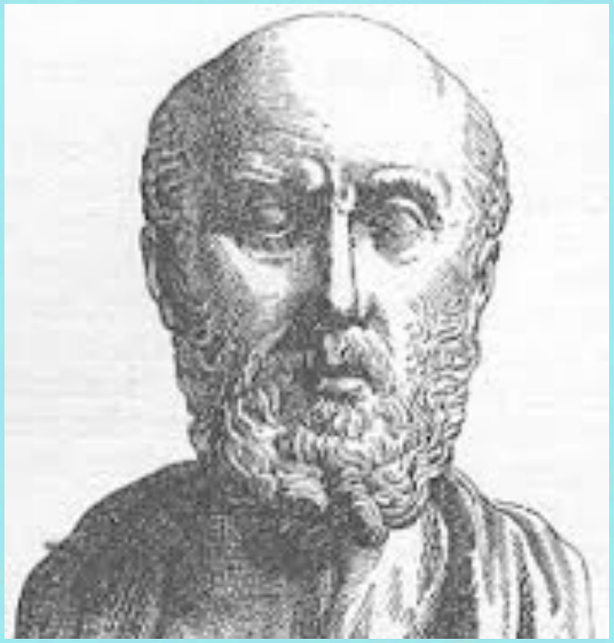
What's new in Therapeutic Hypothermia

Ratchanee Lee, MD.
Cardiology unit, Department of internal medicine
Faculty of Medicine, Ramathibodi hospital

Scopes

- History & Evidence of TH
- Important physiologic change
- Steps by steps of TH
- Futures: Prehospital TH, Cool in children, Cool in non cardiac arrest

History of Hypothermia

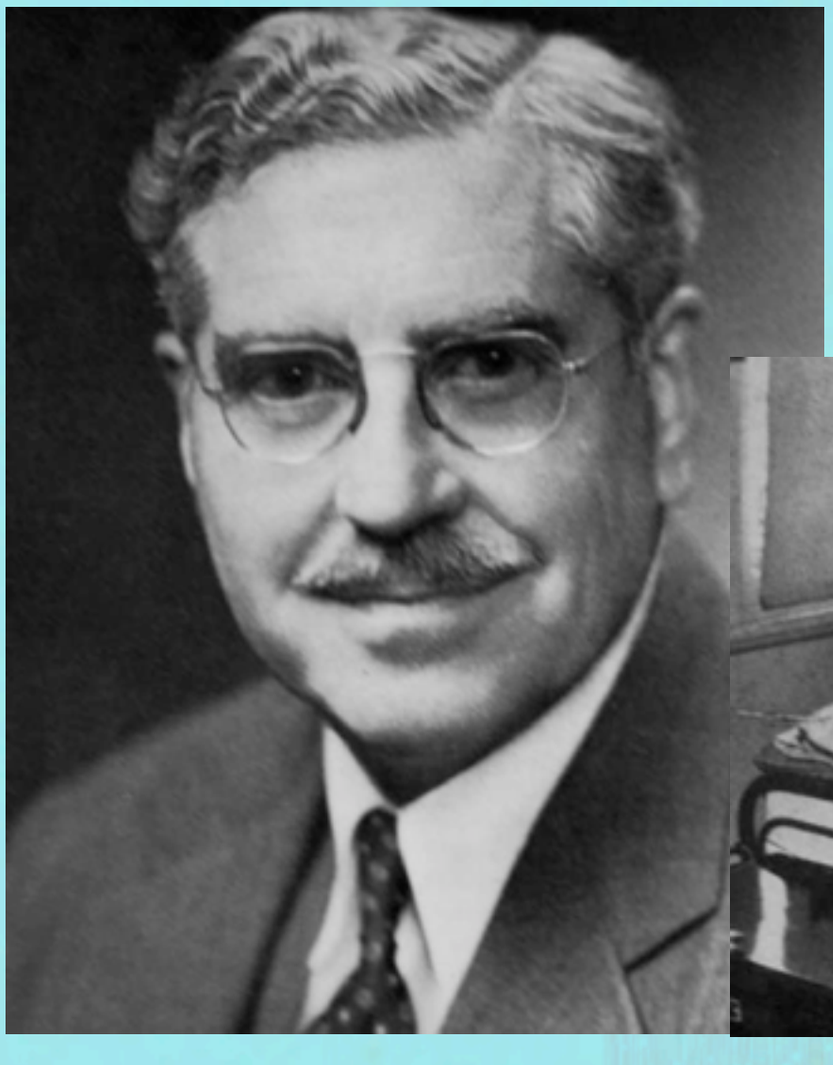


The Greek physician Hippocrates advocated packing of wounded soldiers in snow and ice.

Napoleon's surgeon-general Baron Larrey described that during the Napoleonic wars, wounded soldiers who were put close to campfire died earlier than those who were not rewarmed

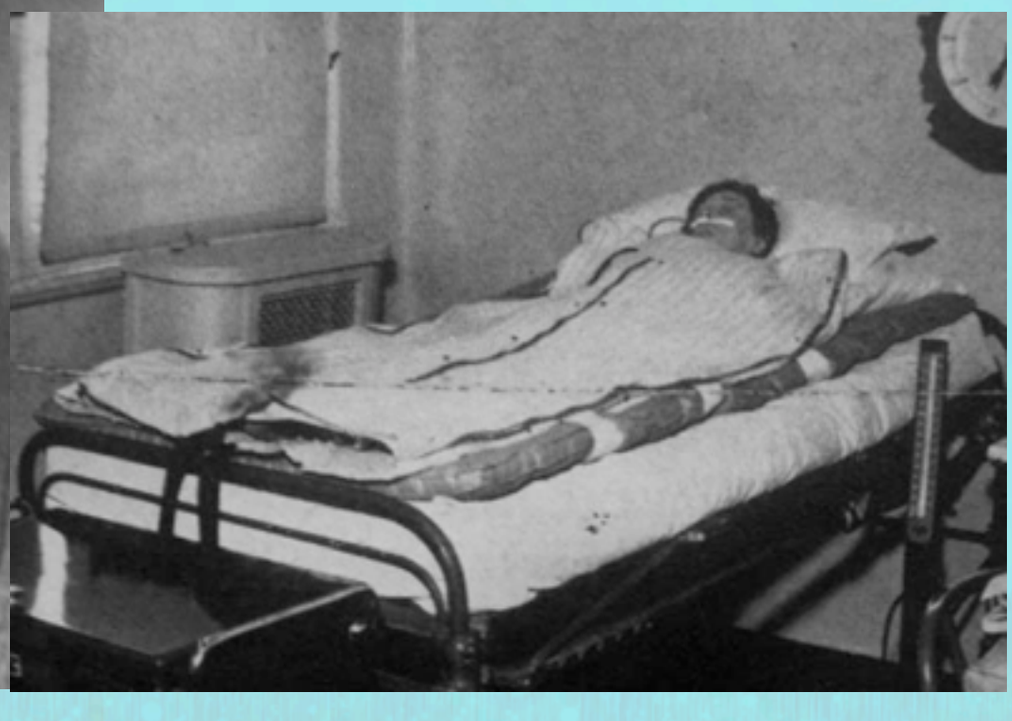
History of Hypothermia

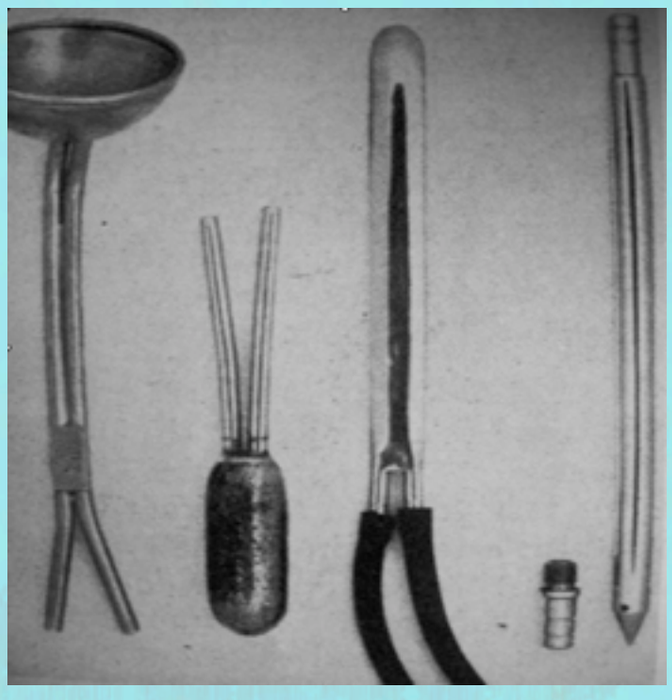
Dr. Temple Fay
Pioneer of hypothermia



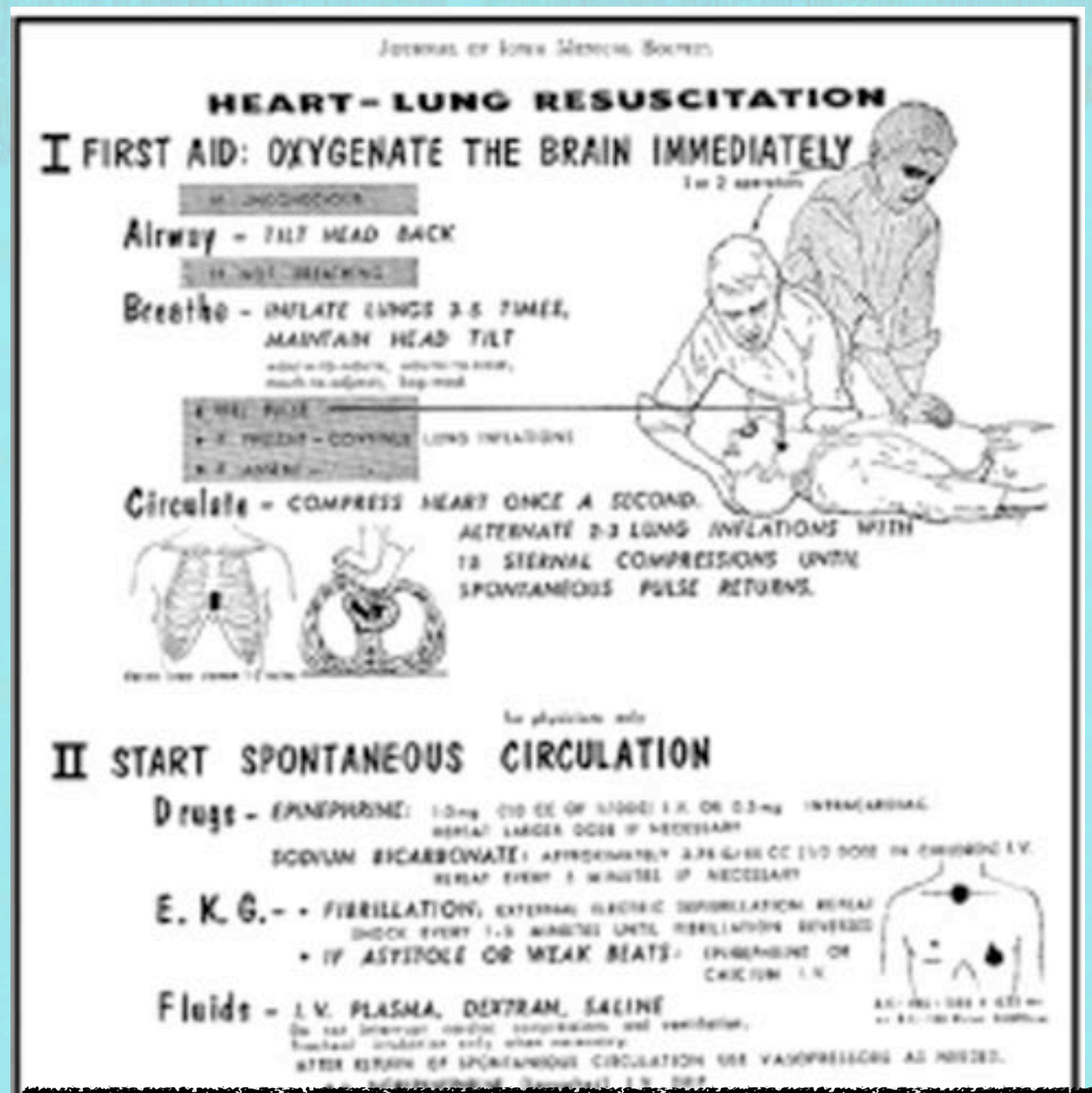
First clinical report use of hypothermia published in 1940's

" Early experience with Local and generalized refrigeration of the human brain"





History of Hypothermia



JOURNAL OF IOWA MEDICAL SOCIETY

HEART–LUNG RESUSCITATION

I FIRST AID: OXYGENATE THE BRAIN IMMEDIATELY

Airway – TILT HEAD BACK

Breathe – INFLATE LUNGS 3-5 TIMES, MAINTAIN HEAD TILT

Circulate – COMPRESS HEART ONCE A SECOND. ALTERNATE 2-3 LUNG INFLATIONS WITH 15 STERNAL COMPRESSIONS UNTIL SPONTANEOUS PULSE RETURNS.

II START SPONTANEOUS CIRCULATION

Drugs – EPINEPHRINE:

SODIUM BICARBONATE:

E. K. G. – • FIBRILLATION:

• IF ASYSTOLE OR WEAK BEATS:

Fluids – I.V. PLASMA, DEXTRAN, SALINE

III SUPPORT RECOVERY (physician-specialist)

Gauge EVALUATE AND TREAT CAUSE OF ARREST

Hypothermia START WITHIN 30 MINUTES IF NO SIGN OF CNS RECOVERY

Intensive Care SUPPORT VENTILATION: TRACHEOTOMY, PROLONGED CONTROLLED VENTILATION, GASTRIC TUBE AS NECESSARY

SUPPORT CIRCULATION
CONTROL CONVULSIONS
MONITOR

Peter J. Safar M.D.

Note TH in Journal of the Iowa Medical Society, November, 1964

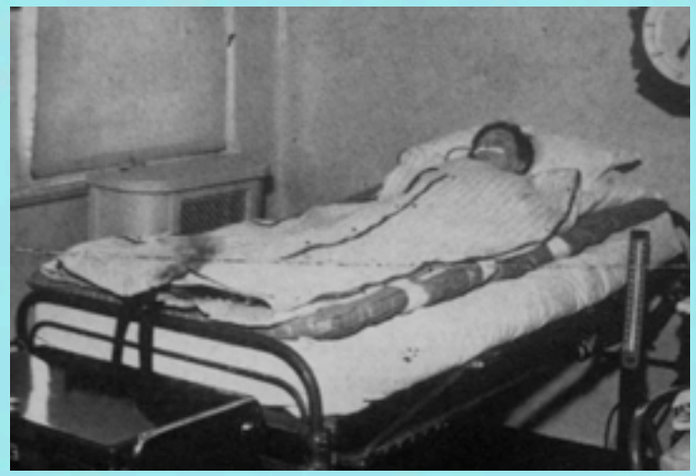
Animal study: hypothermia @ 32-34° C is safer and effective

Definition of hypothermia

- **Mild** = **32-35°C**
- **Moderate** = **28-32°C**
- **Deep** = **20-28°C**
- **Profound** = **<20°C**

Hypothermia after cardiac arrest

- First studies in the 1950's



  - Benson et al. Anesth Analg 1958;38:423-8
  - Williams et al. Ann Surg 1959; 148:462-8
  - Positive effects on neurological outcome of survivor; therapy abandoned because of side effects (which were very difficult to manage in a context without ICU)
  - Temperatures < 30 °C used !!!
- Benefits limited with moderate hypothermia <30 °C owing to arrhythmias, infections, and coagulation problems. *Danzl, Accidental hypothermia, N Engl J Med 1994.*

The New England Journal of Medicine

VOLUME 346 FEBRUARY 21, 2002 NUMBER 8

MILD THERAPEUTIC HYPOTHERMIA TO IMPROVE THE NEUROLOGIC OUTCOME AFTER CARDIAC ARREST

THE HYPOTHERMIA AFTER CARDIAC ARREST STUDY GROUP*

Multicenter European study, VF/VT rhythms

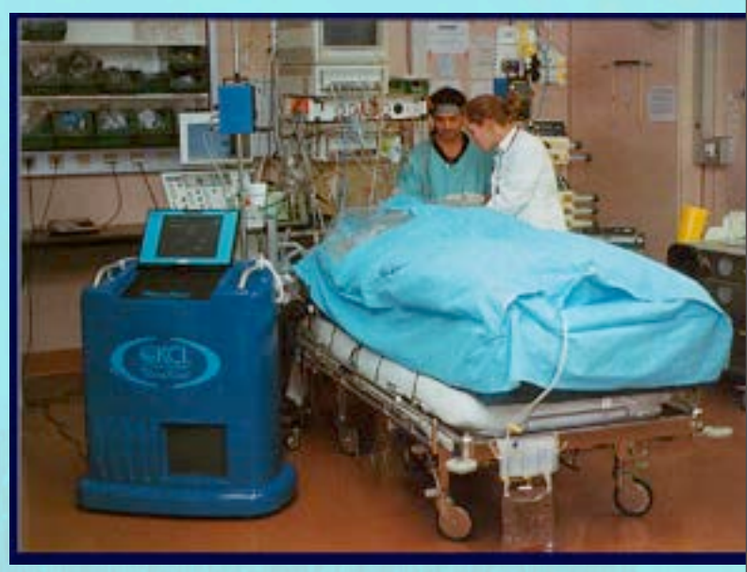
Randomed and started treatment at ER

275 pt enrolled, cooled to 32-34 °C for 24 h

ARR of poor neurological outcome 16%, NNT =6

ARR of mortality 14%, NNT =7

Statistically significant



INDUCED HYPOTHERMIA AFTER OUT-OF-HOSPITAL CARDIAC ARREST

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

STEPHEN A. BERNARD, M.B., B.S., TIMOTHY W. GRAY, M.B., B.S., MICHAEL D. BUIST, M.B., B.S., BRUCE M. JONES, M.B., B.S., WILLIAM SILVESTER, M.B., B.S., GEOFF GUTTERIDGE, M.B., B.S., AND KAREN SMITH, B.SC.

Australian multicnter study

Only 77 pt, VF/VT rhythm

Cooling initiated by paramedics, cooling packs

Goal Temp 33 °C withing 2 h for 12 h

ARR of poor neurological outcome 23%

ARR of mortality 17%

Statistical not significant, insufficient power

Study in Non VF/VT arrest !! Need more power

- **Hachimi-Idrissi Resuscitation 2001 (Belgium)**

  - **Asystole/PEA cardiac arrest**, Single center, Cool 34 °C for 4 h.

  - Survival to favorable neurological recovery: Hypothermia group 2/16 (13%) VS Normothermia group 0/14 (0%), **Not statistically significant**

- **Oddo 2006 (Switzerland):** Retrospective cohort assess **good neuro outcome in ANY rhythm** arrest => Hypothermia

  - VT/VF group: CPC 1-2; Hypothermia = 24/43 (56%), Control = 11/43 (26%)(P = .004) ARR 30% NNT = 3

  - Asystole or PEA group: CPC 1-2; Hypothermia= 2/12, Control group= 0/11 **Not statistically significant, but trend toward good outcome**

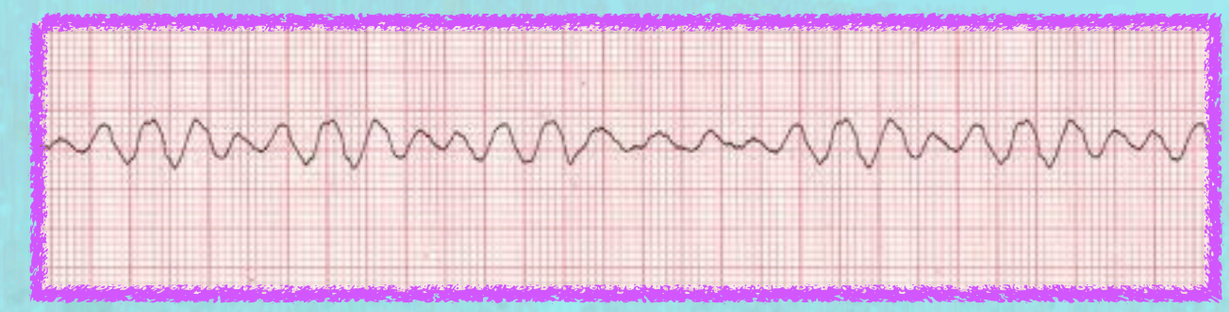
- **Holzer stroke 2006 (Austria) : ANY rhythm (29% non-VF) Cool to 33 °C 24 h** ; 30 day survival with a favorable neurological outcome Hypothermia group 51/79 (53%), Normothermia group 320/941 (34%) **p = .0003, ARR 19%, NNT 5**, No significant adverse events

Hypothermia after cardiac arrest

- Based on 2002 studies, in 2003 International Liaison Committee on Resuscitation (ILCOR) recommended all unconscious adult pt with ROSC following out-of-hospital arrest due to VF should be cooled to 32-34°C for 12-24 h

- 2005 AHA guideline recommended as class IIa and change to class I indication in 2010 guideline.

- The Cochrane Database's systematic review in 2009 found NNT 5-7 for improve 1 outcome, Aspirin (NNT=40), thrombolysis NNT = 100 for MI in comparison.



Summary of Practice Guideline Recommendations for Therapeutic Hypothermia

AHA Guidelines for CPR and ECC(2010)

- Comatose (ie, lack of meaningful response to verbal commands) adult patients with ROSC after **out-of-hospital VF cardiac arrest** should be cooled to 32°C–34°C (89.6°F–93.2°F) for 12 to 24 h **(Class I; Level of Evidence: B).**

- Induced hypothermia also may be considered for comatose adult patients with ROSC after **in-hospital cardiac arrest of any initial rhythm** or after **out-of-hospital cardiac arrest with PEA or asystole (Class IIb; Level of Evidence: B).**

- Active rewarming should be avoided in comatose patients who spontaneously develop a mild degree of hypothermia (>32°C [89.6°F]) during the first 48 h after ROSC (Class III; Level of Evidence: C).

European Resuscitation Council Guidelines for Resuscitation (2010)

- Use of therapeutic hypothermia should include comatose survivors of cardiac arrest associated initially with nonshockable rhythms and shockable rhythms. The lower level of evidence for use after cardiac arrest from nonshockable rhythms is acknowledged.

International Liaison Committee on Resuscitation (2008)

- Therapeutic hypothermia should be part of a standardized treatment strategy for comatose survivors of cardiac arrest.

Circulation. 2013;127:244-250

Lessons from the history

- In order to properly use hypothermia, we need to understand the physiology and mechanism underlying its protective effects.
- It's not just about reducing metabolism! but O_2 and Glu consumption
- Mild hypothermia (32-34, 30-35?) is low enough (same benefits, less side effects)
- Need intensive care facilities to care for these pt. and properly manage side effects.
- should be a part of good intensive care for brain-injured pt. but implementation strategies are important.

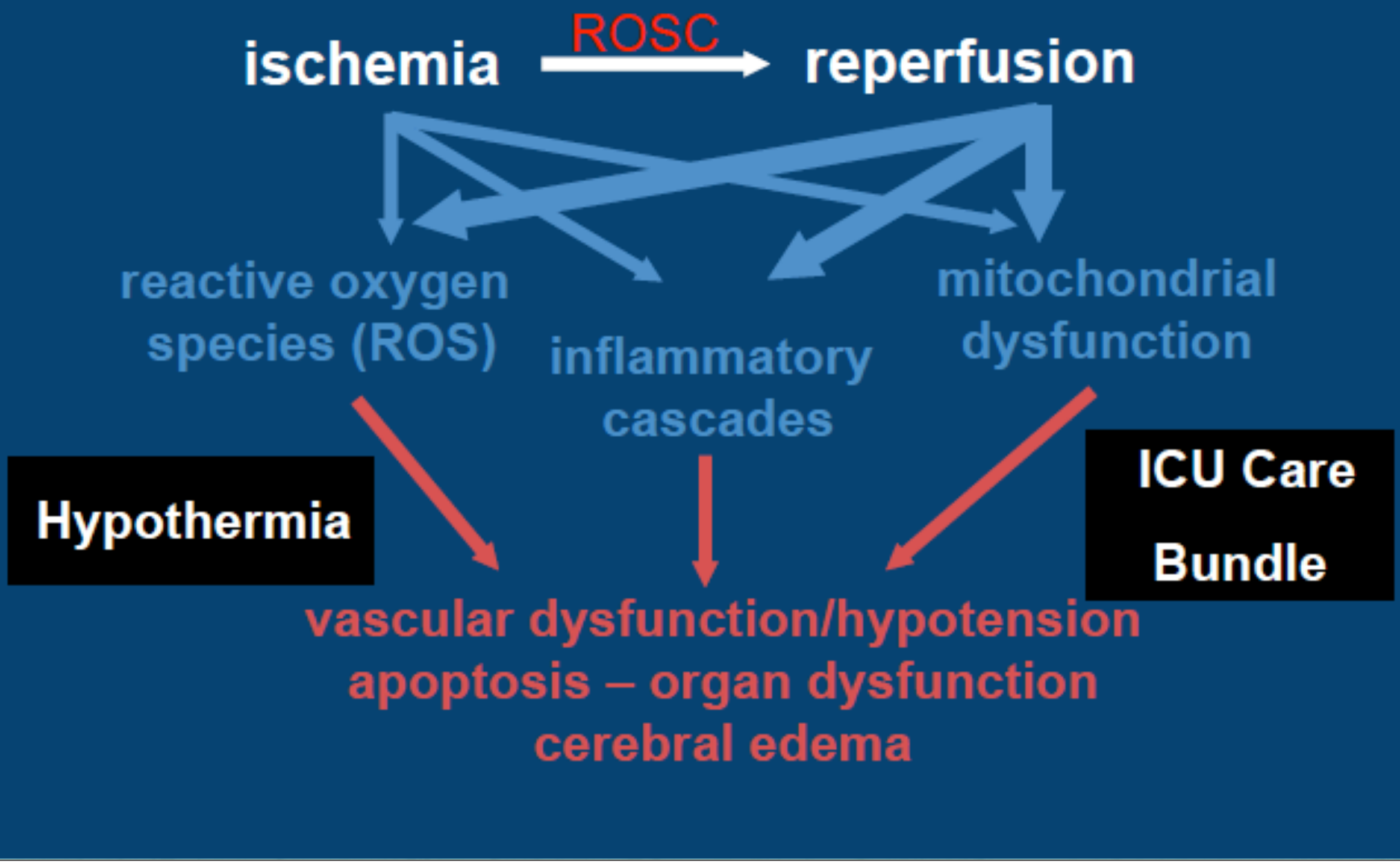
Physiologic changes associated with hypothermia

The NEW ENGLAND JOURNAL of MEDICINE

Severity of Hypothermia	Body Temperature	Central Nervous System	Cardiovascular	Respiratory	Renal and Endocrine	Neuromuscular
Mild	35°C (95°F) to 32.2°C (90°F)	Linear depression of cerebral metabolism; amnesia; apathy; dysarthria; impaired judgment; maladaptive behavior	Tachycardia, then progressive bradycardia; cardiac-cycle prolongation; vasoconstriction; increase in cardiac output and blood pressure	Tachypnea, then progressive decrease in respiratory minute volume; declining oxygen consumption; bronchorrhea; bronchospasm	Cold diuresis; increase in catecholamine, adrenal steroids, triiodothyronine, and thyroxine; increase in metabolism with shivering	Increased preshivering muscle tone, then fatiguing shivering-induced thermogenesis; ataxia
Moderate	<32.2°C (90°F) to 28°C (82.4°F)	Electroencephalographic abnormalities; progressive depression of level of consciousness; pupillary dilatation; paradoxical undressing; hallucinations	Progressive decrease in pulse and cardiac output; increased atrial and ventricular arrhythmias; nonspecific and suggestive (J-wave) electrocardiographic changes; prolonged systole	Hypoventilation; 50% decrease in carbon dioxide production per 8°C drop in temperature; absence of protective airway reflexes; 50% decrease in oxygen consumption	50% increase in renal blood flow; renal autoregulation intact; no insulin activity	Hyporeflexia; diminishing shivering-induced thermogenesis; rigidity
Severe	<28°C (82.4°F)	Loss of cerebrovascular autoregulation; decline in cerebral blood flow; coma; loss of ocular reflexes; progressive decrease in electroencephalographic activity	Progressive decreases in blood pressure, heart rate, and cardiac output; reentrant dysrhythmias; decreased ventricular arrhythmia threshold; asystole	Pulmonic congestion and edema; 75% decrease in oxygen consumption; apnea	Decrease in renal blood flow parallels decrease in cardiac output; extreme oliguria; poikilothermia; 80% decrease in basal metabolism	No motion; decreased nerve-conduction velocity; peripheral areflexia

Danzl D and Pozos R. N Engl J Med 1994;331:1756-1760

Hypothermia mechanism



Benefit of Cooling

- **↓Temp. strengthen cell membrane, ↓disruption to environment.**
- Stabilized blood-brain barrier.
- ↓Cerebral metabolism 7-10% / 1 °C body temp drop.
- **Hypothermia moderates inflammation & reduces free radical production**
- ↓ATP & glucose consumption
- ↓inflammation & cerebral edema ==>↓ ICP

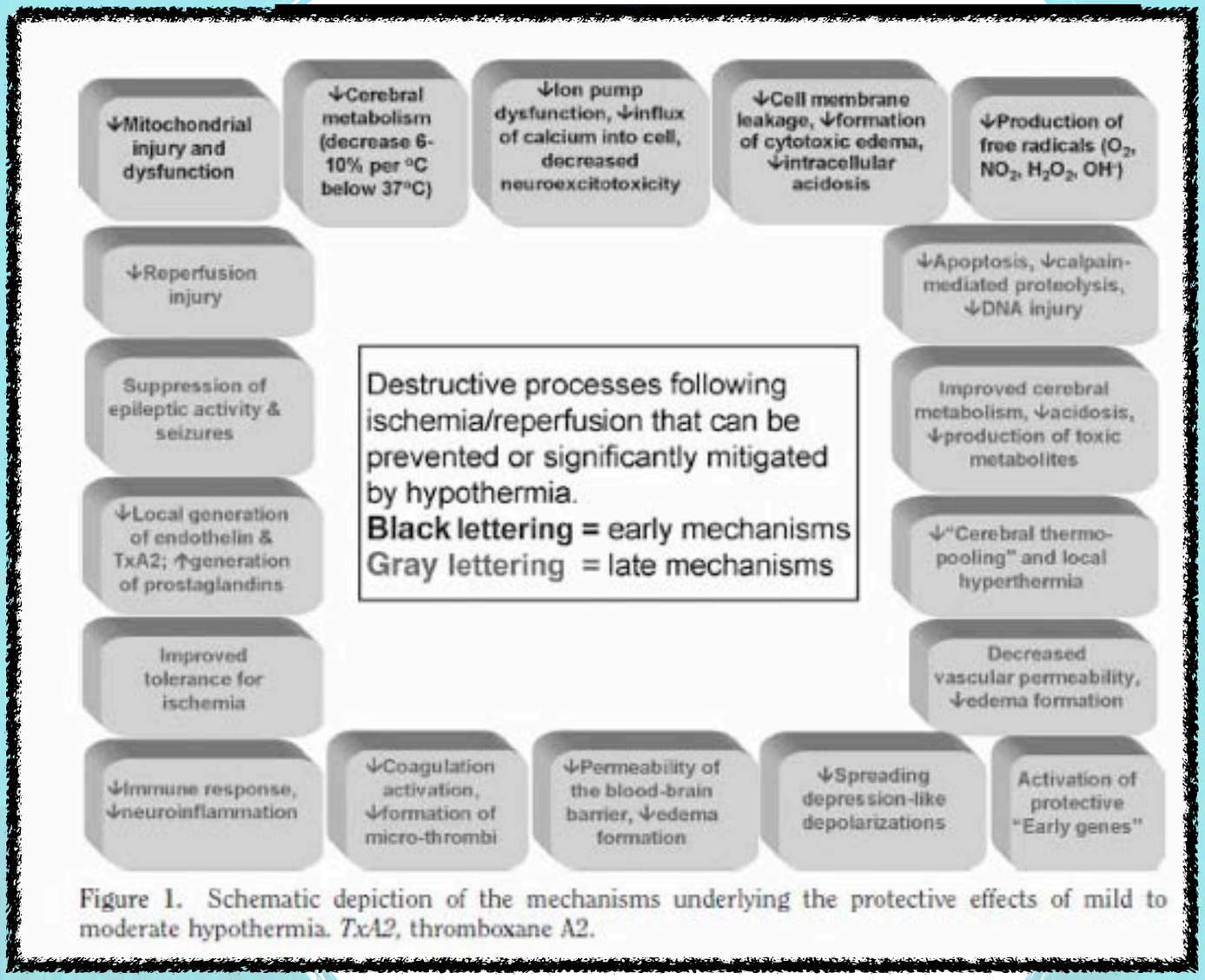
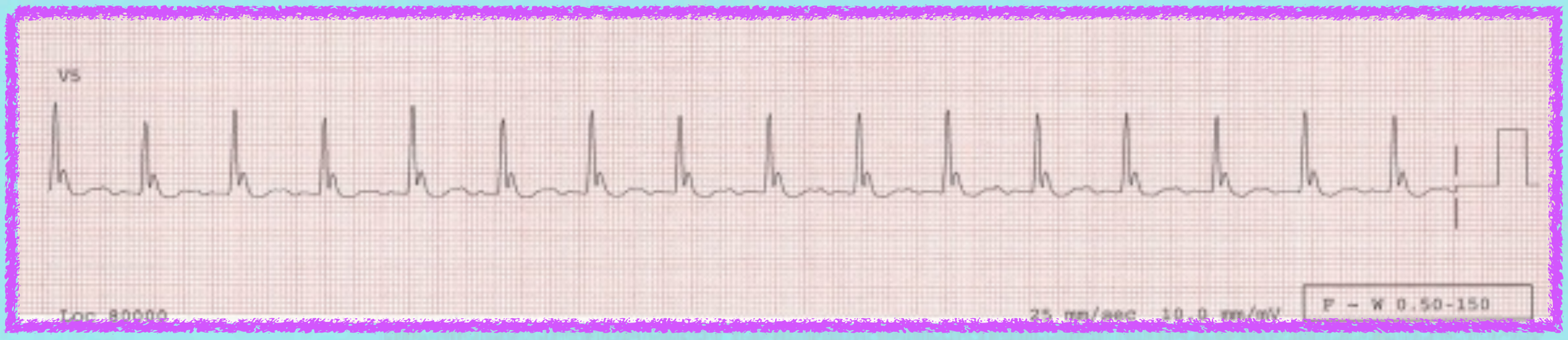


Figure 1. Schematic depiction of the mechanisms underlying the protective effects of mild to moderate hypothermia. *TxA2*, thromboxane A2.

Cardiovascular

- Tachycardia, then bradycardia when T < 35°C
- Increased contractility
- Cardiac cycle prolongation (PR, QRS, QT)
- Vasoconstriction –Stable or Increased BP
- ↑CVP due to venoconstriction
- Decreased C.O. 25-40%
- Arrhythmias very rare at Temp > 30°C



Polderman, KH. Crit Care Med 2009; 37: S186-202
Hovdenes, J. Acta Anaesthesiol Scand 2007; 51: 137-142
Boddicker, KA. Circulation 2005; 111: 3195-3201

Respiratory

In TH after OHCA, ventilation controlled

↑Solubility of O2 & CO2 ->↓PaO2, PaCO2
Bronchorrhea, bronchospasm
Left shift of Oxy-HgB dis curve→↓DO2
Ventilator settings require frequent changes during induction

Renal/ Electrolyte

Cold diuresis

Increased venous return, venoconstriction
↑ANP, ↓ADH, & tubular dysfunction
If uncorrected, causes hypovolemia, hemoconcentration

↓Electrolytes (K, Mg, Phos) due to

Diuresis-induced, ↑renal excretion
Intracellular electrolyte shifts

Musculoskeletal

Induction hypothermia →activate counter-regulatory mechanisms

Vasoconstriction begins @ ≈ 36.5°C

 # Shivering begins @ ≈ 35.5°C

In awake patients

increased VO2 (40-100%); ↑Myocardial VO2

increased metabolic rate; ↑WOB, ↑HR

These are suppressed with sedatives

Removed with paralytics

Lopez M, Anesthesiology, 1994; 80: 780-788
Polderman KH, Crit Care Med, 2009; 37: 1101-1120

Endocrine/ Metabolic

↑Drug levels/effects

- ↓hepatic clearance, ↓speed of enzymatic reactions
- ↓blood flow, bile excretion
- Affected drugs: pressors, sedatives, analgesics, NMB, etc

Hyperglycemia

- Decreased insulin sensitivity
- Decreased insulin secretion by pancreatic islet cells
- Hyperglycemia is damaging to the injured brain

↑Lactate, ketones, free fatty acids

Gastrointestinal

 # Ileus: impaired bowel function

 # Delayed gastric emptying

 # Gastric stress ulcers

 # Hepatic dysfunction – LFT's (transaminitis)

 # Pancreatic dysfunction – ↑amylase, but no clinical pancreatitis

Povlishock, JT. Acta Neurochir Suppl (Wein) 1999; 73: 15-20

Hematologic

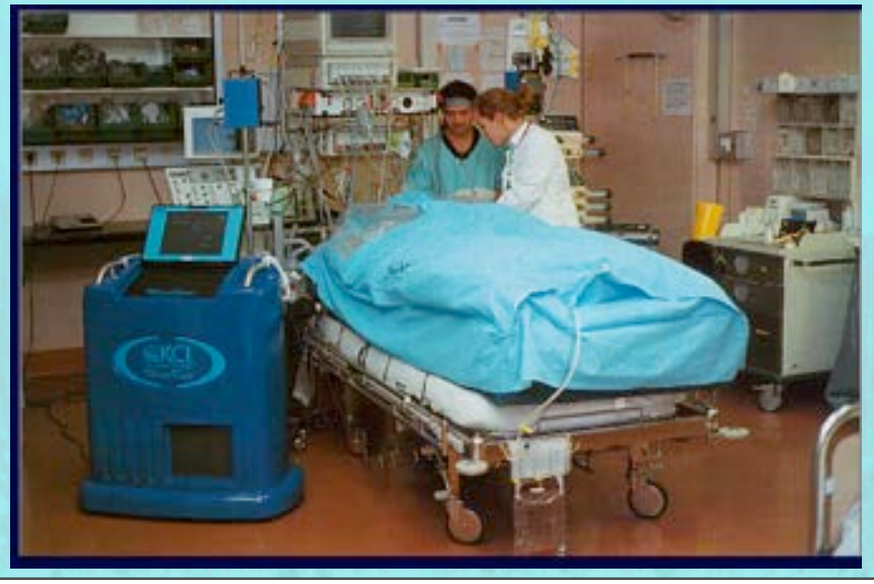
↑Hb
↓platelet & WBC count (>24 hrs)
Mild hypothermia→Mild Coagulopathy
↓platelet function, count (@ < 35˚C)
↓function of plasma proteins (@ < 33˚C)
Risk of spontaneous bleeding is very low

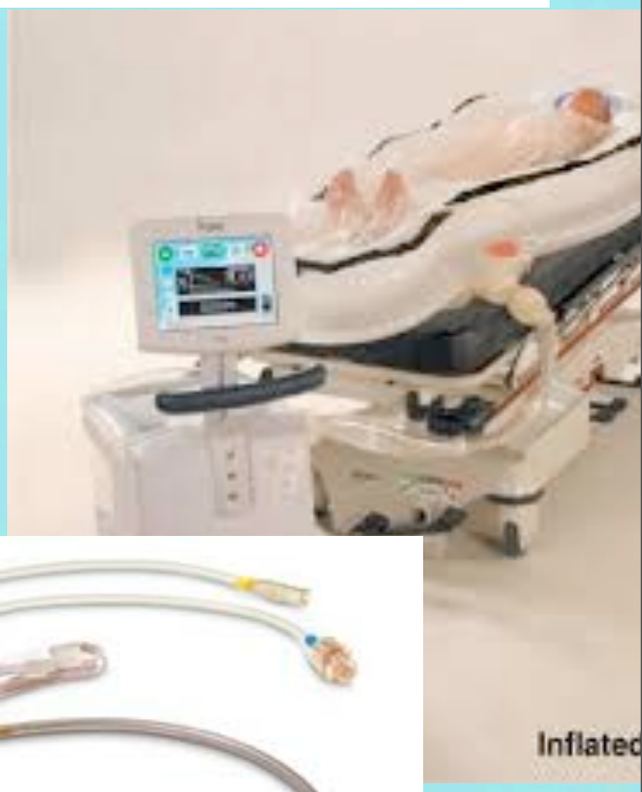
Infectious risk

Impairs immune/inflammatory response
(?mechanism of improved CNS outcome)
Inhibition of leukocyte migration, phagocytosis
↑ Risk of Pneumonia when hypothermia > 24 hrs
↑Wound infections
↓WBC migration, ↑skin vasoconstriction
Contact point of cooling pads

Methods of cooling

- Endovascular cooling
- Surface cooling





Indication and Contraindication

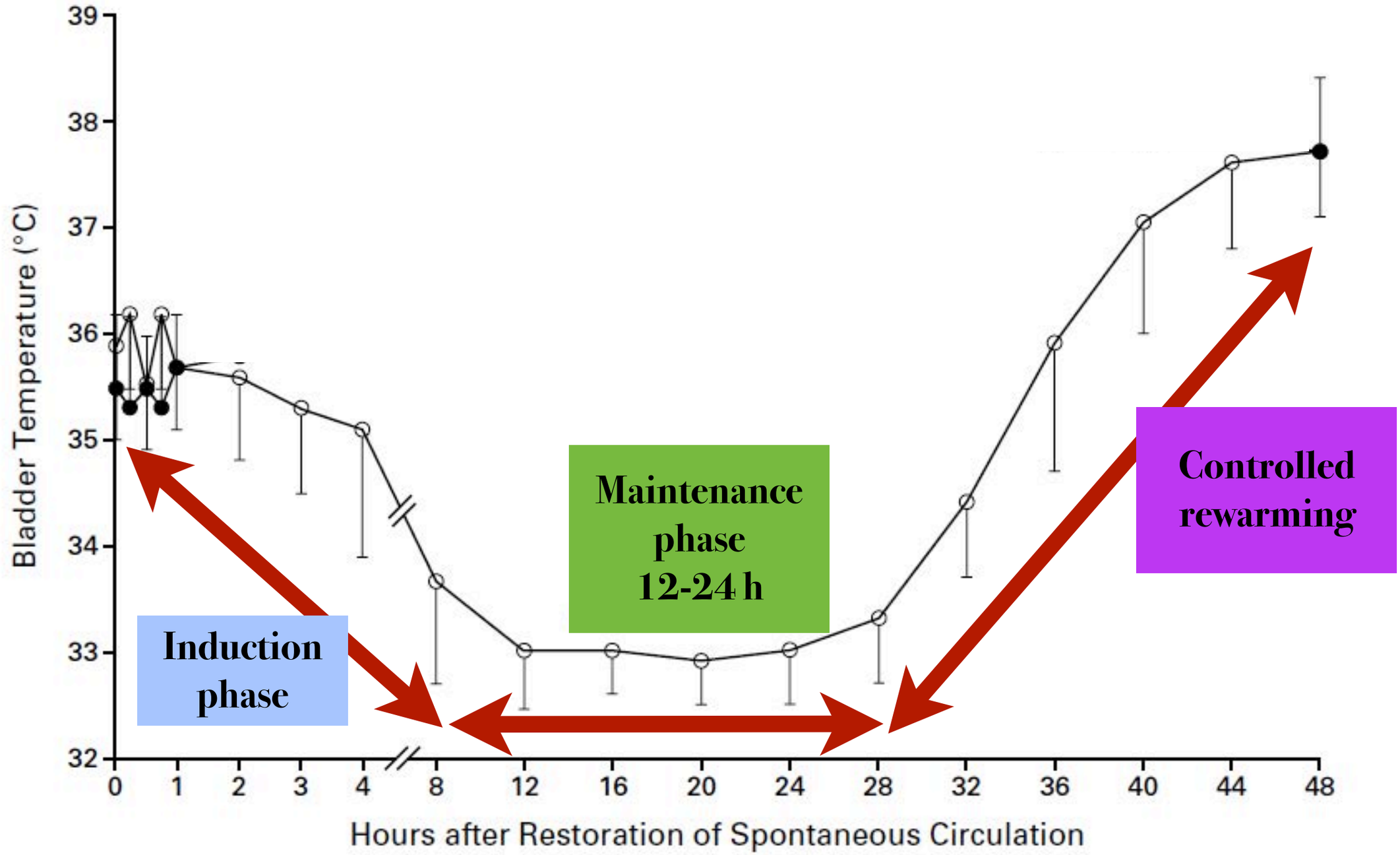
Indication

- Post-cardiac arrest with ROSC: Out hospital cardiac arrest from VF is class I recommendation, other setting & rhythm may be considered
- Less than 12 hours since ROSC
- Patient's pre-arrest cognitive status is not severely impaired
- Patient is comatose GCS< 8 without sedation.

Contraindications

- Documented intracranial hemorrhage
- Severe hemorrhage
- Refractory hypotension
- Severe uncontrolled sepsis
- Pregnancy.

Temperature curve during hypothermia



Getting started

- **Temp. probe**
  - Esophageal
  - Rectal
  - Bladder
- **Hemodynamic monitoring**
  - A-line
  - CVP
- **Foley catheter, ET tube with controlled ventilator**

Monitor-Induction phase

- **Induction phase may be started with 4 °C saline 30-40 cc/kg rapid infusion**
- **ABG:**
  - Minimized FiO2; goal O2 Sat ≥ 94%
  - Ventilated to ETCO2 35-40 mmHg, PaCO2 40-45 mmHg.
- **MAP goal 80-100 mmHg;** fluid resuscitation and vasopressor.

Monitor-Induction phase

- **Shivering:**
  - Thermoregulatory response to hypothermia
  - DDx from seizure, infection
  - Create heat, undesired effects
  - Sedative, Pethidine, Mg^{2+}, NMB (trigger ventilator) and encourage vasodilatation .
  - Subclinical shivering may considered if targeted temp is not achieved.

Monitor-Induction phase

- **Metabolic:**
  - High blood sugar, treat when > 200 mg%, higher insulin requirement
  - Hypokalemia from cellular shift, no need to correct unless level < 3.4 mEq/L; based on Bernard study
  - Hypomagnesemia
  - Hypophosphatemia
- **Continuous temp monitoring**

Monitor- Maintenance phase

- **Arrhythmia:** Bradycardia is common, no treatment if perfusion is good.
- **Bleeding:** mild coagolapathy no treatment if no active bleeding
- **Skin** for evidence of frostbite
- **Vulnerable area** (bony prominences)
- **Infection surveillance:** Serial lactate level, leukocytosis, CRP may helpful

Monitor-Rewarming phase

- Ideal rate 0.1-0.5 °C/h
- Vasodilatation cause hypotension, need fluid resuscitation
- Hyperkalemia from cellular shift
- Less insulin need, stop insulin when Glu < 200 mg%
- Keep sedation and anlgesia until temp 36 °C
- Avoid “ rebound hyperthemia” after reach 37 °C, may keep normothermia for 2 days.

Evaluation of Outcome at 72h, at discharge, 6 and 12 Mo

Cerebral Performance Categories scale (CPC)

CPC 1. Good cerebral performance: conscious, alert, able to work, might have mild neurologic or psychologic deficit.

CPC 2. Moderate cerebral disability: conscious, sufficient cerebral function for independent activities of daily life. Able to work in sheltered environment.

CPC 3. Severe cerebral disability: conscious, dependent on others for daily support because of impaired brain function. Ranges from ambulatory state to severe dementia or paralysis.

CPC 4. Coma or vegetative state: any degree of coma without the presence of all brain death criteria. Unawareness, even if appears awake (vegetative state) without interaction with environment; may have spontaneous eye opening and sleep/awake cycles. Cerebral unresponsiveness.

CPC 5. Brain death: apnea, areflexia, EEG silence, etc.

Futures in Hypothermia treatment

Circulation

Prehospital Cooling

American Heart Association®

Induction of Therapeutic Hypothermia by Paramedics After Resuscitation From Out-of-Hospital Ventricular Fibrillation Cardiac Arrest: A Randomized Controlled Trial

Stephen A. Bernard, Karen Smith, Peter Cameron, Kevin Masci, David M. Taylor, D. James Cooper, Anne-Maree Kelly and William Silvester

Circulation. 2010;122:737-742; originally published online August 2, 2010;
doi: 10.1161/CIRCULATIONAHA.109.906859
7272 Greenville Avenue, Dallas, TX 75231

SSN: 1524-4539

!! No survival benefit to cooling in the field with chilled saline

Table 3. Outcomes at Hospital Discharge

	Paramedic Cooling (n=118)	Hospital Cooling (n=116)	P*
Favorable outcome, n (%; 95% CI)	56 (47.5; 38.2–56.9)	61 (52.6; 43.1–61.9)	0.433
Discharge to home, n (%; 95% CI)	24 (20.3; 13.5–28.7)	34 (29.3; 21.2–38.5)	…
Discharge to rehabilitation, n (%; 95% CI)	32 (27.1; 19.3–36.1)	27 (23.3; 15.9–32.0)	…
Discharge to nursing home awake, n	0	0	…
Discharge to nursing home comatose, n (%; 95% CI)	0	1 (0.9; 0.02–4.7)	…
Dead, n (%; 95% CI)	62 (52.5; 43.1–61.8)	54 (46.6; 27.2–56.0)	…

CI indicates confidence interval.
*P calculated by χ^2 test.

Limitation

- Enroll by paramedics may lead to over/undertreatment
- Tympanic membrane temp is not true core temp
- No lab before cooling

Hypothermia in pediatric pt.

EVIDENCE-BASED CHILD HEALTH: A COCHRANE REVIEW JOURNAL
Evid.-Based Child Health **8:5**: 1584–1613 (2013)
Published online in Wiley Online Library (onlinelibrary.wiley.com). DOI: 10.1002/ebch.1939

Hypothermia for neuroprotection in children after cardiopulmonary arrest (Review)

Scholefield B, Duncan H, Davies P, Gao Smith F, Khan K, Perkins GD, Morris K

Unable to make any recommendations for clinical practice.
Randomized controlled trials are needed

Ongoing study in pediatric pt.

Trial name or title	Hypothermia for Cardiac Arrest in Paediatrics (HypCAP)
Methods	Randomized, single blind (outcome assessor), parallel assignment efficacy Phase II study
Participants	≥ 38 weeks gestation up to and including 17 yrs Chest compressions ≥3 minutes In-hospital and out-of-hospital arrest GCS ≤ 10 at 1 hour post-cardiopulmonary arrest Invasive mechanical ventilation Randomized within six hours
Interventions	1) Therapeutic hypothermia: 48 hours at 33°C to 34°C with rewarming 0.5°C every 2 hours to 36.5°C 2) Therapeutic normothermia: 48 hours at 36.5°C to 37.5°C

Evid.-Based Child Health 8:5: 1584–1613 (2013)

Ongoing study in pediatric pt.

Trial name or title	Therapeutic Hypothermia to Improve Survival After Cardiac Arrest in Paediatric Patients-(THAPCA-OH) (Out of Hospital) Trial
Methods	Randomized, single blind (outcome assessor), parallel assignment, safety and efficacy Phase III study
Participants	> 48 hours (with a corrected gestational age ≥ 38 weeks) and < 18 years chest compressions ≥ 2 minutes out-of-hospital cardiopulmonary arrest only mechanical ventilation Randomized within six hours
Interventions	1) Therapeutic hypothermia: 48 hours at 33°C±1°C with gradual rewarm to 36.75°C±0.75°C maintained until 120 hours 2) Therapeutic normothermia: 120 hours at 36.75°C±0.75°C
Trial name or title	Duration of Hypothermia for Neuroprotection After Paediatric Cardiac Arrest
Methods	Randomized, open label, parallel assignment, safety and efficacy Phase II study
Participants	1 week - 17 years Chest compressions by a healthcare worker In-hospital and out-of-hospital arrest GCS ≤ 8 PICU physician decision to use therapeutic hypothermia Central venous or arterial catheter in situ
Interventions	1) Therapeutic hypothermia: 72 hours at 33 ± 1°C 2) Therapeutic hypothermia: 24 hours at 33 ± 1°C

Evid.-Based Child Health 8:5: 1584–1613 (2013)

Potential indications for induced hypothermia:

- Acute disseminated encephalomyelitis — Level IV
- Grand mal seizures — Level IV
- Cardiac arrest due to non-coronary causes — Level IV
- Sepsis/septic encephalopathy — Level IV
- Preventing/delaying cardiac arrest in severe hypovolemic shock — Level IV
- Perioperative (vascular, cardiac and neurosurgery) — Level III
- Stroke — Level III
- Post-anoxic encephalopathy VT/VF — Level I
- Post-anoxic encephalopathy Asystole/PEA — Level III
- Traumatic brain injury – improving outcome — Level IIA
- Mitigating myocardial injury during Ischemia/reperfusion — Level III
- Traumatic brain injury - reducing ICP — Level I
- Reversing cardiac shock following cardiac surgery — Level III
- Hepatic encephalopathy (reducing ICP) — Level III
- Subarachnoid haemorrhage — Level IV
- Fever in presence of neurological injury — Level IIB
- Perinatal asphyxia — Level I
- Preventing cardiac injury during cardiac surgery — Level III
- Delayed spinal ischemia — Level IV
- ARDS — Level IV
- Bacterial meningitis — Level IV
- Spinal cord contusion — Level IV

Polderman KH. Therapeutic hypothermia in the ICU: problems, pitfalls and opportunities (review). Part 1: Indications and evidence. Intensive Care Med 2004; 30:556-75. Polderman KH. Yearbook of Intensive Care & Emergency Med 2004 p830-843

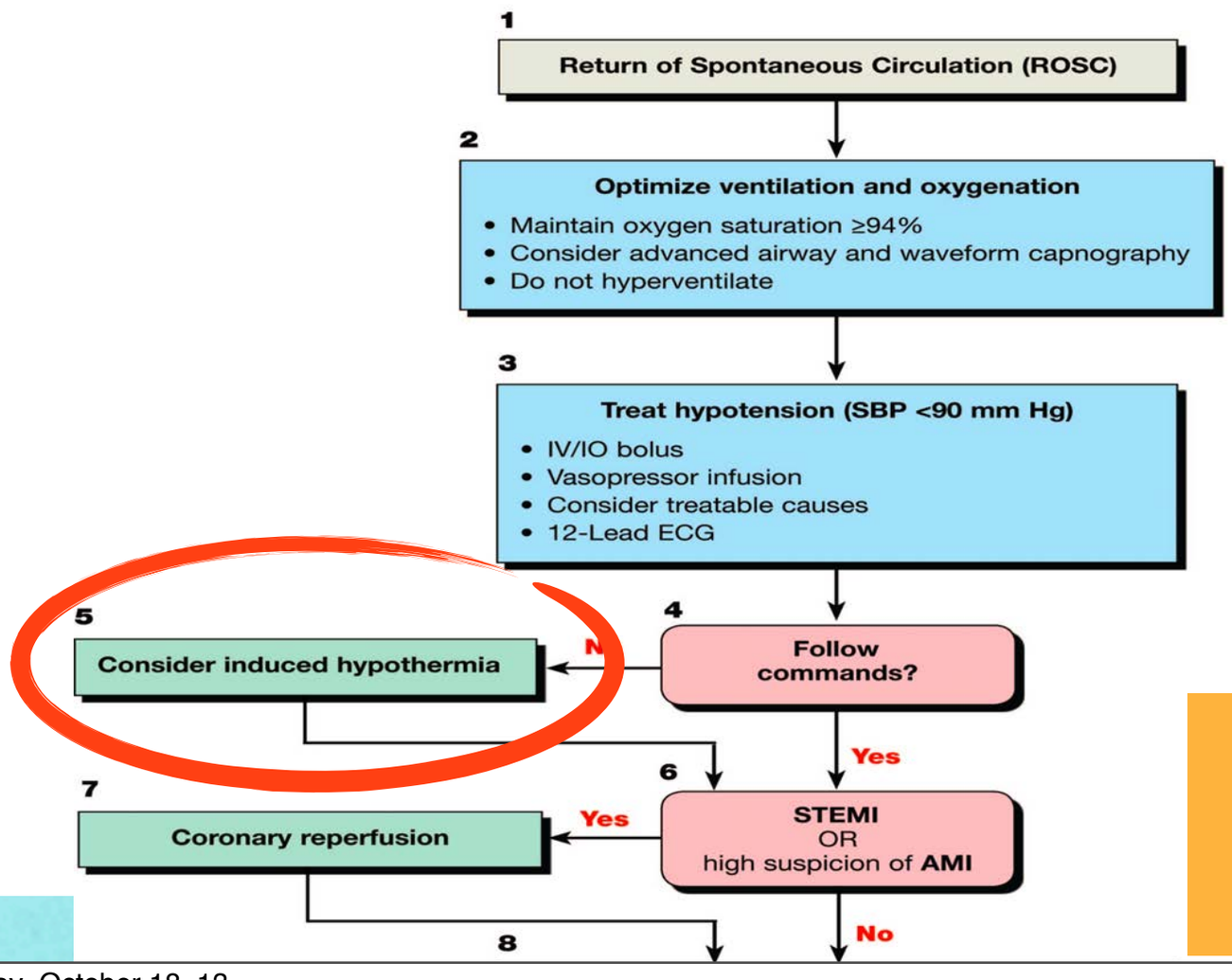
Post-anoxic encephalopathy
VT/VF
Level I

The strongest evidence...

Traumatic brain injury - reducing ICP
Level I

Perinatal asphyxia
Level I

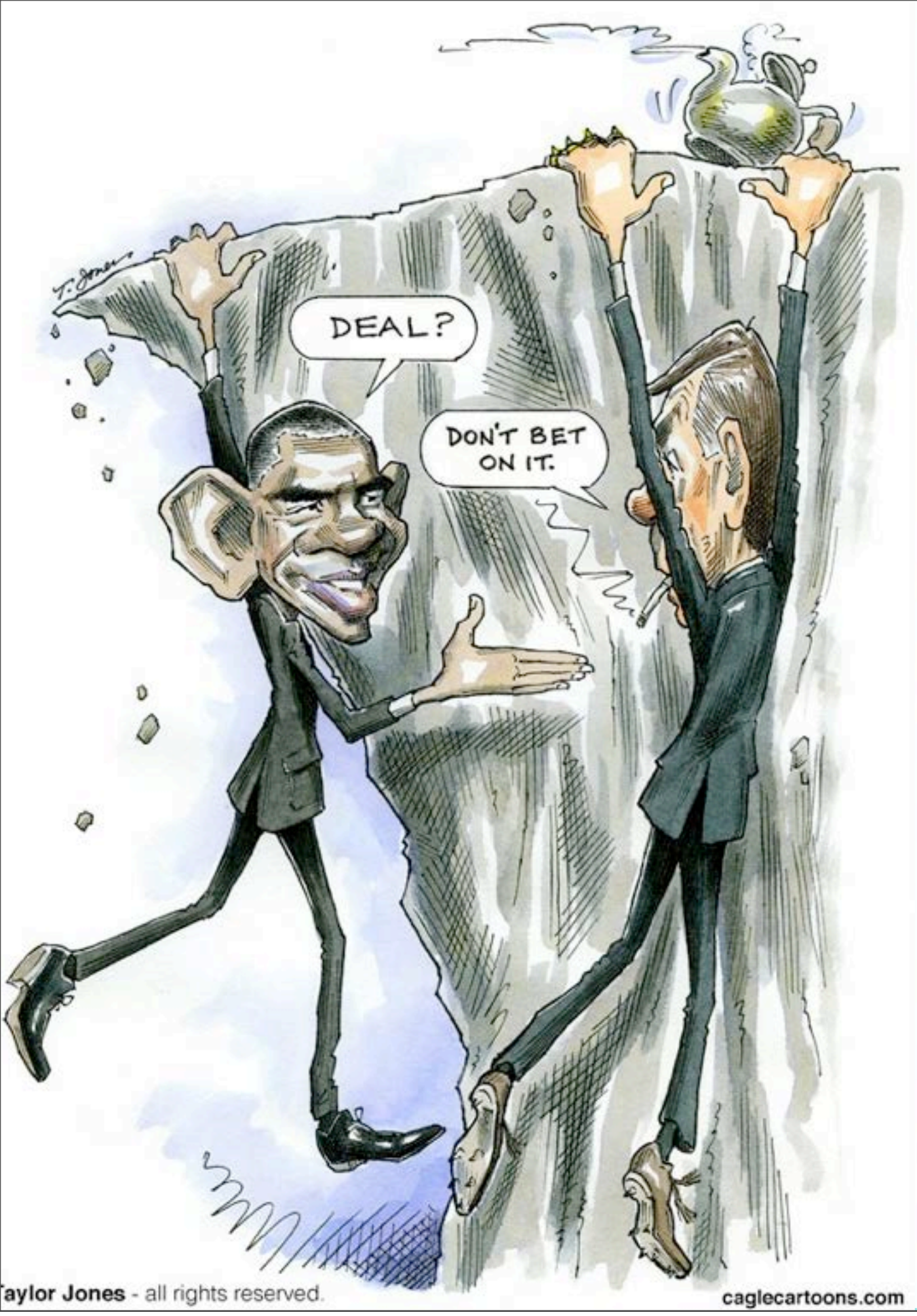
Fever in presence of neurological injury
Level IIB



2010 AHA guideline introduced hypothermia into post-arrest care algorithm

Hypothermia in non cardiac arrest

- **STEMI:** feasible and safe, ?? limit infarct size or reduce MACE, thus not currently recommended
- **Stroke:** feasible, ↓brain edema, effective as adjuvant treatment, may need more rapid cool to targeted temp (endovascular prefered), very slow rate of rewarming (< 0.1 °C/h) (prevent rebound ↑ICP)
- **TBI:** most study is negative, high rate of complication esp. infection (pneumonia)
- **Spinal cord injury:** Moderate- Mild hypothermia may be effective, Cool in the field may work, Adjuvant to standard treatment.



Induced hypothermia: "can be risky, but is potentially highly rewarding"

Question and discussion