Whats Cool in HIE!

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Declaration of Disclosure

I have no actual or potential conflict of interest in relation to this program.

I also assume responsibility for ensuring the scientific validity, objectivity, and completeness of the content of my presentation.

Patrick McNamara, MD

Learning Objectives:

At the end of this session, you will be able to:

- Understand the benefits/limitations of Therapeutic Hypothermia and how it works?

- Identify patients who may benefit from treatment.

Scenario I

Full term male — Birth weight 3.43 Kg

Meconium stained liquor — Fetal bradycardia to 60

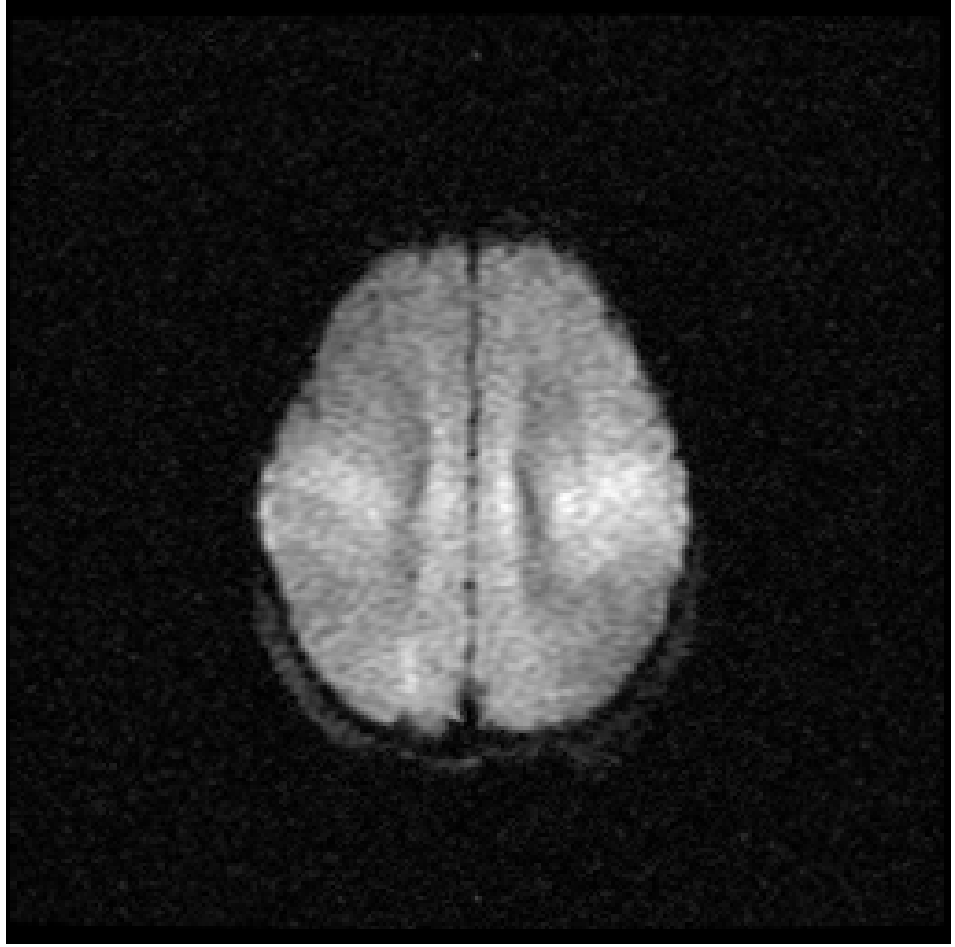
High forceps delivery → CPR for 20 mins

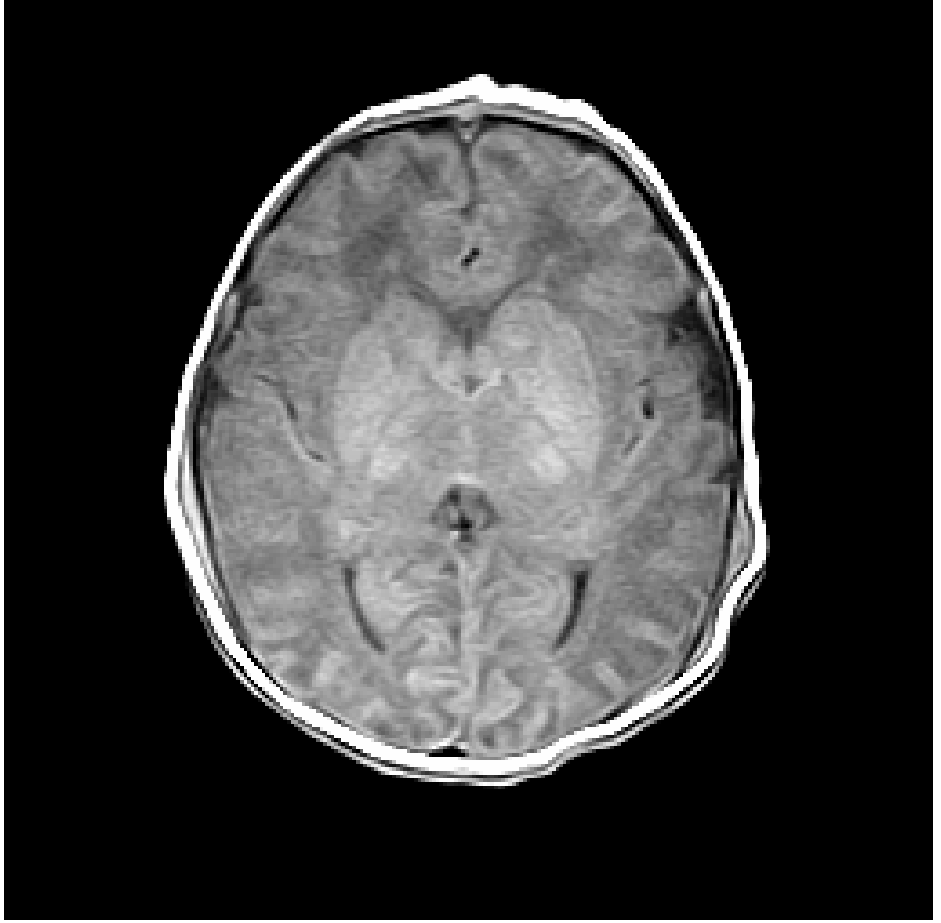
Cord pH 6.91 — Apgars 1^{1} 1^{5} 2^{10} 7^{15}

Transferred from Level II community hospital

Severe Encephalopathy with Intractable seizures → Phenobarbitone & mizadozalam

<u>EEG:</u> Severely abnormal trace with global low voltages





- **<u>MRI:</u>** Diffuse hypoxic-ischemic changes
- ICU support withdrawn on day 3 of life

Hypoxic-ischemic Encephalopathy

- Intrapartum hypoxia 3-5/100 live births

Levene 1986 Lancet

- Complicates ~1/1000 live births
  - Neurological sequelae: > 25%
  - Mortality: 10-60% (23% of global neonatal deaths)

Vannuci 1990 Pediatrics

- HIE accounts for 20-30% cerebral palsy

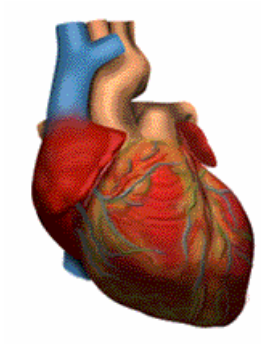
Hagberg 2001 Acta Paed

- Burden: Lifetime cost: $5,000,000 for care worldwide

Is there an opportunity to intervene?

Hypoxic-ischemic insult

Prevention



Resuscitation

Post-Resuscitation Care

Improved Outcome

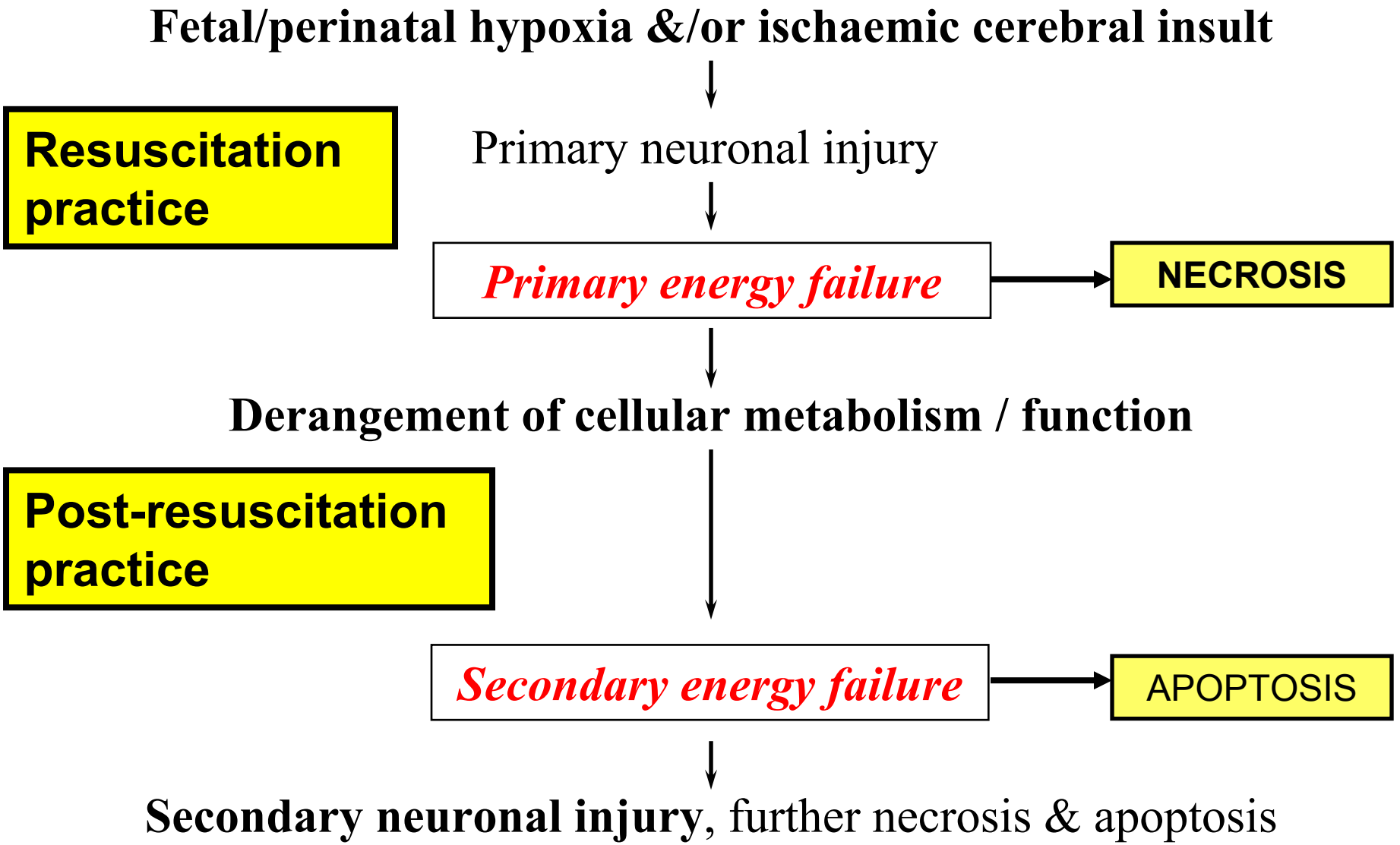
Resuscitation Data

	Neonate	Child	Adult
Oxygen	Yes *	No	No
Ventilation	No	No	Yes
Chest compressions	No	No	Yes
Epinephrine	No	Yes *	Yes *
Sodium Bicarbonate	No	No	Yes *

Established Insult

But if the horse has bolted…….

Pathophysiology



Hypothermia & Delayed Energy Failure

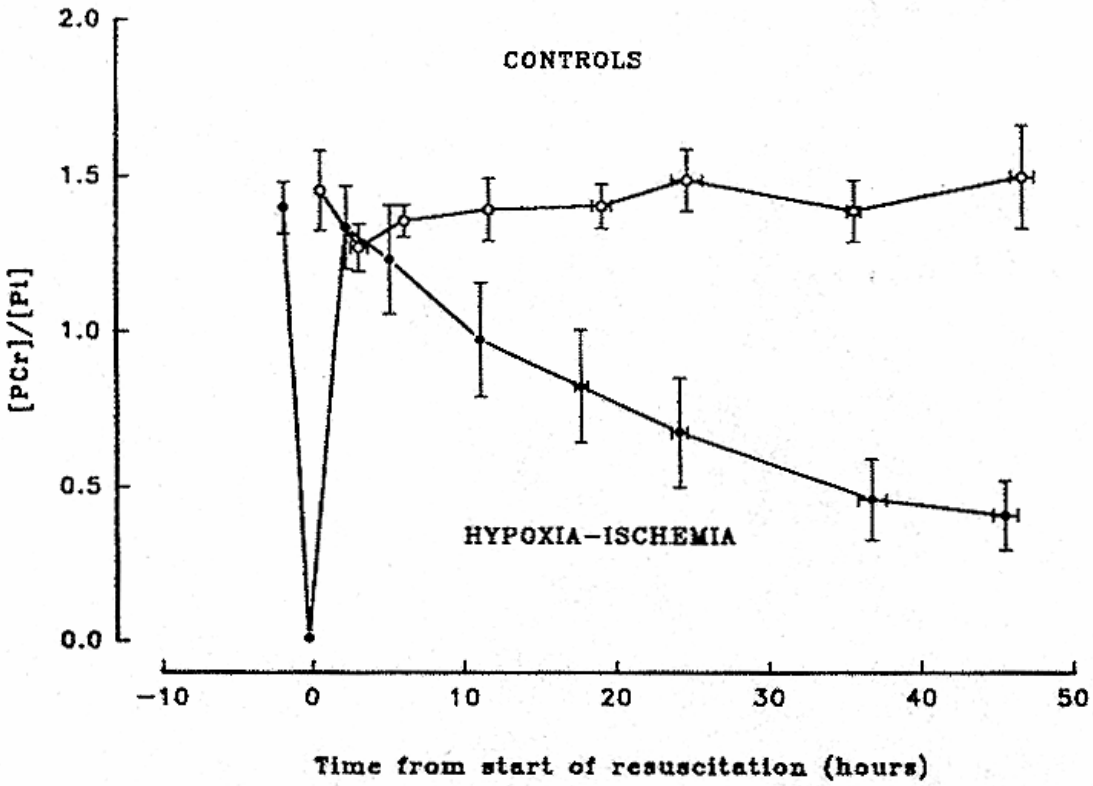


Figure 3. [PCr]/[Pi] in the control group ($n = 6$) and the experimental group of piglets whose brains were subjected to acute hypoxia-ischemia ($n = 12$). Values are means and SEM.

Pediatr Res 1994;36:699-706

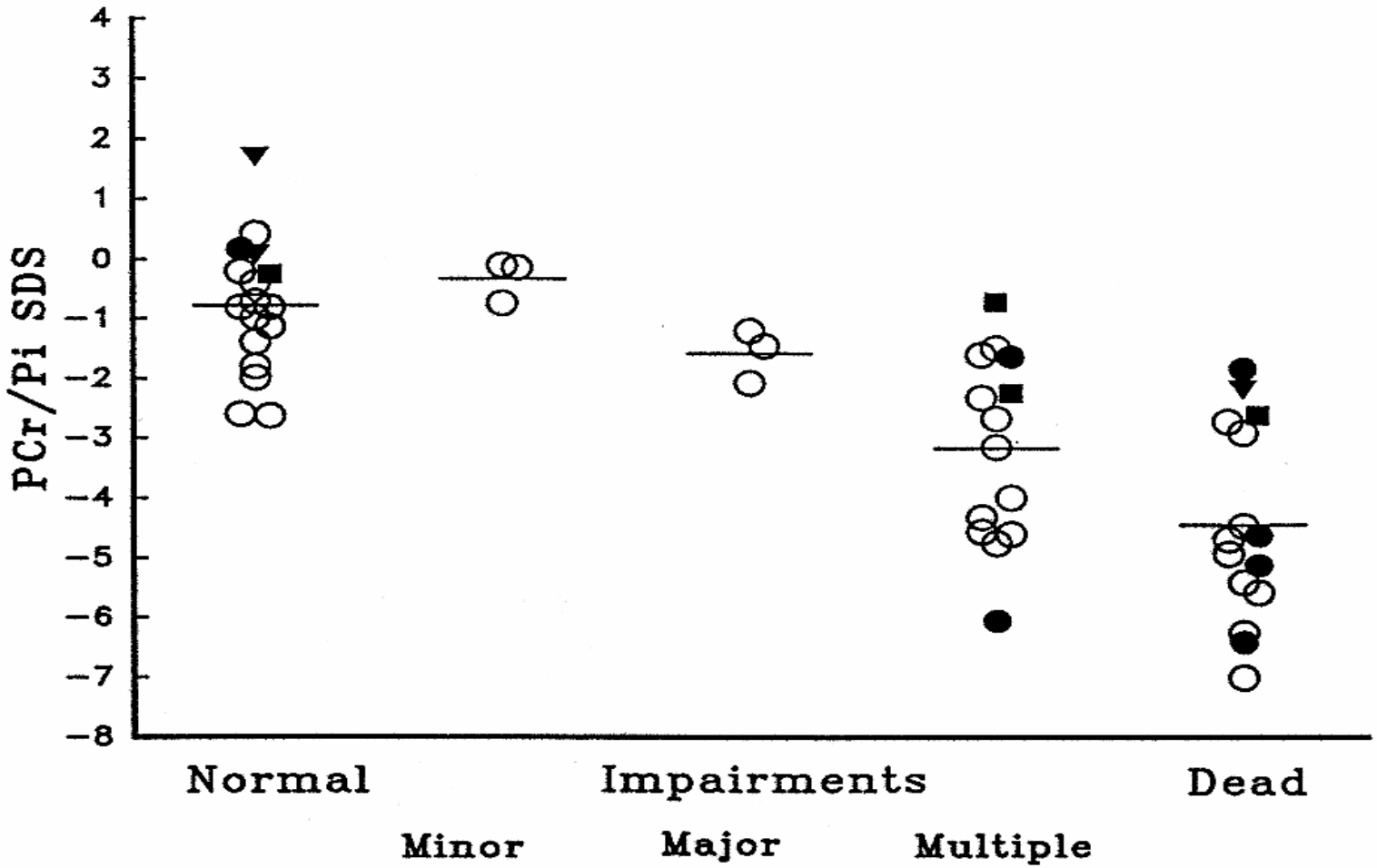


Fig. 2. Values for PCr/Pi SDS, according to neurodevelopmental outcome group: ○ term AGA infants; ● term SGA infants; ▼ preterm AGA infants; □ preterm SGA infants.

Dev Med and Child Neurol 1992;34:285-295

Abnormal outcome is related to abnormal brain cellular metabolism…..

Is brain injury reversible?

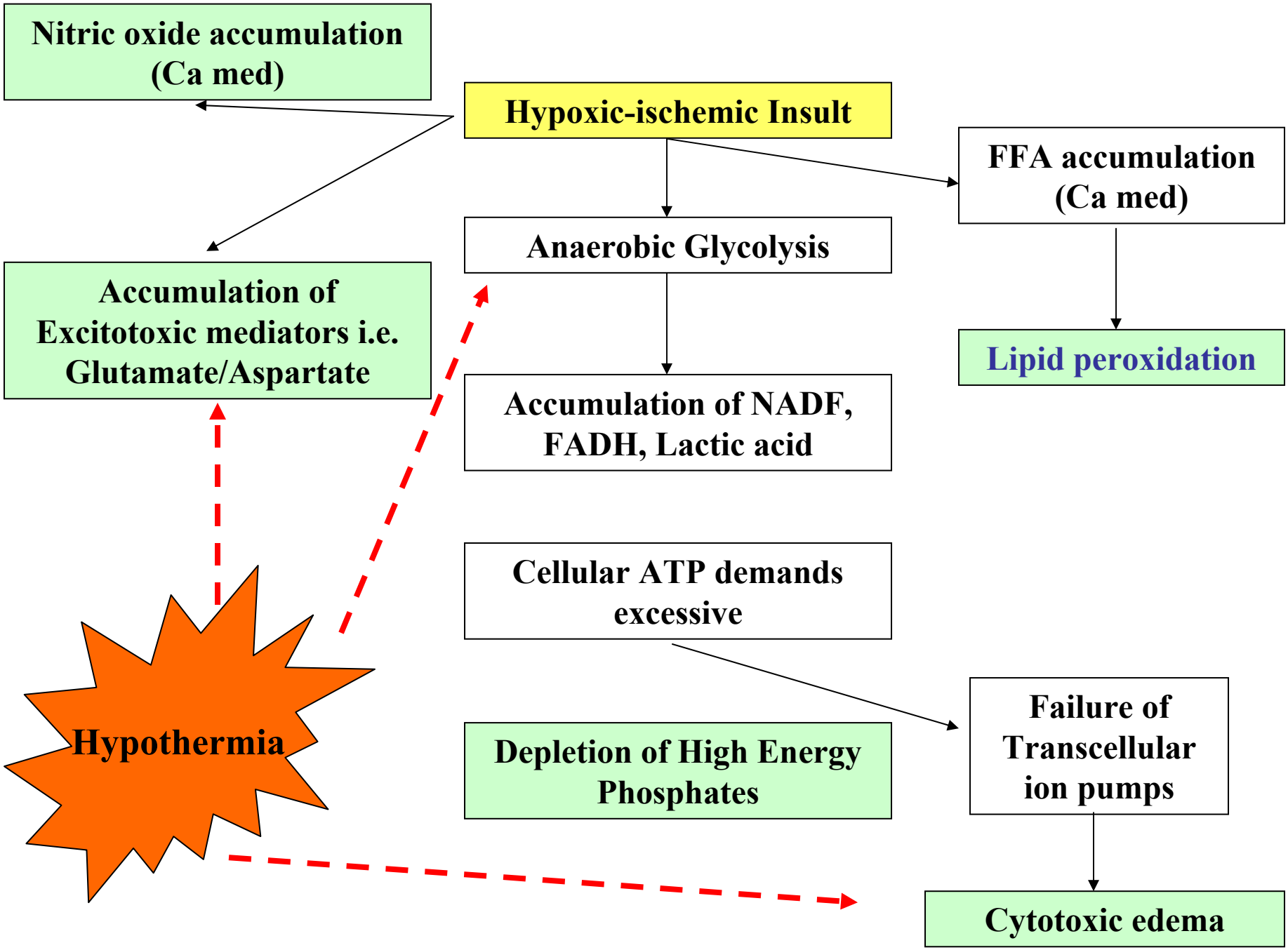
Neuroprotective therapies

Pharmacological

- Oxygen free radical scavengers (i.e Vit E, Vit C, allopurinol, indomethacin)
- Excitatory AA antagonists (i.e NMDA, MK801)
- Calcium channel blockers (i.e. nicardipine, flunarizine)
- Inhibition of NO production (NOS inhibitors)
- Corticosteroids
- Barbiturate coma (phenobarbitone, Thiopental)

Non-Pharmacological

- Hyperglycemia (conflicting rodent vs porcine data)
- Therapeutic hypercapnia


Nitric oxide accumulation (Ca med)
Hypoxic-ischemic Insult
FFA accumulation (Ca med)
Anaerobic Glycolysis
Accumulation of Excitotoxic mediators i.e. Glutamate/Aspartate
Lipid peroxidation
Accumulation of NADF, FADH, Lactic acid
Cellular ATP demands excessive
Hypothermia
Depletion of High Energy Phosphates
Failure of Transcellular ion pumps
Cytotoxic edema

An Era of Cooling

- **Westin B**, Miller JA, Nyberg R, Wedenberg E Neonatal asphyxia pallida treated with hypothermia alone or with hypothermia and transfusion of oxygenated blood. *Surgery.* 1959; 45:868-879

- **Westin B**, Nyberg R, Miller JA, Wedenberg E. Hypothermia and transfusion with oxygenated blood in the treatment of asphyxia neonatorum. *Acta Paediatr Scand.* 1962;(suppl)139:1-80

- **Westin B** Infant resuscitation and prevention of mental retardation. *Am J Obstet Gynecol.* 1971; 110:1134-1138 [

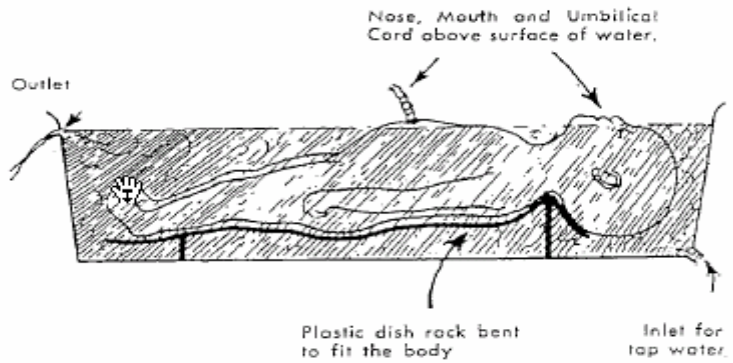


Figure 1. The immersion bath used by Westin *et al.* [3.3] to resuscitate and cool newborn infants who were unresponsive (Apgar 0–3) after 5 min. Infants were taken out of the cold bath when breathing resumed. Reproduced with permission from the publisher.

The influence of the thermal environment upon the survival of newly born premature infants

WA Silverman, JW Fertig and AP Berger
3975 Broadway, New York 32, New York.

Pediatrics, Nov 1958, 876-886, Vol 22, No. 5

- *"Survival overall was 68% in the hypothermic group vs 83% in the warmer incubators".*

- *Majority of the effect was in infants with birth weights <1000 g*

Hypothermia & Brain Cell death

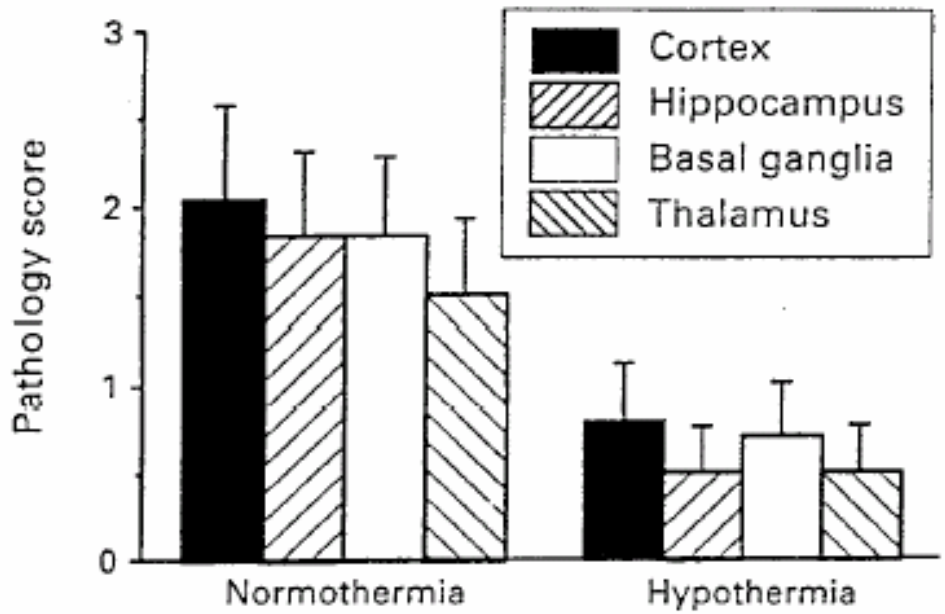


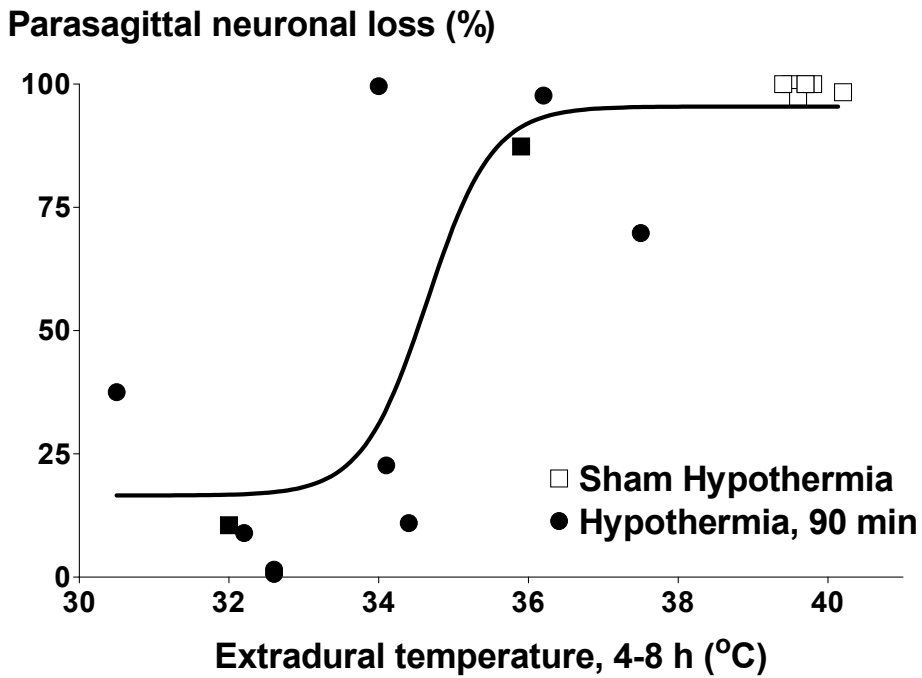
Figure 3. The total pathology score (mean +SEM) in different regions of the brain of newborn rats who survived 1 week after an experimental H-I insult and were randomized to normothermia or hypothermia (32°C) for the first 3 h after the insult. There is significant protection by hypothermia in all regions of the brain [16]. Reproduced with permission from the publisher.

Thoreson 1996 Arch Dis Child

Mechanics I

Magnitude of Hypothermia

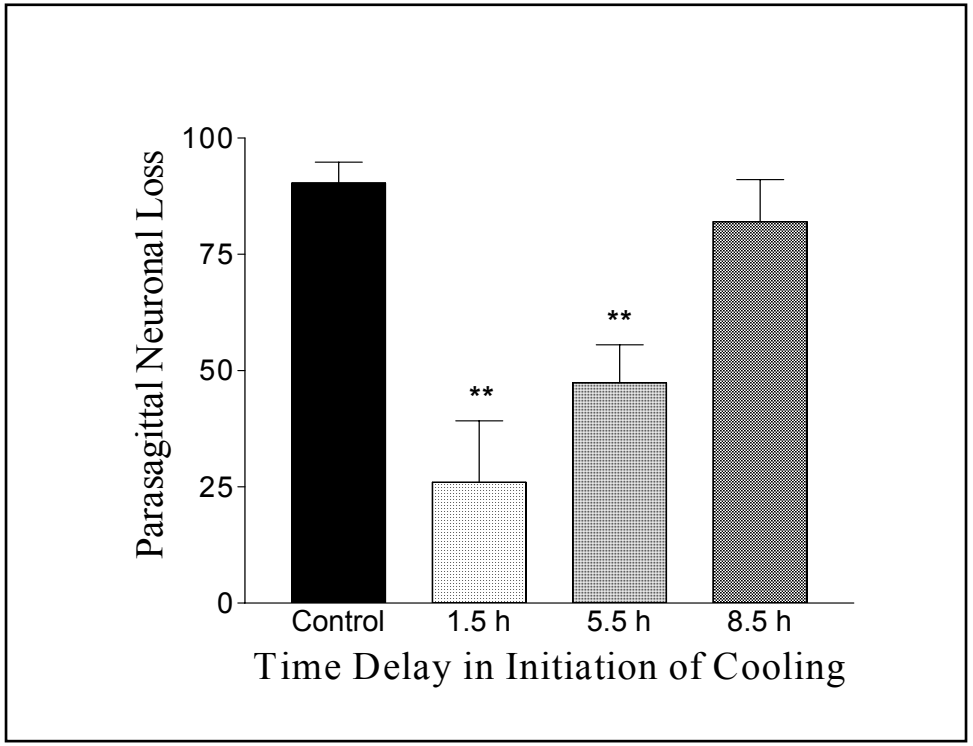
- Critical depth of cooling (Deep brain structures)
  - 1°C fall = ↓ Cerebral metabolic rate 6-7%



- Critical brain temperature < 35°

Mechanics II

'Temporal Window of Opportunity'

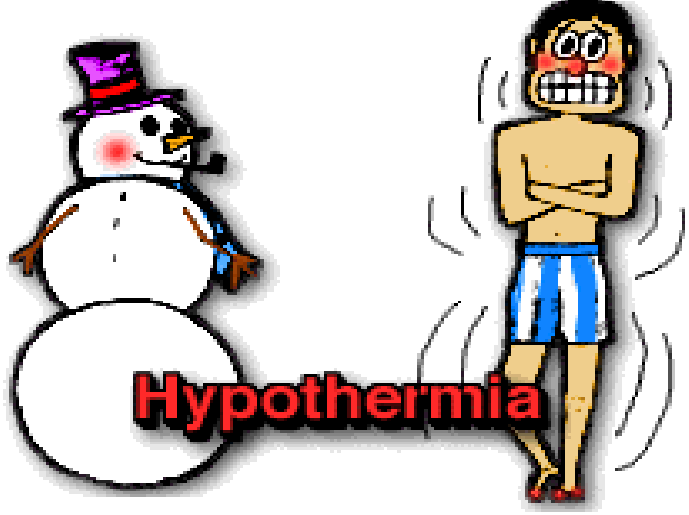


- Neural protection is long lasting, but benefit is reduced if cooling is delayed.

Duration of cooling

- Long enough to prevent, not delay cell loss
- Continued throughout period of secondary energy failure [**Presumption 72 hours**]
  - Seizures on rapid rewarming - fetal ovine data
  - Extrapolation to the human [heterogenous insult] is difficult

Summary



Cell death is preventable

…..but only if applied **early** and a **critical temperature range** is achieved

Is Hypothermia Effective in Humans?

Hypothermia

Whole Body

Cooling blanket

Selective Head

Infant with CoolCap

Coolcap method

ICE trial method

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

◂ Previous Volume 353:1574-1584 October 13, 2005 Number 15 Next ▸

Whole-Body Hypothermia for Neonates with Hypoxic–Ischemic Encephalopathy

Seetha Shankaran, M.D., Abbot R. Laptook, M.D., Richard A. Ehrenkranz, M.D., Jon E. Tyson, M.D., M.P.H., Scott A. McDonald, B.S., Edward F. Donovan, M.D., Avroy A. Fanaroff, M.D., W. Kenneth Poole, Ph.D., Linda L. Wright, M.D., Rosemary D. Higgins, M.D., Neil N. Finer, M.D., Waldemar A. Carlo, M.D., Shahnaz Duara, M.D., William Oh, M.D., C. Michael Cotten, M.D., David K. Stevenson, M.D., Barbara J. Stoll, M.D., James A. Lemons, M.D., Ronnie Guillet, M.D., Ph.D., Alan H. Jobe, M.D., Ph.D., for the National Institute of Child Health and Human Development Neonatal

Reduction in death or moderate/severe disability from 62% (n=64) to 42% (n=45) with whole body cooling

Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: multicentre randomised trial

Peter D Gluckman, John S Wyatt, Denis Azzopardi, Roberta Ballard, A David Edwards, Donna M Ferriero, Richard A Polin, Charlene M Robertson, Marianne Thoresen, Andrew Whitelaw, Alistair J Gunn, on behalf of the Cool Cap Study Group

Lancet 2005; 365: 663–70

See Comment page 632

No difference in death or moderate/severe disability between control [66%, (n=73)] and selective head cooling group [55%, (n=59)]

Hypothermia : Overview

Death / Disability

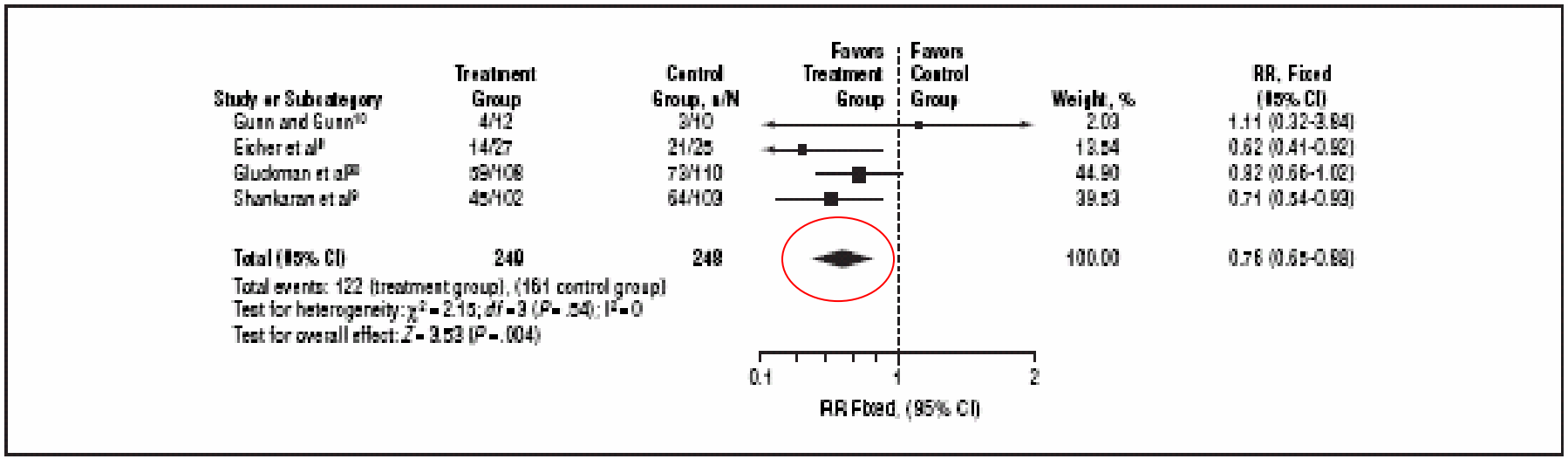


Figure 2. Death or moderate to severe neurodevelopmental disability in survivors. CI indicates confidence interval; RR, relative risk.

Shah 2007 Arch Pediatr

TOBY TRIAL

Table 2. Main Neurodevelopmental Outcomes at 18 Months.

Outcome	Cooled Group	Noncooled Group	P Value	Relative Risk (95% CI)
	no./total no. (%)			
Primary outcome				
Combined death and severe neurodevelopmental disability	74/163 (45)	86/162 (53)	0.17	0.86 (0.68–1.07)
Secondary outcomes*				
Death	42/163 (26)	44/162 (27)	0.78	0.95 (0.66–1.36)
Severe neurodevelopmental disability	32/120 (27)	42/117 (36)	0.13	0.74 (0.51–1.09)
Survival without neurologic abnormality	71/163 (44)	45/162 (28)	0.003	1.57 (1.16–2.12)
Multiple neurodevelopmental disabilities	21/112 (19)	33/110 (30)	0.05	0.63 (0.39–1.01)
BSID-II Mental Developmental Index score			0.03 for trend	
<70	28/115 (24)	38/110 (35)	0.09	0.70 (0.47–1.06)
70–84	6/115 (5)	12/110 (11)		
≥85	81/115 (70)	60/110 (55)	0.01	1.29 (1.05–1.59)
BSID-II Psychomotor Developmental Index score			0.03 for trend	
<70	27/114 (24)	37/109 (34)	0.09	0.70 (0.46–1.06)
70–84	9/114 (8)	14/109 (13)		
≥85	78/114 (68)	58/109 (53)	0.02	1.29 (1.04–1.60)
GMFCS score			0.01 for trend	
No abnormality	85/120 (71)	63/117 (54)	0.007	1.32 (1.07–1.61)
1–2	11/120 (9)	18/117 (15)		
3–5	24/120 (20)	36/117 (31)	0.06	0.65 (0.41–1.02)
Cerebral palsy	33/120 (28)	48/117 (41)	0.03	0.67 (0.47–0.96)
Hearing loss not corrected by aids	4/114 (4)	7/108 (6)	0.31	0.54 (0.16–1.80)
No useful vision	8/119 (7)	12/114 (11)	0.30	0.64 (0.27–1.50)
Seizures requiring anticonvulsant agents at time of assessment	12/116 (10)	16/116 (14)	0.42	0.75 (0.37–1.51)
Head circumference at follow-up >2 SD below the mean	24/114 (21)	28/112 (25)	0.48	0.84 (0.52–1.36)

Azzopardi 2009 NEJM

Whole-body hypothermia for term and near-term newborns with hypoxic-ischemic encephalopathy.

A randomized controlled trial

Susan E. Jacobs, M.D., Colin J. Morley, M.D., Terrie E. Inder, M.D., Michael J. Stewart, M.D., Katherine R. Smith, MBiostat., Patrick J. McNamara, M.D., Ian M.R. Wright, M.D., Haresh M. Kirpalani, M.D., Brian A. Darlow, M.D., Lex W. Doyle, M.D., for the ICE Collaboration.

OUTCOMES ICE TRIAL

Outcome	Cool Group	Control Group	Risk Ratio (95% CI)	P Value
	n/total n (%)			
Primary outcome				
Death or major disability	55/107 (51.4)	67/101 (66.3)	0.77 (0.62, 0.98)	0.03
Encephalopathy at assessment:				
Mild	4/16 (25.0)	8/24 (38.1)	0.53 (0.17, 1.66)	0.27
Moderate	26/62 (42.6)	34/54 (66.7)	0.64 (0.45, 0.91)	0.01
Severe	25/30 (83.3)	24/29 (88.9)	0.94 (0.76, 1.15)	0.54
Moderate or severe	51/92 (55.4)	58/83 (69.9)	0.75 (0.60, 0.94)	0.01
Secondary outcomes				
Death	27/108 (25.0)	42/109 (38.5)	0.65 (0.43, 0.97)	0.04
Major sensorineural disability	28/80 (35.0)	25/59 (42.4)	0.83 (0.54, 1.26)	0.37
Neuromotor delay	23/79 (29.1)	19/59 (32.2)	0.90 (0.55, 1.50)	0.70
Cerebral palsy	21/79 (26.6)	17/59 (28.8)	0.92 (0.54, 1.59)	0.77
Moderate or severe CP	16/79 (20.3)	13/59 (22.0)	0.92 (0.48, 1.76)	0.80
GMFCS 2-5	16/79 (20.3)	12/58 (20.7)	0.98 (0.50, 1.91)	0.95
Motor score on Bayley scales <-2 SD	19/73 (26.0)	14/50 (28.0)	0.93 (0.52, 1.68)	0.81
Developmental score on Bayley scales <-2 SD	17/73 (23.3)	14/50 (28.0)	0.83 (0.45, 1.53)	0.55
Legal blindness	1/78 (1.3)	0/58 (0)		0.99
Survival free of any disability	42/106 (39.6)	22/97 (22.7)	1.75 (1.13, 2.70)	0.01

Jacobs 2010 PAS

Cooling in Toronto

- ICE TRIAL terminated in 2008 on the basis of loss of equipoise

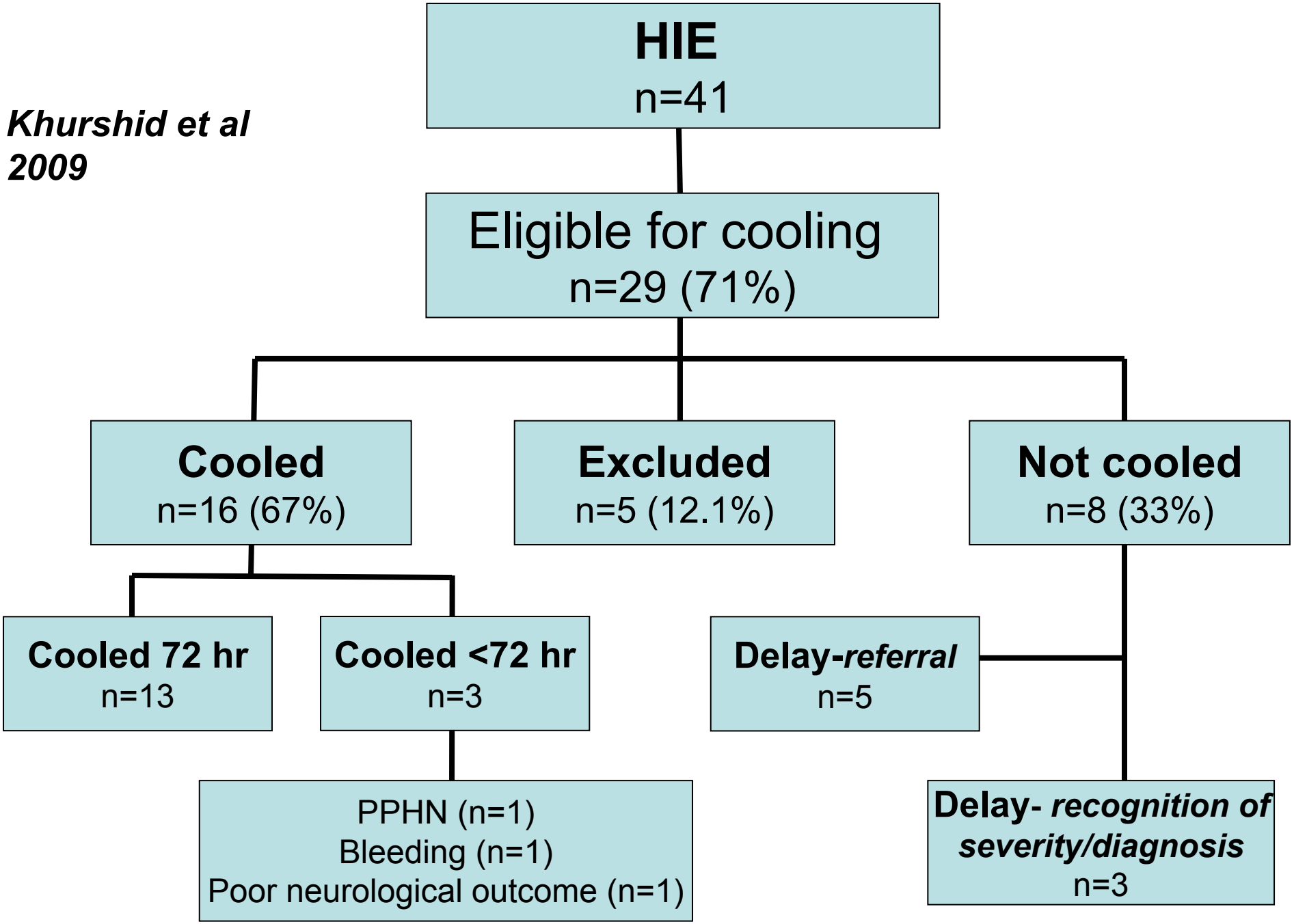
- ICE method in transport
- Blanketrol III in NICU

- Cooling offered at all three tertiary sites
- 40-50 cases per year

Inclusion criteria

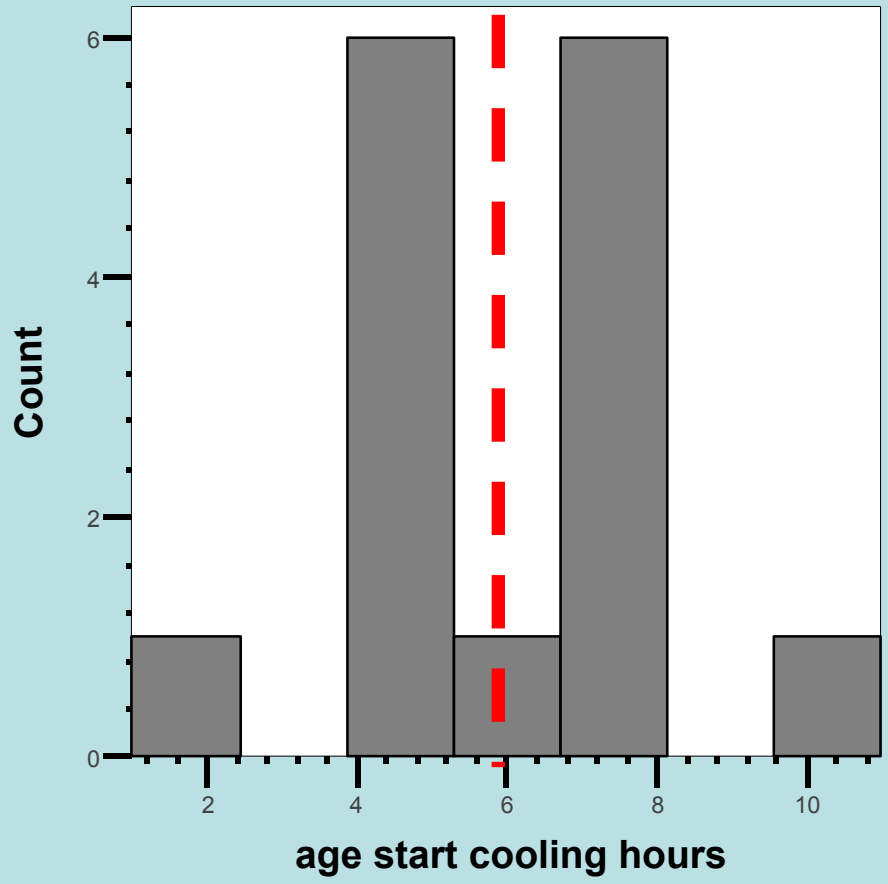
- < 6 hours (maximum of 12 hours)
- > 35 weeks gestational age
- Evidence of **intrapartum hypoxia**
  - Apgar score < 5 at 10 minutes
  - need for mechanical ventilation or resuscitation beyond 10 minutes,
  - cord pH < 7 or arterial pH < 7, base deficit > 16 within 60 minutes of birth.
- **Moderate or severe encephalopathy**

Khurshid et al 2009

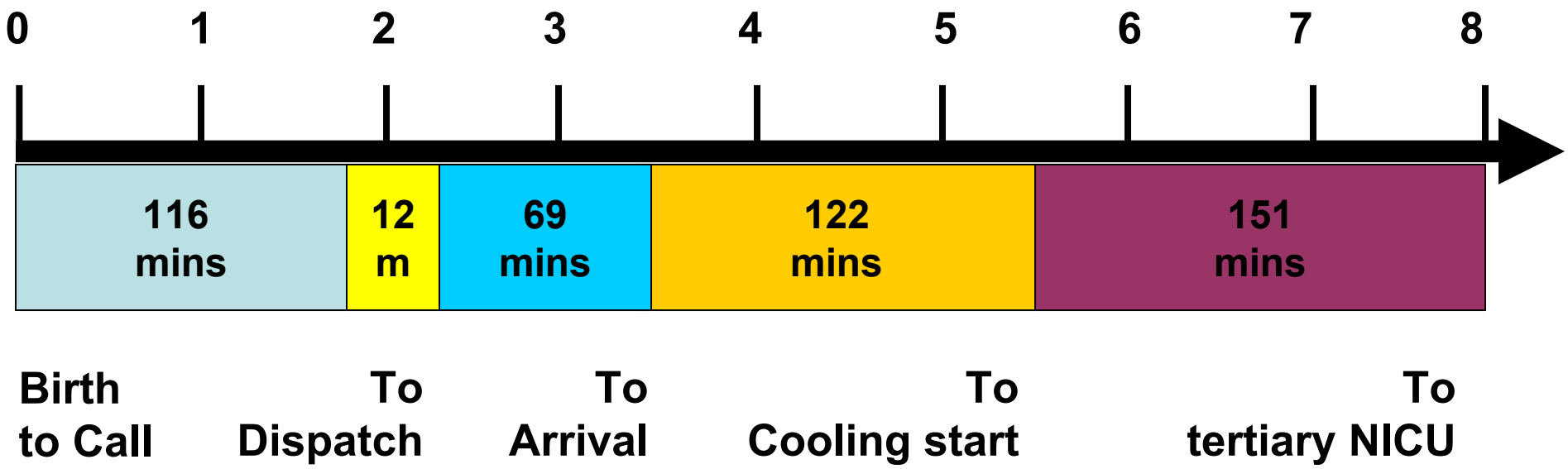


Hypothermia [Age at Initiation]

Median 6 hours (range 1, 11; IQR



Khurshid et al 2009


0
1
2
3
4
5
6
7
8
116 mins
12 m
69 mins
122 mins
151 mins
Birth to Call
To Dispatch
To Arrival
To Cooling start
To tertiary NICU

Therapeutic hypothermia on neonatal transport

1. ***Decision to implement*** based on the geographics of the referral base and neonatal transport team capabilities

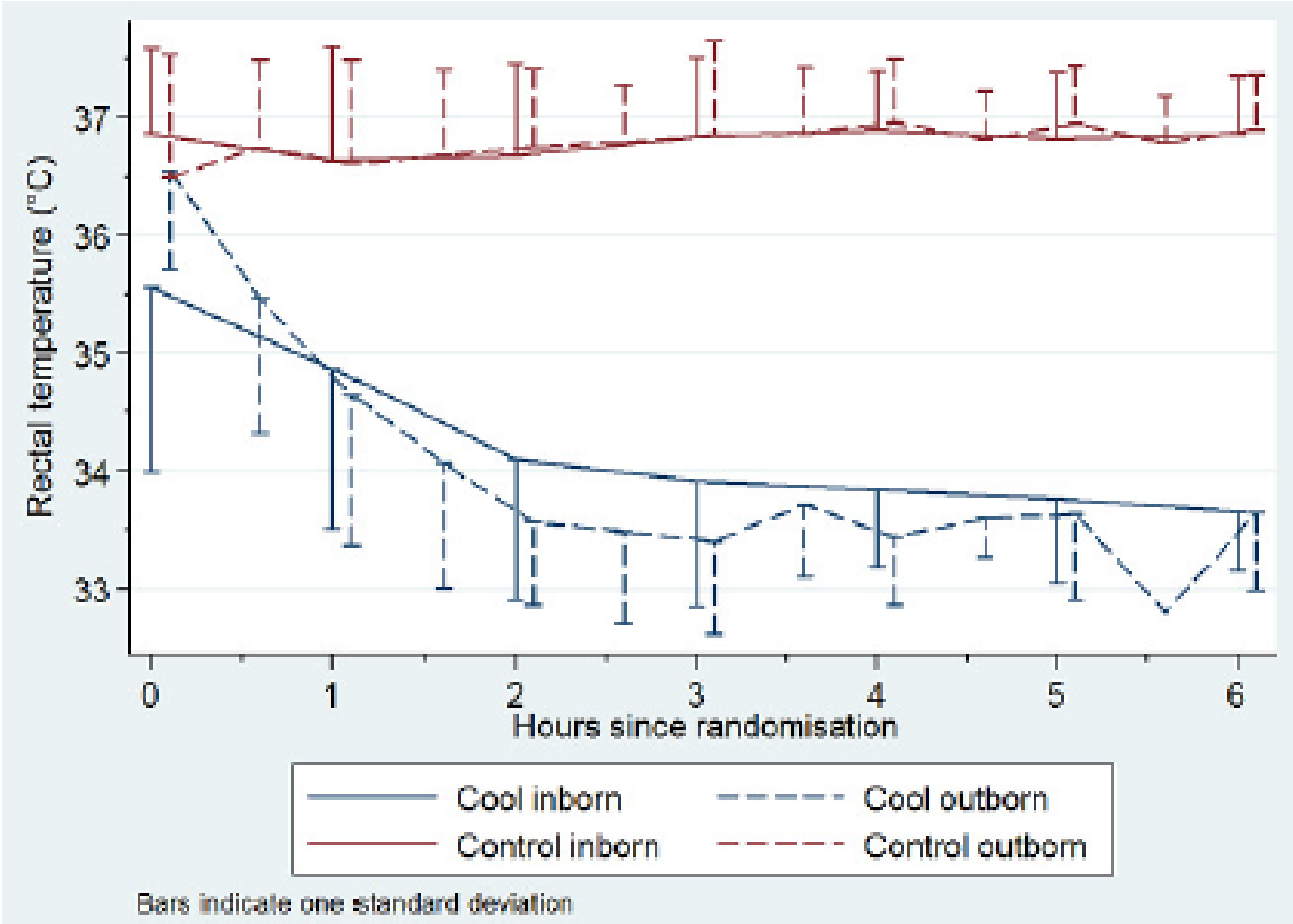
2. Establish ***protocols*** and organize ***education*** sessions (including neurological assessment)

3. ***Equipment***: system for continuous rectal temperature monitoring throughout cooling and transport, cool gel packs, receiving blankets and transport incubator

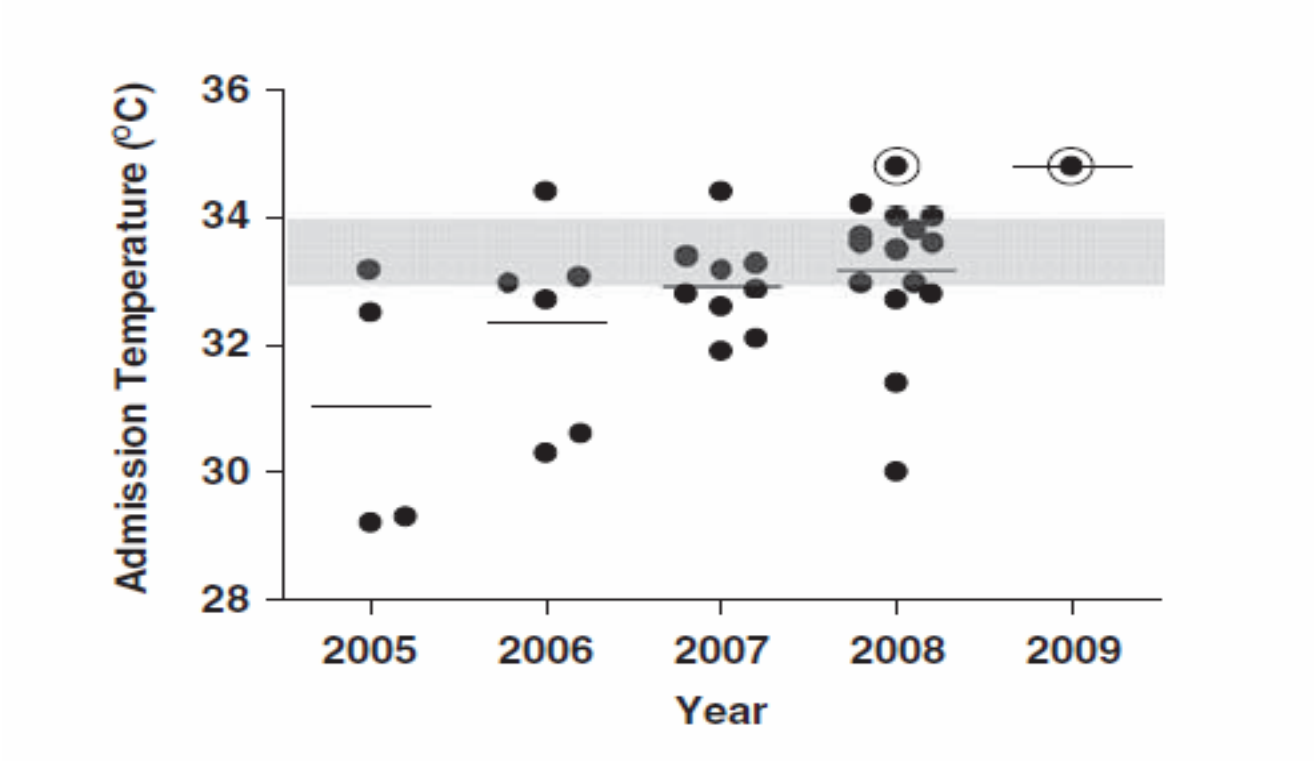
4. Consider ***passive cooling*** and/or targeting temperature **34–35ºC** in start-up phase to avoid overcooling

5. Maintain flow sheets and ***database*** for recording clinical data for quality assessment and improvement

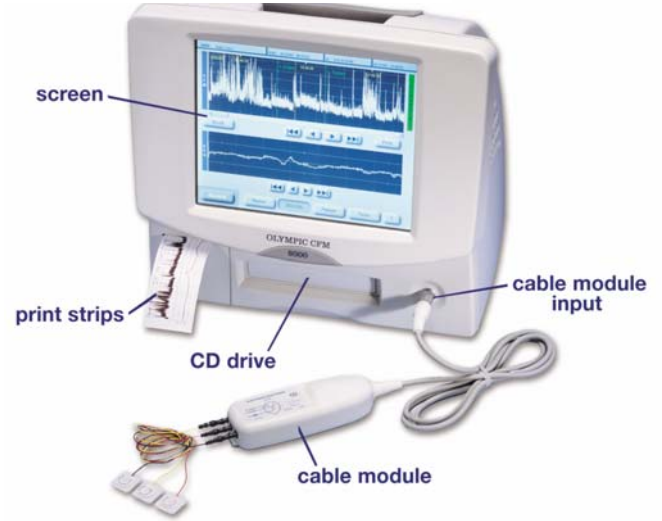
Figure 2B Temperature during transport and the 6 hour initiation of intervention period by birth hospital status

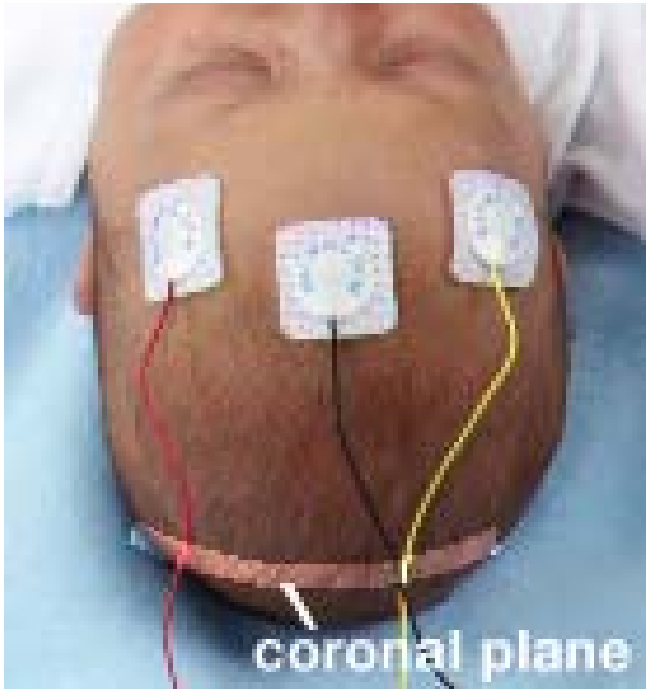


Cooling in Transport

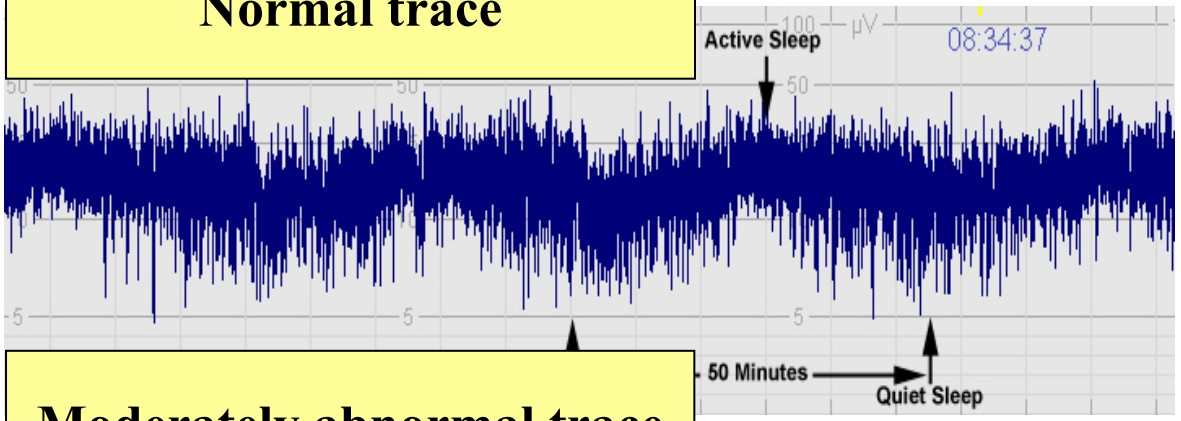


Fairchild 2010 J Perinat

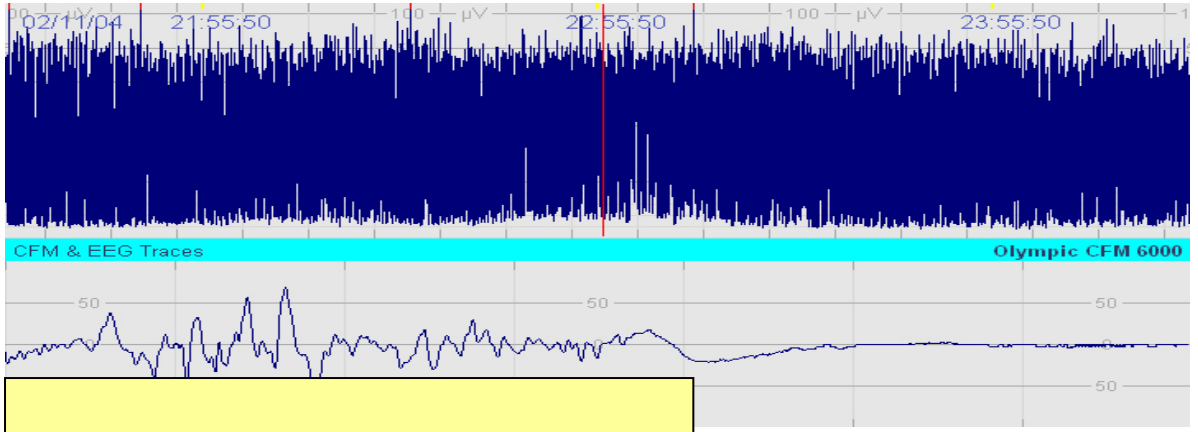




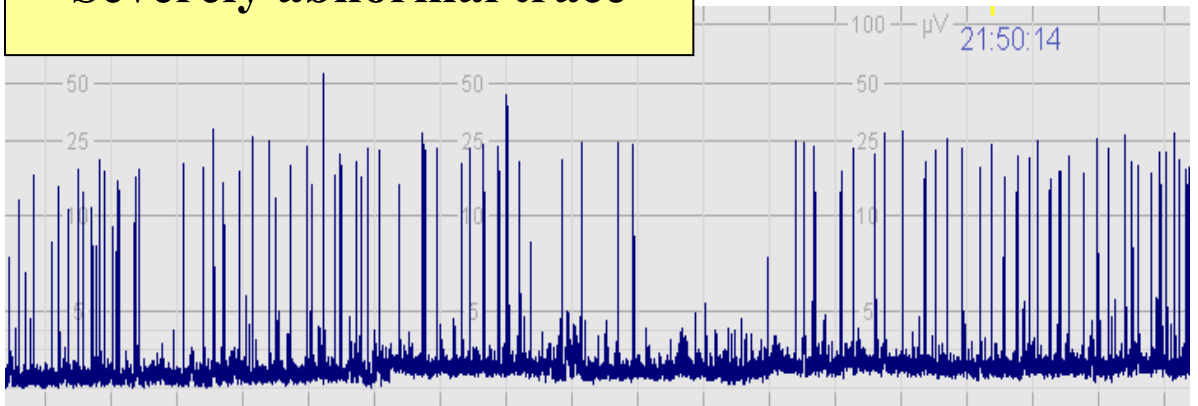
Normal trace



Moderately abnormal trace



Severely abnormal trace



Selective Head Cooling

	Cooled	Control	p value
Intermediate aEEG group, n=172			
Died or severe disability at 18 months	40 (48%)	58 (66%)	0·02
Died	24 (29%)	34 (39%)	0·20
Severe neuromotor disability	7 (12%)	15 (28%)	0·03
Bayley MDI† <70	15 (25%)	20 (40%)	0·15
Bilateral cortical visual impairment	4 (7%)	7 (14%)	0·34
Secondary outcomes			
Multiple disabilities	8 (14%)	14 (28%)	0·10
Bayley PDI <70	14 (24%)	18 (39%)	0·13
Bilateral sensorineural hearing loss	3 (6%)	1 (2%)	0·63
Epilepsy	8 (13%)	8 (15%)	0·79
Continuous BSID II scores (median, range)			
Bayley MDI	85 (49–116)	77·0 (49–119)	0·04
Bayley PDI	89·5 (49–127)	84·5 (49–125)	0·047
Severe aEEG group, n=46			
Died or severe disability at 18 months	19 (79%)	15 (68%)	0·51
Died	12 (50%)	8 (36%)	0·39
Severe neuromotor disability	7 (58%)	6 (43%)	0·70
Bayley MDI§ <70	6 (55%)	4 (36%)	0·67
Bilateral cortical visual impairment	3 (25%)	4 (31%)	1·00
Secondary outcomes			
Multiple disabilities	7 (58%)	6 (43%)	0·70
Bayley PDI <70	7 (64%)	5 (50%)	0·67
Bilateral sensorineural hearing loss	2 (22%)	2 (17%)	1·00
Epilepsy	3 (25%)	3 (21%)	1·00

Tips for Community Hospitals

- **Early Referral** (risk factors & any encephalopathy)
- **Avoid Hyperthermia** – maintain normal temperature

Is there harm from elevated temperature?

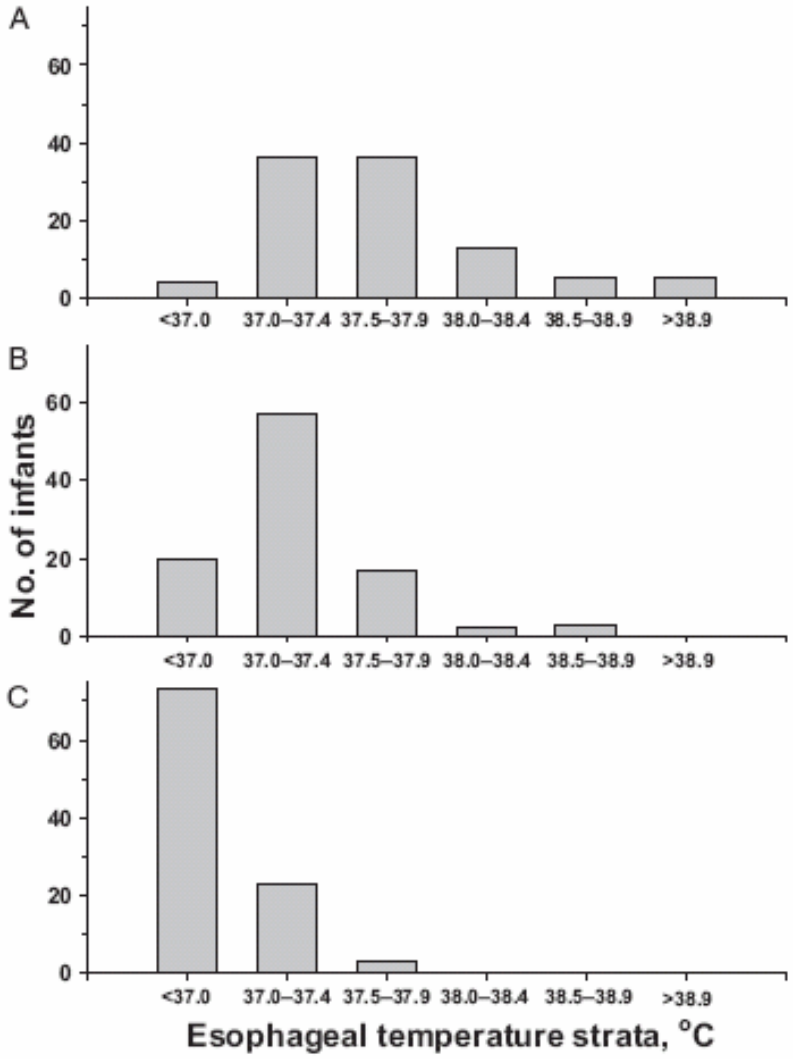


TABLE 1 ORs Relating Esophageal Temperatures to Adverse Outcomes for Control Infants

Esophageal Temperature	OR (95% CI)		
	Death or Disability (n = 99)	Death (n = 99)	Disability (n = 65)
Highest quartile	4.0 (1.5–11.2)	6.2 (2.1–17.9)	1.8 (0.4–8.2)
Median	3.2 (0.9–11.2)	5.9 (1.5–22.7)	1.0 (0.2–5.1)
Lowest quartile	1.5 (0.6–3.5)	1.4 (0.6–3.3)	1.1 (0.3–3.5)

Need for Adjunctive Therapy

- > 40% patients fail to respond to therapeutic hypothermia – ***biological*** constraints
- Access to expensive equipment – ***financial*** constraints
- Challenges of maintaining target temperature outside of NICU setting – ***logistic*** constraints
- Temporal delay in initiation of hypothermia – ***geographical*** constraints

Adjunctive Phenobarbitone

GABA agonist

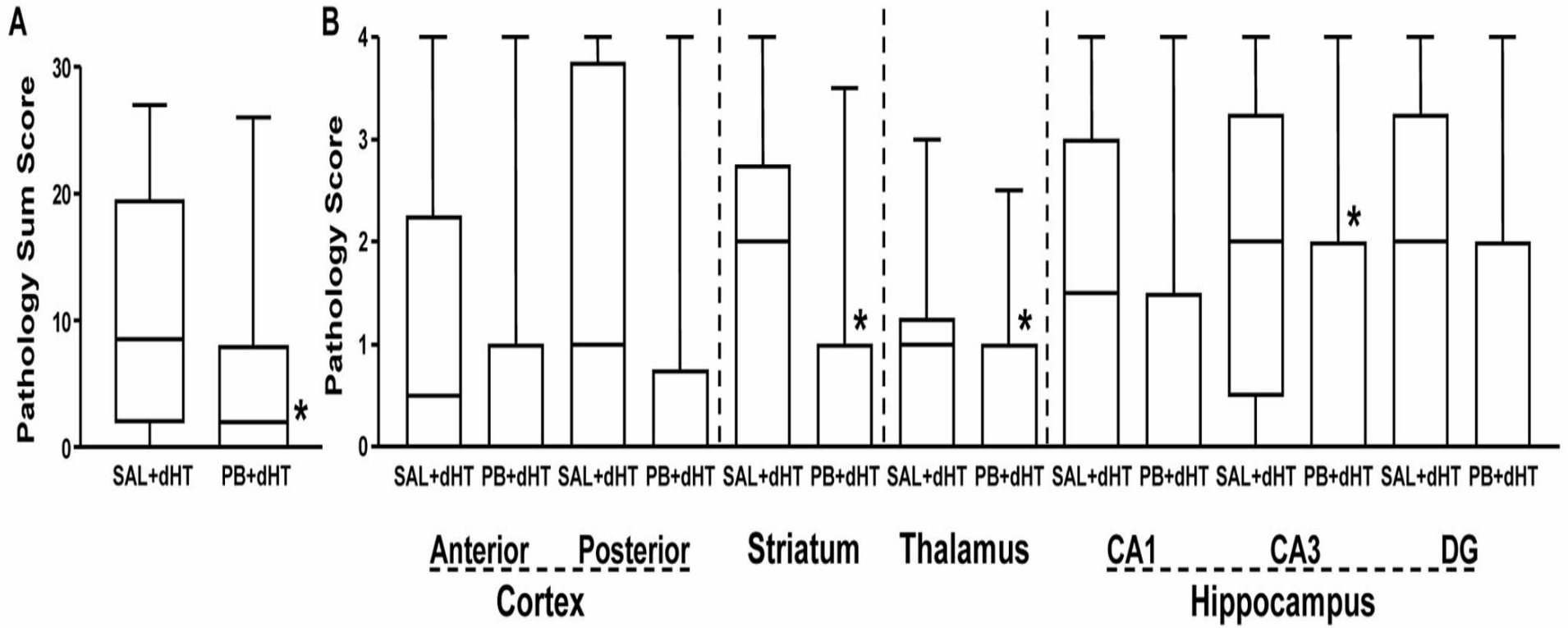
- Reduced cerebral metabolic demand
- Antioxidant
- Decreased cerebral edema

  Nilsson 1971 Acta Neurol, Crane 1978 Stroke, Singh 2004 J Perinat Med

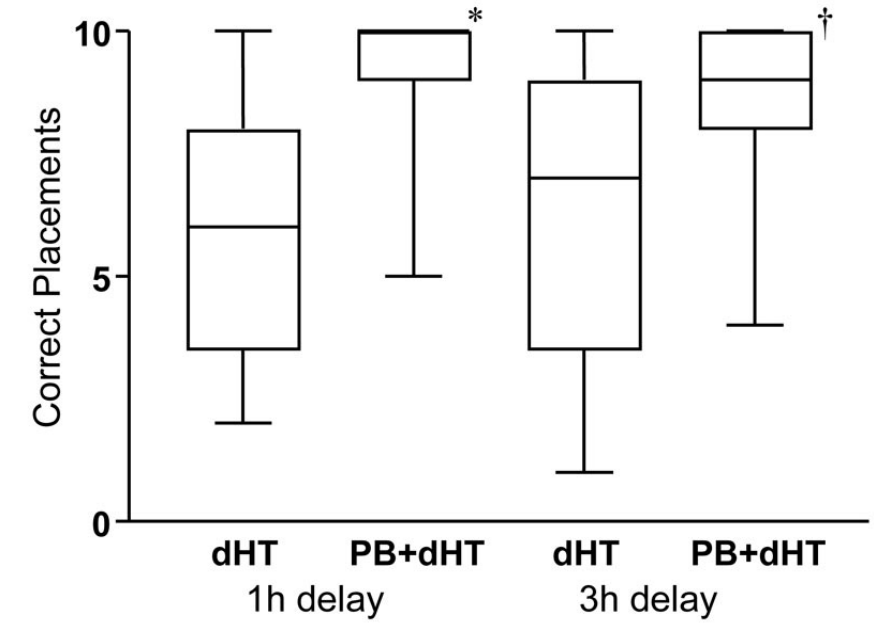
- Potential synergism with bumetanide
  - maturational changes in neuronal chloride transporter expression on GABA receptor function
  - blocking the neonatal neuronal chloride transporter with bumetanide can augment the inhibitory activity of GABA agonists

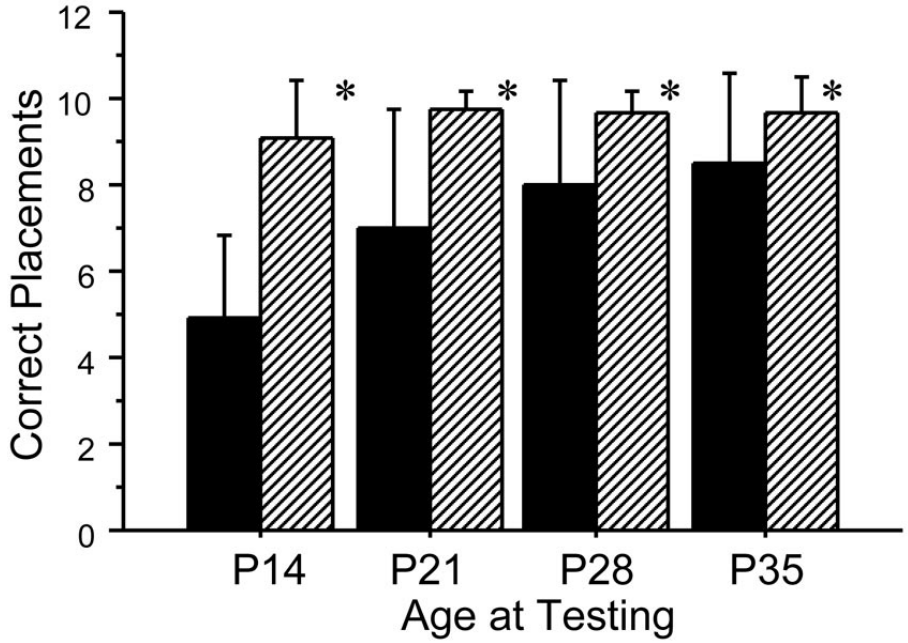
Dzhala 2008 Ann Neurol

Phenobarbitone and Neuroprotection



Barks 2010 Ped Res





Barks 2010 Ped Res

Adjunctive Xenon

- Acts postsynaptically
  - reduce excitotoxicity (inhibition of NMDA subtype of glutamate receptor)
  - prevents apoptosis by actions preceding translocation of Bax.

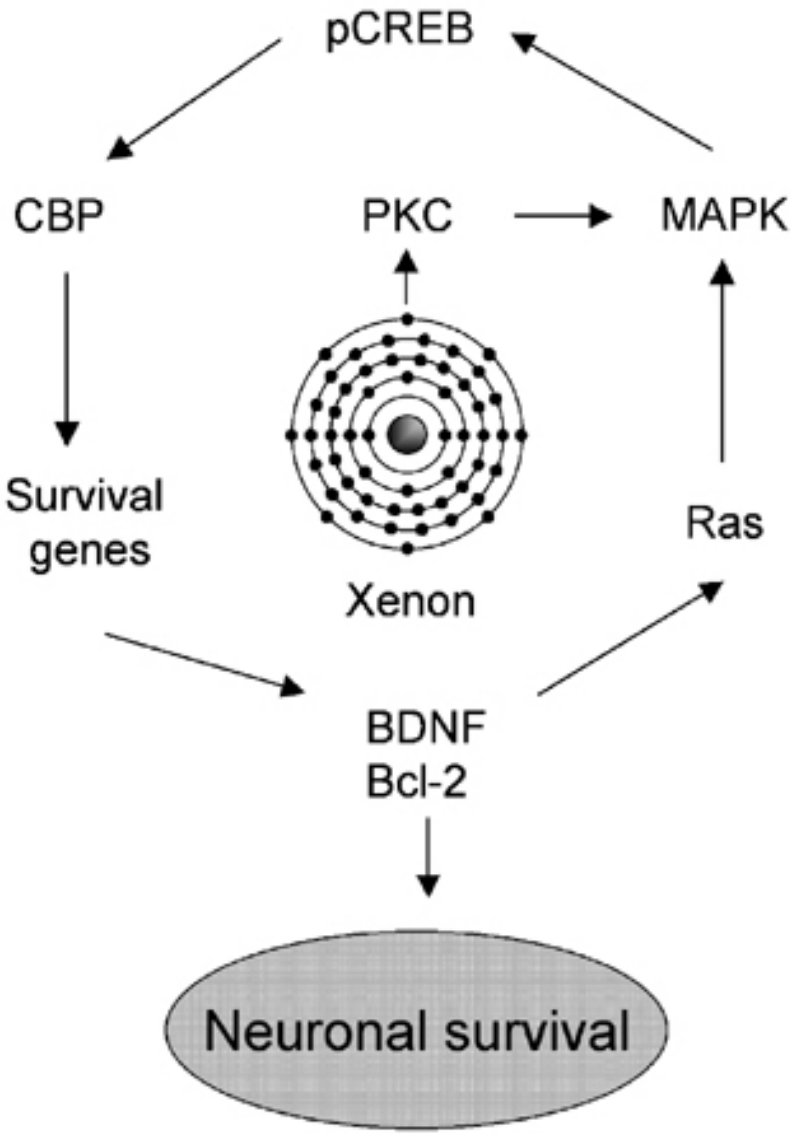
Ma 2005 Ann Neurol

- Efficacious in various models of pharmacological induced apoptosis
  - protein kinase inhibitor-induced
  - soflurane-induced apoptosis

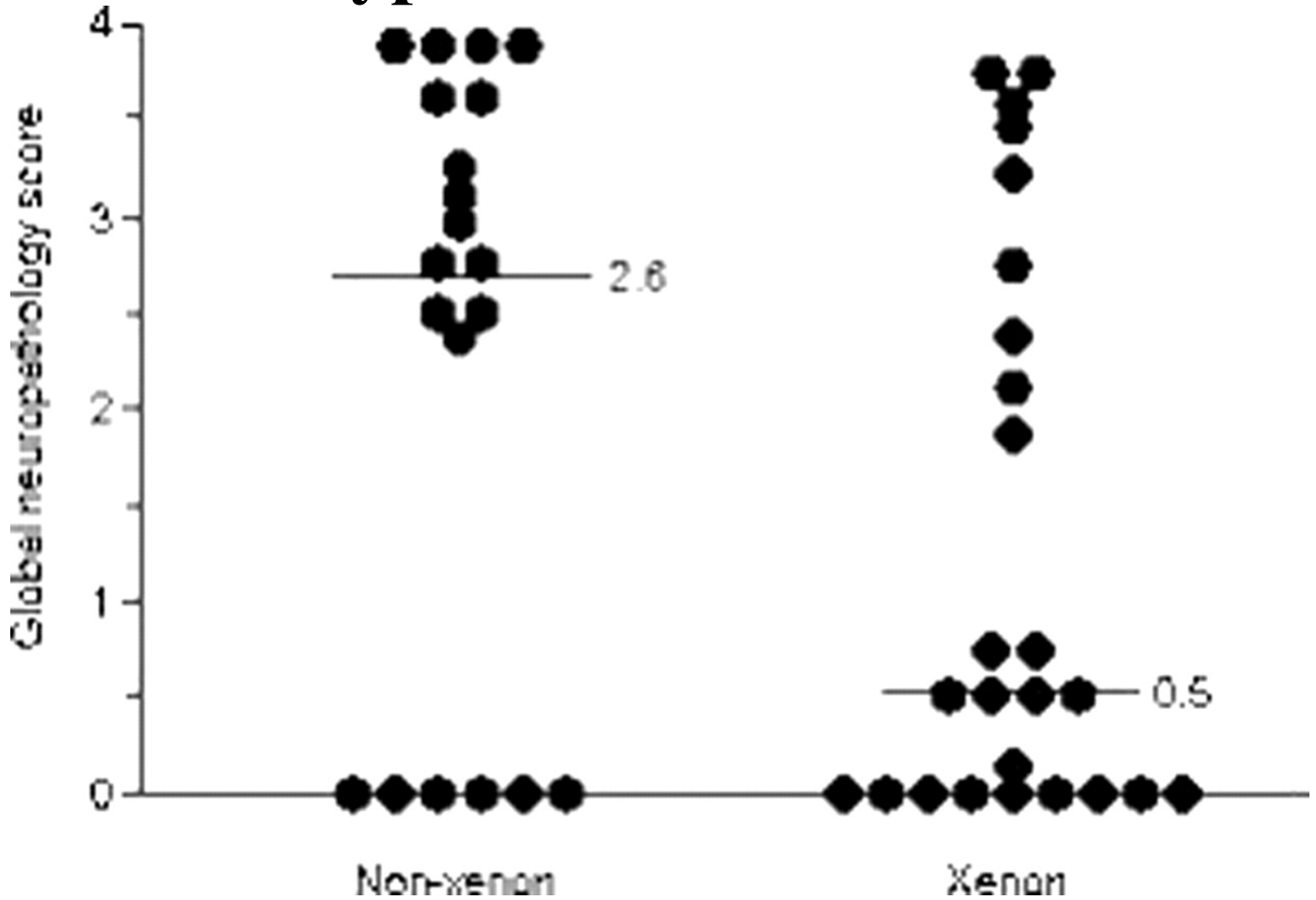
Sanders 2005 Anesthesiol

- Upregulates anti-apoptotic proteins in a preconditioning paradigm

Ma 2006 J Cereb Blood Flow Metab



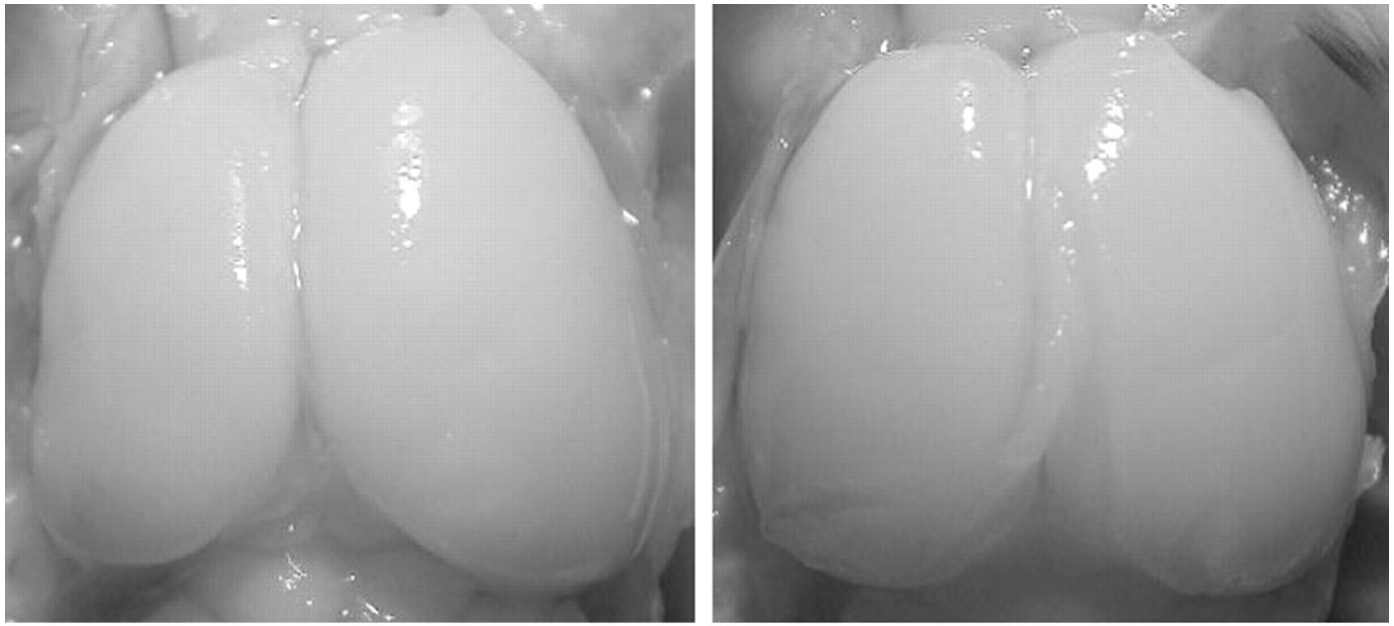
NEUROPATHOLOGY SCORES – Hypoxia Rodent Model



Dingley, J. et al. Stroke 2006;37:501-506

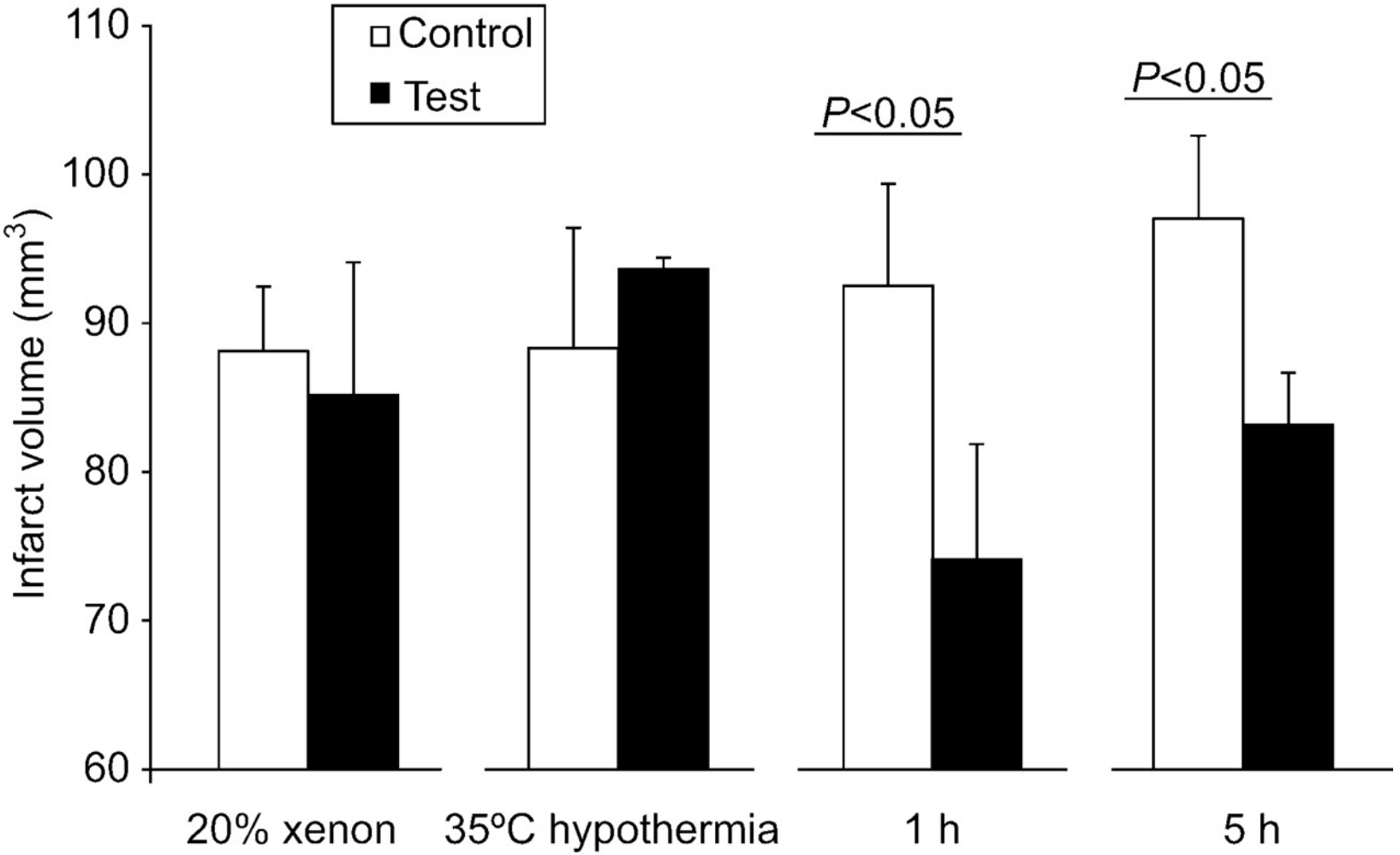
Stroke

Dorsal views of typical brains from both groups



Dingley, J. et al. Stroke 2006;37:501-506

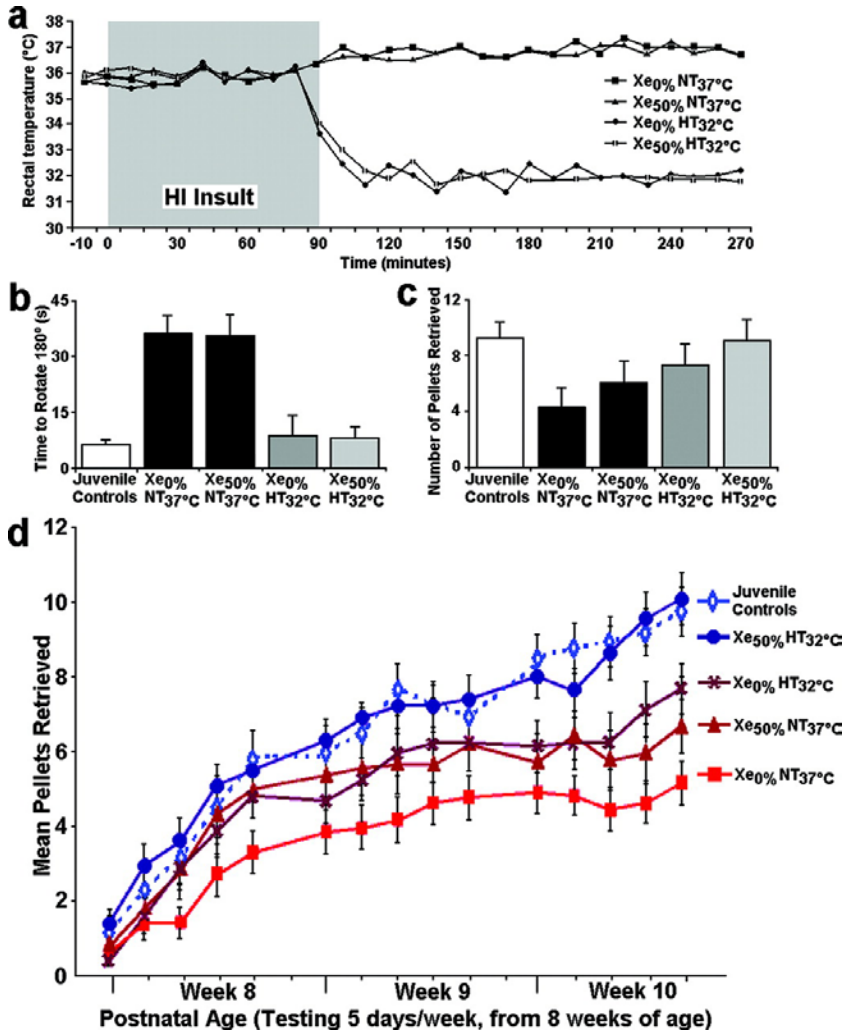
Infarct size and Hypothermia / Xenon



Martin J L et al. Br. J. Anaesth. 2007;98:236-240

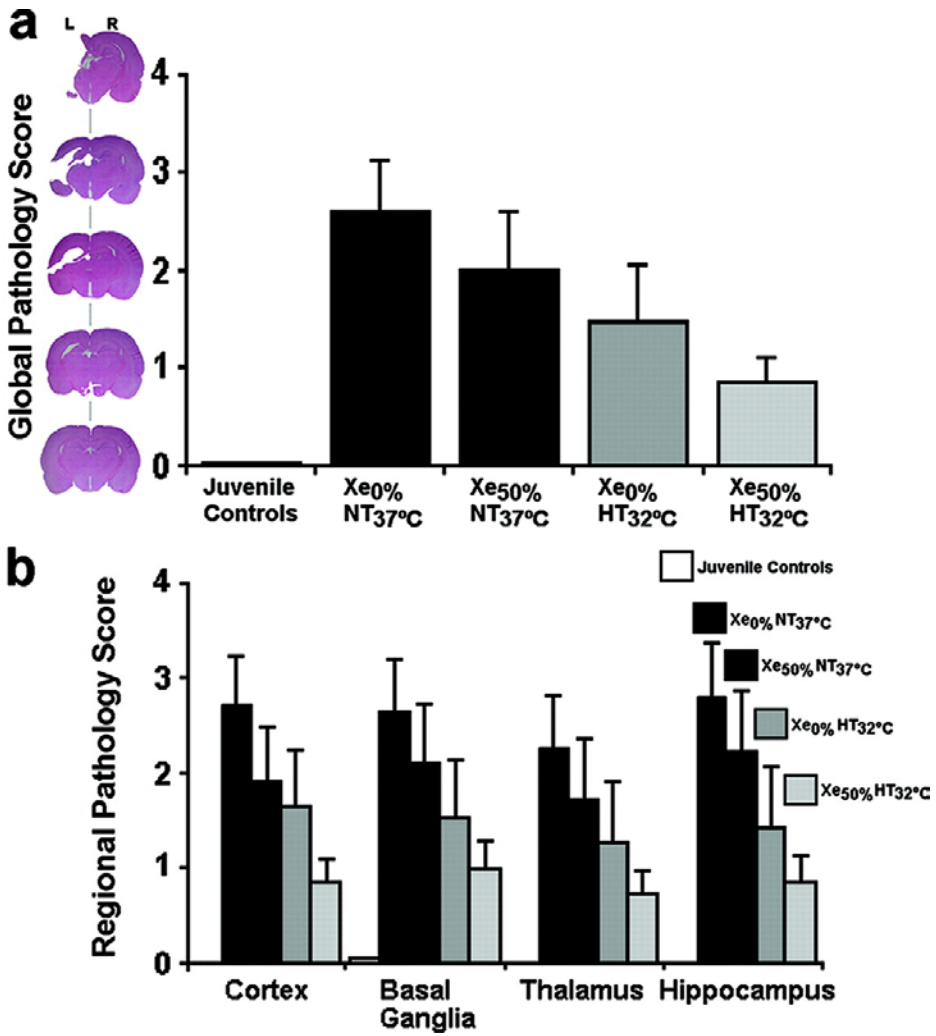
BJA British Journal of Anaesthesia

ion Xenon – Hypothermia & Outcomes



Hobbs, C. et al. Stroke 2008;39:1307-1313

Pathology -Treatment effects at 10-week survival



Hobbs, C. et al. Stroke 2008;39:1307-1313

Stroke

Other strategies

- Oral **topirimate** (anti-glutamataergic)
  - Animal data suggest benefit with/out hypothermia
  - No adverse short term effects in humans *Filippi 2010 J Pediatr*
- **Erythropoeitin** sc
  - Improves sensorimotor function after neonatal rodent HI and protects against cerebral injury (dose-dependent and only females) *Fan 2010 Ped Res*
  - Recent adminsitration to human neonates demonstrated feasibility with lower iNO concentrations *El Mahdy 2010 Pediatrics*
- **Melatonin** (Free radical scavenger/ potent anti-oxidant)
  - Maternal administration to mice model reduced cerebral injury *Hutton 2009 Dev Neurosci*
  - Administration before or after HI in immature rats led to reduced cerebral injury *Carloni 2008 J Pineal Res*

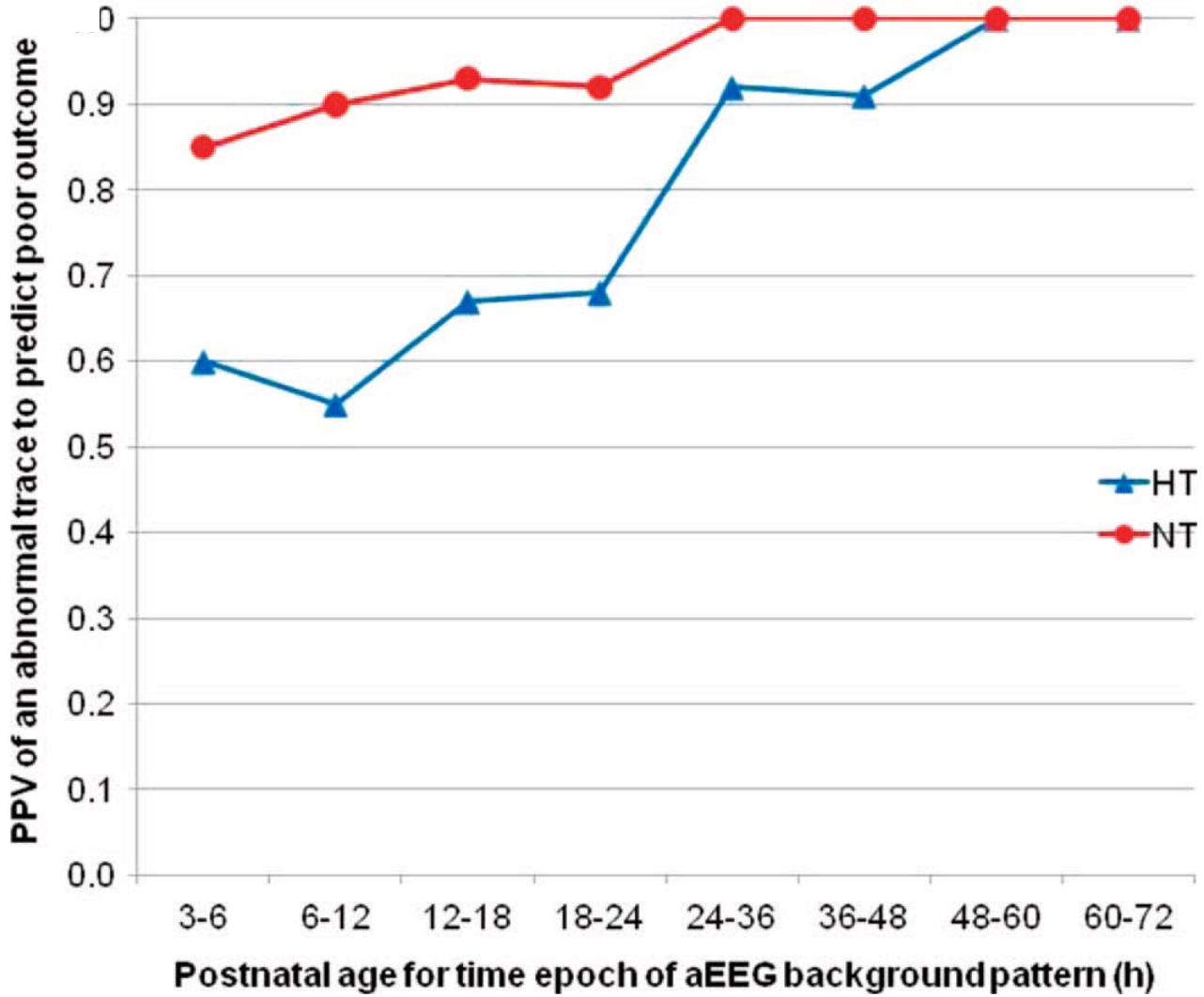
Evaluating Prognosis

- Serial aEEG, EEG predict outcome
  - < 6 hour background
  - Time to recovery of SWS (96% good outcome if recovered by 36 hours)
- MRI scans (Day 2–3) during hypothermia seem to predict later irreversible brain injuries in asphyxiated newborns.

Wintermark 2010 ADC

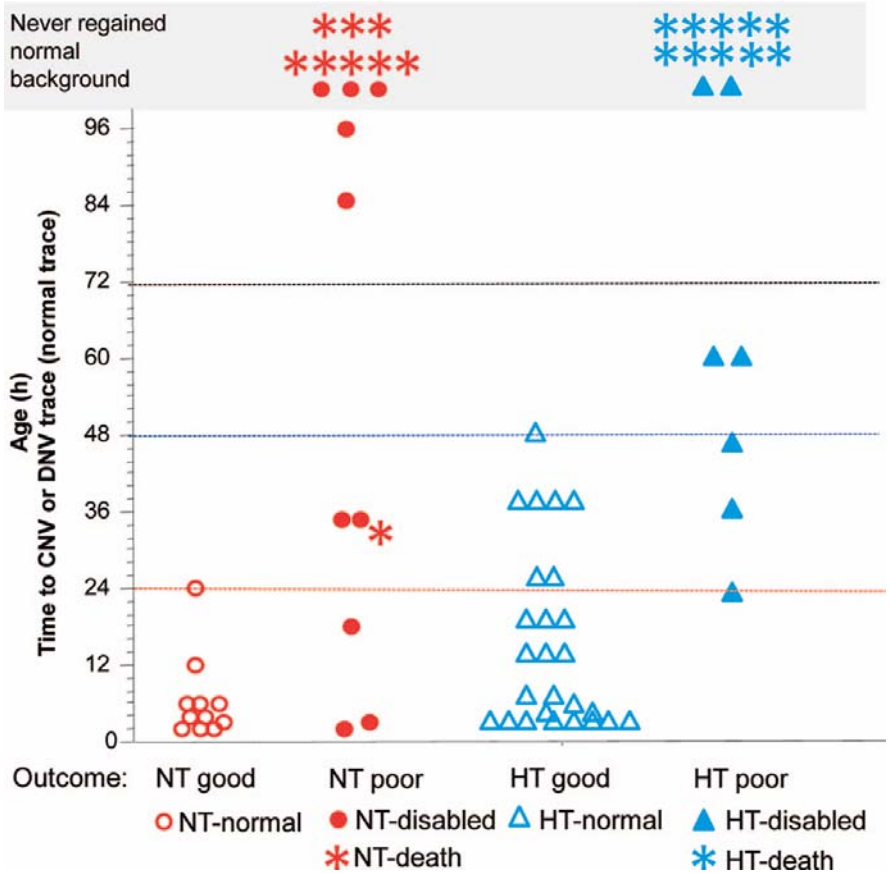
aEEG Transition 0 – 72 hours

Thoreson 2010 Pediatrics

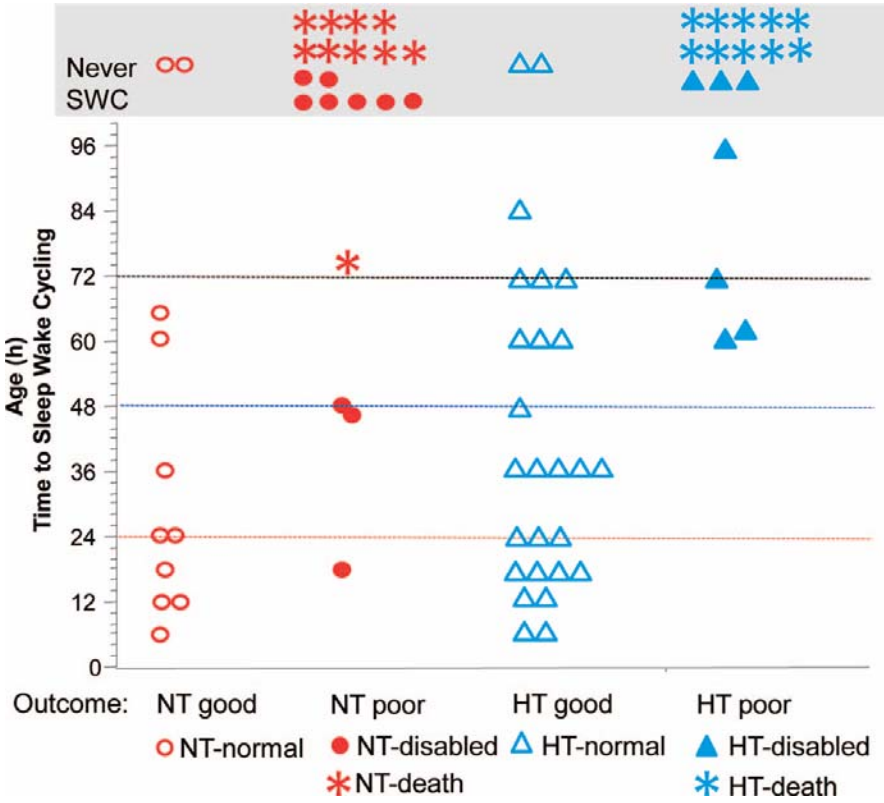


At 36 hours, the odd ratio (OR) for an abnormal trace to predict poor outcome was 10.70 (95% confidence interval [CI]

Normal Background



SWS



MRI FINDINGS

	Cooled (n=64)	Non-cooled (n=67)	Adjusted*		Unadjusted*	
			OR (95% CI)	p	OR (95% CI)	p
Basal ganglia and thalami						
0	26	14	0·36 (0·15–0·84)	0·02	0·39 (0·18–0·84)	0·02
1	11	14				
2	11	14				
3	16	25				
Posterior limb of internal capsule						
Normal	34	23	0·38 (0·17–0·85)	0·02	0·46 (0·23–0·93)	0·03
Equivocal	2	5				
Abnormal	28	39				
White matter						
Normal	23	11	0·30 (0·12–0·77)	0·01	0·35 (0·15–0·80)	0·01
1	19	26				
2	15	21				
3	7	9				
Cortex†						
0	34	24	0·62 (0·27–1·41)	0·25	0·65 (0·29–1·42)	0·28
1	16	22				
2	10	16				
3	4	4				
Intracranial haemorrhage	25	22	Not done		1·31 (0·64–2·68)	0·11

Data are number or OR (95% CI). *Odds ratio for presence or absence of MRI abnormalities in cooled and non-cooled infants, with and without adjustment for severity of amplitude integrated EEG and postnatal age. OR=odds ratio. †Cortex could not be assessed in one infant in the non-cooled group.

Table 2: **Grades of cerebral lesions seen on MRI in cooled and non-cooled infants**

Rutherford 2010 Lancet

Conclusion

- **Hypothermia** is now a **standard therapeutic option** for *neonates with moderate/severe encephalopathy*

- Recommended by AAP, Canadian NRP, NICHD & ILCOR

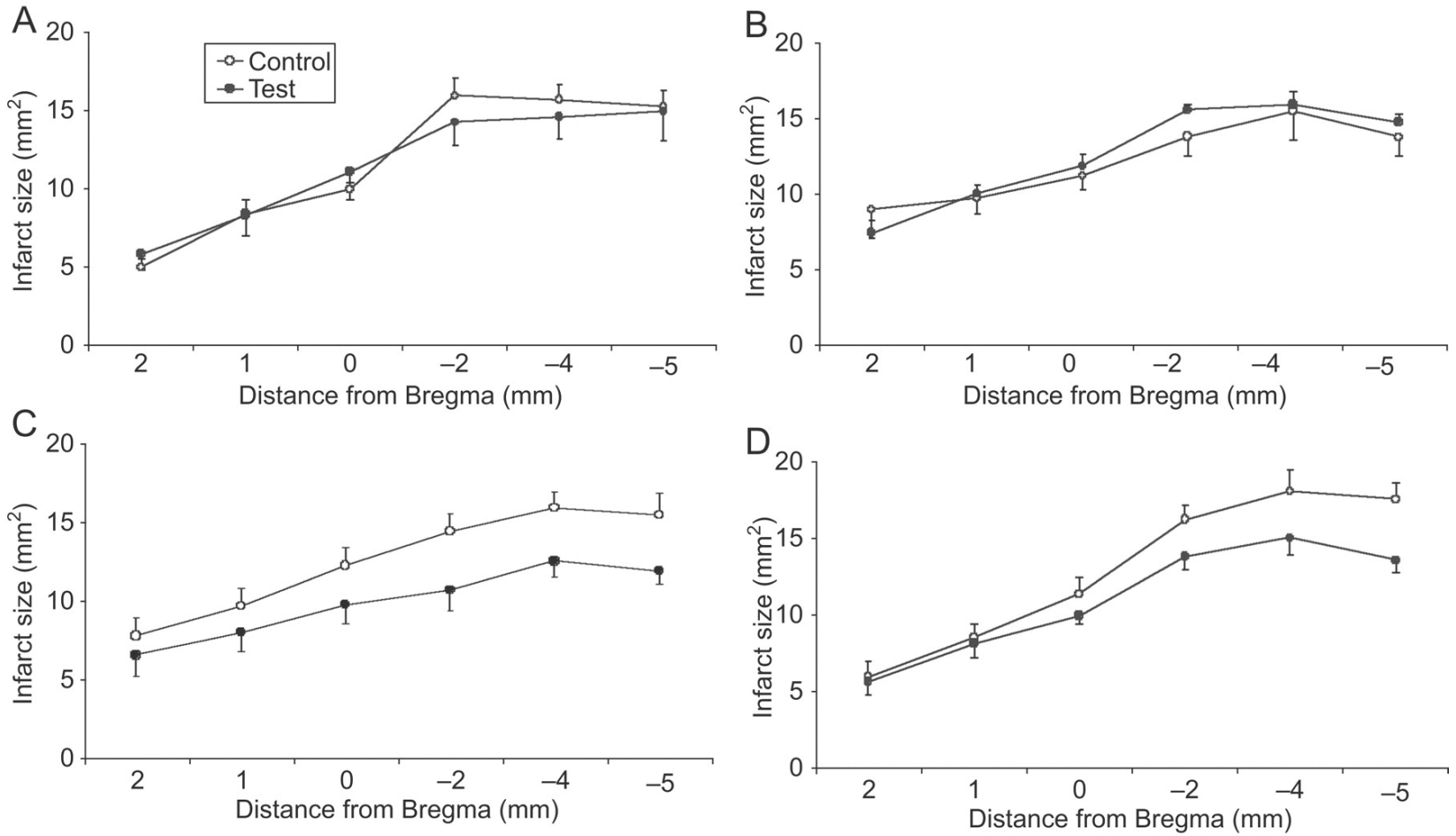
- Challenges of patient selection remain

Future Initiatives

- Gender and genetic influences
- Hypothermia in other clinical settings e.g. post-cardiac arrest, preterm brain injury
- Beyond 6 hours, duration of cooling, rewarming rate
- Combination therapies (anticonvulsants, anti-inflammatory agents)

Thankyou ……

Infarct size in rat pups exposed to hypothermia or xenon



Martin J L et al. Br. J. Anaesth. 2007;98:236-240

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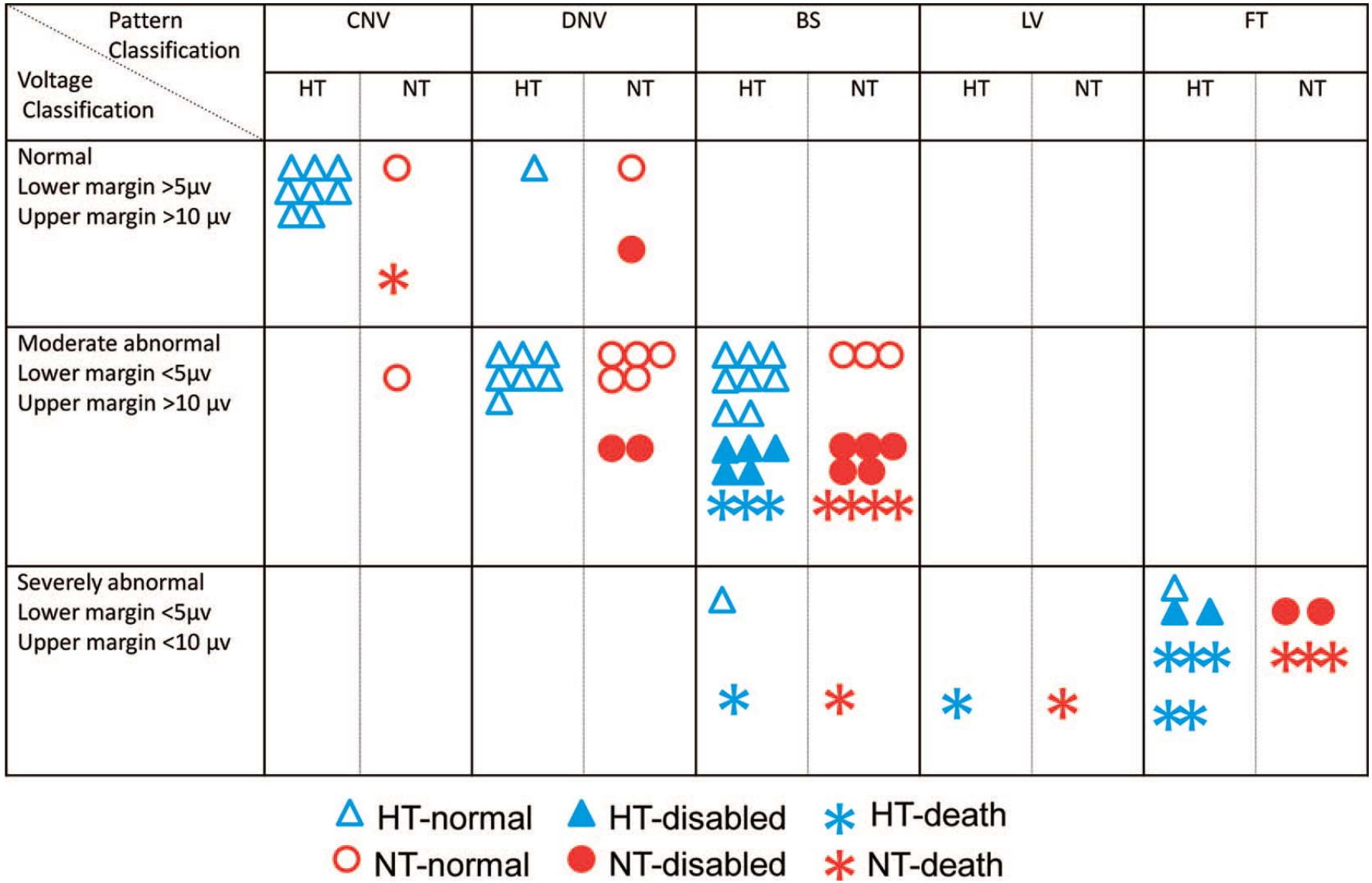
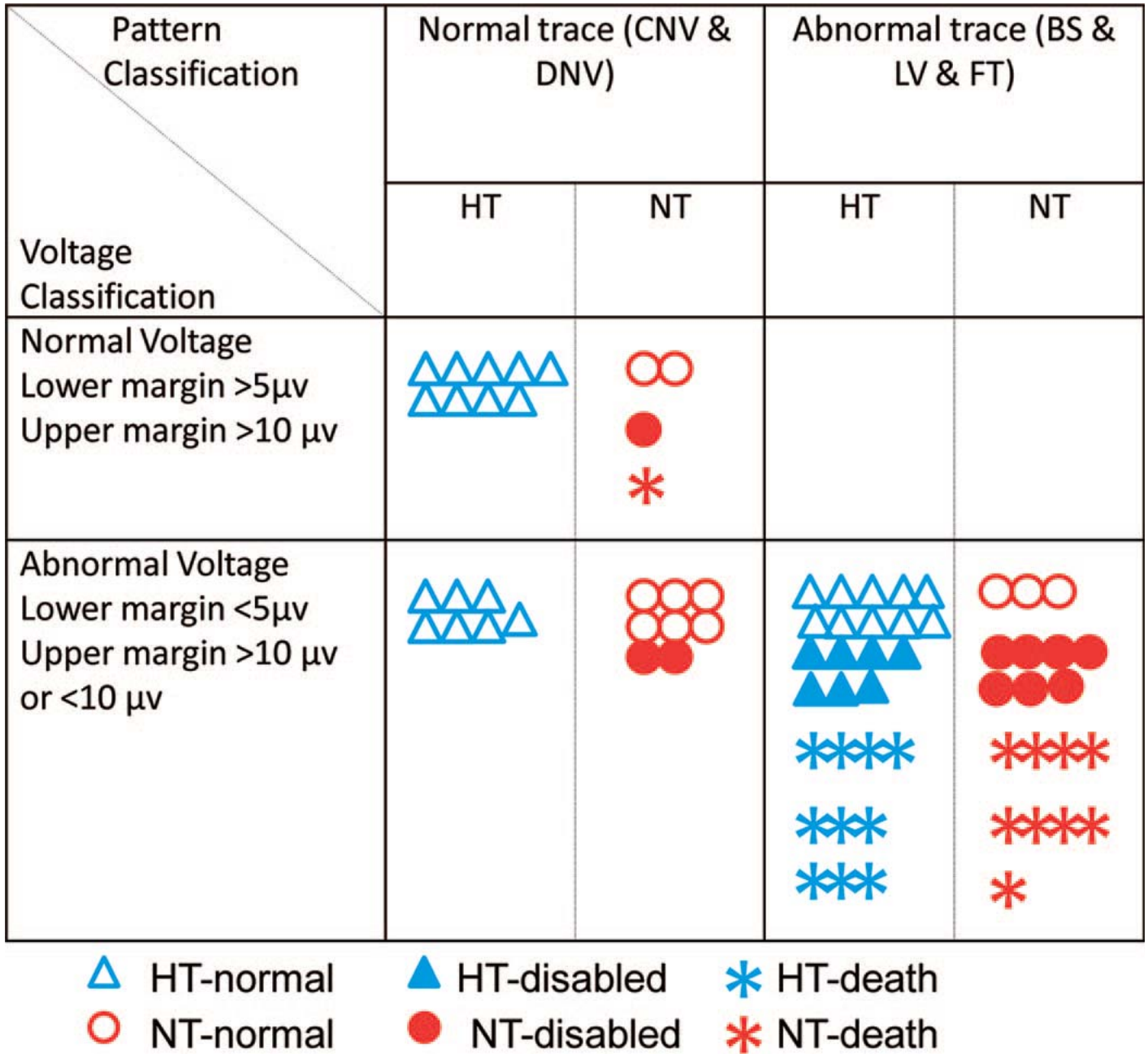

Pattern Classification
Voltage Classification
CNV
DNV
BS
LV
FT
HT
NT
Normal
Lower margin >5μv
Upper margin >10 μv
Moderate abnormal
Lower margin <5μv
Upper margin >10 μv
Severely abnormal
Lower margin <5μv
Upper margin <10 μv
HT-normal
HT-disabled
HT-death
NT-normal
NT-disabled
NT-death


Pattern Classification
Voltage Classification
Normal trace (CNV & DNV)
Abnormal trace (BS & LV & FT)
HT
NT
HT
NT
Normal Voltage
Lower margin >5μv
Upper margin >10 μv
Abnormal Voltage
Lower margin <5μv
Upper margin >10 μv
or <10 μv
HT-normal
HT-disabled
HT-death
NT-normal
NT-disabled
NT-death