The Advances in Cerebral Resuscitation, Protection & Preservation from Ischemia

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Disclaimer/Disclosure

- I am in the Speaker's Bureau of the University of Louisville for continuing education of physicians & other health professionals & for public information.
- Some of my research projects were supported by grants obtained from drug companies on a competitive/merit basis & I have no financial interests or investment in them.
- The opinions expressed during this presentation are my own & do not necessarily reflect those of the University of Louisville or organized medicine (A.M.A.).

Scope of Presentation

- Stages/phases of resuscitation.
- Definition of terms & classification of cerebral hypoxia/ischemia.
- Patho-physiology of cerebral ischemia & mechanisms of neuronal destruction.
- Clinical applications of cerebral protection.
- Methods of cerebral protection with emphasis on pharmacologic & non-pharmacologic methods.
- State of the art in cerebral protection – "Gold Standard" & the "Strokes".
- Summary & Conclusion.

Classification – Therapeutic Interventions

Class	Supporting Evidence	Clinical Intervention
1	At least one randomized clinical trial (RCT)	Always useful
2a	Multiple studies with positive results	Useful & safe
2b	Evidence is generally but always positive	Within standard of care
Intermediate	Inconsistent	Inconclusive
3	Studies confirm harm	Harmful

Definition of Terms

- **Anoxia** (*an-ok'se-ah*) – Absence or lack of oxygen; reduction of oxygen in body tissue below physiologic levels.
- **Hypoxia** (*hi-pok'se-ah)* – Low oxygen content or tension; deficiency of oxygen in the inspired air.
- **Cerebral Ischemia** *(ce-re'b-ral is-ke"me-ah)* – Deficiency of blood in the cerebrum due to functional constriction or actual obstruction of a blood vessel.
- **Stroke** *(strok)* – A syndrome characterized by a host of neurological events that have a rapid onset & that usually progress over a 24-hour period. The cause is generally attributed to an interruption of the blood flow to the brain.

CPR - Stages

- **B.L.S. (Basic Life Support)** – The A,B,Cs of resuscitation.
- **Intermediate Life Support** – AEDs & Advance Airway Devices (Class 1).
- **ACLS, PALS & ATLS** (Advanced Cardiac/Trauma Life Support) with emphasis on airway & circulation

  - I.V. accesses (Class 1).

  - Drugs - cardiac, respiratory arrest & treatment of acute coronary syndrome (ACS) – Class 2a.
- Cerebral resuscitation, protection & preservation.

CRC

CEREBRAL ISCHEMIA *and* RESUSCITATION

Avital Schurr
Benjamin M. Rigor

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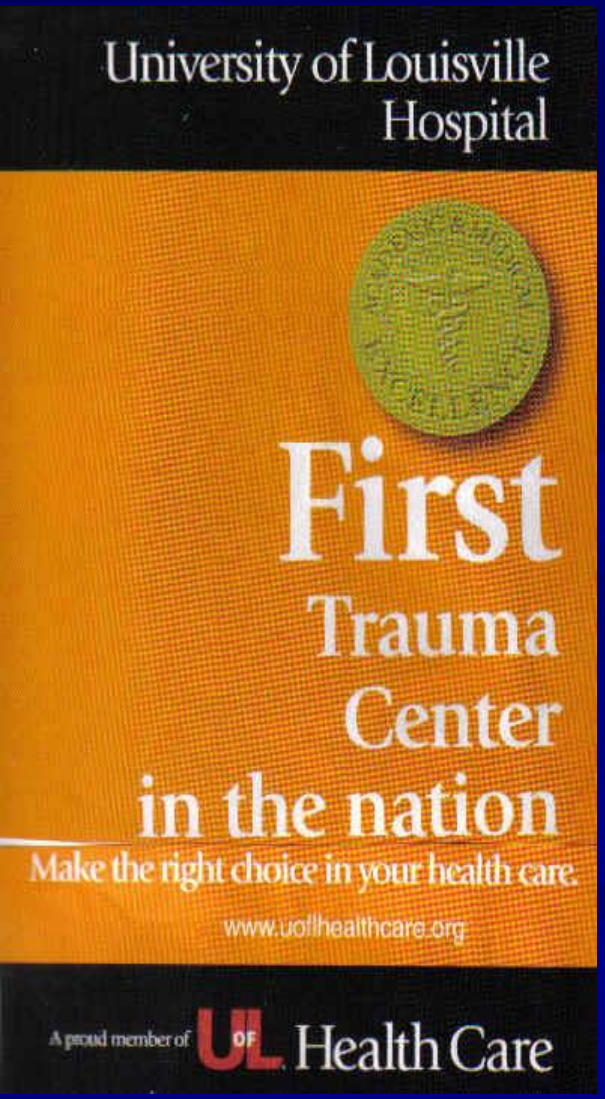
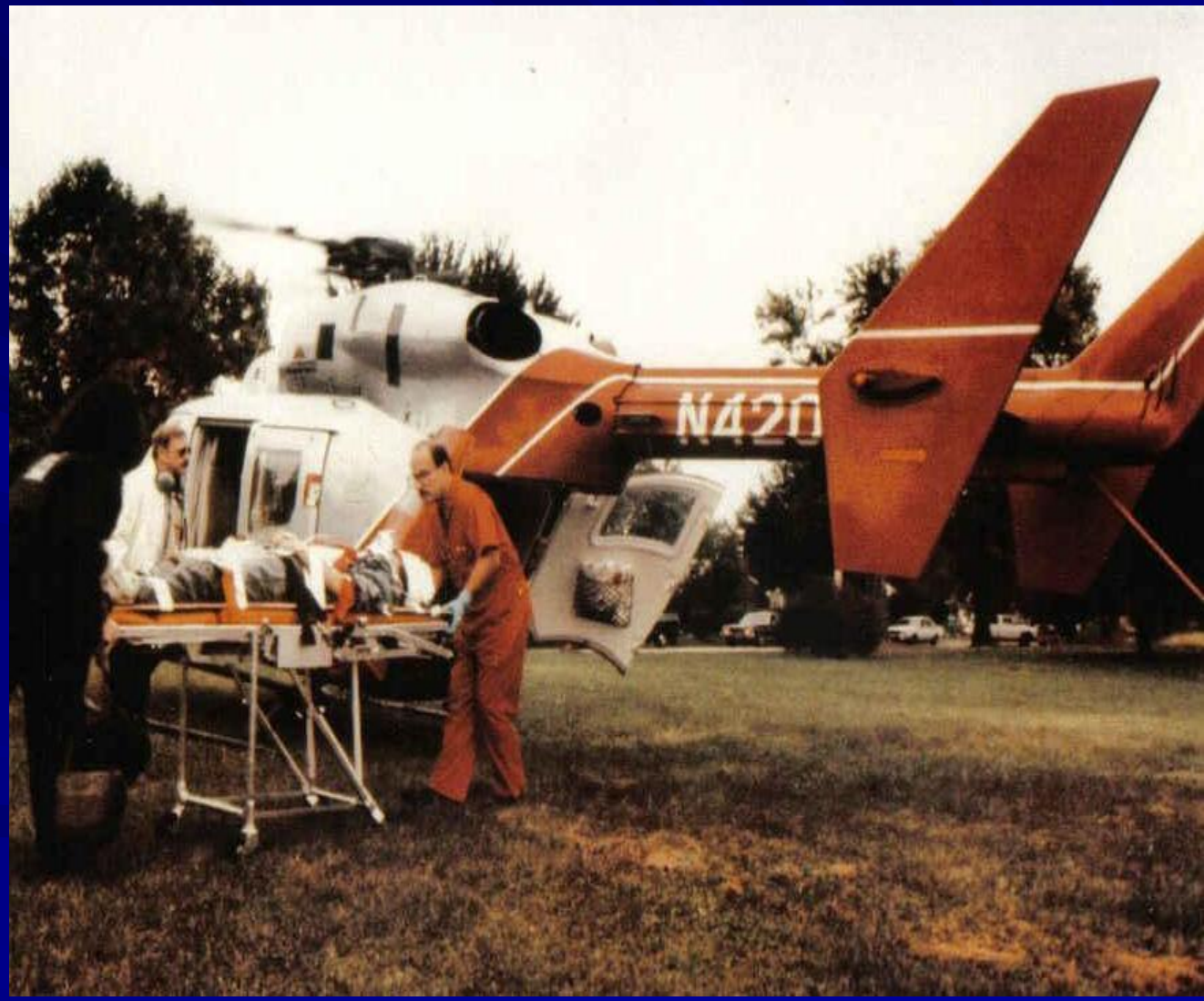
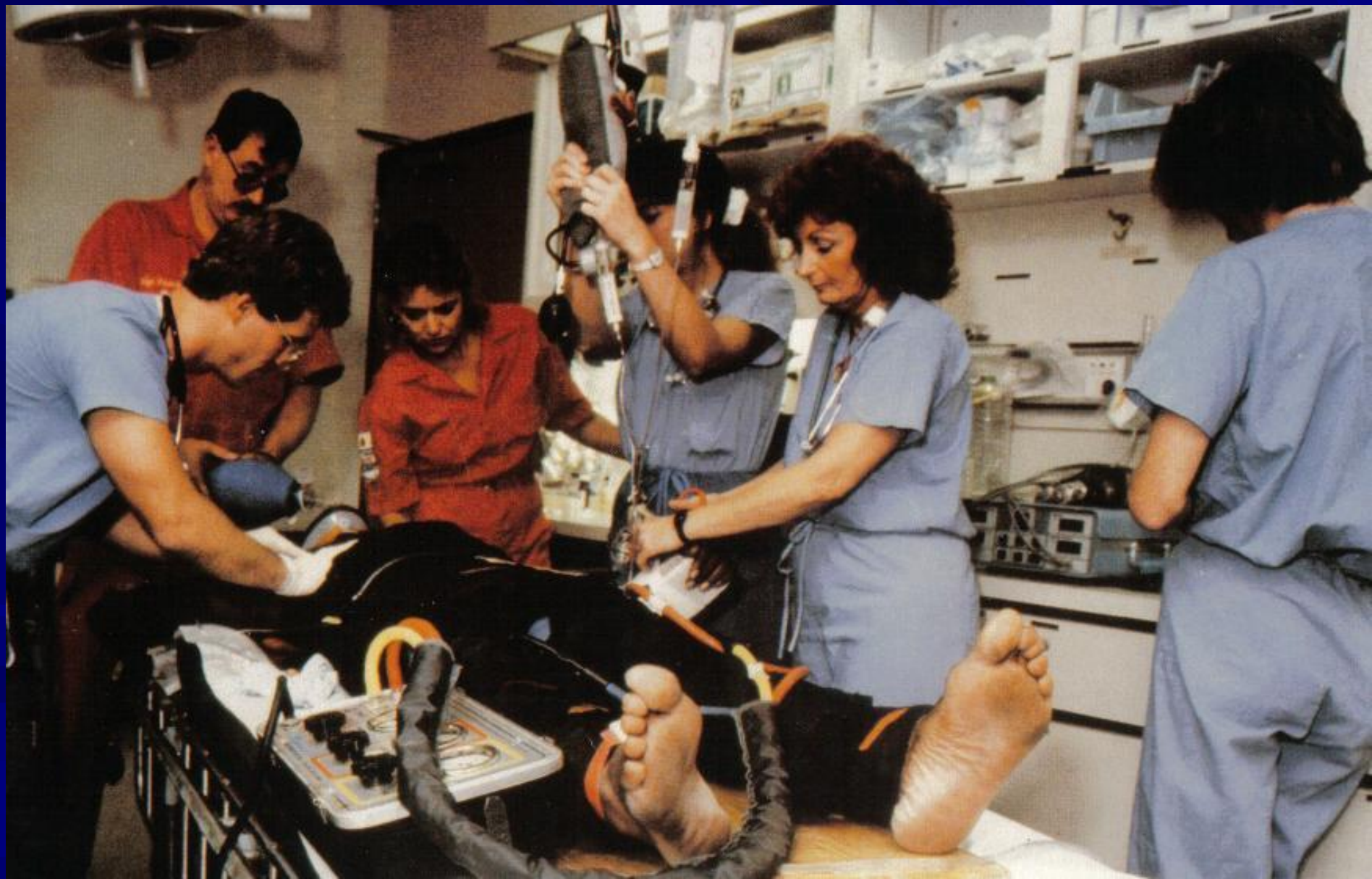
Emergency Resuscitation





Emergency Resuscitation



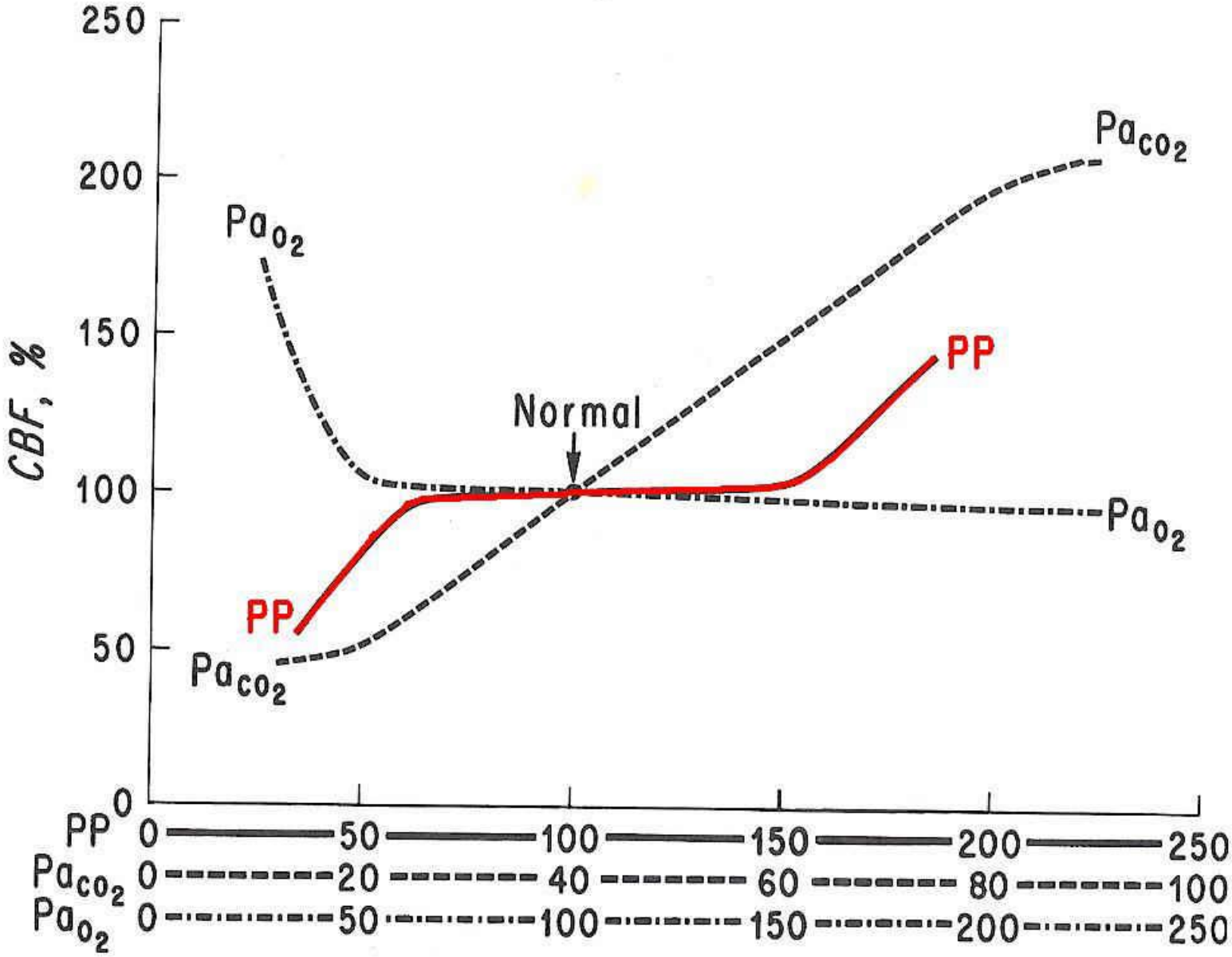
Pathophysiology of the Brain

- The skull is a rigid vault.
- Glucose is the primary substrate for cerebral metabolism. Lactate can serve as an alternate substrate under severe anaerobic conditions (Schurr, Rigor). Outcomes are poor with hypo- or hyperglycemia.
- pCO_2 is the greatest determinant of vascular caliber - ↑ pCO_2 = cererbal vasodilatation, ↓ intracellular pH, watch out for inverse-steal!!

Pathophysiology of the Brain

- Mild to moderate hypothermia, barbiturates & anesthetics - ↓ $CMRO_2$ (cerebral metabolic rate).
- BBB abnormalities are still present after an initial insult (hypoxia, global ischemia, stroke) up to 4 – 6 wks.
- ↑ Hct. (hematocrit) - ↑ blood viscosity → ↓ cerebral blood flow – stay at 30-35% Hct.
- What is the safe lower limit of cerebral autoregulation??

Cerebral Autoregulation



Causes of Tissue Hypoxia

	Levels of Interference	Causes of O_2 Lack
Tissues –	Cellular metabolism	Metabolic blockage
		↑ O_2 need
	Cell membrane/wall	↓ Cell permeability
	Extracellular space	↑ Tissue edema
CVS -	RBC	Blood loss, anemia
	Blood supply	A-V shunting, arterial occlusion
	Heart	Pump failure
Respiratory -	Alveolar membrane	↓ Permeability
	Lung perfusion	V/Q mismatch
	Alveolar ventilation	Hypoventilation
	Inspired air	Low O_2 tension

Classification of Brain Ischemia

- **Based on Location** –
  1. Global – Cardiac arrest
  2. Focal (Regional) – Embolization
- **Degree of Permanence** –
  1. Temporary – Shunt placement
  2. Permanent – Infarction
- **Degree of Completeness** –
  1. Complete – Infarction
  2. Incomplete – ICA occlusion
- **Combination of the Above** –
  Protection vs Resuscitation

Selective Vulnerability

(Based on Increasing Vulnerability)

A. **Neuronal Elements**:

Neurons → Glial Cells (oligodendroglia, astrocytes, microglia) → Blood Vessels → Other Syncitial Tissues (endothelial & meningeal cells).

B. **Brain Structures**:

Neocortex (Lamina 3 & 5) → Hippocampus (Sommer sector) → Allocortex (end folium) → Caudate Nucleus & Putamen → Cerebellum (Purkinje cells).

Cardiac Arrest

Time

30 sec. Depletion of Cerebral O_2

1 min. Depletion of Cerebral Glucose

Depletion of ATP

Na^+-K^+ Pump Inhibition

4 min. Intracellular H_20 Increase

Cytotoxic Edema

5 min. Neuronal Death

Blood Brain Barrier Disruption

Re-establishment of Flow in <20 minutes

↓

Hyperperfusion (lasts 10-30 min)

↓

Hypermetabolism

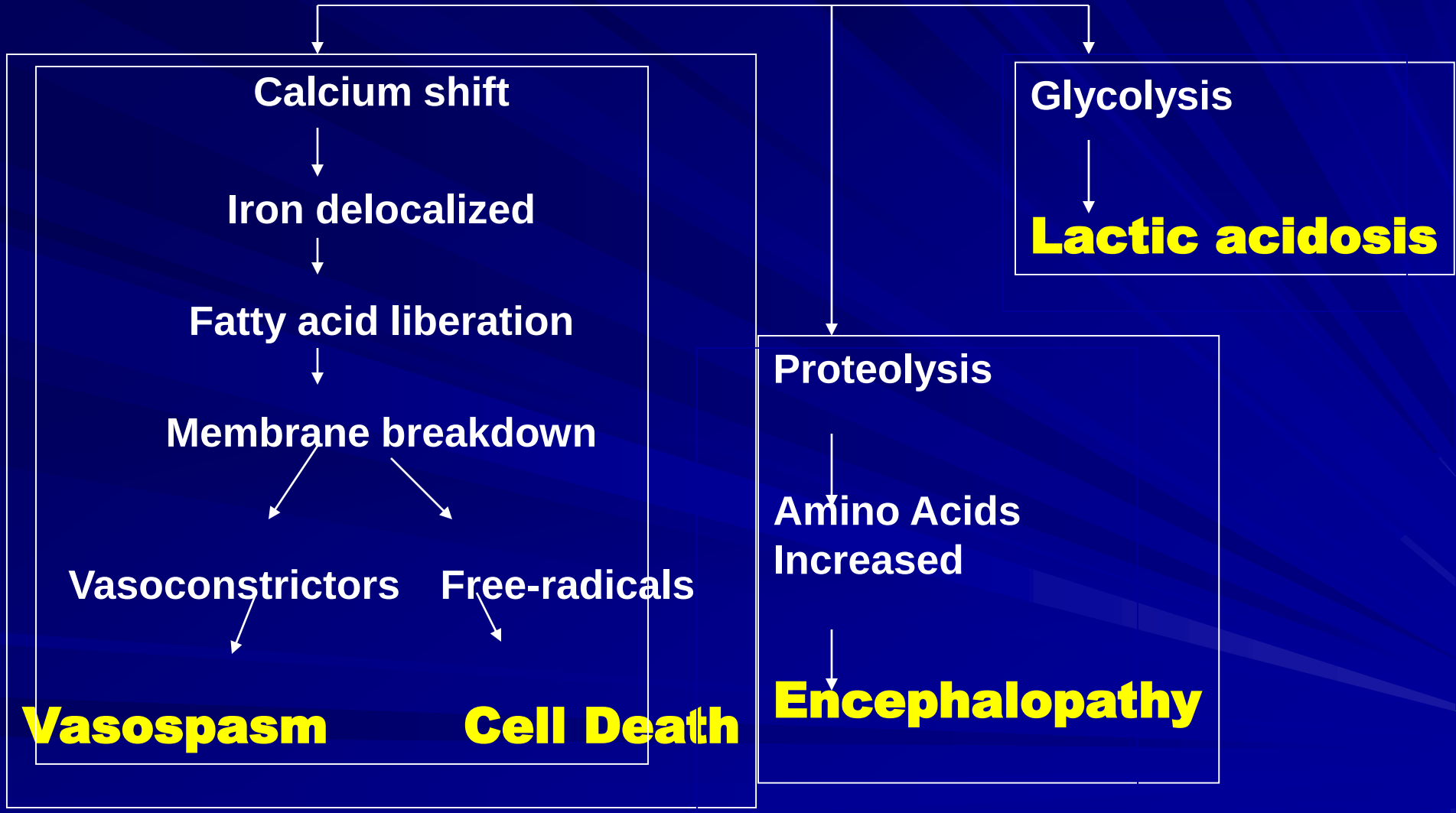
↓

Catecholamine Release & Synthesis

↓

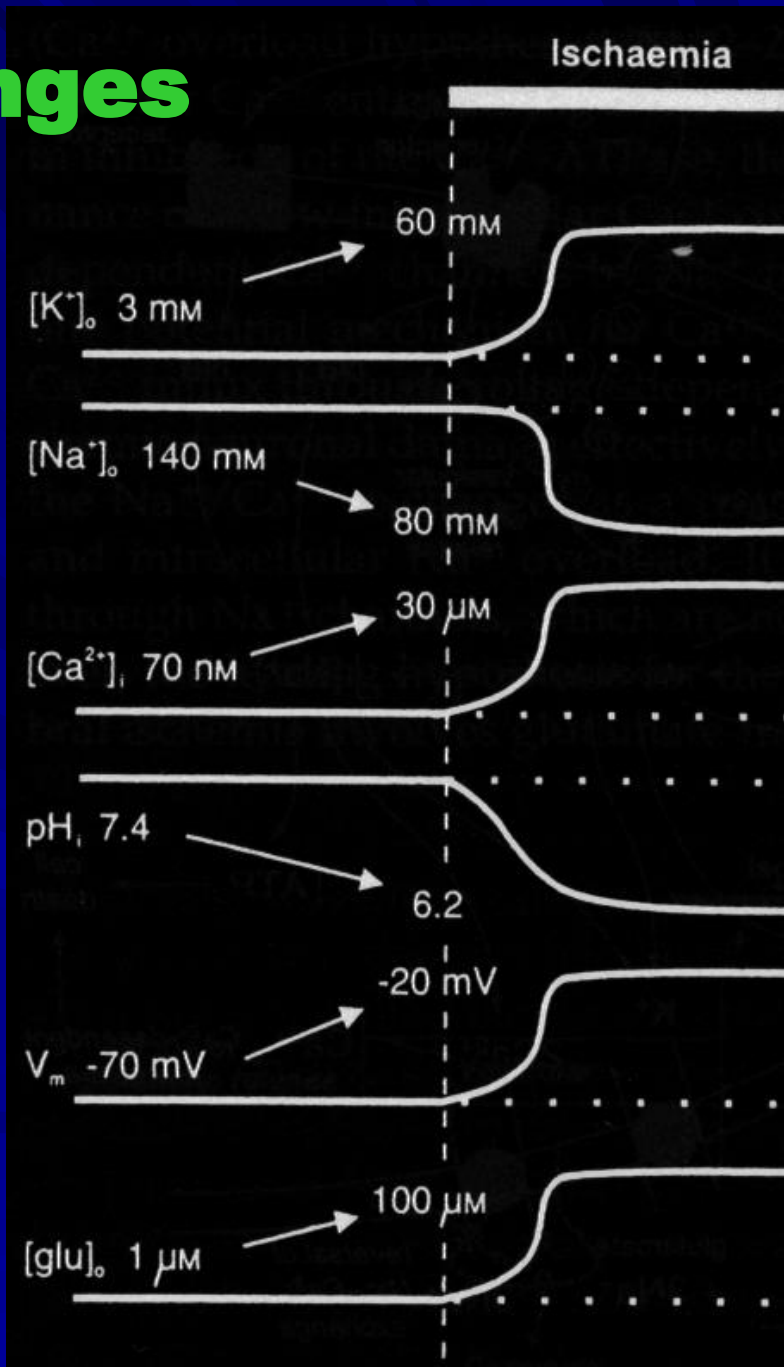
Increased O_2 Consumption

Hypoperfusion (6-18 hours)



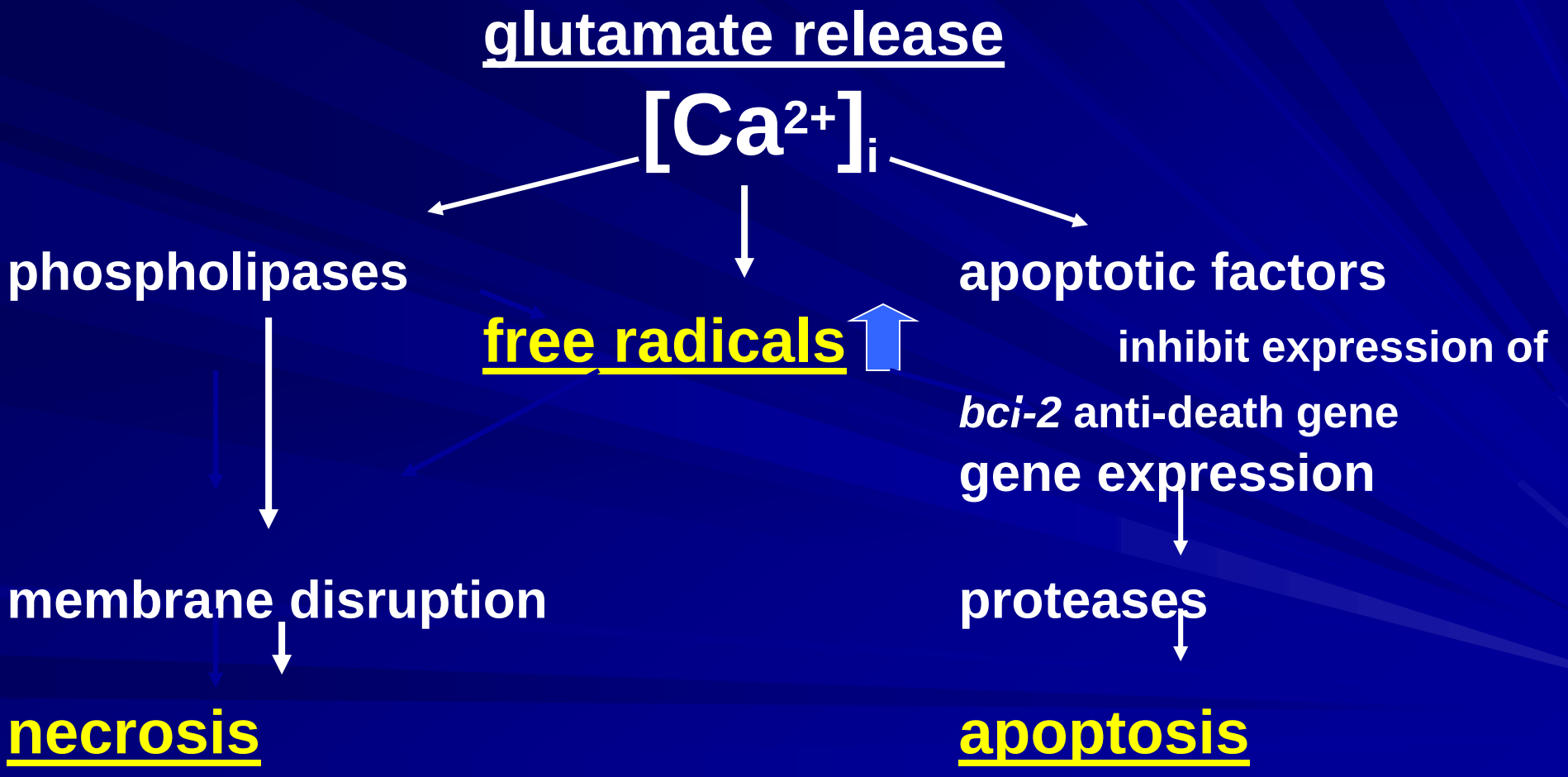
Ischemic/hypoxic Changes

- potassium efflux
- sodium influx
- calcium influx
- acidosis
- depolarization
- glutamate release



Hemmings HC Jr Neuroprotection 1997, p. 23

Excitotoxicity, Ca^{2+} Overload and Cell Death



Tirilizad improves outcome of subarachnoid hemorrhage.
Lanzino G et al. J Neurosurg 1999;90:1018

Neonatal Resistance

- CBF is 60 – 90% greater.
- Lower cerebral metabolic demand.
- Better ionic homeostasis.
- ↑Brain glycogen content.
- ↓Na^{++} channels.
- ↑Taurine level →↓Ca^{++} influx.
- ↓Glutamate levels (storage).
- Underdeveloped & immature neuronal elements.

Mechanisms of Cerebral Hypoxic-Ischemic Damage

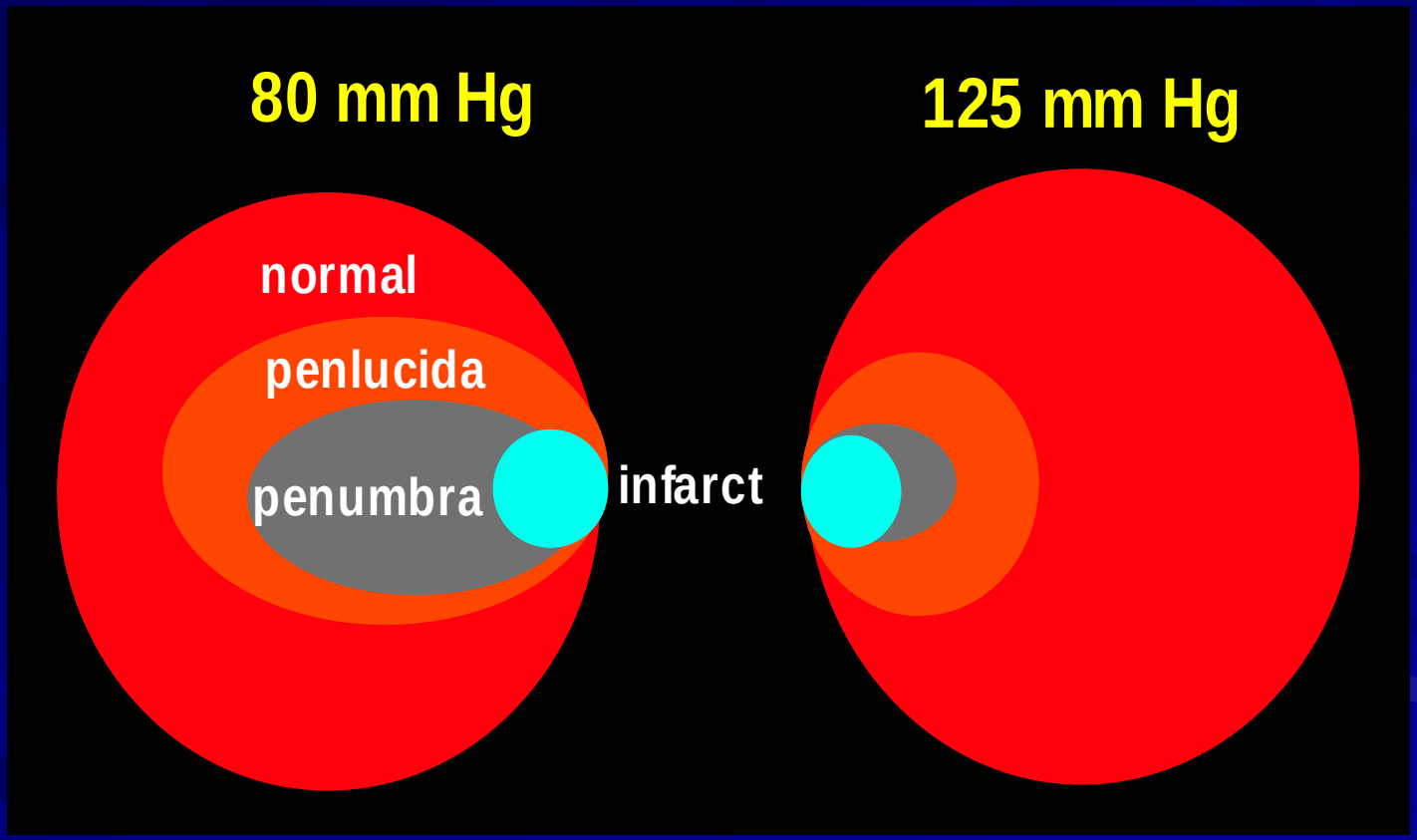
- Acidosis due to anaerobic ↑ lactic acid.
- Ca^{++} influx & intracellular accumulation
  - Pump failure
  - ↑ Membrane permeability
- Neurotoxicity of excitatory transmitters – NMDA, AMPA, glutamate, etc.
- Formation of O_2 free radicals – Reperfusion & re-oxygenation of hypoxic/ischemic tissues.
- Mucosal damage of blood vessel, platelet aggregation, sludging & aggravation of the low- or no-flow state.

(*Schurr A, Rigor BM: Hippocampus, 2:221-228, 1999*)

Compromised Neuronal Viability

- C.P.P. (cerebral perfusion pressure) is less than 30 mmHg.
- gCBF less than 15 ml/100 Gm/min.
- Cerebral venous pO_2 less than 20 torr.
- I.C.P. (intra-cranial pressure) – >8 – 12 mm. Hg.

Controlled Hypertension May Reduce Injury



Young, W.L. Problems in Anesthesia 7(1):140, 1993

Clinical Applications

- Cardiac arrest from all causes.
- Brain preservation in cardiac & neurosurgery.
- Asphyxia & drowning (submersion).
- Traumatic brain injury (T.B.I.).
- Neonatal resuscitation & OB misadventures.
- Reye's Syndrome
- Total circulatory arrest for complex congenital heart surgery.
- Surgery for giant vertebro-basilar aneuryms & A-V malformations.

Goals of Cerebral Protection

- Preserve functions & viability of the penumbral region.
- ↓ Extension of neuronal damage.
- Preserve functions beyond the vegetative state.
- ↓ Oxygen consumption/metabolic demand of viable or "stunned" neuronal elements.
- Prevent or stop associated complications in other organ systems.
- Maintain homeostasis at the pre-injury level.

Clinical Endpoints

- Reversal of EEG patterns.
- ↑Cerebral blood flow.
- ↓Size of the infarct.
- ↓Neurologic deficit(s).
- Improvement of behavioral patterns.
- **Survival beyond vegetative state!**

Neurologic deficit/ injury correlates more with the anatomical location rather than the size of the infarct!!

What will you do with the tight brain?

- Continuous use of ICP monitors.
- Optimal positioning.
- Permissive hyperventilation.
- I.V. narcotics/sedatives/tranquilizers.
- Osmodiuretics.
- Spinal fluid drainage, if necessary.
- Surgical decompression.
- Keep airway patent/unobstructed – O_2!!!

"The brain softens before the lungs stiffen".

Methods of Cerebral Protection

A. **Improve O_2 Supply (Vascular)** –

1. Improve Rheology –
   a. ↓ Viscosity – hemodilution, anti-aggregation, ↑deformability (RBCs).
   b. Anticoagulation & Anti-thrombosis
2. Flow Enhancement –
   a. Vasodilators - Nimodipine
   b. Controlled hypertension
   c. Anti-vasospasmodic agents - Ca^{++} blockers, magnesium, etc.
3. ↑ O_2 delivery – Fluosol, RBC-Hb ghost cells, EPO, Hyperbaric O_2, etc.

Methods of Cerebral Protection

B. **Metabolic Demands (Neuronal)** –

1. Synaptic Depression – Local anesthetics.
2. Metabolic Suppression – Barbiturates, propofol, general anesthetics, hypothermia, etc.

C. **Membrane Protection** –

1. Ionic & Membrane Stabilization – Steroids, local anesthetics, etc.
2. Antioxidation/Free Radical Scavenging – NMDA antagonists (N_2O, ketamine, dextromethorphan, MK-801), 60% xenon & remacemide.

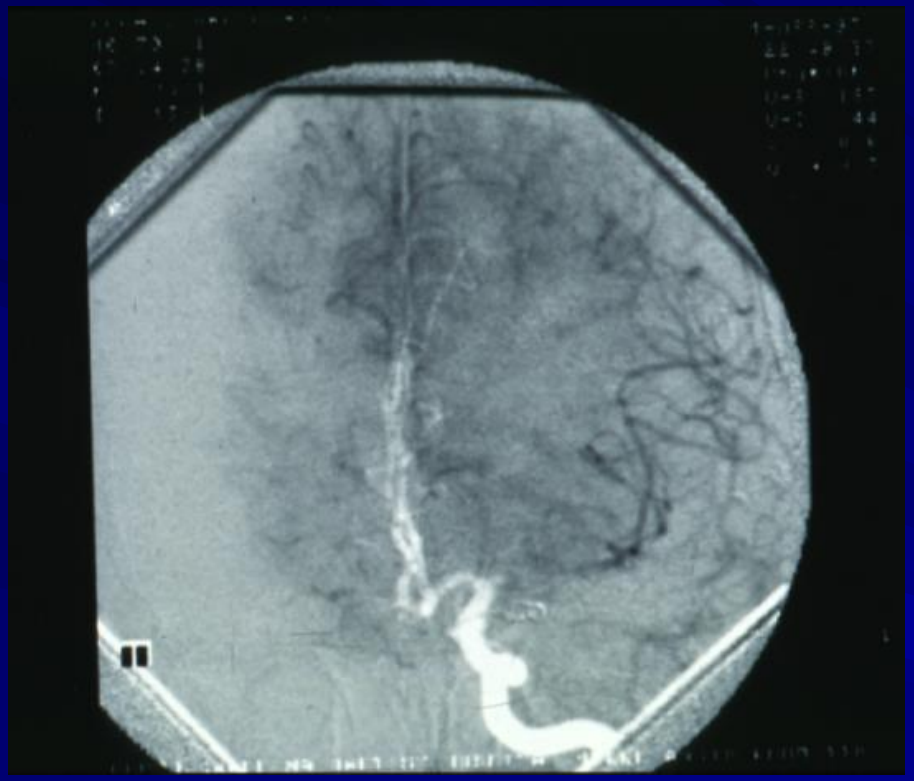
Neuroprotection – Na^+ Channel Blockers

- Block ischemic depolarization (penumbra).
- Retard voltage dependent Na^+ intracellular accumulation.
- Slow glutamate-induced Na^+ & Ca^{++} during reperfusion.
- Prevent post-anoxic repetitive neuronal firing (post-hypoxic seizures.

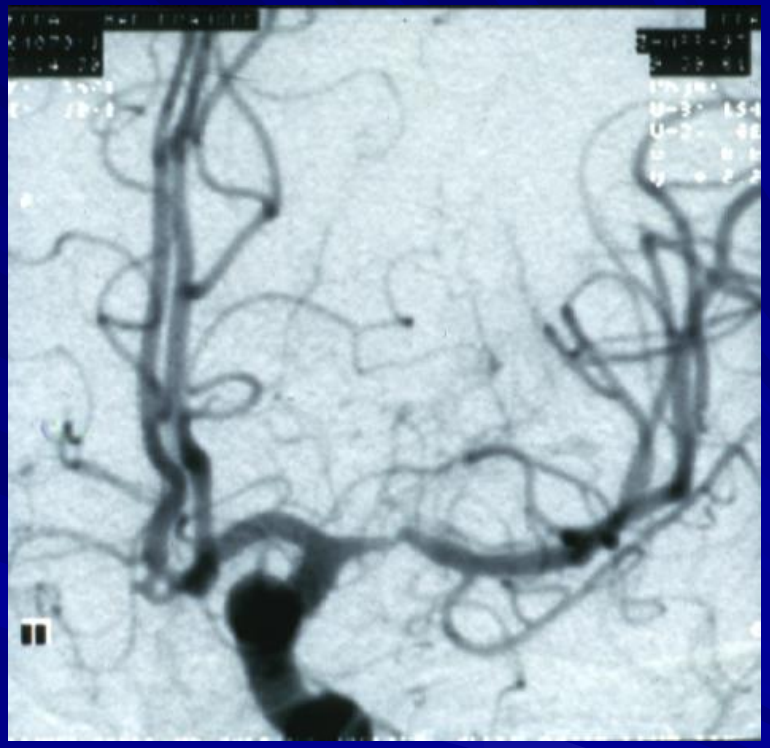
Neuroprotection – Ca^{++} Channel Blockers

- Hydrophilic – cannot penetrate BBB!
- Heterogenous group – multiple sites of action.
- Problems with posology – What dose??
- Possible direct effects of the drug.
- Other pharmacologic effects – anti-serotinergic, NMDA antagonist, membrane stabilization, etc.
- Can open other pores or channels!!.

Controlled Hypertension to Reverse Developing Embolic Injury



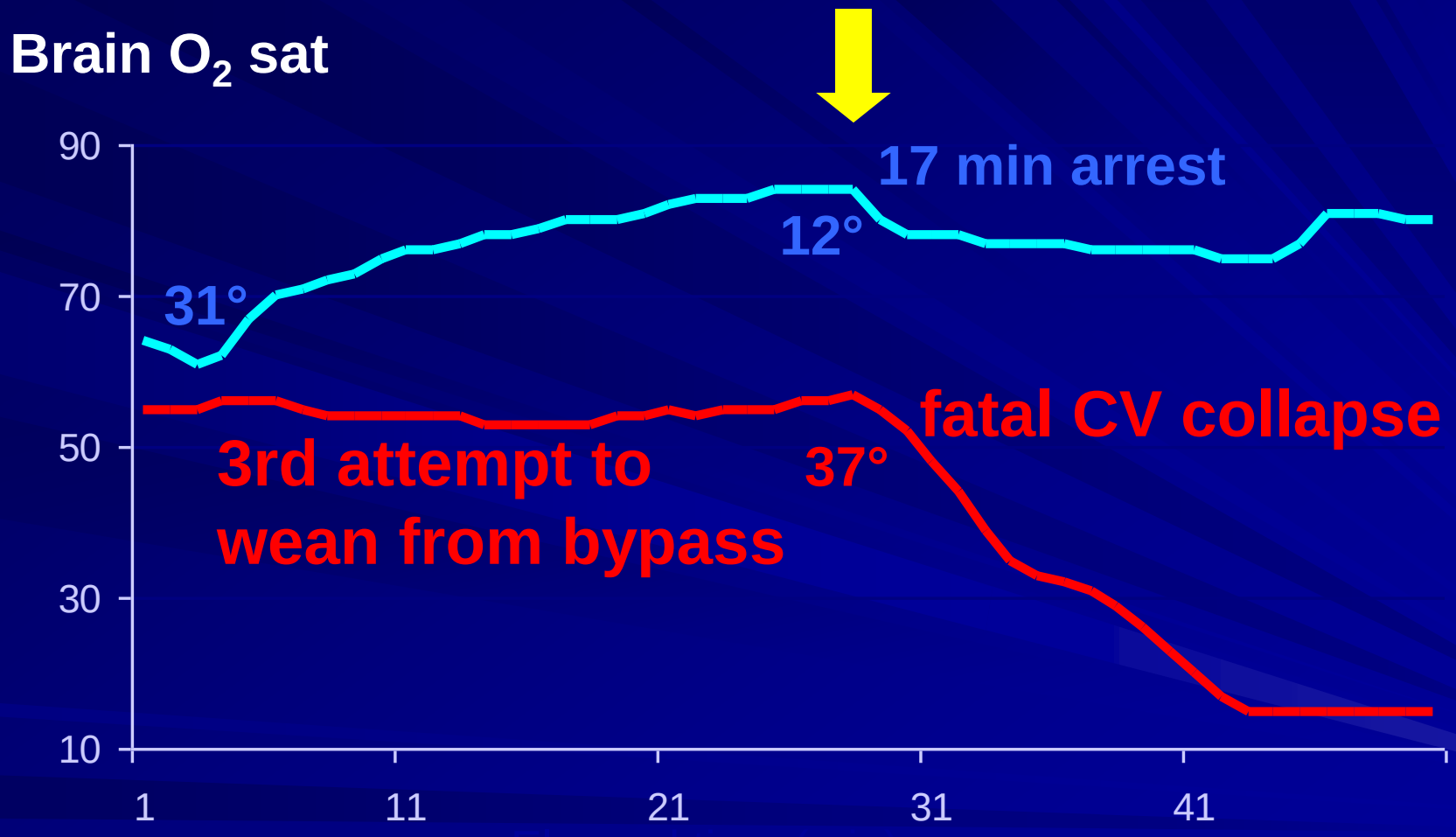
MCA occlusion @ angiography
hemiparesis develops
systolic 120 mm Hg



Hemiparesis subsides
systolic 160 mm Hg
leptomeningeal collateral perfusion

Courtesy of Dixon Woodbury MD

Hypothermia and Neuroprotection



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Beneficial Effects - Hypothemia

- ↓Release of glutamine, glycine & dopamine.
- Recovery of ubiquitin synthesis.
- Inhibition of protein kinase C.
- ↓Free radical-triggered lipid peroxidation.
- ↓Metabolic rate & oxygen consumption.
- ↓Primary synergists of ischemic metabolic cascade.
- ↓Apoptosis.

Adversed Effects - Hypothermia

- ↑Cardiac irritability (VF).
- ↑Airway resistance.
- ↓Immuned responses (infections).
- Coagulopathy & platelet dysfunction.
- Shift of O_2 dissociation curve.
- Altered membrane permeability.
- Acidosis & glucose intolerance.
- Shivering & ↑O_2 consumption.

Methods of Cerebral Protection

D. Miscellaneous –

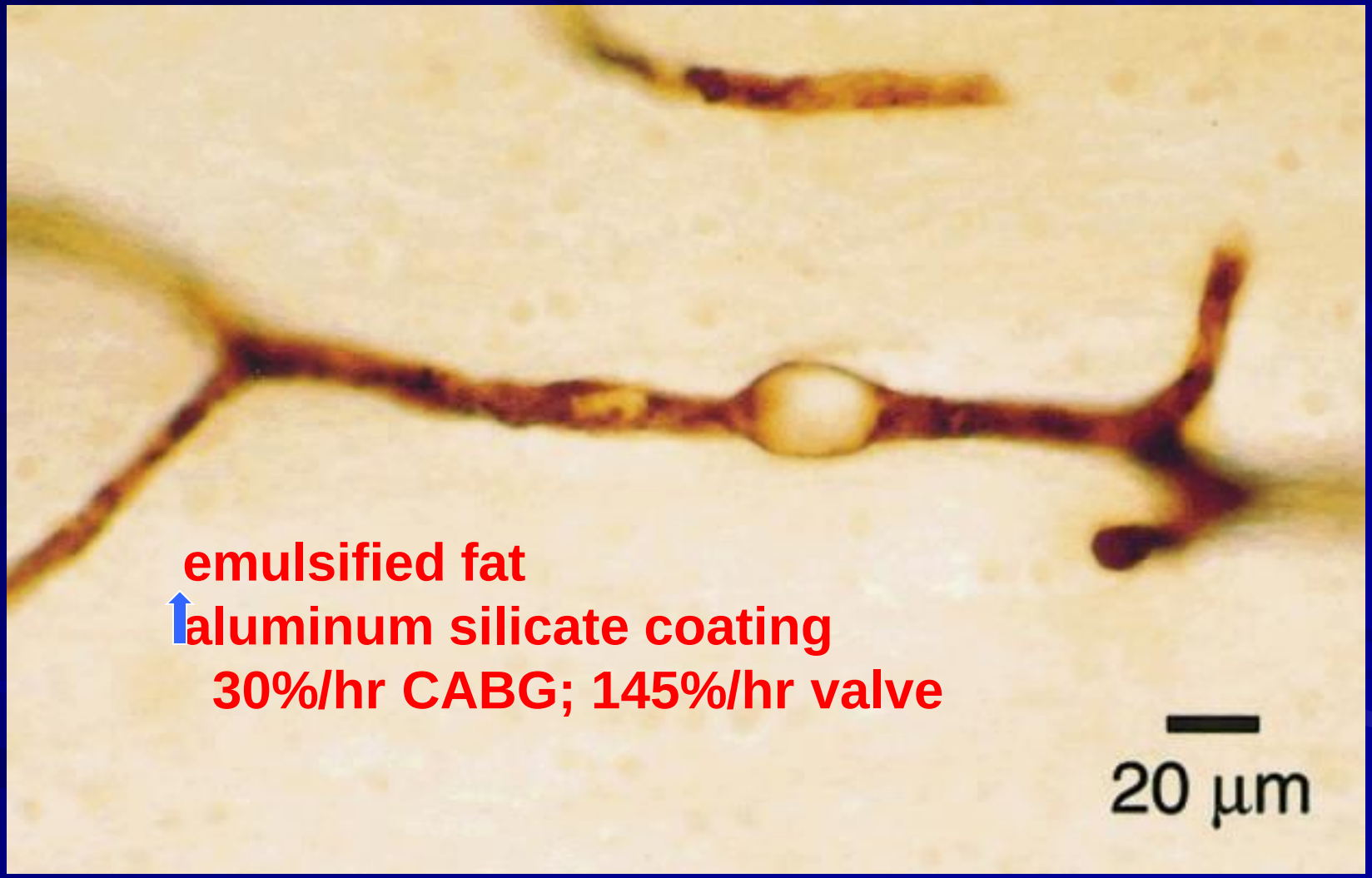
1. Perioperative neuromonitoring.
2. Stents, shunts, filters & flow modifications with cerebral protection in carotid surgery.
3. Synaptic stimulation.
4. Alkaloids & other pharmacological agents.
5. Cerebral preconditioning - Sevoflurane, xenon, EPO, previous TIA, etc.

Cerebral Preconditioning

- Stimulates proteins of repair.
- ↓Neuronal excitotoxicity.
- ↓Inflammation & the inflammatory cascade.
- Inhibits neuronal apoptosis.
- Stimulation of neuro- & angiogenesis.

The perioperative brain injuries were caused by hypoperfusion, dysoxygenation, and embolization (*fat, air, microaggregates, etc.*)

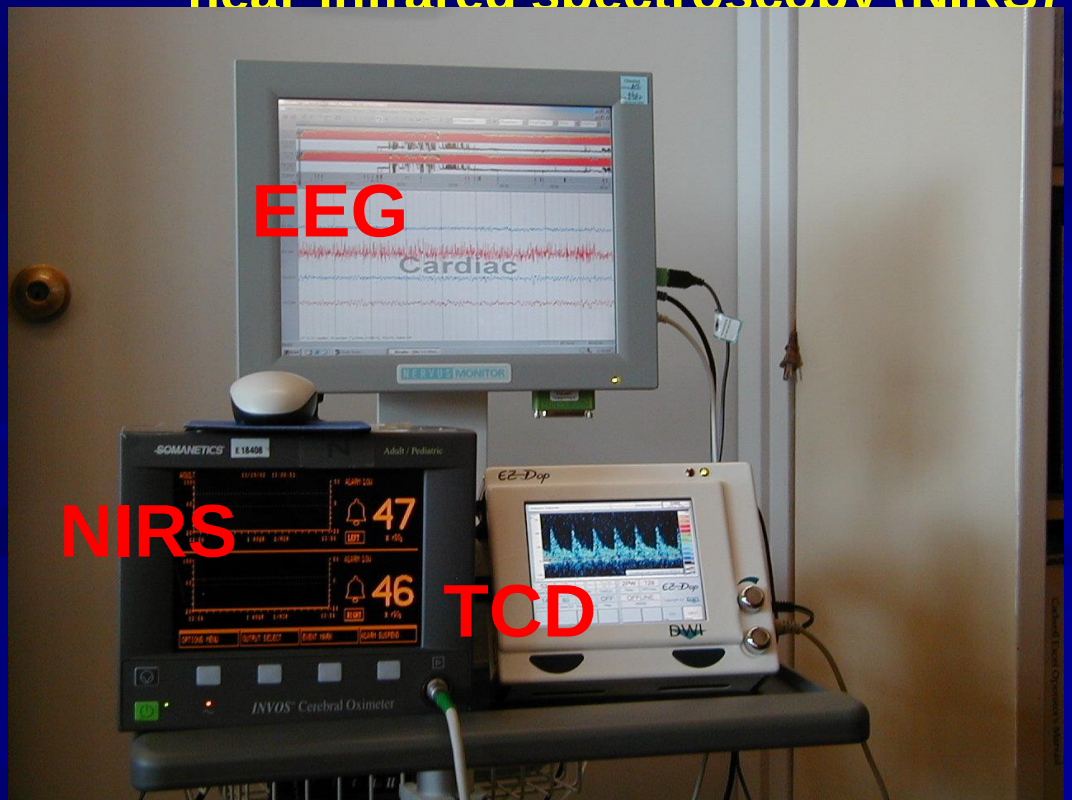
Small Capillary and Arteriolar Dilatation (SCAD)

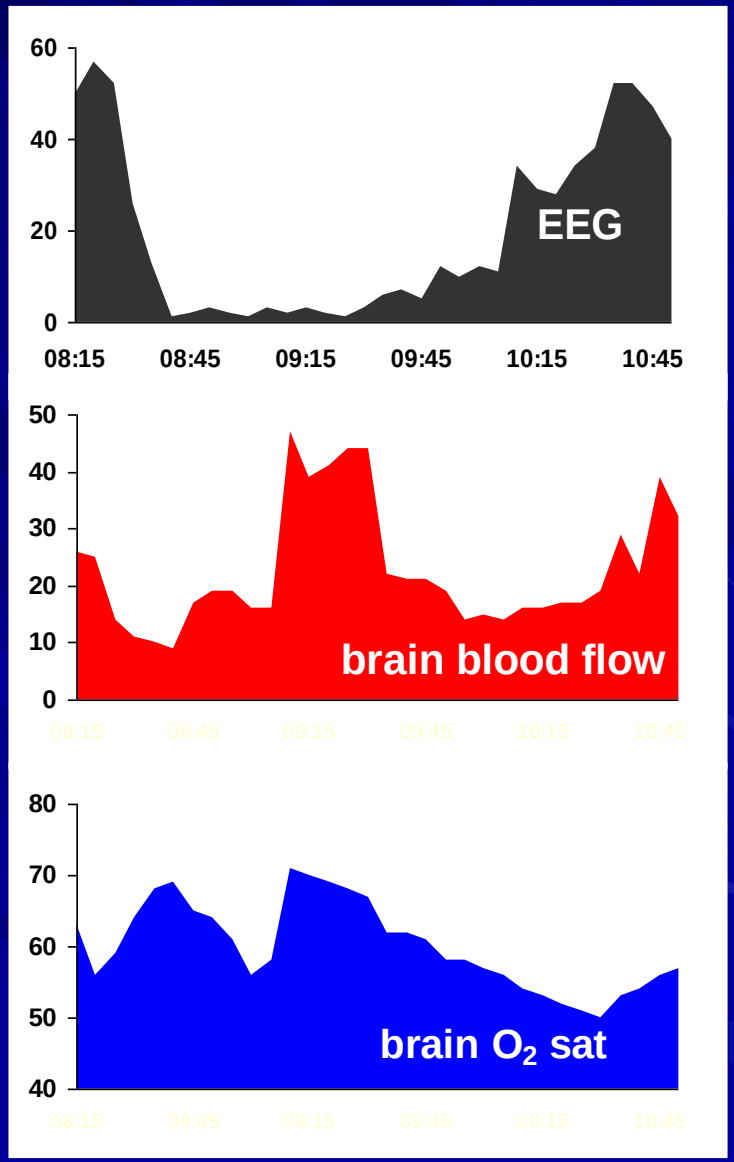


Brown WR et al. Stroke 2000;31(3):707

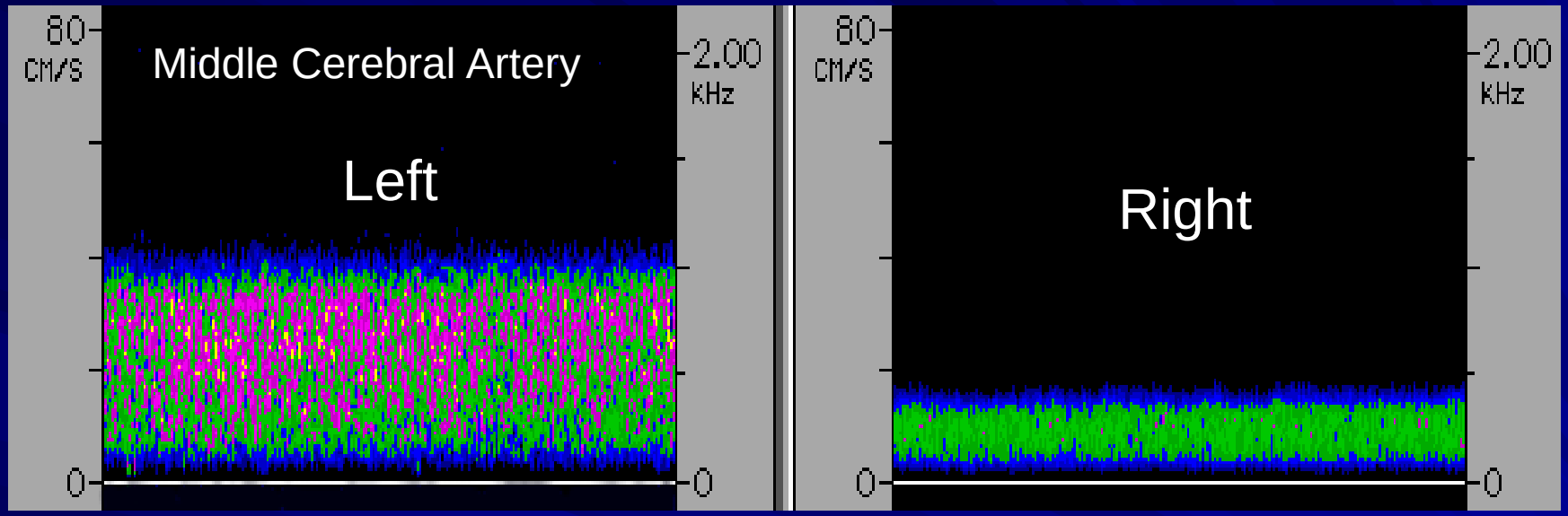
Multi-modality Neuromonitoring

- Synaptic Function
  - EEG
- Large Cerebral Vessel Perfusion
  - transcranial Doppler (TCD)
- Small Cerebral Vessel Oxygenation
  - near-infrared spectroscopy (NIRS)

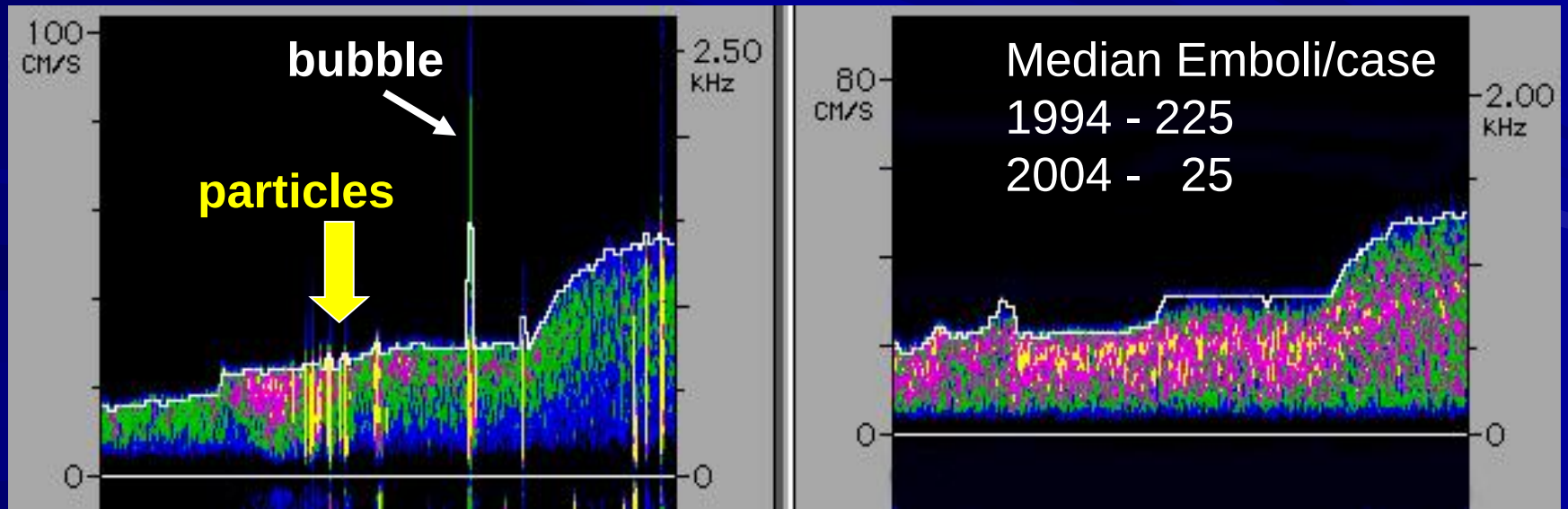




TCD Identifies Brain Blood Flow Abnormalities



and the Presence of Microemboli



What is Known About Brain Resistance to Hypoxia?

- Neonatal/perinatal brain is more resistant to hypoxia/ischemia but more vulnerable.
- Recovery of metabolic/electrical activity after I hr. of global ischemia *(in vivo).*
- Functional recovery after 2-3 hrs. of focal ischemia *(in vivo).*
- Hypoxia of 5 min. does not necessarily cause irreversible neuronal damage.
- Drugs / physiologic manipulations can modify the extend of damage & recovery.
- The success of resuscitation is **time dependent**!!
- Very few neurobehavioral/outcome studies.

Cerebral Protection/Resuscitation – State of the Art

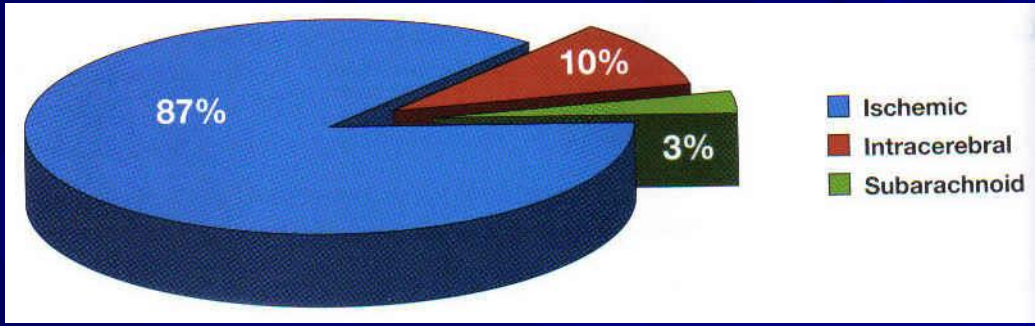
- Airway maintenance/patency & mechanical ventilation – Normocarbia (Class 1).
- Prevention of seizures/convulsions (Class 1).
- Prevention & control of ↑I.C.P. & cerebral edema (Class 1).
- Support & maintain hemodynamic parameters (Class 1).
- Sustained continuous mild to moderate hypothermia (32-34 ^{0}C) & gradual rewarming (8 hrs.) – Global ischemia & TBI (Traumatic Brain Injury) - (Class 2a).
- Osmotic diuretics for ↑ICP (Class 2a) & ICP monitoring (Class 2a).

Cerebral Resuscitation/Protection – State of the Art

- Glycemic control (Euglycemia) – Class 2a.
- Use of neuromonitoring modalities improve anticipation & prediction of insults – BIS, Transcranial Doppler, Cerebral oximetry (Class 2a).
- Metabolic depression & synaptic suppression – barbiturates, propofol, anesthetics, etc. (Class 2b).
- Other supportive therapies –

  - Control of sepsis & infections (Class 1).
  - Control of acid/base, fluid & electrolytes abnormalities (Class 1).
  - Prevention of other complications – Stress ulcers, diabetes insipidus, etc. (Class 1)

Cerebral Resuscitation/Protection – State of the Art



- **Chain of Survival – Stroke – 8 "D's" (Class 2a)**
  Detection, Dispatch, Delivery, Door, Data, Decision, Drugs & Disposition.

Critical Time Limits – Cincinnati Prehospital Stroke Scale -

- General Assessment – 10 min.
- Neurologic Assessment – 25 min.
- Acquisition of CT Scan – 25 min.
- Head CT Scan Interpretation – 45 min.
- Fibrinolytic Therapy – IV rTPA 60 min. ED arrival or 3 hrs. from onset of symptoms.
- Door-to-Admission time of 3 hours or up to 4.5 hrs. (Stroke Unit).

Most Useful Initiatives

- **Thrombolytic agents** – Alteplase IV r-tPA 3 hrs. or up to 4.5 hrs of having a stroke (**Class 1**) & the **Standard of Care**.
- **Endovascular Therapy** with a stent retriever if it meets the following criteria (**Class 1**, **Level of Evidence A**):
  - Pre-stroke mRS score 0 to 1.
  - Acute IS receiving IV tPA within 4.5 hrs. of onset of symptoms.
  - Occlusion of the ICA or proximal MCA(M1).
  - Age is > or = 18 years old.
  - NIHSS score of > or = 6.
  - Rx can be initiated (groin puncture) w/in 6 hrs. of onset of symptoms.

Newer Initiatives

- Statins & Antiplatelet Therapy – Simvastatin & clopidogrel - ↑Endothelial NO, anti-inflammatory, ↓ oxidative stress & plaque stabilization.
- Magnesium (16mmol over 15 min., then 65 mmol for 24 hrs. within 6-12 hrs. of stroke) – Smooth blood vessels relaxation - ↑ Cerebral circulation.
- Glucocorticoids (Class 3) – Very poor outcome studies.

Newer Initiatives

- Cerebral Preconditioning – Stimulates protein repair, ↓ neuronal excitotoxicity, ↓inflammation & the cascade,↓ neuronal apoptosis & stimulate neuro- & angiogenesis.
- In carotid artery surgery, use of embolus blockers, stents & flow dynamics modifications – Class 2b.
- Improved RBC rheology/O_2 delivery – Hyperbaric oxygenation, fluosol, EPO, etc. (Class Int.)

Suggested Reading List

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