Physiology and Pharmacology of CBF/CSF/ICP

I. Physiology

A. Blood Flow

Cerebral Blood Flow = Cerebral Perfusion Pressure (CPP) / Cerebrovascular Resistance (CVR)

1. Normal Values

a) Cerebral blood Flow

total flow in humans is ≈ 54ml/100gm/min (≈ 750 mls/m, ≈15% of the CO)
Flow via the carotids ≈ 700 mls/min, vertebrales ≈ 50 mls/min
grey matter ≈ 75ml/100gm/min.
white matter ≈ 15-20 ml/100gm/min
overall flow normally ↓ with age ↓ in grey matter)

b) EEG (unanaesthetised, 37°C)

(1) ≈ 20-24mls/100gm/min → ↓ frequency
(2) ≈ 15-19mls/100gm/min → becomes isoelectric

c) Somatosensory Evoked Potentials (unanaesthetised, 37°C)

(1) ≈ 20mls/100gm/min → ↓ amplitude and ↓ latency
(2) ≈ 15mls/100gm/min → absent

d) Cellular Changes

(1) < 20 mls/100gm/min → astrocytes and neuronal mitochondria swell
(2) ≈ 10 mls/100gm/min → ↑ density of neural parikaryon. ↑electron density of nuclei.
(3) < 10 mls/100gm/min → cell death if maintained (unanaesthetised, 37°C)

e) Spinal Cord Blood Flow

white matter of the cord ≈ 15-20ml/100gm/min
gray matter flow ≈ 60ml/100gm/min

B. Methods of Measurement

Some methods of measuring cerebral and spinal cord blood flow are applicable only to animal studies because they require extensive surgical manipulation or tissue sampling. These techniques include the use of radioactive microspheres, classic autoradiography, and venous outflow.

1. Inhalation of Inert Gas

This method, as originally developed by Kety and Schmidt in 1945, used nitrous oxide (N_2O) as the tracer gas. It determines the mean transit time for N_2O molecules through the brain by measurement of the gas in arterial and jugular venous blood samples collected during a 10 to 15 minute period of gas inhalation. Not an entirely practical technique.

It is important to understand that the caveat; that N_2O has no effect on CBF, is only true with low concentrations of N_2O (see later).

Other inert gases that have been used include argon, krypton-85 (^{85}Kr), and xenon-133 (^{133}Xe) (these are most commonly used today).

Regional as well as total flows can be obtained with the use of multiple collimated scintillation detectors placed in various positions over the skull. These detect photons (ionising radiation), and the rate of photons received by a detector is directly related to the concentration of the photon-emitting radionuclide (^{133}Xe) in the volume of tissue seen by the detector. The problem with these radioisotope techniques is the confounding influence of extra-cerebral blood flow.

2. Intra-arterial Injection of Inert Gas

This method, described by Lassen and Ingvar in 1961, also measures the mean transit time of a freely diffusible tracer molecule. Although ^{85}Kr was originally used as the tracer, ^{133}Xe is now most commonly employed. The gas is dissolved in saline solution and injected as a bolus into the internal carotid or the vertebral artery. Scintillation detectors are used to measure the radionuclide, as in the inhalation method. Neither of the inert gas methods is useful for obtaining spinal cord blood flow owing to the difficulty of selective recording from the cord. There are two slopes on the activity decay curve, fast and slow washout phases. The initial fast washout phase is thought to represent gray matter flow and the later white matter flow. There are problems with "look through" where a region of low flow is missed because of gamma emission distal to the region that we are interested in.

3. Topical application of ^{133}I to cortex
   ^{133}I in saline is applied to an exposed area of cortex and the decay is measured as for 2). Allows very localised measurements of rCBF.
4. Intra-arterial Injection of Radioactive Oxygen
   ^{15}O-labelled water injected into the internal carotid artery can be followed with scintillation detectors, and the same equations as are used with ^{133}Xe can be used to determine CBF. In addition, with this technique, it is possible to obtain regional oxygen consumption. The disadvantage of this method is that the half-life of ^{15}O is 2.05 minutes. Thus, it can only be undertaken where a cyclotron is immediately available.
5. Single Photon emission CT (SPECT scans)
   Uses radioisotope labelled Iodine, thallium, and technetium with initial distribution proportional to CBF with almost complete extraction by the brain without redistribution. They therefore allow tomographic imaging. These are currently used at RPAH to localise the focus of focal epilepsy. The technetium is injected within 90s of the start of the fit and localises in the area of ↑ rCBF. The scan can be taken ≤6 hrs later. The usual material is technetium HMPAO.
6. Stable Xenon enhanced CT
   In sufficient concentrations non-radioactive (stable) Xenon is radio-dense. CT is enhanced by inhalation of 30-40% Xenon/Oxygen mixture. Gives local flows with reasonable resolution (2+mm). Xenon anaesthetic effects have to be considered but are minor at the concentrations used. Quantative measurement. Currently only 3 slices can be done at a time and it requires the patient to lie still for 7-9 mins. Has the huge advantage that it can be done very early in patients with acute intracranial problems (at the time of initial CT).
7. MRI
   Using paramagnetic tracers that can be excited in a magnetic field (eg gadolinium-labelled agents) one may directly examine cerebral perfusion. Using capillary transit times one can get indirect indices of CBF and CBV. With the development of freely diffusible paramagnetic drugs we will be able to get wash in and wash out curves similar to current isotope techniques.
8. Positron Emission Tomography (PET)
   Uses radionuclides that emit positrons (^{11}C, ^{15}O, ^{13}N, ^{18}F). The radionuclide is administered through inhalation or intravenous injection. PET has proven useful for determining cerebral blood volume and metabolism. A satisfactory method of measuring regional CBF employing this technique is under development. A cyclotron is required to generate the positron-emitting radionuclides.
9. Trans-cranial Doppler
   This is used to measure the blood velocity of the carotid vessels or the middle cerebral arteries. Dopplers used extensively for non-invasive assessment of carotid narrowing. They are also being used in the management of vasospasm for qualitative assessment of flow. The problem with this technique is that unless the vessel diameter, the flow velocity profile within the vessel, and the angle the probe is to the vessel is known then flow can not be calculated. It is therefore used predominantly as a qualitative measure. Even with this velocity and flow do not always move in the same direction. In the diagnosis of vasospasm it is an increase in velocity that is considered diagnostic!
10. Laser Doppler
    This uses a probe that is placed directly onto an area of cerebral cortex. It uses the reflection of light from RBCs in the area of cortex immediately below the probe to calculate a rCBF equivalent. The bandwidth of the reflected light is proportional to the flow. The amount of activity at these shifted frequencies gives an indication of the number of RBCs in the volume of cortex looked at (i.e. a measure of blood volume) It monitors a small (several mm deep) area of tissue. It must be positioned over an area of cortical tissue and not a major vessel for accurate results. Gives relative values but it is claimed it can be calibrated against some other technique to give an absolute value. It looks at flow in very small vessels and probe orientation is not a problem and is therefore much more reliable than ultrasound doppler.
11. Thermal Diffusion
    CBF is measured by thermal diffusion. The thermal diffusion is constant without blood flow, but with an increased blood flow, the thermal conductivity increment was a linear function of the rate

of flow in the tissue. A distal circular gold plate (6mm) is heated (with a fixed amount of power) while a smaller proximal gold plate (2mm) is held at a neutral temperature by the cortex it is resting on. The temperature gradient between the two plates is inversely proportional to CBF. An alternative type exists where the temperature difference between the two plates is held constant and the amount of power needed to do this is proportional to the flow.

The device is placed subdurally and may contain facility to monitor ICP as well. It should be over an area of cortex not a major vessel for accurate measurement. It correlates well with other techniques. It measures cortical blood flow (in the top 2-3mm) not global flow.

It appears that it still needs to be calibrated against some other device however it seems to be possible to do this in a given probe on an experimental animal.

12. Hydrogen Clearance

Electrical potential measured in reference to an implanted polarized electrode following IV bolus or inhalation of H_2. The platinum electrode is polarised positive with respect to a reference electrode (usually Ag/AgCl). H_2 is administered and then is allowed to wash out. The H_2 in the vicinity of the platinum electrode (the electron receiver or anode) is oxidised to 2 protons and 2 electrons ($H_2 \rightarrow 2H^+ + 2e^-$), the later being accepted by the platinum electrode, thus generating a current flow that is proportional to the relative concentration of H_2 in the vicinity of the electrode. The current decreases as the $[H_2] \downarrow$, ie a washout curve is created. Used in animal experiments. It allows multiple measurements to be made but is somewhat invasive and there is some concern about the effects of the implanted electrodes themselves (they may cause a local decrease in flow).

13. Autoradiographs

Uses the uptake of ^{14}C iodoantipyrene and thin slices on brain tissue placed against X-ray film. Very high resolution but once only experiment. Animal killed.

14. Radio-isotope labelled microspheres

Maximum of 6 different isotopes in the one animal (with different energy emissions). Animal then sacrificed and radioactivity measured to give rCBF. Not accurate for very low flows as some blood flow is needed to carry the spheres to the capillaries

15. Venous Outflow

If one collects the total outflow of the sagittal sinus a very reliable indicator of total CBF is possible (only reliable in dogs).

C. **Regulation of Cerebral and Spinal Cord Blood Flow**

1. Cerebral Perfusion Pressure

CPP = MAP – (Cerebral Tissue Pressure or Cerebral Venous Pressure)
(whichever is greater)

nb measured at the level of the area of brain we are interested in.

Cerebral tissue pressure usually = ICP but not always. Tissue pressure is usually the limiting factor. When the cranium is open ICP = atmospheric pressure but when the surgeon uses retractors the tissue pressure may become very high.

Normal CPP ≈ 80 mmHg

CPP < 50 mmHg → slowing of the EEG (37°C)
< 25-40 mmHg the EEG → flat EEG
< 20 mmHg → cell death if prolonged.

2. Cerebrovascular Resistance

a) Vessel Diameter

The major site of resistance is at the level of the 30-100μm diameter arterioles.

(1) Autoregulation

In the normal person, CBF remains almost constant, despite wide variation in the mean arterial blood pressure (MAP). This phenomenon, termed *autoregulation,* occurs not only in the cerebral vasculature but in the vessels of many other organs, including the heart and the kidneys, as well.

Autoregulation is an active vascular response; during increases in MAP, the cerebral vessels constrict (i.e. cerebrovascular resistance increases), and during decreases in arterial pressure, the cerebral vessels dilate (i.e. cerebrovascular resistance decreases). The lower limit of autoregulation is about 50 to 60mmHg and the upper limit is about 150mmHg. When MAP falls below 50 to 60mmHg, CBF decreases. When MAP exceeds 150mmHg,

"autoregulatory breakthrough" occurs. This breakthrough is associated with an increase in CBF, disruption of the blood-brain barrier at many sites and the formation of cerebral oedema. It is imperative to understand that these are average values in healthy young people. The "normal" CBF varies considerably and the limits of autoregulation are variable both in normal people and more importantly, in disease. One can not predict with certainty that a given CPP will ensure adequate cellular function.

(a) Cerebral perfusion independent of perfusion pressure
≈ 30 to 120 seconds to compensate for acute changes
hypertensive patients have the curve shifted to the right
treated hypertensive's curves return towards normal
some evidence that similar autoregulation occurs in the spinal cord

(b) Mechanism
The exact contribution of all these factors is not fully defined yet.

i) Myogenic
This hypothesis states that autoregulation is an intrinsic response of the smooth muscle of the arterial wall. When the smooth muscle is stretched by increasing pressure, it contracts, producing vasoconstriction. The response of the smooth muscle to a reduction in systemic arterial tension is relaxation, thus producing vasodilatation. This is probably an important mechanism especially in the acute response.

ii) Metabolic
According to the metabolic hypothesis, blood flow is regulated by the metabolic activity of the tissue. Therefore, anything that interferes with oxygen delivery to the tissue (e.g. hypotension) results in the liberation of acid metabolites, which then produce local vasodilatation and increased blood flow.

iii) Neurogenic
There is some evidence that neural release of neurotransmitters may play some role in autoregulation. Gamma amino-butyric acid (GABA), Neruopeptide Y, substance P, vasoactive intestinal peptide (VIP), and some others may be involved.

(c) Loss of autoregulation:
i) Hypoxia
ii) Hypercapnia
iii) Trauma
iv) Some anaesthetic agents

(d) ↑ ICP ↑ brainstem ischemia ↑ MAP
i) Cushings Triad
(1) ↑ ICP
(2) ↑ BP
(3) ↓ HR

(2) Arterial Blood Gases and pH

(a) PaCO2
i) CBF varies linearly with $PaCO_2$ between 20-80mmhg
PaCO2 = 20 mmhg → CBF ≈ 25 mls/100gms/m
PaCO2 = 80 mmhg → CBF ≈ 100 mls/100gms/m
in persons with initially normal $PaCO_2$
ii) response time ≈ 30 s
iii) The exact mechanism not completely understood
The prevailing theory is that changes in CO_2produce alterations in the pH of the CSF surrounding the vessels and in the walls of the arterioles. This alteration occurs because CO_2crosses the blood-brain barrier freely whereas bicarbonate crosses more slowly. Thus, increases in Pa CO_2 decrease pH in the CSF and arteriolar walls. Because bicarbonate ions do cross the blood-brain barrier, changes in CSF pH and CBF resulting from alterations in Pa CO_2 last only 24 to 36 hours. After this time, CBF returns to normal despite continuing hypocapnia or hypercapnia.
CSF half-life for resolution of pH changes is ≈6/24
iv) Spinal cord blood flow changes similarly

(b) PaO2

i) ↑ with $PaO_2 < 50$mmhg

The mechanism for the increase in flow with hypoxia is not clear but probably results from accumulation of acid metabolites.

ii) ↓ 10-12% with $PaO_2 > 300$ mmHg

(c) pH (PaCO2 = 40 mmHg)

i) acidaemia → slight ↑

ii) alkalaemia → slight ↓

(3) Cerebral Metabolism

(a) Total CBF

Total CBF generally parallels overall cerebral metabolism. Metabolism, and consequently CBF, is closely correlated with brain activity. When the level of activity is lowest, as in coma, metabolism and CBF are lowest. When overall brain activity is high, as in a grand mal convulsion, metabolism and CBF are high.

(b) Regional CBF (rCBF)

The same is true of activity, metabolism, and CBF at the regional level. The exact controlling mechanism for rCBF is unclear. The ↑ in flow precedes a ↓ in local pH so this can not be the primary mechanism. Flow also ↑ more than local oxygen consumption does so presumably oxidative metabolism is also not the key. Recently it has been suggested that neuronal mechanisms may be responsible. Whether this is via local release of vasodilator substances eg Substance P or due to the release of K that occurs during depolarisation is not settled. A recent suggestion is that the glial cells take up the released K and then release it at their end-feet (on the capillaries). This "syphoning" would result in larger rises in [K] at the vessel wall than would occur via diffusion alone.

Nitric oxide may also play a role but again this is not fully elucidated.

(c) Sleep

Changes in CBF occurring during sleep and unrelated to variations in either PaCO2 or MAP appear to reflect alterations in cerebral metabolism. CBF is reduced approximately 10% during slow-wave sleep and is increased about 10% during rapid eye movement (REM) sleep.

(d) Body Temperature

acts via changes in metabolism

i) ↓ → ↓ CBF

This is not a simple relationship. The relationship between temperature and metabolic rate is often expressed by the Q10. This is simply the ratio between two metabolic rates separated by 10°C ie a Q10 of 2.0 means a 50% reduction of metabolic rate. The Q10 between 37° and 27° (when continuous EEG activity is present) is ≈2.0 however between 27° and 17°C EEG activity ceases and there is a step reduction in metabolic rate. The Q10 over this next step is ≈5.0! This explains how at 17° it is possible to tolerate 50 minutes of complete cerebral ischaemia without damage. In the absence of EEG activity eg barbiturate coma the Q10 is ≈ 2.0 over the entire temperature range.

The relationship between CMRO2 and CBF is maintained, as is the CO2 response curve. Uncorrected values for PaCO2 at 37°C should be used for defining hypo and hypercarbia during hypothermia.

ii) ↑ → ↑ CBF

> 42°C → ↓↓ in CMR indicating the threshold for toxic effects of hyperthermia

(4) Neurogenic Factors

(a) little direct actions↑→↓

The physiologic importance of the sympathetic and parasympathetic innervation of the cerebral vasculature has been extensively debated and is still a matter of some controversy (Gross, 1979). Although neurogenic influences appear to be less important for overall cerebrovascular regulation than the factors just discussed, they may be operative at the upper and lower limits of autoregulation.

Marked ↓ BP from hypovolaemia result in a right shift in the autoregulatory curve suggesting that there is some sympathetic innervation.

b) Viscosity

(1) Hematocrit

The hematocrit affects CBF primarily by altering blood viscosity. Measurable changes in CBF are not seen with hematocrits between 30 and 50%. There is some evidence that in patients with cerebral vasospasm that reducing the haematocrit to ≈ 30% may provide optimal oxygen delivery.

(a) ↑ → ↓ CBF

(b) ↓ → ↑ CBF

(2) Plasma Viscosity

This is not physiologically variable however therapeutically decreasing plasma viscosity can increase CBF eg mannitol in patients with cerebral vasospasm.

II. Cerebral Metabolism

A. Cerebral Metabolic Rate for Oxygen ($CMRO_2$)

1. ≈ 20% of resting oxygen uptake (50 mls/m)
   1.3 - 1.6 μmol/gm/min (3.0–3.8ml/100gm/min)
   $CBF / CMRO_2$ is normally ≈ 15
   $CMRO_2$is higher in children than in adults.
   The $CMRO_2$of the cerebral cortex is the highest in most species studied.
2. Processes that require oxygen
   a) reduction of molecular oxygen
      The most important oxygen-consuming process in the brain is by the electron transport system. This process produces high-energy phosphate compounds and water.
   b) The mixed function oxidase system
      oxygen transferase system
      two processes that require oxygen they are involved in synthesis and detoxification. These systems contribute little to the overall oxygen consumption of the brain.
3. Oxygen stores in the brain are almost nonexistent
   Consciousness is lost when $PaO_2 < 30$mmHg
   If delivery of oxygen to the brain ceases ↓ LOC within 5-11 s

B. Cerebral Metabolic Rate for Glucose (CMRgl)

1. Glucose consumption ≈ 0.25 μmol/gm/min (5mg/100gm/min)
   ≈ 95% of glucose consumption is aerobic
   A small amount of "anaerobic" metabolism occurs normally → lactic acid
   The normal cerebral venous lactate/pyruvate ratio is ≈15. This increases with hypoxia
   This small amount of "anaerobic" metabolism does not signify a lack of oxygen, the normal oxygen tensions in the brain do not limit cellular respiration. The production of lactic acid has to do, rather, with lactate concentration gradients, since if lactate levels in the brain rise, lactate production stops and, in fact, the brain can take up and metabolise lactate.
2. Relationship Between $CMRO_2$and CMRgl
   fixed relationship under normal conditions
   The general equation for the reaction is:
   $Glucose + 6\ O_2 \rightarrow 6\ CO_2 + 6\ H_2O$
   $\therefore\ CMRO_2 / CMRgl \approx 6$ (normally)
   Under certain conditions, including hypoxia (which activates glycolysis), hypercapnia (which inhibits glycolysis), and hypoglycaemia (when ketone bodies are produced), the relationship does not hold. In these instances, CMRgl is not synonymous with cerebral metabolic rate.
3. Metabolism of Alternative Substrates
   During starvation, the brain can metabolise acetoacetate and beta-hydroxybutyrate
   These compounds appear to be the only substrates that can support cerebral energy production in the absence of glucose. Amino acids are not important in the absence of glucose, and fatty acids are not used by the brain.

C. **Production of High-Energy Phosphate Compounds**

1. The aerobic metabolism of glucose produces ATP according to the equation:
   Glucose + 6 O_2 + 38 ADP + 38 Pi → 6 CO_2 + 6 H_2O + 38 ATP
   The hydrolysis of ATP into adenosine diphosphate (ADP) and inorganic phosphate (Pi) is accompanied by a release of energy. Thus the oxidation of glucose provides energy for the various synthetic and transport processes of the brain. 36 of these ATP come from oxidative phosphorylation.
2. [ATP] is not an accurate indicator of the energy level of the brain as the storage form of ATP is phosphocreatine (PCr)
   Also ATP can be produced from ADP:
   ADP + ADP ↔ ATP + AMP (adenylate kinase)
   Phosphocreatine can provide ATP according to the equation.
   PCr + ADP + H^+ ↔ ATP + Cr
   During periods of hypoxia, ATP levels are preserved, at the expense of PCr and ADP, until the hypoxic stress becomes severe. The earliest changes with ischaemia are ↓ [PCr] and ↑ lactate/pyruvate ratio.
3. Energy Charge (EC) of the brain
   $EC = \frac{[ATP] + {}^1/_2 [ADP]}{[ATP + ADP + AMP]}$
   This is a measure of the energy state of the brain and a normal value is ≈ 0.9. Used in animal experiments. It decreases with hypoxia.

III. **Cerebrospinal Fluid**

A. **Secretion and Circulation of Cerebrospinal Fluid**

1. CSF is formed at ≈ 0.35ml/min/70 kg (500mls/d)
   The total volume of CSF ≈130 to 150ml
   ≈50% is intracranial (this figure varies from source to source)
2. Sites of Formation
   Most CSF is formed in the choroid plexus (≈ 70%) and the ependymal lining of the cerebral ventricles. Some CSF is formed extrachoroidally by the cerebral capillary endothelium, and some may be derived from the water of oxidative metabolism.
3. Mechanism of formation
   The capillary endothelium of the choroid is fenestrated forming a protein rich fluid within the choroidal stroma. The choroidal epithelial cells which separate this from the CSF contains apical tight junctions which constitutes a blood-CSF barrier. Water moves freely across this barrier via hydrostatic pressure. The passage of most ions and glucose is via active transport or facilitated diffusion resulting in a tight control of CSF concentration.
4. Composition
   CSF is actively secreted by the choroid plexus and other sites
   [Na] ≈ 141 mmol/
   [K] ≈ 2.9 mmol/l
   [Ca] ≈ 1.2 mmol/l
   [HCO3] ≈ 21 mmol/l
   [glucose] ≈ 3.3 mmol/l
   [Cl] ≈ 124 mmol/l
   [Mg] ≈ 1.2 mmo/l
   The pH ≈ 7.32
   PCO2 ≈ 51mmHg
   CSF is isotonic to plasma ≈ 285 mosmoles/kg
   [K], [Mg], [Ca] in newly formed CSF is constant despite changes in plasma []s.
   Protein concentration in the CSF is extremely low, ≈ 0.28 gm/l. Whilst the concentration of most proteins are very low, the transport proteins transthyretin, transferrin, and ceruloplasmin are secreted by the choroid, they transport thyroid hormones, iron, and copper respectively.

5. Factors Affecting Secretion
   a) Physiologic Parameters → ↓ production
      (1) ↓ choroidal blood flow
          ↓ choroidal capillary hydrostatic pressure.
          It is thought that the rate of CSF production is controlled by choroid plexus arterioles changing size so that the pressure in the plexus capillaries is constant, until the MAP (at the head) < 50-60 mmhg.
      (2) ↓ body T°
      (3) ↑ serum osmolality.
      (4) ↑ intraventricular hydrostatic pressure (minimal)
          The rate of secretion is independent of the CSF pressure until the cerebral perfusion pressure falls below the lower limits of autoregulation.
   b) Drugs that ↓ production
      Ouabain and corticosteroids produce their effect by inhibiting Na/K ATPase. The mechanism of action of the other drugs is less clear; it may be related to their effects on sodium transport, or, in the case of acetazolamide, the effect on bicarbonate formation
      (1) acetazolamide
      (2) ouabain
      (3) corticosteroids
      (4) spironolactone
      (5) furosemide
      (6) vasopressin
      (7) mannitol
6. Circulation
   CSF flows from the lateral ventricles into the third ventricle and then into the fourth ventricle. It leaves the ventricular system via the medial (foramen of Magendie) and lateral (foramina of Luschka) foramina of the fourth ventricle into the cerebellomedulary cistern (cisterna magna). The fluid circulates in the subarachnoid spaces surrounding the brain and spinal cord. The flow in the spinal subarachnoid space is extremely sluggish compared to the flow in the cranial subarachnoid space.

B. **Absorption of Cerebrospinal Fluid**
1. Sites of Absorption
   The major sites of absorption of CSF are the arachnoid villi that protrude into the cerebral venous sinuses. Ten to fifteen percent of the absorption occurs in the spinal subarachnoid space, while the ependyma and meningeal lymphatics take up small amounts of CSF as well. From these sites, CSF is returned to the venous system.
2. The Mechanism of Absorption
   The mechanism of CSF absorption is not completely understood. At one time it was thought that the arachnoid villi had valves that prevented back-flow of CSF from the cerebral sinuses to the subarachnoid space. Another theory was that the arachnoid villi consisted of a number of tubes that provided direct communication between the subarachnoid space and the venous sinuses and permitted CSF to move into the sinuses by bulk flow. There is no histologic evidence, however, for either valves or open channels in the arachnoid villi.
   More recently, giant vacuoles in the lining cells of the arachnoid villi have been described. These appear to develop from invaginations of the basal cell surface and open onto the apical cell surface, thus forming in essence a dynamic system of channels through the cells. These channels allow bulk flow of CSF to occur through the cells of the arachnoid villi.
3. Factors Affecting Absorption
   The absorption of CSF is governed by a hydrostatic force
   linear relationship between pressure and absorption
   Below a CSF pressure of 7cmH20 absorption ceases
   a) ↑ in CSF pressure → ↑ absorption
   b) ↑ in cerebral venous pressure → ↓ absorption.

4. Functions
   a) Shock absorbtion
      The net weight of the brain in the CSF is ≈ +50 gms. This obviously limits the damage that can occur with skull movement even if these are quite severe. This is the major function of CSF as anyone who has had a hangover can attest to!
   b) Stable milleau for electrical activity
      The brains function depends on a precise relationship between neurotransmitter release and electrical response. The CSF provides a stable background for this to occur. The three most important ions ([K], [Mg], [Ca]) for a neurones electrical responses are held stable in the CSF.
   c) Cirulation of nutrients and neurotransmitters
      This is probably a minor role
   d) Circulation of neuromodulators eg endorphins
      specialised ventricular cells and neurons within brain parenchyma secrete these neuroendocrine factors into the CSF where they can diffuse throughout the CSF.
   e) Removal of metabolic products

IV. Intracranial Pressure

A. General Principles

1. Intracranial pressure (ICP)
   ≈ 5-10mmhg in the recumbent person (mid-cranium)
   The term as currently used means *supratentorial CSF pressure;* that is, the pressure in a lateral ventricle or in the subarachnoid space over the convexity of the cerebral cortex. This definition is a simplification of the concept of CSF pressure, as this pressure may be markedly different in different areas of the cranium, and as CSF pressure in the cranial subarachnoid space may differ from pressure in the spinal subarachnoid space. In a normal person in the recumbent position, the CSF pressure measured at the lumbar cistern accurately reflects ICP. However, many factors, including the assumption of the upright position, can alter the relationship between cranial and spinal CSF pressure. In addition, in the presence of intracranial mass lesions, infratentorial CSF pressure (as measured in the cisterna magna or lumbar cistern) often falls while supratentorial pressure rises. Despite these problems, the measurement of supratentorial CSF pressure is a useful clinical tool.
2. Volume of Cranial Contents ≈1500mls
   Monro-Kellie doctrine:
   Because the cranial vault is a rigid structure the volume within must be constant. That volume is made up of Brain, CSF, and Blood, any increase in volume in one or more must be associated with a decrease in one or both of the others.
   a) Brain volume - 1350mls (gms) (≈90%)
   b) Blood volume - 75mls (≈5%) (recumbent)
      Note that changes in CBF will only producing ↑ ICP when there is an ↑ CBV. Usually however these move in the same direction. Over the limits of autoregulation there is vasoconstriction as CPP↑ → ↓ CBV. The reverse happens when CPP ↓ and vasodilation occurs → ↑CBV.
      (1) Venous ≈75%
      (2) Arterial ≈24%
      (3) Capillary ≈1%
   c) CSF volume - 75mls (≈5%) (recumbent)

B. Intracranial Compliance

1. Pressure-Volume Curve (Elastance Curve)
   Intracranial compliance can be illustrated diagrammatically by the pressure-volume curve.
   a) No single curve, varies with:
      (1) which compartment the increase in volume occurs in
         The best compensated is when the increase occurs in brain volume as both blood and CSF compensatory mechanisms are available to help. An increase in either CSF or blood volume will leave only the other to help. Squeezing the brain out through the foramin magnum is not an effective compensatory mechanism!
      (2) MAP

(3) $PaCO_2$

b) phases of the curve:

(1) flat horizontal portion (representing high compliance)

During the phase of high compliance, a considerable increase in total intracranial volume may take place before ICP increases. This initial stability occurs because there is a certain degree of elasticity in the craniospinal system; in addition, an increase in the volume of one of the intracranial contents can be partially compensated for by a decrease in the volume of the remaining contents.

(2) intermediate portion (representing a transition stage)

(3) steep terminal portion (representing low compliance)

2. Testing Intracranial Compliance

A patient may have normal or nearly normal ICP and yet be at the limit of compensatory mechanisms. Further perturbations, such as those which can occur during the induction of anaesthesia, may therefore be associated with large increases in ICP and a worsening of neurologic status. A method for determining which patients are in this category would be clinically useful. Miller et al (1973) devised a method for testing intracranial compliance in patients whose ICP is being monitored continuously by an intraventricular catheter. The ICP response to the injection of one millilitre of fluid through the catheter is assessed. An increase of greater than 4mmHg is almost always associated with a significant mass lesion and is an indication of poor compliance.

3. Effects of ↑ ICP

a) Brain herniation

Ischaemia of the brainstem probably arises from the downward movement of the brainstem kinking vessels entering it rather than the effects of ↓ CPP. Death occurs due to terminal brainstem ischaemia.

b) ↓ CPP

V. Blood Brain Barrier (BBB)

A. Structure

The cerebral microcirculation behaves quite differently to the rest of the body. In the majority of the bodies capillaries there are fenestrations ≈6.5nm between capillary endothelium. In the brain the endothelial cells are joined by tight junctions and the foot processes of the astrocytes completely end-sheath the capillaries. They are only separated only by an attenuated basal lamina.

B. Function

It behaves as if it had fenestrations of ≈0.8nm and ∴ only H_2O and lipid soluble substances can freely cross it. Specific transport mechanism exist for ions, amino acids, glucose and other substances.

The relative impermeability to ions as well as protein means that total plasma osmolality rather than plasma oncotic pressure is the critical factor for fluid movement (cf with normal capillaries).

Certain areas of the brain do not have this BBB and are affected by plasma concentration of substances. These areas are known as the Circumventricular organs. They are the posterior pituitary and adjacent ventral part of the median eminence of the hypothalamus, area postrema, organum vasculosm of the lamina terminalis, and the subfornical organ. These areas are important in water and sodium balance, blood pressure control, and hormone secretion.

C. Dysfunction

Results in leakage of protein into the brain interstitium and cerebral oedema.

1. Acute severe hypertension
2. Trauma
3. Ischaemia

VI. Pharmacology

One of the major mysteries of cerebral pharmacology is the effects of drugs on cerebral blood flow. Recently it has been realised that the net effect is the result of the sometimes conflicting direct and indirect effects. The direct effects are what the drug does directly to the cerebral vasculature ie vasodilation/constriction. These effects depend partly on the ability of the drug to access the site where this effect might occur (ability to cross the BBB). The indirect effects are mediated by the drugs effect on cerebral metabolism. If a drug decreases CMR then it would usually cause a decrease

in CBF. The net effect is going to be dependant on the degree to which that same drug effects autoregulation. This balance of effects probably explains the apparently paradoxical effects of the inhalational agents on CBF.

A. **Inhalational Anaesthetics**

1. **Nitrous Oxide**

a) CBF and $CMR0_2$

The effect on nitrous oxide (N_2O) on cerebral blood flow (CBF) and metabolism is somewhat controversial (Smith, 1972). The variant results obtained probably reflect differences in species, methodology, and the effects of other drugs given concomitantly with N_2O.

(1) Rat (60% to 70% N_2O) nb MAC in rats is ≈275%!

(a) CBF none

(b)≈ 10% ↓ $CMR0_2$

(2) Dog

>11% ↑ in CMR/CBF

In dogs that were given high spinal anaesthesia, protected from external stimuli, and paralysed and artificially ventilated, inhalation of 70% N_2O and 30% O_2 produced an increase of 11% in the cerebral metabolic rate for oxygen ($CMRO_2$), as compared with 70% N_2 and 30% O_2 (Theye, 1968). The addition of the high spinal anaesthesia, paralysis, and ventilation to the regimen was necessary, as N_2O is always administered at less than 1 MAC (minimal alveolar concentration). Therefore, the possibility existed that the effects of external stimuli and catecholamine release on CBF and $CMRO_2$ might have been misinterpreted as an N_2O effect unless these stimuli were blocked by other means. Other investigators found even larger increases in flow (≈103%) and metabolism (≈21%) when 60% N_2O was added to halothane (0.2%) and oxygen (Sakabe, 1978). Pre-treatment with reserpine for two days before the experiment did not modify the responses, suggesting that the effect was not due to catecholamines. Prior administration of thiamylal attenuated the influence of N_2O both on flow and on metabolism.

(3) Goats

43% ↑ CBF

10% ↑ $CMRO_2$

These animals had nitrous only.

(4) Rabbits

50% ↑ CBF (70% N_2O added to 1 MAC of halothane)

(5) Human Beings

Volunteers pre-treated with Thiopentone little change

Morphine 3 mg/kg prevented any ↑ in CBF/$CMRO_2$

60% N_2O was added to 0.84% halothane ↑ CBF equivalent by 300% (a 300% ↑ in CBF or a similar ↑ in $CMRO_2$ or a combination of these changes)

other studies have showed less effect but all show some ↑

b). ICP

↑ ICP esp. in patients with already ↑ ICP

The rise in pressure is thought to result from cerebral vasodilatation that leads to increases in CBF and cerebral blood volume (CBV). Increases may be attenuated or prevented by prior administration of thiopental or diazepam but, at least in one study, not by mild hyperventilation ($PaCO_2$ ≈ 33) before introduction of N_2O. Hyperventilation to a $PaCO_2$ of ≤ 29 mm/hg prevented this ↑.

c). Autoregulation and Carbon Dioxide Response

Autoregulation is well-preserved with 70% N_2O

CO2 responsiveness unchanged by 70% N_2O

B. **Volatile Anaesthetics**

In general, the volatile anaesthetics produce dose-dependent increases in CBF, thus increasing cerebral blood volume and ICP. Other dose-related effects of volatile anaesthetics include a decrease in cerebral metabolic rate and abolition of autoregulation.

1. **Halothane**

a) CBF and $CMRO_2$

↑ CBF and ↑ $CMRO_2$

uncoupling

↑ CBF dose dependent (0.5%-4.0%)

metabolism and flow

1% → 25-50% ↑ CBF (cf awake)

25% ↓ $CMRO_2$

2% → 100% ↑ CBF

50% ↓ $CMRO_2$

The ↑ in flow precedes the ↓ $CMRO_2$

in dogs, $CMRO_2$, 25% ↓ for the first 1% and then ≈ 15% ↓ per % ↑ in [] this continued beyond EEG isoelectricity

very high levels → cerebral lactic acidosis and ↓ high energy phosphates

That CBF may actually be decreased by low inspired concentrations of halothane was demonstrated by a study done on monkeys (Morita, 1977). During the inhalation of 0.5% halothane, CBF decreased by 17% and $CMRO_2$by 30%. In contrast, at 1% and 2% halothane, CBF increased by 26% and 97% respectively, although CMRO2 continued to fall. The authors suggested that at low concentrations, the decrease in CBF might result from the marked reduction in $CMRO_2$, which the vasodilatory effect of halothane is unable to overcome. At higher concentrations, there is little further reduction in $CMRO_2$ (40% at 1% halothane, 50% at 2% halothane), and the direct dilator effects of halothane predominate. The cerebral metabolic rate for glucose (CMRgl is decreased by halothane in proportion to the reduction in $CMRO_2$ (Shapiro, 1978). Regional differences in the reduction of glucose metabolism have been demonstrated; the greatest change occurs in the occipital lobes.

b) ICP

may → ↑↑ ICP

Pre-treatment with thiopental, diazepam or hyperventilation may prevent or moderate the increase

Prior hyperventilation to a $PaCO_2$ ≈25 mmhg completely prevents this ↑ ICP with 1% halothane (in patients with intracranial pathology). Simultaneous introduction of both does not prevent ↑'s but the rise is small and only lasts ≈30 minutes.

This increase can be devastating in a patient who has an intracranial disorder, particularly since, in addition to raising ICP, halothane often decreases mean arterial pressure (MAP). Thus, cerebral perfusion pressure (CPP) may be severely compromised.

c) Autoregulation and CO2 Response

Dose-dependent impairment of autoregulation

At 0.5%, it is partially intact

1% to 2% → abolished

Carbon dioxide responsiveness is retained

2. **Enflurane**

a) CBF and $CMRO_2$

↑ CBF ≈ 40% (maximal) Enflurane is a potent depressor of $CMRO_2$and CMRgl

1 MAC ≈ 35% ↓

2 MAC ≈ 50% ↓

the appearance of a seizure pattern in the EEG → ↑↑ $CMRO_2$ (>1.5% and $PaCO_2$ < 30 mmhg

48% ↑ in $CMRO_2$in one study

b) ICP

may → ↑↑ ICP (less than for halothane)

if seizures occur → ↑↑↑ ICP

↑ CSF ICP

may → ↑ ICP (less than Halothane, Enflurane)
This may be prevented by ↓ $PaCO_2$

c) Autoregulation and CO_2 Response
dose dependent depression of autoregulation
Carbon dioxide responsiveness is retained

3. Isoflurane

a) CBF and CMRO2
↑ CBF ≈ 33% at 1 MAC (less than Halothane or Enflurane
↓ $CMRO_2$ ≈ 23% at 1 MAC
≈ 50% at 1.5-2.0 MAC (isoelectric EEG)
Isoflurane can produce an isoelectric EEG in clinically obtainable doses. Doses greater than this do not ↓ $CMRO_2$further or result in abnormal brain metabolism.

b) ICP
may → ↑ ICP (less than Halothane or Enflurane
This may be prevented by ↓ $PaCO_2$

c) Autoregulation and CO_2 Response
dose dependent depression of autoregulation
less than Halothane or enflurane
Carbon dioxide responsiveness is retained

4. **Sevoflurane**

a) CBF and $CMRO_2$
Similar to overall to Isoflurane but slightly less vasodilator responses. Probably the best of the inhalational agents for neuro-Anaesthesia. This is accompanied by slowing of the EEG. The EEG is isoelectric at ≈ 2.0 MAC. As BP is less effected by Sevoflurane than Isoflurane the CPP is better preserved.

b) ICP
may →↑ ICP (similar to Isoflurane)
This may be prevented by ↓ $PaCO_2$

c) Autoregulation and CO_2 Response
Preserved with low concentrations.

5. **Desflurane**

a) Essentially the same as for Isoflurane up to 1.5MAC. This is accompanied by slowing of the EEG. The EEG is isoelectric at ≈ 2.0 MAC.

b) ICP
may →↑ ICP (similar to Isoflurane)
This may be prevented by ↓ $PaCO_2$

c) Autoregulation and CO_2 Response
Doses > 1.0 MAC impair autoregulation
Carbon dioxide responsiveness is retained ≤ 1.5 MAC.

C. **Intravenous Anaesthetics**

1. **Barbiturates**

a) CBF and CMRO2
Coupling of CBF/ $CMRO_2$ maintained
↓ CBF
↓ $CMRO_2$ ≈ 50% at EEG isoelectricity (maximal)
high energy phosphates preserved with large doses
Barbiturates, in doses large enough to produce unconsciousness, constrict cerebral vessels and increase cerebrovascular resistance, thereby decreasing CBF and CBV. The reduction in flow parallels a reduction in $CMRO_2$ and CMRgl, and the alteration in flow has been attributed entirely to metabolic changes. The cerebral effects of barbiturates are dose-dependent; neither CBF nor metabolism is markedly altered by sedative doses. The onset of anaesthesia with barbiturates, as defined by loss of response to pain in one study and by EEG changes in another, occurs when CBF and $CMRO_2$ have declined 25% to 30%. With increasing doses of barbiturates, CBF and $CMRO_2$ are further decreased to the point at which the EEG becomes

isoelectric. At this point, both flow and metabolism are approximately 50% of normal, and additional doses of drug have little effect on either. nb barbiturates placed directly onto cerebral vessels (in vitro) are actually vasodilators.

b) ICP
dose dependent ↓, maximal with EEG isoelectricity
magnitude of ↓ depends on starting ICP

c) Autoregulation and CO2 Response
both preserved

d) Cerebral Protection
Demonstrated in models of focal incomplete ischaemia

2. **Propofol**

a) CBF and $CMRO_2$
dose dependent ↓, maximal with EEG isoelectricity
parallel decreases in both, ie. coupling maintained

b) ICP
dose dependent ↓, maximal with EEG isoelectricity
magnitude of ↓ depends on starting ICP
Propofol commonly causes marked falls in MAP and if this exceeds the ↓ in ICP then the CPP may actually worsen. Patients with mildly elevated or normal ICPs may have ↓ CPP but those with markedly elevated ICPs don't (at least if doses are limited to that which produces the maximal effect on ICP)

c) Autoregulation and CO_2 Response
both preserved

d) CSF
No effects

e) Cerebral Protection
Evidence conflicting. In comparative models of focal incomplete ischaemia cf barbiturates it has sometimes shown benefit and sometimes not.

3. **Narcotics**

Analgesic and premedicant doses of narcotics have little effect on either CBF or ICP unless arterial blood carbon dioxide tension (PaCO2) increases secondary to respiratory depression.
The figures below assume blood gases remain normal ie patient ventilated.

a) **Morphine and Pethidine**

(1) CBF and $CMRO_2$

(a) Dogs
↓ $CMRO_2$
↓ CBF
maximal at 1.2mg/kg → $CMRO_2$ ↓ 15%
CBF ↓ 55%.
nb in control dogs, CBF decreased 35% during the course of the experiment. Thus, the vasoconstrictor effect of morphine accounted for about 20% of the reduction in flow.
The effect of pethidine on the $CMRO_2$ in dogs is similar to the effect of morphine. This is in the presence of N_2O, in its absence there is little effect

(b) Humans
CBF
$CMRO_2$/CMRgl essentially unchanged cf awake values (3mg/kg with 70% N_2O and 30% O_2). This probably means that the vasodilating effects of N_2O are blocked.

(2) Effect on ICP
Unchanged in normocapnic, normotensive individuals

(3) Effect on Autoregulation and CO_2 Response
both preserved

b) **Fentanyl**

(1) CBF and $CMRO_2$

(a) Dogs (6ug/kg)
CBF ↓ ≈ 47%

$CMRO_2 \downarrow \approx 18\%$

(b) Humans

$CBF/CMRO_2$ little effect

(2) Effect on ICP

little or no effect on ICP

c) **Alfentanil/ Surfentanil/Remifentanil**

(1) $CBF/ CMRO_2$

If CPP is held constant they will decrease $CMRO_2$ and therefore CBF. They do not produce an isoelectric EEG. They have no direct effects on the cerebral vasculature. If BP falls then there may be autoregulatory vasodilation that may lead to increased ICP.

4. **Neuroleptics**

Neuroleptanesthesia is most commonly induced by combining fentanyl with droperidol. The two drugs may be given as a premixed combination (Innovar).

a) CBF and $CMRO_2$

b) Dogs

(1) Droperidol 0.3mg/kg

$CBF \downarrow \approx 40\%$

$CMRO_2$ unchanged

(2) Innovar

$CBF \downarrow \approx 50\text{-}60\%$

$CMRO_2 \downarrow 23\%$.

Thirty minutes after injection, the effects resembled droperidol alone. Thus droperidol acted as a potent, long-lasting cerebral vasoconstrictor, and the effects of droperidol and fentanyl on CBF and $CMRO_2$ appeared to be additive in the first 30 minutes.

c) Humans

(1) Droperidol

no human data

(2) Innovar

$CBF/ CMRO_2$ unchanged

d) ICP

droperidol, 5mg and fentanyl, 0.1mg $\rightarrow \downarrow$ ICP

droperidol in large doses (7.5mg – 12.5mg) did not effect the ICP (normocapnic patients who had space-occupying lesions) but MAP was depressed and CPP was decreased significantly.

This blood pressure response is most likely related to the alpha-adrenergic blocking effect of droperidol. The addition of fentanyl, 0.2mg to 0.3mg, did not affect ICP but produced a further decrease in MAP and CPP. Hyperventilation reduced ICP, causing CPP to rise. Neurolept-anaesthesia may be used safely in patients who have increased ICP, provided that hyperventilation is used concurrently and hypotension is avoided.

Note that as in many situations in medicine these studies are not consistent.

e) Effect on Autoregulation and CO_2 Response

(1) Dogs

Droperidol and fentanyl produces marked cerebral vasoconstriction and hypocapnia ($PaCO_2$ = 20mmHg) has no further effect. The vessels, however, respond to hypercapnia.

Therefore, CO_2 responsiveness is not lost, but the vessels are maximally constricted by droperidol/fentanyl and unable to respond further when hypocapnia is induced. The cerebral autoregulatory response during Droperidol/Fentanyl anaesthesia has not been examined.

(2) Humans

no data

5. **Ketamine**

a) CBF and $CMRO_2$

$CBF \uparrow \approx 60\%$

$CMRO_2/CMRgl \uparrow \approx 10\text{-}20\%$

Marked regional differences have been found

direct vasodilation may also occur

These facts lead some investigators to speculate that the change in CBF may be due to regional increases in metabolism that are not apparent when overall metabolism is measured.

b) ICP

Ketamine ↑↑ ICP
secondary to ↑ CBF
can be minimized, but not completely prevented, by hyperventilation.
For this reason, it is best to avoid ketamine altogether in patients who have intracranial disorders.

c) Autoregulation and CO_2 Response

There is presumptive evidence to indicate that autoregulation remains intact during ketamine anaesthesia.
Cerebrovascular CO_2 responsiveness appears to be maintained, since hypocapnia lowers ICP during ketamine anaesthesia, suggesting that it decreases CBF.

6. **Benzodiazepams**

a) **Diazepam**

(1) CBF and $CMRO_2$

(a) Dogs
CBF ↓ ≈ 15%
$CMRO_2$ ↓ ≈ 15%

(b) Head injured humans
CBF ↓ ≈ 25%
$CMRO_2$ ↓ ≈ 15%

(c) Nitrous Anaesthesia in humans
CBF ↓ ≈ 45%
$CMRO_2$ ↓ unchanged

(2) ICP
↓ proportionate to ↓ CBF

(3) Autoregulation and CO_2 Response
unchanged

b) **Lorazepam**

(1) CBF and $CMRO_2$ (Monkeys)
CBF ↓ ≈ 26%
$CMRO_2$ ↓ ≈ 21-30%%

(2) ICP
presumably ↓

(3) Autoregulation and CO_2 Response
unchanged

c) **Midazolam**

(1) CBF and $CMRO_2$ (Humans)

(a) 0.15 mg/kg
CBF ↓ ≈ 33%
$CMRO_2$ ↓ ≈ 21-30%

(b) Nitrous Anaesthesia
moderate dose as for diazepam
high dose $CMRO_2$ ↓ ≈ 45%

(2) ICP
presumably ↓

(3) Autoregulation and CO_2 Response
Autoregulation unchanged
0.15 mg/kg ↑ carbon dioxide responsiveness

D. **Vasoactive Agents**

Except for agents that act at extracranial sites eg Trimethaphan these agents must cross the BBB to be directly cerebrally active. They may , of course, have effects related to changes in systemic BP.

1. Sympathomimetic agents

a) Vasoconstrictors

little direct action
if sudden ↑↑ in MAP can → exceed autoregulatory limits and cause leaks in the BBB

b) Isoprenaline, Histamine, and Acetycholine
↑ CBF

c) Tyramine, and 5-hydroxytrptamine
↓ CBF

2. Hypotensive agents: Nitroprusside, Nitro-glycerine, Hydralazine, Diazoxide
↑ CBF if MAP does not fall to far. One study showed that if MAP falls below 70% of baseline then ICP is not increased.

a) Nitropruside

(1) CBF
If the MAP is allowed to fall there is no change or even a ↓ in CBF.
When the MAP is supported there is an ↑ CBF

(2) ICP
Consistently ↑ unless the MAP falls considerably (in one study unless the MAP ≤70% of control the ICP ↑).
In view of the minimal effects on CBF there may be more marked effects on capacitance vessels.

b) Nitro-glycerine

(1) CBF
↑ demonstrated in rats

(2) ICP
Consistent ↑ more marked than with SNP
As it is an unreliable hypotensive agent there is little to recommend its use during neurosurgery except in patients with acute myocardial ischaemia.

c) Trimethaphan

(1) CBF
No effect

(2) ICP
Usually no change however if very rapid falls in MAP are allowed then ICP may ↑.

d) Hydralazine/Diazoxide
Little direct evidence but one would presume both are cerebral vasodilators and may ↑ CBF/ICP

3. Esmolol/Propanolol/Metoprolol
Have no direct effect on the cerebral vasculature and therefore if MAP is unchanged CBF is unchanged.

4. Labetalol
As for Esmolol
Theoretically this would be an ideal agent to control BP in neurosurgical patients as there are few α receptors in the cerebral circulation so it should not effect CBF directly. Unfortunately it is not available in an IV form in Australia.

E. **Muscle Relaxants**

1. Currare/Atracurium/Mivacurium
All release histamine if given as a bolus. This can cause cerebral vasodilation and ↑ ICP as well as falls in MAP. This may compromise cerebral perfusion. Better avoided if used as a bolus.

2. Pancuronium
May cause an increase in MAP and this may exceed the autoregulatory limits especially in patients with impaired autoregulation. This may → ↑ CBF/ICP. Best avoided in a bolus dose.

3. Suxamethonium
Reports of ↑ ICP in some patients and in some clinical settings
Minton et al in a study of patients with brain tumours compared the effects before and after vecuronium. Prior to vecuronium there was a consistent rise in ICP of ≈5 mmHg that was prevented by vecuronium. It was postulated that stimulus of muscle afferents caused a reflex ↑ in $CMRO_2$ and CBF.

Stirt et al also showed increases of ICP of ≈12mmHg that was prevented by metocurine pre-treatment.

Lanier et al in dogs showed that there was an ↑ in CBF that paralleled the ↑ ICP (1% Halothane)
There was also an ↑ $PaCO_2$ however this could only explain the later part of the ↑ ICP

A follow-up study by this group also showed that the increase paralleled the ↑ in afferent muscle nerve activity. This ↑ afferent nerve activity started with fasciculations and lasted for ≈30 minutes.

It is probable therefore that the mechanism relates to ↑ afferent activity to the brain causing ↑ $CMRO_2$ and a coupled ↑ in CBF leading to ↑ ICP. This should be blocked by reflex suppressants as well as non-depolarising relaxants.

Practically if Suxamethonium is given with a thiopentone induction there have not been reports of clinically important degrees of ↑ ICP.

4 Vecuromium/Rocuronium/Cis-Atracurium

None of these have any cardiovascular effects and will have no effect on CBF/ICP.

F. **Diuretics**

1. **Mannitol**
   a) 6 carbon sugar, non-metabolised
   b) Osmolality 1098mosmoles/kg
   c) ↓ ICP by:
      (1) Osmotic action - normal brain mainly
      (2) Vasoconstriction - ↓ viscosity → ↑ CBF → Vasoconstriction and CBF returns to normal (viscosity autoregulation)
   d) Maximum effect - large dose given rapidly
   e) Acute side effects:
      (1) Hypotension
      (2) ↑ K^+ (2gm/kg)
   f) 1.5gm/kg over 20 minutes is "safe"
2. **Frusemide**
   a) 1mg/kg decreases ICP by an unknown mechanism (not related to its diuretic effects)
   b) 0.3mg/kg augments the ICP lowering effects of mannitol. Probably by prolonging the hyperosmolarity.