بسم الله الرحمن الرحيم

Cerebral Protection

Presented by: Dr. Ashraf Arafat Abdelhalim, MD

Professor of Anesthesia

Alexandria of University, Egypt

- Up to 50% of patients with acute subarachnoid hemorrhage (SAH) suffer from some degree of neurological impairment after aneurysm clipping
- **Cerebral protection** : preemptive use of therapeutic interventions to improve neurologic outcome in patients who will be at risk for cerebral ischemia.

- **Resuscitation** : therapeutic interventions initiated after an ischemic event.

CNS PHYSIOLOGY•

Brain

- 2% body weight
- 15% CO

Energetic tissue, utilize

- 3-5 mls O2/min/100gm
- 5mg glucose/min/100gm•

Brain energy

- 60% sustain synaptic function
- 40% maintain cellular integrity

CBF (ml/min per 100g brain)	CHANGES
50	Normal
25-30	Abnormal EEG
15-25	Loss of electrical activity (i.e; isoelectric EEG)
10-15	Sufficient to maintain ATP to support ionic pump funtion
≤10	Membrane failure due to a critical loss of ATP, which causes ionic imbalance between the cell and the extracellular
<10 + prolonged (min) + worsened	Permanent neurological impairment due to cell death

CHANGES IN ICP

ICP documented in 50-70% cases.

Causes :

- Mass lesion (EDH, SDH, ICH ; Contusion)
- Cerebral hyperemia
- Cerebral edema (vasogenic & cytotoxic)
- Hydrocephalus
- Uncontrolled ICH ⇨ ⇩perfusion ⇨ Ischemia ⇨ Brain Swelling ⇨ Brain herniation

Primary brain damage

Many etiologies:

Vascular insufficiency or disruption

Trauma

Infection or inflammation

Tumour

Metabolic and nutritional derangement

Global brain injury

- Hypoxemia, cardiovascular insufficiency or arrest lead to hypoxic and low or or complete hypoperfusion of entire organ•
- No potential for recruitment of collateral flow•
- Recovery depend on severity and duration of insult•
- After 5-6 min have permanent histological damage and neurological deficit in survivors•
- Outcome worsens significantly after 15 min

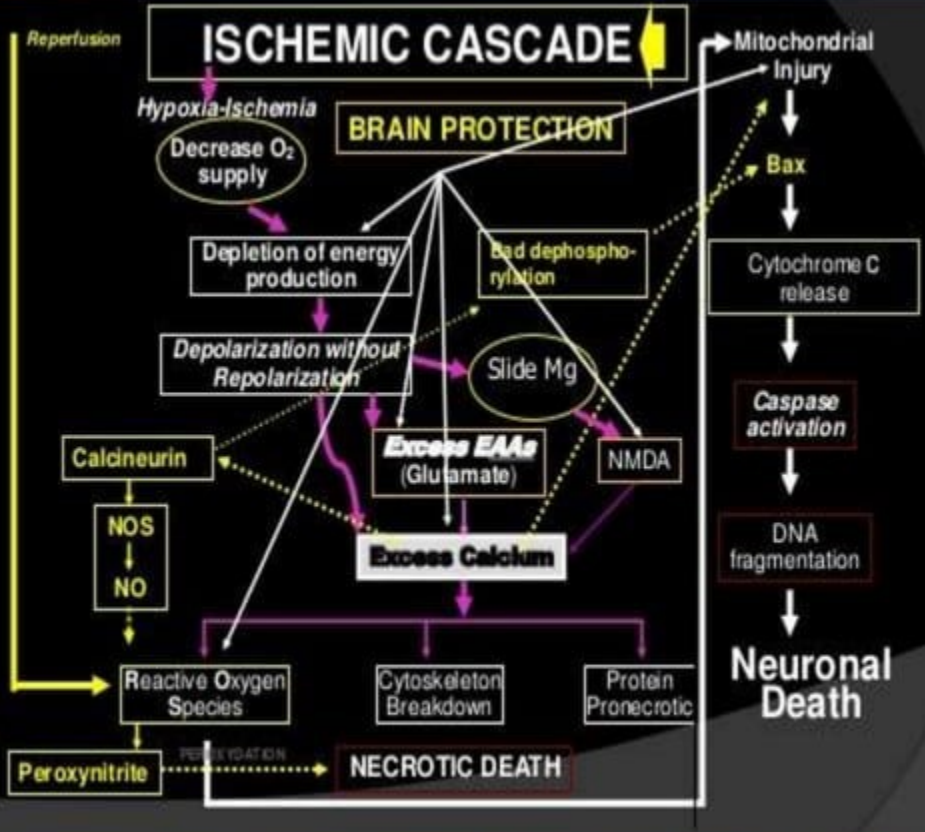
Focal brain injury

- Occlusion of an arterial distal to circle of willis
- Permit some collateral flow•
- Dense ischaemic core with a partially perfused surrounding penumbral zone and tissue more salvageable and target for neuroprotection•
- The time course for infarction and irreversible damage around 30-60 mins

Secondary brain damage

Neural injury is worsen by

- Hypoxemia
- Hypercapnia
- Hyperglycemia
- Hypotension
- Hypothermia
- Anemia
- Electrolyte imbalance


ISCHEMIC CASCADE
Reperfusion
Hypoxia-Ischemia
Decrease O_2 supply
BRAIN PROTECTION
Depletion of energy production
Bad dephospho-rylation
Depolarization without Repolarization
Slide Mg
Excess EAAs (Glutamate)
NMDA
Calcineurin
NOS
NO
Excess Calcium
Reactive Oxygen Species
Cytoskeleton Breakdown
Protein Pronecrotic
Peroxynitrite
PEROXYDATION
NECROTIC DEATH
Mitochondrial Injury
Bax
Cytochrome C release
Caspase activation
DNA fragmentation
Neuronal Death

CELLULAR EVENTS

Ischaemia→ Biochemical events→ Neuronal death

Mediators of Cellular cascade are :

- Calcium
- EAA (aspartate & glutamate)
- Free radical (SO dismutase, H_2O_2, OH^-)
- Cerebral Lacto-acidosis
- Ionic fluxes of K^+ & Mg^{++}
- Inflammatory mediators- Cytokines

CNS MONITORING

- General monitoring brain injury patient include;

• Continuous IABP – ABG analysis and blood glucose
• Pulse oximeter
• ETCO2 – early correction of hypercapnia induce high ICP
• CVP
• Temperature
• Clinical monitoring - GCS

- **SPECIFIC MONITORING**

• Pressure within the cranial cavity (ICP)
• Changes in brain oxygenation
• Metabolism (jugular venous oxygen saturation, brain tissue monitoring)
• Cerebral hemodynamics (transcranial doppler)
• Electrical activity of the CNS

Indication for cerebral protection

Majority associated with high ICP:

- Cerebral oedema
- Post myocardial infarction
- Post cranial surgery
- Seizures
- Head injury
- Cerebral hypoxia
- Post cardio respiratory arrest
- Brain infection
- Space occupying lesion

Aims

- Prevent further cerebral damage
- Reverse cerebral damage
- Improve cerebral functions and neurological outcome
  - Maintain of cerebral perfusion
  - Maintain of systemic hemodynamics
  - Maintain adequate oxygenation and ventilation

Nonpharmacologic treatment

Hypothermia for cerebral protection

Pathophysiology:

- Reduction of CMRO2 of 6-7% per 1o drop in temp
- Reduction in ICP
- Decreases excitatory amino acids and lactate in ischaemia/reperfusion injury
- Reduces intracellular Ca++ sequestration
- Reduces neutrophil adhesion
- Reduces apoptosis
- Reduces free radical production •

International Journal of Cardiology 151 (2011) 333–341

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Hypothermia after cardiac arrest should be further evaluated—A systematic review of randomised trials with meta-analysis and trial sequential analysis

Niklas Nielsen [a,*], Hans Friberg [b], Christian Gluud [c], Johan Herlitz [d], Jørn Wetterslev [c]

Hypothermia for neuroprotection in adults after cardiopulmonary resuscitation

- Conventional cooling methods to induce **mild** therapeutic hypothermia seem to improve survival and neurological outcome after cardiac arrest.

- **Aim** for mild (33-34°C) to moderate (26-31°C) hypothermia
- **Avoid shivering-** increase CMRO2 & CBF, may require muscle relaxant
- Tympanic membrane or nasopharyngeal temperature are a more accurate estimate of brain temperature.
- **Avoidance of hyperthermia** is paramount as it markedly increase $CMRo_2$ and exacerbate ischemic damage.

- **Deep hypothermic circulatory arrest** to core temperatures of 13Â°C to 21Â°C might be indicated for clipping giant or complex basilar artery aneurysms.
- **Avoid hypoxia, and hypercapnia.**
- **Hemodilution :** to a hematocrit of 32% to 34% increases CBF by decreasing viscosity& improving oxygen delivery.
- **Correction of acidosis and electrolyte imbalance**

Hypertension

Aim

- ✓ To limit ischemia by increasing regional CBF
- ✓ To overcome regional vasospasm
- ✓ Done usually with drugs - vasopressors •

During ischemia

- ❖ Autoregulation is impaired
- ❖ CBF is pressure dependent
- Maintain CPP 70-80 mmHg

INTRAOPERATIVE BRAIN PROTECTION

CBF is Normally Autoregulated over a MAP **Range of 50 to 150 mmHg**.

Maintenance of CBF with a **CPP in excess of 60 mmHg**.

Adequate CPP is to **Maintain Perfusion** in a **Brain Ischemic Injury.**

TBI: **Higher than normal CPP (>70 mmHg)** to maintain normal CBF.

Patients who have **Sustained an Ischemic cerebral injury** may benefit from :

Induced Hypertension; Increase MAP > 20% baseline, Augmentation CBF

Hypotension to be **Deleterious** to ischemic or traumatic injured brain.

- **Normalization of increased ICP :** by
  - moderate hyperventilation [Paco2] of 25 to 30 mm Hg
  - head elevation to 30Â°,
  - mannitol and/or furosemide diuresis,
  - cerebrospinal fluid (CSF) drainage via ventriculostomy,
  - limited fluid restriction,
  - barbiturate coma.

Anticonvulsant

- Severe TBI – 20% seizures
- Highest in depressed skull fractures, IC hematoma and contusion
- Efficient in reducing of early post traumatic seizure
- First line therapy – phenytoin (a week duration)

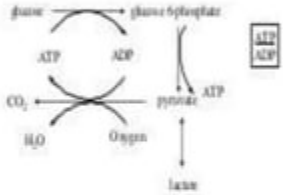
INTRAOPERATIVE BRAIN PROTECTION

Targets Blood Sugar Levels between **100-180 mg/dl.**

- **Anaerobic Glucose** metabolism product Lactic Acid and ATP.
- The **Lactic Acid** contributes to the **Tissues Acidosis.**

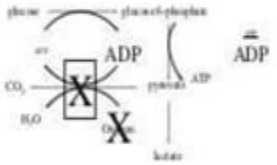
Brain Does Not have Glucose Stores : If **During Hyperglycemia.**

- **Increased Neuronal Glucose**, Increase Lactic Acid.
- **Promote tissue Acidosis**, contributes **Neuronal Death**.



During Hypoglycemia is also associated with Cerebral Injury.

- 40 mg/dl, Shift or Changes EEG Wave **.**
- 20 mg/dl, **Suppression of the EEG (flat)**.
- Persistence of this level: Seizure and **Neuronal Death**.



Osmotherapy

Mannitol

- ✓ Increase plasma osmolality – withdrawal of brain across bbb
- ✓ Reduction ICP after 20-30mins
- ✓ Need to monitor plasma osmolality, not > 320 mosmol/ml•

Hypertonic saline (5or 7.5%)

- ➢ Reduces brain water by establish osmotic gradient across bbb
- ➢ Hypernatremia, <155 mmol/L
- ➢ Cause tissue necrosis and thrombophlebitis

Physical manipulation

Patient position

- Important for both prevention and treatment of elevated ICP

Aim :

- Allow proper cerebral venous drainage (venous return)
- Maintain the head and neck elevated 30°
- Maintain neutral position
- Avoid obstruction to jugular vein i.e; ETT anchoring, cervical collar
- Avoid increase in intrathoracic & intraabdominal pressure

Avoid ;

- ✓ Excessive stimulation e.g suctioning, only do it when necessary
- ✓ Sudden movement to head
- ✓ Rough handling of patient
- ✓ Painful stimulation
- ✓ Hyperthermia >38°C

Pharmacologic treatment
Barbiturates coma

- Barbiturates decreases ICP & CBF
- Can lower ICP refractory to other measures
- Dose titrated to burst suppression on EEG
- Reduction in CMRo2 of up to 55% to 60% at which EEG becomes isoelectric
- An effective anticonvulsant.
- Thiopental does not improve outcome in global or complete ischemia after cardiac arrest.

- Other possible mechanisms : (GABA) agonism, free radical scavenging, membrane stabilization, NMDA antagonism, Ca channel blockade, and maintenance of protein synthesis.

Barbiturate Coma

Indications:

- Potentially survivable head injury
- No surgically treatable lesion accounting for intracranial hypertension (except when used for preparation for surgery)
- Other conventional therapies of controlling ICP have failed (posture, hyperventilation, osmotic and tubular diuretics, corticosteroids)
- ICP > 20 to 25 mmHg for more than 20 min, or >40 mmHg at any time
- Unilateral cerebral hemispheric edema with significant (>.7 mm) shift of midline structures shown on CT
- A low Glasgow Coma score

- **Etomidate** reduces CMRo2 (up to 50%), CBF, and ICP
- EEG burst suppression occurs with higher doses.
- Maintaining cardiovascular stability and CPP.
- CO2 reactivity is preserved.
- **Adrenocortical suppression** for up to 24 hours after a single induction dose (inhibition of 11 beta-hydroxylase).
- Myoclonic activity has been reported with etomidate, and seizures may occur.
- Side effects : nausea, vomiting, and pain on injection.

Propofol

- Decreases CMRo2, ICP, and CBF .
- Hemodynamic depression decreases CPP more than with barbiturates.
- Burst suppression on EEG occurs with larger doses of propofol.
- Decrease postoperative nausea and vomiting.

- **Ketamine**, a phencyclidine derivative, produces dissociative anesthesia.
  - Markedly increases ICP and CBF (60%) via cerebrovasodilatation.
  - The $CMRo_2$ is unchanged or slightly increased. Autoregulation is abolished.
  - Seizures can occur.
  - Although it is a noncompetitive NMDA antagonist, **ketamine is not recommended** for patients who have intracranial pathology.

Opioid

- **Morphine** . can cause hypotension secondary to histamine release.
- **Meperidine** may increase the heart rate. Its metabolite Normeperidine that can cause CNS excitation and seizures.
- **Fentanyl** is 100 times more potent than morphine. Fentanyl does not cause histamine release, is shorter acting than morphine, and decreases ICP and CBV slightly while maintaining CPP.
- **Sufentanil** is more potent than fentanyl and may increase ICP (via vasodilatation) in patients who have severe head trauma.
- **Remifentanil** is a very short-acting (t1/2 = 3 to 10 minutes) esterase-metabolized , reduce ICP and CBV and maintain CPP in a recent clinical trial.

Potent inhaled anesthetics

- All vasodilatators & increase CBF and ICP to different degrees.
- This effect can be attenuated by prior hyperventilation.
- The volatile anesthetics also decrease $CMRo_2$
- Autoregulation is impaired but CO_2 reactivity is preserved.

- **Isoflurane** is the least potent vasodilator causes the greatest decrease in CMRo2 (40% to 50%).
- ✓ The EEG becomes isoelectric at 2 (MAC) or 2.4%.
- ✓ It has no effect on the production of CSF .
- ✓ Studies of isoflurane in animal models have shown some limited protection from isoflurane.
- ✓ Preconditioning with isoflurane seems to confer tolerance to ischemia and some neuroprotection.
- ✓ **In vitro studies** have also shown improved recovery after ischemia and a reduction in cell death through the postischemic activation of ATP-regulated K channels & protein kinases.

- **sevoflurane** similar to isoflurane; it cause a slight increase in CBF and ICP and a decrease in $CMRo_2$.
- Nephrotoxic inorganic fluoride may accumulate when receiveing sevoflurane for prolonged periods of time.
- Sevoflurane may offer protection after brain ischemia through preconditioning.
- Cerebral protection have been demonstrated during incomplete ischemia in vitro.
- Improved recovery in CA1 pyramidal cells in rats has occurred at clinical concentrations known to be useful in humans.

- **Desflurane** is similar to isoflurane but ICP might increase despite normocapnia with desflurane compared to isoflurane.
- Induction and emergence with desflurane are rapid.
- Desflurane may also be protective after brain ischemia.
- Studies after hypoxia and after incomplete cerebral ischemia in rats have shown cerebral protective effects.

Local anesthetics (Lidocaine)

- When administered after EEG isoelectricity induced by pentobarbital, it may decrease CMRo2 by an additional 15% to 20%.
- At clinically recommended doses (1.5 mg/kg), lidocaine may reduce ischemic damage.
- It blunts the hemodynamic response to intubation by increasing anesthetic depth.
- At lower doses, it possesses anticonvulsant activity .
- At toxic doses, lidocaine causes seizures.

Ca channel-blocking drugs

- **Nimodipine :**
  - Decreases vasospasm after aneurysmal (SAH).
  - It may increase CBF to underperfused areas by redistribution through an inverse steal effect.
  - **The dose**: oral form, is 60 mg every 4 hours for 21 days after SAH. Hypotension may occur with the administration of nimodipine.
- **Nicardipine**,
  - available for IV administration,
  - has decreased ischemic damage in animal studies, but clinical trials have not shown improved neurologic outcome after ischemia.

NMDA receptor antagonists

- **Dizocilpine maleate (MK-801)**
  - beneficial effects in laboratory experiments
  - not approved for use in humans .
- **Magnesium,** a noncompetitive NMDA antagonist, binds within the ion channel, preventing ion flux, and may be helpful after brain injury.
- Glycine binding site antagonism with **HA-966 and 7-chlorokynurenic acid** is still in the investigational stage
- AMPA receptor antagonism with **2, 3-dihydroxy-6-nitro-7-sulfamoylbenzo (f)quinazoline (NBQX)** has proved beneficial when given after the ischemic insult in experimental models.

- **Dexmedetomidine,** an alpha$_2$ agonist,
  - decreases the MAC for halothane and isoflurane and decreases CBF without significantly altering CMRo$_2$.
  - decreases central sympathetic activity by decreasing plasma norepinephrine release.
  - neuroprotective in a model of focal ischemia

- **Sodium channel-blocking drugs** :
- **riluzole** may reduce glutamate release during ischemia.
- **Lamotrigine**, an anticonvulsant with Na channel-blocking activity, is known to reduce glutamate release and ischemic damage.

- **Tirilazad,** a lipid-soluble 21-aminosteroid,
- crosses the blood-brain barrier and acts as a lipid antioxidant, inhibiting free radical formation and lipid peroxidation.
- Studies indicate protection only when tirilazad is administered before an ischemic event.

Free radical scavengers :

- Superoxide dismutase (SOD), deferoxamine, vitamin E, mannitol, and glucocorticoids.
- The utility of SOD has been limited by its short t1/2 (8 minutes) & poor blood-brain barrier penetration.
- glucocorticoids have membrane-stabilizing properties & decrease cerebral edema from brain tumors, they have not been shown to improve outcome in cerebral ischemia.
- The clinical usefulness of free radical scavengers is still under investigation.

- Modification of arachidonic acid synthesis.
- Ischemia-induced excess of the vasoconstrictor thromboxane relative to the vasodilator prostacyclin (PGI_2)
- Led to the development of thromboxane synthetase inhibitors and PGI_2 synthetase stimulation to prevent the formation of excessive thromboxane.

- **NO** is a free radical with complex neuronal activity. It decreases neuronal damage in experimentally induced focal ischemia

- **1. Neuronal NOS (nNOS)** enhances glutamate release & NMDA-mediated neurotoxicity. Selective nNOS inhibition has been shown to be neuroprotective.
- ✓ **2.Immunologic NOS (iNOS)** is not detectable in healthy tissue. Induction of iNOS exacerbate glutamate excitotoxicity.
- ✓ Inhibition of iNOS by aminoguanidine reduces ischemic damage in experimental models.
- ✓ **3.Stimulation of endothelial NOS (eNOS) :**has been shown to reduce ischemic damage in a rodent model.

- Erythropoietin (EPO) is a substance produced in the brain after hypoxic or ischemic insults.
- Stimulates neurogenesis, & diminishes neuronal excitotoxicity, reduces inflammation, and inhibits neuronal apoptosis.
- It has been used in humans for cerebral preconditioning in patients after ischemic stroke.
- **Nonhematopoietic analogs of EPO, such as asialoEPO**, have been developed and are showing equivalent potency as neuroprotectants in the laboratory.
- These analogs do not increase the hematocrit and thus do not exacerbate the ischemia injury through an increase in blood viscosity.

- **Experimental results** have shown that all of the following modalities can be used to accomplish cerebral preconditioning :
  - Preoperative hyperbaric oxygen,
  - Normobaric 100% oxygen exposure,
  - Electroconvulsive shock,
  - Potassium channel-opening drug,
  - Diazoxide,

Conclusion

- Perioperative brain damage may result in new postoperative neurological deficits including transient ischaemic attack, stroke, and postoperative cognitive decline .
- Pharmacological perioperative neuroprotection has yielded conflicting results.
- Recent evidence provides conflicting results, and more randomized control trials are needed to draw significant conclusions that guide clinical management.

Thank you