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Pediatric Traumatic Brain Injury

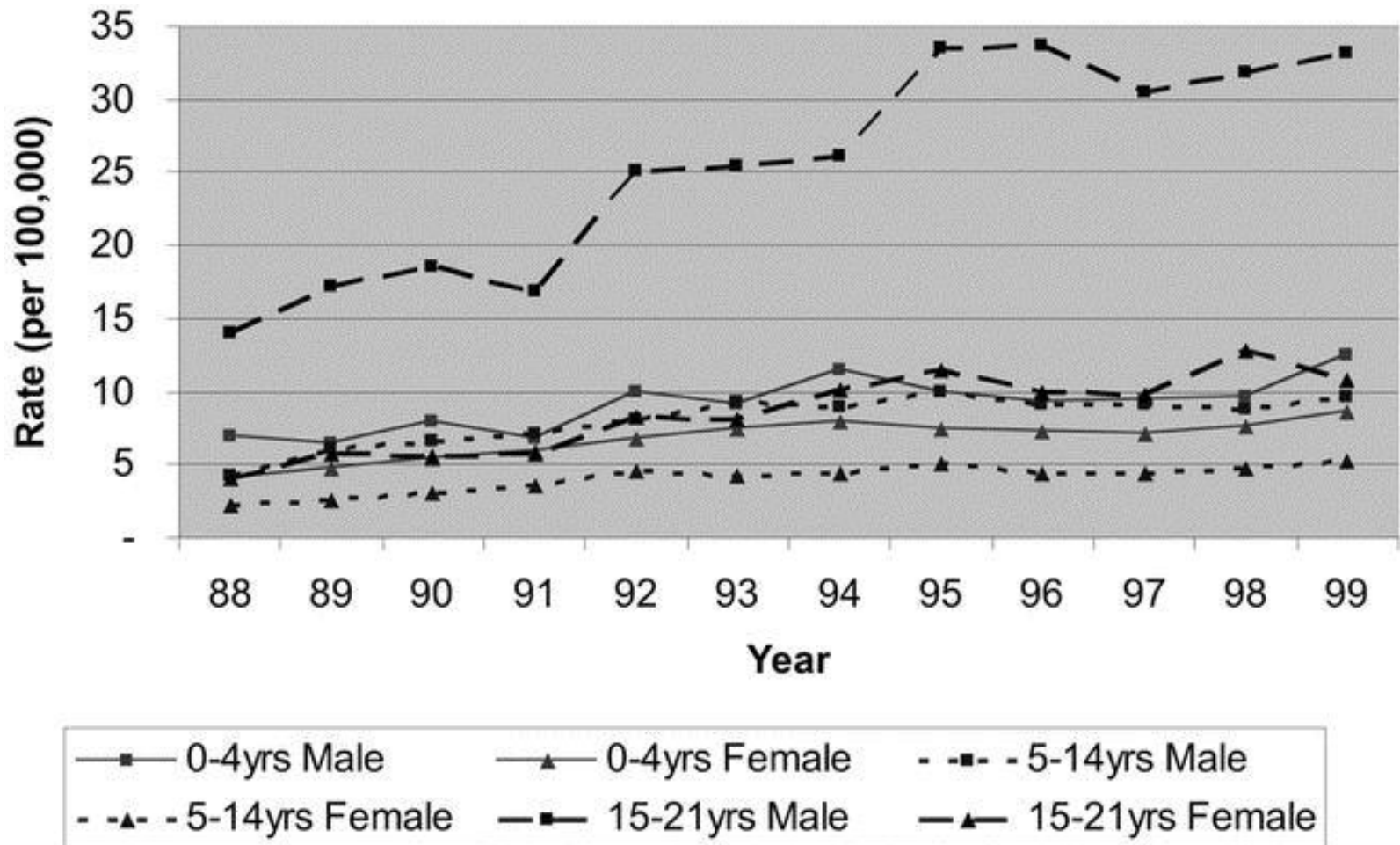
Objectives

- Review TBI pathophysiology
- Treatment of TBI
- Hypothermia in TBI

TBI Epidemiology

- Children < 14 years, annually
 - 3000 deaths
 - 29,000 hospitalizations
 - 400,000 emergency department visits
 - 10-15% TBI cases severe
 - Death rate
 - 20 times the number of deaths from asthma
 - 40 times the number of deaths from cystic fibrosis

Incidence of TBI requiring Intubation by Age



Mechanisms of Injury

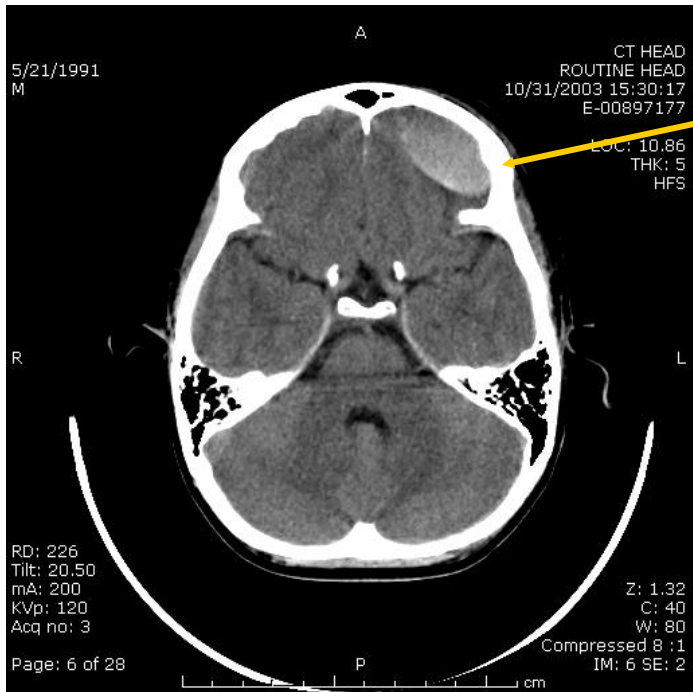
- Direct tissue injury
- Hematoma/hemorrhage
- Swelling
- Shearing forces
- Secondary injury



**Subarachnoid
hemorrhage**

**Subdural
hemorrhage**

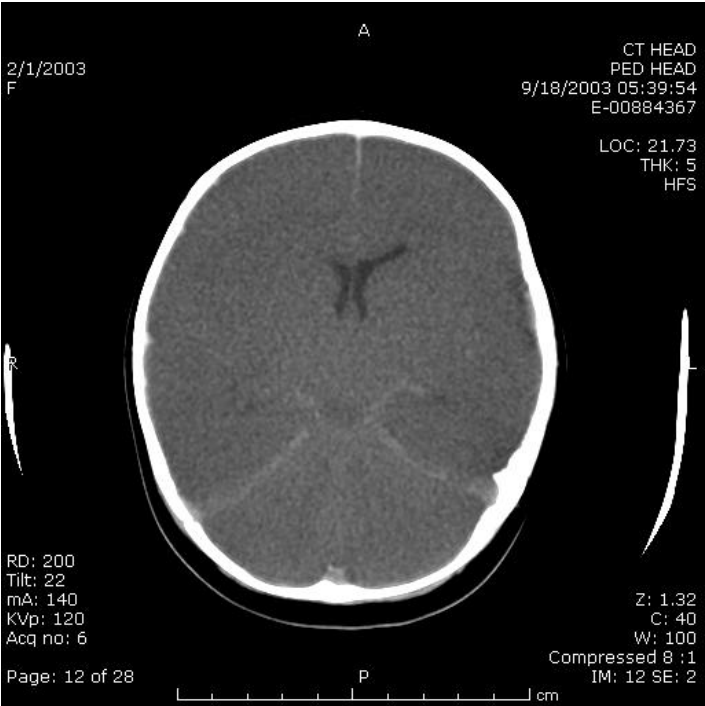




**epidural
hemorrhage**



**intraparenchymal
hemorrhage**



Types of Cerebral Edema

- Cytotoxic
 - Astrocyte Swelling- uptake of substrates (e.g. glutamate), acidosis, Na and H₂O accumulate, increased glucose
 - Other cells swell (e.g. neurons)- Trauma/Ischemia induced ion pump failure
- Osmolar swelling- contusion necrosis, increased local osmolarity
- Vasogenic- forms in extracellular space secondary to BBB disruption (seems increasingly less important- so perhaps more benefit to hyperosmolar therapies now, rather than decreasing CBF)

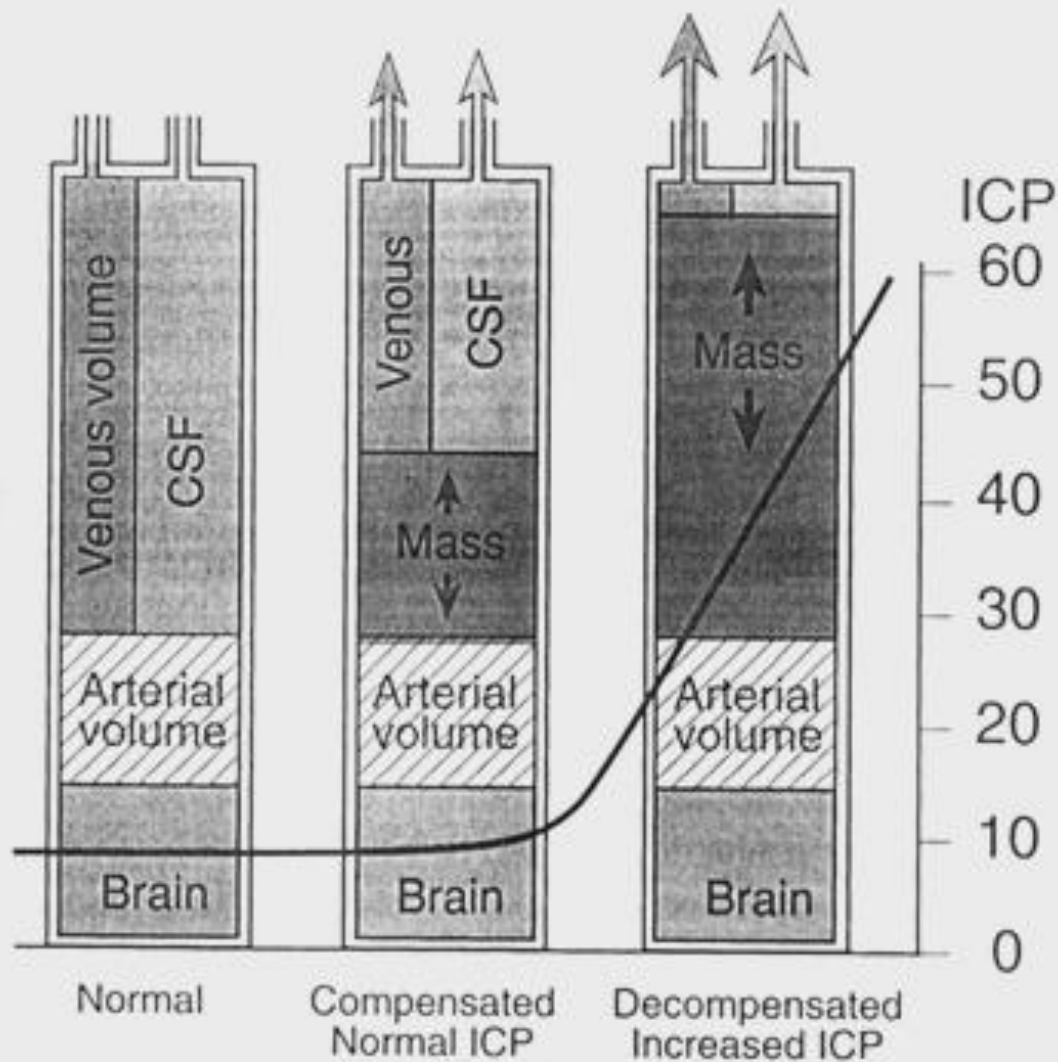
Hemodynamic phases after TBI

- **Phase 1 (day 0) Hypoperfusion phase**
 - CBF reduced, normal AVDO₂, normal SjO₂
 - CMRO₂ about 50% normal
 - ? Normal response or increased microcirculatory resistance
- **Phase 2 (days 1-3) Hyperemia phase**
 - CBF increase, AVDO₂ falls, increased SjO₂
 - CMRO₂ depressed
 - ? Decreased microcirculatory resistance from local vasodilators
- **Phase 3 (days 4-15) Vasospasm phase**
 - CBF gradually falls, AVDO₂ low, SjO₂ remains elevated
 - Persistently reduced CMRO₂ (maybe cell death)
 - Vasospasm may contribute to worsening ischemia - debate about Triple H therapy normally employed for SAH (Hypertension, Hemodilution, Hypervolemia)

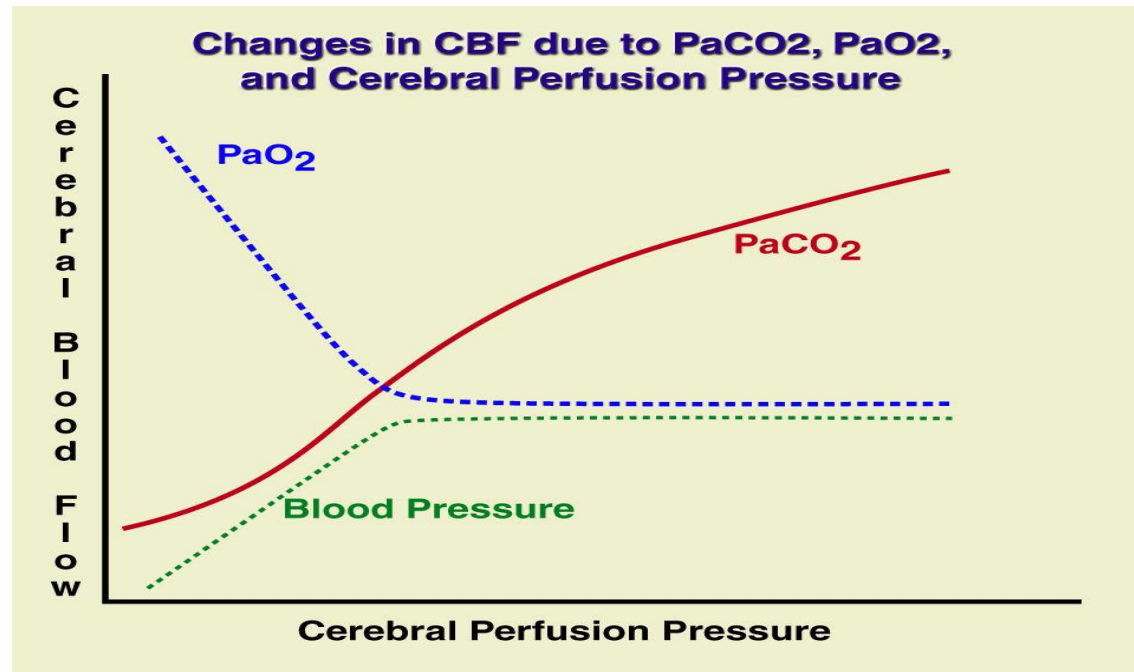
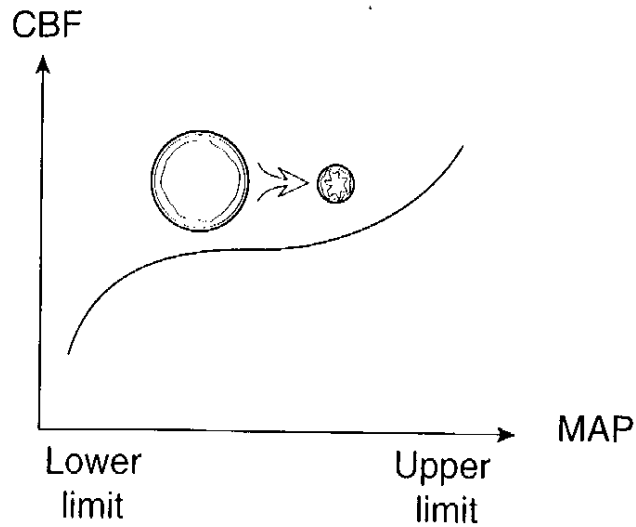
Physiologic principles of severe TBI

- Monroe Kelley Doctrine
- Cerebral Autoregulation
- Cerebral Perfusion Pressure

Monroe Kelley Doctrine



Autoregulation

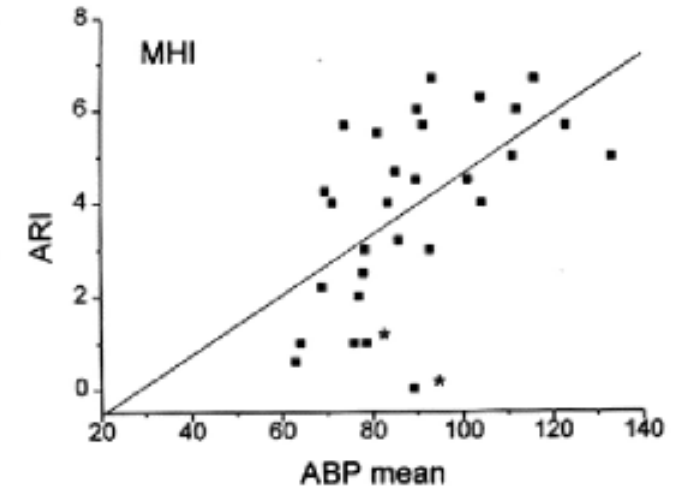
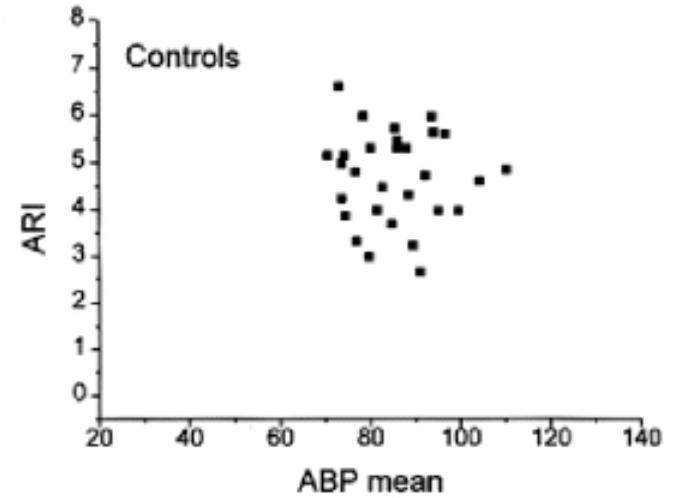
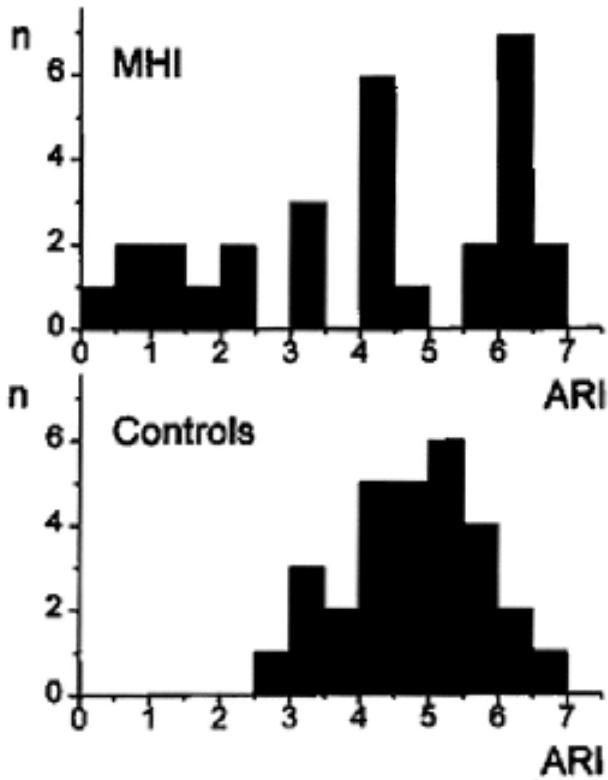


Rogers, et al

Assumptions

- Autoregulation is intact in Trauma
 - Junger et al., 1997, found that a subgroup of 28% of adults even with minor trauma had defective autoregulation
 - Czosnyka et al., 1996, found that worse autoregulation was associated with worse GCS and worse outcomes.
- Autoregulation ranges in Children ?

Disruptions in Autoregulation by Trauma: Adults



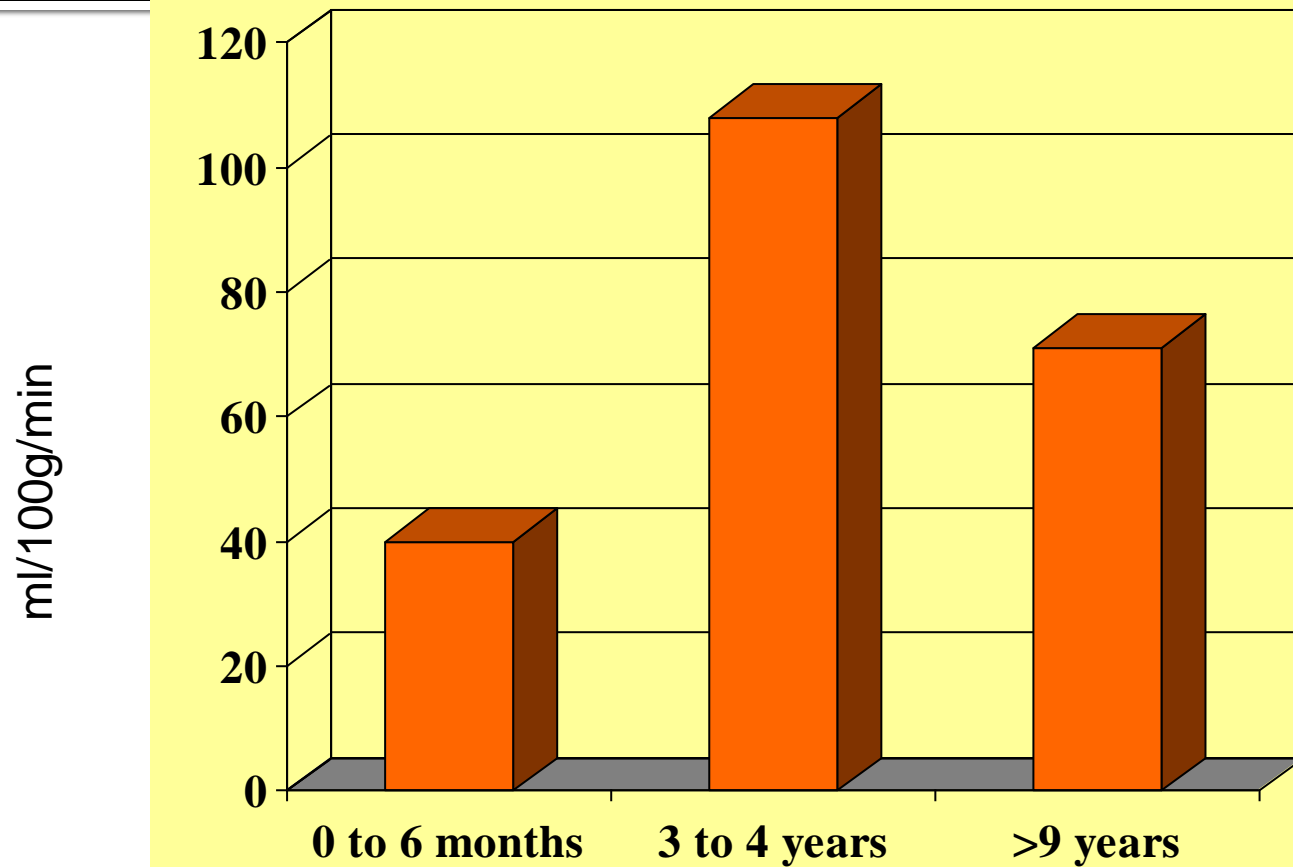
$ARI = \% \text{ Change CVR} / \% \text{ Change MAP}$

Junger et al

Cerebral Perfusion Pressure

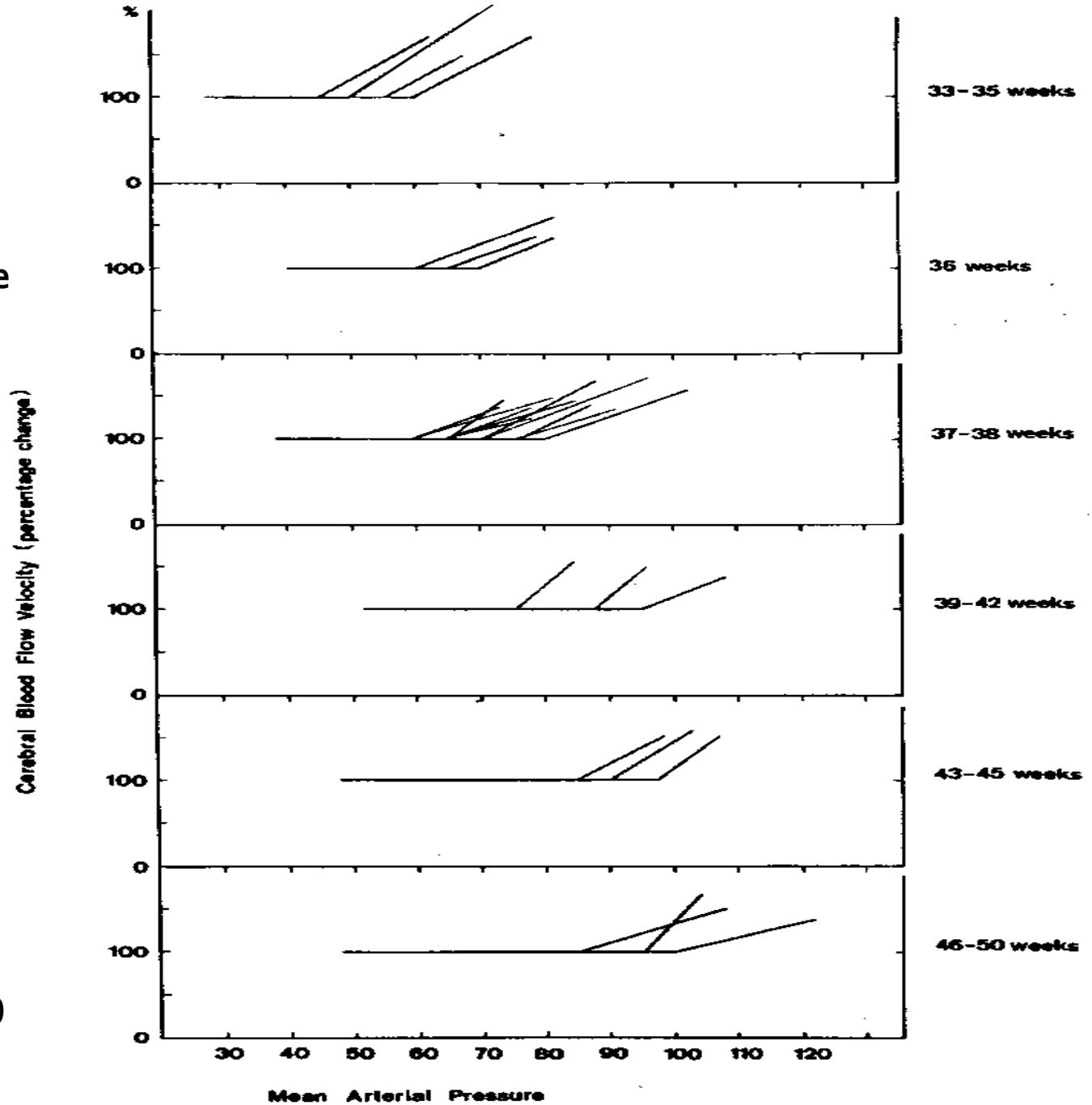
- $CPP = MAP - ICP$
 - Recommendations for CPP are extrapolated from effects in normal individuals with intact cerebral autoregulation
- Adults target CPP >60 mmHg
- Goal CPP in infants/ children?
 - Autoregulatory curve unclear
 - Pediatric TBI guidelines suggest
 - Infants/toddlers 40-50 mmHg
 - Children 50-60 mmHg
 - Adolescents > 60 mmHg

CBF by age



Zwieneberg M, 1999 J. Neurotrauma

Autoregulation Ranges in Newborns and Infants by Gestational Age



Ramaeker, 1990

Blood Pressure goals

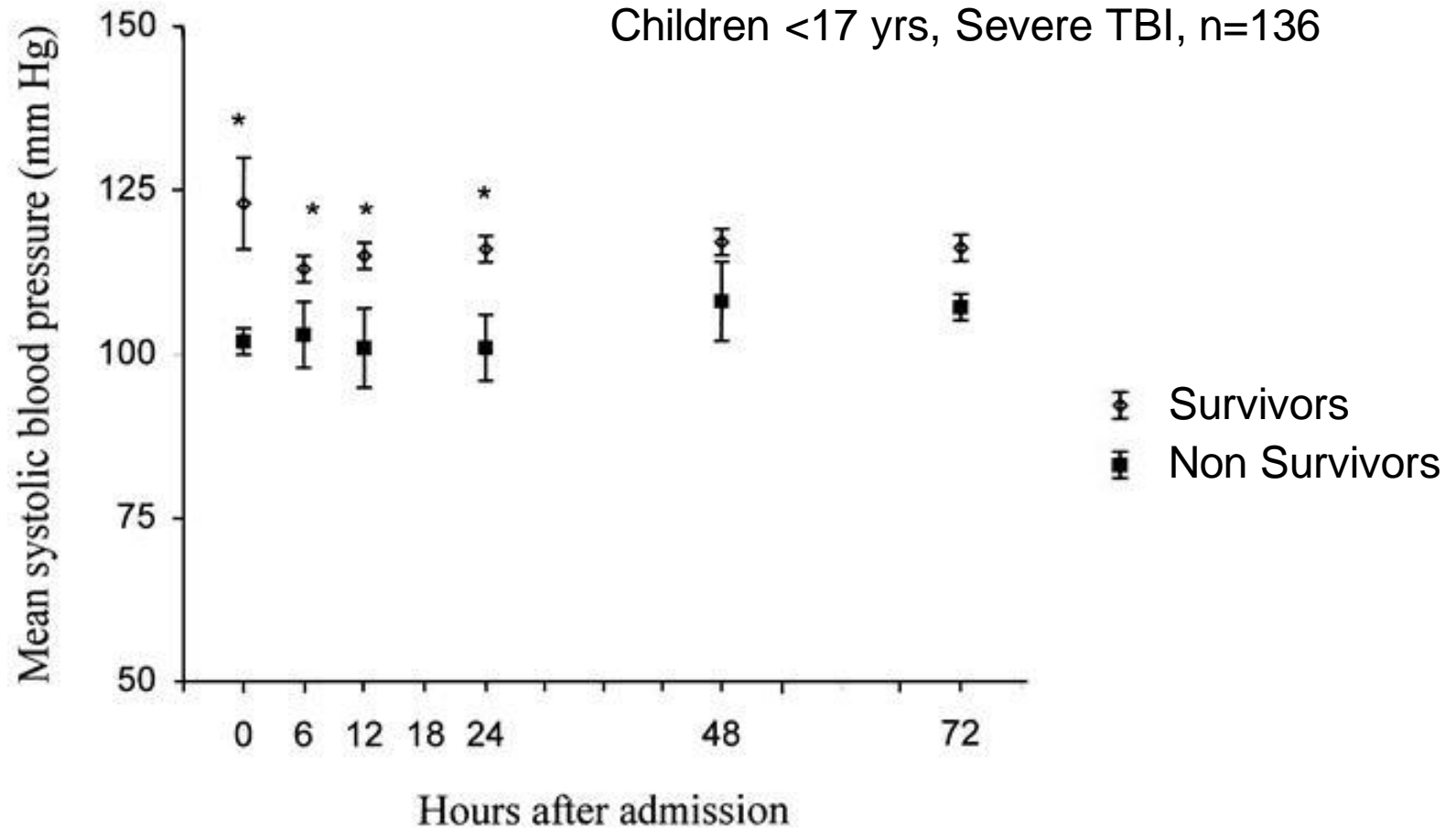
- Hypotension should be avoided and corrected as rapidly as possible.
 - Poorer outcomes, increased mortality for children and adults hypotensive at any point during their resuscitation
- Hypertension?
 - Initially implicated with worse outcome.
 - However, more recent data has shown an almost 20 fold increased odds of survival with “supranormal (>135) ” systolic blood pressures, especially in the first 6-12 hours.

Adelson et al.. S12-18: 2003 Jul.

Kanter RK et al, 1985; 24:320-323.

White JR, et al. Critical Care Medicine 2001; 29:534-540.

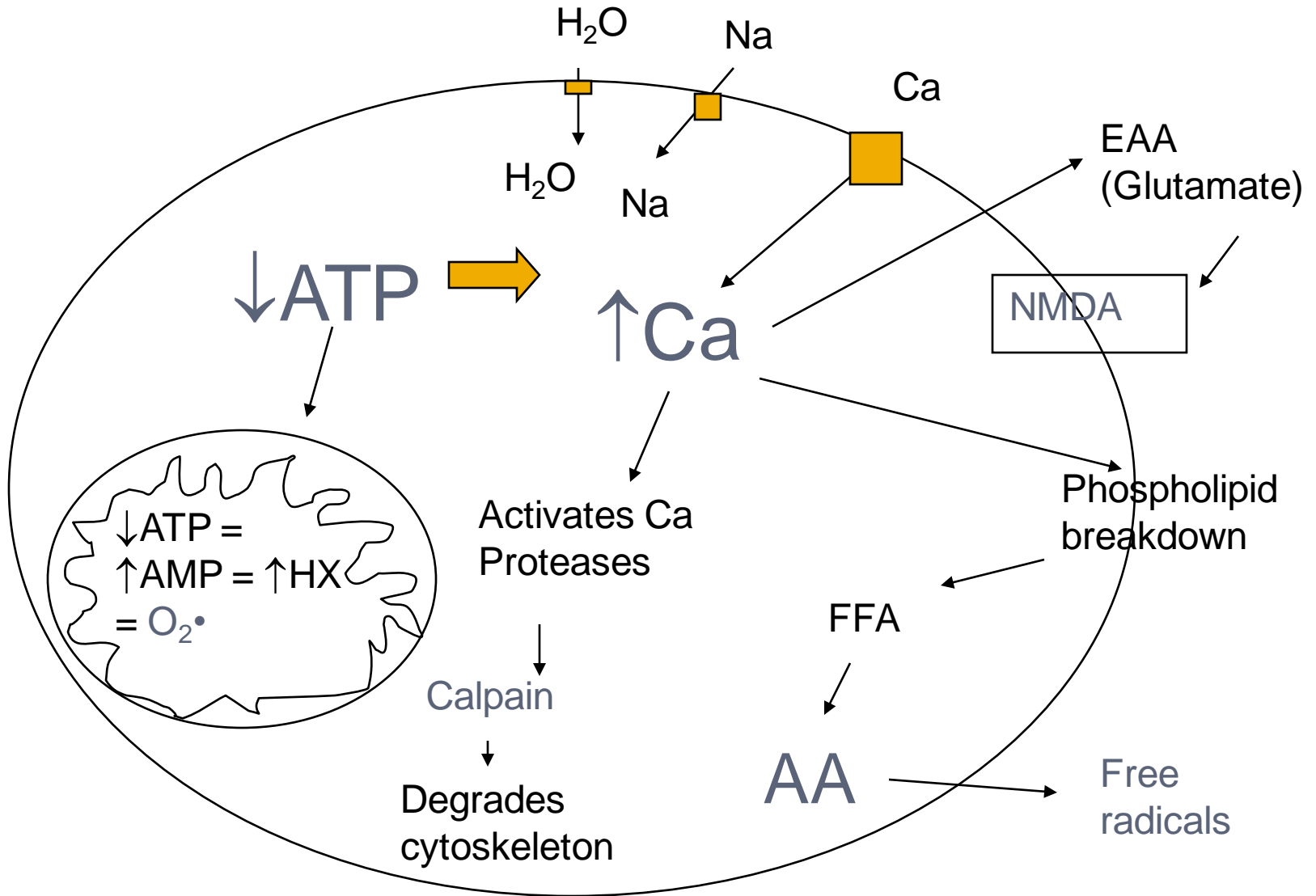
Blood Pressure Differences



Cellular injury

- Cell rupture and death
- Energy depletion
- Free radical toxicity
- Protein breakdown
- Glucose release

ATP energy failure (depletion of substrates \approx 5 minutes)



Traumatic Brain Injury: Initial Stabilization

- ABC's
- Identification and correction of airway obstruction, inadequate ventilation, and shock take priority over a detailed neurologic assessment
- Brain specific interventions in the absence of signs of herniation or other neurologic deterioration are not recommended.
- Mannitol may be counterproductive for initial management of IC Hypertension during initial resuscitative efforts
- Hypertonic saline (3%) may be a better choice.

Traumatic Brain Injury

- Studies consistently show increased morbidity and mortality associated with **hypotension** and **hypoxemia**
- In the UK, over 11 yr period, Endotracheal intubation and ventilation rates increased from 11-82%,
 - reduced hypoxemia from 22 to 8%
 - reduced mortality rate from 45 to 32%
- When should you intubate?

Criteria for Intubation of the Head-Injured Child

- GCS score ≤ 10
- Decrease in GCS of >3 , independent of initial GCS
- Anisocoria >1 mm
- Cervical Spine injury compromising ventilation
- Apnea
- Hypercarbia ($\text{PaCO}_2 > 45$ mm Hg)
- Loss of pharyngeal reflex
- Spontaneous hyperventilation causing $\text{PaCO}_2 < 25$ mmHg

What should you use to intubate?

- Neurologic and hemodynamic status directs pharmacologic strategy
- Hemodynamically unstable: the combination of etomidate, lidocaine, and muscle relaxant *OR* fentanyl, lidocaine, and muscle relaxant
- Stable patients: same meds but can add Midazolam and/or thiopental
- Etomidate & thiopental ultrafast acting, reduce cerebral metabolism
- Avoid ketamine
 - Animal (dog) experiments linking to increases in ICP
 - Small case series in adults with CSF obstruction

Lidocaine

- Intended to blunt sympathetic (aka pressor) response to Laryngoscopy- to avoid CVA, dysrhythmias, rise in ICP
 - Based on adult studies, and must be given 3 minutes before DL
 - Pressor response larger in adults than kids
- Pediatric Data does not support its use

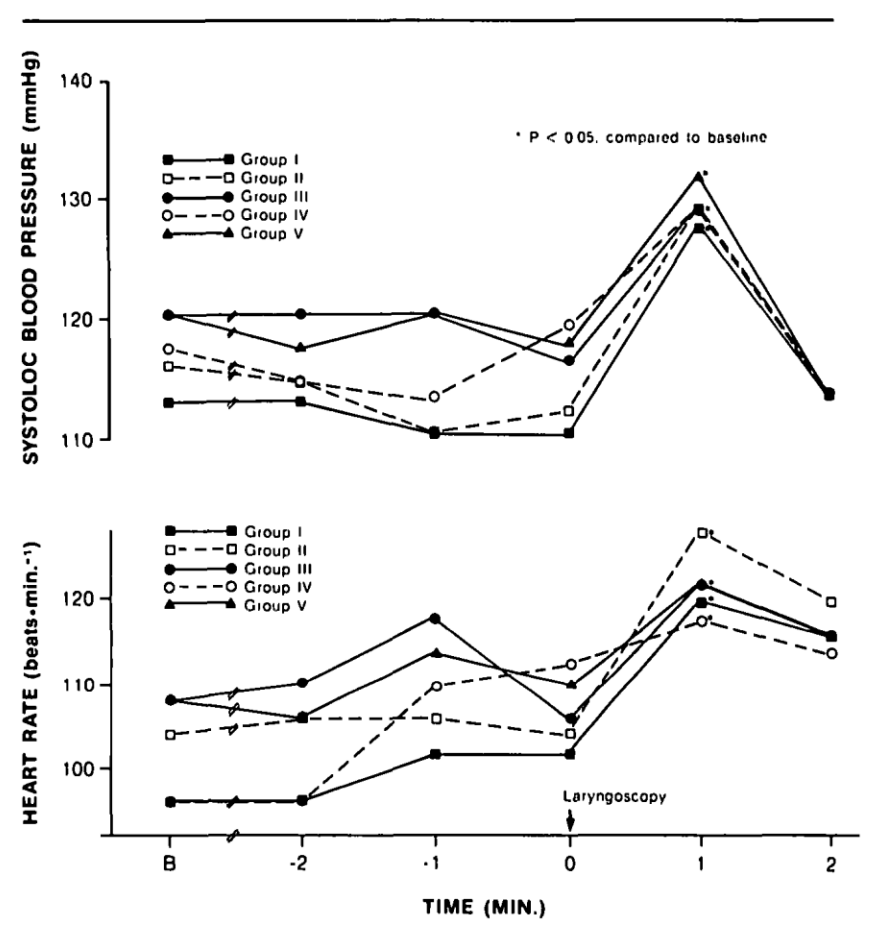


FIGURE The heart rate and systolic blood pressure at rest (time = B; operating room baseline), during induction of anaesthesia, and before and after tracheal intubation in patients treated with thiopentone only (Group V), and in combination with lidocaine one, two, three and four minutes before laryngoscopy, Groups I-IV, respectively.

Controversies of Ketamine?

- Potential neuroprotective effects in animal models
 - mediated by antagonism of N-methyl-D-aspartate (NMDA) channels located on central neurons.
 - prevents calcium influx during states of neurocellular ischemia (Pfenninger, 1997; Fitzal, 1997; Lin, 1996)
- Similarly, in a prospective trial of patients with head injuries and in animal models of stroke and head injury may have neuroprotective effects
- Ketamine use controversial with head injuries (or stroke) (Kolenda, 1996; Shapira, 1994; Reeker, 2000)

Safety of sedation with ketamine in severe head injury patients: Comparison with sufentanil

Aurélie Bourgoin, MD; Jacques Albanèse, MD; Nicolas Wereszczynski, MD; Martine Charbit, MD;
Renaud Vialet, MD; Claude Martin, MD, FCCM

Objective: The aim of the study was to compare the safety concerning cerebral hemodynamics of ketamine and sufentanil used for sedation of severe head injury patients, both drugs being used in combination with midazolam.

Design: Prospective, randomized, double-blind study.

Setting: Intensive care unit in a trauma center.

Patients: Twenty-five patients with severe head injury.

Interventions: Twelve patients received sedation with a continuous infusion of ketamine-midazolam and 13 with a continuous infusion of sufentanil-midazolam. All patients were mechanically ventilated with moderate hyperventilation.

Measurements and Main Results: Prognostic indicators (age, Glasgow Coma Scale scores, computed tomography diagnosis, and Injury Severity Scale score) were similar in the two groups at study entry. Measurements were carried out during the first 4 days of sedation. The average infusion rates during this time were $82 \pm 25 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ketamine and $1.64 \pm 0.5 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ midazolam in the ketamine group and $0.008 \pm 0.002 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ sufentanil and $1.63 \pm 0.37 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ midazolam in the sufentanil group. No significant differences were

observed between the two groups in the mean daily values of intracranial pressure and cerebral perfusion pressure. The numbers of intracranial pressure elevations were similar in both groups. The requirements of neuromuscular blocking agents, propofol, and thiopental were similar. Heart rate values were significantly higher in the ketamine group on therapy days 3 and 4 ($p < .05$). With regard to arterial pressure control, more fluids were given on the first therapy day and there was a trend toward greater use of vasopressors in the sufentanil group. Sedative costs were similar in the two groups.

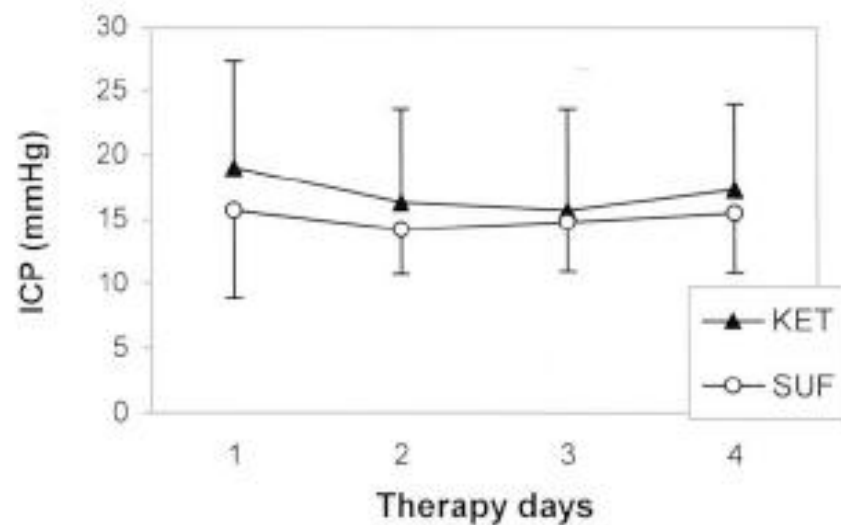
Conclusion: The results of this study suggest that ketamine in combination with midazolam is comparable with a combination of midazolam-sufentanil in maintaining intracranial pressure and cerebral perfusion pressure of severe head injury patients placed under controlled mechanical ventilation. (Crit Care Med 2003; 31:711-717)

KEY WORDS: severe head injury management; ketamine; sufentanil; midazolam; sedation; intracranial pressure; cerebral perfusion pressure; adverse effects of anesthetic agents; intensive care unit

Mean daily intracranial pressure

1a

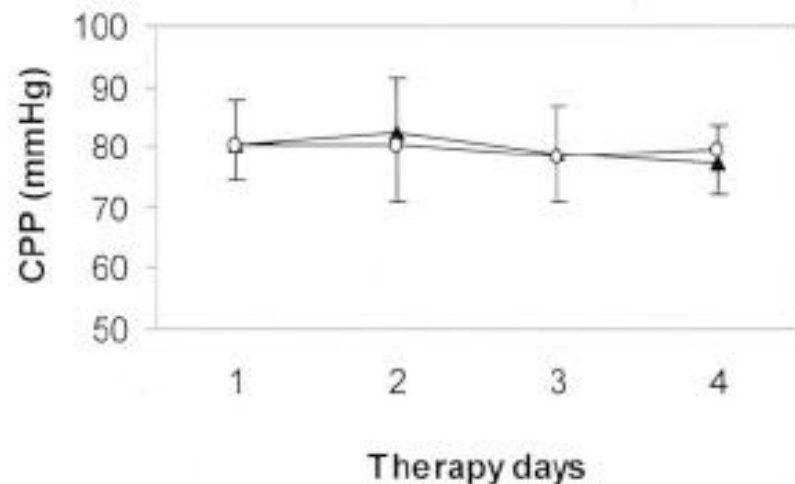
n=K	12	10	8	7
n=S	13	12	9	7



Mean daily cerebral perfusion pressure

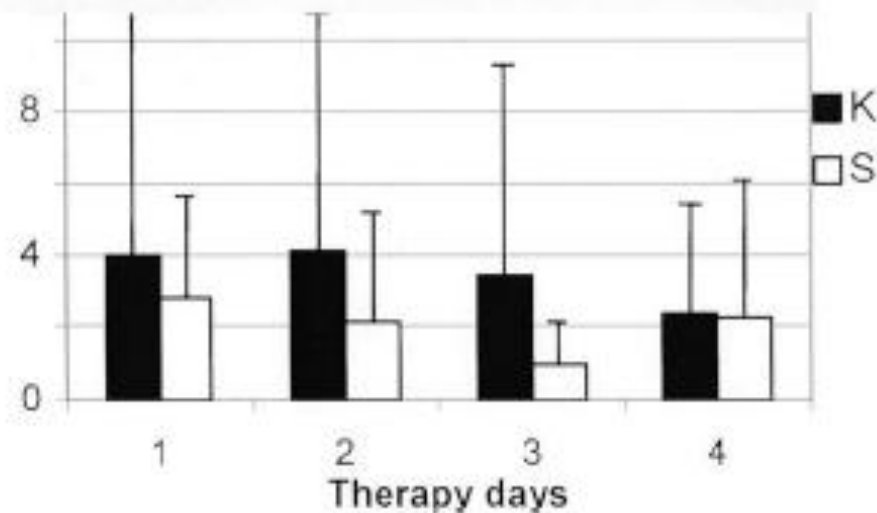
1b

n=K	12	10	8	7
n=S	13	12	9	7



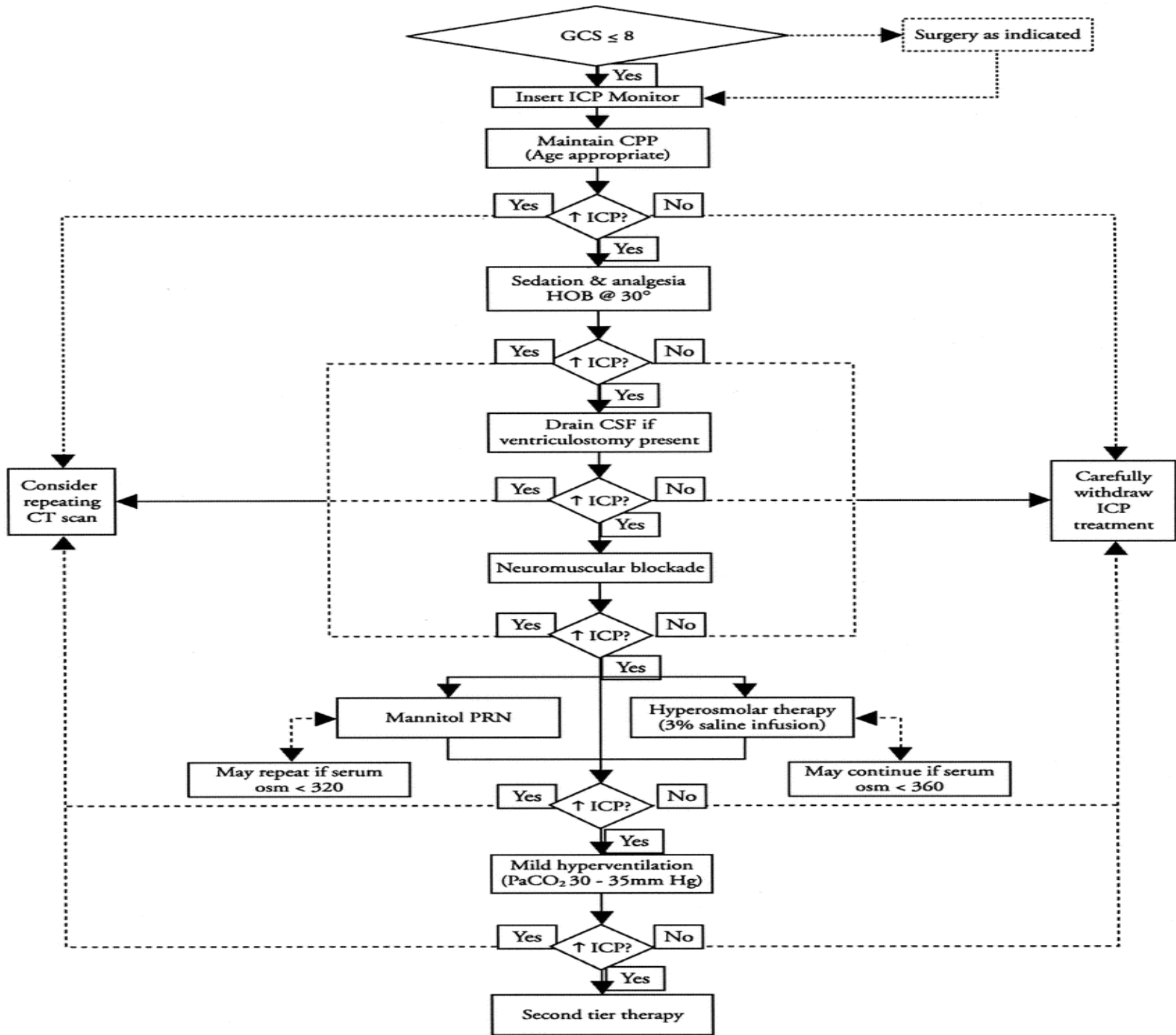
1c Numbers of ICP elevation per day

n=K	12	10	8	7
n=S	13	12	9	7



Pediatric TBI Treatment

- 2003 PCCM:4(3) Suppl.
Guidelines for management of pediatric TBI



SECOND TIER THERAPY

↑ ICP despite first tier tx?
No surgical lesion on CT?

Yes

Working ventriculostomy?
Open cisterns on concurrent CT?

Consider lumbar drain

Salvageable patient?
Evidence of swelling on CT?

Unilateral swelling?

Consider unilateral decompressive craniectomy with duraplasty

Bilateral swelling?

Consider bilateral decompressive craniectomy with duraplasty

Active EEG?
No medical contraindications to barbituates?

Consider high dose barbituate therapy

Evidence of hyperemia?
No evidence of ischemia?

Consider hyperventilation to a PaCO₂ < 30 mm Hg
(Consider monitoring CBF, S_jO₂, AFDO₂)

Evidence of ischemia?
No medical contraindications to hypothermia?

Consider moderate hypothermia (32 - 34° C)

Pediatric Critical Care Management Guidelines

Severe TBI with GCS \leq 8

Management Goals

Maintain ICP \leq 20

Maintain Cerebral Perfusion

Cerebral perfusion pressure age based goals:

- < 2 years \geq 45mm Hg
- 2-6 years \geq 50mm Hg
- 7-10 years \geq 55mm Hg
- 11 years \geq 60mm Hg

Prevent Hypoxia and Hypotension

- Maintain adequate MAP to keep CPP in range
- Goal SpO₂ $>$ 96%
- Goal PaCO₂ 36 - 40 to maintain cerebral blood flow
- Keep hematocrit \geq 28

Basic Management

Intubation

- Modified rapid sequence
- C-spine precautions
- Lidocaine (1.5mg/kg IV)
- Fentanyl (4mcg/kg)
- Versed (0.05mg/kg; if BP normal)
- Rocuronium (1.2mg/kg)
- Normal Saline at bedside

ICP monitor placement

- Correct coagulopathy prior to placement
- Camino fiberoptic or ventriculostomy catheter
- Check ICP monitor for patency & waveform

Bedside

- Keep head midline with HOB 30 degrees
- Arterial line, CVP set-up
- Foley in place
- Indwelling temp probe (goal 35.5 - 37.5° C)
- Neuro checks q1h
- ICP monitor zeroed & functioning
- Prevent atelectasis with CPT/suctioning q4 & pm
- Log roll to prevent pressure sores

Fluids

- NS for volume replacement
- Call MD for UOP < 1cc/kg/hr or > 4cc/kg/hr
- D5NS +/- KCl @ 2/3rds maintenance
- Goal serum Na+ 145-155
- Goal serum glucose 120-180

Nutrition

- Ulcer prophylaxis while NPO
- Begin TPN/enteral feeds within 72 hrs
- Replace 120% resting metabolism expenditure
- 15-20% nitrogen calories

Labs

- ABG q6
- Chem 8, serum osm, urine dip q12
- CBC qam

Interventions for ICP > 25 for 5 min

Prevent worsening edema

- 3% saline (6ml/kg over 20 minutes)
May repeat if serum osm < 360 & serum Na⁺ < 160
- Mild hyperventilation (PaCO₂ 30-35)
- Drain CSF per Neurosurgery if ventriculostomy in place

Minimize cerebral oxygen demand with sedation & neuromuscular blockade

- Fentanyl/Morphine & Versed infusions
- Lidocaine (1.5mg/kg IV) before noxious stimuli if ICP increases > 10
- Vecuronium for shivering/clonus

Seizures

- Acute treatment with Versed (0.1mg/kg, may repeat)
- Start AED only after 1st seizure requiring treatment
- Load Fosphenytoin 20mg/kg & start maintenance if pt ≥ 2 years of age (goal level 15-20) OR
- Load Phenobarbital 20mg/kg & start maintenance if pt < 2 years of age (goal level 20-30)
- Order EEG if suspect subclinical seizures

Inotropes/Vasopressors

- If CPP/MAP low after adequate volume resuscitation start Dopamine @ 5mcg/kg/min up to 10mcg/kg/min then start
- Epinephrine @ 0.02mcg/kg/min (cool ext) OR
- Norepinephrine @ 0.02mcg/kg/min (warm ext)

Interventions to consider for ICP refractory to medical management (ICP > 25 for 20 minutes)

Discuss with Neurosurgery & Trauma:

- Repeat CT scan
- Brief hyperventilation (PaCO₂ 25-30)
- Barbiturate therapy
- Decompressive craniectomy

ICP

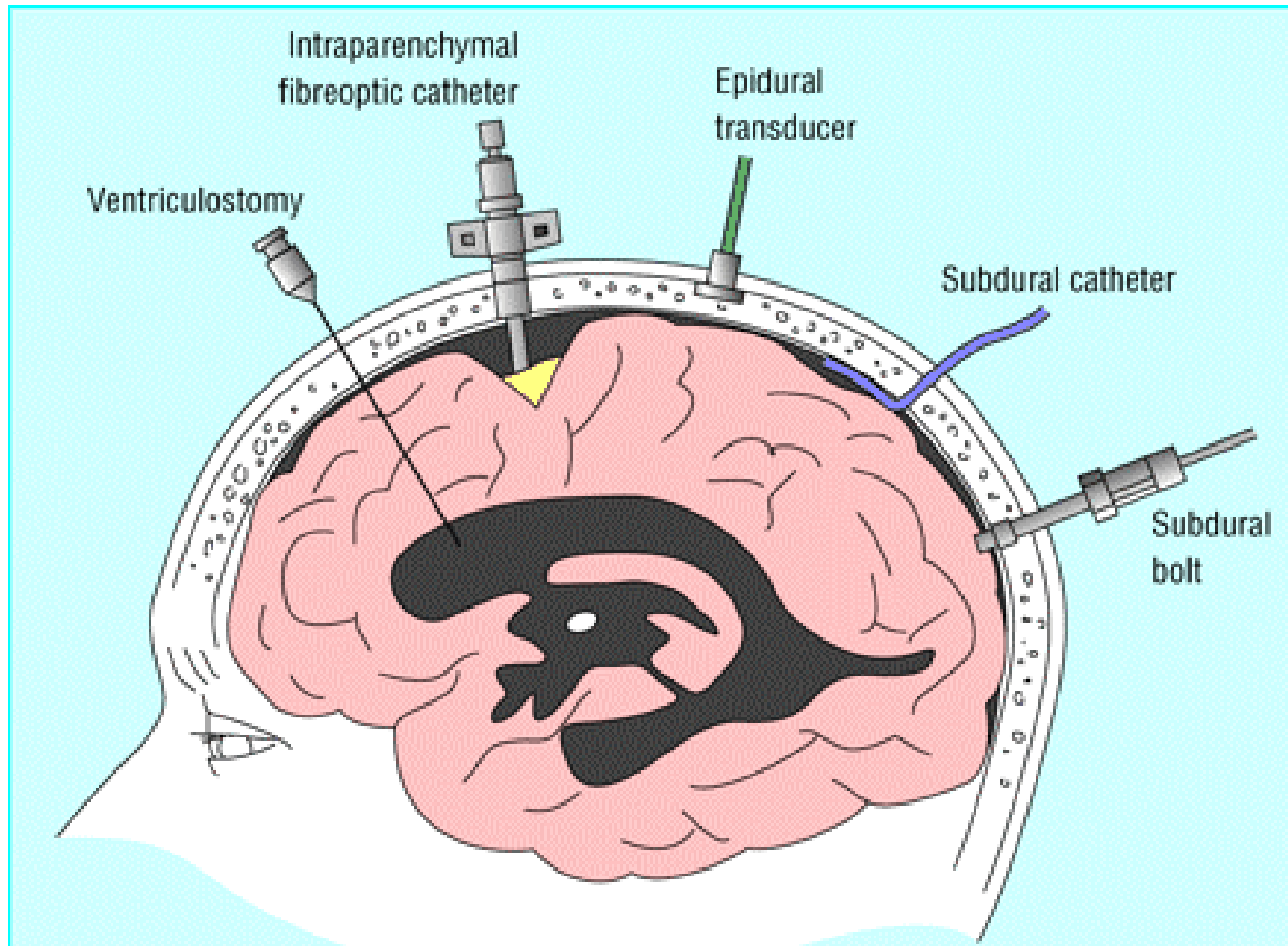
- ICP Monitor indications
 - GCS <8
 - Mechanical Ventilation and Sedation
 - Ability to drain
- What ICP target?
 - ICP <20 is associated with a favorable outcome in several small retrospective pediatric studies.
 - One prospective, double blind, placebo-controlled study that showed better outcome when ICP was kept < 20 (adults too)
 - Few studies that have shown physiologic derangements associated with ICP >20 with respect to diminished cerebral blood flow or pressure volume index, but what impact this has clinically can only be extrapolated.

Eisenberg et al. J Neurosurgery 1988; 69:15-23.

Sharples et al. J Neurology Neurosurgery, and Psychiatry 1995; 58:145-152.

Shapiro K, et al. J Neurosurg 1982; 56:819-825.

ICP Monitoring Options



ICP or CPP

- Is CPP more important, regardless of ICP?
 - Low CPP with poor outcome (retrospect Ped Studies).
 - Donward et al retrospectively found higher mortality in patients with mean CPP < 40 and mean ICP > 20
 - This supported earlier work done by Elias-Jones that again correlated CPP < 40 with poor outcome
 - High CPP better outcome?
 - There seems to be some support in the adult literature that CPP > 80 has beneficial effects

Donward C, et al. J Trauma 2000; 49:654-658.

Elias-Jones AC, et al 1985-90. Archives of Dis Child. 1992; 67:1430-1435.

Intracranial Pressure VII, 1989, pp 839-841.

Head Position/CSF drainage

- HOB 30 degrees
 - In adult TBI studies ICP decreased at this level, without affecting CBF or CPP
 - Improves Jugular venous and CSF drainage
- Ventricular CSF drainage
 - Monroe Kelley Doctrine, lower ICP
 - Documented benefit in adults with greater increase in jugular venous saturations

Feldman Z, et al; J Neurosurg 76:207-211, 1992

Fortune, JB, J Trauma 39:1091-1099, 1995

Sedation

- Facilitate daily care and handling
- Decrease cerebral metabolic demands by diminishing pain and stress
- Can have negative effect with vasodilation and Hypotension- lowering CPP
- Advocate use when ICP monitor in place, with caveat of being less able to follow clinical exam
- Derived from adult data, no good pediatric data that it improves outcome
- Particularly important before procedures

Neuromuscular Blockade

- Not great pediatric data, but most advocate use based on reduction in metabolic demands
- Small pediatric study, showing decreased oxygen consumption (only 6 patients had TBI)
- Prophylactic use has been associated with increased VAP and LOS

Hyperosmolar Therapy

- Mannitol
 - Rheologic Properties-immediate
 - Osmotic Diuretic- 30 minutes
 - Good Literature lacking.
 - Adult Studies- Cochrane review failed to find efficacy over placebo, but smaller studies find 10% reduction in ICP
 - PICU epidemiologic study- increased LOS, no survival benefit
 - Risks: may accumulate in injured brain regions, reverse shift, renal insufficiency sOSM > 320

White et al. Critical Care Medicine 2001; 29:534-540

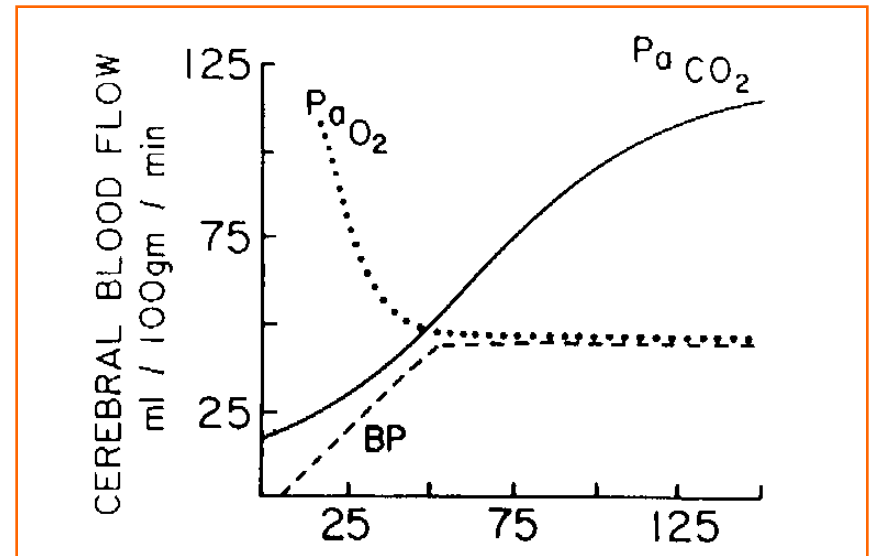
Schierhout Cochrane Database Syst Rev 2000; 2.

Hyperosmolar Therapy

- Hypertonic Saline
 - Given either as bolus doses or continuous infusions to reduce acute rises in ICP
 - Evidence based on a handful of studies showing modest reductions in ICP
 - May lead to shorter length of stay and ventilation
 - Can tolerate higher sOSM >365 without much renal insufficiency; theoretical risk of Extrapontine Myelinolysis
 - No direct comparison studies with mannitol

Hyperventilation

- Hypocapnea, cerebral vasoconstriction, decrease cerebral blood flow
- This reduction may be detrimental to focal areas of injury that rely upon adequate CBF for perfusion



- Prophylactic hyperventilation ($CO_2 < 25$) associated with worse outcomes (RCT in adults)
- Goal Normocapneic, with acute hyperventilation used for impending herniation

Muizelaar et al Journal Neurosurgery 1991; 75: 731-739.

Adelson et al.

Barbiturates

- Mechanism of controlling intracranial hypertension
 - lowering metabolic demands
 - altering vascular tone
- Evidence for children from few small case control studies in 1980's- Barbiturate coma
- Detrimental effects on hemodynamics- lower BP and CPP

Temperature Control

- Avoid Fever!!
 - Occurs in 30% of Pediatric TBI patients
 - Increases Metabolic Demands
 - Worse outcome

Temperature Control : to cool or not to cool?

- Clifton GL, J Neurotrauma 1993
 - Phase II RCT showed 16% increase in good recovery/moderate disability in cooled group
- Marion DW, NEJM 1997
 - Small RCT (80 adults)
 - Cooled 33°C x 24 hrs
 - “Trend toward better outcome”
- Clifton GL, NEJM 2001
 - RCT 392 adults with closed head injury
 - Cooled to 33°C for 48 hrs
 - Cool group lower ICP
 - No change in outcome (poor 60% in both groups)
 - No change in mortality (27/27%)

Temperature Control : to cool or not to cool?

- Hypothermia (Moderate 32-34 °C)
 - Meta analysis and retrospective studies in adults showed some benefit.
 - Did not affect outcome in Adult RCT, but younger patients did better than older patients
 - Phase II RCT in Children demonstrated safety, but no efficacy benefit
 - Phase III RCT in Children no benefit

Temperature Control : to cool or not to cool?

- Shankaran S, NEJM 2005
 - RCT 239 full term infants with moderate/severe encephalopathy from perinatal injury
 - Cooled to 33.5°C for 72 hrs
 - Hypothermic group less disability and death
- Gluckman PD, Lancet 2005
 - RCT 234 infants with moderate/severe encephalopathy from perinatal injury
 - Cooled 34-35°C for 72 hrs
 - No benefit overall or in severe injury, may benefit less severe pts.

Moderate Hypothermia in Pediatric TBI

- Hutchinson JS, NEJM 2008
 - RCT 225 children ages 1-17 with presenting GCS \leq 8, CT with TBI, mechanically ventilated
 - Cooled to 32.5°C for 24 hours
 - 6 month unfavorable outcome 31% vs. 22%
 - Mortality 21% vs. 12%

Moderate Hypothermia in Pediatric TBI

Outcome	Hypothermia Group (N=108)	Normothermia Group (N=117)	Relative Risk or Absolute Difference (95% CI)	P Value
Primary				
PCPC score 4–6 — no./total no. (%)	32/102 (31)	23/103 (22)	1.41 (0.89 to 2.22)	0.14
Secondary				
Overall mortality — no. (%)	23 (21)	14 (12)	1.40 (0.90 to 2.27)	0.06
Duration of care — days				

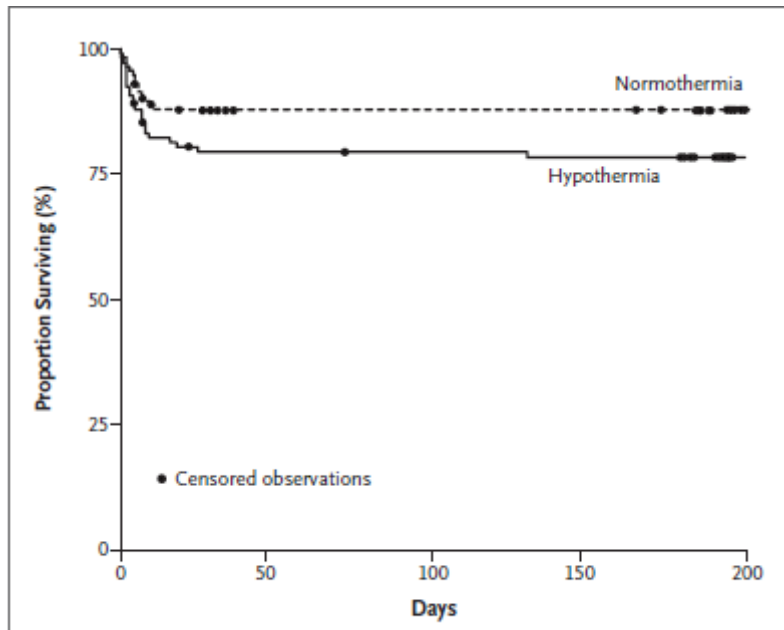


Figure 2. Kaplan-Meier Estimates of Survival.

	Hypothermia Group (N=108)	Normothermia Group (N=117)	P Value
Physiological variables at 25 to 72 hr			
ICP — mm Hg (95% CI)	17.1±7.1 (15.6 to 18.5)	17.4±10.7 (15.4 to 19.4)	0.77
CPP — mm Hg (95% CI)	60.8±7.8 (59.2 to 62.4)	66±10.8 (64 to 68.1)	<0.001
Mean blood pressure — mm Hg (95% CI)	77.7±7.6 (76.2 to 79.2)	83.4±8 (81.9 to 84.9)	<0.001
Heart rate — beats/min (95% CI)	100.7±18.3 (97.1 to 104.3)	105.3±18.2 (101.9 to 108.6)	0.07
Adverse events — no. (%)			
Hypotension			
0–24 hr	27 (25)	18 (15)	0.07
25–72 hr	49 (45)	38 (32)	0.047

Outcomes

- GCS probably has highest predictive ability (<5 first 24 hours)
- Age dependent
- Severe TBI (GCS < 8)
 - Age 5-10 good outcome in 70%
 - Age <4 death rates as high as 60%, with poor outcome with rest (mostly because of mechanism)
 - Inflicted and gun shot wounds do worse

Levin HS, et al. Neurosurgery 1982

Peterson B, et al. CCM 2000

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