG changes suggestive of ischaemia showed tolerance of much lower levels of CBF during isoflurane anaesthesia,

a. halothane & enflurane **~ 18** ml/100g/min
b. isoflurane **~ 8** ml/100g/min (?? method of CBF measurement)

NB: conversely, data from primates subjected to regional ischaemia with either control, thiopentone or isoflurane "protection", showed those in the isoflurane group had ***no advantage*** with respect to neurological outcome

---

• it has been suggested that a bolus of ***thiopentone*** should be administered immediately prior to carotid cross clamping, however,

a. there is ***no evidence*** that this influences the incidence or severity of stroke

b. most CVA's ***do not*** occur during the cross clamp period

c. this will render the EEG ***isoelectric*** for a period and prevent the detection of ischaemia which could be treated by shunting, induced hypertension, or both

• there is better ***rationale*** for giving a bolus of thiopentone when,

a. the patient has ***multiple critical stenosis***, suggesting a lack of contralateral flow, or

b. cross clamping results in ***EEG changes*** suggestive of ischaemia

• the wide swings in BP commonly seen during CEA are thought to relate to induced dysfunction of the ***carotid baroreceptors***
• these variations may be reduced by infiltration around the baroreceptor with ***local anaesthetic***
• postoperative hypertension is more common in patients suffering intraoperative ischaemia
• there are two main approaches to these variations in BP,

1. variation of anaesthetic depth
2. administration of vasoactive agents

• a recent study suggested that control of hypotension by reduction in ***anaesthetic depth*** was associated with a lower incidence of wall motion abnormalities, whereas ***phenylephrine*** was associated with a higher incidence and severity of wall motion abnormality
• however, frequent alteration of anaesthetic level is associated with alteration of the EEG data and difficulty in interpretation

• $\mathbf{P_{aCO2}}$ being a potent cerebral vasodilator must also be controlled intraoperatively
• generalised vasodilatation may result in cerebral "steal" to non-ischaemic areas
• ***hypocapnia*** may result in "reverse steal" and be useful during periods of regional ischaemia
• however, this has ***not*** been demonstrated reliably and hypocapnia may aggravate the effects of ischaemia on cerebral metabolism

NB: therefore, ***normocapnia*** should be maintained during CEA,
hypocapnia should only be used if cerebral ischaemia is monitored

• animal studies have shown greater susceptibility to ischaemic injury if ***glucose*** is administered during the period of insult
• patients with a new stroke have a worse outcome if the presentation BSL is high
• this suggests withholding glucose, and tightly controlling BSL in the diabetic may be useful
• however, there are no ***outcome*** data to support this statement

• patients with severe carotid stenosis are at greater risk of ***postoperative hypertension***
• the distal intracerebral vasculature is maximally dilated and no longer autoregulates
• with restoration of perfusion pressure, there is greatly increased CBF and ***cerebral oedema*** and ICH may occur
• those patients who suffer ICH have an extremely high mortality
• patients with ***severe preoperative stenosis*** must have tight control of postoperative hypertension

ANAESTHESIA FOR SPINAL CORD INJURY (SCI)

a. age ~ 70-80% are between **11-30 yrs**

b. sex ~ 2/3 are ***males***

c. ***mortality*** ~ 30% die before reaching hospital
~ 10% during the first year
~ normal for age thereafter

Pathophysiology

- injury results from both primary and secondary injury
- the anatomic and histological findings associated with ***primary injury***,
  a. direct neurilemmal & neuronal disruption ± destruction
  b. petechial haemorrhages
  c. gross haematomyelia
  d. total cord transection * a rare event

- subsequent ***secondary injury*** involves,
  a. progressive haemorrhagic necrosis
  b. oedema
  c. inflammatory response

  NB: → proportional to the extent of the 1° injury

- the proposed mechanism of the ***2° injury*** includes,
  a. activation of ***phospholipase*** $\mathbf{A_2}$, due to release of
     i. Ca^{++}
     ii. bradykinin
     iii. thrombin
  b. formation of arachidonic acid & other FFA's from cell membrane
  c. metabolism of arachidonic acid to,
     i. prostaglandins * mainly ***thromboxane***
     ii. leukotrienes → microcirculatory thrombosis & stasis
     vasogenic oedema
     tissue ischaemia
     chemotaxis of inflammatory cells
  d. free radical formation & hydrolysis of membrane lipid fragments
     → ***lipid fragment peroxides***

e. lipid hydrolysis and peroxidation of fragment membrane phospholipids

→ further release of Ca^{++} & positive feedback

f. increased $PGF_{2\alpha}$ and thrombin augment phospholipase activity

g. raised intracellular Ca^{++} leads to disordered energy metabolism and maintenance of cell integrity (Na^{+}/K^{+}-ATP'ase)

h. increased endogenous kappa opioid agonist ***dynorphin***, plus an increase in receptor binding capacity following experimental SCI in rats

■ ***Effects On Spinal Cord Blood Flow***

• immediately following SCI there is a marked ***reduction*** in SCBF, resulting in ischaemia and biochemical changes as above
• these changes may not commence for up to 1-4 hrs post SCI
• therefore postulated that interruption of the above cascade may protect against ischaemia
• the normal mean ***SCBF* ~ 40-50 ml/100g/min**
• this is partitioned between grey & white matter ~ 3:1
• SCBF normally ***autoregulates*** between ~ 60-150 mmHg MAP in rats
• SCBF has been shown to vary with P_{aCO2} ~ 1:1 ratio (1 ml/mmHg)
• most of the decrease in SCBF following SCI is in the central cord region
• work with cats has shown that autoregulation is ***abolished*** following SCI

Management of Acute SCI

a. pharmacological
   i. ***steroids***
      - given before, or shortly after decrease 2° injury in animals
      - Braken (1990) showed high dose methylprednisolone improved motor and sensory function at 6 weeks & 6 months
      - benefit is statistically significant only when administered ***≤ 8 hrs*** of SCI
      - there was no increased incidence of septic complications
      - subsequent RCT's have not suported this finding and use currently controversial
   ii. mannitol
      - effective in reducing parenchymal volume
      - also causes a vigorous osmotic diuresis
      - intravascular volume must be maintained to ensure SCBF

b. spinal cord perfusion
   - following experimental SCI ***autoregulation*** is lost → ***pressure passive***
   - hypotension leads to cord hypoperfusion & ischaemia
   - hypertension leads to increased oedema and haemorrhage
   - therefore the aim is to maintain ***MAP ~ normal***

c. experimental*
   - hypothermia
   - hyperbaric oxygen
   - catecholamine antagonists
   - dimethyl sulphoxide
   - naloxone (opioid antagonism)

NB: *none of these has consistently demonstrated a benefit in human clinical trials

Associated Problems

- ***Airway Management***

NB: any patient with a significant ***closed head injury*** potentially has a fractured ***cervical spine***

• ***neutral position*** must be maintained during intubation
• non-incremental traction without radiological control ***does not*** protect against further injury
• blind nasal & fibreoptic intubation may be attempted if base of skull fracture can be excluded, however both tend to produce coughing & bucking which may be deleterious

NB: RSI & oral intubation are indicated in the presence of,

i. complete apnoea
ii. associated head injury with GCS < 9
iii. an uncontrollable patient

- ***Respiratory Complications***

• ***anoxia/hypoxia*** is the most common cause of death in acute SCI
• ***pneumonia*** is the 2nd most common cause of death
• the degree of respiratory embarrassment depends upon SCI level
• ***phrenic paralysis*** ($C_{3,4,5}$) arises with ***lesions*** $\geq \mathbf{C_4}$, leaving only the accessory muscles

→ severe hypoventilation

• intercostal & abdominal paralysis results in significant reduction in pulmonary function $\geq \mathbf{T_7}$
• pulmonary oedema, ***DVT & PTE***, also contribute significantly to early mortality
• ***pulmonary oedema*** has been seen in up to 44% of patients following resuscitation from spinal shock
• this most likely results from over-enthusiastic volume resuscitation, and attempts to maintain a "normal" arterial BP

- ***Cardiovascular Complications***

1. ***acute changes***
   - in experimental SCI there is an abrupt, brief (2-3 min) increase in MAP, ? due to sympathoadrenal outflow
   - this is associated with significant increases in CBF/ICP, BBB permeability, extravascular lung water, CVP, PAP, PAOP, and CO
   - this supports the tendency for these patients to develop ***cerebral & pulmonary oedema*** early in resuscitation
   - rarely seen by the time of admission to a 3° centre

2. ***hypotension*** ≡ᵗ "spinal shock"
   - varying degrees of hypotension, bradycardia, decreased TPR, low-normal CVP and a normal or slightly elevated CO
   - decreased myocardial function, with ↓ LVSWI (~ 26%) and CI (~ 18%) in response to volume loading in patients for spinal stabilisation surgery
   - loss of the cardioaccelerator fibres (T_{1-4}) produces ***bradycardia***
   - ? the Bainbridge reflex (decreased RAP) may contribute as bradycardia is seen in below T_4 SCI
   - lesions ≥ $\mathbf{T_1}$ leave only the Frank-Starling mechanism to increase contractility, and may produce a MAP < 40 mmHg
   - the β-***endorphin*** surge with SCI may also depress contractility by either a direct action on the heart, or by centrally mediated increases in parasympathetic tone
   - ***orthostatic reflexes*** are absent & positioning important
   - severe hypotension is observed above a ***critical level*** ~ $\mathbf{T_{6-7}}$
   - this phase may last days to weeks but is usually ***less than*** the period of flaccid muscle paralysis
   - cautious addition of fluid is recommended in view of the decreased CVS reserve and tendency to ***oedema formation***
   - monitoring by PAOP is frequently indicated as the venous compliance curve is abrupt in the absence of resting tone

3. ***autonomic hyperreflexia***
   - this follows the phase of hypotension/flaccid paralysis in patients with ***lesions*** ≥ $\mathbf{T_{6-7}}$, usually at 1-3 weeks
   - MAP returns to ~ normal or below, with episodes of severe hypertension in **~ 85%** of patients
   - triggered by common noxious stimuli, bladder or rectal distension, labour or surgical pain
   - this generalised response begins ***below*** the level of the lesion, due to the loss of control of the higher centres
   - it may spread above the lesion due to ***sympathetic divergence***
   - symptoms include nasal congestion, severe headache, dyspnoea and nausea
   - signs include pallor, sweating, intense somatic & visceral muscle contraction, & piloerection below the lesion
   - above the lesion there is flushing & severe hypertension with reflex bradycardia
   - SAH & retinal haemorrhages have been observed, with syncope, convulsions and death if unabated
   - management has included ganglionic blockers, catecholamine storage depletion, α-adrenergic blockade, and direct vasodilators
   - however the studies have been small & lacked controls
   - the main aim is to ***avoid*** known stimuli

4. ***arrhythmias & ECG abnormalities***
   - mid thoracic SCI results in sinus or nodal bradycardia ± PAC's, PVC's, AV dissociation, or ventricular tachyarrhythmias
   - ***atropine*** is usually effective for bradyarrhythmias, which are frequently seen with airway manipulations
   - β-***blockers*** may be useful for ventricular tachyarrhythmias
   - the ECG frequently shows LV strain ± subendocardial ischaemia
   - similar arrhythmias are seen in ~ 75% of autonomic hyperreflexic episodes

- ***Other Systems***

1. ***genitourinary***
   - ARF may occur 2° to hypotension, dehydration, sepsis, nephrotoxic drugs, acute obstruction, associated renal trauma, or other factors
   - in the chronic phase of SCI, renal failure accounts for ~ 20-75% of mortality
2. ***disordered thermoregulation***
   - afferent information to the hypothalamus may be interrupted
   - sympathetic denervation causes heat loss
   - inability to shiver reduces heat production
   - general tendency to become ***poikilothermic***
3. ***fluid & electrolytes***
   - chronic SCI patients tend to be ***hypovolaemic & anaemic***
   - hypercalcaemia and hypercalcuria follow immobilisation, especially in young male patients (peak ~ 10/52 post-SCI)
4. ***gastrointestinal complications***
   - ~ 20% of SCI patients develop ***GIT bleeding*** acutely
   - nonspecific liver dysfunction with a normal bilirubin occurs commonly
   - gastric distension & ileus are common
   - increased risk of regurgitation / ***aspiration***
5. ***suxamethonium hyperkalaemia***
   - may be seen as early as **3 days**
   - the magnitude of the rise is more a function of the muscle mass affected than the amount of drug given
   - the underlying overgrowth of receptors may occur well ***before*** spasticity replaces flaccid paralysis
   - pretreatment with a nondepolarising agent ***does not*** reliably prevent the occurrence of significant hyperkalaemia

Management

- between 25-65% of SCI patients have associated problems, most commonly,
    1. head injury
    2. thoracic trauma
    3. abdominal trauma
    4. major skeletal trauma

- these may compromise respiratory or circulatory function coincident with spinal shock and require a high index of suspicion
- during the acute phase, maintenance of "normal" acid-base & blood gas parameters and adequate cord perfusion are paramount
- experimental animal work has shown ***no advantage*** in either hypercapnia or hypocapnia in neurological recovery or histological tissue damage
- although not statistically significant, there is some date to suggest hypercapnia is more harmful than hypocapnia
- therefore, should aim for a P_{aCO2} ~ 35-40 mmHg and ***hypoxaemia*** should be avoided at all costs
- ***contributing factors*** such must be suspected and managed accordingly,
    i. pulmonary contusion
    ii. pneumothorax, haemothorax
    iii. pulmonary embolism (fat or thrombus)
    iv. foreign body
    v. gastric aspiration
    vi. non-cardiogenic pulmonary oedema

- similar to the findings for CNS ischaemia, an elevated ***plasma glucose*** has been shown to be deleterious upon neurological outcome
- mild to moderate increases of BSL $\leq$ 2.5 mmol/l, tripled the incidence of paraplegia in rabbits following aortic occlusion
- notably there was a lack of correlation between the degree of BSL rise and the extent of neurological injury
- therefore, as for head injury, the administration of dextrose containing fluids should be restricted to proven hypoglycaemia
- the present data are insufficient to recommend active reduction of an elevated plasma glucose

- Cole (1989) looked at various anaesthetic techniques following SCI in the rat
- of the techniques studied, halothane, fentanyl, N_2O, and SA lignocaine, ***all*** increased the duration of ischaemia required to produce SCI
- no one technique was superior in terms of final ***neurological outcome***

POSTOPERATIVE CNS DYSFUNCTION

Post Routine Anaesthesia & Surgery

• all agents used for premedication, induction and maintenance have some lingering effects and contribute to subtle CNS dysfunction in recovery,

a. ***midazolam*** affects memory for a similar duration to diazepam

b. methohexital affects psychomotor performance for > 12 hrs

c. ***propofol*** affects memory function for < 24 hrs

d. induction & maintenance with ***halothane/enflurane*** for 3.5 mins impairs psychomotor function for ~ 5 hrs;
the duration of impairment increasing with the duration of anaesthesia

e. REM sleep is abnormal for days following surgery & anaesthesia

• previous allegations that the ***elderly*** are more susceptible to these effects have ***not*** been supported by recent studies
• effects in the elderly may actually be a part of the "whole" hospitalisation experience

NB: elderly patients receiving ***regional anaesthesia*** (especially with sedation) have psychic and cognitive dysfunction similar to those receiving a GA (Chung CJA 1989)

▪ ***Delirium***

a. cerebral hypoxia
- hypoventilation, pulmonary oedema, etc.
- hypotension
- cerebral ischaemia

b. anaesthetic medications
- ketamine
- anticholinergics (atropine, scopolamine)
- propofol, benzodiazepines

• factors associated with an increased risk of postoperative delirium,

a. extremes of age

b. pre-existing organic brain disease or psychiatric disease

c. type of surgery
- ophthalmic
- cardiac
- hip repair

d. endocrine & metabolic disturbances

e. language difficulties

f. postoperative pain

g. covert drug abuse

■ ***Perioperative Stroke***

• following non-cardiac, non-neurological surgery the reported ***incidence*** is uncommon

→ 1:2,500 to 1:20,000

• an asymptomatic carotid bruit ***does not*** increase the risk of perioperative stroke
• studies are divided as to whether symptomatic CVD (TIA, RIND) increases the risk

NB: recommended that surgery be delayed for ***≥ 6 weeks*** following an acute CVA, due to the risk of reinfarction, though there is no controlled study to justify this practice

• the relationship between intraoperative ***hypotension & stroke*** is tenuous,

a. hypotension is very common, whereas stroke is uncommon
b. many patients suffering postoperative stroke, survived intraoperative hypotension without neurological sequelae
c. a study of TIA patients exposed to a 60% reduction in MAP, showed a large percentage had no focal findings

NB: not suggesting hypotension is benign, but less sinister than previously thought

• ***thrombotic*** and ***embolic*** events are probably the most common form of perioperative CVA
• Hart (1982) in a series of 12 cases found 5 of ***cardiogenic*** origin (related to MI or atrial fibrillation), and nearly all occurred ***postoperatively***
• Oliver (1987) reported 3 cases, 2 due to embolism (1 cardiogenic, 1 paradoxical CO_2) and 1 due to haemorrhage

■ ***Clinical Evaluation of the CNS in Recovery***

• a prospective study of all patients admitted to recovery over a 1 month period found 9% were unrousable for up to 15-90 minutes
• most patients awake promptly but the variability is large
• delayed arousal is more commonly due to ***drug effects*** than a CNS event
• a brief CNS examination looking for ***focal deficits*** should be performed,

1. findings common in ***normal*** patients
   i. absent pupillary reflexes
   ii. clonus, hyperreflexia
   iii. upgoing plantars

   however, these are ***bilateral*** if due to anaesthesia

2. other findings, which may also be ***drug induced***,
   i. opisthotonus
   ii. difficulty with eye opening
   iii. extrapyramidal signs
   iv. seizures

- signs ***unlikely*** to be due to anaesthesia and indicating a possible CNS event,
    1. unilateral or focal neurological abnormalities
    2. positive snout, palmomental, grasp & Hoffmann's reflexes

- management / evaluation of delayed recovery includes,
    a. review history
        i. medical & drugs
            - seizures, TIA's, SAH
            - cardiac history (recent MI etc.)
            - diabetes
            - prescribed & illicit drug use
        ii. anaesthetic
    b. examine to exclude significant pathology
        i. brief neurological examination
        ii. cardiac examination
            - arrhythmias
            - intracardiac shunts
            - recent MI
            ± echocardiogram
    c. allowing ***time*** for recovery from anaesthesia
    d. reversing those agents which can be reversed,
        i. ***naloxone***
            - small doses, 40-80 µg
            - allows assessment without adverse effects or increase of pain
        ii. ***physostigmine***
            - effective for anticholinergics
            - unreliably reverses volatile agents and the benzodiazepines
        iii. ***flumazenil***
            - benzodiazepines
    e. neurological I_x
        - EEG is not usually helpful, except for ongoing seizures
        - ***CT head*** delineates mass lesions, but does not exclude stroke
        ± angiography for carotid or vertebrobasilar disease

Following Specific Surgical Procedures

▪ ***Carotid Endarterectomy***

• the incidence of perioperative stroke ***~ 2-20%***
• possible causative, or associated factors include,

a. hypoperfusion during ***cross clamping***

b. ***embolic events*** during,

i. shunt insertion

ii. reperfusion of the carotid

c. ***reperfusion hyperaemia*** ∝ severe preoperative stenosis
postoperative hypertension

• strategies rely on the concept that cerebral ischaemia can be recognised prior to permanent damage being caused
• recognition of cerebral ischaemia is probably best achieved with either an ***awake patient***, or using ***processed EEG***,

a. studies comparing the 2 indicate that both false positive and negative EEG's occur, however the agreement between the 2 is usually good

b. whether EEG monitoring improves outcome ***has not*** been ascertained, there are no controlled trials

c. untreated cross-clamp induced EEG changes indicative of ischaemia are predictive of stroke in some patients

NB: indirect evidence in support of EEG monitoring,
however, most CEA associated strokes ***do not*** occur during cross-clamping

- preservation of $CMRO_2$ balance,
    a. ***shunting*** - not performed routinely due to the risk of ***emboli***
       - standard practice in response to EEG changes
    b. loss of vascular reactivity and the potential for "steal" and "inverse steal" has led to debate regarding optimal P_{aCO2} and blood pressure;
       studies are small and the influence of these on outcome is uncertain

       → maintenance of ***normocarbia*** is recommended
    c. a retrospective review of 2000 CEA's showed that ischaemic EEG changes were less common with ***isoflurane*** (18%) than with either halothane or enflurane (25%); however, there was no difference in neurological ***outcome*** in the 3 groups
    d. ***critical CBF*** for EEG ischaemia,
        i. with isoflurane ~ 8 ml/100g/min
        ii. halothane/enflurane ~ 18 ml/100g/min
        iii. however, animal models of focal cerebral ischaemia have failed to show a protective effect with isoflurane
    e. ***barbiturates*** have been traditionally used for brain protection, however, evidence for their efficacy in focal ischaemia is variable (specifically during CPB)

- reducing the effects of ischaemia,
    a. ***glucose***
        - models of focal incomplete ischaemia (≡ CEA) are not consistent
        - the ***threshold*** for adverse effects has not been defined
        - still recommended however, to avoid glucose unless indicated

    b. ***nimodipine***
        - * improves neurological outcome and reduces mortality in ischaemic stroke if commenced within 24 hours of stroke
        - oddly the benefit is confined to ***men***
        - ? role in perioperative stroke

■ ***Cardiopulmonary Bypass***

• estimates of the incidence of neurological dysfunction post-CPB ***~ 2-61%***
• subtle deterioration in cognitive or neuropsychological function occurs in ≤ 80% of patients undergoing CPB
• both ***cerebral hypoperfusion*** and ***embolic phenomena*** have been implicated,

a. most, but not all, recent studies argue that perfusion is ***not*** a major determinant following routine CPB

b. conversely, there is evidence for "***luxury perfusion***", preserved coupling of $CBF/CMRO_2$ and, with ***alpha stat*** management, intact autoregulation

c. ***microemboli*** of fat, air, cellular elements etc. are probably responsible for most post-CPB dysfunction; efforts to minimise these include,

i. membrane oxygenators
ii. arterial filters
iii. short bypass times

NB: evidence of reduced incidence or extent of CNS dysfunction is ***equivocal***

• factors which compound the risks for CNS dysfunction include,

i. open chamber surgery
ii. prolonged bypass period
iii. symptomatic cerebrovascular disease
iv. advancing age

• the controversy over optimal CO_2 management continues, as to what represents a "normal" $PaCO_2$ in a hypothermic patient and the possible effects of,

a. hypercapnia increasing CBF and predisposing to emboli, or

b. hypocapnia leading to relative hypoperfusion

NB: although there are measurable differences in CBF between alpha-stat and pH-stat methods, there is ***no data*** to suggest one is associated with a worse CNS ***outcome***; Bashein (1990) in a randomised controlled trial failed to demonstrate differences in CNS outcome as a function of CO_2 management

• the role of ***barbiturate protection*** during CPB is also in dispute
• Nussmeier (1986) showed in a prospective controlled trial of patients undergoing open chamber, normothermic CPB, that ***burst suppression*** doses of thiopentone, prior to aortic cannulation reduced the incidence of stroke and neuropsychiatric dysfunction, however,

a. the accompanying higher requirement for ***pressor support*** and prolonged ***ventilation*** times, plus the questionable applicability to alternative CPB routines has discouraged the widespread use of thiopentone, also

b. Zaiden (1991) in a randomised controlled trial of closed ventricle, hypothermic CPB procedures, found ***no evidence*** for protection

NB: thus the role of barbiturates during CPB is uncertain

■ ***Thoracoabdominal Aortic Surgery***

• ***paraplegia*** occurs with an incidence from,

a. coarctation repair ~ 0.1%

b. emergency thoracic dissection repair ~ 24%

• spinal cord blood supply comes partly from the segmental vessels arising from the aorta, the artery of ***Adamkiewicz*** ($\mathbf{T_8}$-$\mathbf{L_3}$) predominantly
• spinal hypoperfusion may occur during cross-clamping or when this segment of the aorta is sacrificed during repair
• cross-clamping also increases CBF and therefore ***ICP*** & spinal CSF pressure, which contributes to the decreased spinal cord perfusion pressure
• efforts to reduce the incidence include,

a. SSEP's
- assesses dorsal column, not motor tracts
? effects of hypoperfusion on peripheral nerve axon function
? effects on outcome

b. bypass shunts
- considered beneficial by some workers
? unnecessary, ineffective ± harmful by others

c. CSFP
- attempts to lower ICP/CSFP will improve perfusion pressure
* lumbar SA catheter for pressure monitoring
± drainage of CSF
± protective agents (papaverine ↑SCBF)
→ reduced incidence of paraplegia

NB: study was to small to draw definitive conclusions
considered experimental at this stage

d. the effectiveness of large doses of ***steroids*** post acute SCI cannot be extrapolated to ischaemic injury, but may well prove beneficial in the future

e. as the cord is particularly susceptible to the effects of ***hyperglycaemia***, avoidance of glucose containing solutions seems prudent

■ ***Less Common Neurosurgical Procedures***

a. stereotaxic brain biopsy

b. ablation of seizure foci

c. resection for movement disorders

d. extracranial-intracranial anastomosis