



**CEREBRAL PROTECTION**

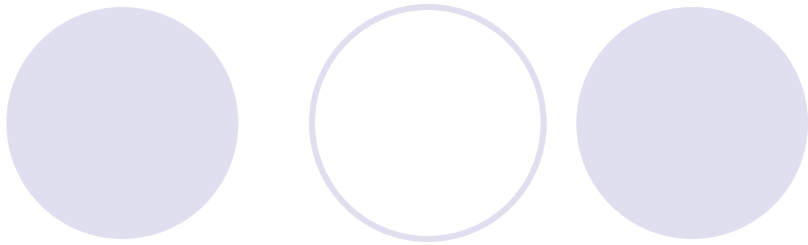
# Cerebral protection



**“ Treatment initiated before onset of ischaemia, intended to modify intra-ischaemic cellular and vascular biological responses to deprivation of energy supply so as to increase tolerance of tissue to ischaemia resulting in improved outcome.”**

- **Goal of therapy**

**increase oxygen supply**  
**decrease oxygen demand**



- **To achieve this goal**

**preserve the cerebral blood flow**  
**avoid Hypoxia and hypoxemia**



- **Aim** of brain protection is to prevent or minimise the pathological sequelae of inadequate cerebral perfusion, regardless of its cause.
- **Type**
  - Complete global ischemia
  - Focal (incomplete) ischemia
- **Global ischemia** is characterized by a complete cessation of CBF (e.g., cardiac arrest). Time window for the restoration of flow is very small because death of neurons is rapid.
- **Focal ischemia** is characterized by a region of dense ischemia (the so called “core”) that is surrounded by a larger variable zone that is less ischemic (the penumbra).

# Complete Global ischemia



## Cascades of Death

- 5–6 s after the onset of circulatory arrest, the patient loses consciousness.
- Cerebral tissue oxygen tension declines continuously reaching 0 after about 2 min.
- Simultaneously, neuronal energy in terms of adenosine triphosphate is depleted and metabolites, such as adenosine, lactate, and hydrogen ions, accumulate in the cells.

**Rossen R, et al. Arch Neurol Psychiatry 1943;50:510–2**  
**Cavus E, et al. Resuscitation 2006;71:97–106**

- Dysfunction of the cell membrane ion pumps leads to a severe breakdown in cellular homeostasis.



- **Calcium overload is considered a key factor in cellular toxicity.**
- **Massive accumulation of calcium in the cell cytosol when calcium efflux pumps fail, voltage-gated calcium channels open, and ligand gated channels are activated by released excitatory amino acids, such as glutamate and aspartate.**

**Kristiain T, et al. Stroke 1998;29:705–18**



- **If neuronal energy is recovered rapidly upon return of spontaneous circulation-reperfusion does stop neuronal degeneration to a certain degree.**
- **During reperfusion, free radicals aggravate cellular damage.**

**Sakamoto A,et al. Brain Res1991;554:186–92**



- **During reperfusion period, adenosine triphosphate gives the cell the opportunity to actively react to the damage.**
- **This is associated with the expression of immediate early genes, a complex machinery involving both cell survival and cell death cascades.**
- **The morphological correlate of “subnecrotic” cellular damage is delayed neuronal death, which shows typical signs of apoptosis and occurs mainly in the vulnerable brain areas such as the hippocampus, the nucleus reticularis thalami or distinct layers of the cortex.**

***Schmitz B, et al. J Cereb Blood Flow Metab 1998;18:1077–87***

***Chen J, et al. J Neurosci 1998;18:4914–28***





## Cerebral Circulation Disorders

- Return of cardiac function does not automatically restore normal cerebral circulation.
- Depending on the duration of the ischemic period, cerebral vessel dysfunction develops, which likely contributes to neuronal damage.
- Reperfusion fails completely in circumscribed areas of the brain (no-reflow phenomenon). These areas increase with the duration of ischemia.
- No-reflow is probably caused by capillary congestion because of edema of endothelium and perivascular glia, blood cell sludging, leukocyte adhesion, and disseminated intravascular coagulation.

*Fischer M, et al. Intensive Care Med 1995;21:132–41.  
Boettiger BW, et al. Circulation 1995;92:2572–8*



- **Local no-reflow is paralleled by global cerebral hyperemia during the early period of reperfusion.**
- **This is probably caused by the accumulation of metabolites such as adenosine, lactate, or hydrogen ions during ischemia, which are potent vasodilators.**
- **Within the first hour after reperfusion, reactive hyperemia is followed by a global reduction in cerebral blood flow (delayed hypoperfusion).**
- **This phenomenon is probably caused by cerebral vasospasms because of dysfunctional nitric oxide and endothelin metabolism.**

**Lemiale V, et al. Resuscitation 2008;76:17–24**



## **Systemic Sequelae**

- **In addition to cerebral injury, ischemic damage also occurs in other vital organs - post resuscitation disease.**
- **Typically, myocardial function is markedly reduced after circulation is restored.**
- **Both systolic contractility and diastolic relaxation are impaired, leading to pronounced hemodynamic instability.**



- **Cardiac arrest induces systemic inflammation, whereby leukocytes and complement are activated and levels of cytokines increased.**
- **Coagulatory cascades are activated immediately but without concomitant stimulation of endogenous fibrinolysis.**
- **Activation of coagulation contributes to cerebral no-reflow**
- **Systemic inflammation impairs myocardial function.**
- **Hemodynamic instability worsens cerebral perfusion, because autoregulation of the cerebral vessels is often defective after cardiac arrest.**

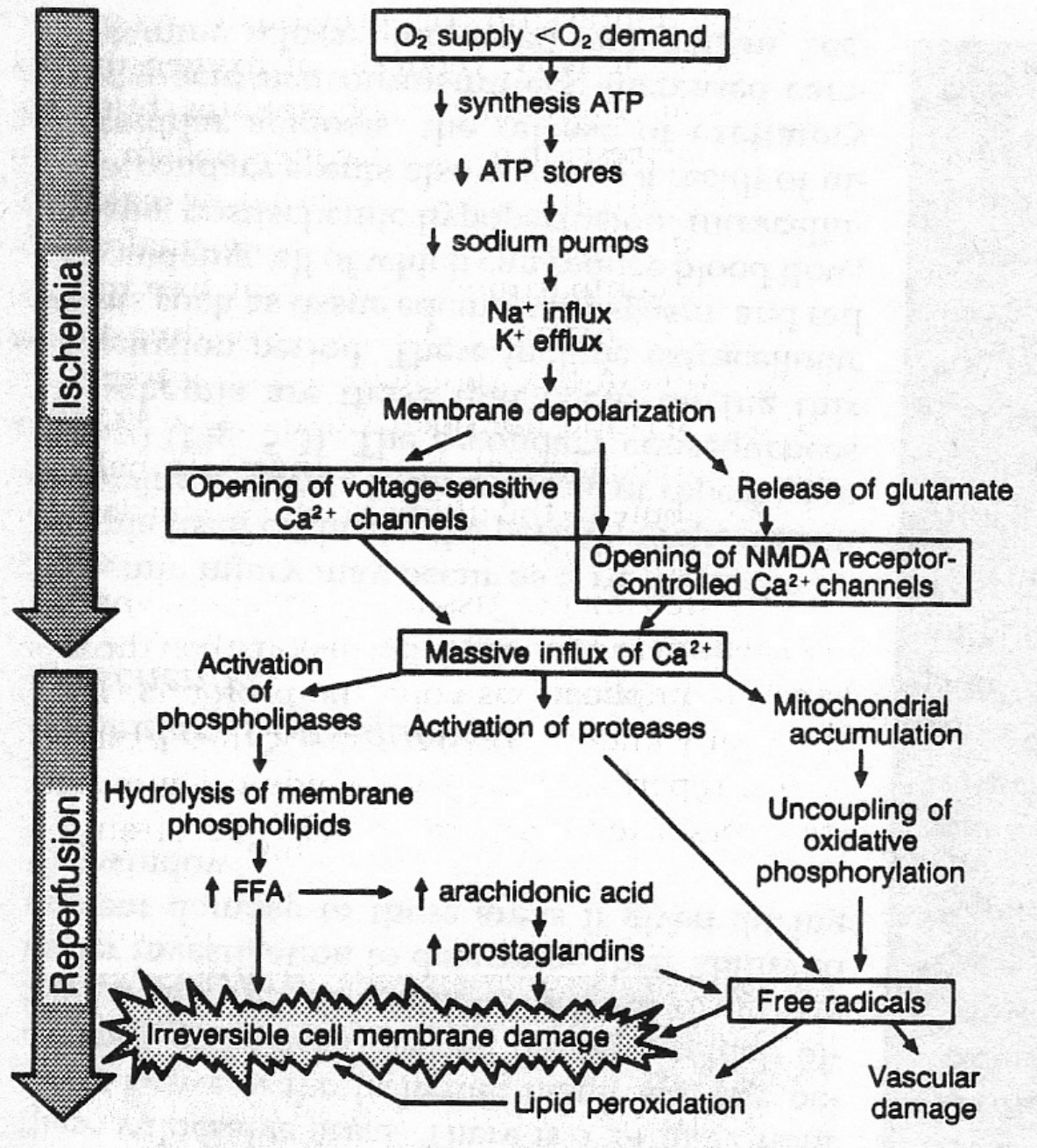
***Niemann JT, et al. Crit Care Med 2004;32:1753–8***

***Sundgreen C, et al. Stroke 2001;32:128–32***

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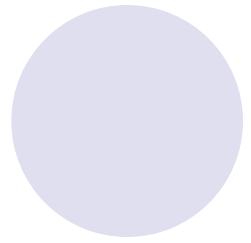
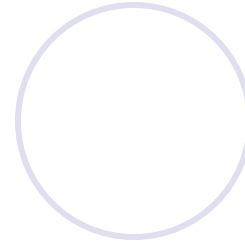
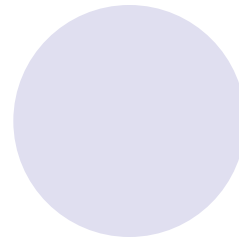
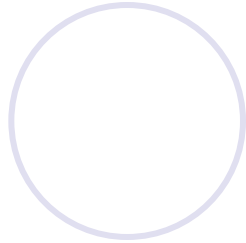
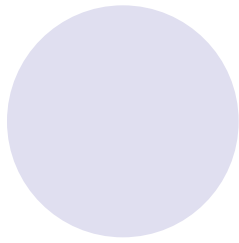
# Nonpharmacological treatment

- Hypothermia
- Avoidance of hyperglycemia
- Prevention and treatment of
  - Hypotension
  - Hypoxia
  - Hypercapnia
- Hemodilution
- Normalisation of increased ICP
- Correction of acidosis and electrolyte imbalance

# Pharmacological treatment



- **Barbiturate**
- **Inhaled anaesthetic agent**
- **Other intravenous anaesthetic agent**  
(propofol, etomidate, benzodiazepine, lignocaine)
- **Calcium channel blocking drug**
- **Anticonvulsant**
- **Steroids**
- **Experimental modalities under investigation**  
(Prostanoids, Free radical scavengers, Lipid membrane peroxidation inhibitors, NMDA receptor antagonists, 21-aminosteroids, Erythropoietin (EPO), Sodium channel blocking drug, Potassium channel-opening drug, NO)



## **MILD THERAPEUTIC HYPOTHERMIA**

- **The first reports of postischemic therapeutic hypothermia were published in the late 1950s.**

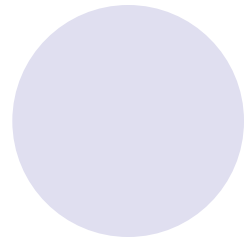
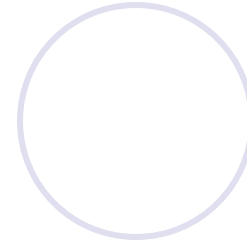
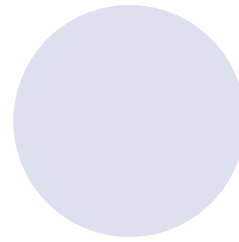
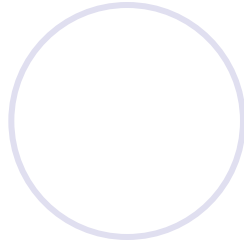
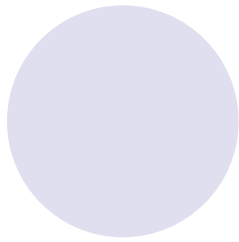
***Benson DW, et al. Anesth Analg 1959;38:423–8***

- **Beneficial effects of mild therapeutic hypothermia after cardiac arrest is provided by two major randomized clinical trials that were published in 2002.**
- **Both studies investigated mild therapeutic hypothermia in comatose adult patients after out-of-hospital cardiac arrest because of ventricular fibrillation**

***Bernard SA, et al. Ann Emerg Med 1997;30:146–53***

***Hypothermia after Cardiac Arrest Study Group. N Engl J Med 2002;346:549–56***





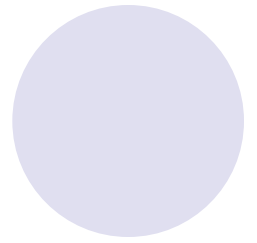
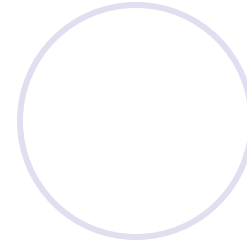
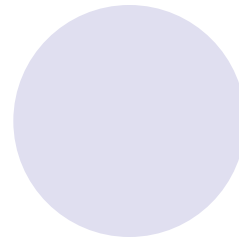
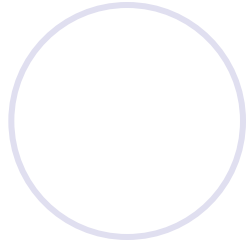
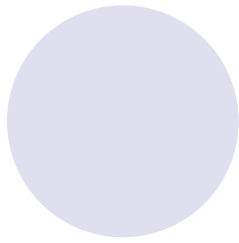
- **The European multicenter trial - Hypothermia After Cardiac Arrest study group included 275 patients, of whom 137 were cooled to 32°C–34°C for 24 h while body temperature in the control group was not decreased.**
- **Regarding outcome at 6 month, mortality was reduced by 26% (41% vs 55%, *P* 0.02) and the favorable neurological outcome increased by 40% (55% vs 39%, *P* 0.09)**

**Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med* 2002;346:549–56**



- **The Australian trial by Bernard et al., covered 77 patients; hypothermia of 33°C for 12 h was applied in 43 patients.**
- **At hospital discharge, the likelihood for good neurological outcome was 85% higher in the hypothermic group (49% vs 26%, *P* 0.046).**

**Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med* 2002;346:557–63**



- **The International Liaison Committee on Resuscitation recommended ( 2003) that mild therapeutic hypothermia be used in comatose adult patients after out-of-hospital cardiac arrest because of ventricular fibrillation.**
- **This recommendation was implemented into the revised international guidelines on CPR in 2005.**



**Table 1.** Indications for Mild Therapeutic Hypothermia<sup>53</sup>

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Unconscious adult patients with spontaneous circulation after out-of-hospital ventricular fibrillation cardiac arrest should be cooled to 32°C–34°C. Cooling should be started as soon as possible and continued for at least 12–24 h.

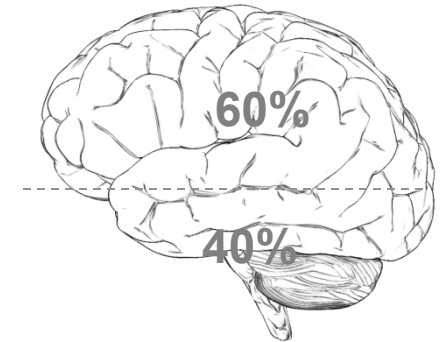
Induced hypothermia might also benefit unconscious adult patients with spontaneous circulation after out-of-hospital cardiac arrest from a nonshockable rhythm or cardiac arrest in hospital.

A child who regains a spontaneous circulation but remains comatose after cardiopulmonary arrest may benefit from being cooled to a core temperature of 32°C–34°C for 12–24 h.

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# physiological effects of hypothermia

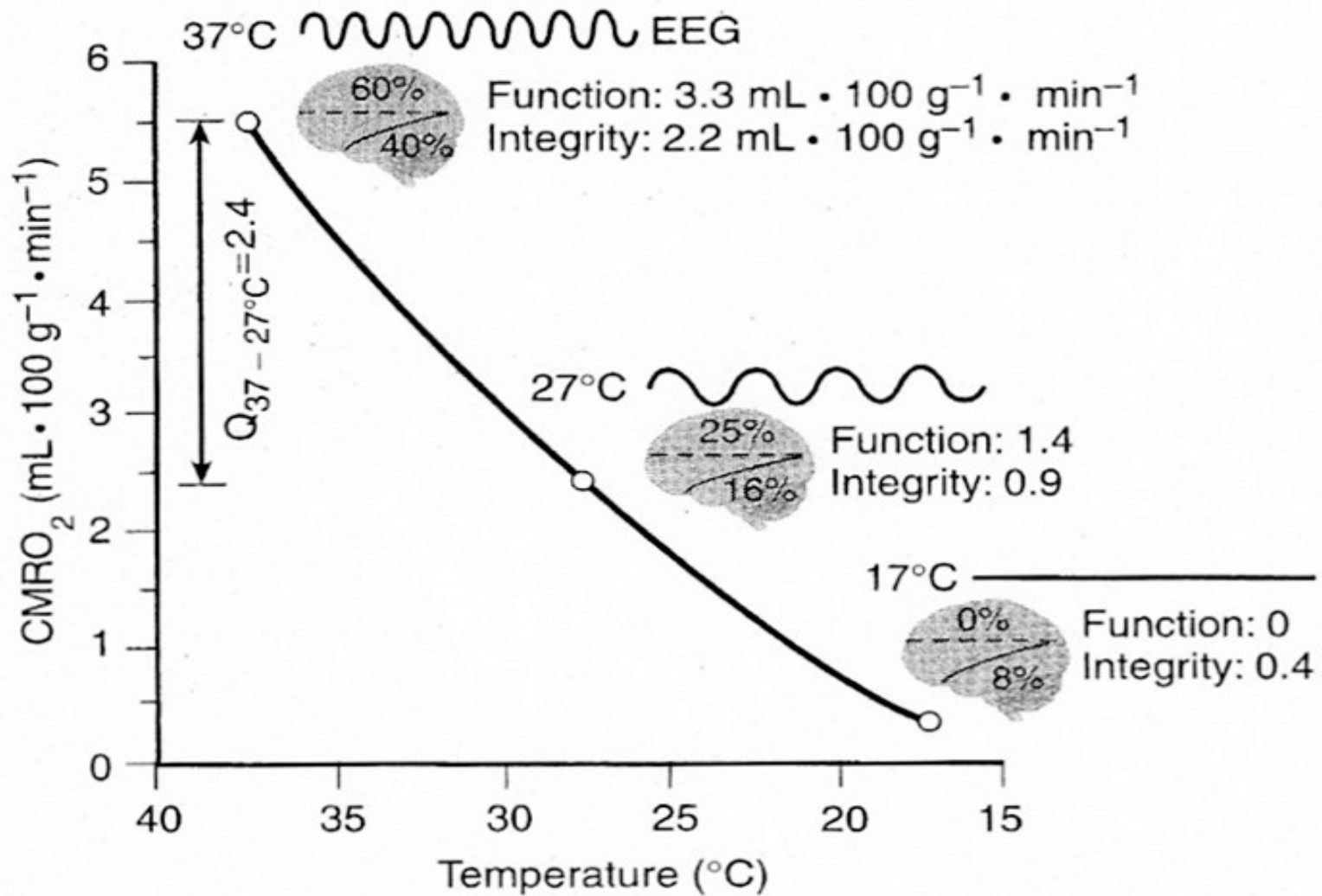
- **Decrease in cerebral metabolism**
- **Maintains integrity of membranes**
- **Preserves ion homeostasis**
- **Decreases excitatory AA release**
- **Decrease Ca influx**
- **Decrease lipid peroxidation**
- **Decrease free radical formation**
- **Decrease nitric oxide synthase activity**
- **direct inhibition of apoptosis**
- **inhibition of coagulation cascades and inflammatory reaction**
- **alters gene expression by enhancing the expression of brain-derived neurotrophic factor (BDNF), the antiapoptotic protein Bcl-2, and suppressing the proapoptotic protein Bax or matrix metalloproteinase-9.**



# Hypothermia

- **Temperature Coefficient - Q10**
  - defines relationship between temperature and global cerebral metabolism
- **$CMRO2_{37deg} = 3ml/min/100gm$  brain**
- **$CMRO2_{27deg} = 1.4ml/min/100gm$  brain**
- **$Q10_{37-27deg} = 2.1$**
- **$Q10_{27-17deg} = 4.5$**

# Temperature





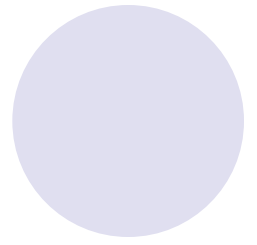
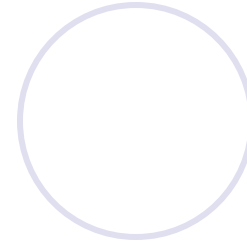
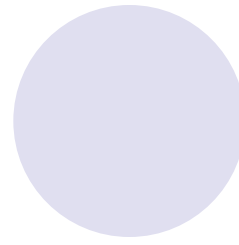
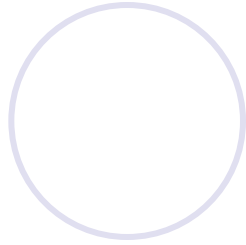
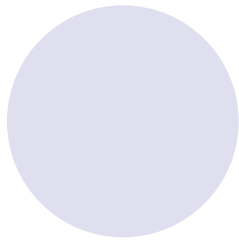
- Hypothermia can be induced by different methods, surface cooling, ice-cold infusions or endovascular cooling catheters.
- Recommendation is that hypothermia should be initiated with minimal delay after cardiac arrest.  
*Circulation 2005;112:IV1–IV211*
- Surface cooling or ice-cold infusions can be used preclinically.
- Kim et al. conducted a randomized clinical trial in which patients were assigned to either receiving 4°C normal saline or not in the out-of-hospital setting, Survival rates was higher in patients who had received out-of-hospital cooling treatment  
*Circulation 2007;115:3064–70*



## Detrimental Effects of hypothermia



- **Circulatory:** ↑ afterload, 3<sup>rd</sup> spacing, viscosity, diuresis, hypovolemia, hypotension
- **cardiac:** cardiac output, arrhythmias
- **Pulmonary:** pulm edema
- **Neurologic:** ICP w/ rewarming, affects neuromonitoring
- **Coagulation:** plt dysfxn , fibrinolysis , bleeding
- **Metabolic:** shifts O2 dissociation curve left, metabolic acidosis, respiratory alkalosis (CO2 more sol), drug metabolism
- **Immunologic:** leuk mobility & phagocytosis



**Questions that still need to be addressed include**

**-establishing the indications for therapeutic hypothermia (intra-hospital cardiac arrest and treatment in children)**

**-cooling characteristics (target temperature, cooling rate, and duration of hypothermia)**

**-cooling methods (external or internal).**

# Hypothermia in neurosurgery



- **1<sup>st</sup> reported use of therapeutic hypothermia in TBI in 1943.**
- **1<sup>st</sup> reported use as a protective adjunct to neurosurgery in 1955.**
- **Abandoned from common practice in 70' s-80' s d/t associated complications.**
- **Revived interest in 90' s after multiple animal studies showed neuroprotective benefit with even mild hypothermia.**

# Mild Intraoperative Hypothermia during Surgery for Intracranial Aneurysm (IHAST)

A total of 1001 patients with a preoperative World Federation of Neurological Surgeons score of I, II, or III ("good-grade patients"), who had had a subarachnoid hemorrhage no more than 14 days before planned surgical aneurysm clipping, were randomly assigned to intraoperative hypothermia (target temperature, 33°C, with the use of surface cooling techniques) or normothermia (target temperature, 36.5°C).

- **Results-** There were no significant differences between the group assigned to intraoperative hypothermia and the group assigned to normothermia in the duration of stay in the intensive care unit, the total length of hospitalization, the rates of death at follow-up .
- **Postoperative bacteremia** was more common in the hypothermia group than in the normothermia group (5 percent vs. 3 percent,  $P=0.05$ ).
- **Conclusions-** Intraoperative hypothermia did not improve the neurologic outcome after craniotomy among good-grade patients with aneurysmal subarachnoid hemorrhage.

**New England Journal of Medicine Vol: 352, No2, January, 13 2005**

# ***No Association between Intraoperative Hypothermia or Supplemental Protective Drug and Neurologic Outcomes in Patients Undergoing Temporary Clipping during Cerebral Aneurysm Surgery***

**Anesthesiology 2010; 112:86 –101**

- **Patients undergoing temporary clipping (n 441) were assigned to intraoperative hypothermia ( $33.3^{\circ} \pm 0.8^{\circ}\text{C}$ , n 208) or normothermia ( $36.7^{\circ} \pm 0.5^{\circ}\text{C}$ , n 233), with 178 patients also receiving supplemental protective drug (thiopental or etomidate) during temporary clipping.**
- **Neither hypothermia ( $P$  0.847; odds ratio 1.043, 95% CI 0.678– 1.606) nor supplemental protective drug ( $P$  0.835; odds ratio 1.048, 95% CI 0.674–1.631) were associated with better 3-month Glasgow Outcome Score.**
- **The effect of supplemental protective drug did not significantly vary with temperature. The effects of hypothermia and protective drug did not significantly vary with temporary clip duration.**
- **Conclusion: In the Intraoperative Hypothermia for Aneurysm Surgery Trial, neither systemic hypothermia nor supplemental protective drug affected short- or long-term neurologic outcomes of patients undergoing temporary clipping**

# Hypothermia in brain injury pt.

- Initial pilot studies showed neuroprotective effect but later studies did not.
- Bench-to-bedside review: Hypothermia in traumatic brain injury  
*Critical Care 2010, 14:204*
- The use of hypothermia in patients with traumatic brain injury may have beneficial effects in both ICP reduction and possible neuro-protection, supported by the Eurotherm3235Trial protocol.

# Hypothermia in stroke

- Studies demonstrated the efficacy of induced moderate hypothermia

## ***Moderate Hypothermia in the Treatment of Patients With Severe Middle Cerebral Artery Infarction***

**S. Schwab, et al. *Stroke* 1998;29:2461-2466**

***Methods***—Moderate hypothermia was induced in 25 patients with severe ischemic stroke in the middle cerebral artery (MCA) territory for therapy of postischemic brain edema. Hypothermia was induced within  $14\pm 7$  hours after stroke onset and achieved by external cooling with cooling blankets, cold infusions, and cold washing.

- Patients were kept at 33°C body-core temperature for 48 to 72 hours, and intracranial pressure (ICP), cerebral perfusion pressure, and brain temperature were monitored continuously.
- Outcome at 4 weeks and 3 months after the stroke was analyzed with the Scandinavian Stroke Scale (SSS) and Barthel index. The side effects of induced moderate hypothermia were analyzed.



**Results**—Fourteen patients survived the hemispheric stroke (56%). Neurological outcome according to the SSS score was 29 (range, 25 to 37) 4 weeks after stroke and 38 (range 28 to 48) 3 months after stroke. During hypothermia, elevated ICP values could be significantly reduced.

Herniation caused by a secondary rise in ICP after rewarming was the cause of death in all remaining patients.

The most frequent complication of moderate hypothermia was pneumonia in 10 of the 25 patients (40%). Other severe side effects of hypothermia could not be detected.

**Conclusions**—Moderate hypothermia in the treatment of severe cerebral ischemia is not associated with severe side effects. Moderate hypothermia can help to control critically elevated ICP values in severe space-occupying edema after MCA stroke and may improve clinical outcome in these patients.



# Cooling for Acute Ischemic Brain Damage (COOL AID): An Open Pilot Study of Induced Hypothermia in Acute Ischemic Stroke

**Derk W. Krieger et al, *Stroke* 2001;32;1847-1854**

## ***Methods—***

patients presented with major ischemic stroke (National Institutes of Health Stroke Scale [NIHSS] score >15) within 6 hours of onset. patients with a persistent NIHSS score of >8 were treated with hypothermia to  $32\pm 1^{\circ}\text{C}$  for 12 to 72 hours depending on vessel patency. A modified Rankin Scale was measured at 90 days and compared with concurrent controls.

## ***Results—***

Ten patients with a mean age of  $71.1\pm 14.3$  years and an NIHSS score of  $19.8\pm 3.3$  were treated with hypothermia. Nine patients served as concurrent controls. The mean time from symptom onset to thrombolysis was  $3.1\pm 1.4$  hours and from symptom onset to initiation of hypothermia was  $6.2\pm 1.3$  hours. The mean duration of hypothermia was  $47.4\pm 20.4$  hours. Target temperature was achieved in  $3.5\pm 1.5$  hours.



**Non critical complications in hypothermia patients included bradycardia (n5), ventricular ectopy (n3), hypotension (n3), melena (n2), fever after rewarming (n3), and infections (n4). There were 3 deaths in patients undergoing hypothermia. The mean modified Rankin Scale score at 3 months in hypothermia patients was  $3.1 \pm 2.3$ .**

***Conclusion—***

**Induced hypothermia appears feasible and safe in patients with acute ischemic stroke even after thrombolysis. Refinements of the cooling process, optimal target temperature, duration of therapy, and, most important, clinical efficacy, require further study.**

# Avoid Hyperthermia

- **Brain metabolic rate alters in direct proportion to core temp.**
- **Above normal temp. markedly increase CMRo2 and exacerbate ischemic injury**
- **Ischemia that normally results in scattered neuronal necrosis produces cerebral infarction when body temperature is elevated.**



# Hyperventilation or Normocapnia

- Available data do not support reduction of PaCO<sub>2</sub> as a routine intervention to reduce cerebral injury, but its important for reduction in ICP

*ASA Refresher Courses (29) 2001*

*ASA Annu Rev (54)*

- In head injury pt, application of prophylactic hyperventilation is associated with a worse outcome as the ischemic regions increase dramatically with hypocapnia.
- The Brain Trauma Foundation has recommended that prophylactic hyperventilation be avoided during the early stages after head injury.

*J Neurotrauma 2000;17:513-20.*

- Prophylactic hyperventilation has not been shwon to be of any benefit in patients with stroke.

*Ruta TS, et al. Anesthesiology 1992;78:134-40.*

# **“Therapeutic Hypercapnia” after Ischemic Brain Injury**

## ***Is There a Potential for Neuroprotection?***

**Zhou et al. Anesthesiology 2010; 112:274 – 6**

- **Induction of transient global cerebral ischemia in adult Wistar rats by bilateral occlusion of the common carotid arteries and controlled hypotension for 15 min.**
- **After the release of the carotid clamps, the animals were exposed for 2 h to defined concentrations of inhaled carbon dioxide to achieve PaCO<sub>2</sub> goals of mild, moderate, and severe hypercapnia (60–80, 80–100, and 100– 120 mmHg, respectively).**
- **Physiologic variables including mean arterial pressure, arterial blood gases, and intracranial pressure (ICP) were measured during ischemia and early reperfusion.**
- **The animals were evaluated at 24 and 72 h of recovery for functional performance (neurologic deficit score). Subsequently (at 72 h), the brains were analyzed for histopathologic changes, protein expression, and tissue edema formation.**



- **Mild and moderate hypercapnia were associated with better neurologic deficit scores, fewer ultrastructural histopathologic changes, and reduced neuronal apoptosis compared with normocapnia.**

## **conclusion**

- **the neuroprotective effects observed with mild and moderate hypercapnia (PaCO<sub>2</sub> 60–100 mmHg) involves modulation of apoptosis regulating proteins. In contrast, the absence of neuroprotection with severe hypercapnia (PaCO<sub>2</sub> 100–120 mmHg) could potentially be attributed to more pronounced brain edema formation.**

# Glycemic control for neuroprotection

- **Why to maintain normoglycemia**  
**expansion of ischemic lesion**  
**delayed recovery after ischemic insult**

## **Target**

**Non diabetic- 80 to 155 mg/dL**

**Poorly-controlled diabetes 100 to 200 mg/dL.**

**Wass CT,et al . Mayo Clin Proc. 1996;71:801–812.**

**-evidence is against strict glycemic control**

## INTENSIVE INSULIN THERAPY IN CRITICALLY ILL PATIENTS

N Engl J Med 2001;345:1359-67

- prospective, randomized, controlled study involving adults admitted to surgical intensive care unit on mechanical ventilation were randomly assigned to receive intensive insulin therapy ( 80 -110 mg/dl) or conventional treatment ( 180 - 200 mg/ dl).

### *Results*

- At 12 months, with a total of 1548 patients enrolled, intensive insulin therapy reduced mortality during intensive care from 8.0 percent with conventional treatment to 4.6 percent.
- The benefit of intensive insulin therapy was attributable to its effect on mortality among patients who remained in the intensive care unit for more than five days. The greatest reduction in mortality involved deaths due to multiple-organ failure with a proven septic focus.
- Intensive insulin therapy also reduced overall in-hospital mortality by 34 percent, bloodstream infections by 46 percent, acute renal failure requiring dialysis or hemofiltration by 41 percent, the median number of red-cell transfusions by 50 percent, and critical-illness polyneuropathy by 44 percent, and patients receiving intensive therapy were less likely to require prolonged mechanical ventilation and intensive care.

### *Conclusions*

- Intensive insulin therapy to maintain blood glucose at or below 110 mg per deciliter reduces morbidity and mortality among critically ill patients in the surgical intensive care unit.



## Intensive Insulin Therapy in the Medical ICU

N Engl J Med 2006

- prospective, randomized, controlled study of adult patients admitted to medical ICU, requiring intensive care for at least three days were randomly assigned to strict normalization of blood glucose levels (80-110 mg/dl) with the use of insulin infusion or to conventional therapy (<180 mg/dl ). There was a history of diabetes in 16.9 percent of the patients.

### Results

- In the analysis of 1200 patients, intensive insulin therapy reduced blood glucose levels but did not significantly reduce in-hospital mortality (40.0 percent in the conventional-treatment group vs. 37.3 percent in the intensive-treatment).
- but morbidity was significantly reduced by the prevention of newly acquired kidney injury, accelerated weaning from mechanical ventilation, and accelerated discharge from the ICU and the hospital.

### Conclusions

- Intensive insulin therapy significantly reduced morbidity but not mortality among all patients in the medical ICU.

# Intensive versus Conventional Glucose Control in Critically Ill Patients

The NICE-SUGAR Study Investigators\*

**NEJM 2009**

- Within 24 hours after admission to an intensive care unit (ICU), adults requiring treatment in the ICU on 3 or more consecutive days were randomly assigned to undergo either intensive glucose control (81 - 108 mg/dl), or conventional glucose control (< 180 mg/dl). the primary end point as death from any cause within 90 days after randomization.

## Results

- Of the 6104 patients who underwent randomization, 3054 were assigned to undergo intensive control and 3050 to undergo conventional control. The two groups had similar characteristics at baseline.
- A total of 829 patients (27.5%) in the intensive-control group and 751 (24.9%) in the conventional-control group died .
- The treatment effect did not differ significantly between operative (surgical) patients and non -operative (medical) patients .
- Severe hypoglycemia (blood glucose level,  $\leq 40$  mg/dl) was reported in 206 of 3016 patients (6.8%) in the intensive-control group and 15 of 3014 (0.5%) in the conventional-control group (P<0.001).
- There was no significant difference between the two treatment groups in the median number of days in the ICU or hospital or the median number of days of mechanical ventilation or renal-replacement therapy

## Conclusions

- Intensive glucose control has increased mortality among adults in the ICU, a blood glucose target of <180 mg/dl resulted in lower mortality than did a target of 81 - 108 mg/dl.



**Insulin therapy protects the central and peripheral nervous system of intensive care patients.**

**Van den Berghe G, et al. Neurology 2005; 64: 1348–1353.**

- **surgical patients admitted with isolated brain injury showed reduced mean and maximum intracranial pressure with IIT, while cerebral perfusion pressures were maintained identical with eightfold less vasopressors.**
- **Seizures occurred less frequently and there was a trend towards a reduction in diabetes insipidus.**

## Differential temporal profile of lowered blood glucose levels (3.5 to 6.5 mmol/l versus 5 to 8 mmol/l) in patients with severe traumatic brain injury

**Regula Meier, *Critical Care* 2008, 12:R98**

- 228 propensity matched patients (age, sex and injury severity) treated in intensive care unit (ICU) from 2000 to 2004, were retrospectively evaluated the influence of different predefined blood glucose targets (3.5 to 6.5 versus 5 to 8 mmol/l) on frequency of hypoglycaemic and hyperglycaemic episodes, insulin and norepinephrine requirement, changes in intracranial pressure and cerebral perfusion pressure, mortality and length of stay on the ICU.

### Results

- Mortality and length of ICU stay were similar in both blood glucose target groups.
- Blood glucose values below and above the predefined levels were significantly increased in the 3.5 to 6.5 mmol/l group, predominantly during the first week. Insulin and norepinephrine requirements were markedly increased in this group.
- The rates of bacteraemia and urinary tract infection are significantly increased when reducing blood glucose levels to 3.5 to 6.5 mmol/l as compared with 5 to 8 mmol/l during the first week, followed by a significant decrease in the second week.

### Conclusion

- Maintaining blood glucose within 5 to 8 mmol/l appears to yield greater benefit during the first week. During the second week, 3.5 to 6.5 mmol/l is associated with beneficial effects in terms of reduced intracranial hypertension and decreased rate of pneumonia, bacteraemia and urinary tract infections.

**The Effect of Intensive Insulin Therapy on Infection Rate, Vasospasm, Neurologic Outcome, and Mortality in Neurointensive Care Unit After Intracranial Aneurysm Clipping in Patients With Acute Subarachnoid Hemorrhage: A Randomized Prospective Pilot Trial,**

- **78 patients were prospectively enrolled and randomly assigned either to conventional insulin therapy or to intensive insulin therapy (38 and 40 patients, respectively).**
- **The infection rate during the study was significantly higher in patients who received conventional insulin therapy than in patients who received intensive insulin therapy (42% vs. 27%;  $P < 0.001$ ).**
- **The benefit of strict glycemic control on postoperative vasospasm, neurologic outcome, and mortality rates does not seem to be affected by intensive insulin therapy.**

**Journal of Neurosurgical Anesthesiology: July 2007 - Volume 19 - Issue 3 - pp 156-160**

# Insulin-related decrease in cerebral glucose despite normoglycemia in aneurysmal subarachnoid hemorrhage

Florian S, et al. *Critical Care* 2008, 12:R9

- In prospective, nonrandomized study, 31 SAH patients in an intensive care unit (age  $52 \pm 10$  years, World Federation of Neurological Surgeons grade  $2.9 \pm 1.6$ ). A microdialysis catheter was inserted into the vascular territory of the aneurysm after clipping.
- Blood glucose levels above 140 mg/dl were treated with intravenous insulin and the microdialysates were analyzed hourly for the first 12 hours of infusion.

## Results

- Twenty-four patients were treated with insulin for glucose control. Higher age and World Federation of Neurological Surgeons score were risk factors for need for insulin treatment ( $P < 0.05$ ).
- blood glucose remained stable after initiation of insulin infusion, insulin induced a significant decrease in cerebral glucose at 3 hours after onset of the infusion until the end of the observation period ( $P < 0.05$ ), reflecting high glucose utilization.
- The lactate/pyruvate ratio and glutamate did not increase, excluding ischaemia as possible cause of the decrease in glucose.
- Glycerol tended toward higher values at the end of the observation period (9 to 12 hours), reflecting either tissue damage after SAH or the beginning of cellular distress after insulin infusion.

## Conclusion

- Higher SAH grade was among the risk factors for need for insulin.
- Intensive glycaemic control using insulin induced a decrease of cerebral glucose and a slight increase in glycerol.



# Hemodilution

- Target hematocrit 30%- 35%
- Beneficial effect by
  - decreasing viscosity
  - increases CBF
  - increase oxygen delivery

-No role in stroke,

-Definitive role in vasospasm

**The Lancet Neurology, Volume 2, Issue 10, 2003**



# Avoid hypotension

Hypotension has been shown to be deleterious to the injured (ischemic or traumatic) brain

Hypotension can increase cerebral infarct volumes significantly and should be avoided

- In head injured patients ,a higher than normal CPP is required to maintain normal CBF.
- Chan and colleagues have shown that CPP of about 70 mmHg is adequate in head injured patients.

**Chan KH, et al. Neurosurgery 1993;32:547-52.**





- **Patients who have sustained an ischemic cerebral injury may benefit from an augmentation of cerebral blood flow by induced hypertension.**

**Schwarz S, et al. Stroke 2002;33:998-1004**

- **Induced hypertension, with an increase in mean arterial pressure 20% above baseline pressure, can lead to a clinical improvement in a patients with acute stroke in whom thrombolysis is not feasible. The potential risk for hemorrhagic conversion of the stroke exists.**

**Rordorf G, et al. Neurology 2001;56:1210-3.**

- **Maintenance of an adequate MAP and CPP**
  - MAP 70-80 mmHg**
  - CPP >60 mm Hg**
  - SAH induced vasospasm- SBP 180-220 mm Hg**
- **Elevation of MAP by alpha agonists**



## **Thrombolysis**

**Rationales for using thrombolytics during CPR.**

- **Cardiac arrest is caused by acute myocardial infarction or pulmonary embolism in 50%–70% of patients.**
- **Coagulation disorders are involved in the no-reflow phenomenon.**
- **Microscopic examination of cerebral vessels shows that multiple microemboli develop during cardiac arrest and resuscitation.**



- **The European multicenter Thrombolysis in Cardiac Arrest trial.**

**After inclusion of 1050 patients, the study was prematurely stopped, because preliminary findings indicated that there was no likely benefit of thrombolytic therapy over placebo.**

***Thrombolysis in Cardiac Arrest (TROICA) Study. Eur J Clin Invest 2005;35:315–23***



- **Studies have consistently shown that thrombolysis during CPR is largely safe and not associated with increased bleeding complications.**

***Abu-Laban RB, et al. N Engl J Med 2002;346:1522–8  
Resuscitation 2004;61:309–13***

- **Thrombolytic therapy during CPR was included in international CPR guidelines in 2005 but only when pulmonary embolism or myocardial infarction is suspected**

# Hypertonic, Hyperoncotic Infusions to promote microcirculation

- Several animal studies have shown that hypertonic-hyperoncotic solutions given during CPR, or immediately after restoration of spontaneous circulation, decrease cerebral no-reflow.

*Krep H, et al. Resuscitation 2004; 63:73–83*

*Noppens RR, et al. Crit Care Med 2006;34:2194–200*

- Besides having positive effects on cerebral microcirculation, hypertonic saline also seems to ameliorate cardiac function during and after CPR.



- **Bender et al. randomized 66 patients who suffered out-of-hospital cardiac arrest into two groups. The patients received 2 mL / kg/ 10 min of either hypertonic saline with HES (7.2% NaCl with 6% HES 200,000/0.5) or HES alone during continuous CPR.**
- **Resuscitation success tended to be higher in patients receiving hypertonic saline with HES (66.7%vs 51.5%, *P* 0.21) and hospital admission rates were also increased (57.6% vs 39.4%, *P* 0.14)**

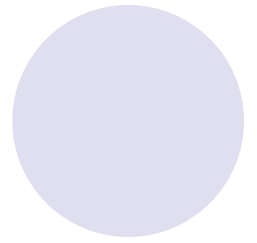
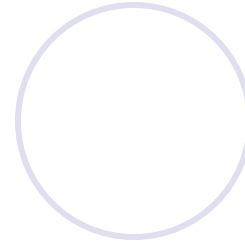
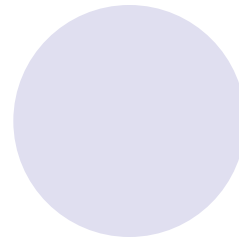
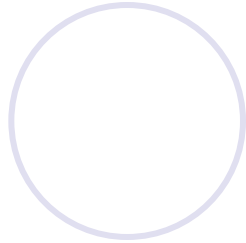
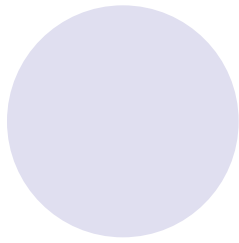
***Resuscitation 2007;72:74–81***

# Barbiturates



- **The Brain Resuscitation Clinical Trial failed to demonstrate any improved outcome due to thiopental therapy following cardiac arrest.**
- **Barbiturates selectively reduced metabolism associated with synaptic transmission, and is effective in the presence of EEG activity**
- **During cardiac arrest, the EEG becomes isoelectric within 20-30 sec and this persists for several minutes after resuscitation.**

***Brain Resuscitation Clinical Trial 1 Study Group. N Engl J Med 1986; 314:397 -403.***



- **Thiopentone, methohexital**

**Do not improve outcome in global or complete ischemia after cardiac arrest**

- **Pentobarbital**

**mechanism similar to thiopental**

**long acting ,Current clinical indication- BARBITURATE COMA**

- **Barbiturates have been found to be efficacious in the treatment of focal ischemia and can reduce the extent of cerebral injury.**

**Warner DS, et L. J Cereb Blood Flow Metab 1991;11:794-802.**

**Drummond JC. Anesthesiology 1993;78:611-3.**





## **BARBITURATES IN HEAD TRAUMA**

- **Barbiturates provide a means of reducing and maintaining intracranial pressure but not necessarily corresponds to improved outcome.**

***Ward JD, et al. J Neurosurg 1985; 62: 383-8***

# Propofol



- **Similar to barbiturate**
- **Anti-inflammatory property**
- **Anti-emetic**
- **Anti pruritic**
  
- **Unique feature-provide neuroprotection in post ischemic period but is not sustained.**

**Bayona NA, et al, Anesthesiology 100:2004**

# Etomidate



- Reduces CMRO<sub>2</sub>(50%)
  - Decreases CBF
  - Decreases ICP
  - But maintains cardiovascular stability and CPP
  - CO<sub>2</sub> reactivity is preserved
- 
- Models of focal ischemia revealed that etomidate actually increased the volume of brain infarction by reducing nitric oxide levels in ischemic brain tissue .

**Drummond JC, et al. Anesth Analg 2005;100:841-6**

**Available data do not support the use of etomidate as a neuroprotective agent.**

# Benzodiazepine



- **Stimulate inhibitory neurotransmitter GABA**
- **Decreases CMRO<sub>2</sub>, CBF while preserving CO<sub>2</sub> reactivity**
- **Commonly used are diazepam, midazolam, lorazepam**
- **Diazepam improved the oxygen supply:demand ratio**
- **Reduces energy required for synaptic transmission**  
**Marana E, et al. Resuscitation 1982 10: 89-100.**  
**Cotev S, et al. Anesthesiology 1975; 43:117-22**

**May be neuroprotectant in both global and focal ischaemia.**

# Lidocaine

A decorative graphic consisting of six circles arranged in two rows. The top row has two circles: a solid light purple one on the left and an outlined light purple one on the right. The bottom row has three circles: a solid light purple one on the left, an outlined light purple one in the middle, and a solid light purple one on the right.

- **The mechanism of action**

- **selective blockade of Na channels in neuronal membranes, Depolarization is blocked**

- **At high doses,( 160 mg/kg ) like the barbiturates, abolishes synaptic electrical activity ( isoelectric EEG) and thus reduces the CMRO<sub>2</sub>**

- reduces intracranial hypertension**



**It was demonstrated by Astrup *et al.* in a canine global ischaemia model that in the functionally arrested brain (i.e., an isoelectric EEG induced by barbiturates), lidocaine can further reduce the metabolic rate by 15-20 per cent.**

**This reduction in metabolism was attributed to lidocaine's ability to reduce ion leaks (block Na<sup>+</sup> influx and K<sup>+</sup> efflux) and thus reduce the energy requirement for ionic homeostasis by the Na pumps.**

***Astrup J, et al. Anesthesiology 1981; 55: 263-8.***

**This effects of lidocaine (i.e., metabolic inhibition beyond that achievable with an isoelectric EEG alone and a delay in the ischaemic potassium efflux) resemble those of hypothermia.**

# Volatile anaesthetics



- **Protects both against focal and global ischemia**
- **Mechanism**
  - Metabolic electrical suppression**
  - Inhibition of excitatory neurotransmitter**
  - Potentialiation of inhibitory receptor**
  - Decrease Ca<sup>+</sup> influx**
  - Activation of mitoATP k<sup>+</sup> channels**
- **Adequate anesthesia per se has protective effect versus awake state.**
- **No difference in neuroprotective effect among volatile anesthetics.**



- **When compared with other volatile anaesthetics, isoflurane has demonstrated superior protection during focal ischaemia.**
- **Michenfelder *et al.* compared the frequency of cerebral ischaemia during carotid endarterectomy (a model of transient incomplete regional ischaemia) when isoflurane, enflurane and halothane were used.**
- **This retrospective study confirmed that different volatile anaesthetics differ in their cerebral vascular properties.**
- **Majority of patients developed ipsilateral EEG changes of ( ischaemia within three minutes of carotid occlusion) is lowest for isoflurane (10 ml/ 100 g/ min) then enflurane (15 ml./ 100 g/ min) and finally halothane (20 ml/100 g/min). Thus it appears that cerebral vasodilation and critical CBF are related.**

***Michenfelder JD, et al. Anesthesiology 1987; 67: 336-40.***





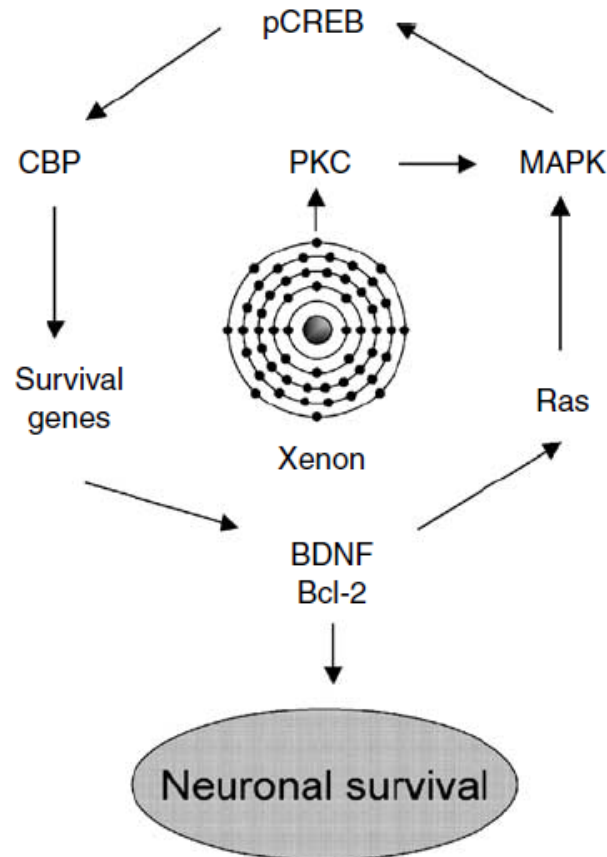
# Nitrous oxide

- **N<sub>2</sub>O exposure during incomplete global cerebral ischemia enhanced ischemic damage and resulted in poor neurological outcomes as compare with inhalational agent anesthesia.**
- **N<sub>2</sub>O may also suppress the neuroprotective properties of other inhalational anesthetics in ischemic brain when administered as a combination treatment.**

# xenon

- NMDA antagonist
- Upregulation of genes and synthesis of the CREB-dependent survival (proteins Bcl-2 ,BDNF,Ras protein).

D Ma et al, *Journal of Cerebral Blood Flow & Metabolism* (2006) 26, 199–208





# Calcium entry blockers

- **The role of CEB in CNS protection has centred around effects on the cerebral vasculature.**
- **Exact mechanism of cerebral protective action is not known.**
- **But it is presumed to be their ability to reduce Ca influx across plasma and mitochondrial membranes.**



- **The Ca ++ channel entry blocking agents as a group display differential effectiveness as cerebral protectants.**
- **Agents appears to be tissue,organ,and species specific.**
- **The tissue specificity of CEBs can be attributed to the variation that exists among Ca channels**

***Gelmers HJ et al. Am J Cardiol 1985; 55: 144-8B.***



## LIDOFLAZINE AND FLUNARIZINE

- The results of studies of the cerebral protective effects of lidoflazine and flunarizine during complete cerebral ischaemia are conflicting and inconclusive.
- Desphande *et al.* demonstrated a significantly improved histological outcome in flunarizine-treated rats that were exposed to severe incomplete global ischaemia.

***Desphande JK, et al. Anesthesiology 1986; 64: 215-24.***



## **NIMODIPINE**

- **Blocks the L-type of voltage-sensitive ca channels.**
- **Nimodipine has an effect on CBF particularly after complete ischaemia where it ameliorates post-ischaemic hypoperfusion thus increasing CBF once reperfusion has been established.**
- **Even in the non-traumatized brain, nimodipine increases the CBF without increasing the cerebral metabolic rate.**

***Harper AM, et al. J Cereb Blood Flow Metab 1981; 1: 349-56.***



### ***Nimodipine in Sub-arachnoid haemorrhage***

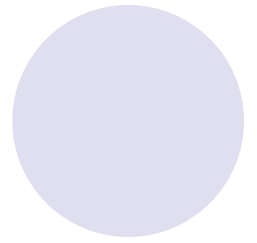
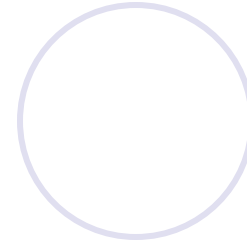
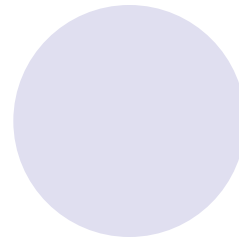
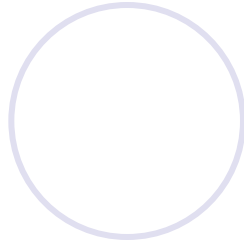
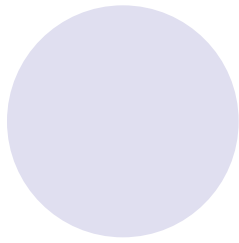
- **The protective effect was attributed to the inhibition of cerebral arterial spasm by nimodipine.**
- **Allen *et al.* demonstrated a beneficial effect due to nimodipine as the occurrence of neurologic deficits and death were significantly reduced in treated patients.**

***Allen GS, et al. N Engl J Med 1983; 308: 619-24.***

### ***Nimodipine in head injury***

- **Nimodipine is efficacious in treating patients with severe head trauma but without producing adverse changes in ICP or systemic blood pressure.**

***Kostron H, et al. Neurol Res 1984; 6: 29-32.***



## ***Nimodipine in stroke***

- **In a double-blind, placebo-controlled prospective study, nimodipine significantly reduced mortality from all causes during acute ischaemic stroke in man.**
- **During a six-month follow-up, patients in the nimodipine group continued to show significant improvement when compared with the placebo group.**

***Gelmers H J, et al. N Engl J Med 1988; 318: 203-7.***



# Dantrolene as neuroprotectant

- ↓ EAA
- Upregulation of antiapoptotic gene Bcl-2
- Membrane stabiliser
- Prevents protein unfolding in ischemic zone

**Susanne M. Neurocrit Care (2009) 10:103–115**

# Magnesium



- **Maintains of cellular ATP levels through Ca ++ channels blockade**
- **NMDA receptor antagonist**
- **Inhibition of neuronal transmission**
- **Free radical scavenger**
- **Membrane stabiliser**

# Prophylactic intravenous magnesium sulfate for treatment of aneurysmal subarachnoid hemorrhage: A randomized, placebo-controlled, clinical study

Crit Care Med 2010; 38:1284 –1290

- 110 patients were randomized to receive intravenous magnesium sulfate or to serve as controls.
- Magnesium treatment was started with a bolus of 16 mmol, followed by continuous infusion of 8 mmol/hr. Serum concentrations were measured every 8 hrs, and infusion rates were adjusted to maintain target levels of 2.0–2.5 mmol/L.
- Intravenous administration was continued for 10 days or until signs of vasospasm had resolved. Thereafter, magnesium was administered orally and tapered over 12 days.

## *Results*

- The incidence of delayed ischemic infarction was significantly lower in magnesium-treated patients (22% vs. 51%).
- Delayed ischemic neurologic deficit was non significantly reduced (9 of 54 vs. 15 of 53 patients) and transcranial Doppler-detected/angiographic vasospasm was significantly reduced in the magnesium group (36 of 54 vs. 45 of 53 patients)

***Conclusion:*** The high-dose intravenous magnesium can reduce cerebral ischemic events after aneurysmal subarachnoid hemorrhage by attenuating vasospasm and increasing the ischemic tolerance during critical hypoperfusion.



- **Magnesium sulfate for neuroprotection after traumatic brain injury: a randomised controlled trial**
  - Continuous infusions of magnesium for 5 days given to patients within 8 h of moderate or severe traumatic brain injury were not neuroprotective and might even have a negative effect in the treatment of significant head injury.  
**Lancet , Volume 6, Issue 1, January 2007**
  
- **Mg in stroke**
  - early administration of intravenous magnesium does not reduce mortality or disability in the 90 days following onset of acute stroke.  
**IMAGES Trial, Lancet. 2004;363:439–45.**

# Anticonvulsant

A decorative graphic consisting of six circles arranged in two rows. The top row has three circles: a solid light purple circle on the left, a hollow light purple circle in the middle, and a solid light purple circle on the right. The bottom row has three solid light purple circles.

- **Untreated seizures can produce neuronal necrosis even with normal cerebral perfusion.**
- **Target is Prevention of and rapid treatment of seizures**
- **Seizures can be rapidly treated with benzodiazepines, barbiturates, etomidate and propofol , phenytoin.**

# Phenytoin



- Two separate studies, by Aldrete *et al.* and Cullen *et al.*, demonstrated that treatment with phenytoin improved neurological recovery and reversed histopathological changes in animals subjected to complete global ischaemia.

*Aldrete JA, et al. Crit Care Med 1979; 7: 466-7 I.*  
*Cullen JP, et al. Analg 1979; 58: 165-9 Anesth.*

*Artru et al.* proposed that phenytoin exerts its protective effects through slowing the release of K<sup>+</sup> from ischaemic neurons, and by stabilization of cellular membranes.

- Phenytoin limit cerebral extracellular K<sup>+</sup> accumulation, improving the distribution of CBF, energy/substrate delivery, and prevent the accumulation of metabolites and toxic substances

# Agents with potential but unproven efficacy

## *Corticosteroids*

- **Antiinflammatory properties, alter the normal response to injury and may alter the neurological outcome following an ischaemic insult.**
- **Steroids reduces edema but evidence for benefit from use is weak**
- **Insufficient evidence to define role of glucocorticoids in focal ischemia**  
**(Cochrane Database Syst Rev 2002)**
- **In double-blind study, administration of dexamethasone to acute stroke victims concluded that dexamethasone can be a useful adjunct to the treatment of the patient with a severe stroke and the beneficial effects of steroids are in part due to their ability to decrease brain oedema secondary to massive brain infarction.**  
***Patten BM, et al. Neurology 1972; 22: 377-83.***

**Glucocorticoids exacerbate injury from global ischemia by increasing plasma glucose**



## **Other agents under investigation**

- **Prostanoids**
- **Free radical scavengers**
- **Lipid membrane peroxidation inhibitors**
- **NMDA receptor antagonists**
- **21-aminosteroids**
- **Erythropoietin (EPO)**
- **Sodium channel blocking drug**
- **Potassium channel-opening drug**
- **NO**



# INFLUENCING APOPTOSIS



## Inhibitors of Apoptosis

- **Delayed neuronal death after cardiac arrest is caused by apoptosis.**
- **Apoptosis is characterized by activation of proteolytic cascades, which ultimately result in degradation of cellular components.**
- **The proteolytic enzyme, caspase 3, is one of the key executioners of apoptosis.**
- **Pathophysiology of neuronal degeneration is too complex to be reduced to only one molecule.**
- **Inhibition of apoptotic cascades is still in a experimental phase.**



## Growth Factors

- **Endogenous nerve growth factor (NGF) and BDNF are upregulated in neurons after cerebral ischemia and have antiapoptotic effect**
- **The expression of BDNF is even enhanced by therapeutic hypothermia.**
- **Administration of exogenous growth factors after cerebral ischemia has produced inconclusive results.**



### ***Free radical scavengers***

- **Damage produced by free radicals may be prevented or decreased with the use of free radical scavengers -barbiturates, vitamins C and E, edaravone, mannitol, with enzymes that promote metabolism of free radicals (catalase, superoxide dismutase).**

### ***Prostaglandin inhibitors***

- **Indomethacin is a cyclo-oxygenase inhibitor that has been shown to inhibit the increase in prostaglandins that accompanies post-ischaemic reperfusion and to improve post-ischaemic CBF in experimental models of ischaemia.**



## ***Iron chelators***

- **Fe<sup>2+</sup> as a catalyst in oxygen-free radical mechanisms that lead to lipid peroxidation which in turn leads to cell damage,**
- **By eliminating iron as a catalyst, lipid peroxidation and cell damage may be prevented.**
- **The iron chelator deferoxamine has been shown to inhibit post-ischaemic lipid peroxidation and thus may help to prevent reperfusion injury due to membrane injury by lipid peroxidation.**

## **Erythropoietin(asialoEPO)**

- **Stimulates neurogenesis,angiogenesis**
- **Inhibits excitotoxicity,neuronal apoptosis**
- **Reduces inflammation**

**Grasso G.et al, JNA 2006;18:91**

# Gene therapy for neuroprotection

- **Direct application of neurotrophic factors (VEGF, GDGF, ILGF-1 ) through adenoviral construct(Ad-p65).**
- **ZFP transcription factor gene therapy to increase expression of the full complement of VEGF-A splice variants is a promising avenue for the treatment of nerve injury and neurodegeneration.**

**Gene Therapy (2009) 16, 1292–1299**

- **Topical application of GDNF protein greatly reduced the infarct size and brain edema at 24 hr of continuous MCAO in rats. GDNF protein showed a direct protective effect against ischemic brain damage, but not secondary by improving CBF.**

**Clinical Neurology.43;11;894-896(2003)**