Ipotermia terapeutica nel bambino: manca l'evidenza?

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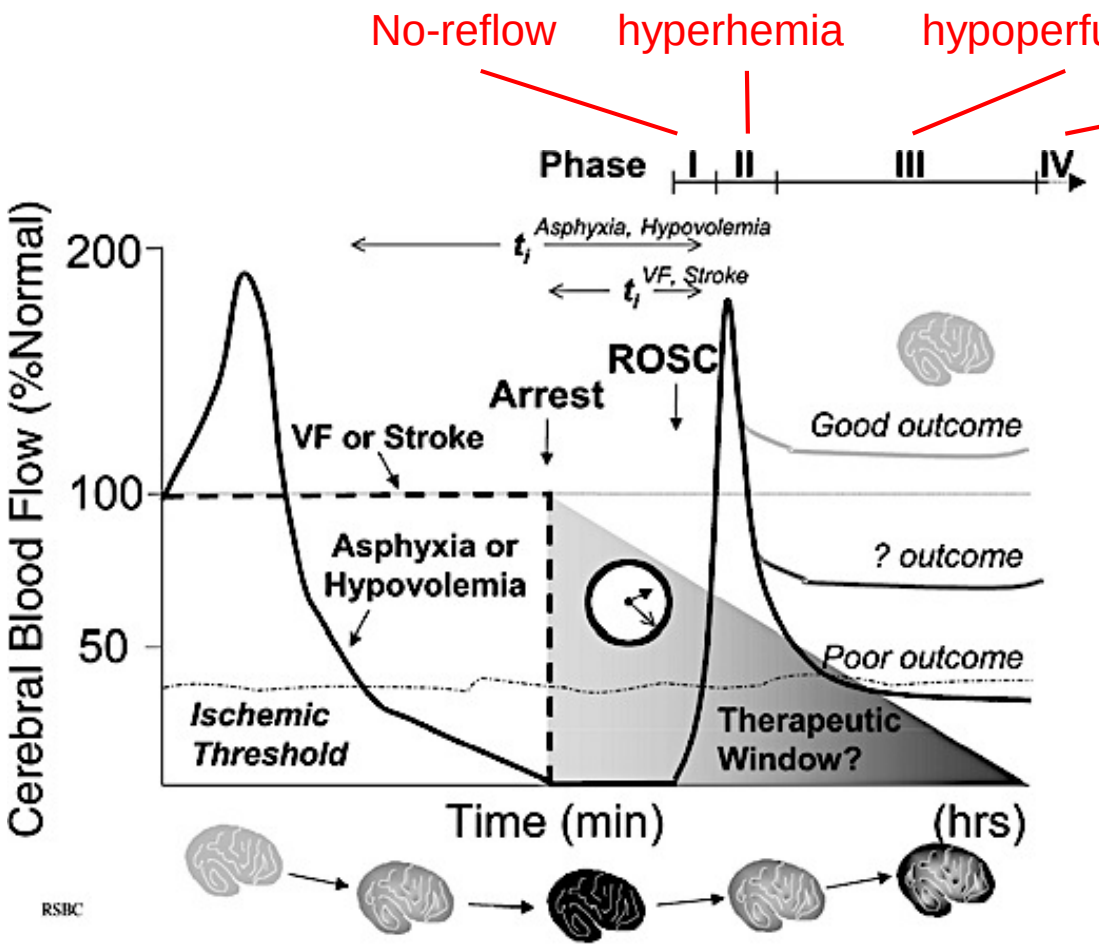
13 E 14 OTTOBRE
CENTRO CONGRESSI MAGAZZINI DEL COTONE
PORTO ANTICO GENOVA
CONGRESSO NAZIONALE IRC 2017
IRC Italian Resuscitation Council

Cardiac arrest in children

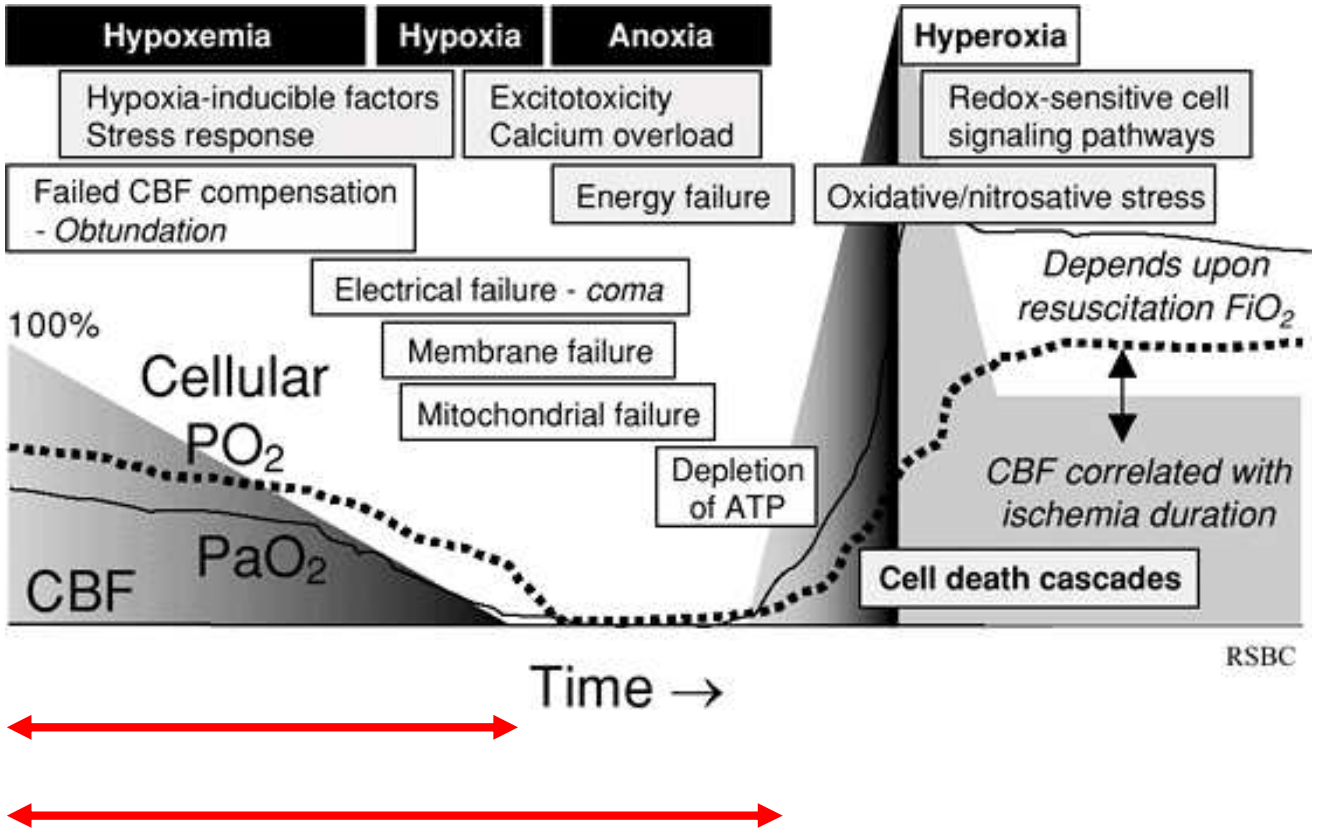


- 80-90% asphyxial
- 10-20% arrhythmias
- OHCA survival VT/VF 30%, asystole/PEA 5%
- IHCA survival VT/VF 35%, asystole/PEA 27%

Roger's Textbook of Pediatric Intensive Care, 4th Edition, Ch. 59

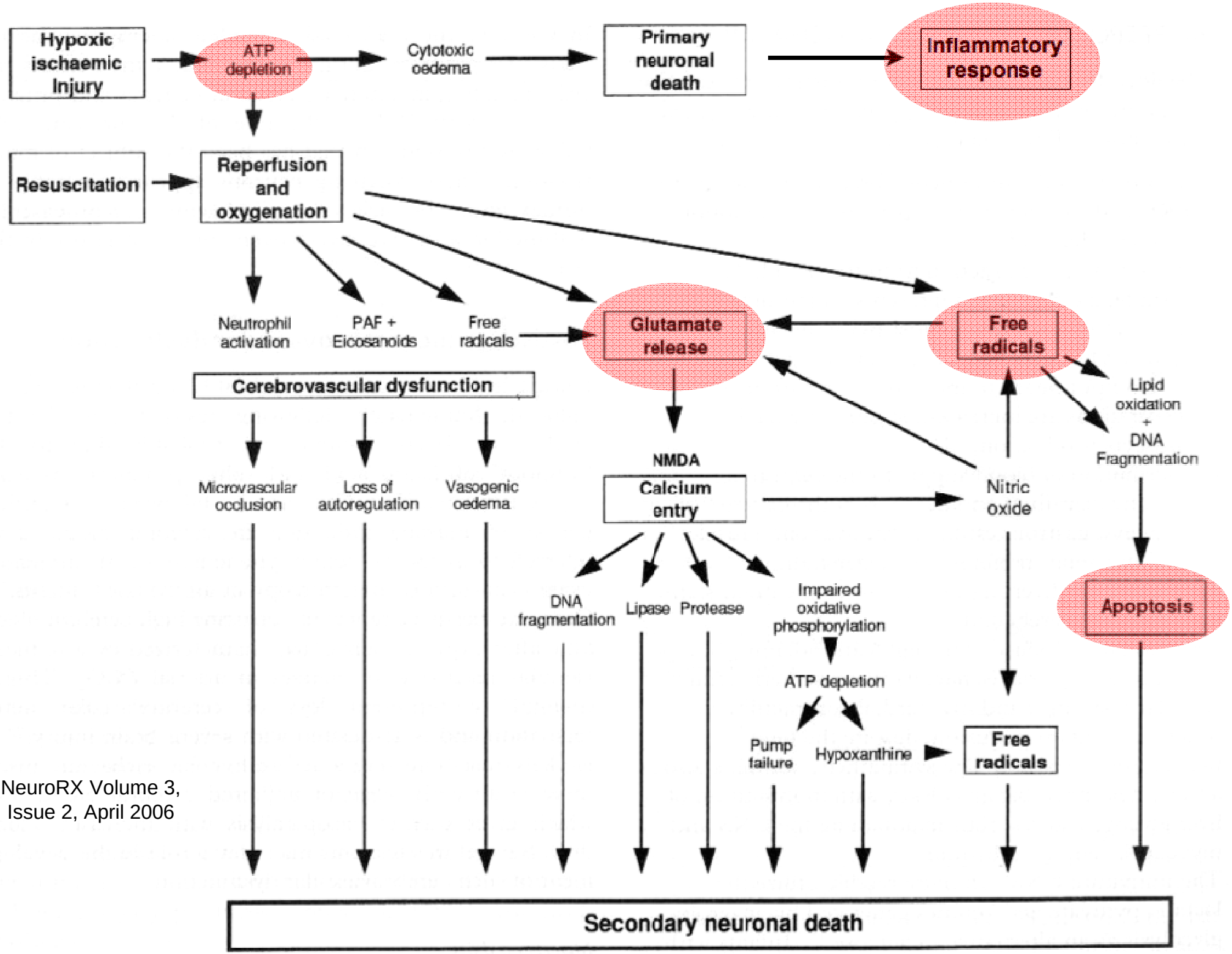
Fischer M, Hossmann KA. No-reflow after cardiac arrest. Intensive Care Med. 1995 Feb;21(2):132-41.

Asphyxial brain injury



Roger's Textbook of Pediatric Intensive Care, 4th Edition, Ch. 59

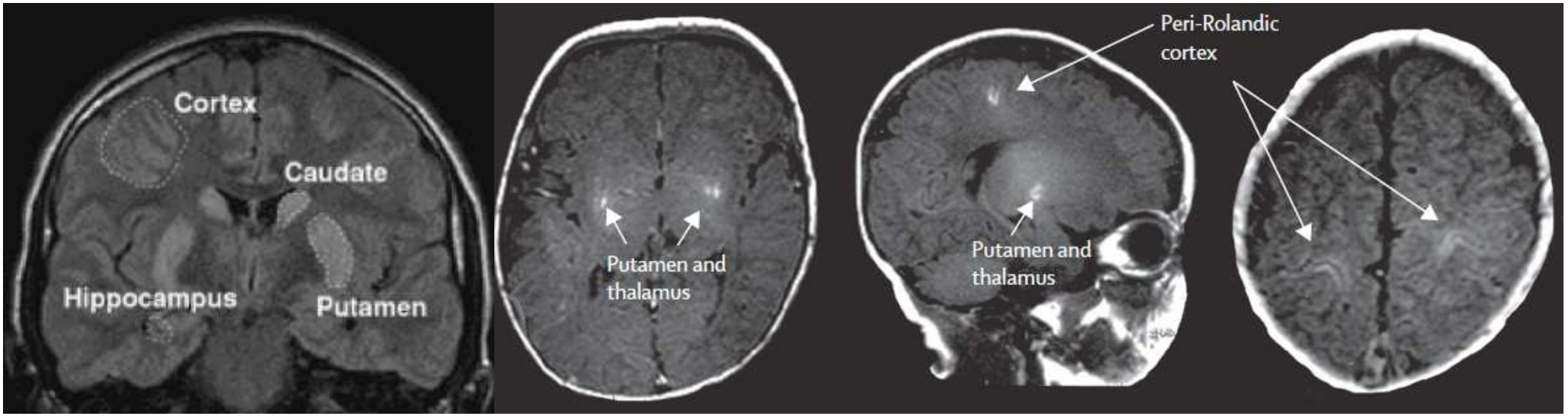
Pearigen, P., Gwinn, R., & Simon, R. P. (1996). The effects in vivo of hypoxia on brain injury. Brain Research, 725(2), 184–191.



NeuroRX Volume 3, Issue 2, April 2006

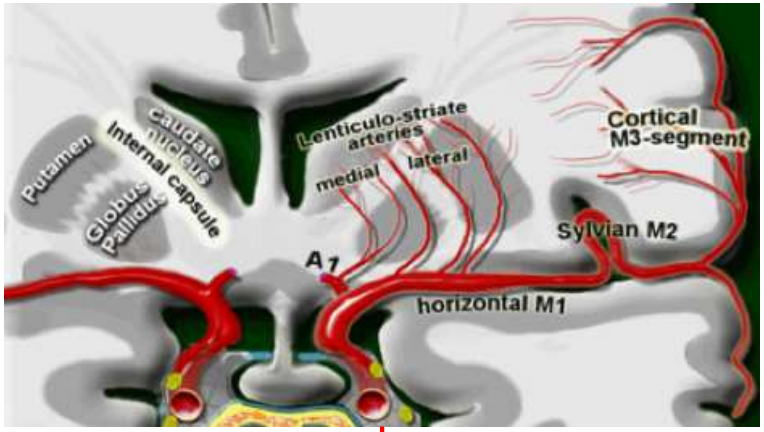
Hypoxic-ischemic brain injury

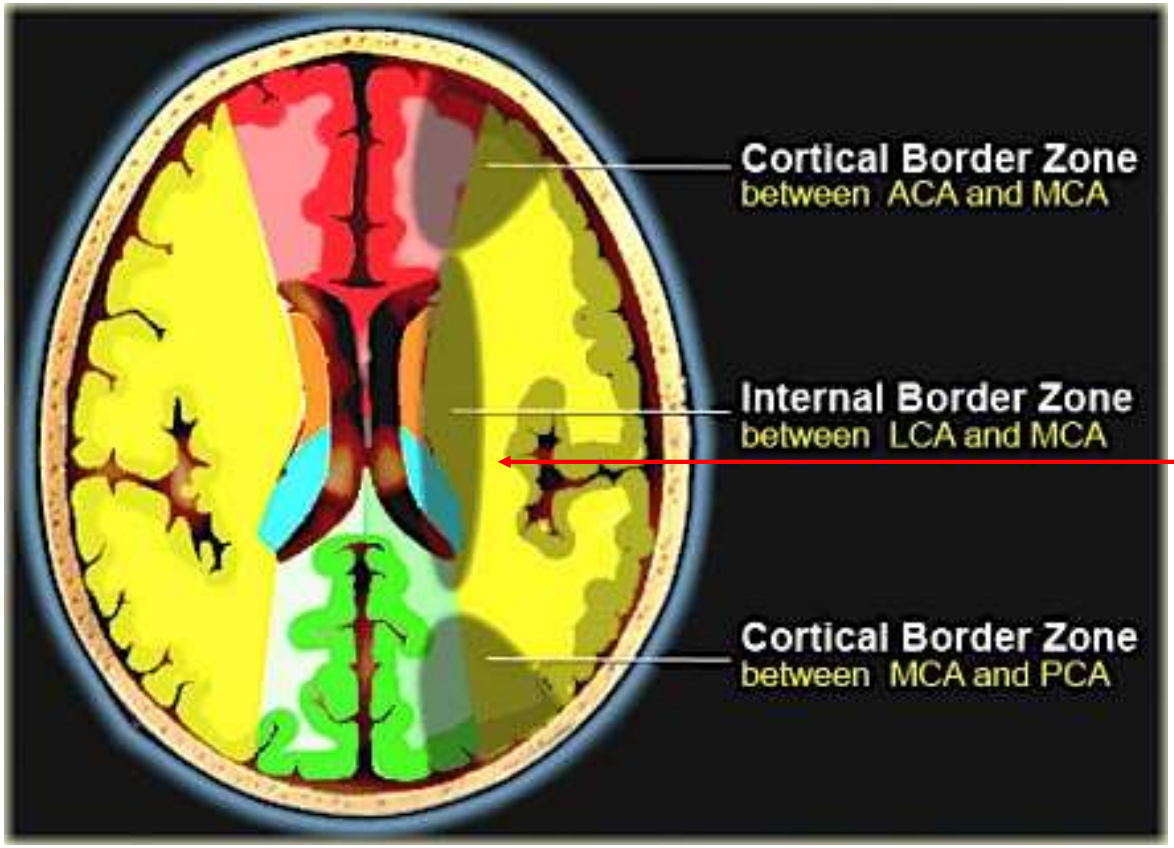
- CA1 region hippocampus
- Cerebral cortical layers 3-5
- Basal ganglia, amigdala
- Cerebellar Purkinje cells



Johnston, M. V. (2005). Excitotoxicity in perinatal brain injury. Brain Pathology (Zurich, Switzerland), 15(3), 234–240.

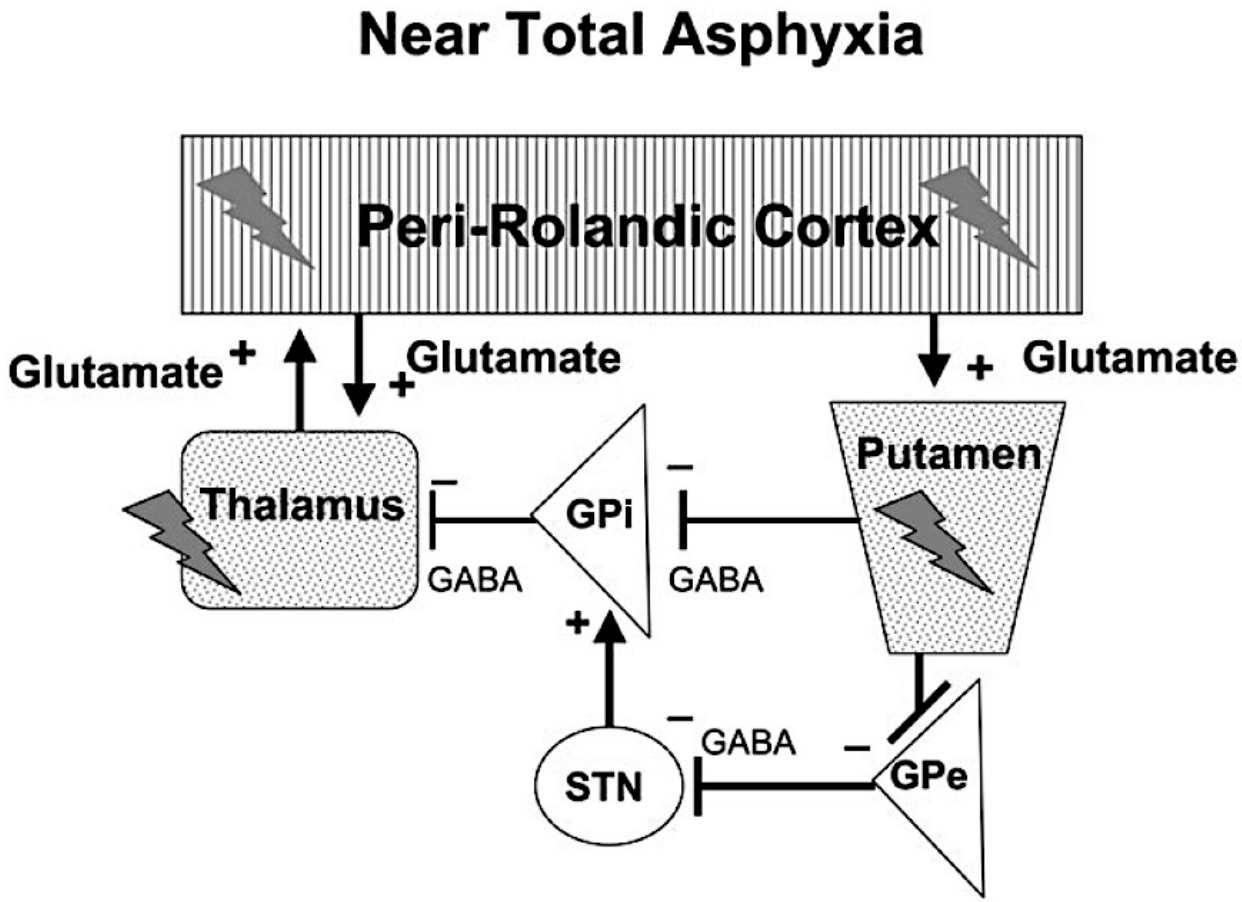
Hypoxic-ischemic brain injury





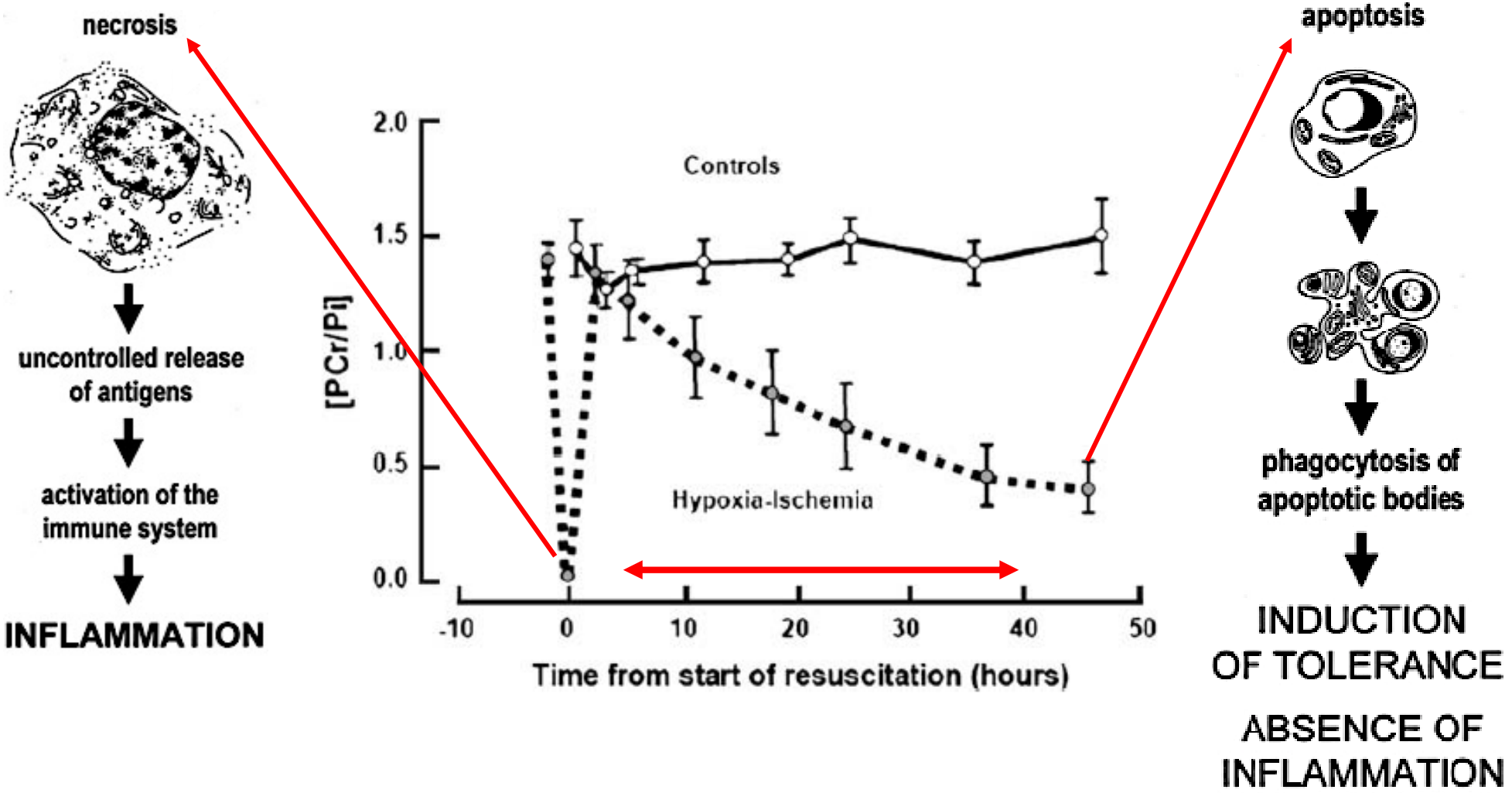
http://www.radiologyassistant.nl.

Hypoxic-ischemic brain injury

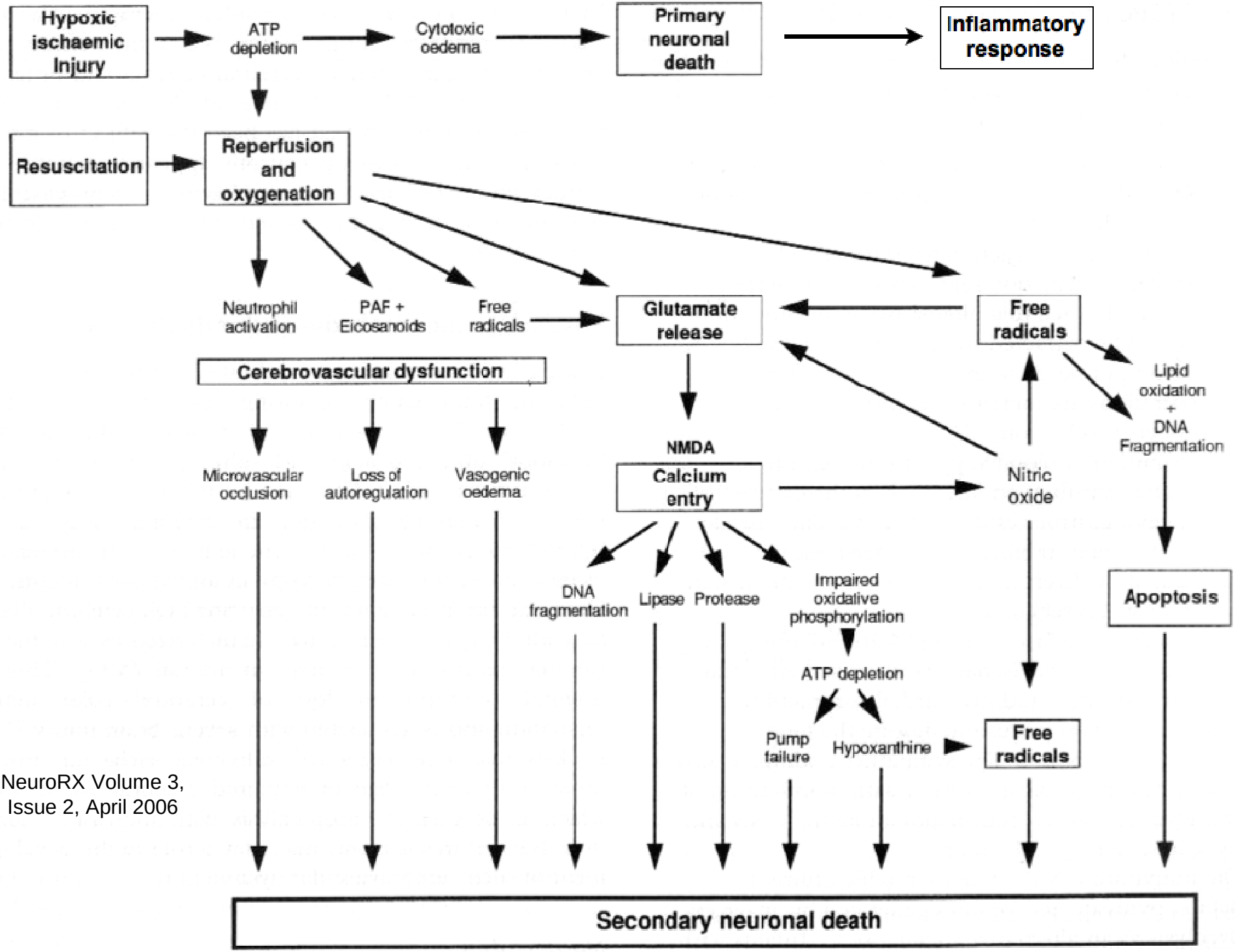


Johnston, M. V. (2005). Excitotoxicity in perinatal brain injury. Brain Pathology (Zurich, Switzerland), 15(3), 234–240.

Mechanisms of neuronal death



Pediatr Res 1994;36:699–706



NeuroRX Volume 3,
Issue 2, April 2006

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Neonatal Resuscitation: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations

- Newly born infants born at or near-term with evolving moderate to severe hypoxic-ischemic encephalopathy should be offered therapeutic hypothermia.
- Treatment should be consistent with the protocols used in the randomized clinical trials (ie, begin within 6 hours of birth, continue for 72 hours after birth, and rewarm over at least 4 hours).

Perlman, J. M., Wyllie, J., Kattwinkel, J., Atkins, D. L., Chameides, L., Goldsmith, J. P., et al. (2010). Neonatal Resuscitation: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. Pediatrics, 126(5), e1319–e1344.

Wyckoff MH, Aziz K, Escobedo MB, Kapadia VS, Kattwinkel J, Perlman JM, Simon WM, Weiner GM, Zaichkin, JG. Part 13: neonatal resuscitation: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2015;132(suppl 2):S543–S560.

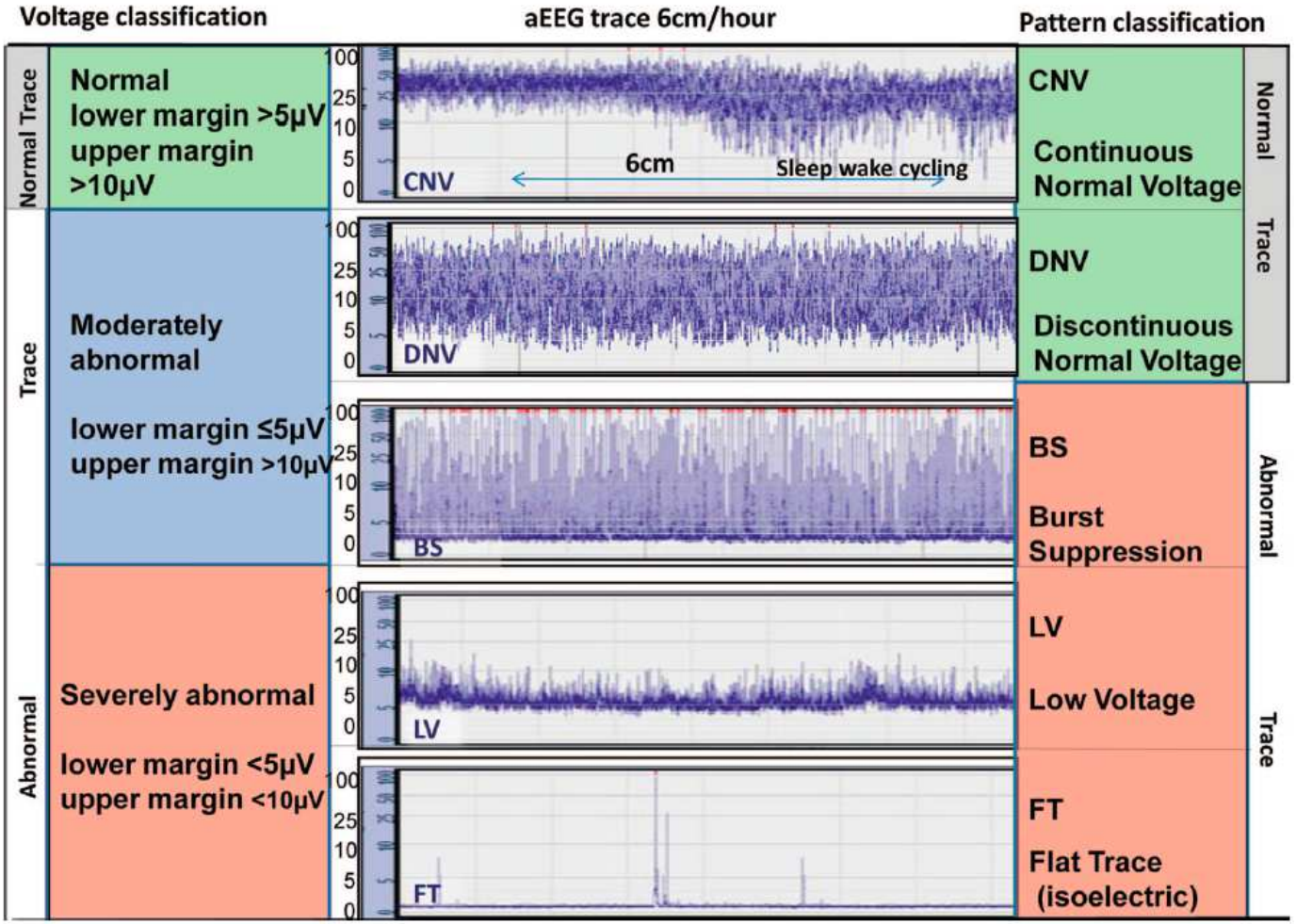
Patient's selection

1 Evidence of peripartum asphyxia – at least two of:
   - Apgar score of 5 or less at 10 min
   - Ongoing resuscitation or ventilation at 10 min
   - Cord pH < 7.1, or if cord pH not available
   - Arterial pH < 7.1 or base deficit of 12 or more within 60 min of birth
2 Moderate or severe encephalopathy
3 No recognisable major congenital abnormality
4 Less than 6 h of age

Category	Moderate encephalopathy	Severe encephalopathy
Level of consciousness	Lethargy	Stupor/coma/obtunded
Spontaneous activity	Decreased activity	No activity
Posture	Arms flexed, legs extended (decorticate)	Arms and legs extended (decerebrate)
Tone	Hypotonia	Flaccid
Primitive reflexes	Weak suck, gag and Moro	Absent suck, gag and Moro
Autonomic system		
Pupils	Constricted	Dilated/deviated/non-reactive
Heart rate	Bradycardia	Variable heart rate
Respirations	Periodic breathing	Apnoea

Journal of Paediatrics and Child Health 46 (2010) 568-576

aEEG

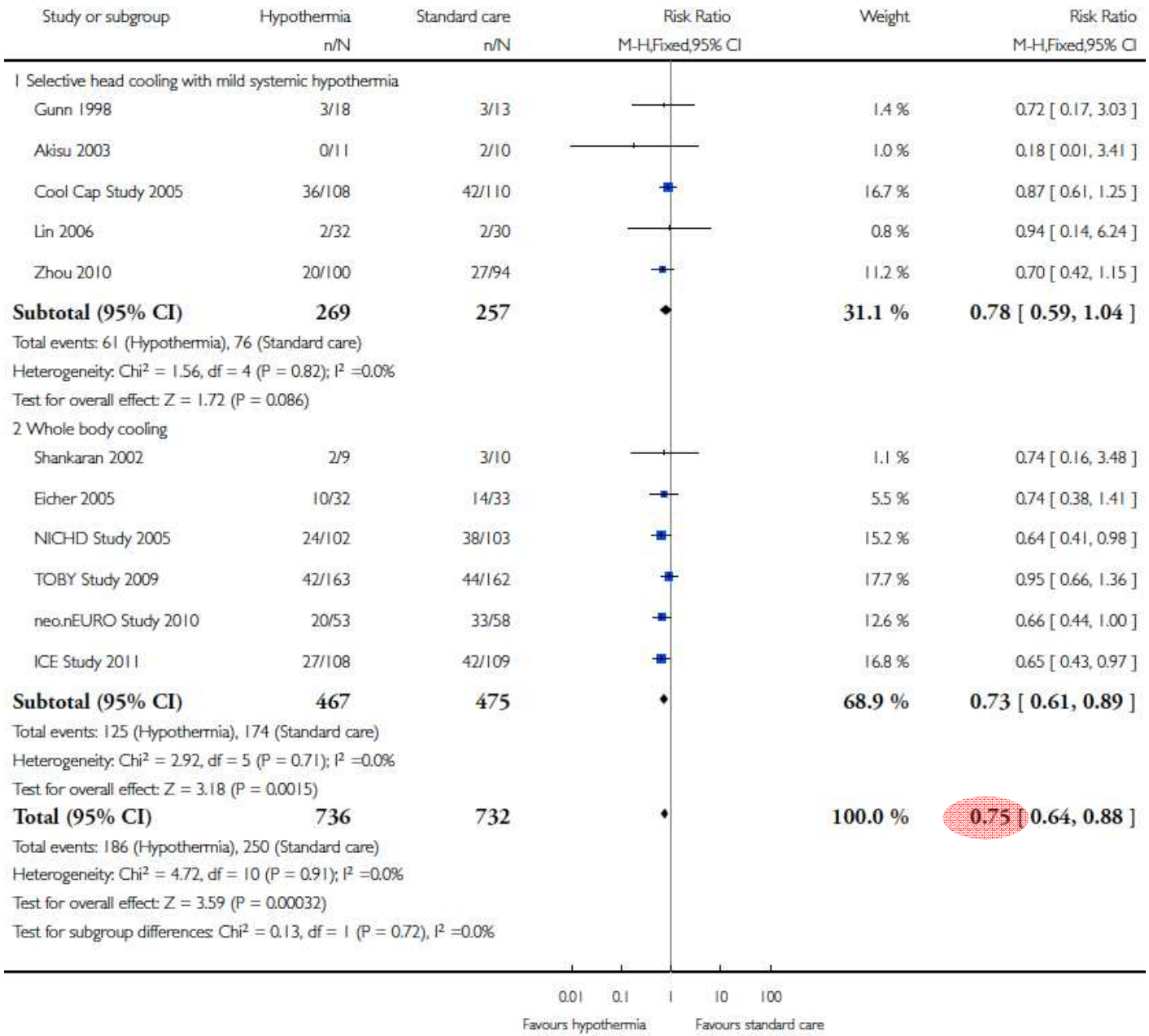

Voltage classification
aEEG trace 6cm/hour
Pattern classification
Normal Trace
Trace
Abnormal
Normal
lower margin >5μV
upper margin
>10μV
Moderately
abnormal
lower margin ≤5μV
upper margin >10μV
Severely abnormal
lower margin <5μV
upper margin <10μV
100
25
10
5
0
CNV
6cm
Sleep wake cycling
DNV
BS
LV
FT
CNV
Continuous
Normal Voltage
DNV
Discontinuous
Normal Voltage
BS
Burst
Suppression
LV
Low Voltage
FT
Flat Trace
(isoelectric)
Normal
Trace
Abnormal
Trace

25%

Review: Cooling for newborns with hypoxic ischaemic encephalopathy

Comparison: 1 Therapeutic hypothermia versus standard care: subgroup analysis by method of cooling

Outcome: 2 Mortality, by method of cooling



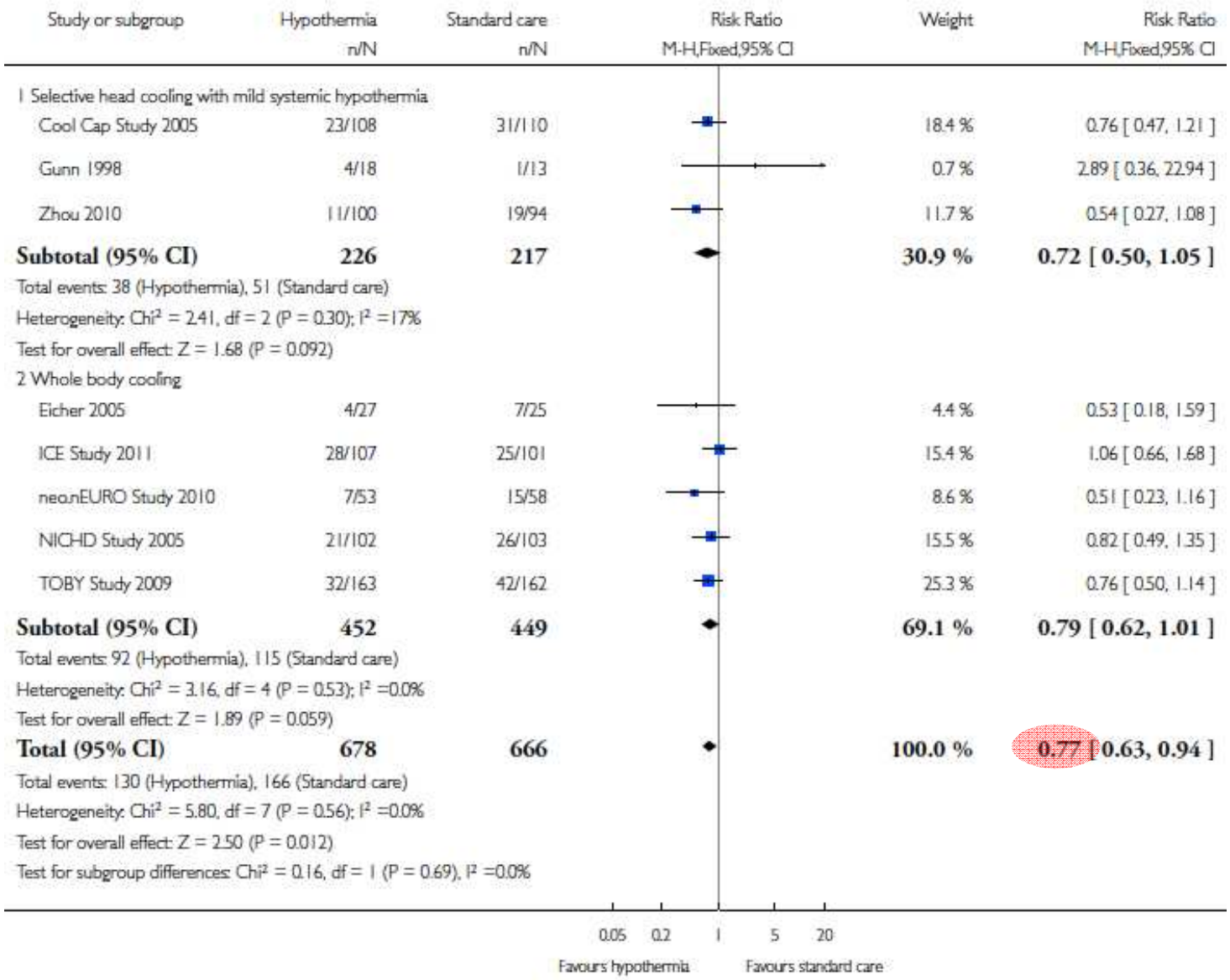
23%

Cochrane Database Syst Rev2013;(1):CD003311.

Review: Cooling for newborns with hypoxic ischaemic encephalopathy

Comparison: 1 Therapeutic hypothermia versus standard care: subgroup analysis by method of cooling

Outcome: 3 Major neurodevelopmental disability by method of cooling (CP, blindness, deafness)



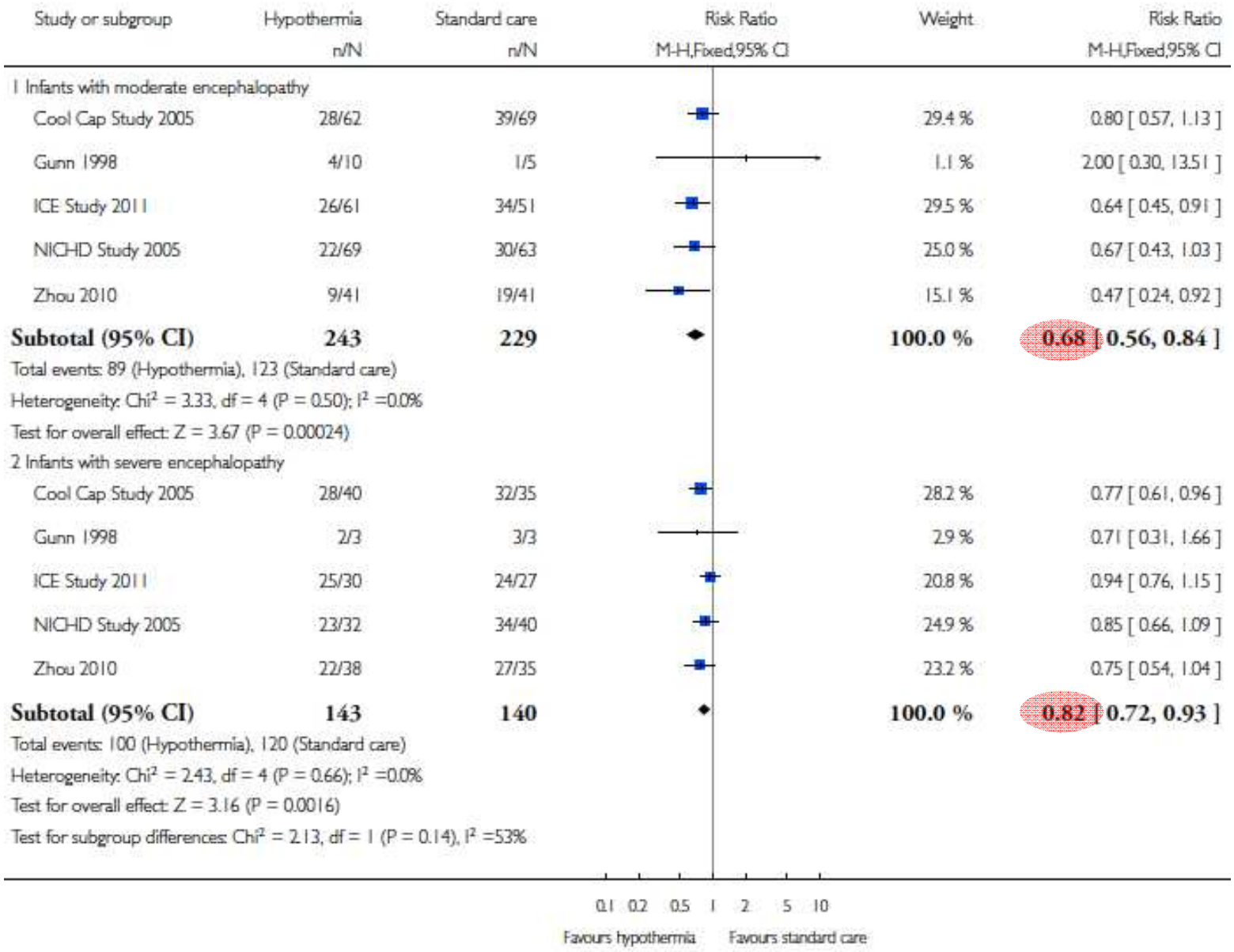
25%

Cochrane Database Syst Rev2013;(1):CD003311.

Review: Cooling for newborns with hypoxic ischaemic encephalopathy

Comparison: 2 Therapeutic hypothermia versus standard care: subgroup analysis by baseline severity of encephalopathy

Outcome: 1 Death or major disability in survivors assessed



Adverse effects

- Sinus bradycardia and prolongation of the QT interval on electrocardiogram
- The reported rates of coagulopathy, sepsis, and pneumonia were essentially the same in treated and control infants
- Aggregated data from published studies (meta-analysis): increase in sinus bradycardia and a significant increase in thrombocytopenia (platelet count <150 000/mm^3).

COMMITTEE ON FETUS AND NEWBORN. (2014). Hypothermia and Neonatal Encephalopathy. Pediatrics, 133(6), 1146–1150.

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European Resuscitation Council Guidelines for Resuscitation 2015 Section 6. Paediatric life support

After ROSC, a strict control of the temperature must be maintained to avoid hyperthermia (>37.5 °C) and severe hypothermia (<32 °C)

Resuscitation 95 (2015) 223–248

Part 6: Pediatric Basic Life Support and Pediatric Advanced Life Support

We suggest that for infants and children with OHCA, TTM be used in the post–cardiac arrest period

It is reasonable to use either hypothermia (32°C–34°C) or normothermia (36°C–37.5°C)

For pediatric survivors of IHCA, the confidence in effect estimates for the use of TTM is so low that the task force decided that a recommendation was too speculative

Circulation. 2015;132[suppl 1]:S177–S203

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TREATMENT OF COMATOSE SURVIVORS OF OUT-OF-HOSPITAL CARDIAC ARREST WITH INDUCED HYPOTHERMIA

- Comatose patients (77) after VF - OHCA (94.5% witnessed)
- Hypothermia (33°C target core temp. within 2 hrs after ROSC for 12 hrs) or normothermia
- 49% good outcome (discharged home or to rehablitation) vs 34%

OUTCOME*	HYPOTHERMIA (N=43)	NORMOTHERMIA (N=34)
	number of patients	
Normal or minimal disability (able to care for self, discharged directly to home)	15	7
Moderate disability (discharged to a rehabilitation facility)	6	2
Severe disability, awake but completely dependent (discharged to a long-term nursing facility)	0	1
Severe disability, unconscious (discharged to a long-term nursing facility)	0	1
Death	22	23

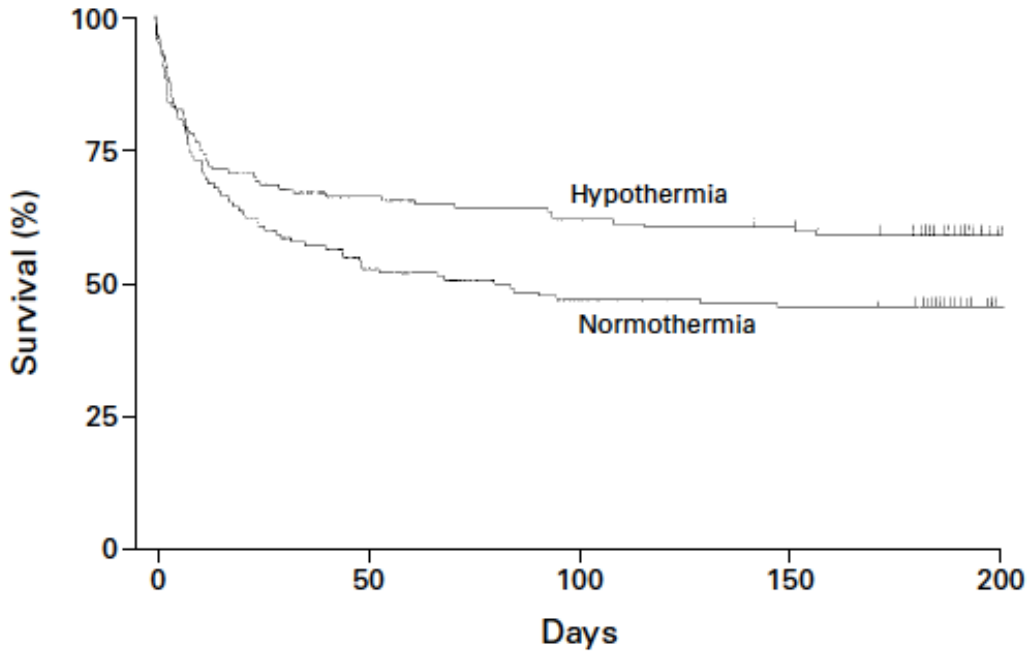
Limitations: pseudo-randomisation, 43 hypothermia v 34 controls, better neurologic outcome p = 0.046 (barely statistically significant), mortality p = 0.145 (not statistically significant).

If either 1 fewer patient in the hypothermia group had a poor outcome or 1 more patient in the control group had a good outcome, the differences in outcome between the 2 groups would no longer be statistically significant.

N Engl J Med, Vol. 346, No. 8

MILD THERAPEUTIC HYPOTHERMIA TO IMPROVE THE NEUROLOGIC OUTCOME AFTER CARDIAC ARREST

- VF-VT out of hospital witnessed (100%) cardiac arrest (275 pts)
- Hypothermia (target temperature, 32°C to 34°C, measured in the bladder) over a period of 24 hours or to receive standard treatment with normothermia

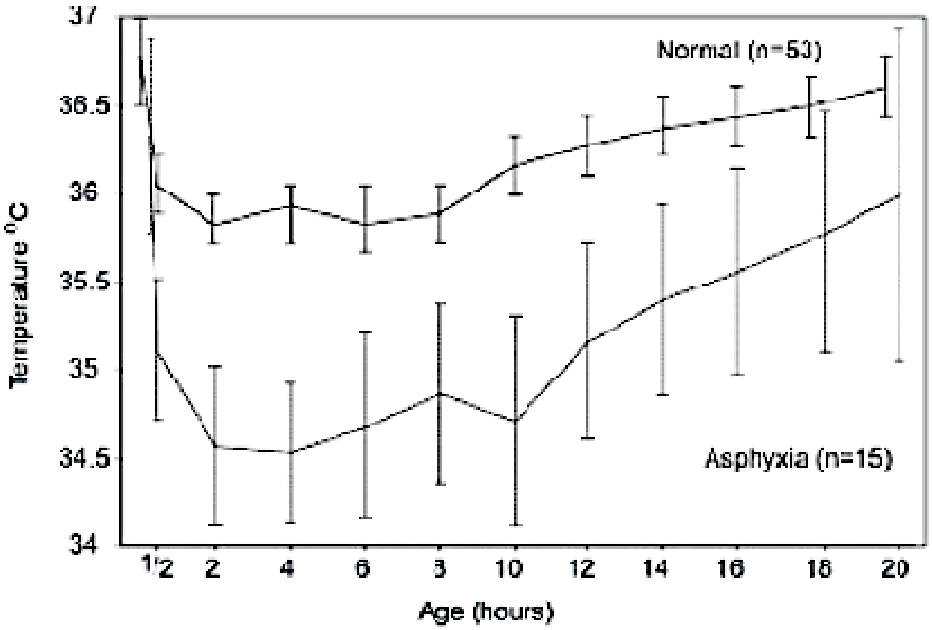


- Increased rate of favourable neurologic outcome (55% vs 39%, good recovery-moderate disability)

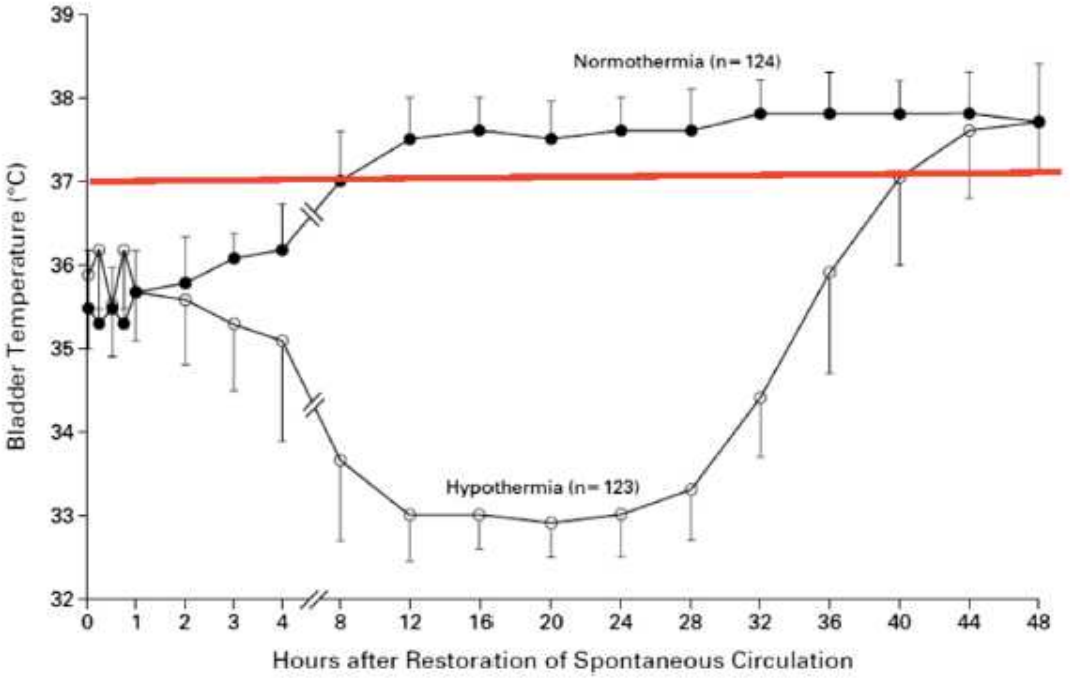
N Engl J Med, Vol. 346, No. 8

Therapeutic hypothermia

Newborn



Adult



Hypothermia after Cardiac Arrest Study Group. (2002). Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. The New England Journal of Medicine, 346(8), 549–556.

BURNARD, E. D., & CROSS, K. W. (1958). Rectal temperature in the newborn after birth asphyxia. British Medical Journal, 2(5106), 1197–1199.

TTM Trial: Targeted Temperature Management at 33°C versus 36°C after Cardiac Arrest

- Patients >18 years, unconscious (GCS <8) on admission to the hospital after OHCA of presumed cardiac cause, irrespective of the initial rhythm
- Target (core) Temperature Management of 33°C versus 36°C
- After 28 hours, gradual rewarming to 37°C in hourly increments of 0.5°C was commenced in both groups
- At 36 hours, mandatory sedation was discontinued or tapered
- Maintain the body temperature for unconscious patients below 37.5°C until 72 hours after the cardiac arrest, with the use of fever-control measures at the discretion of the sites

N Engl J Med 2013;369:2197-206.

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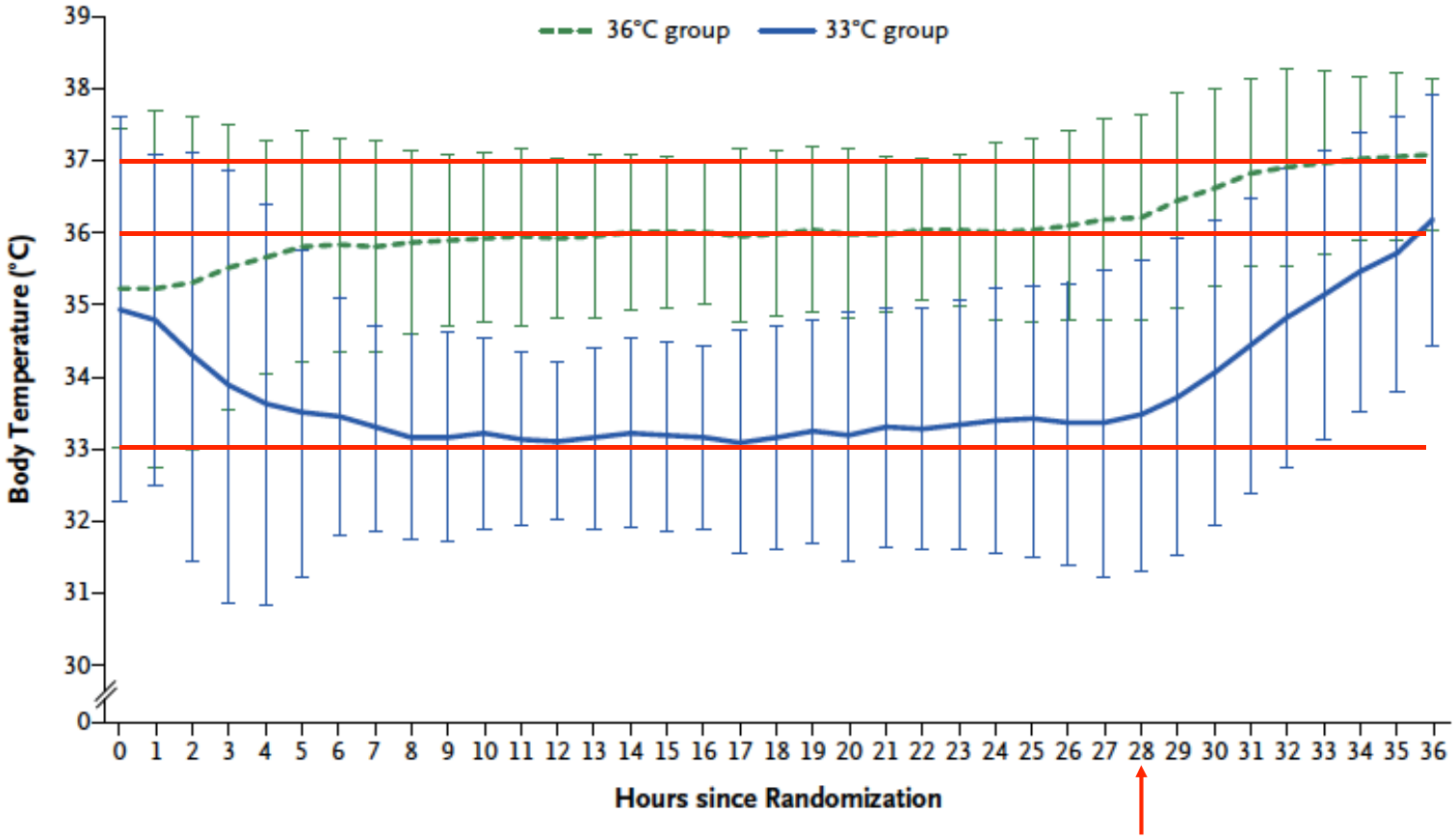
TTM Trial: Targeted Temperature Management at 33°C versus 36°C after Cardiac Arrest



No difference in death or poor neurological outcome

N Engl J Med 2013;369:2197-206.

In-Hospital Cardiac Arrest

- There is “insufficient evidence to determine the effects of therapeutic hypothermia on participants with IHCA, asystole or non-cardiac causes of arrest” *Cochrane Database of Systematic Reviews, 2(8), CD004128.*
- More than 75% of IHCAs are due to nonshockable rhythms
- IHCA is often due to hemorrhage, respiratory insufficiency, or pulmonary embolism (instead of primary arrhythmias or an acute coronary event) *Crit Care Med 38: 101-108, 2010*
- Patients with IH-CA are often“sicker”and have more co-morbidities (44% respiratory insufficiency, 29% hypotension, 20% heart failure, 17% sepsis, 15% pneumonia; 58% admitted to ICU, 31% on mechanical ventilation, and 29% receiving intravenous vasopressors). *Resuscitation 81:302-311, 2006*
- Between 12% and 48% of IH-CA are unwitnessed

Resuscitation 82: 845-852, 2011

Journal of Cardiothoracic and Vascular Anesthesia, 28(3), 789–799, 2014. http://doi.org/10.1053/j.jvca.2014.01.015

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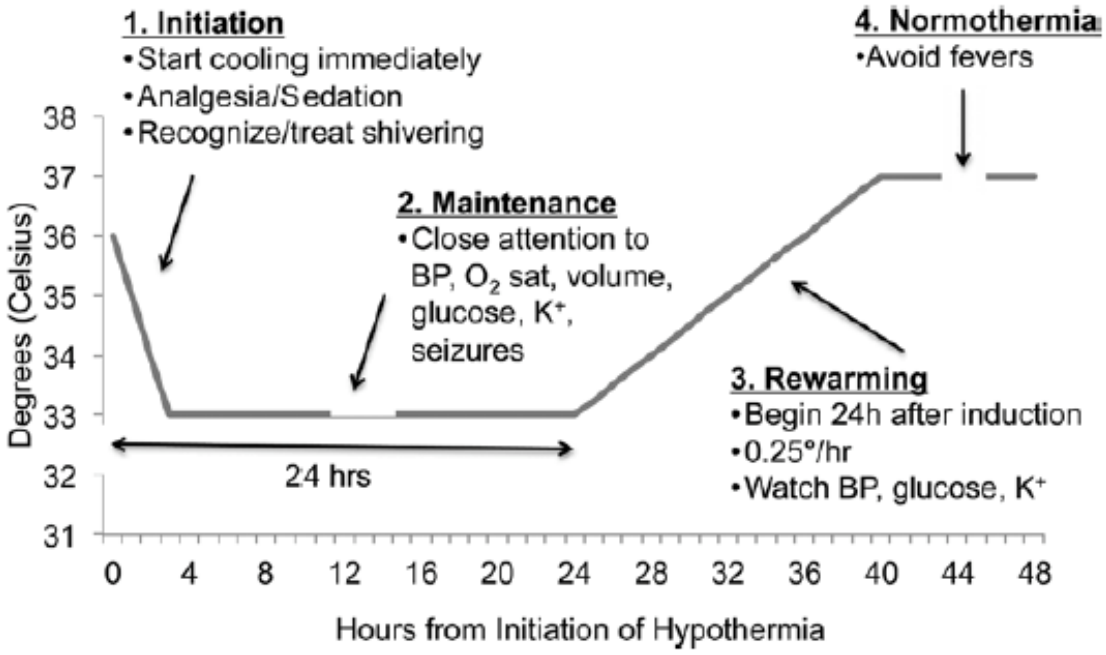
What is the harm in applying TH if it might help?

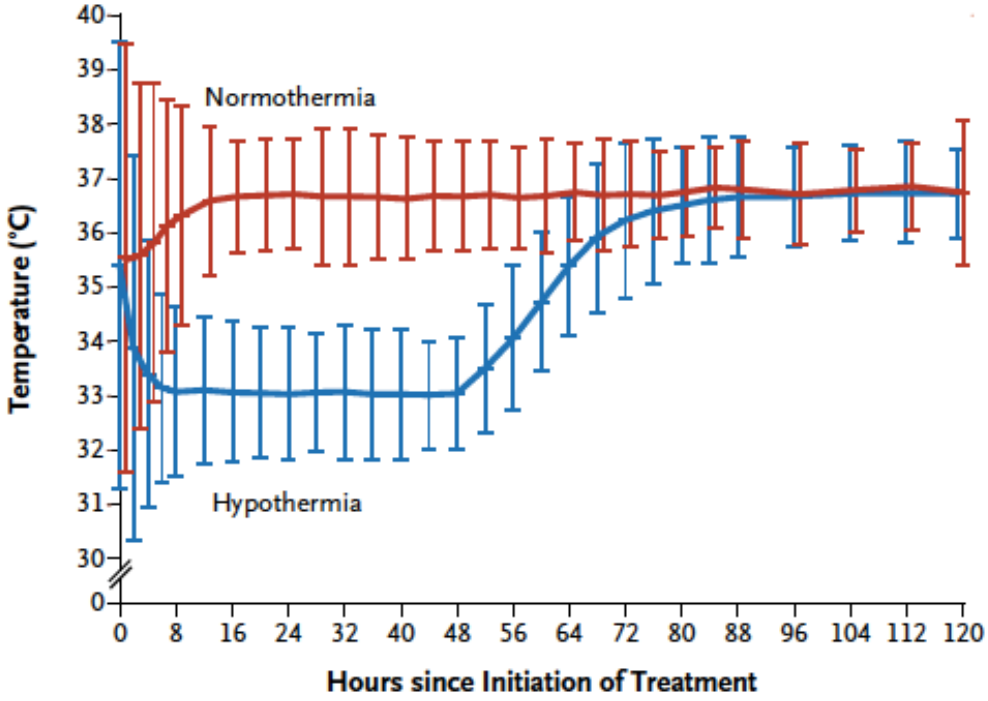


- Shivering (37-35°C)
- Hemodynamics (bradicardia, PR and QT prolongation, vasoconstriction/dilation)
- Hyperglycemia (< insulin secretion, > insulin resistance)
- Hypopotassemia (cellular influx, renal wasting)
- Infections (suppression of cellular and antibody immunity)
- Bleeding, coagulopathy, < PLT

TTM Trial: no difference in incidence of serious adverse events or causes of death with the lower targeted temperature

Scirica, B. M. (2013). Therapeutic Hypothermia After Cardiac Arrest. Circulation, 127(2), 244–250.

Therapeutic Hypothermia after Out-of-Hospital Cardiac Arrest in Children



- Within 6 hours after ROSC, comatose patients > 2 days < 18 years of age were randomly assigned to therapeutic hypothermia (target temperature, 33.0°C) or therapeutic normothermia (target temperature, 36.8°C)
- Cardiac arrest requiring chest compressions for at least 2 minutes and remained dependent on mechanical ventilation after ROSC
- Exclusion if: score of 5 or 6 at GCS motor sub-scale

72% respiratory cause vs 100 cardiac in adults, 8 vs 80% shockable rhythms

n engl j med 372;20 nejm.org may 14, 2015

Therapeutic Hypothermia after Out-of-Hospital Cardiac Arrest in Children

- No significant between-group difference in the primary outcome of survival with a good neurobehavioral outcome (VABS-II composite score of ≥70) at 12 months (20% vs. 12%; relative likelihood, 1.54; 95% CI, 0.86 to 2.76; P=0.14)
- The groups had similar incidences of infection and serious arrhythmias, as well as similar use of blood products and 28-day mortality

The study was, underpowered to show a significant difference for survival, for which the lower 95% confidence interval approached 1

Therapeutic Hypothermia after In-Hospital Cardiac Arrest in Children

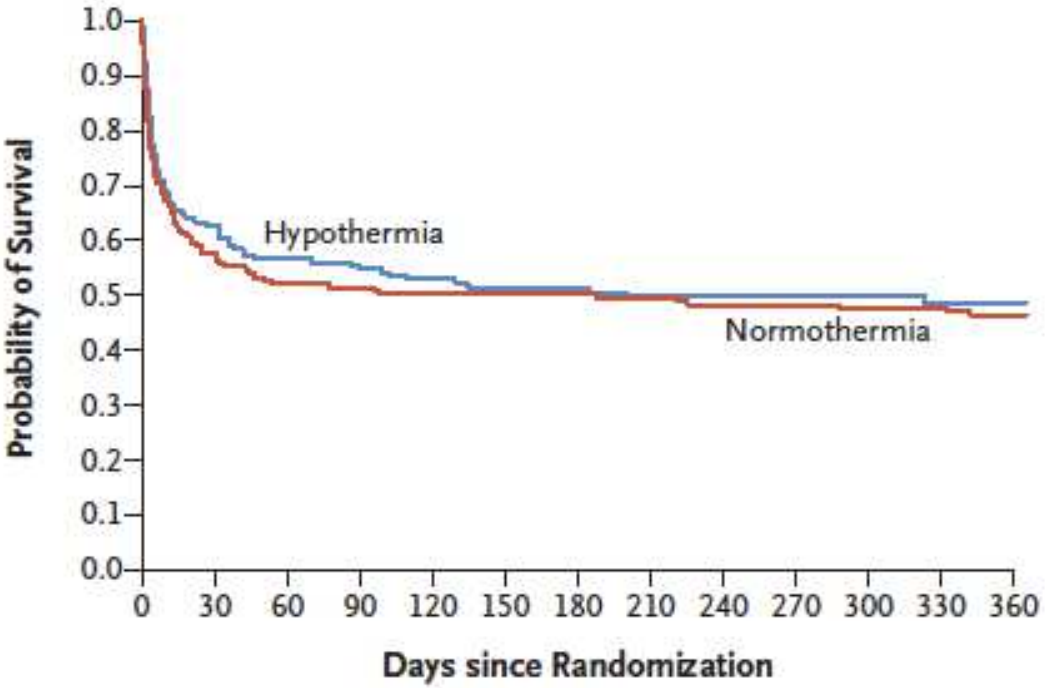
- Within 6 hours after ROSC, comatose children older >2 days and <18 years of age were randomly assigned to therapeutic hypothermia (target temperature, 33.0°C) or therapeutic normothermia (target temperature, 36.8°C)
- Cardiac arrest requiring chest compressions for at least 2 minutes and remained dependent on mechanical ventilation after ROSC
- Exclusion if: score of 5 or 6 at GCS motor sub-scale

A cardiac cause or a cause related to congenital heart disease in 50% and 16% of patients, respectively, or in 65% of patients combined (vs 72% respiratory in the THAPCA-OH)

THAPCA-IH vs THAPCA-OH:

- asystole 7% vs 58%
- bradycardia 57% vs. 6%
- shockable rhythms 8 vs 10% of patients

Therapeutic Hypothermia after In-Hospital Cardiac Arrest in Children



- 257 pts: survival with a favorable neurobehavioral outcome at 12 months of follow-up did not differ significantly between the hypothermia group and the normothermia group (36% [48 of 133 patients] and 39% [48 of 124 patients], respectively; relative risk, 0.92; 95% CI, 0.67 to 1.27; P=0.63)
- No difference in: blood-product use, infection, serious adverse events, and 28-day mortality

n engl j med 376;4 nejm.org January 26, 2017

Conclusions and future directions

- Fever commonly occurs after hypoxic–ischemic brain injury *Pediatrics 2000; 106:118-22*
- In initial trials of hypothermia for neonatal asphyxial encephalopathy and adult out-of-hospital cardiac arrest, the control groups did not receive therapeutic normothermia

N Engl J Med 2002; 346:549-56 N Engl J Med 2002; 346:549-56 N Engl J Med 2002; 346:549-56 Arch Pediatr Adolesc Med 2011; 165: 692-700

- Therapeutic normothermia is probably also beneficial
- No trends toward higher mortality or higher incidences of infection, arrhythmias, blood product use, or other serious adverse events in the therapeutic hypothermia group than in the therapeutic normothermia group *(TTM, THAPCA-IH and THAPCA-OH)*

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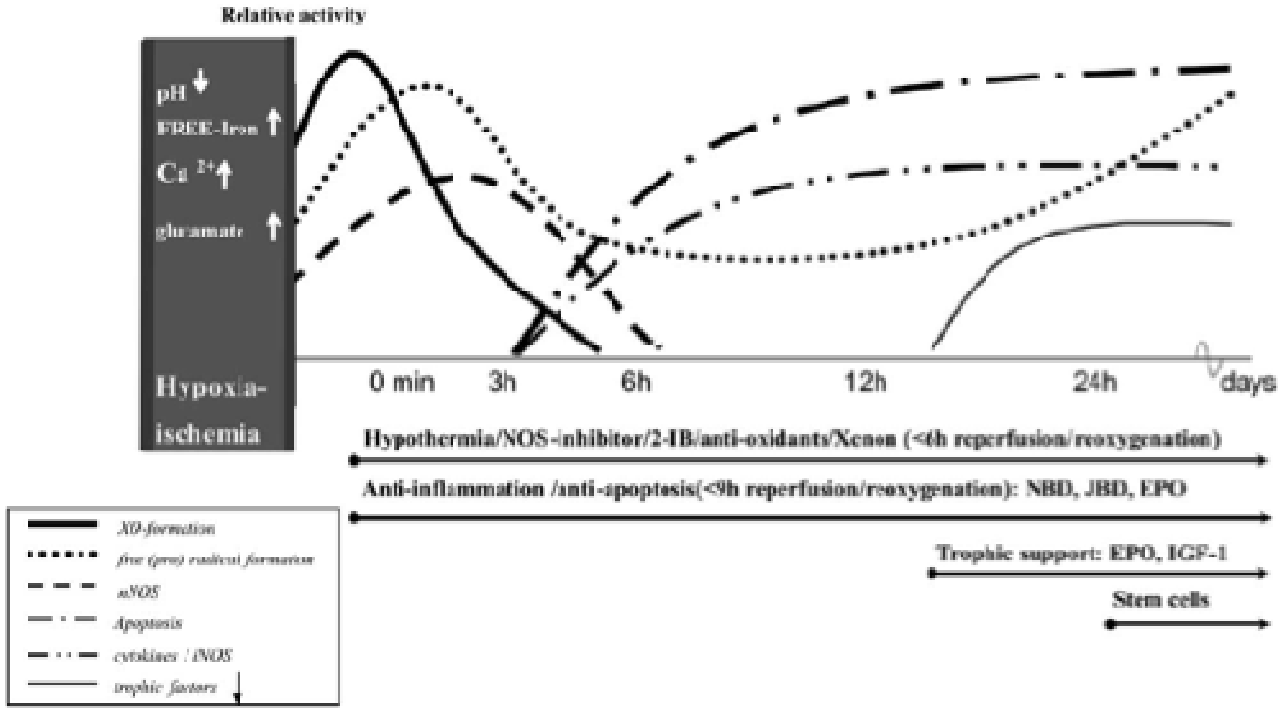
Conclusions and future directions

- Shorter therapeutic window for attaining the target temperature
- Longer or shorter duration of temperature control
- Higher or lower depths of temperature control

Conclusions and future directions

"Because the incidence of death and disability remains high after treatment with cooling (approximately 40%), there is an urgent need for additional therapies to further improve outcomes"



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COMMITTEE ON FETUS AND NEWBORN. (2014). Hypothermia and Neonatal Encephalopathy. Pediatrics, 133(6), 11461150 Fan, X., et al (2010). Pharmacological neuroprotection after perinatal hypoxic-ischemic brain injury. Current Neuropharmacology, 8(4), 324–334.

Therapeutic Hypothermia after Out-of-Hospital Cardiac Arrest in Children

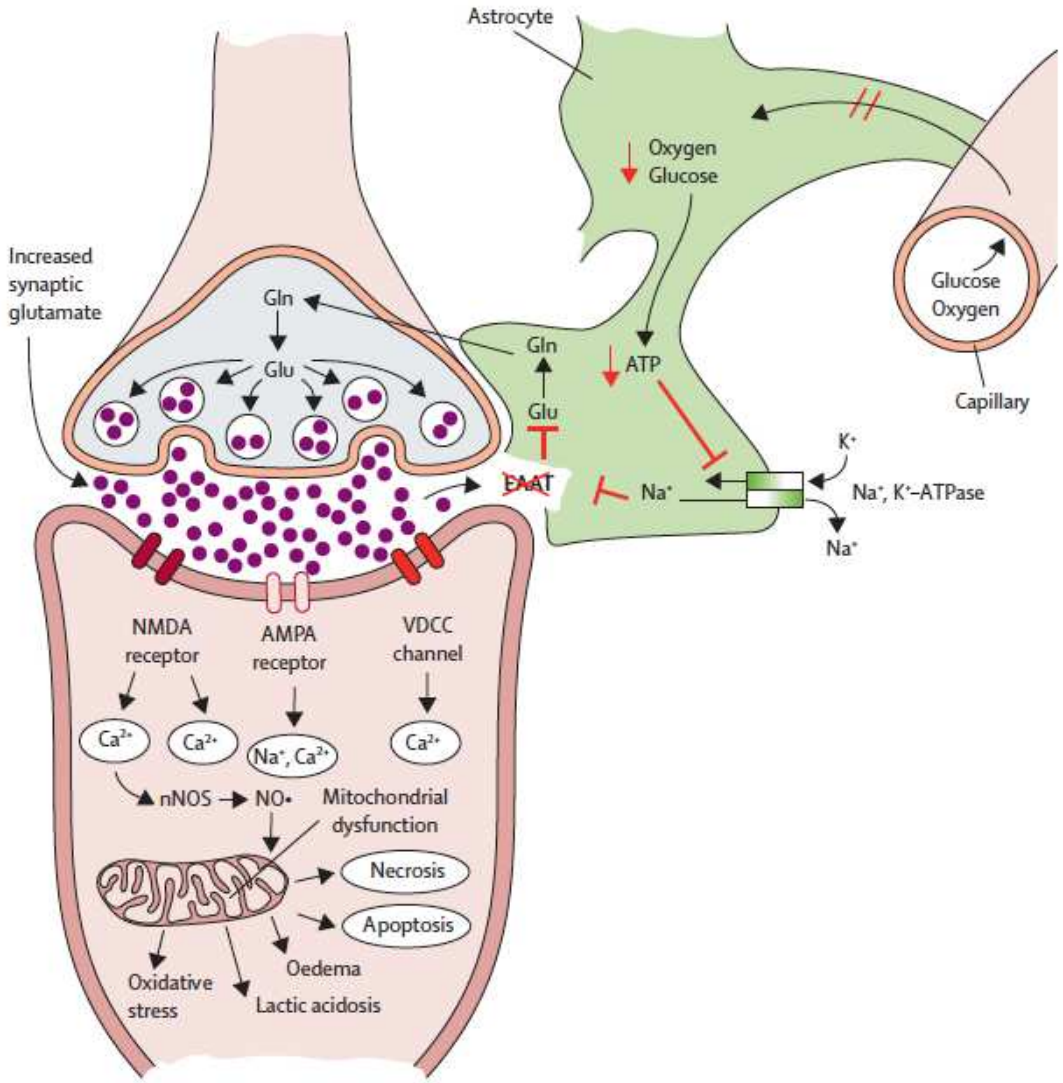
- No significant between-group difference in the primary outcome of survival with a good neurobehavioral outcome (VABS-II composite score of ≥70) at 12 months (20% vs. 12%; relative likelihood, 1.54; 95% CI, 0.86 to 2.76; P=0.14)
- The change in the VABS-II score from baseline to 1 year, did not differ between the groups (38% in the hypothermia group vs. 29% in the normothermia group; relative likelihood, 1.29; 95% CI, 0.93 to 1.79; P=0.13)
- The groups had similar incidences of infection and serious arrhythmias, as well as similar use of blood products and 28-day mortality

The study was, underpowered to show a significant difference for survival, for which the lower 95% confidence interval approached 1

Therapeutic Hypothermia after In-Hospital Cardiac Arrest in Children

- 257 pts: survival with a favorable neurobehavioral outcome at 12 months of follow-up did not differ significantly between the hypothermia group and the normothermia group (36% [48 of 133 patients] and 39% [48 of 124 patients], respectively; relative risk, 0.92; 95% CI, 0.67 to 1.27; P=0.63)
- 317 pts who could be evaluated for change in neurobehavioral function, the change in VABS-II score from baseline to 12 months did not differ significantly between the groups (P=0.70)
- Among 327 pts who could be evaluated for 1-year survival, the rate of 1-year survival did not differ significantly between the hypothermia group and the normothermia group (49% [81 of 166 patients] and 46% [74 of 161 patients], respectively; relative risk, 1.07; 95% CI, 0.85 to 1.34; P=0.56)
- No difference in: blood-product use, infection, serious adverse events, and 28-day mortality

Asphyxial brain injury



Johnston, M. V., Fatemi, A., Wilson, M. A., & Northington, F. (2011). Treatment advances in neonatal neuroprotection and neurointensive care. Lancet Neurology, 10(4), 372–382.