Neurophysiology in Critical Care

Noosa April 2017

Monitoring

- Physical examination
- ICP measurement
- Electrophysiology
  - BIS
  - EEG
  - aEEG
  - EPs
- Assessment of Blood Flow and/or Metabolism
  - Xenon
  - Trans Cranial Doppler
  - Jugular Bulb Oximetry SjvO2
  - NIRS
  - Microdialysis
  - MR Spectroscopy

Physical Exam

TABLE 33–2 Glasgow Coma Scale for Assessment of Coma in Infants and Children

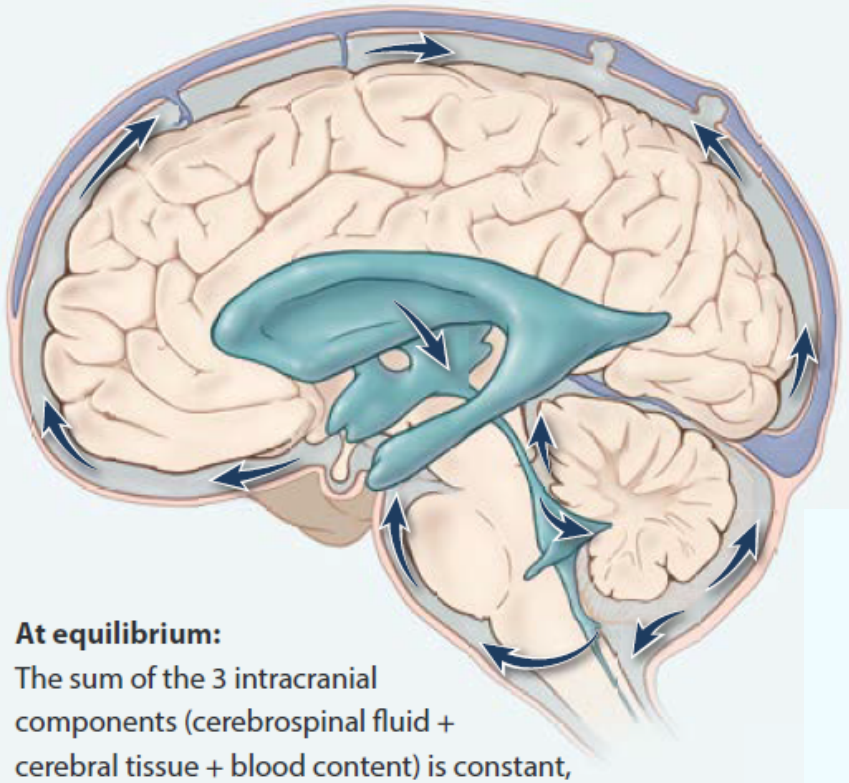
CATEGORY	SCORE*	INFANT AND YOUNG CHILD CRITERIA	OLDER CHILD AND ADULT CRITERIA
Eye opening	4	Spontaneous opening	Spontaneous
	3	To loud noise	To verbal stimuli
	2	To pain	To pain
	1	No response	No response
Verbal response	5	Smiles, coos, cries to appropriate stimuli	Oriented to time, place, and person; uses appropriate words and phrases
	4	Irritable; cries	Confused
	3	Inappropriate crying	Inappropriate words or verbal response
	2	Grunts, moans	Incomprehensible words
	1	No response	No response
Motor response	6	Spontaneous movement	Obeys commands
	5	Withdraws to touch	Localizes pain
	4	Withdraws to pain	Withdraws to pain
	3	Abnormal flexion (decorticate)	Flexion to pain (decorticate)
	2	Abnormal extension (decerebrate)	Extention to pain (decerebrate)
	1	No response	No response

Serial assessment of:

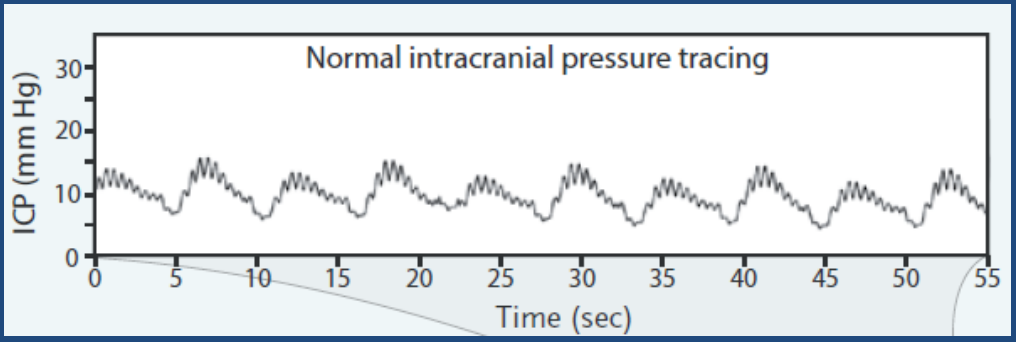
- Recognition and response to family members
- Following command
- Symmetry of movement
- Pupillary reactions and extraocular movements

ICP Monitoring

A Intracranial pressure under normal conditions, sagittal section



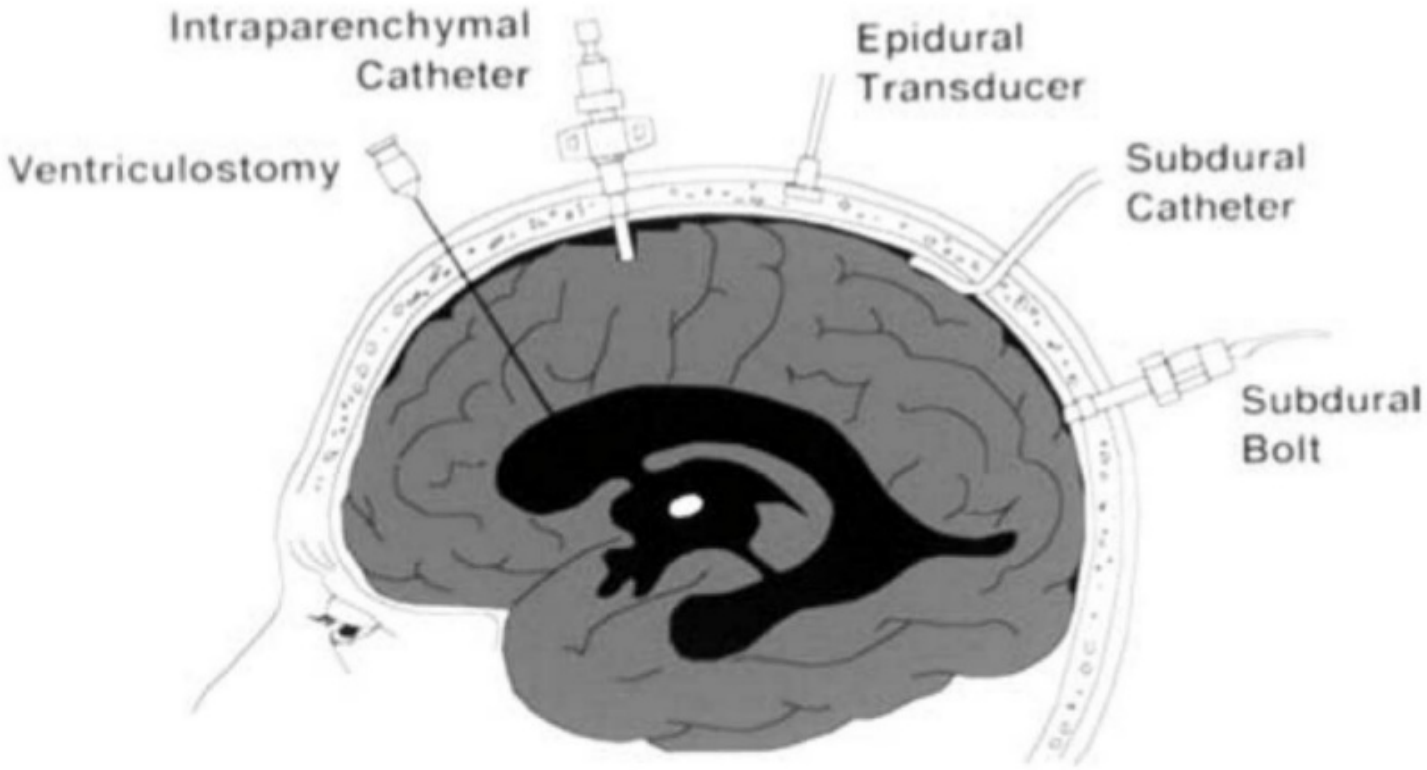
At equilibrium:
The sum of the 3 intracranial components (cerebrospinal fluid + cerebral tissue + blood content) is constant, corresponding to a normal (10–15 mm Hg) intracranial pressure.

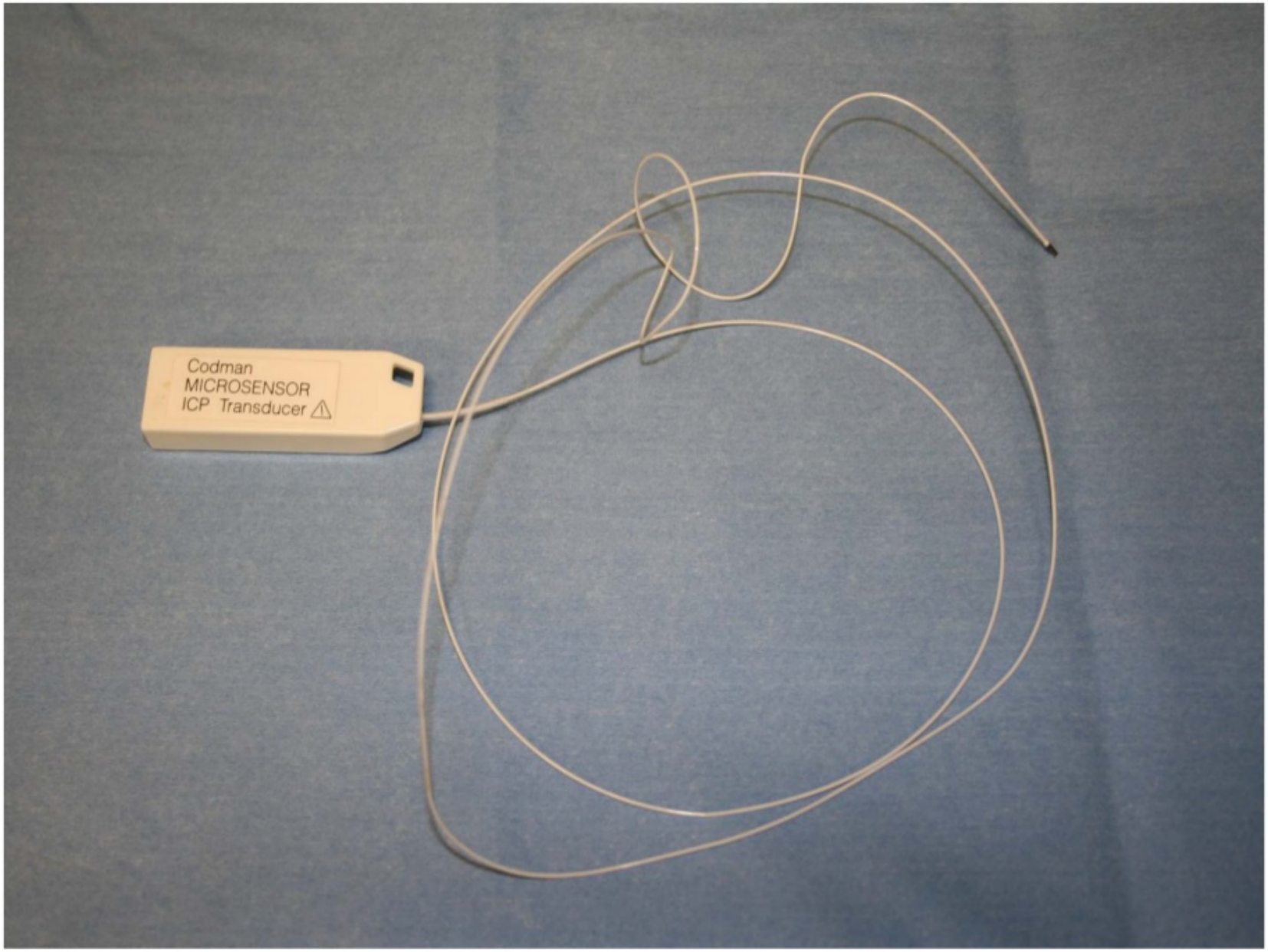


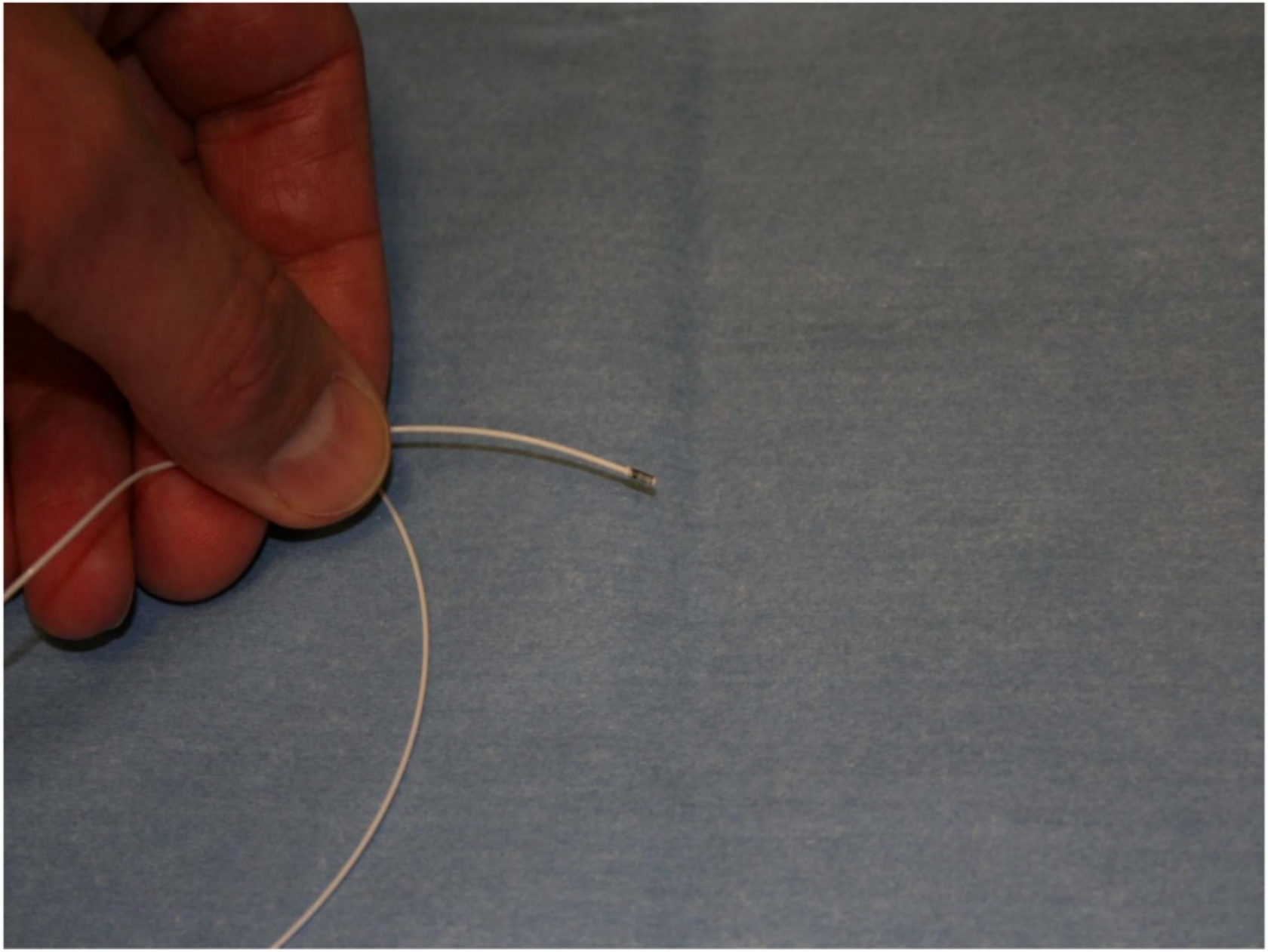
Intracranial Pressure

- ICP is the pressure inside the cranial vault relative to atmosphere
- The intracranial contents can be divided into four compartments
  - Solid material ~10%
  - Tissue Water ~75%
  - CSF (150ml) ~10%
  - Blood (50-75ml) ~ 5%
- Raised ICP causes brain damage by reducing CPP or by focal compression of brain tissue due to distortion and herniation of intracranial contents

Methods to measure ICP




Codman
MICROSENSOR
ICP Transducer



Codman
ICP
15
ICP Express

Ideal ICP monitor

- No limitation on duration of monitoring
- Minimal drift
- Allows in vivo recalibration
- Allows waveform analysis
- Easy to insert and read
- Cost-effective

UPS/T/IO
ESS/T/IO

Indications for ICP monitoring

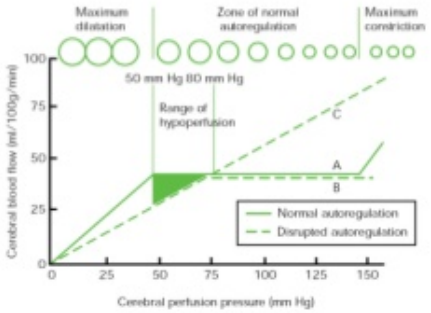
- Severe head injury (GCS 3-8)
- Moderate head injury (GCS 9-12)
  if
  - anesthetised/sedated
  - abnormal CT scan
- Aim for ICP <20mmHg

Complications

- Infection
- Haemorrhage
- Malfunction
- Malposition

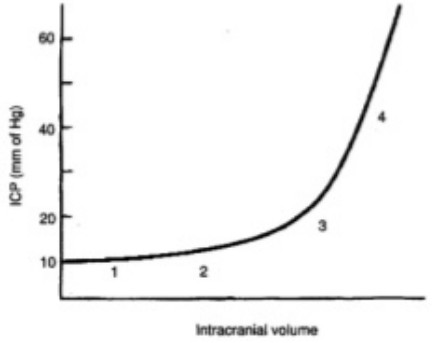
ICP Monitoring

Cerebral Autoregulation



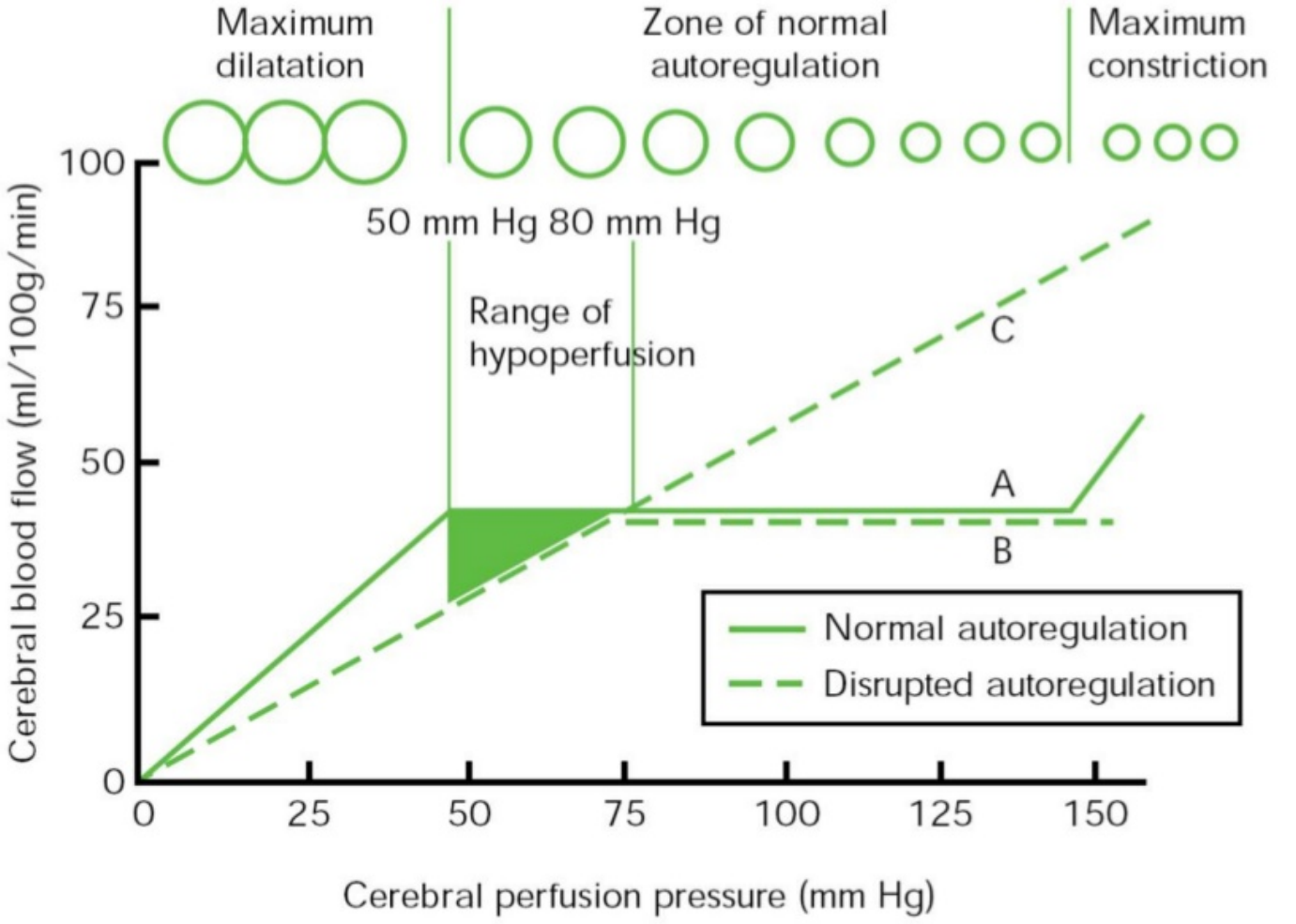
Vascular reactivity

Craniospinal Compliance

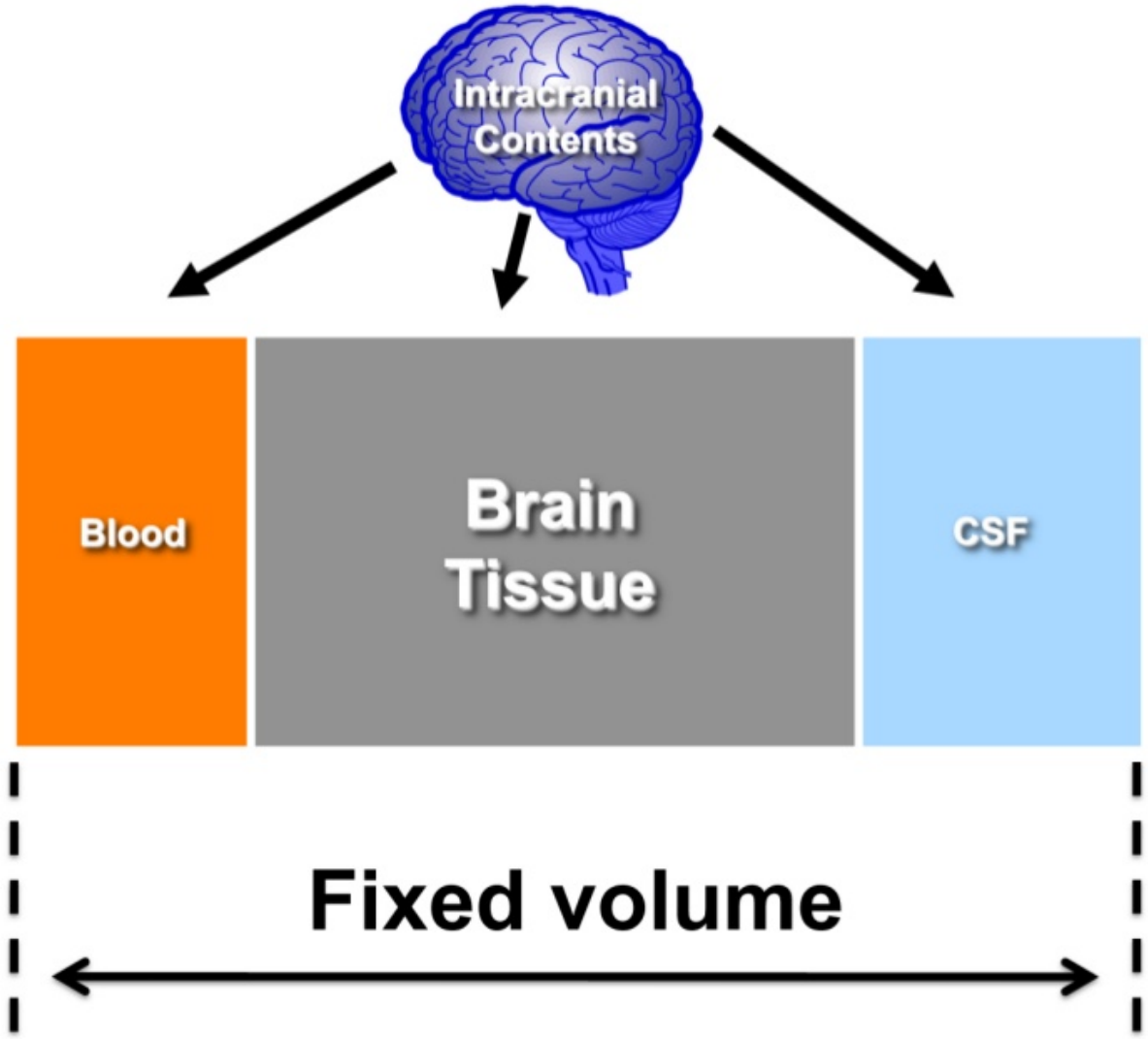


Pressure-Volume regulation

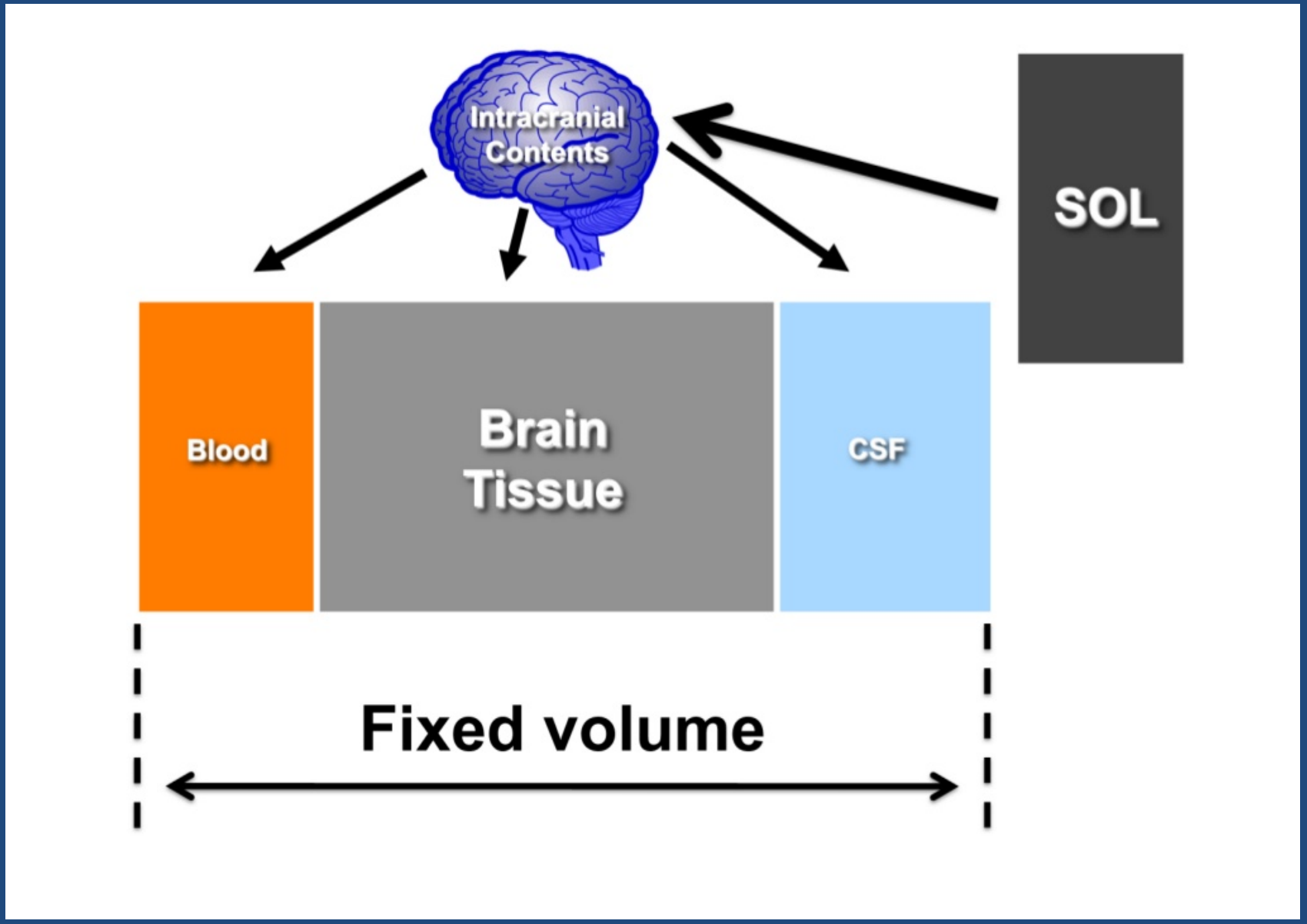
Cerebral Autoregulation



Dunn et al. JNNP 2002; 73: i23-i27

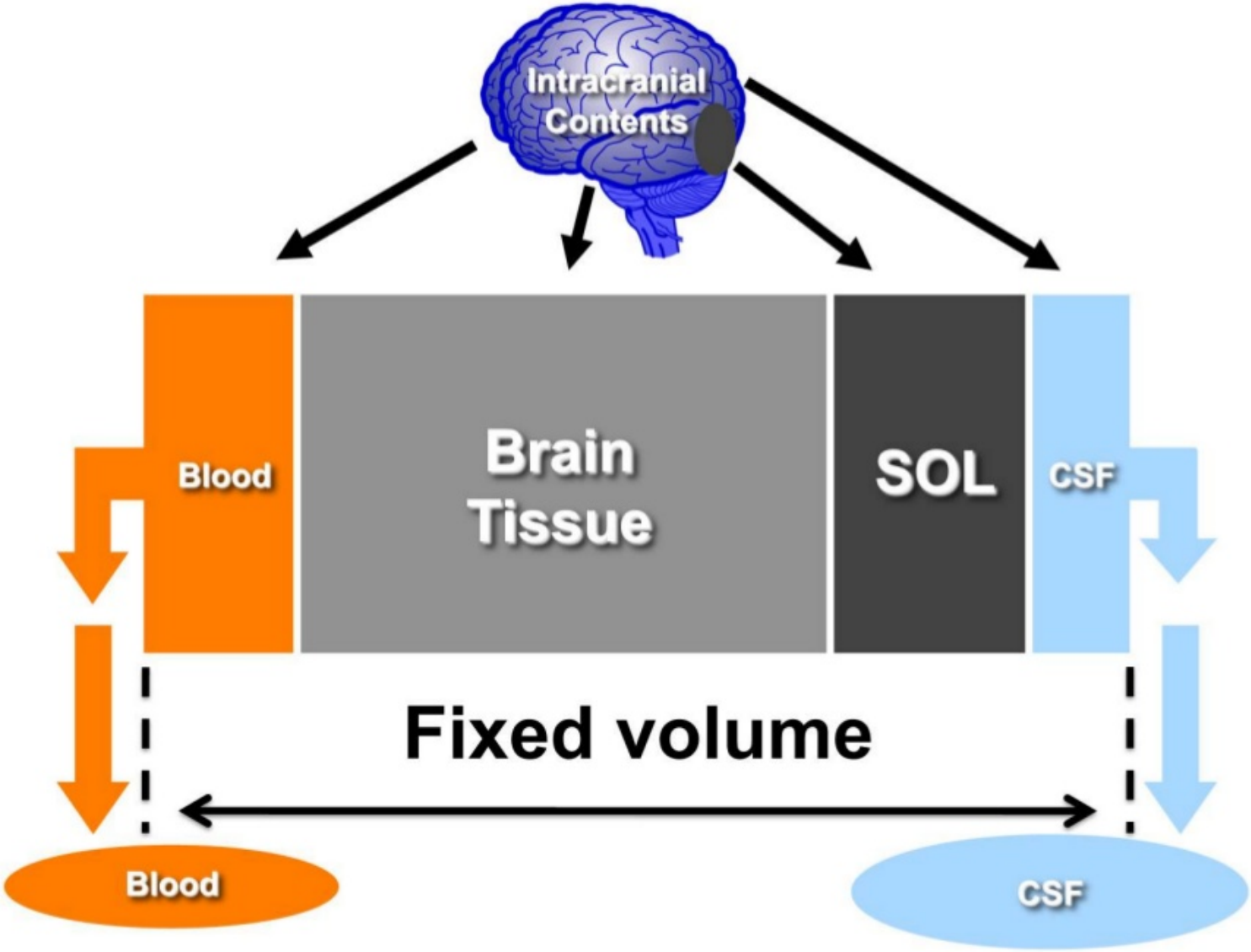


Monro Kelli Doctrine



Monro Kelli Doctrine

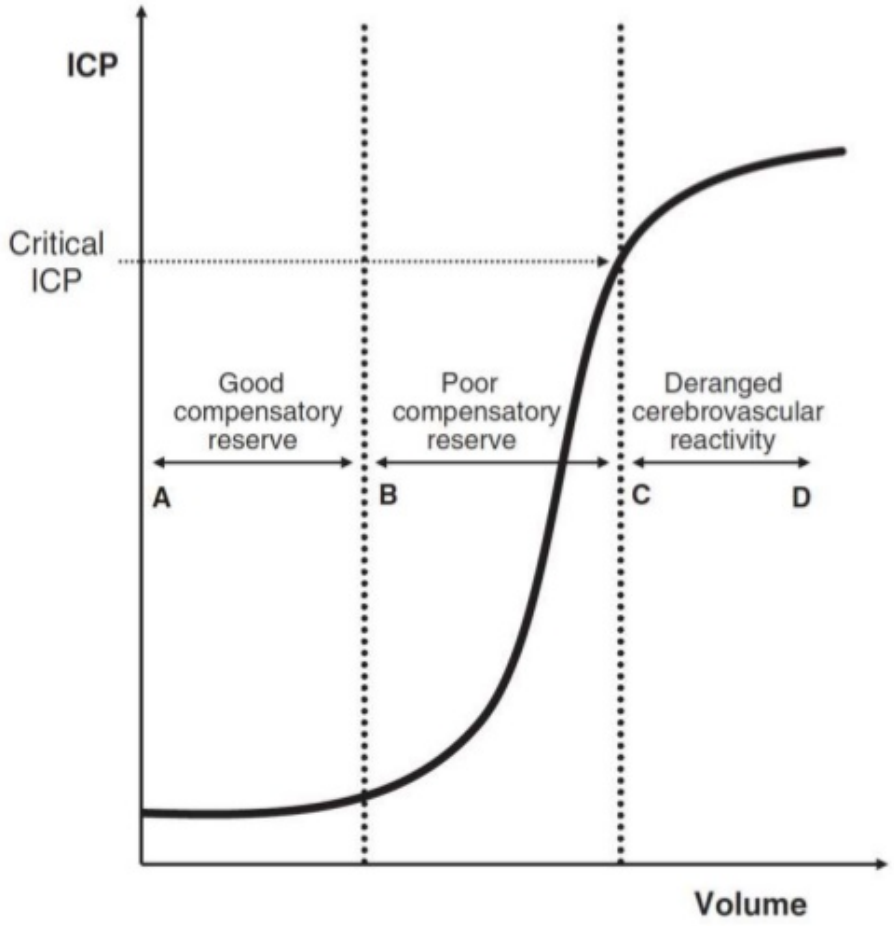
Right
Left

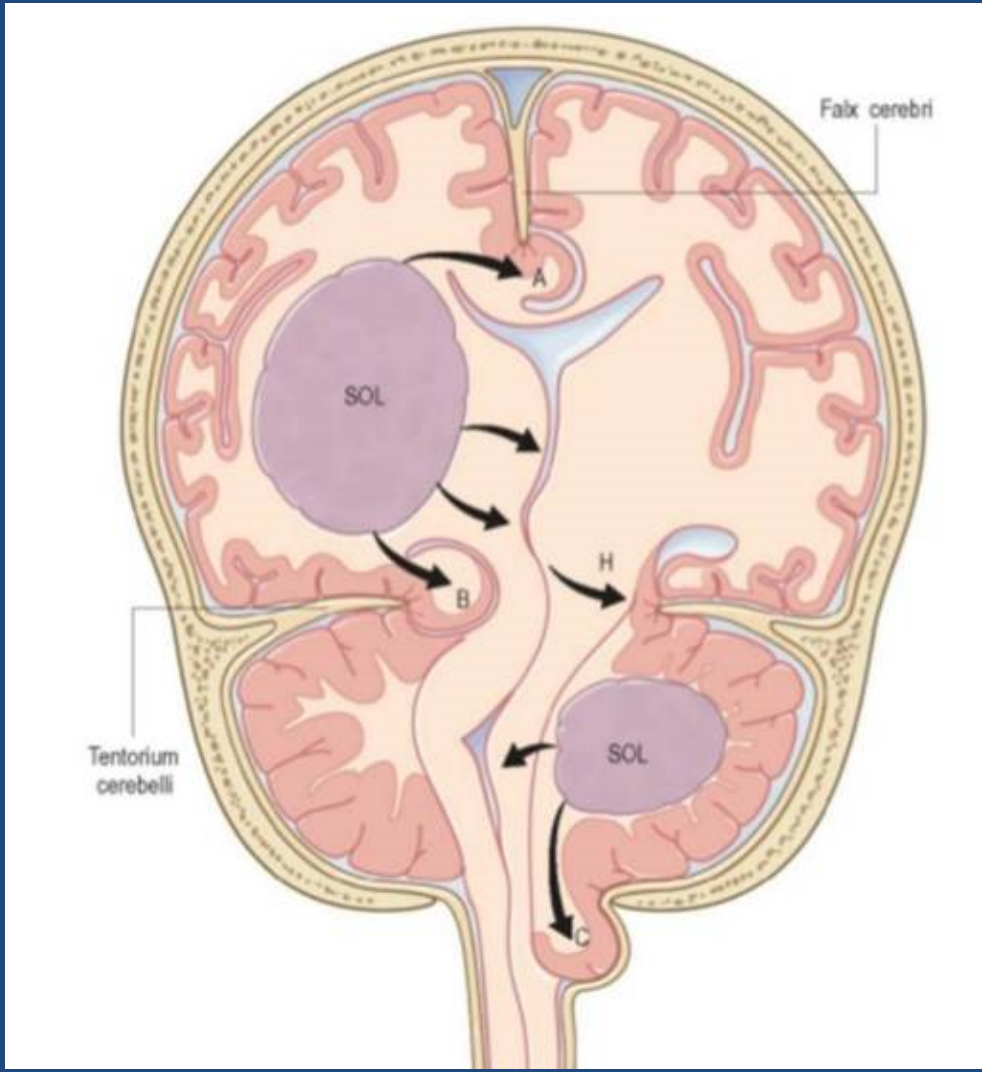


Monro Kelli Doctrine

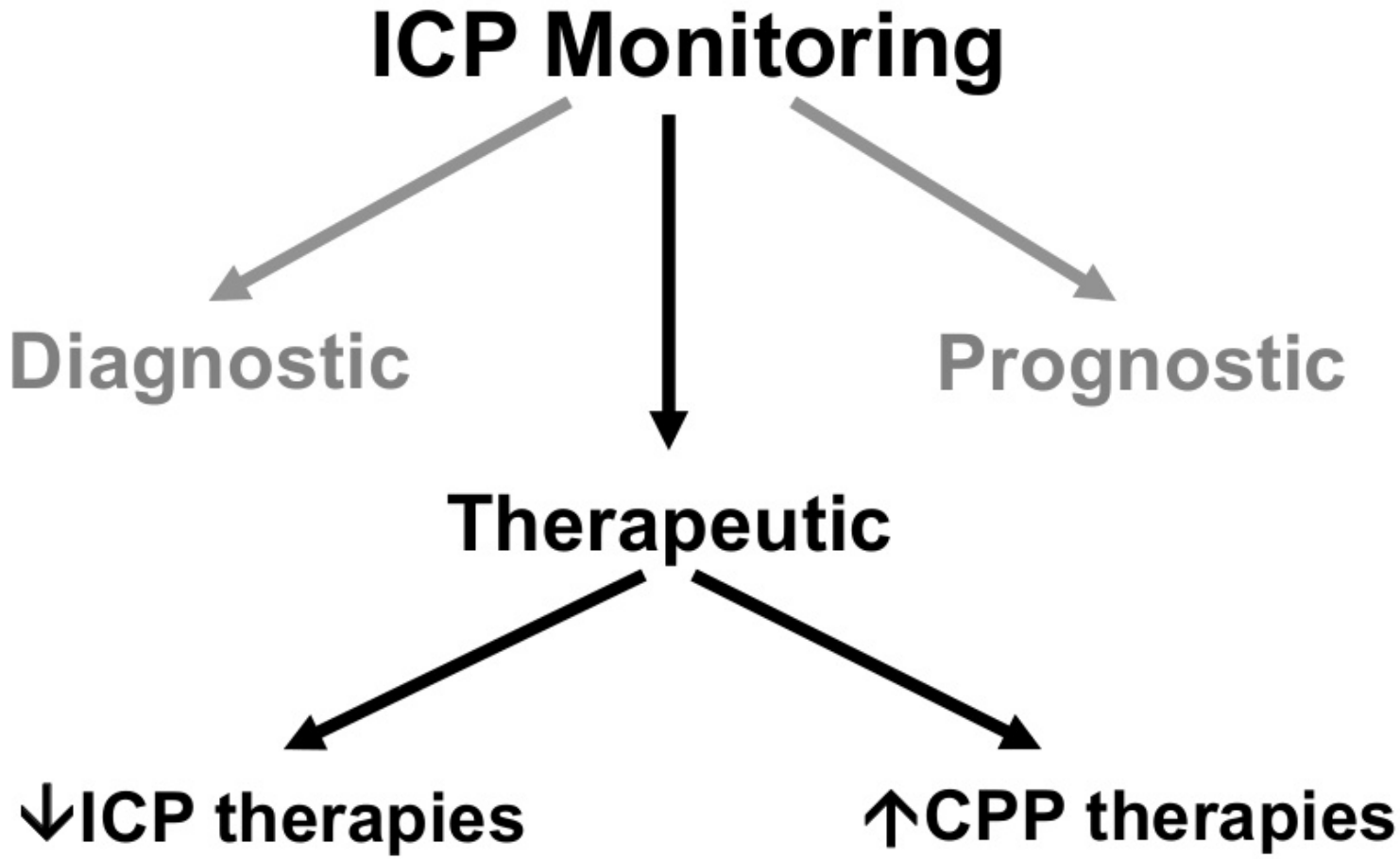
Pressure-Volume regulation

(Spatial compensation)





A	Herniation of cingulate gyrus under the falx
B	Tentorial herniation of parahippocampal gyrus
C	Herniation of cerebellar tonsils through foramen magnum
H	Compression of cerebral peduncle against free edge of tentorium cerebelli


ICP Monitoring
Diagnostic
Prognostic
Therapeutic
↓ICP therapies
↑CPP therapies

Traumatic Intracranial Hypertension: Rx

- Avoid exacerbating factors (fever, hypoxia, hypotension, hypercarbia)
- Surgical evacuation if possible
- First Tier
  - Analgesia, sedation and muscle relaxation
  - 30° head up, avoid neck lines
  - Continuous CSF drainage
  - Hyperosmolar Rx
  - Optimise CPP
  - Mild hyperventilation
- Second Tier
  - Barbiturates
  - Hypothermia
  - Decompressive craniectomy

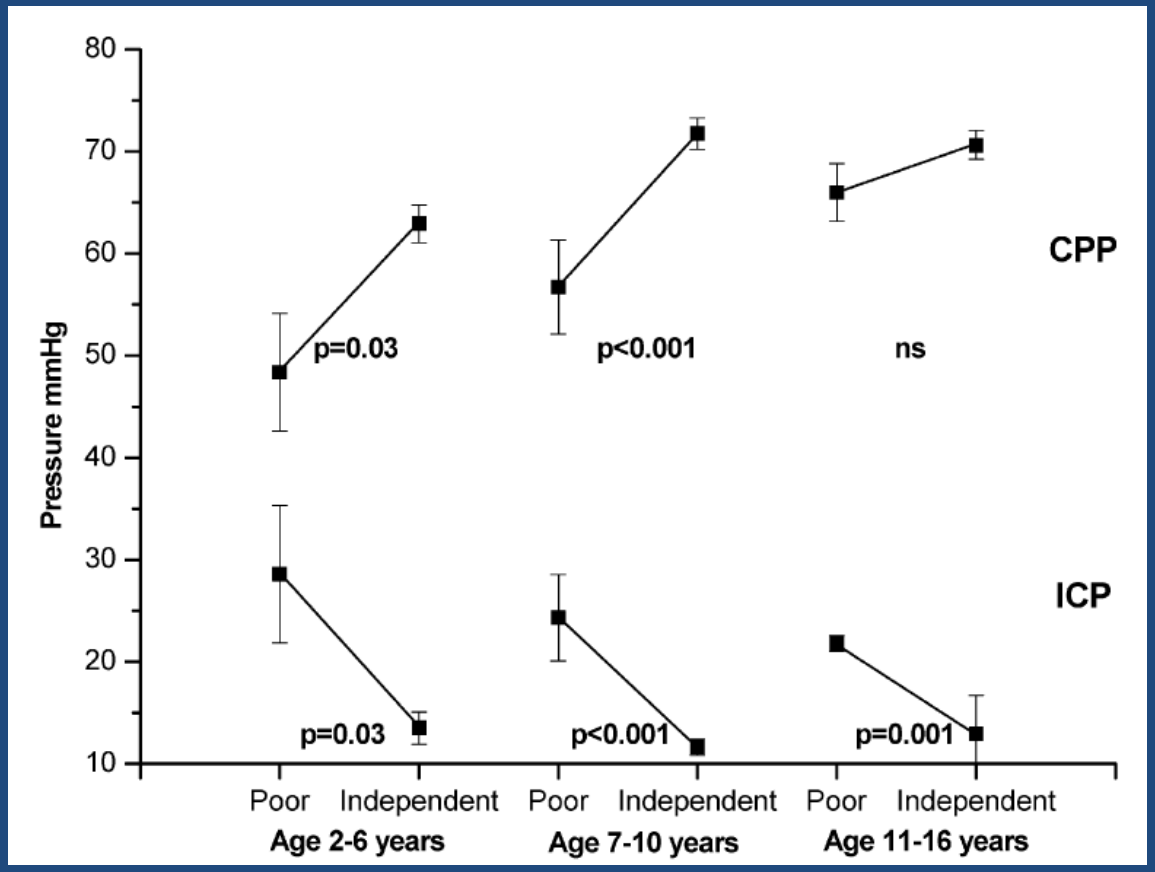
Modified 2007 BTF Guideline
ICP- accepted limits

	ICP	CPP
Adults	<20mmHg	60-70mmHg
Children	< 15 mmHg	50-60mmHg
Infants	5-10 mmHg	40-50mmHg

Age-related differences in intracranial pressure and cerebral perfusion pressure in the first 6 hours of monitoring after children's head injury: association with outcome

I. R. Chambers Childs Nerv Syst (2005)

- 235 UK children 1982-2003 with ICP measured for TBI mean measures for first 6h
- 104 good outcome, 71 moderately disabled, 29 severely disabled and 31 deaths



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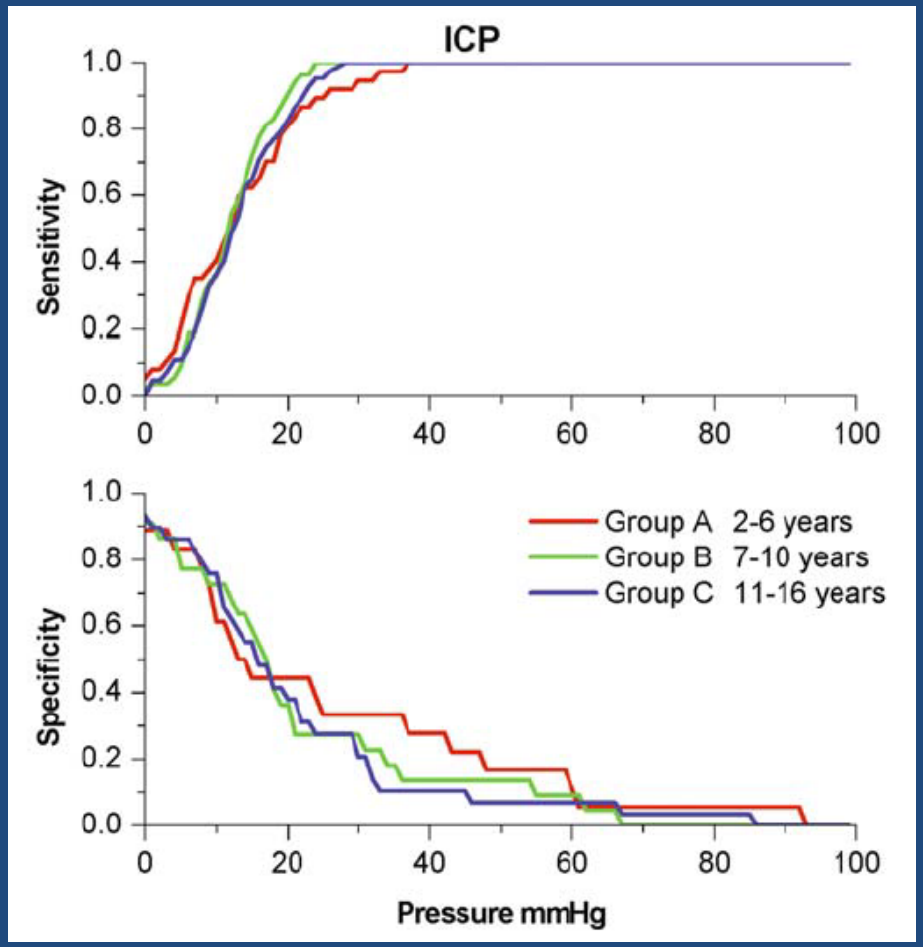
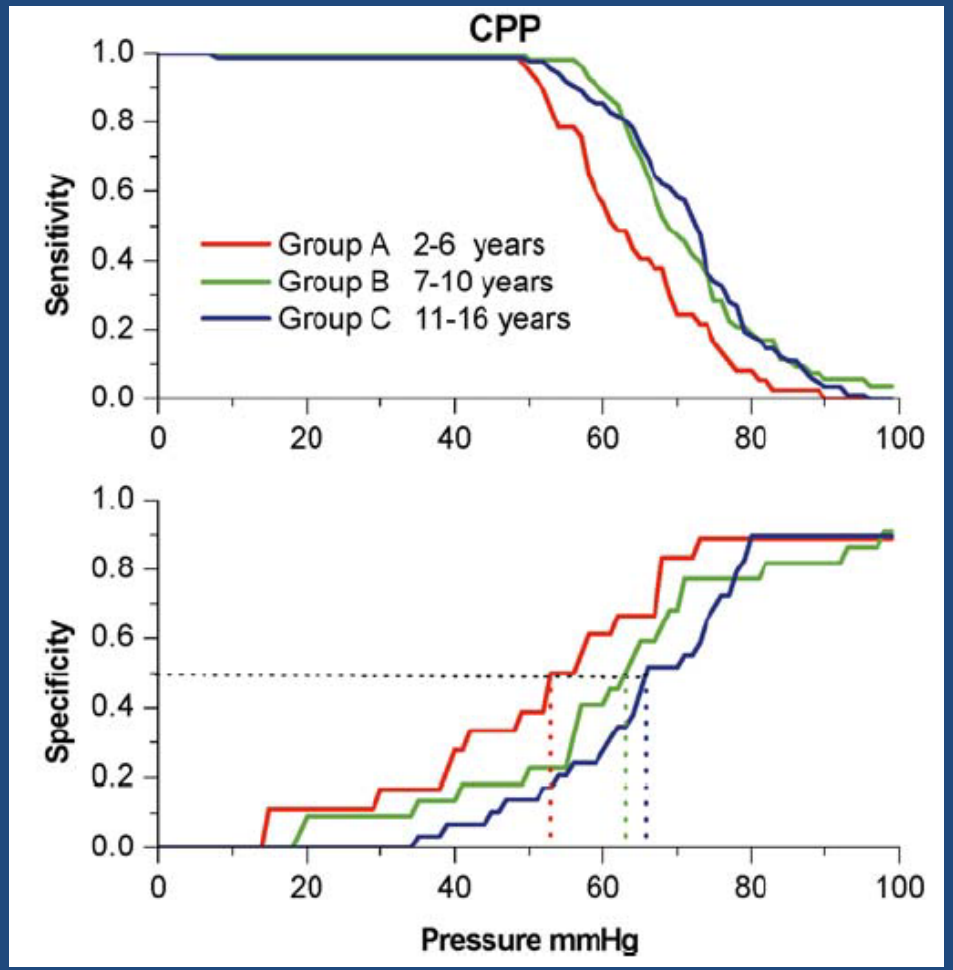




A Trial of Intracranial-Pressure Monitoring in Traumatic Brain Injury

N Engl J Med 2012;367:2471-81

- 4 Bolivian and 2 Ecuadorian hospitals with intensivists, 24h CT and neurosurg cover
- Inclusion: TBI, ≥ 13y, GCS 3-8 (with motor component 1-5 if pt intubated) (NB.GCS 3 + fixed and dilated or injury believed to be unsurvivable excluded)
- Multicentre parallel-group trial with randomisation to ICP monitoring or imaging and exam
- 528 eligible, 204 excluded, recruited Sept 08→Oct 2011
- Primary outcome: composite of 21 components (av%?)
  - Survival
  - Duration and level of impaired consciousness
  - Functional status and orientation 3mo post injury
  - Functional and neuropsych status 6mo post injury

A Trial of Intracranial-Pressure Monitoring in Traumatic Brain Injury

N Engl J Med 2012;367:2471-81

Table 2. Clinical Outcomes *

The value of knowing the precise intracranial pressure is not being challenged here, nor is the value of aggressively treating severe traumatic brain injury being questioned. Rather our data suggest that a reassessment of the role of manipulating monitored intracranial pressure as part of multimodality monitoring and targeted treatment of severe traumatic brain injury is in order.

Effect of hyperventilation on regional cerebral blood flow in head-injured children.

Skippen et al, CCM Aug 1997

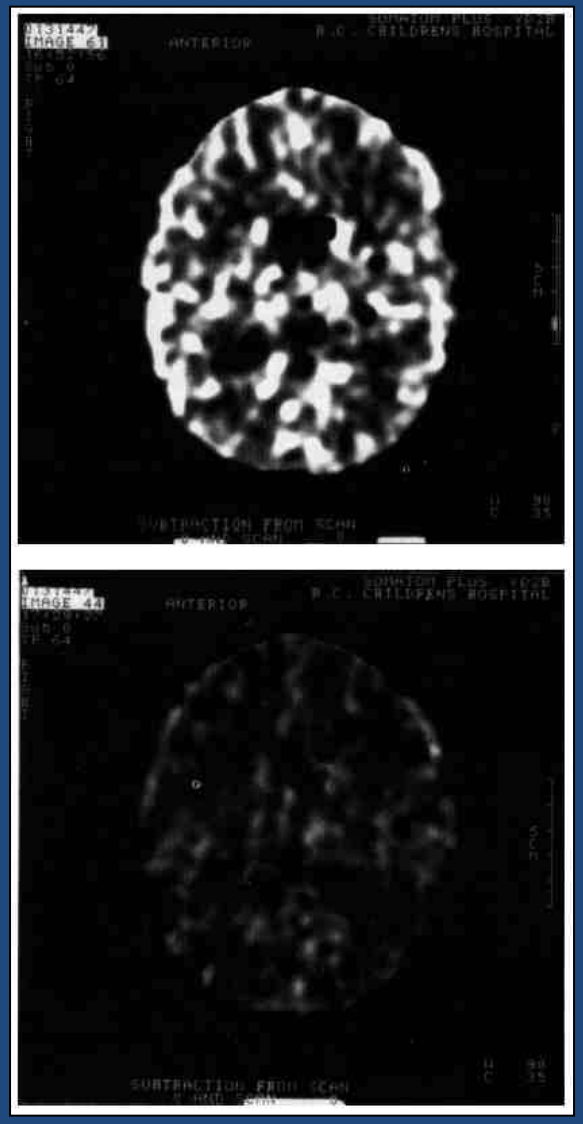
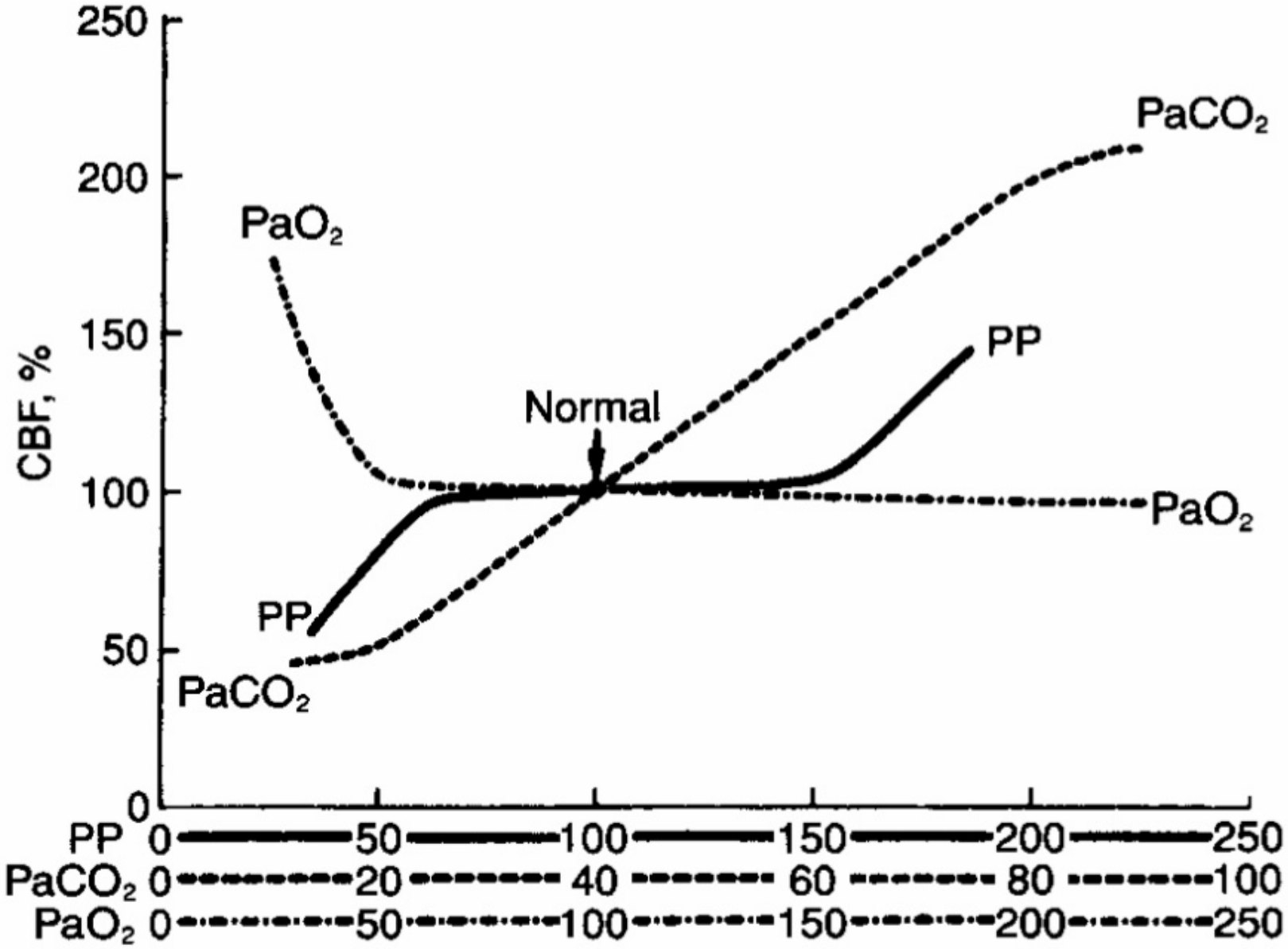


Figure 6 . Xenon-enhanced CT flow images from a child 16 h post MVA. GCS O/A 5

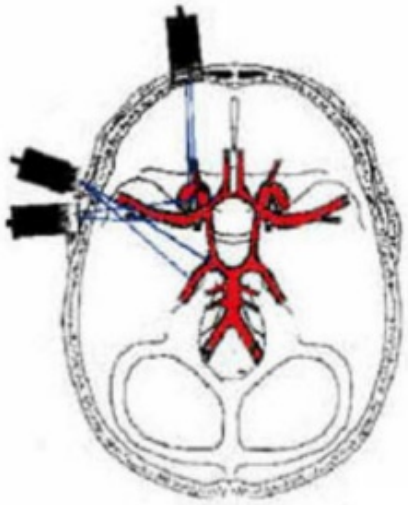
Top: Scan performed at P_aCO_2 45, ICP 44, CPP 54, and global CBF 59 mL/min/100 g.

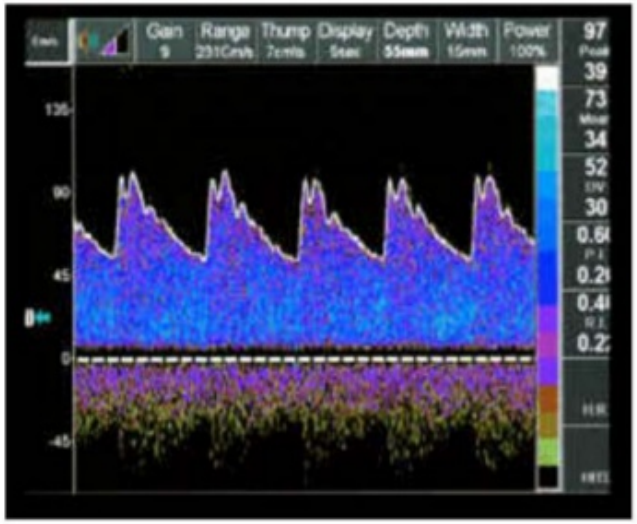
Bottom: Scan at same level, 15 mins after hyperventilation, shows clinically important cerebral ischemia. Scan performed at P_aCO_2 30, ICP 15, CPP 82 and global CBF 14 mL/min/100 g. (Several local areas of this scan had regional cerebral blood flow rates of <10 mL/min/100 g.)


250
200
150
100
50
0
CBF, %
PaO2
PaCO2
PP
Normal
PaO2
PP
PaCO2
PP 0 50 100 150 200 250
PaCO2 0 20 40 60 80 100
PaO2 0 50 100 150 200 250

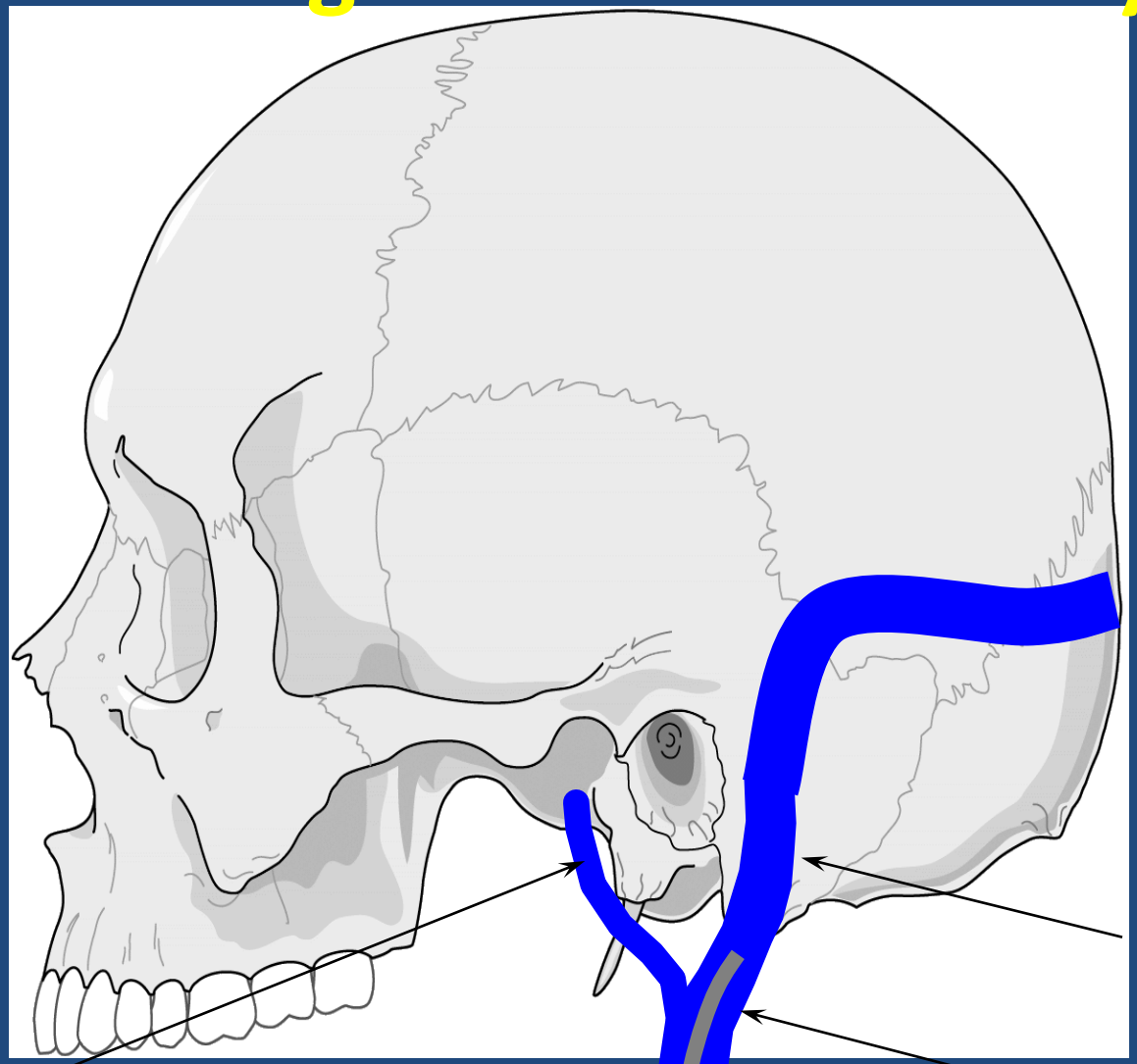
Transcranial doppler (TCD)

- Non-invasive method of assessing the state of the intracranial circulation
- Velocity can be measured in the middle, anterior and posterior cerebral arteries, the ophthalmic artery and the internal carotid
- Inverse relationship between the severity of head injury and middle cerebral artery velocity
- Useful for detecting vasospasm





Jugular bulb oximetry



Jugular bulb oximetry

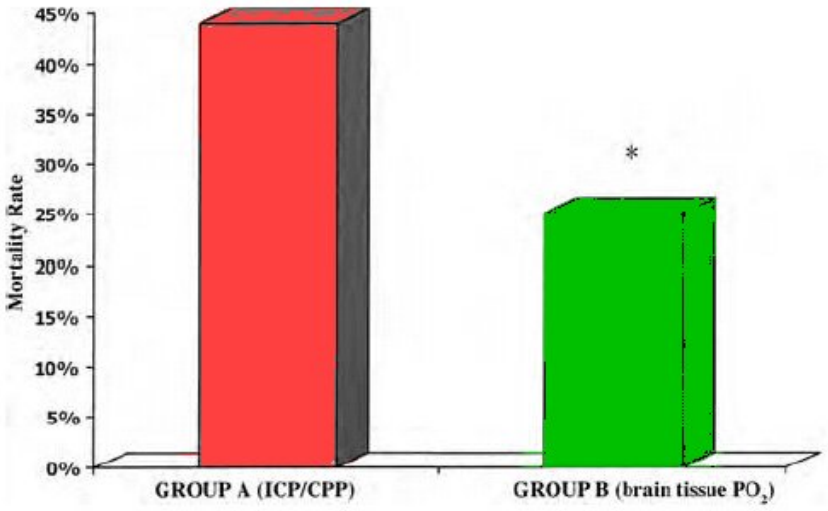
- Sampling catheter inserted into internal jugular vein directed upwards, so that tip rests in the jugular bulb at base of brain
- Normal mixed venous oxygen saturation range ($S_{jv}O_2$) 50-70%
- $S_{jv}O_2$ falls when there is imbalance between oxygen consumption and delivery
- A fall in $S_{jv}O_2$ but maintained CPP, signifies increased cerebrovascular resistance
- An increase in $S_{jv}O_2$ to 85% implies either hyperaemia, shunting or brain death

Reduced mortality rate in patients with severe traumatic brain injury treated with brain tissue oxygen monitoring

Michael F. Stiefel, M.D., Ph.D., Alejandro Spiotta, M.D., Vincent H. Gracias, M.D., Alicia M. Garuffe, M.S.N., Oscar Guillamondegui, M.D., Eileen Maloney-Wilensky, M.S.N., Stephanie Bloom, M.S.N., M. Sean Grady, M.D., and Peter D. LeRoux, M.D.

Department of Neurosurgery and Division of Trauma Surgery and Surgical Critical Care, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

J Neurosurg 103:805–811, 2005



Bar graph illustrating the mortality rates in patients who received traditional ICP/CPP therapy (Group A, 25 patients) or combined ICP/CPP and brain tissue PO_2 treatment (Group B, 28 patients). *$p < 0.05$.

neurocritical care society Neurocrit Care
DOI 10.1007/s12028-011-9621-9 August 2011

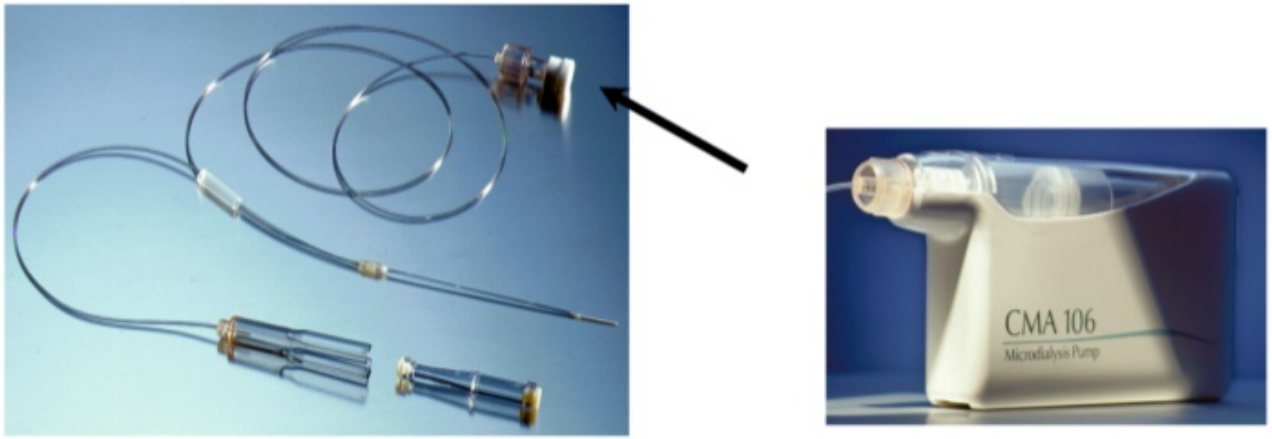
REVIEW

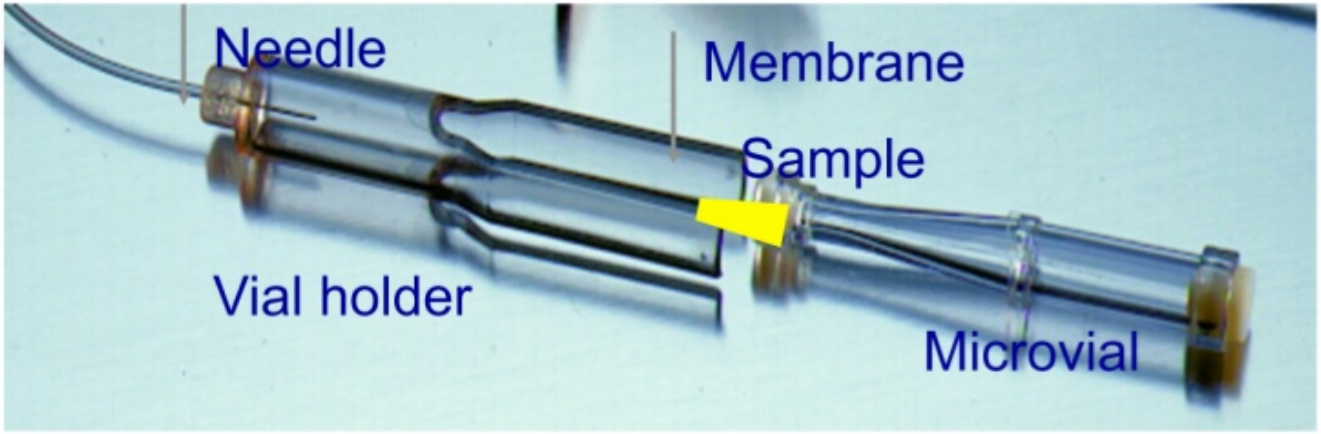
Brain Tissue Oxygen-Based Therapy and Outcome After Severe Traumatic Brain Injury: A Systematic Literature Review

Raj Nangunoori · Eileen Maloney-Wilensky · Michael Stiefel · Soojin Park · W. Andrew Kofke · Joshua M. Levine · Wei Yang · Peter D. Le Roux

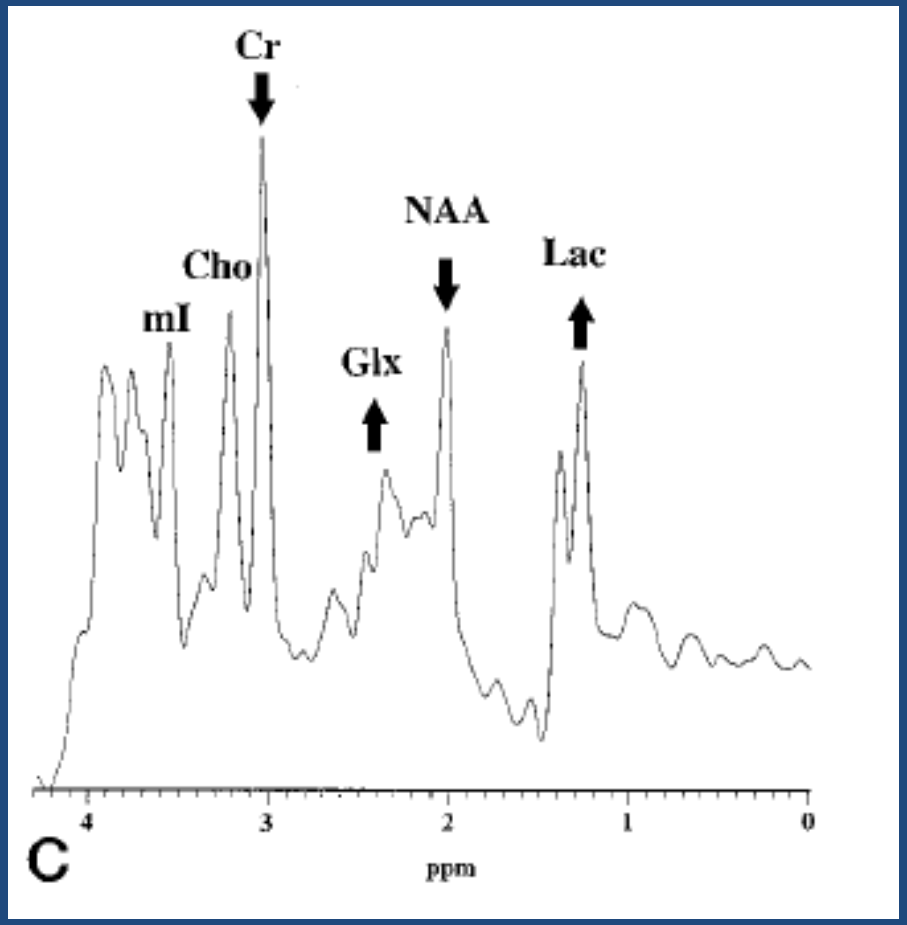
	Favourable	Unfavourable
ICP/CPP	42%	58%
PbtO2	61%	39%

Cerebral microdialysis





MR Spectroscopy



- Single time point
- Localised volume of brain tissue
- Quantitate:
  - Lactate / pyruvate
  - Neurotransmitters
  - Markers of neuronal injury (NAA)
  - Glial destruction (choline compounds)

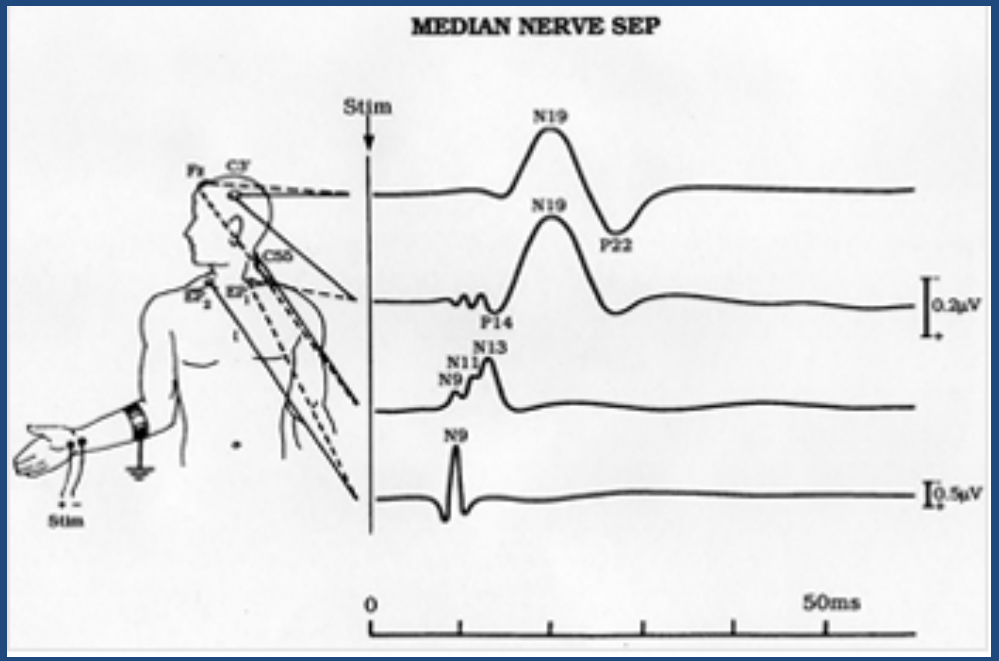
Electrophysiology: BIS

BIS Index Range and Clinical State

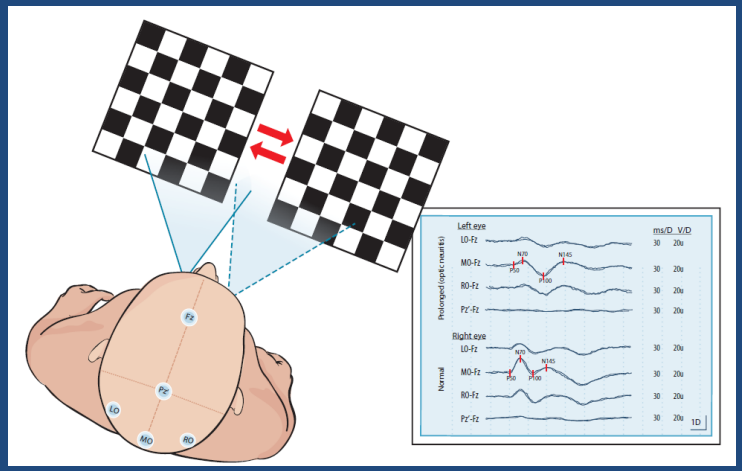
BIS INDEX	CLINICAL STATE
100	Awake
80	Light/Moderate Sedation
60	General Anesthesia
40	Deep Hypnotic State
20	Burst Suppression
0	Flat Line EEG

- Two surface electrodes placed over frontal cortex and examines power, frequency and phase of EEG signal to generate BIS index
- ICU series have failed to demonstrate good correlation with bedside sedation scores –> not standard
- Possible role in paralysed patients
- Applicability in situation of evolving brain injury uncertain

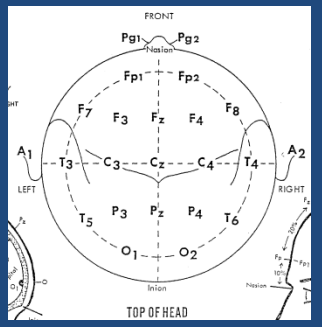
Electrophysiology: Evoked Potentials



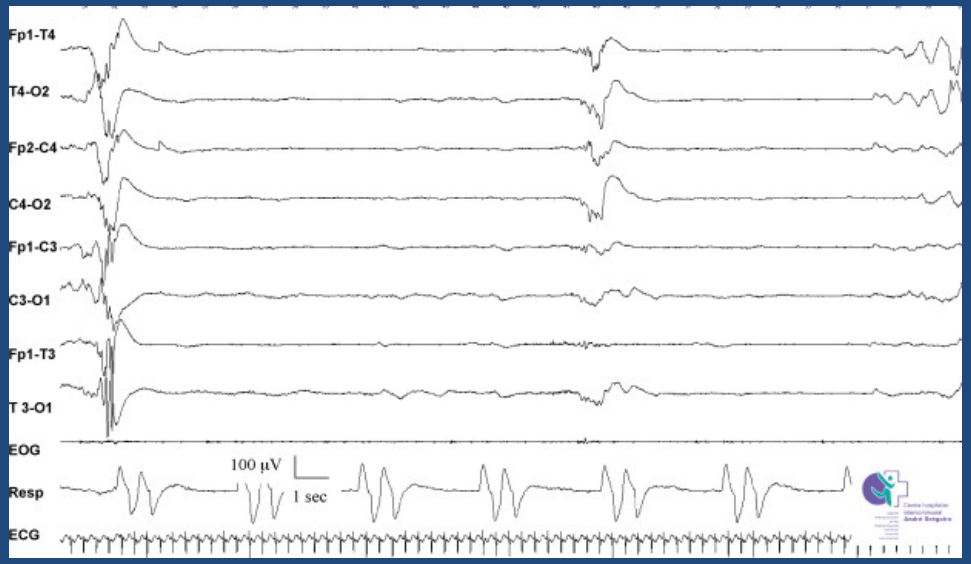
Best studied in ICU are SSEPS where peripheral stimulus applied and then presence, amplitude and latency of cortical response examined
Cortical component has good correlation with injury post trauma or hypoxia ischaemia
Unaffected by sedation
Requires significant technical expertise

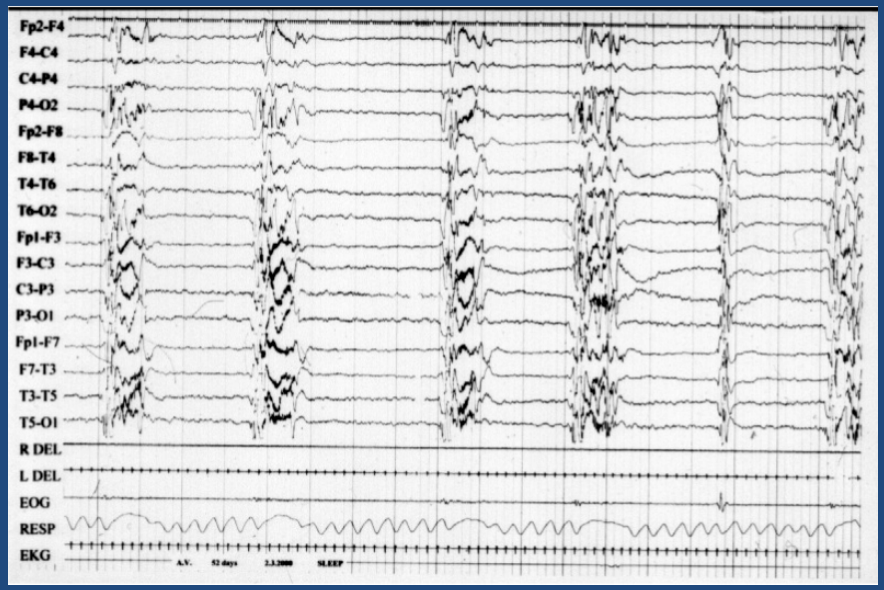


Electrophysiology: EEG



- Amplified electrical potential difference measured over skull & frequency, amplitude and location of wave forms reported
  - α 8-13Hz over post portions of skull normal during wakefulness
  - β >13Hz common with ICU sedation
  - Θ 4-7Hz common in young children but if asymmetric indicative of localising pathology
  - ∂ <4Hz very likely pathologic
- Extreme discontinuity can be due to immaturity: the term burst suppression not applicable prior to 35 weeks





- BS: bursts of high voltage (75-200µV) lasting 1-10s alternating with periods of marked background attenuation (<10µV, 2-45s) due to volleys from intrinsic “pacemaking” thalamo cortical neurons→cyclic bursts over a cortical background which is depressed or totally inactive

Neonatal EEG score – term neonate

Holmes and Lambroso 1993

1. Normal pattern
   - Transient discontinuity (<50%), distinct state changes
2. Excessively discontinuous
   - Discontinuity >50%, amplitude >5 and <25, IBI >6", poor state changes
3. Low voltage and undifferentiated
   - Persistent 5-15µV and without normal features
4. Burst suppression
   - As above, invariant and unreactive
5. Extremely low voltage
   - Persistent <5µV with no discernable cerebral activity

….value of continuous EEG monitoring in NICU / PICU ?

Video-EEG monitoring in newborns with hypoxic-ischemic encephalopathy treated with hypothermia

K.B. Nash, MD* Neurology® 2011;76:556-562

- 41 newborns >36w with HIE who underwent TH in UCSF 2007-2009
- Electrographic sz identified in 34% (13/14 in first 18h) and ~50% of these never showed a clinical correlate including 3 with sublinical SE
- Greatest prognostic value of EEG for predicting mod-severe injury was after 24h TH

Table 2 Evolution of EEG background with hypothermia by severity of MRI injury[a]

	Phase of therapeutic hypothermia							
	Beginning		Mid		End		Post	
EEG background	None/mild injury	Moderate/severe injury	None/mild injury	Moderate/severe injury	None/mild injury	Moderate/severe injury	None/mild injury	Moderate/severe injury
Normal	8 (100)	0	14 (93)	1 (7)	11 (92)	1 (8)	15 (94)	1 (6)
Excessively discontinuous	11 (73)	4 (27)	10 (77)	3 (23)	13 (81)	3 (19)	8 (73)	3 (27)
Depressed and undifferentiated	2 (50)	2 (50)	2 (40)	3 (60)	2 (29)	5 (71)	2 (33)	4 (67)
Burst suppression	2 (29)	5 (71)	0	4 (100)	0	2 (100)	0	4 (100)
Extremely low voltage	3 (43)	4 (57)	0	3 (100)	0	3 (100)	0	2 (100)

Subclinical early posttraumatic seizures detected by continuous EEG monitoring in a consecutive pediatric cohort

Epilepsia, 54(10):1780–1788, 2013

- Consecutive acute TBI pts of all severities (GCS 3-15) at CHLA and CHC
- All pts monitored for a minimum of 24h
- Standard international 10-20 system placement of gold-plated or plastic electrodes with standard filter settings and sampling rate

Results

- Seizure detected in 43% (62% if < 1y), varied with cause: most likely AHT (77%) and less likely blunt (20%), falls (27%), bicycle (33%) and MVA (25%)
- Subclinical Seizure: detected in 16% (43% of these (or 7% overall) **only** subclinical) - Regression analysis → intraaxial blood only sig predictor
- Subclinical SE: 14% of all pts studied

Subclinical early posttraumatic seizures detected by continuous EEG monitoring in a consecutive pediatric cohort

Epilepsia, 54(10):1780–1788, 2013

Discussion

The incidence of 42.5% (37/87) for EPTS and 16.1% (14/87) for subclinical seizures in this study are higher than those reported in a comparable adult cohort (22.3% and 11.7%, for EPTS and subclinical seizures, respectively) (Vespa et al., 1999b). This suggests a greater risk for EPTS in pediatric patients. The rate was also higher than found in two retrospective pediatric TBI evaluations without standardized cEEG (EPTS 12.0%) (Chiaretti et al., 2000; Liesemer et al., 2011). The use of cEEG to detect subclini-

Subclinical early posttraumatic seizures detected by continuous EEG monitoring in a consecutive pediatric cohort

Epilepsia, 54(10):1780–1788, 2013

Proposed indications for and value of cEEG use after TBI in children

We propose that cEEG monitoring for subclinical EPTS be strongly considered for all children younger than the age of 2 years admitted to the PICU for acute TBI. In addition, presence of intraaxial blood or demonstration/suspicion of AHT indicates greater risk for subclinical EPTS and thus signifies high-risk groups for cEEG monitoring. This would allow selective intervention with AEDs in patients who have EPTS, without indiscriminately exposing all patients to potential adverse effects. Severity of injury and skull fracture on CT has been shown to be possible risk factors based on other literature and may be considered as well.

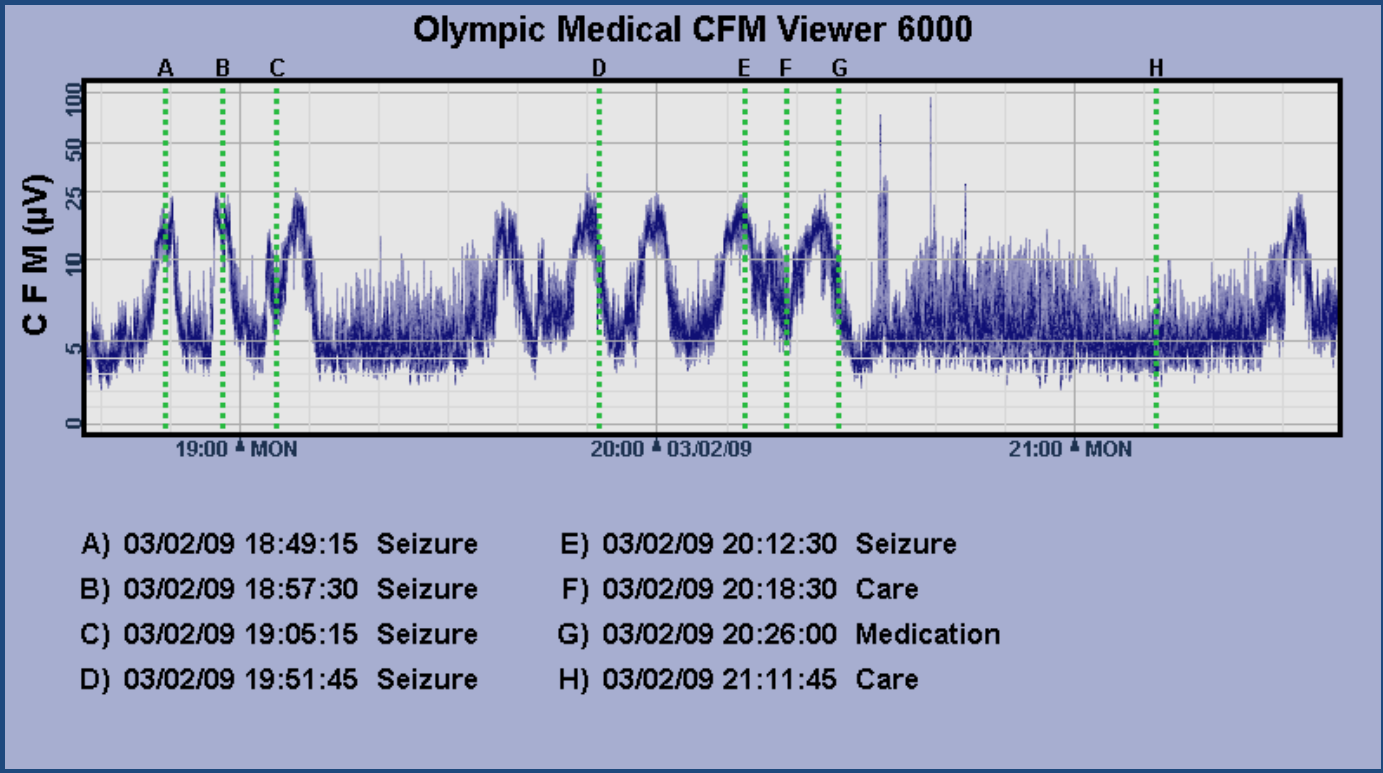
Consensus Statement on Continuous EEG in Critically Ill Adults and Children, Part I: Indications

Journal of Clinical Neurophysiology • Volume 32, Number 2, April 2015

- American Clinical Neurophysiology Soc
- Indications for Critical Care continuous EEG
- Diagnosis of non convulsive seizures, NCSE and other paroxysmal events:
  - Recommended with
    - Persistently abnormal mental status following generalised convulsive SE or other clinically evident seizures
    - Acute supratentorial brain injury with altered mental status
    - Fluctuating mental status or unexplained alteration of mental status without known acute brain injury
    - Generalised periodic discharges GPDs, lateralising (LPDs) or bilateral independent periodic (BIPDs)
    - Paralysis and risk of seizures
    - Clinical paroxysmal events suspected to be seizures
    - Assessment of therapy for sz (NCSE, Refractory SE)
  - Suggested:
    - as adjunct to identify ischaemia in pts at high risk
    - Monitoring of sedation and high dose suppressive therapy
  - May be of value: assessment of severity of encephalopathy and prognostication

aEEG

- Compressed array of EEG amplitude over extended time period on a logarithmic scale
- Certain patterns correlate with cerebral states
- Discharges without substantial increase in amplitude will be missed
- Localisation of seizure onset often precluded
- Requires correlation with standard EEG



Seizure Pathophysiology & Rx

Status Epilepticus

- Commonest neurologic emergency in childhood, responsible for 2-4% of PICU admissions
  - Status = > 5 mins continuous or electrographic seizure activity
  - RSE = seizure persisting despite adequate benzo + load of another appropriate med'n
  - Super RSE = persistence after anaesthetic agent
- Seizure initiation and seizure perpetuation are different
- More refractory the seizure, greater likelihood of underlying genetic predisposition: 141 genes associated with resistant status
  - Cortical dysplasias
  - Altered biochem (inborn errors, mitoch disease)
  - Altered membrane or transmitter function
- ...Clinical utility of finding genetic mutation currently of little impact

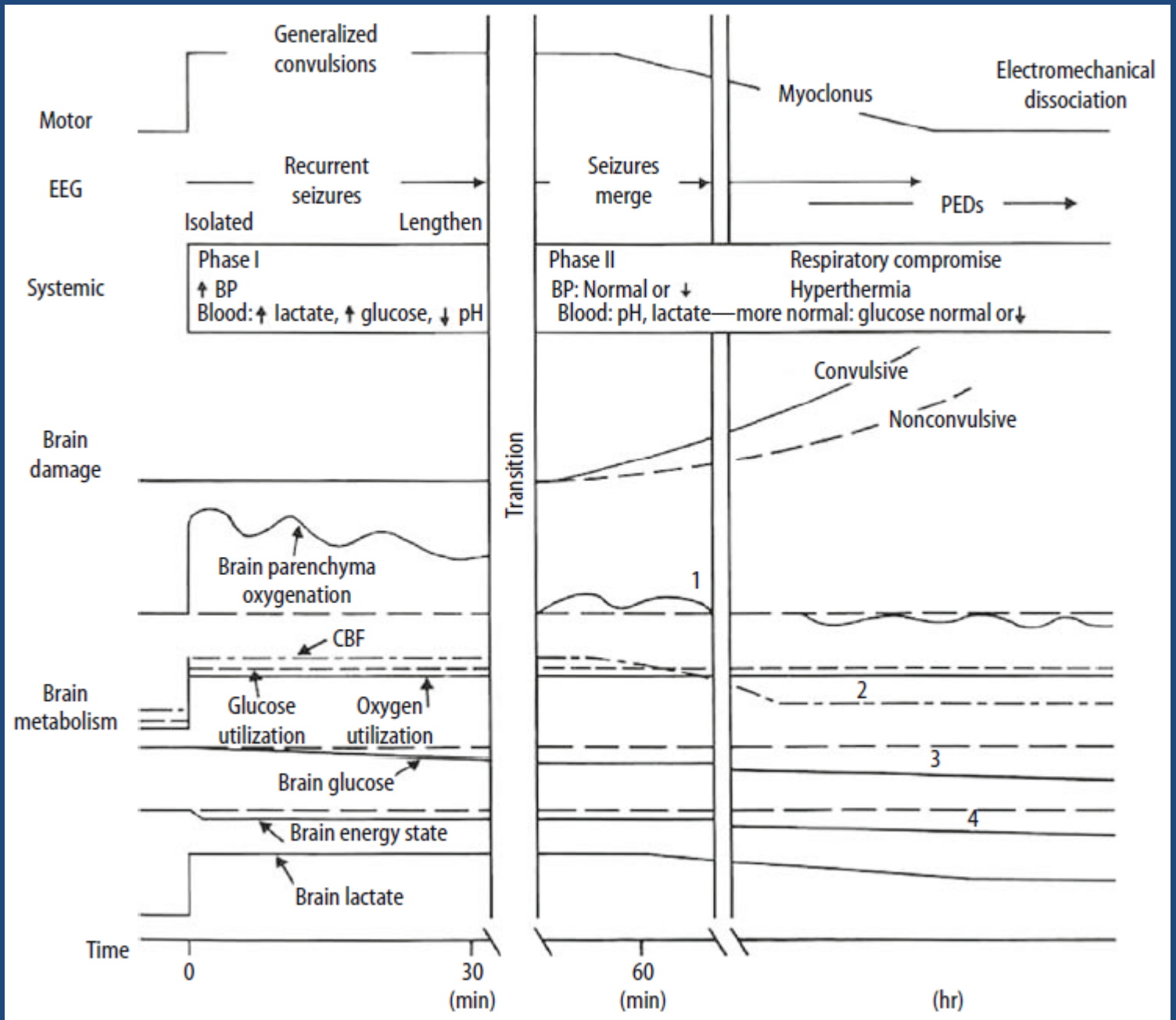


FIGURE 11.1. Pathophysiologic characteristics during the phases of compensation (within 30 min of onset) and decompensation (after 30 min of onset) of status epilepticus. BP, blood pressure; PEDs, periodic epileptiform discharges. (Adapted from Lothman E. The biochemical basis and pathophysiology of status epilepticus. Neurology 40[5 Suppl 2]:15. © 1990 with permission from Lippincott Williams & Wilkins.)

Admissions to paediatric intensive care units (PICU) with refractory convulsive status epilepticus (RCSE): A two-year multi-centre study

I. Tully et al. / Seizure 29 (2015) 153–161

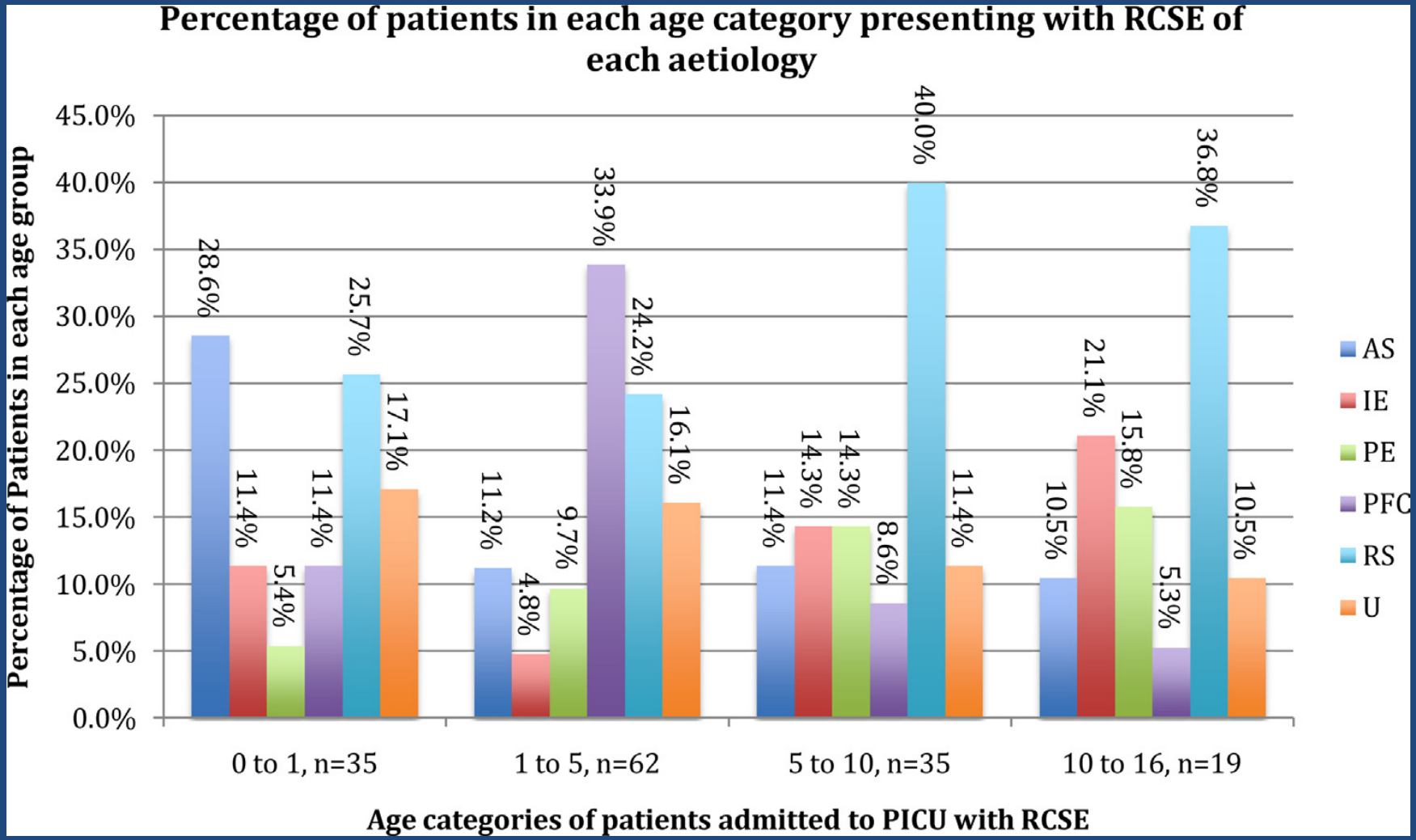


Fig. 3. Numbers of patients by age is presented on the axis label. AS = acute symptomatic epilepsy; IE = idiopathic epilepsy; PE = epilepsy as a feature of a progressive encephalopathy; PFC = prolonged febrile seizure; RS = remote symptomatic epilepsy; U = unclassified.

Hypothermia for Neuroprotection in Convulsive Status Epilepticus

Legriel et al NEJM Dec 22 2016

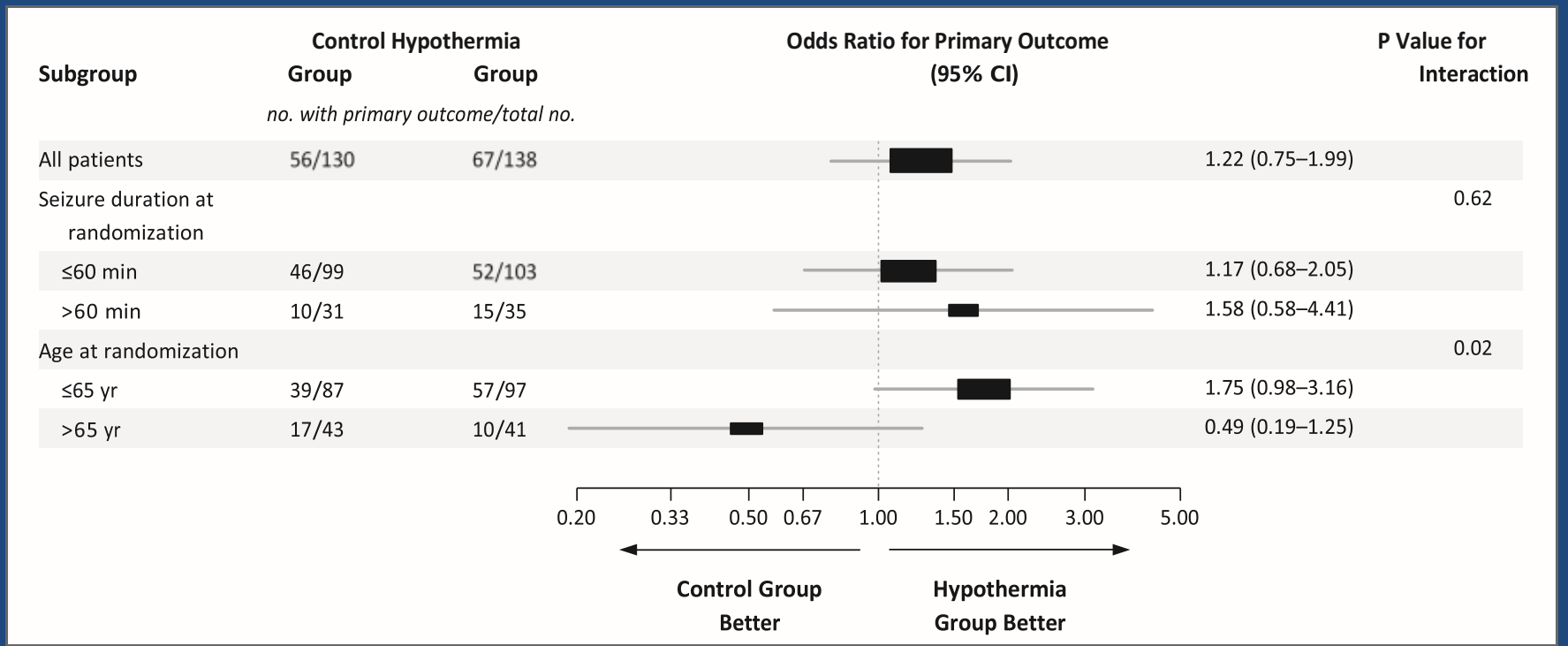


Figure 2. Prespecified Subgroup Analyses.

The primary outcome was the absence of functional impairment at 90 days, as defined by a score of 5 on the Glasgow Outcome Scale (GOS; range, 1 to 5, with 1 representing death and 5 representing no or minimal neurologic deficit). The sizes of the data markers reflect the relative size of each subgroup. P values were calculated with the use of the Gail and Simon test.

Peripheral Nervous System Disorders

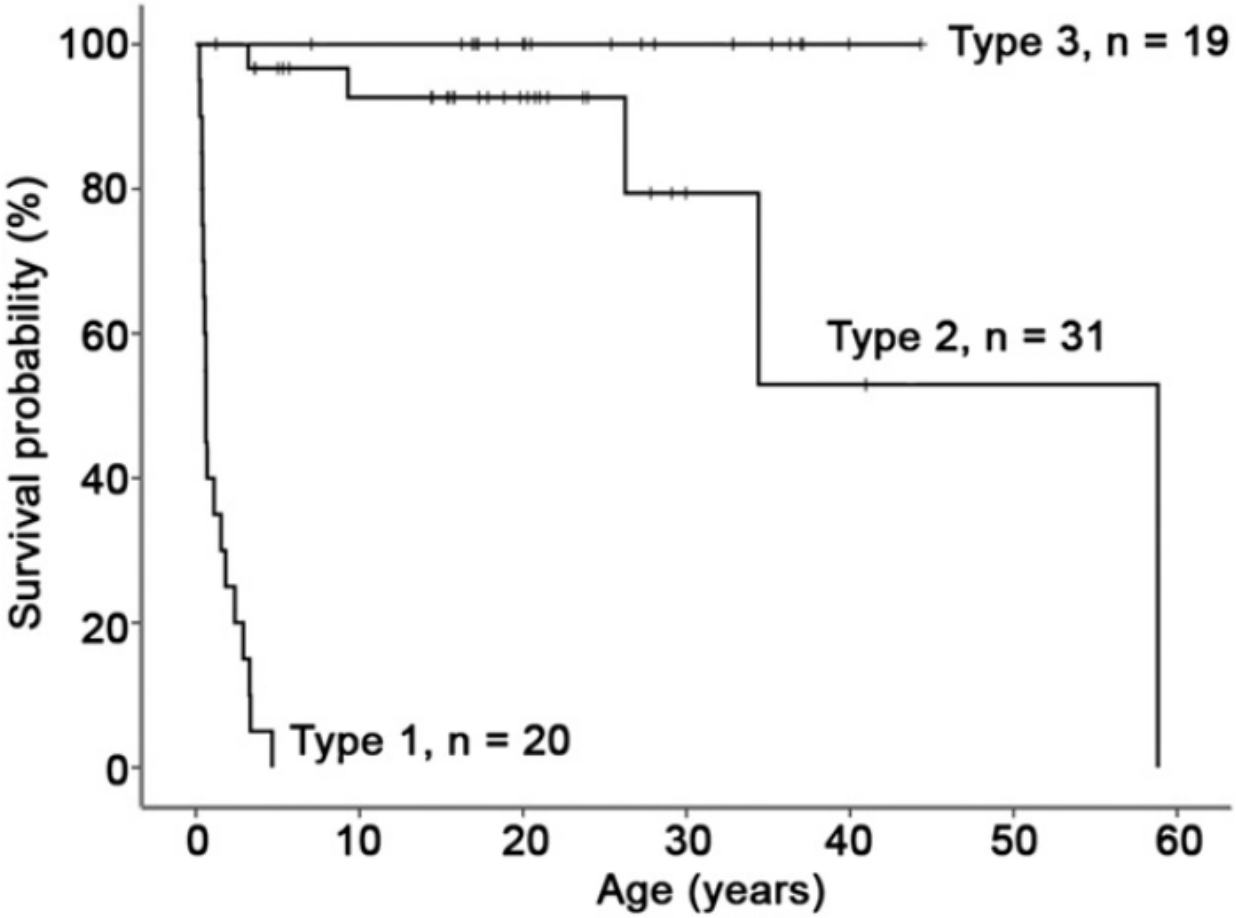
- Cause admission to PICU
- Occur as secondary consequence of critical illness

Anterior Horn Cell

- SMA
  - Types I-III correlate with SMN protein expression (involved in RNA metabolism and expressed in most tissues of the body)
  - Dx is clinical and confirmed by genetic analysis and NCVs (if performed) are usually WNL with EMG demonstration of denervation
  - Rx options?

Pathophysiological Insights Derived by Natural History and Motor Function of Spinal Muscular Atrophy

Michelle A. Farrar, MBBS[1,2], Steve Vucic, MBBS, PhD[1,3], Heather M. Johnston, MBChB[2], Desirée du Sart, MBBS, PhD[4], and Matthew C. Kiernan, MBBS, PhD, DSc[1,5]



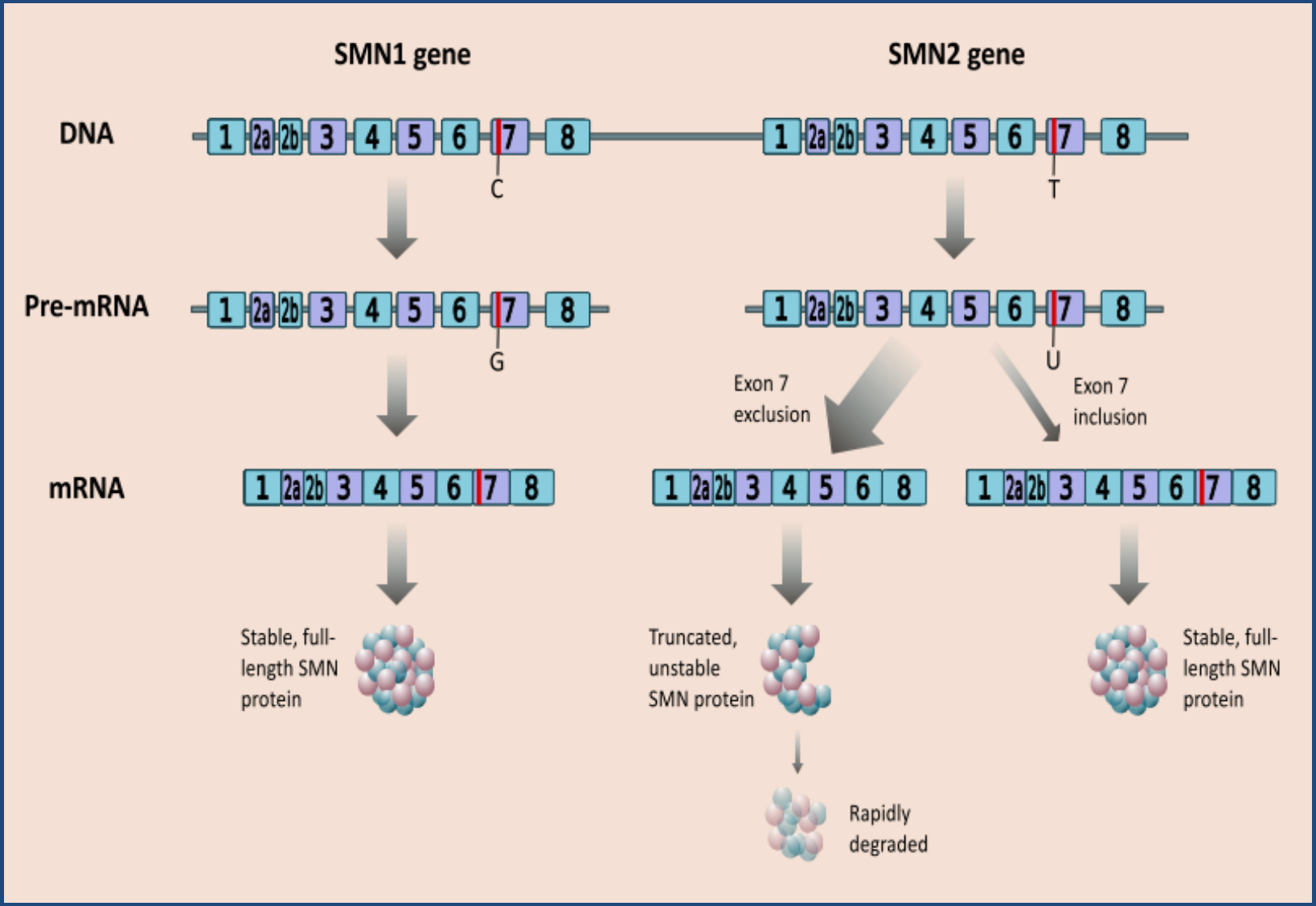
Long term ventilation in SMA type 1: Ethical debate

- Spinal muscular atrophy type 1: Do the benefits of ventilation compensate for its burdens – Case report
- Spinal muscular atrophy type 1: is long term mechanical ventilation ethical? - Editorial
- Letters to the Editor:
  Will this be a life worth living
  Medical impasse: a problem as big as Texas?
  Is a life worth living?

Gray et al J Paed Child Health 2013

- Interim analysis of the phase 3 trial found that patients receiving drug "nusinersen" experienced a significant improvement in motor milestone compared to placebo.
- The study will be stopped, with all participants transitioning into an open label study
- Plans to open a global expanded access program in the last quarter of 2016 for infants with SMA type 1
- Plan to submit the drug to regulatory bodies for approval

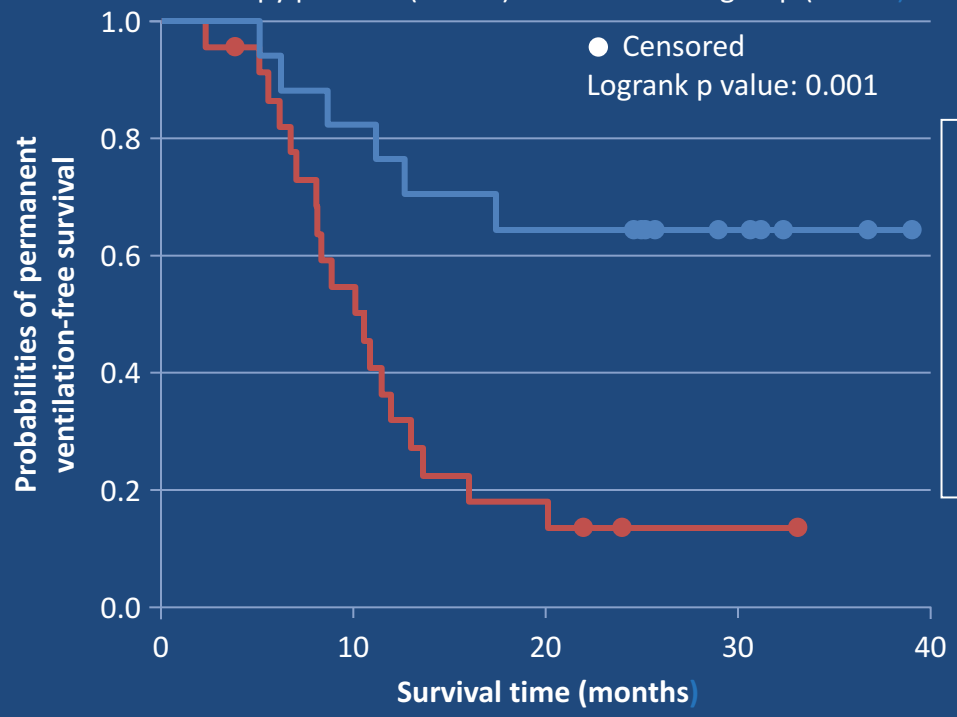
Genetics of SMA



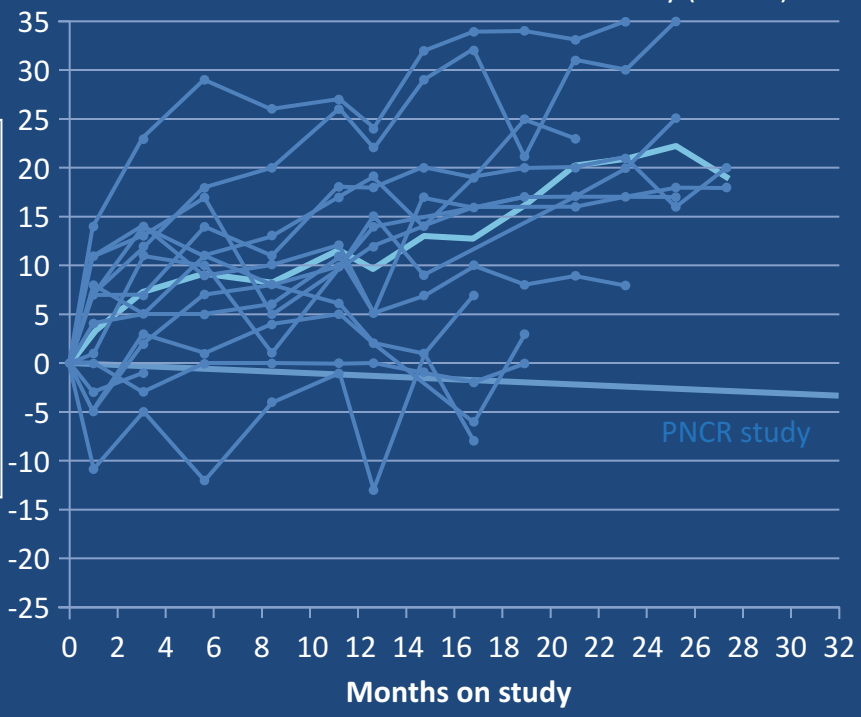
Increased event-free survival and muscle function scores observed in nusinersen-treated infants with SMA: CS3a

(As of January 2016 compared to natural history [PNCR])

Increased permanent ventilation-free survival



Increases in disease-specific motor function scores (CHOP INTEND)



Finkel R. Presented at AAN 2016. Poster # 004.
1. Glanzman AM, et al. Neuromuscul Disord. 2010;20:155-61.

Anterior Horn Cell

- SMA
  - Types I-III correlate with SMN protein expression (involved in RNA metabolism and expressed in most tissues of the body)
  - Dx is clinical and confirmed by genetic analysis and NCVs 9if performed) are usually WNL with EMG demonstration of denervation
  - Recent Rx option?
- Juvenile ALS – C/S & C/bulbar pathways
- West Nile Virus infection – meningoencephalitis or AFP
- Poliomyelitis-like Syndromes
  - JEV, EV71 & vaccine-associated polio
  - Ant horn cells, nuclei in ventral pons, widespread
  - Weakness asymmetric, prox, worse in LLs, may have bulbar involvement
  - MRI changes predominantly ventral cord
  - NCV and SNAP N but reduced CMAP

Peripheral Nerve

Characteristic	Polio-like syndrome	Guillain-Barre	Transv myelitis
Onset	During infection	Post	Post
Fever	Always	Uncommon	Uncommon
Weakness	Asymmetric, prox	Usu. symmetric	Symmetric
Sensory symptoms	No sensory loss. Pain	Painful distal parasthesias and sensory loss	Sensory level
Concurrent encephalopathy	Common	Absent	With ADEM
Resp insufficiency	If bulbar involvement	Common	Uncommon
Bowel / bladder	Common WNV, rare in polio	Rare	Common
CSF	Pleocytosis & inc protein	Inc protein without pleocytosis	Pleocytosis and inc protein, may have OCB
Spinal MRI	Inc T2/FLAIR SC or cauda equina	Cauda equina only	SC only (predilection for WM)
EPS	Dec/absent CMAPs, preserved SNAPs	Slow NCV, cond block, temp dispersion, red SNAPs	NCV, EMG N but delayed/absent SSEPs

Guillain Barre Subtypes

Condition	Features	Pathophysiology	Prognosis
Acute Inflammatory Demyelinating Polyneuropathy	Weakness, areflexia, sensory loss	Demyelination M and S nerves Axonal degeneration in severe cases Anti-GM2	Often rapid and complete recovery
Acute motor axonal neuropathy	Weakness, areflexia, little or no sensory loss	Axonal degen of motor nerves A/W *Campylobacter jejuni* infection Ant-GM1 to axon cell membrane	Variable
Acute motor-sensory axonal neuropathy	Weakness, areflexia, sensory loss, muscle atrophy	Axonal degeneration motor and sensory nerves	Delayed and poor recovery
Miller-Fisher	Ataxia, areflexia, ophthalmoplegia, ± nonrecive pupils	A/W *Campylobacter jejuni* infection Anti GQ1B directed at occulomotor nerves, sensory nerve ganglia and cerebellar neurons	Rapid and complete recovery

Neuromuscular Junction

- Myasthenia Gravis
  - Transient neonatal, autoimmune or congenital
  - Decremental CMAP response on repetitive 2-3Hz stimulation
- Botulism
  - Neurotoxin binds irreversibly to presynaptic nerve terminal
  - Weakness begins cranial nerves and descends
  - Repetitive stimulation (20-30Hz → facilitation) but decrement with 2-3Hz, NCV normal
  - Diagnosis confirmed by bioassay
- Tetanus
  - Toxin enters nerve peripherally and retrograde transport to AHCs where it blocks transmission primarily of GABA'ergic inhibitory interneurons
- Tick poisoning
  - Toxin mechanism not well characterised; non specific pattern of low amplitude CMAPs with preservation of sensory responses

Critical illness Polyneuropathy and Myopathy

- While disorders of peripheral nerve, NMJ and muscle are distinct (and have different electrophysiologic features and pathology) many now argue that they are on a continuum and differentiation largely unimportant
- Clearly more of an adult ICU phenomenon
  - One prospective study in children: incidence 1.7%
  - Adult ICU: pts treated >24h in ICU incidence > 10%, ventilated >7d → 25%*
- EPS studies and clinical weakness do not always correlate
  - "….identifying functional weakness and addressing it …more important…" *(Brussells Rountable 2009)*
- Epidemiologic studies have determined risk factors

MRC Score: shoulder abd, elbow flex, wrist ext, hip flex, knee ext and foot dorsi 0-5 R & L → max 60. By definition score <48→ Dx ICUAW

CIPNM: Risk Factors

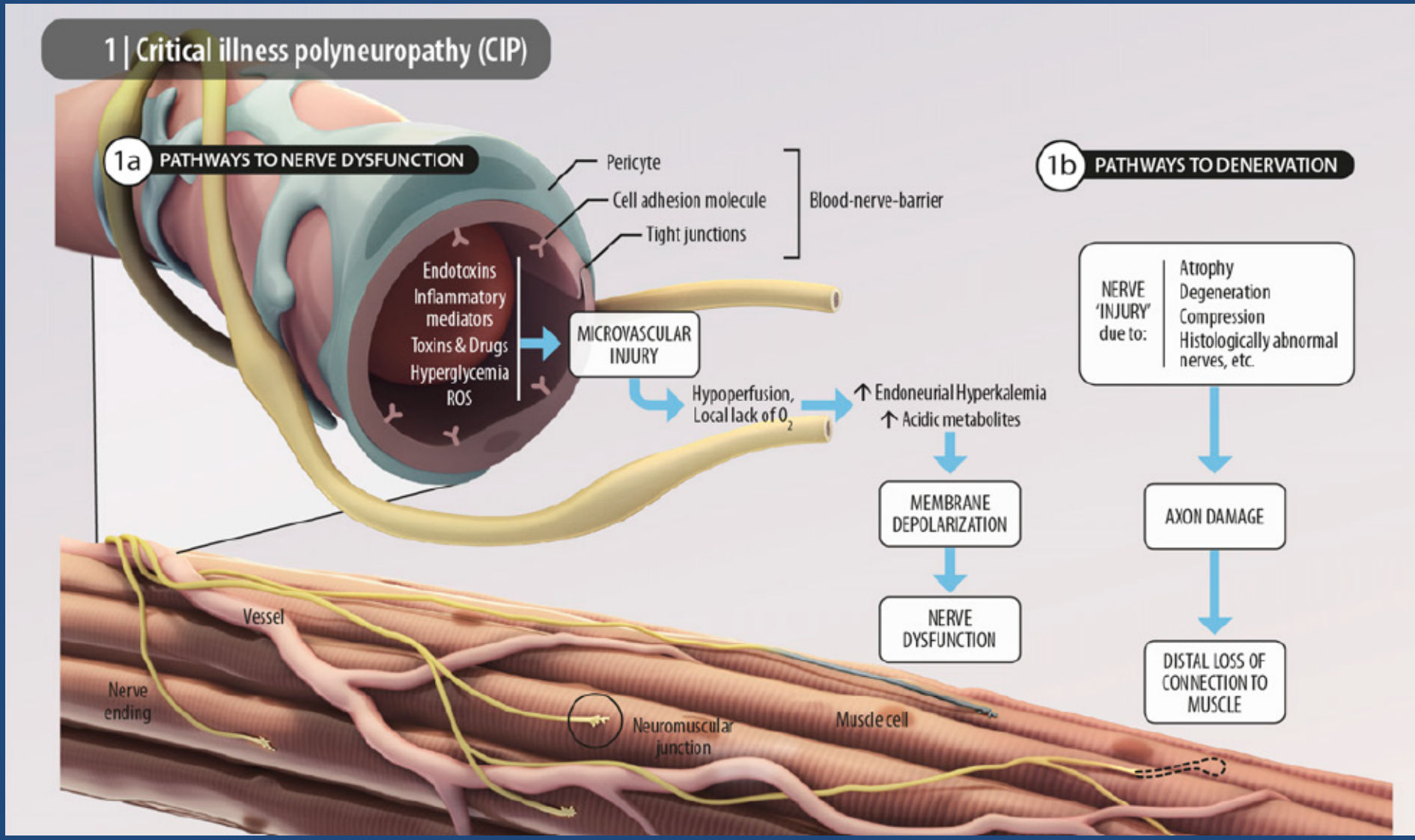
1. Severity of illness
2. Systemic inflammatory response syndrome (SIRS) and multiple organ failure (MOF)
3. Sepsis
4. Hyperglycaemia
5. Immobilisation
6. Corticosteroids, NMBs (anecdotal, not confirmed in prospective trials)
7. Age

CIPNM: Clinical Picture

- Symmetrical and flaccid weakness of limbs more pronounced proximally
- Facial and ocular muscles often spared
- Reflexes usually present and sensory loss absent (but these can be reversed depending on component of CIP)
- Respiratory muscles often affected

- **CIP:** normal or ↓NCV with low amplitude CMAP, and SNAP normal or ↓. Spontaneous fibrillation on EMG with denervation
- **CIM:** NCV normal, SNAP normal and CMAP ↓ (prop to degree atrophy) & EMG polyphasic, spontaneous fibrillation absent (except with significant muscle necrosis)

- Major component of post intensive care syndrome contributing to functional disability and poor HRQOL


1 | Critical illness polyneuropathy (CIP)
1a PATHWAYS TO NERVE DYSFUNCTION
Pericyte
Cell adhesion molecule
Tight junctions
Blood-nerve-barrier
Endotoxins
Inflammatory mediators
Toxins & Drugs
Hyperglycemia
ROS
MICROVASCULAR INJURY
Hypoperfusion, Local lack of O_2
↑ Endoneurial Hyperkalemia
↑ Acidic metabolites
MEMBRANE DEPOLARIZATION
NERVE DYSFUNCTION
1b PATHWAYS TO DENERVATION
NERVE 'INJURY' due to:
Atrophy
Degeneration
Compression
Histologically abnormal nerves, etc.
AXON DAMAGE
DISTAL LOSS OF CONNECTION TO MUSCLE
Vessel
Nerve ending
Neuromuscular junction
Muscle cell

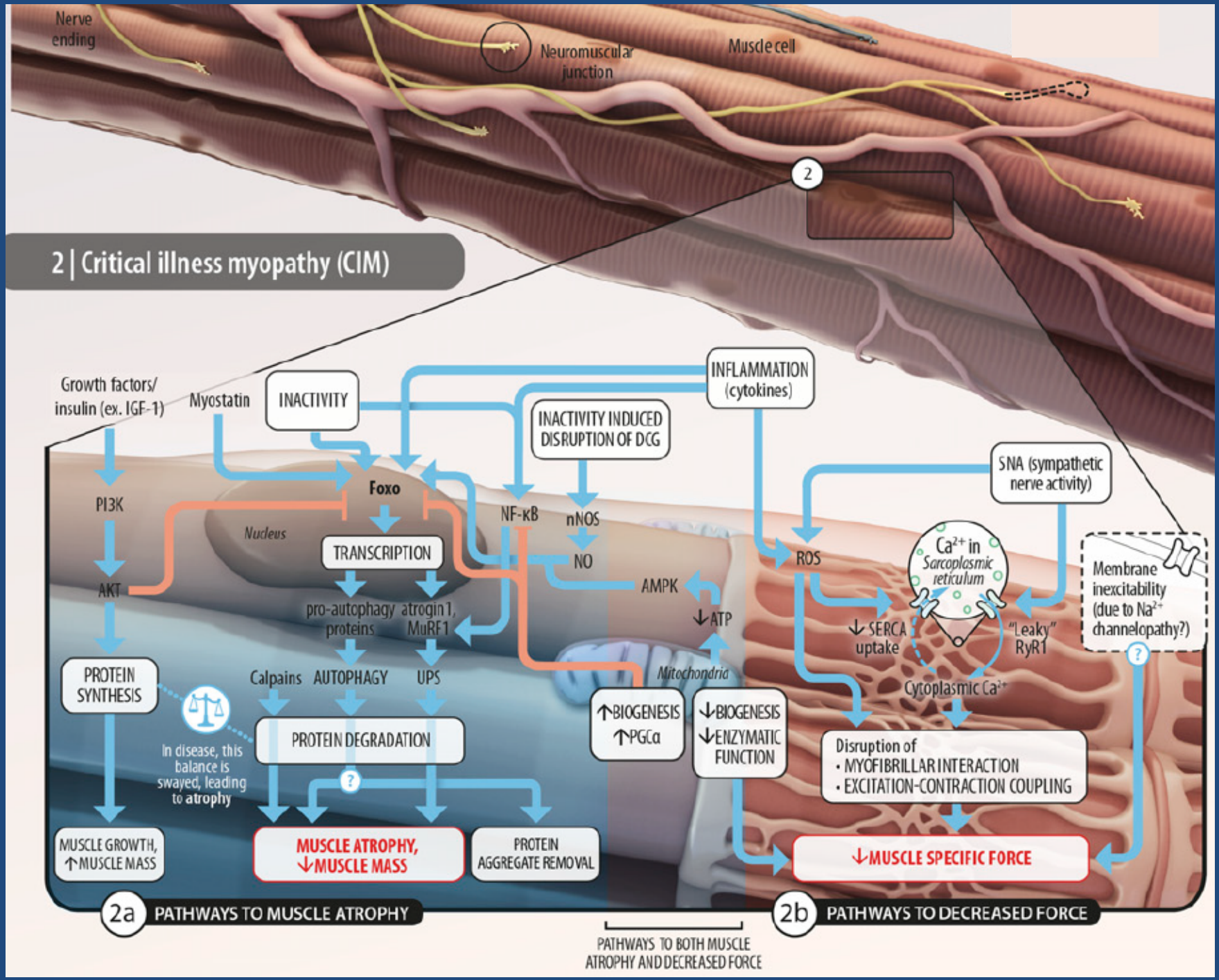

Nerve ending
Neuromuscular junction
Muscle cell
2
2 | Critical illness myopathy (CIM)
Growth factors/ insulin (ex. IGF-1)
Myostatin
INACTIVITY
INFLAMMATION (cytokines)
INACTIVITY INDUCED DISRUPTION OF DCG
SNA (sympathetic nerve activity)
PI3K
Foxo
NF-κB
nNOS
Nucleus
TRANSCRIPTION
NO
ROS
AKT
AMPK
↓ATP
pro-autophagy proteins
atrogin1, MuRF1
Ca2+ in Sarcoplasmic reticulum
Membrane inexcitability (due to Na2+ channelopathy?)
↓SERCA uptake
"Leaky" RyR1
PROTEIN SYNTHESIS
Calpains
AUTOPHAGY
UPS
Mitochondria
Cytoplasmic Ca2+
↑BIOGENESIS ↑PGCα
↓BIOGENESIS ↓ENZYMATIC FUNCTION
In disease, this balance is swayed, leading to atrophy
PROTEIN DEGRADATION
Disruption of
• MYOFIBRILLAR INTERACTION
• EXCITATION-CONTRACTION COUPLING
MUSCLE GROWTH, ↑MUSCLE MASS
MUSCLE ATROPHY, ↓MUSCLE MASS
PROTEIN AGGREGATE REMOVAL
↓MUSCLE SPECIFIC FORCE
2a PATHWAYS TO MUSCLE ATROPHY
2b PATHWAYS TO DECREASED FORCE
PATHWAYS TO BOTH MUSCLE ATROPHY AND DECREASED FORCE

Table 2. Reported cases of pediatric critical illness polyneuropathy (CIP)/critical illness myopathy (CIM) 1986-2003

No. (Reference)	Age, yrs	Gender	Potential Risk Factors	NMBAs	Corticosteroids	First Clinical Signs[a]	Diagnosis (Based on NCS and EMG Findings)	Outcome[b]	Follow-Up, Months
1. (34)	10	F	Asthma	Y	Y	8	Motor CIP	1	12
2. (40)	1.5	F	—	Y	Y	20	Disuse atrophy	2	5
3. (35)	2.5	M	Asthma	Y	Y	13	Motor CIP	1	3
4. (33)	13	F	SIRS	N	N	11	Mixed CIP with demyelination[c]	2	9
5. (33)	0.13	F		Y	N	25	Prolonged neuromuscular blockade	2	9
6. (36)	13	F	—	N	Y	30	CIM	2	3
7. (37)	15	M	SIRS	Y	N	90	Mixed CIP	3	24
8. (11)	15	F	SIRS	Y	Y	<7	Motor CIP	1	1.5
9. (11)	15	M	SIRS	Y	Y	8	Motor CIP	1	17
10. (11)	17	F	Asthma	Y	Y	8	Motor CIP	1	4
11. (11)	6	M	—	Y	N	2	Motor CIP/CIM[c]	0	0
12. (38)	2	F	SIRS	N	N	11	Motor CIP	3	8
13. (39)	6	M	SIRS	Y	N	42	Motor CIP	1	6
14. (39)	2.5	M	SIRS	N	Y	42	Motor CIP	2	15
15. (10)	11	F	SOT	Y	Y	<7	CIM	1	24
16. (12)	8	F	SIRS	N	N	12	Mixed CIP	1	2
17. (12)	14	M	SIRS	Y	Y	15	Mixed CIP	2	15
18. (12)	2	M	SIRS	Y	N	5	Motor CIP[c]	3	N/A
19. (12)	8	F	SOT	Y	Y	8	Motor CIP/CIM[c]	1	6
20. (12)	8	M	Asthma/SIRS	Y	Y	9	CIM	1	0.75

Worse prognosis for CIP than CIM

Outcome different adults V children:

- Children: Of the 20 cases 50% recovered fully, 30% persisting weakness and 15% died or no recovery
- Adults: ARDS lit review, several series: 36% at discharge, 22% ant 3mo, 11% at 6mo, 9% at 2y

When you exercise your muscles do get inflamed (and generate cytokines)

IL-10. Regular exercise acting through IL-6 may reduce systemic vascular inflammation with decreased C-reactive protein (98), prevent atherogenesis, and improve insulin sensitivity. Given that tumor necrosis factor-α may trigger IL-6 release, it is possible that adipose-derived tumor necrosis factor-α is the "bad" driver of inflammatory processes, whereas skeletal muscle IL-6 might be a "defense" mechanism against the proinflammatory actions of tumor necrosis factor (99). Exercise may maintain this important IL-6 regulation of health and disease.

…..but this inflammation is good for you!

Griffiths et al ICU Acquired Weakness CCM 2010, V38, No 3

So, if you find a form of exercise which you enjoy……

You should do it till it hurts…..AND THEN DO IT SOME MORE!

Thank You

Questions ?