Cooling: Is it really as cool as is believed?

Utpal S. Bhalala, MD, FCCM, FAAP, DNB, DCH, MNAMS, MBBS

Assistant Professor, Department of Pediatrics

Director of Research, Pediatric Critical Care Medicine

Associate Medical Director of Volcker Clinical Research Center

The Children's Hospital of San Antonio

Baylor College of Medicine

Past-Chair, SCCM In-Training Section

Past-Chair, SCCM Pediatric Online Module Development Committee

Vice-Chair, SCCM PMCCKAP Committee

Board of Directors, SCCM Texas Chapter

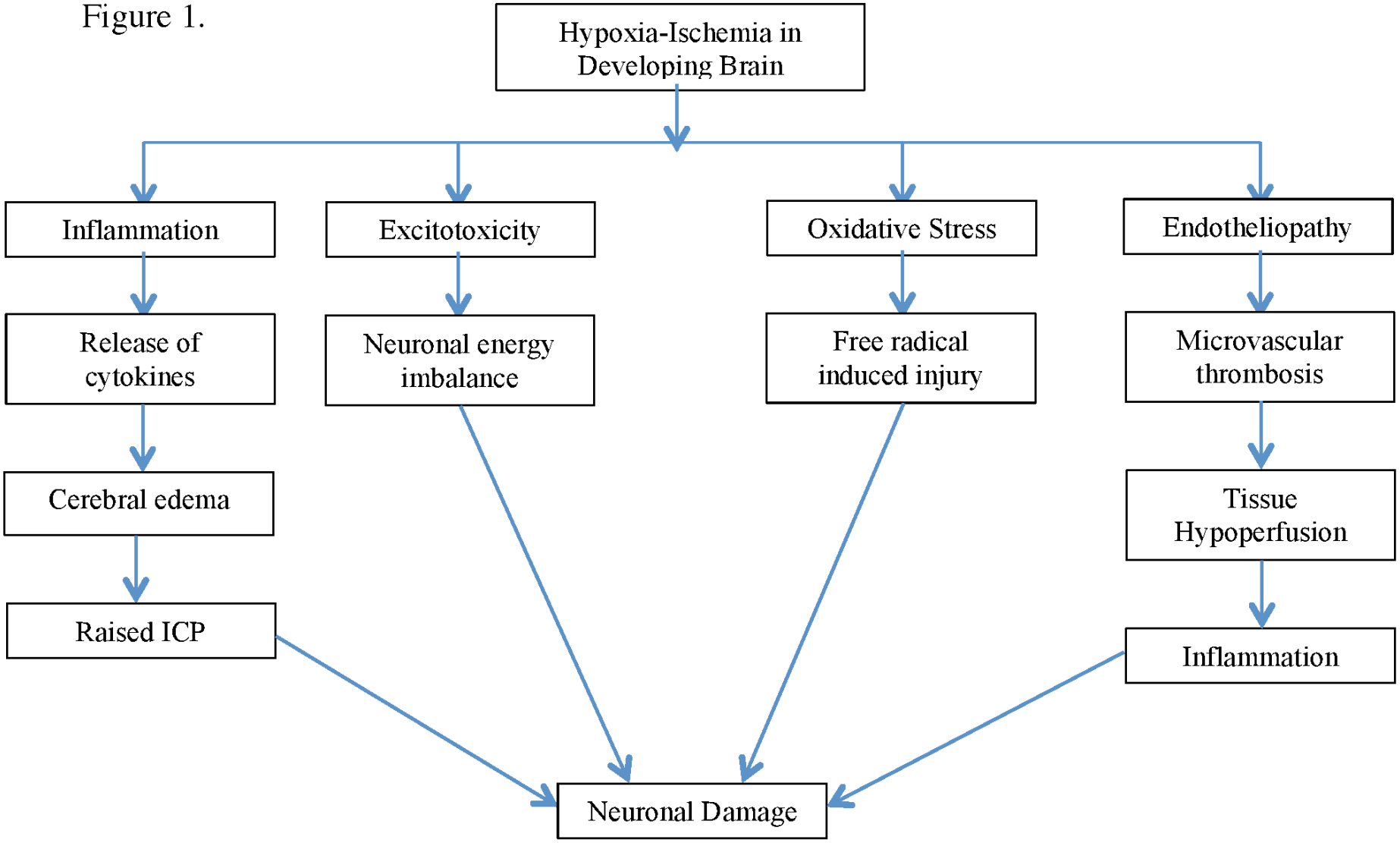
Disclosure

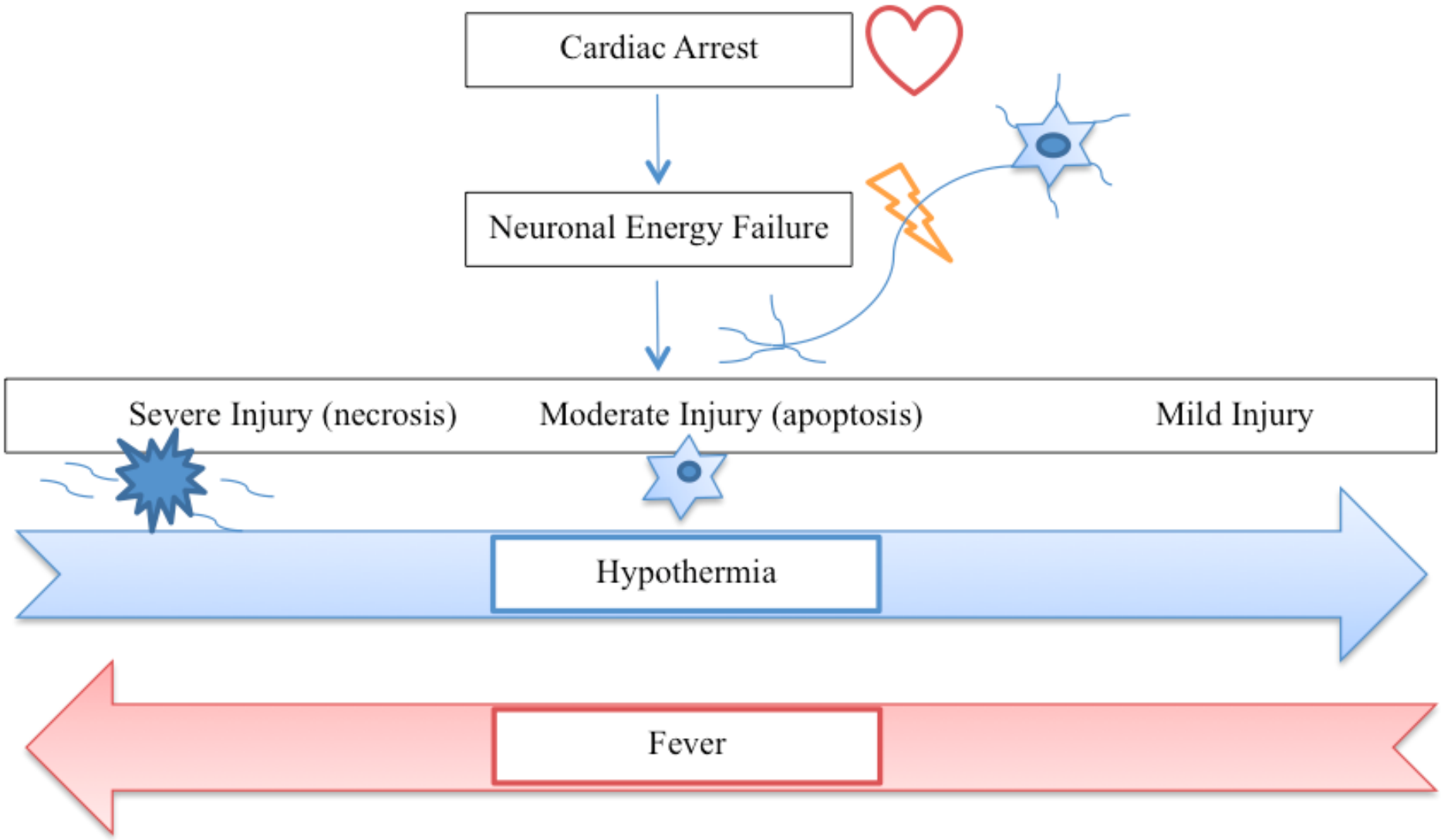
- Johns Hopkins Site PI for THAPCA trials
- PI for NIHCHD-funded project on neuroinflammation in a swine model of cardiac arrest
- No financial disclosure or conflict of interest

History of Therapeutic Hypothermia After Cardiac Arrest

- 1958 – Four cases of cardiac arrest with improved outcome following exposure to therapeutic hypothermia
  - Williams GR, Ann Surg 148:462.
- 1959 - A review of 27 cases of cardiac arrest supporting the hypothermia as a therapeutic intervention in the post-cardiac arrest period
  - Benson DW, Anes Anal 38 (6): 423-8.

Figure 1.


Hypoxia-Ischemia in Developing Brain
Inflammation
Excitotoxicity
Oxidative Stress
Endotheliopathy
Release of cytokines
Neuronal energy imbalance
Free radical induced injury
Microvascular thrombosis
Cerebral edema
Tissue Hypoperfusion
Raised ICP
Inflammation
Neuronal Damage


Cardiac Arrest
Neuronal Energy Failure
Severe Injury (necrosis)
Moderate Injury (apoptosis)
Mild Injury
Hypothermia
Fever

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*

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.

One RCT and 1 quasi-randomized trial enrolling a total of 352 patients provided overall low-quality evidence for decreased poor neurological outcome in patients with OHCA with ventricular fibrillation or pulseless ventricular tachycardia as an initial rhythm who were cooled to 32◦C to 34◦C compared with no cooling.

Journal of the American College of Cardiology
© 2005 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 46, No. 3, 2005
ISSN 0735-1097/05/$30.00
doi:10.1016/j.jacc.2005.04.039

High-Volume Hemofiltration After Out-of-Hospital Cardiac Arrest

A Randomized Study

Ivan Laurent, MD,* Christophe Adrie, MD,† Christophe Vinsonneau, MD,* Alain Cariou, MD,*
Jean-Daniel Chiche, MD,* Alice Ohanessian, MD,‡ Christian Spaulding, MD,‡ Pierre Carli, MD,§
Jean-François Dhainaut, MD, PhD,* Mehran Monchi, MD*

Paris and Saint Denis, France

One additional small RCT of 61 patients evaluated hypothermia in the setting of high-volume hemofiltration and found no increase in survival at 6 months.

Resuscitation Science

Is Hypothermia After Cardiac Arrest Effective in Both Shockable and Nonshockable Patients?

Insights From a Large Registry

Florence Dumas, MD; David Grimaldi, MD; Benjamin Zuber, MD; Jérôme Fichet, MD; Julien Charpentier, MD; Frédéric Pène, MD, PhD; Benoît Vivien, MD, PhD; Olivier Varenne, MD; Pierre Carli, MD, PhD; Xavier Jouven, MD, PhD; Jean-Philippe Empana, MD, PhD; Alain Cariou, MD, PhD

Three cohort studies including a total of 1034 patients provided overall very low-quality evidence for no difference in poor neurological outcome in patients with OHCA

One additional retrospective study using a large registry, analyzing 1830 patients, provided very low-quality evidence for an increase in poor neurological out- come in patients with non-shockable OHCA

Hypothermia After Cardiac Arrest Registry (HACA-R)

- A multicenter observational study
  - 587 patients
  - significantly higher rate of survival to hospital discharge
  - neurologic outcome not significantly better in hypothermia group
  - 2 major limitations –
    - lack of multivariate analysis to account for peri-arrest factors
    - selection bias

Evidence in adults

- French database of adult OHCA
  - mild therapeutic hypothermia
  - VF/VT patients
    - significantly better neurological outcome at discharge
  - non-VF/VT patients
    - trend towards a worse outcome

Evidence in adults

- OHCA RCT -
  - 1359 patients
  - cooled to 34°C using cold saline infusion
  - NO improvement in survival or neurological status
  - increased rate of re-arrest and pulmonary edema in hypothermia arm

Is Cooling good?

Evidence in children

- Reports of no difference in outcome in hypothermia compared to normothermia
- Retrospective, single-center study
  - Doherty DR Circulation 2009
  - Fink EL Crit Care Med 2010

THAPCA Trials

Objective

- *To describe the findings of a randomized clinical trial for pediatric OH cardiac arrest and determine outcomes based on receiving therapeutic hypothermia (TH) versus therapeutic normothermia (TN).*

THAPCA Trials

Methods

- *38 children's hospital PICUs in the United States and Canada.*
- *OH cardiac arrest > 2 days to <18 years of age admitted within 6 hours after the return of circulation were randomly assigned to:*
  - *Therapeutic hypothermia (target temp 33.0˚ C)*
  - *Therapeutic normothermia (target temp 36.8˚ C)*

THAPCA Trials

Methods

- *Primary outcome was survival with a good neurobehavioral outcome at 12 months of follow-up.*
- *Secondary outcomes were survival 12 months after cardiac arrest and change in neurobehavioral function.*

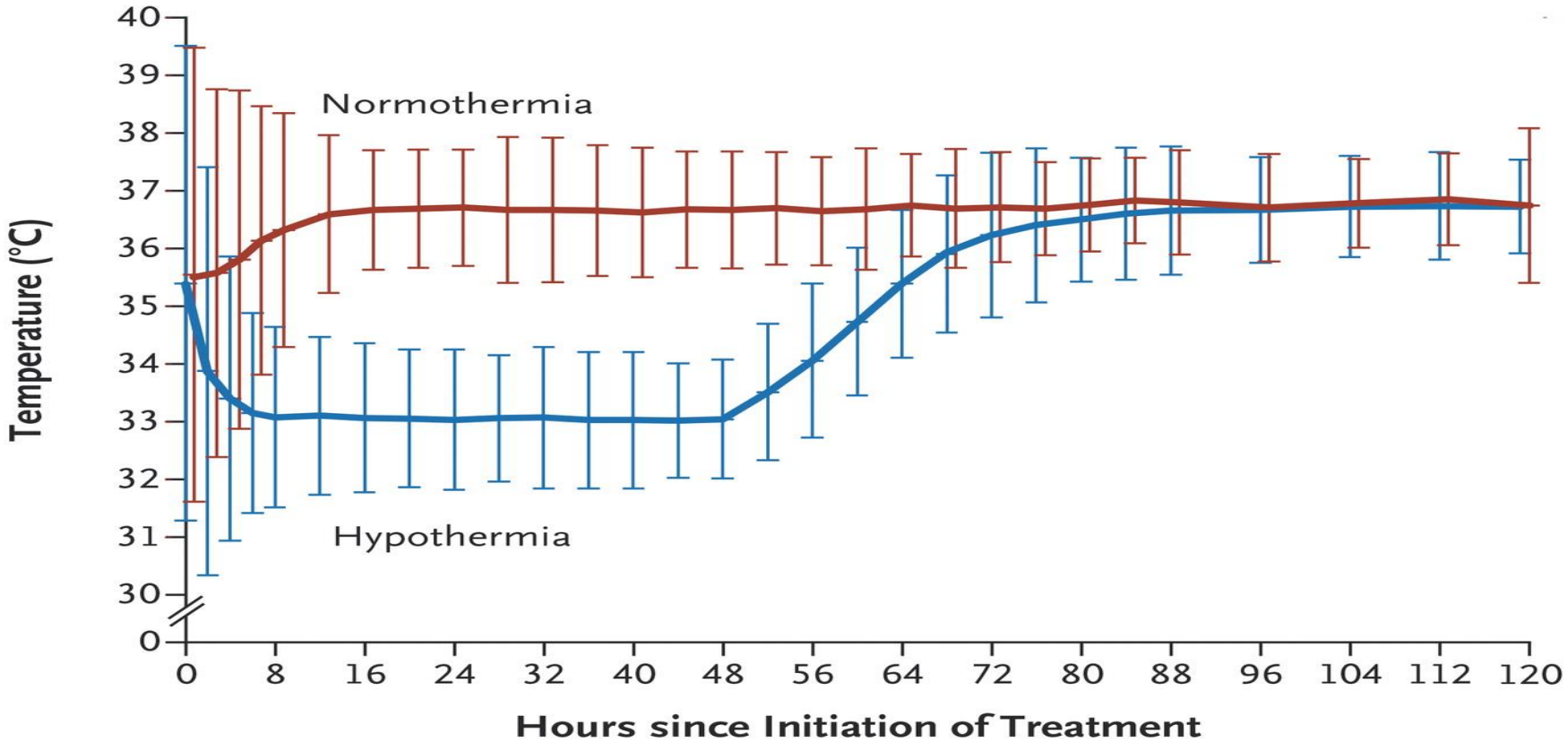
Table 1. Baseline Characteristics of the Patients before Randomization.*

Characteristic	Hypothermia Group (N = 155)	Normothermia Group (N = 140)
Demographic characteristics		
Age — yr		
Median	2.1	1.6
Interquartile range	0.6–10.1	0.4–7.0
Age category — no. (%)		
<2 yr	76 (49)	73 (52)
2 to <12 yr	48 (31)	45 (32)
≥12 yr	31 (20)	22 (16)
Male sex — no. (%)	102 (66)	94 (67)
Medical history — no. (%)		
No preexisting medical condition	81 (52)	71 (51)
Preexisting medical condition		
Lung or airway disease	33 (21)	34 (24)
Neurologic condition	30 (19)	19 (14)
Gastrointestinal disorder	19 (12)	22 (16)
Prenatal condition	15 (10)	22 (16)
Congenital heart disease	14 (9)	21 (15)
Other	34 (22)	37 (26)
Characteristics of the cardiac arrest		
Primary cause of the cardiac arrest — no. (%)		
Respiratory event	111 (72)	102 (73)
Cardiovascular event	14 (9)	18 (13)
Other	11 (7)	4 (3)
Unknown	19 (12)	16 (11)
Bystander witnessed cardiac arrest — no./total no. (%)	58/145 (40)	51/136 (38)
Bystander performed CPR — no./total no. (%)	101/149 (68)	85/134 (63)
Initial rhythm noted by EMS or hospital — no. (%)		
Asystole	85 (55)	87 (62)
Bradycardia	9 (6)	10 (7)
Pulseless electrical activity	25 (16)	18 (13)
Ventricular fibrillation or tachycardia	14 (9)	9 (6)
Unknown	22 (14)	16 (11)
Time from cardiac arrest to CPR in 82 patients — min		
Median	3.0	2.0
Interquartile range	0.0–7.0	0.0–8.0
Duration of CPR in 186 patients — min		
Median	23.0	28.0
Interquartile range	15.0–35.0	19.0–45.0
First hospital patient arrived at was the study hospital — no. (%)	45 (29)	43 (31)
Chest compressions still required at time of arrival at first hospital — no./total no. (%)	97/152 (64)	100/137 (73)
No. of doses of epinephrine		
Administered by EMS in 270 patients†		
Median	2.0	1.0
Interquartile range	0.0–3.0	0.0–2.0
Administered at hospital in 289 patients†		
Median	1.0	2.0
Interquartile range	0.0–3.0	0.0–4.0
All doses administered by EMS and at hospital in 265 patients		
Median	3.0	3.0
Interquartile range	2.0–4.5	2.0–5.0

* CPR denotes cardiopulmonary resuscitation, and EMS emergency medical services.
† $P<0.05$ for the comparison between the two groups.

THAPCA Trials

Temperature of Patients



THAPCA Trials

Outcomes

Table 2. Primary and Secondary Outcomes.*

Outcome	Hypothermia Group	Normothermia Group	Risk Difference	Relative Likelihood (95% CI)	P Value
	no./total no. (%)		*percentage points (95% CI)*		
Primary outcome					
Alive with VABS-II score ≥70 at 1 yr	27/138 (20)	15/122 (12)	7.3 (–1.5 to 16.1)	1.54 (0.86 to 2.76)	0.14†
Detailed supportive analysis					0.14‡
Death	87/138 (63)	88/122 (72)			
Disability					
Profound§	16/138 (12)	11/122 (9)			
Moderate-to-severe¶	8/138 (6)	8/122 (7)			
Good functional status‖	27/138 (20)	15/122 (12)			
Secondary outcomes					
Alive at 1 yr	57/151 (38)	39/136 (29)	9.1 (–1.8 to 19.9)	1.29 (0.93 to 1.79)	0.13†
1-yr change in VABS-II score from baseline					0.13**
Death	94/151 (62)	97/134 (72)			
Lowest possible VABS-II score	6/151 (4)	1/134 (1)			
Decrease in VABS-II score					
>30 points	19/151 (13)	15/134 (11)			
16–30 points	11/151 (7)	4/134 (3)			
≤15 points or improved	21/151 (14)	17/134 (13)			

THAPCA Trials

Outcomes

* The primary outcome was evaluated in patients with a baseline Vineland Adaptive Behavior Scales, second edition (VABS-II), score of 70 or higher at 12 months (scores on the VABS-II range from 20 to 160, with higher scores indicating better function). The secondary outcomes were evaluated in all patients with available data. Denominators reported are for patients whose outcomes were known. CI denotes confidence interval.

† The P value was calculated by means of the Cochran–Mantel–Haenszel test, with adjustment for age category.

‡ The P value was calculated by means of the Mann–Whitney test on the basis of the 1-year continuous VABS-II score, stratified according to age category. Deceased patients and those with the lowest possible VABS-II score were assigned ranks of –2000 and –1000, respectively (i.e., the worst possible scores).

§ Profound disability was defined as a VABS-II score of less than 45 or the lowest possible score.

¶ Moderate-to-severe disability was defined as a VABS-II score of 45 to 69.

‖ Good functional status was defined as a VABS-II score of 70 or higher.

** The P value was calculated by means of the Mann–Whitney test on the basis of the continuous change in VABS-II score, stratified according to age category. Deceased patients and those with the lowest possible VABS-II score were assigned ranks of –2000 and –1000, respectively (i.e., the worst possible scores).

THAPCA Trials

Results

- *1355 children screened, 475 were eligible, and 295 were randomized (155 TH & 140 TN).*
- *The median age was 2 years; two thirds were male. Bystanders witnessed the cardiac arrest in 39% and performed cardiopulmonary resuscitation in 66% of them. The initial rhythm was ventricular fibrillation or ventricular tachycardia in 8%.*

THAPCA Trials

- *The median time from the return of circulation to the initiation of treatment was 5.9 hours (interquartile range, 5.2 to 6.7) in the hypothermia group and 5.8 hours (interquartile range, 5.0 to 6.4) in the normothermia group.*
- *Primary (20% vs 12%) and secondary 12 month survival (38% vs 29%) outcomes were not significantly different between the two groups.*
- *There was no difference in the safety outcomes between the two groups.*

THAPCA Trials

Conclusions

- *In children who survive OH cardiac arrest, therapeutic hypothermia, as compared with therapeutic normothermia, did not confer a significant benefit with respect to survival with good functional outcome at 1 year.*
- *Survival at 12 months did not differ significantly between the treatment groups.*

Cooling is as good as no cooling

Cooling is Bad

Evidence in children

- Cooling trial in children who suffered severe TBI
- Higher mortality in Hypothermia group compared to normothermia group
- Trial stopped early based on futility analysis
- Smaller-than-planned sample size, so difficult to draw conclusions

Is Cooling Bad?

Rewarming

- Therapeutic Hypothermia (TH) improves survival from neonatal HI injury, but does not improve the long-term neurocognitive outcome among survivors.
- Resurgence of inflammation during rewarming from TH potentially contributes to loss of neuroprotective effects of TH.

Rewarming

Journal of Cerebral Blood Flow & Metabolism (2015) 35, 781–793

www.jcbfm.com

ORIGINAL ARTICLE

Rewarming from therapeutic hypothermia induces cortical neuron apoptosis in a swine model of neonatal hypoxic–ischemic encephalopathy

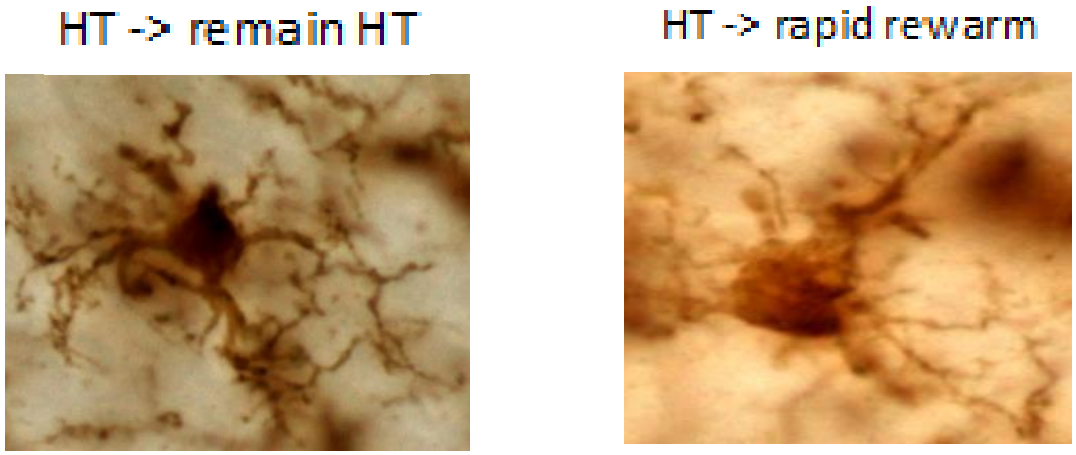
Bing Wang[1], Jillian S Armstrong[1], Jeong-Hoo Lee[1], Utpal Bhalala[1], Ewa Kulikowicz[1], Hui Zhang[1,2], Michael Reyes[1], Nicole Moy[1], Dawn Spicer[1], Junchao Zhu[1], Zeng-Jin Yang[1], Raymond C Koehler[1], Lee J Martin[3] and Jennifer K Lee[1]

Rewarming

Rewarming after hypothermia after cardiac arrest shifts the inflammatory balance*

Laurens L. A. Bisschops, MD; Cornelia W. E. Hoedemaekers, MD, PhD;
Tom E. Mollnes, MD, PhD; Johannes G. van der Hoeven, MD, PhD

Results



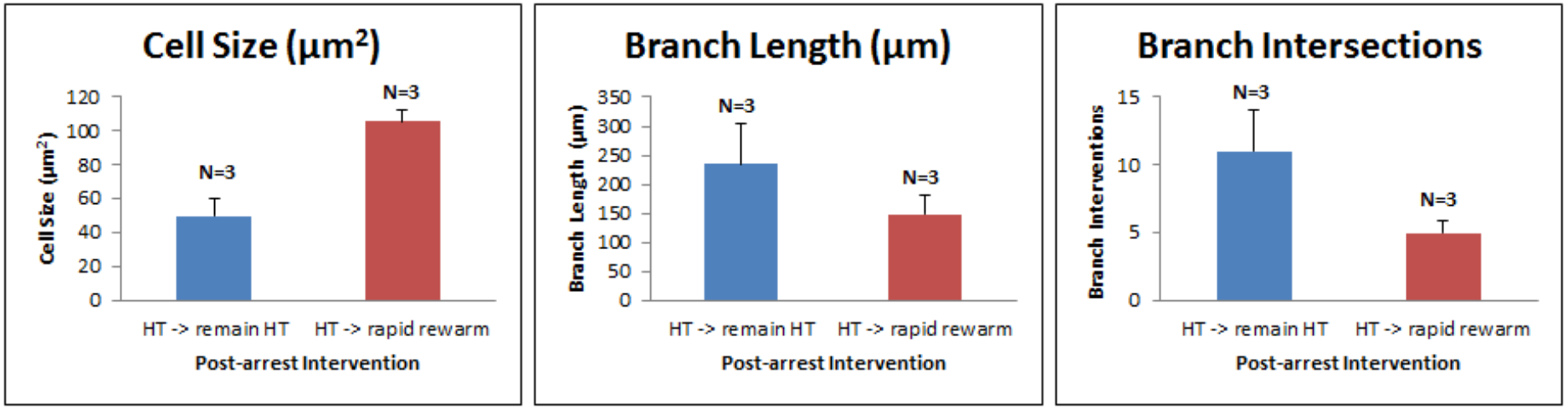
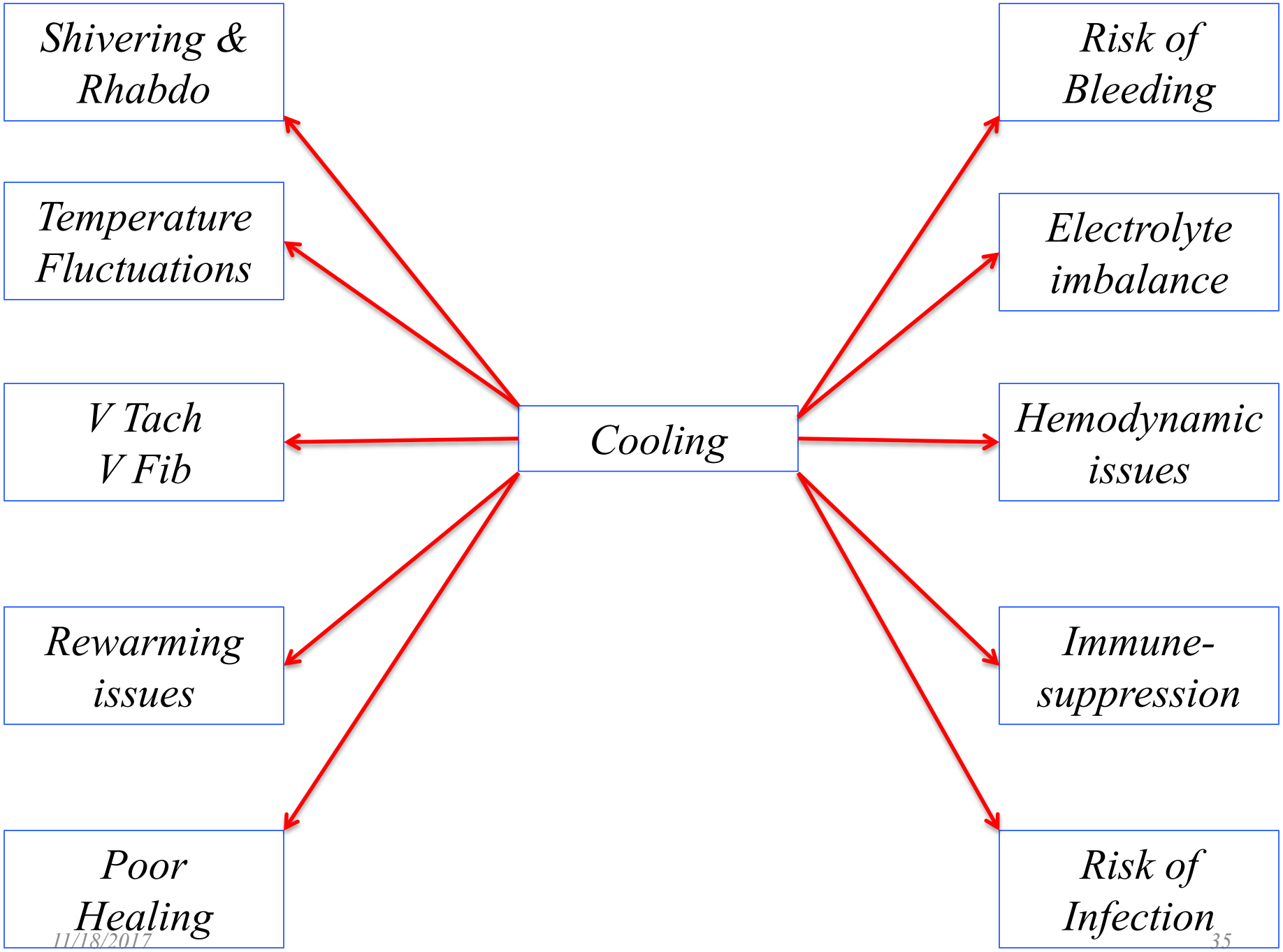


Figure 5: Neurolucida analysis of microglial morphology in male piglets subjected to Hypothermia (HT) alone versus HT followed by rapid rewarming after HA cardiac arrest. Note a significant difference in cell size, branch length and branch intersections in microglia in HT -> remain HT compared to HT -> remain rewarm group.

Cooling is not Bad
Rewarming could be Bad

Summary

- Cooling is good in select HIE patients
- Cooling is as good as normothermia in comatose children after OHCA
- Cooling may not be good in children with TBI
- Inappropriately done cooling and rewarming may be bad
- Fever is certainly bad

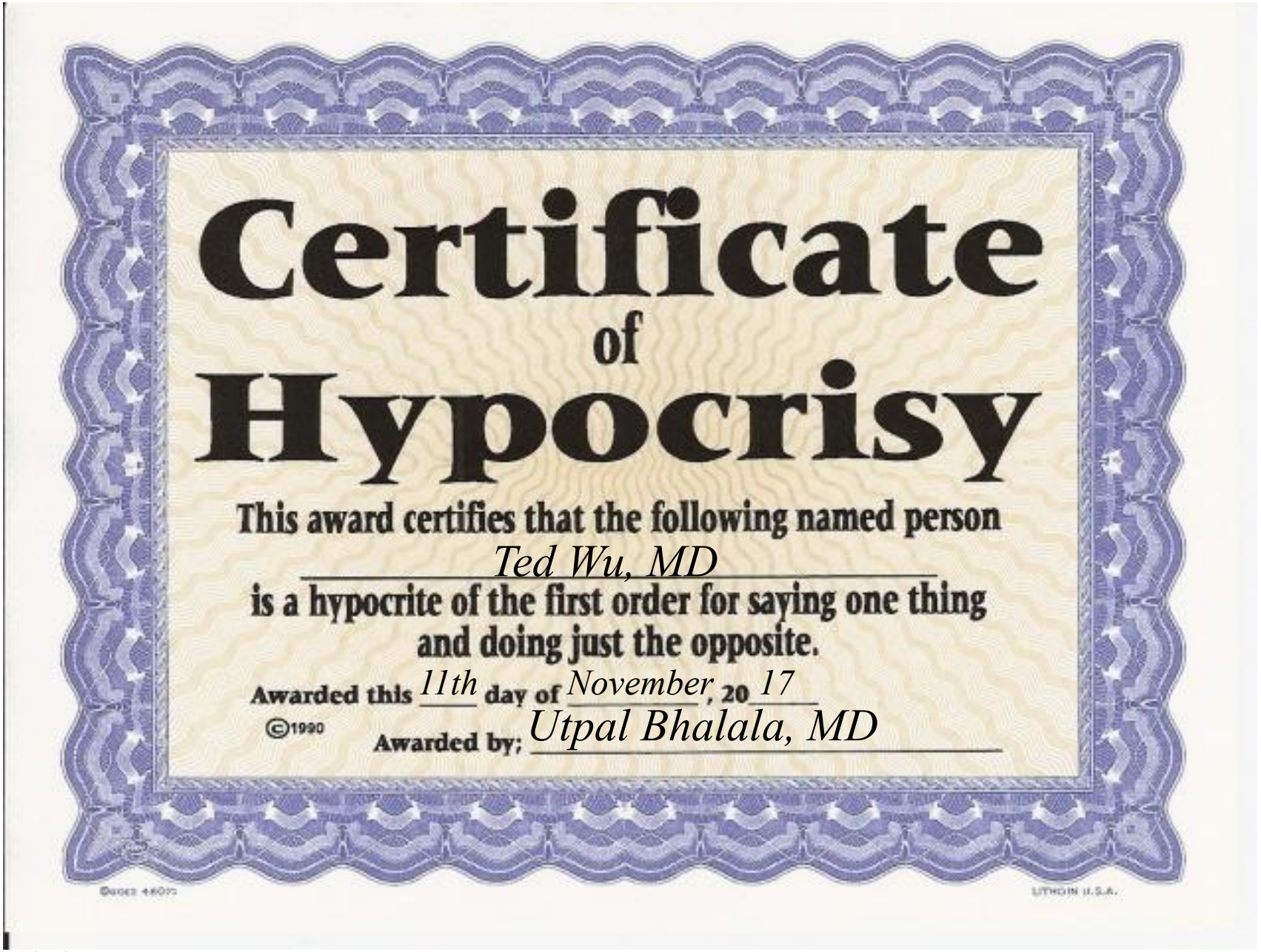

Shivering & Rhabdo
Temperature Fluctuations
V Tach V Fib
Rewarming issues
Poor Healing
Cooling
Risk of Bleeding
Electrolyte imbalance
Hemodynamic issues
Immune-suppression
Risk of Infection

Is cooling really a cool therapy?

Is cooling really worth it?

POLAR BEAR PLUNGE

What is practice in your own institution?


Certificate
of
Hypocrisy
This award certifies that the following named person
Ted Wu, MD
is a hypocrite of the first order for saying one thing
and doing just the opposite.
Awarded this 11th day of November, 20 17
©1990
Awarded by: Utpal Bhalala, MD

Thank You