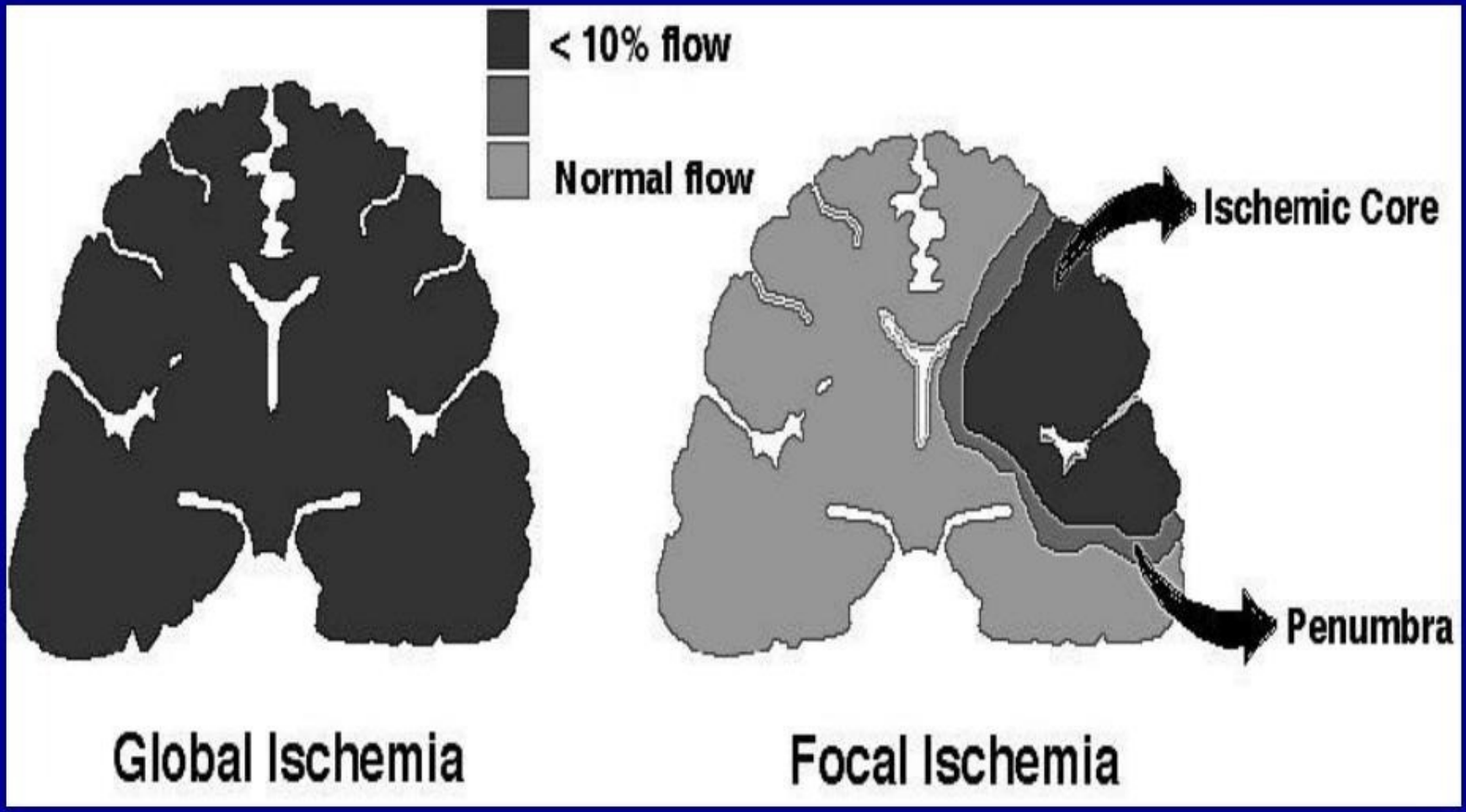
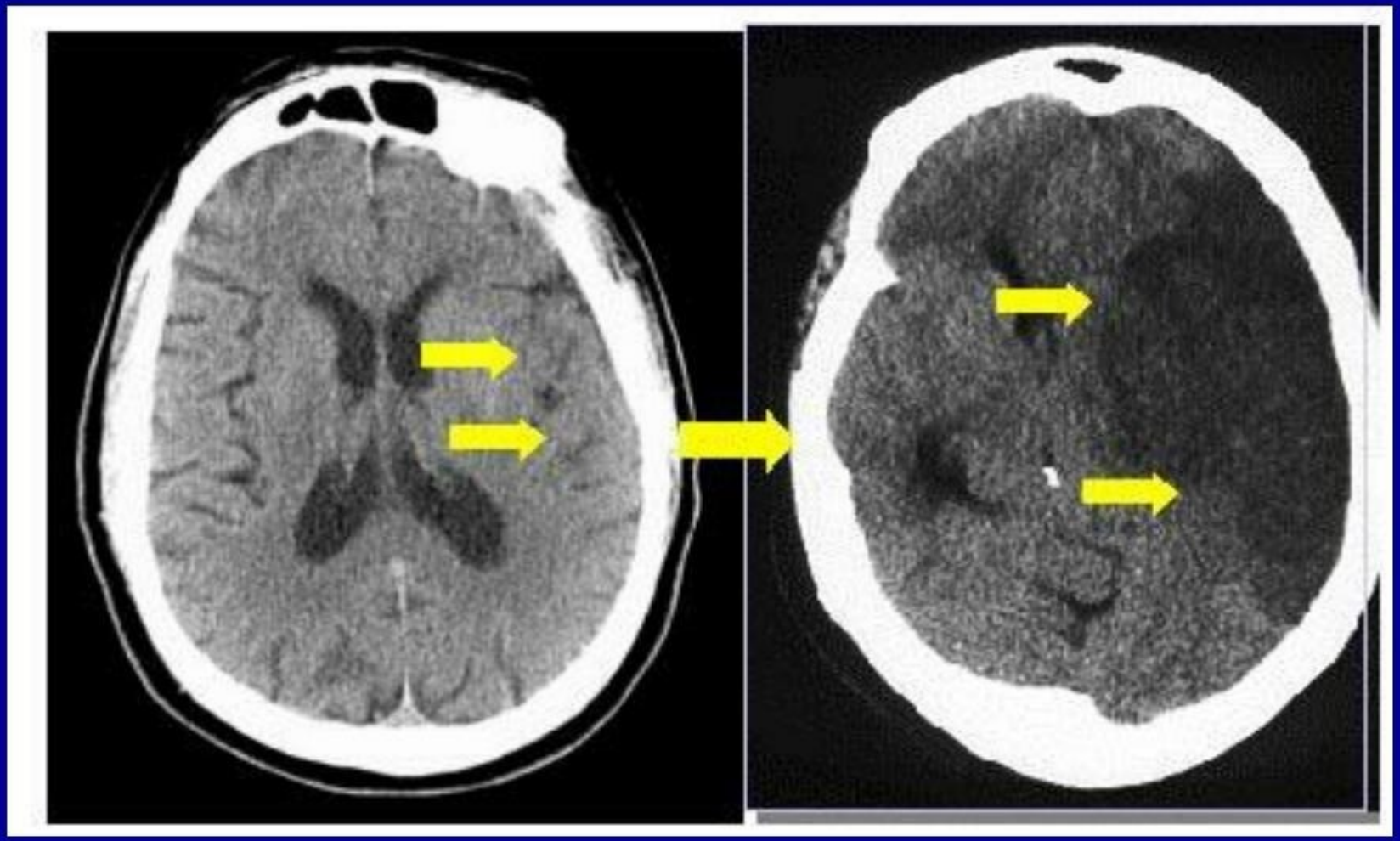
Perioperative Neuroprotection

H. H. Dash

Prof & Head, Neuroanaesthesiology,
Chief of Neurosciences centre,
AIIMS, New Delhi
INDIA

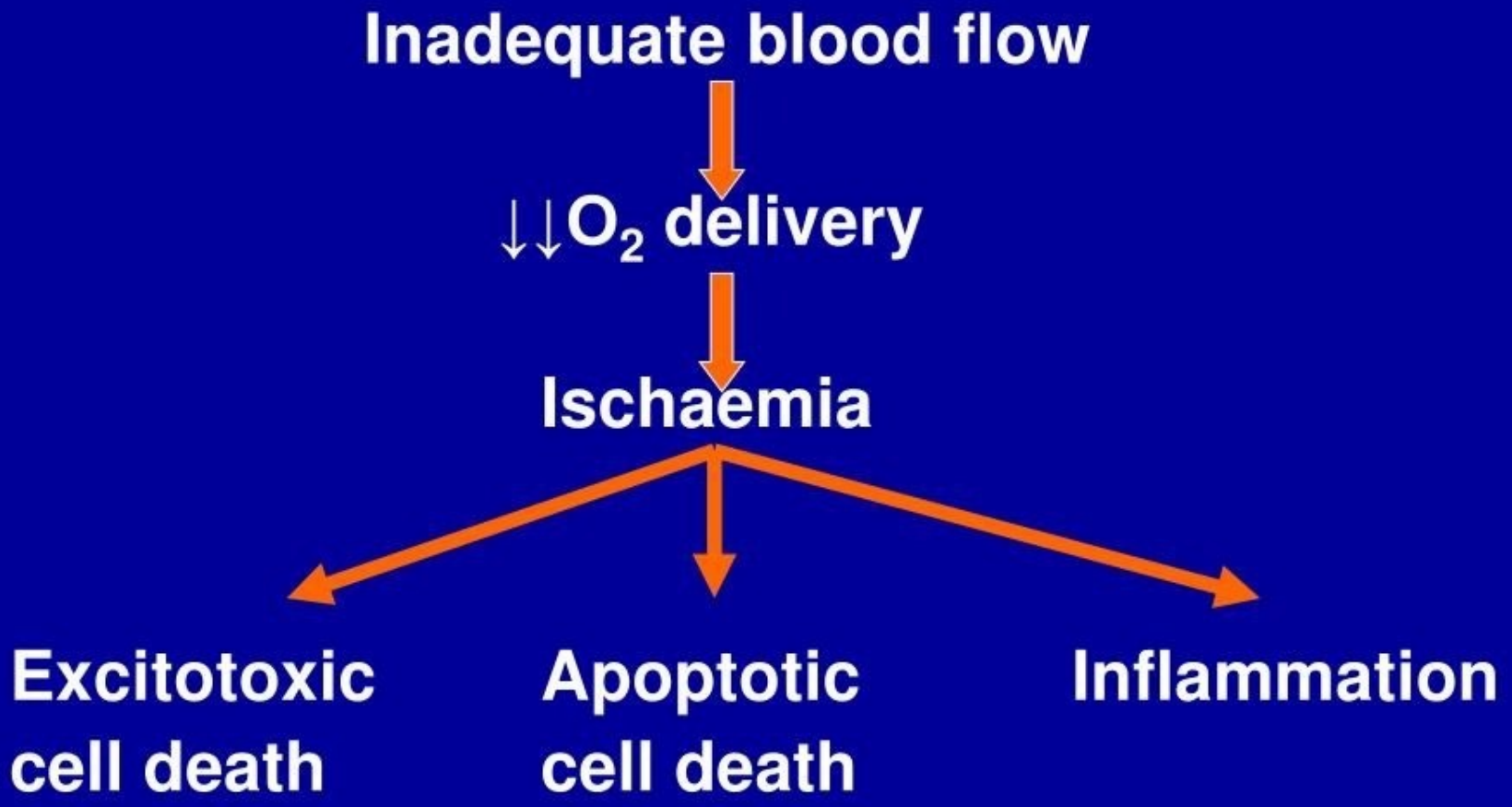

< 10% flow
Normal flow
Ischemic Core
Penumbra
Global Ischemia
Focal Ischemia

Penumbra and Ischemia – CT scan

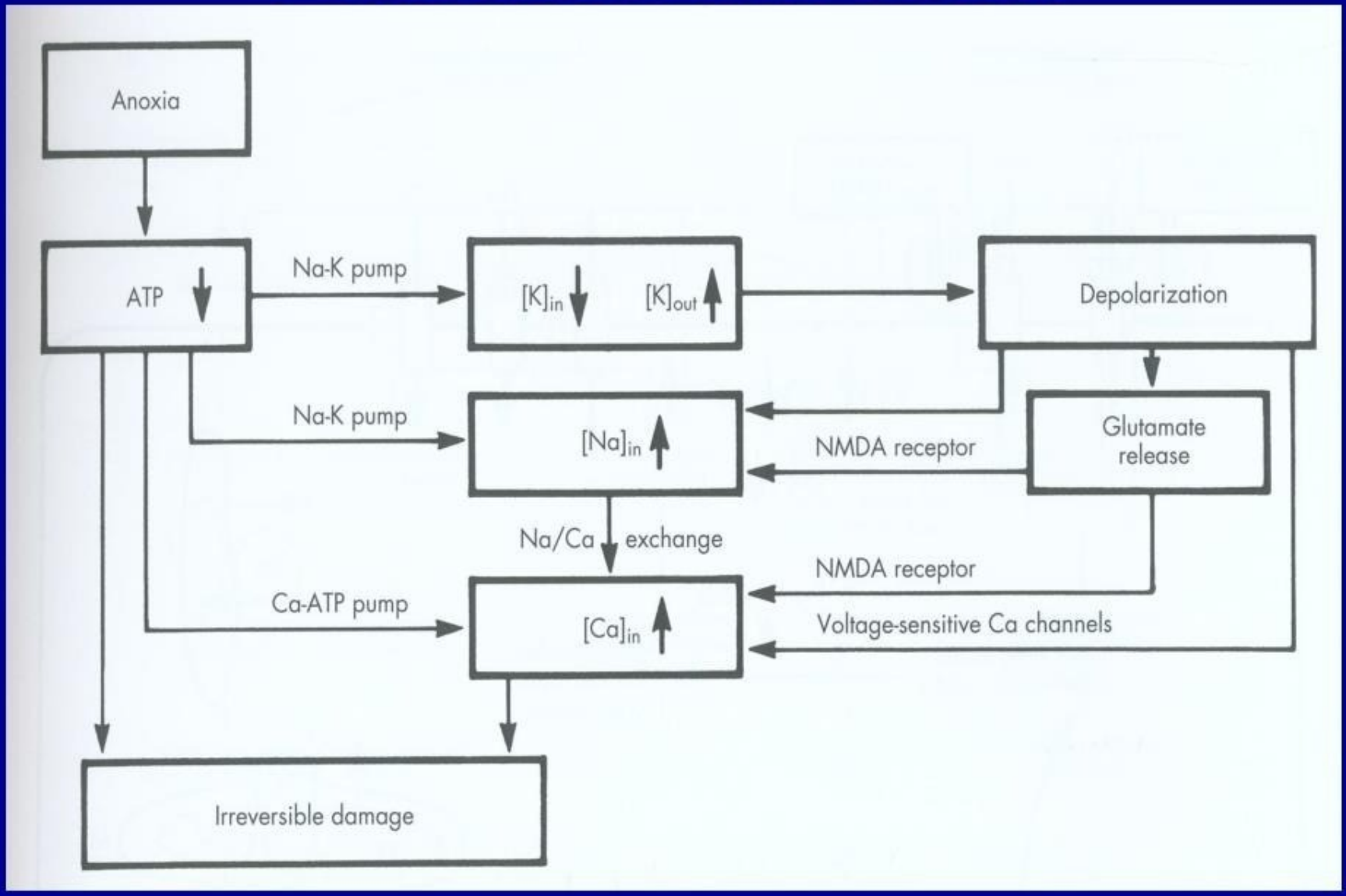



TRAUMA
HYPOXIA
ISCHEMIA
HYPOGLYCEMIA
SEIZURES

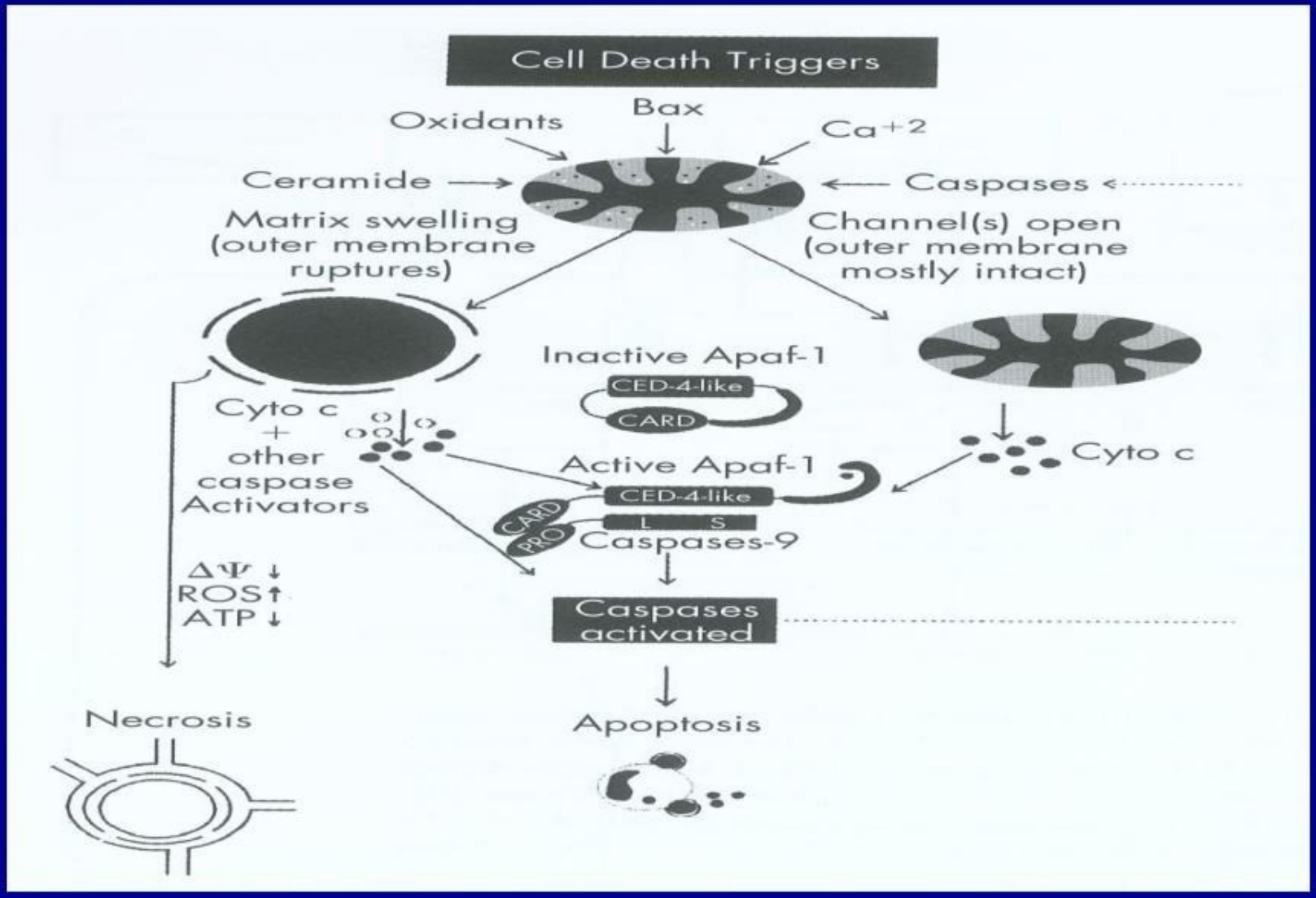
Biochemical & Pathophysiological changes



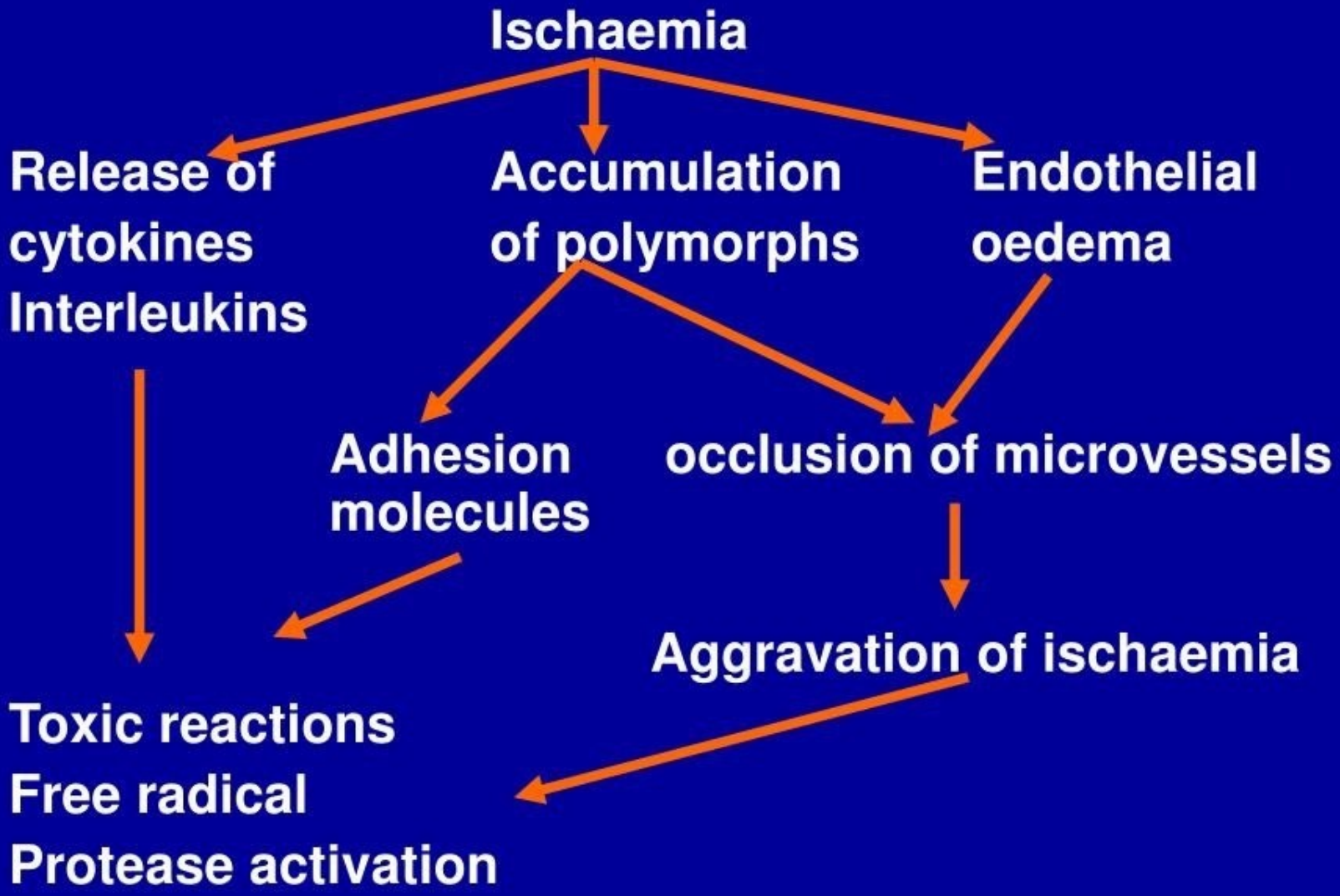
Excitotoxic Cell Death



Apoptotic Cell Death



Inflammation

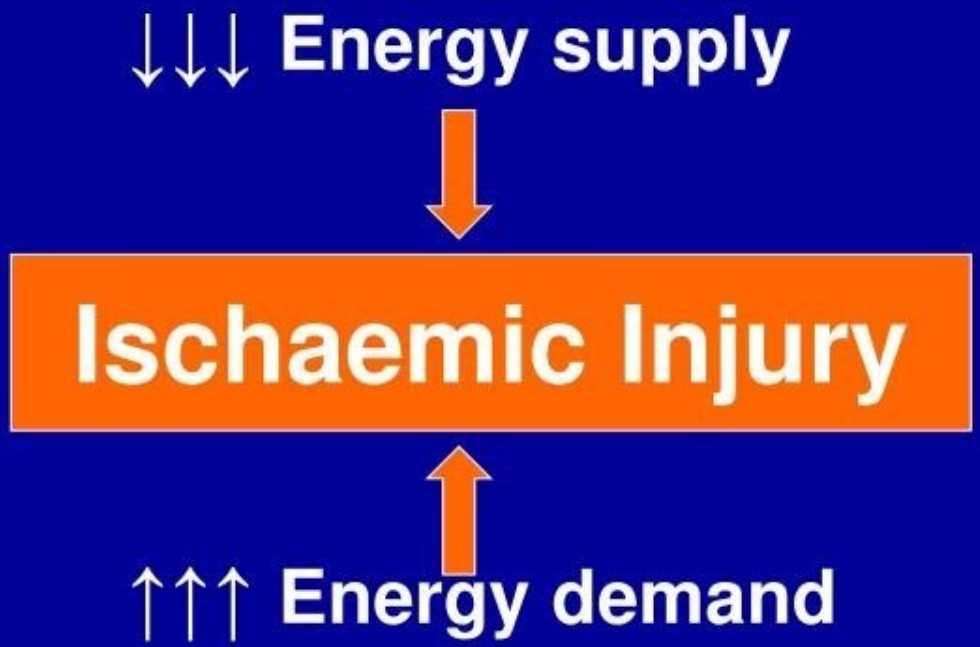


Management

- General care
- Specific care
  - Improve circulation
  - Decrease metabolic demand
  - Treat biochemical changes
- Emerging trends

Blood sugar control

- Hyperglycemia adversely affects stroke pts
  (Parsons MW, et al. Ann Neurol 52:20;2002)
- Hyperglycemia is an independent predictor of poor outcome- long term follow up study
  (Wier CJ, et al. BMJ 314:1303;1997)
- Hyperglycemia was associated with significantly lower odds for desirable clinical outcome and a higher incidence of ICH
  (Bruno A, et al. Neurology 59:669;2002)


↓↓↓ Energy supply
Ischaemic Injury
↑↑↑ Energy demand

Techniques to improve supply



Improve oxygenation

- Stroma free Hb
- Perflurocarbons

Augment blood flow

- Hypertension
- Hypervolemia
- Haemodilution

British Journal of Anaesthesia 95 (5): 669–73 (2005)
doi:10.1093/bja/aei230 Advance Access publication September 9, 2005

BJA

Effects of stellate ganglion block on cerebral haemodynamics as assessed by transcranial Doppler ultrasonography

M. M. Gupta[1], P. K. Bithal[1]*, H. H. Dash[1], A. Chaturvedi[1] and R. P. Mahajan[2]

[1]*Department of Neuroanaesthesiology, All India Institute of Medical Sciences (A.I.I.M.S.), New Delhi, India.*
[2]*University Department of Anaesthesia and Intensive Care, Queen's Medical Centre, Nottingham, UK*
**Corresponding author. E-mail: pkbithal@hotmail.com*

Background. Stellate ganglion block (SGB) causes vasodilatation in the skin of the head and neck because of regional sympathetic block. Its effects on cerebral haemodynamics, in health or in disease, are not clear. We evaluated the effects of SGB on ipsilateral middle cerebral artery flow velocity (MCAFV), estimated cerebral perfusion pressure (eCPP), zero flow pressure (ZFP), carbon dioxide reactivity (CO_2R) and cerebral autoregulation using transcranial Doppler ultrasonography (TCD).

Methods. Twenty male patients, with pre-existing brachial plexus injury, and undergoing SGB for the treatment of complex regional pain syndrome of the upper limb, were studied. For SGB, 10 ml of plain lidocaine 2% was used and the onset of block was confirmed by presence of ipsilateral Horner's syndrome. The MCAFV, eCPP, ZFP, CO_2R, and cerebral autoregulation were assessed before and after SGB using established TCD methods. The changes in these variables were analysed using Wilcoxon's signed rank test.

Results. The block caused a significant decrease in MCAFV from median (inter-quartile range) value of 61 (53, 67) to 55 (46, 60) cm s^{-1}, a significant increase in eCPP from 59 (51, 67) to 70 (60, 78) mm Hg, and a significant decrease in ZFP from 32 (26, 39) to 25 (16, 30) mm Hg. There were no significant changes in CO_2R or cerebral autoregulation.

Conclusion. The increase in eCPP, decrease in ZFP, and no changes in CO_2R or cerebral autoregulation suggest that the SGB decreases cerebral vascular tone without affecting the capacity of the vessels to autoregulate. These effects may be of therapeutic advantage in relieving cerebral vasospasm in certain clinical settings.

Br J Anaesth 2005; **95**: 669–73

Table 2 The eCPP, ZFP, CO_2R, and THRR before and after SGB. The values are given as median (interquartile range)

	Before SGB	After SGB	*P*-value
eCPP (mm Hg)	59 (51, 67)	70 (60, 78)	0.002
CO_2R	26 (18, 27)	22 (17, 24)	NS
THRR	1.26 (1.14, 1.42)	1.27 (1.13, 1.16)	NS
ZFP	32 (26, 39)	25 (16, 30)	0.04

Stellate ganglion block as alternative to intrathecal papaverine in relieving vasospasm due to SAH

Prabhakar H, Jain V, Rath GP, Bithal PK, Dash HH

Anesth Analg 104; 1311-12, 2007

A1853
October 16, 2007
3:30 PM - 5:00 PM
Room Room 301

Effect of Stellate Ganglion Block on Refractory Cerebral Vasospasm

Virendra Jain, M.D., Hari H. Dash, M.D., Rajendra S. Chouhan, M.D., Ashish Suri, M.S., M.Ch., Girija P. Rath, M.D., D.M.
Department of Neuroanaesthesia, All India Institute of Medical Sciences, New Delhi, Delhi, India

Background and Purpose : Stellate ganglion block (SGB) in patients with no intracranial pathology decreases the cerebral vascular tone without affecting the capacity of vessels to autoregulate[1]. The effect of SGB however in patients with cerebral vasospasm has not been studied. A prospective study was undertaken to evaluate the effect of SGB on cerebral hemodynamics in patients with symptomatic cerebral vasospasm following intracranial aneurysm clipping.

Methods: After IRB clearance and informed consent from next of kin, 14 adult patients who underwent surgical clipping of aneurysm and developed cerebral vasospasm refractory to HHH therapy were studied. Diagnosis of cerebral vasospasm was made on clinical and TCD criteria. SGB was performed with 10 ml bupivacaine (0.5%) on side of maximum CBFV. Neurological status, heart rate, NIBP, SpO_2, $EtCO_2$, CBFV and pulsatility index (PI) were assessed by an independent observer before and 10 min, 30 min, 2 hr, 6 hr, 12 hr and 24 hr after SGB.

Generalized estimating equation was applied to compare the difference in mean values over different time intervals since the observations were correlated. Data were expressed in mean (standard error). The p value <0.05 was considered statistically significant.

Results: A significant improvement in GCS from 8.5(0.51) to 10.5(0.51) 24 hours after SGB was seen. Neurological deficits improved in 10 out of 14 patients. A significant decrease in middle cerebral artery (MCA) CBFV from 133.07(8.20) before SGB to 110.14(6.20) at 6 hours and 121.66(6.39) at 24 hours after SGB was observed. There was a significant decrease in anterior cerebral artery (ACA) CBFV from 104.58(6.79) before SGB to 94.75(5.11) 12 hours after SGB. No change in hemodynamic parameters was observed during the study period. No complication was noticed.

Conclusion: SGB seems to be an effective therapy for treatment of refractory cerebral vasospasm in patients following aneurysm clipping.

1. Br J Anaesth 2005; 95: 669-73.[table1]

Anesthesiology 2007; 107: A1853

Cervical Cord Stimulation

Rats with SAH

↓ (CCS)

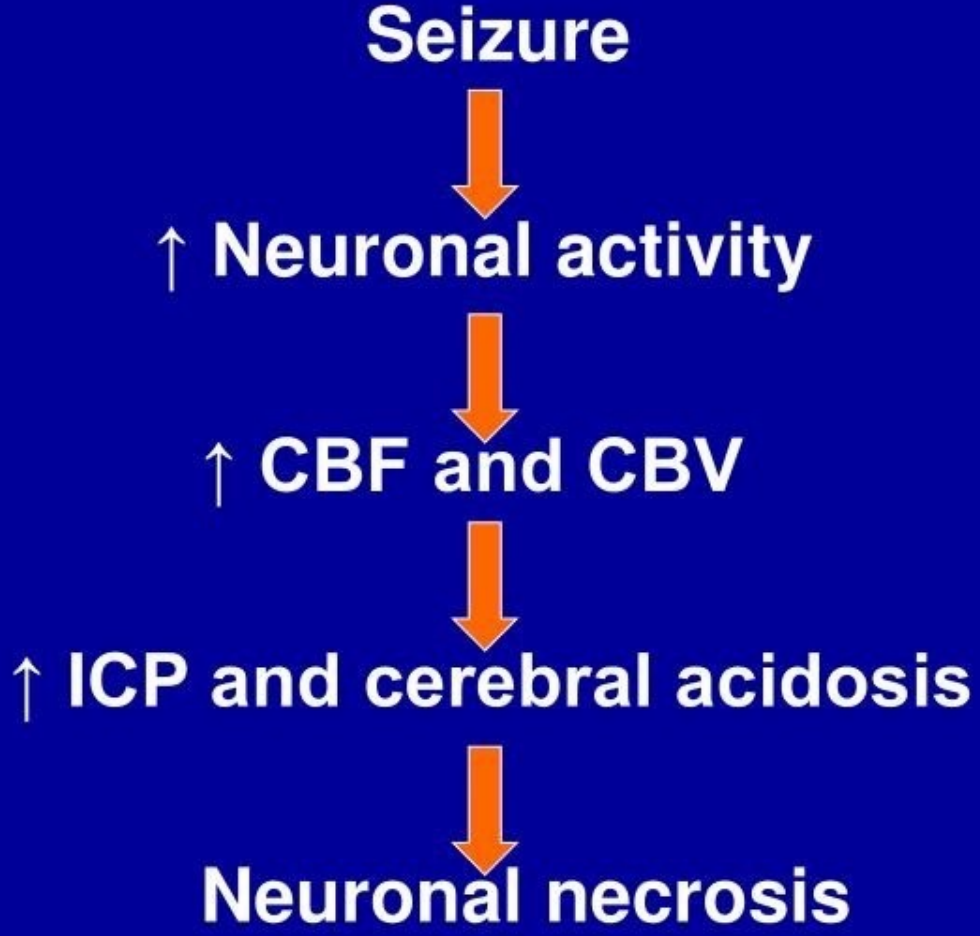
Reverse basilar artery constriction

↓

Improve global CBF

(Lee JY, et al; J Neurosurg 109:1148-54;2008)

Seizure prophylaxis



Techniques to reduce demands

- Barbiturates
- Etomidate
- Propofol
- Hypothermia

Barbiturates and brain protection

- Randomized clinical study of thiopental loading in comatose survivors of cardiac arrest

  (Abraham NS, et al: N Eng J Med 314: 397;1986)

- Neuropsychiatric complications after cardio - pulmonary bypass. Cerebral protection by a barbiturate

  (Nussmeier NA, et al. Anesthesiology 64:165;1986)

Barbiturates & Neuroprotection in Severe Head Injury

Failure of prophylactic barbiturate coma in the treatment of severe head injury

(Ward JD, et al: J Neurosurg 62:383;1985)

Pentobarbital therapy could increase mortality in pts. with diffuse brain injury

(Schwartz M, et al: Can J Neurol Sci 11:434;1984)

Effect of Thio & Propo on NMDA & AMPA mediated glutamate Excitotoxicity

Thiopentone



NMDA & AMPA mediated Glutamate Excitotoxicity



Propofol

(Zhu H, et al : Anesthesiology 87:944;1997)

Long-term Propofol Infusion and cardiac failure in adult Patients with Head Injuries

5 Pts. had cardiac failure and died

Retrospective analysis

6 had cardiac failure - prop>6mg/kg/hr

None had cardiac failure- 4mg/kg/hr

(Cremer OL, et al:Lancet 357:117;2001)

N_2O and Brain Protection

IHAST Study → 1000 pts.
373 pts. → N_2O:O_2
627 pts. → Air:O_2

- No difference in the development of DIND
- At 3 months no difference in outcome variables
  (i.e. – GOS, NIH stroke scol, Rankin disability score)

(McGregor DJ, et al; Anesthesiology 108:568-79;2008
Culley DJ & Crosby G: Anesthesiology 108: 553-54;2008)

Effect of inhalational agents on Brain Protection

The Neuroprotective effects of Xenon and Helium in an in vitro model of Traumatic Brain Injury

(Coburn M, et al: Crir Care Med 36:588-95;2008)

Xenon and Sevoflurane protect against Brain Injury in a neonatal asphyxial model

(Yan L, et al:Anesthesiology 109:782-89;2008)

Body Temperature



Mild hypothermia and head injury

- Multi institutional study - 392 patients

	Hypo	Normo
ICP > 30 mm Hg	41%	59 %
Mortality	28%	27%
Medical problems	More	Fewer

(Clifton GL, et al: N Eng J Med 344:556;2001)

Intraoperative Hypothermia for Aneurysm surgery (IHAST TRIAL)

	Hypo	Normo
No. of pts	499	501
Core Temp	33° C	36.5° C
Good outcome-3 mth	66 %	63%

- Warmer pts. in hypo gp (<33.5°C) had more good outcomes(77%) than the cooler pts(62%)
- ↑ incidence of bacteremia in hypothermia gp

(Todd M, et al: N Eng J Med 352:135;2005)

Mild hypothermia after Cardiac Arrest

- European study – 4 hours of resuscitation, remained cool for 24 hours
- Australian study – cooled at site, cooled for 12 hours

	Hypo	Normo
Favourable outcome at 6 months		
European	55 %	39 %
Australian	39 %	26 %

(HACAS group, N Eng J Med 346:549;2002)
(Bernard SA, et al: N Eng J Med 346:557;2002)

Intraoperative Mild Hypothermia during Intracranial Aneurysm Surgery

- Deliberate mild hypothermia for intracranial aneurysm clipping

  (Chouhan RS, et al: Ind J Anaesth 44:31;2001)

- Intraoperative mild Hypothermia for brain protection during Intracranial aneurysm surgery

  (Chouhan RS, et al: J Anaesth Clin Pharmacol 22:21;2006)

Moderate Hypothermia to treat Perinatal Asphyxial Encephalopathy

Technique	Infants survived	Severe disability	Died	Total
Moderate Hypoth(33.5°C) + ICU care	91	42	32	165
Normothermia + ICU care	76	44	42	162

Azzopadi DV, et al: N Engl J Med 361:1369-58;2009

Effects of IV Methyl Prednisolone on Severe Head Injury

Randomized placebo controlled 10,008 Pts.

within 8 hrs of injury

Placebo
5001pts.

Steroid
5007 pts

Death or severe disability
at 6 months

1728(36.3%)

1828(38.1%)

(Edwards P.,Crash trial collaborators: Lancet 365:1957;2005)

Preconditioning and Neurogenesis

Retina as a model for the CNS

Rats → heat shock (15 min at 41° C)



protect neurons from high intensity light damage after 18 hrs of heat exposure

(Barbe MF, et al: Science 241: 1817;1988)

Preconditioning (contd)

- The phenomenon was soon replicated in a model of cerebral ischaemia

  (Chopp M, et al: Neurology 39:1396;1989)

- Endogenous proteins of repair and the genes that code for them, are now well documented

  (Roth S: Brain Res Bull 62:461;2004)

  (Carmel JB, et al: Exp Neurol 185:81;2004)

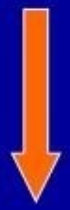
Ischaemic Preconditioning

Homeothermic mammal

Elicits “an evolutionary conserved endogenous response to decreased blood flow and oxygen limitation such as seen during hibernation”

(Stenzel Poore MP, et al: Lancet 362:100;2003)

Prodromal Transient Ischaemic attacks (TIAs)



protects patient's brain during subsequent ischaemic strokes

(Wegner S et al: Stroke 35:616;2004)
(Johnson SC. Stroke 35(S):2800;2004)

Clinical methods of preconditioning

- Pre - op hyperbaric oxygen
- Normobaric 100 % oxygen
- Electroconvulsive shock
- K^+ channel opener→ Diazoxide
- Erythropoietin (EPO)

(Cottrell JE, ASA refresher course lectures 2005)

Erythropoietin

- Cytokine growth hormone
  - -↓ apoptosis
  - -↑ erythrocyte production
- ↑↑ haematocrit

Deleterious effect on ischaemia

- Non haematopoeitic analogues – ASIALO EPO

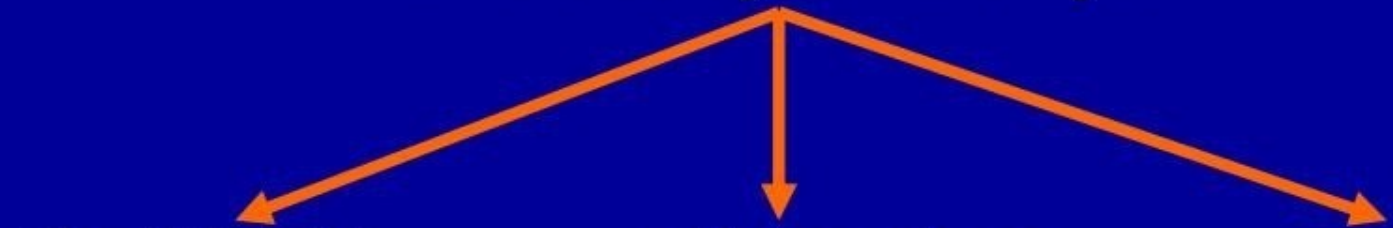
Neuroprotective properties

(Grasso G, et al : Neuroscientist 10:93;2004)

(Leist M, et al: Science 305;239;2004)

Intravenous recombinant erythropoietin

Once daily for 3 days



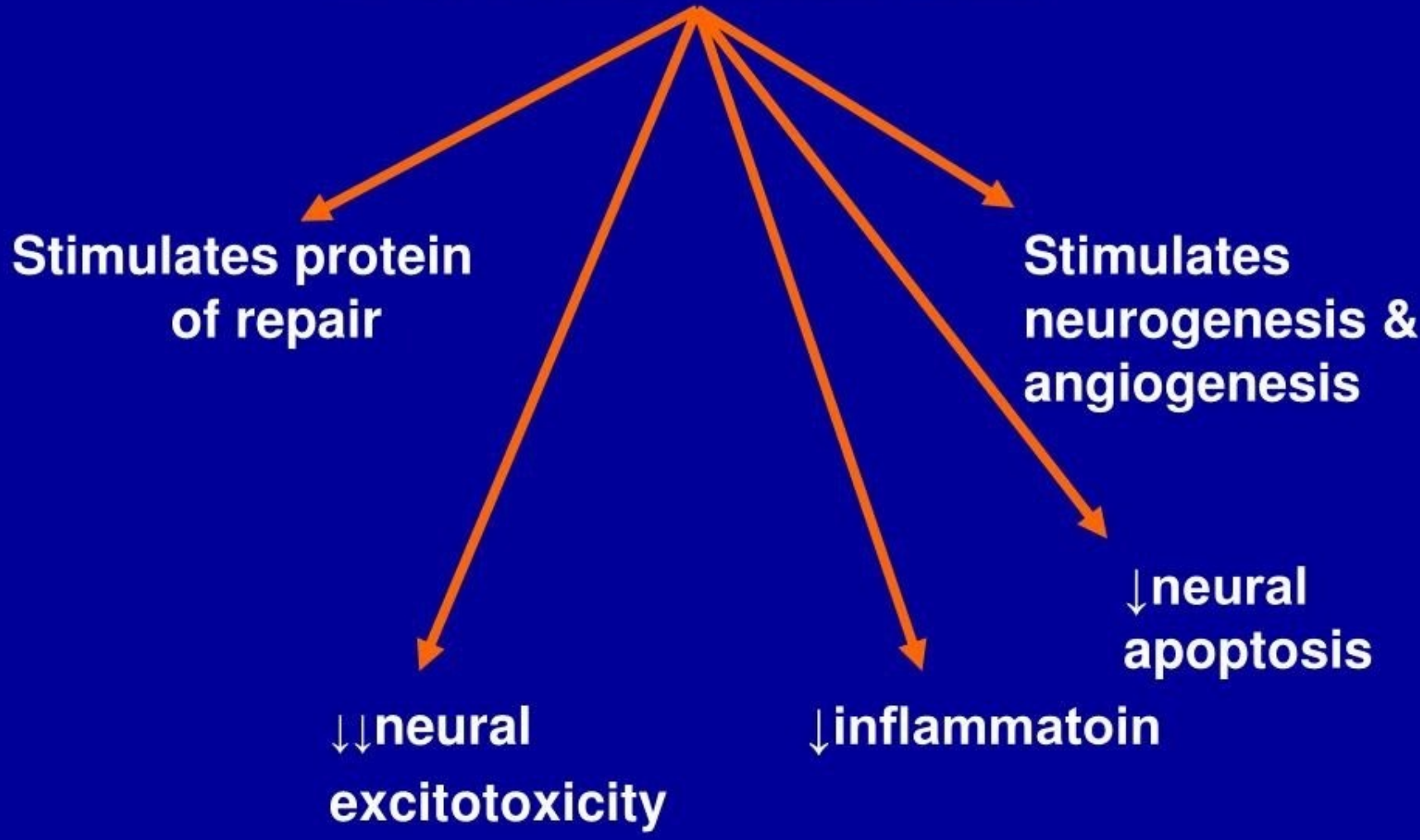
60 -100 fold
↑ of EPO in CNS

↓glial markers
of cerebral
injury
(S 100)

↓ infarct
size &
improved
recovery

(Ehrenreich H, et al: Mol Med 8: 495;2002)

Astrocytes in ischaemic penumbra produces EPO in mammalian brain



Lidocaine

- Blocks Na^+ influx
- Reduces post necrotic injury
- Lidocaine infusion begun in induction and continued for 48 hours (plasma conc 6 -12 µmol/L)



Improved neuropsychological scores following valve surgery and CABG

(Ann Thor Surg 67:1117;1999, Anesth Analg 95:1134;2002)

- Randomized controlled trial is on

Magnesium

- Meta analysis - from 4 small trials in acute ischaemic stroke suggests improved outcome
- Mg^{++} blocks both ligand and voltage dependent Ca^{++} entry
- Randomized controlled trial of administration of $MgSO_4$ (within 12 hrs of stroke) in 2386 pts has shown conclusively that Mg^{++} loading is not neuroprotective

(IMAGES Study Investigators. Lancet 363:439;2004)

Oestrogen protection

- Reduced incidence of stroke in premenopausal women may be due to oestrogen
- Clinical and laboratory studies



oestrogens reduce ischaemic brain injury and provide brain protection in various neurodegnerative disorders

(Wise PM, et al : Front Neuroendo 22: 33;2001)

- Improves microcirculation in pial vessels

(Watanabe Y, et al: Am J Phsiol Heart Circ Physiol 281:H155;2001)

Heat shock / stress protein protection

- Use of viral vectors and transgenic over expression of Hsp 70 protected in animal models
- Hsp 70 over expression using a herpes viral vector has recently been shown to protect from focal ischaemia when given after the onset of ischaemia

(Yenari MA, et al:Mol Med Today 5:525;1999)

(Hoehn B, et al: J Cereb Blood Metab 21:1303;2001)

Bile acid

Uro deoxycholic acid and taurodeoxycholic acid



Inhibit neuronal apoptosis

- Inhibit free radical production
- Stabilizes mitochondrial membrane

(Rodrigues CM, et al: J Cereb Blood Flow Metab 22:463,2002)

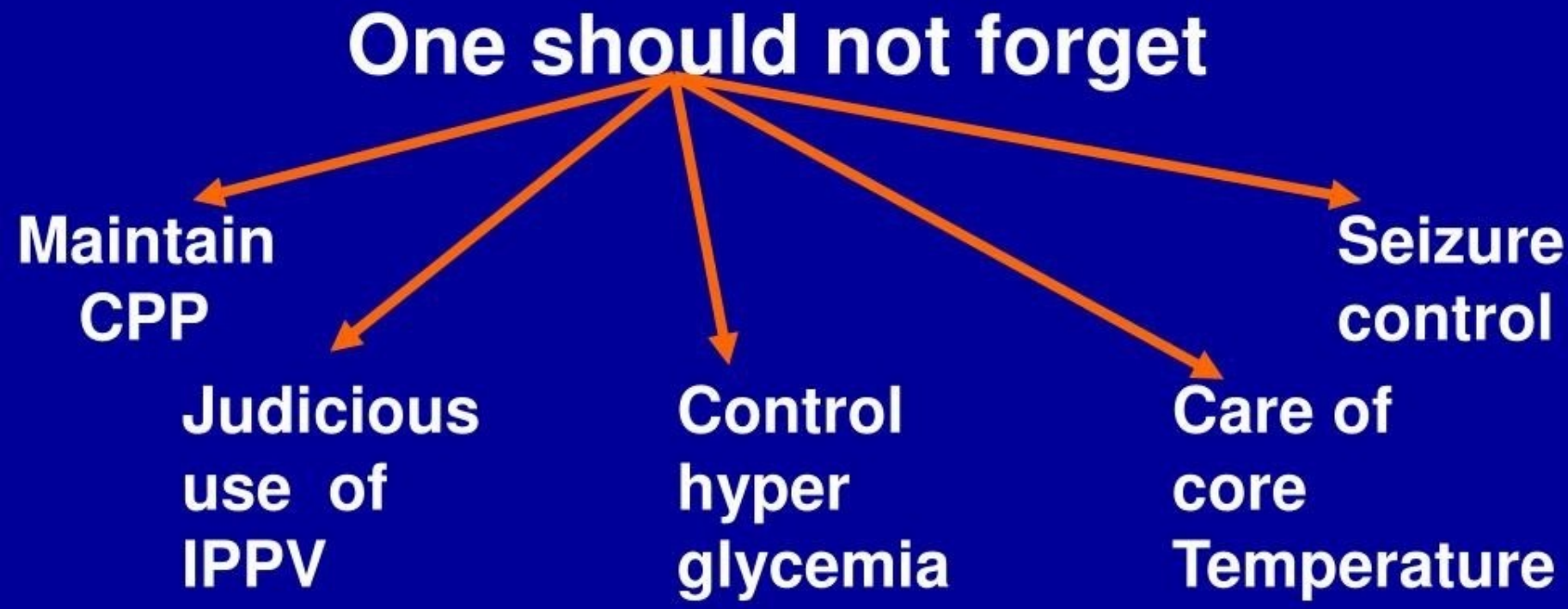
Neurogenesis

- " Activated neural stem cells contribute to stroke induced neurogenesis and neuroblast migration toward the infarct boundary in adult rats"
- "Therapy of stoke infarcts in rats with a nitric oxide donor and human bone marrow stromal cells enhances angio… and neurogenesis" subsequent to 2 hours of MCA occlusion

(Zhang R, et al: J Cereb Blood Flow Metab 24:441;2004)
(Chen J, et al: Brain Res 16:1005;2004)

Conclusion

- Silver bullet for brain protection yet to be discovered








AIIMS
AMBULANCE

Management

- General care
- Specific care
  - Improve circulation
  - Decrease metabolic demand
  - Treat biochemical changes
- Emerging trends

Intra-arterial Procedures

- Transluminal Angioplasty
- Intra-arterial Nimodipine
- Intra-arterial Nicardipine
- Intra-arterial Verapamil
- Intra-arterial Milrinone
- Intra-arterial Fasudil
- Intra-arterial Colforsin daropate

Intra-arterial Milrinone

- Phosphodiesterase III inhibitor
- Inotropic properties
- As effective as Nicardipine

Schmidt U, et al: Anesth Analg 110:895-902;2010