Cerebral blood flow, metabolism and intraoperative cerebral protection:

- The average CBF is 55ml/100gr/min. The CBF in the cortex is about 70-80 ml/100gr/min and in white matter is 20 ml/100gr/min. Cerebral metabolic rate of O2 is 150-160 Micromole mol or 4.5 ml /100gr/min. Cerebral metabolic rate of glucose is 25-30 Micromol or 3.5 ml/100gr/min.Brain constitutes 2-3% of body weight but receives 15-20% of cardiac output.
- **Ischemic thresholds are:** at **25-30 ml**-mild deficit due to **electrical impairment**, at 16-20 ml –severe deficit due to **electrical failure**, at 10-12 ml severe deficit due to **pump failure** and cytotoxic oedema, <10 ml gross **metabolic failure** and death.
- The major metabolic substrate for the brain is **glucose**. It is transported across the BBB by facilitated diffusion using **GLUT-1** (into astrocytes where it is stored as glycogen) and **GLUT-2** (into neurons). Glucose is metabolised through 4 steps with the production of 30-**36 moles of ATP for each mole of glucose.** These steps are 1. Aerobic glycolysis in the cytosol-the end product is pyruvate (2 ATP). 2. Conversion of pyruvate into Acetyl-Coenzyme A in mitochondrial matrix 3. Acetyl coenzyme A is metabolised in the Krebs cycle (in mitochondrial matrix with release of 2 ATP and NADH and FADH) 4. **Oxidative phosphorylation** 'electron transport' in mitochondrial membrane. Electrons donated by NADH and FADH results in the formation of 26 moles of ATP. **During prolonged hypoglycemia ketone bodies** (from fat metabolism) can be utilised as a source of energy (can provide 75% of total cerebral energy. Brain metabolism is a function of brain activity. **60% of the required cerebral energy is used for synaptic transmission** and 40% to maintain cellular integrity

- **Cerebral blood flow is autoregulated (relatively constant) at CPP (MAP-ICP) OF 50-150 mm Hg.** The autoregulation curve may be shifted to the right in patients with chronic hypertension and to the left in patients on ACE inhibitors, prolonged hypoxia and hypercapnia. The autoregulation takes place at the **precapillary arterioles** (the major cerebral resistance vessels). The mechanisms of autoregulation involve 1.**Myogenic** (activation of stretch receptors-activation of stretch activated cation channels –opening of voltage gated Ca channels –influx of Ca into smooth muscles-contraction and decrease in blood flow) 2. **Endothelial factors** (production of vasodilators NO and PG I2 and vasoconstricting factors ET 1 and TXA2. 3. **Neurogenic** factors (cerebral blood vessels have intrinsic and extrinsic sympathetic and parasympathetic innervation. The cerebral autoregulation is disturbed in severe head injury, ischemia and SAH. In these situations increase in CPP results in linear increase in CBF which can lead to cerebral oedema.
- **CBF is coupled with cerebral metabolism**. CBF is high in metabolically active cortex in comparison with less active white matter. Increase in brain activity (excitation) is associated with increase in CBF. **This is mediated through increase in extracellular K, H and adenosine**. The major source of H in aerobic metabolism is CO2 which is converted in the astrocytes into H2CO3 and H and HCO3 (**carbonic anhydrase). PaCO2** exerts profound effect on CBF across its physiological range **(30-50**). There is increase of **1ml for each 1mm Hg** change in PaCO2. This effect is mediated through the

production of H (carbonic anhydrase).Small fluctuations in Pa O2 does not affect CBF , however **severe hypoxia < 50** is associated with cerebral vasodilatation and increase in CBF. **Temperature** also affects CBF. **At T-17C the CMRO2 is reduced to 8% of normal.**

- **CBF** is influenced by other factors including NO (arginine + NOS), endothelines, eicosanoids (prostaglandins and leucotrienes).
- Interruption of blood flow to a brain area results in 2 areas of ischemia 1. **Central core** (severe ischemia-disruption of ionic pumps and cellular integrity and after a few minutes the cells die) 2. **Ischemic penumbra** (the ischemia produces disruption of synaptic transmission but the collateral blood flow is enough to sustain cellular integrity for a variable time. This time provides a window of opportunity for medical intervention. The pathology of ischemic infarction is as follows. Interruption of blood flow- Anaerobic glycolysis-depletion of ATP and acidosis-loss of the function of ionic pumps-depolarisation of neurones and opening of voltage gated Ca channels- Ca influx into the cells-activation of proteases, phospholipases and cell destruction. Also Ca results in increased release of excitatory amino acids (glutamate, glutamine) act on NMDA receptors increasing Ca influx into the cells. The reuptake of glutamate by astrocytes is an energy consuming process and leads to expansion of the infarction. Free radicals (superoxide, hydroxyl ion and NO) produced during ischemia or reperfusion plays a role in the ischemic injury.
- There are three strategies to reduce the focal ischemia during surgery:

1. **Reducing** the duration of ischemia (**clamping time**): the duration of temporary ischemia that can be safely applied is not known and depends on the presence of collateral circulation and varies from patient to patient. It is not known whether brief periods of repetitive occlusion are safer than single long occlusion. Data from animal models is conflicting with some studies showing that repetitive periods of brief occlusion are safer, and others showing no difference if the total occlusion time is less than 2 hours. Clinical retrospective case series studies demonstrated that the temporary occlusion time should be less than 20 min.(Pool, Suzuki and Ogilvie). For MCA shorter period 15 min. is safer (perforators).
2. **Augmentation of collateral** blood flow by increasing MAP by 10% above the basal level.
3. **Reduction of metabolic activity**: A. **Hypothermia** either moderate 33c or part of hypothermic arrest 18C decreases the CMRO2 and CFF.

B. **Barbiturates** at doses causing burst suppression of EEG can reduce CMRO2 by 50%, but they have cardiac suppression, propofol and etomidate can produce similar decrease in CMRO2 with less cardiac side effects.

C. **Serum glucose modulation**: in the absence of O2 glucose is metabolised anaerobically with the production of lactic acid. Acidosis increases ischemic injury. Use glucose free iv fluids intraoperatively.

D. **Experimental agents**: Calcium channel blocker Nimodipine (lipophilic and has better penetration across BBB than nifedipine), glutamate antagonist (Mg blocks NMDA receptor), NOS inhibitor (Tirilasad), lubeluzole (glutamate release inhibitor) and citocoline (contains cytidine and choline, the substrates for the synthesis of phosphatidylcholine, a key membrane component. These agents showed effect in animal models.

- The most commonly used anaesthetic volatile agents in neurosurgery are **isoflurane and sevoflurane (reduce CMRO2 and has minimal vasodilatotory** effect. The most commonly used muscle relaxant is vecuronium (short acting non-depolarising), the most commonly used induction and maintenance iv agents are barbiturates (cardiac suppression), propofol (short acting with less cardio suppression), etomidate, midazolam and opiates morphine and fentanyl)

- Hypothermic Circulatory arrest at **T of 18** C allows the brain to be totally deprived of blood flow for **1 hour** without damage. At this T the **CMRO2 drops to 8% of normal**. The complete deflation of the aneurysm allows safe dissection, endartectomy and thrombectomy. It may be indicated in the management of complex giant aneurysm, particularly those of basilar tip and ophthalmic segment of ICA and those attached to vital structure, with calcified neck and partially thrombosed. The patient should **be fit to have this procedure** (absent of cardiopulmonary disease). ECG, cardiac echo and pulmonary function tests are routinely performed. The procedure should be performed at specialised centres and involve multidisciplinary team. The surgeon starts the dissection of the aneurysm as usual**. Burst suppression of EEG and mild hypothermia are inducted**. The groin region or the chest wall is prepped. Once the decision is made to use the technique, the cardiac team is contacted, **cannulation of the femoral artery and femoral vein** or **aorta and right atrium** is performed after **anticoagulation with heparin** (ACT-400-500 S) and the temperature is allowed to drift to **18.**At T 27 the heart goes into VF. **Cardiac arrest is induced by injection of KCL**. From that point circulation is provided by the pump which has membrane oxygenator and provides flow of **2.5L/min/m^2** once **T is 18** as verified by cortical brain thermal probe the **blood is allowed to exsanguinate through the femoral cannula to drop perfusion pressure to 0**. Overdrainage may predispose to air embolism and failure to re-flow. From that time the surgeon has 45-60 min to clip the aneurysm. If more time is required the patient should be reperfused for 20 min and then the blood is allowed to exsanguinate .Once the procedure is done gradual rewarming of the patient starts and defibrillation of the heart is done (if it does not regain sinus rhythm). **Profound hypothermia has adverse effects** including **coagulopathy, myocardial suppression, renal impairment** and **pulmonitis.** These effects are transient and patients should be managed in ICU after the procedure to correct the coagulopathy and to provide inotropes and ventilatory support until the function of cardiopulmonary system recovers. **Mortality** from this procedure is about **10%**. 87% of patients experience excellent or good outcome (GOS-1, 2).