Yin and Yang of Hypothermia in Trauma and Adult Critical Care

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Before medicine…

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Objectives

- Definitions
- Lessons learned
- Physiology/pitfalls
- History of IH
- Uses of hypothermia
- Future

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Definitions of Hypothermia

	Induced (°C)	Exposure (°C)
Mild	33-36	33-36
Moderate	28-32	28-32
Deep/ Severe	16-27	<28
Profound	6-15	

"Not dead until warm and dead"

Lowest temp documented in survivor:

Infant - 15.2° C (59.4° F)

Adult - 13.7° C (56.8° F)

"Not dead until warm and dead"

- Not reliable in hypothermia:
  - Tissue decomposition
  - Apparent rigor mortis
  - Dependent lividity
  - Fixed/dilated pupils
- Series: 9/27 patients CPR in field, 6/14 survived ED CPR

Danzl DF. Ann Emerg Med 1987.

Lessons from Primary Hypothermia

- Passive vs Active rewarming
  - External-truncal
  - Core
    - Warmed IVF
    - Heated, humidified ventilation
    - Lavage-gastric, colonic, mediastinal, thoracic, peritoneal
    - VV or AV extracorporeal
    - CPB
- Physiology
- For each 1°C ↓ = 6-7% ↓ in cerebral metabolism

Auerbach, Wilderness Medicine, 5th ed.

Lessons Learned

- Intermittent flow may be preferable to no flow
- Difference between warm and cold ischemia time

N	Avg Age (y)	Long-term survival (# pts)	Presentation esophageal temp (mean)	Time to CPB (mean)
32	25.3	15	21.8°C	141 min

Walpoth BH. Eur J Cardiothorac Surg 1990.

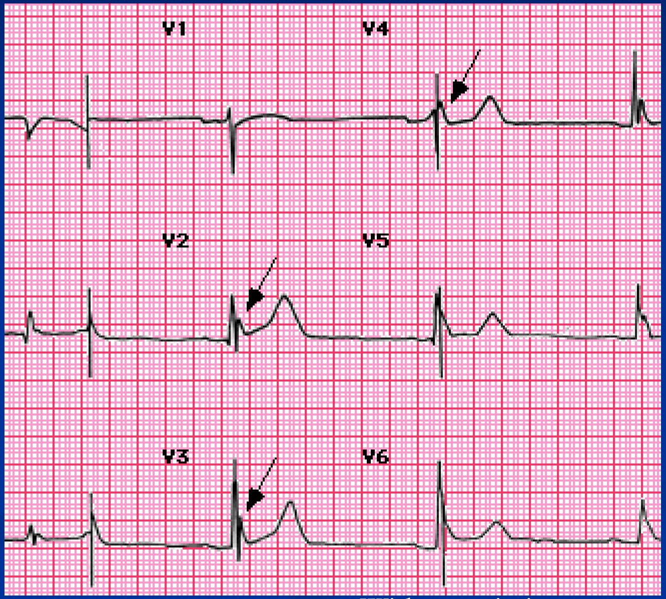
Survival of Hypothermia

- Predictors of survival:
  - Rapid cooling
  - VF during cardiac arrest
  - Narcotic/ethanol intoxication

- Poor prognostic factors:
  - Severe hyperkalemia (>10meq/dL)
  - Pre-hypothermia asphyxiation

Auerbach, Wilderness Medicine, 5th ed.
Silfvast T. Resuscitation 2003.
Schaller MD. *JAMA* 1990.

Cardiovascular



With permission.

- Bradycardia
- Prolonged QT
- Osborn waves
- Arrythmias <32°C
- Most vasopressors relatively ineffective

Hemodynamics

Hypothermia	HR	SVR	CO	CVP	MAP
Mild-mod	↓	↑	↓	↑	↔

- Bradycardia unresponsive to atropine
- Atrial/ventricular fibrillation

Respiratory

- Initial tachypnea → hypopnea
- CO_2 prod =↓ 50% / 8°C ↓
- Decreased ciliary motility and airway reflexes
- VQ mismatch
  - atelectasis
  - bronchorrhea

Renal

- Cold diuresis
  - Increased with EtOH
  - Electrolyte loss
- Renal tubular dysfunction
  - ↓ creatinine clearance—drug dosing
- Hypokalemia – loss and intracellular shift

Polderman KH. Intensive Care Med. 2003.
Macintosh TK. Brain Res. 1989.

Coagulopathy

- Enzyme inhibition
  - Increased PT, possibly PTT
  - Clotting cascade affected below 34°C
- Decreased plt count/function
- Fibrinolysis
- If due to hypothermia: not reversed with FFP, easily reversed with rewarming
- Clinically significant?

Watts DD. J Trauma 1998

Sessler DI. NEJM. 1997.

Infectious

- ↓ function of neutrophils and macrophages
- ? ↑ pneumonia-esp if IH>48hr
- Wound infxn: local vasoconstriction and suppression immune function

Shiozake T, et al. J Neurosurg. 2001.
Schwab S. Stroke. 2008.
Alderson P. Cochran Database Syst Rev. 2008.
Kurtz A, et al. NEJM. 1996.

Neurologic

- Mild hypothermia – confusion, ataxia
- Moderate – obtundation
- Hyperreflexia at 32° C
- <27°C, loss of pupillary light reflex and DTR

Tsuei and Kearney. Injury, Jan 2004.

Spontaneous vs Induced Hypothermia

	Spontaneous	Induced
Cause	Severe ischemia, ↓ cellular reserve Unable to thermoregulate Environmental exposure	Deliberate, controlled Poss more cellular reserve
Significance	Advanced tissue ischemia ↓ cellular substrates Failure of homeostasis Shivering worsens mismatch of tissue supply/demand	↓ metab rate Preservation of substrates ↓ free radical ↓ oxidative stress ↓ vasc permeability Active shivering prevention
Clinical Implication	Lethal triad Poor prognostic sign	Therapeutic strategy with potential benefit

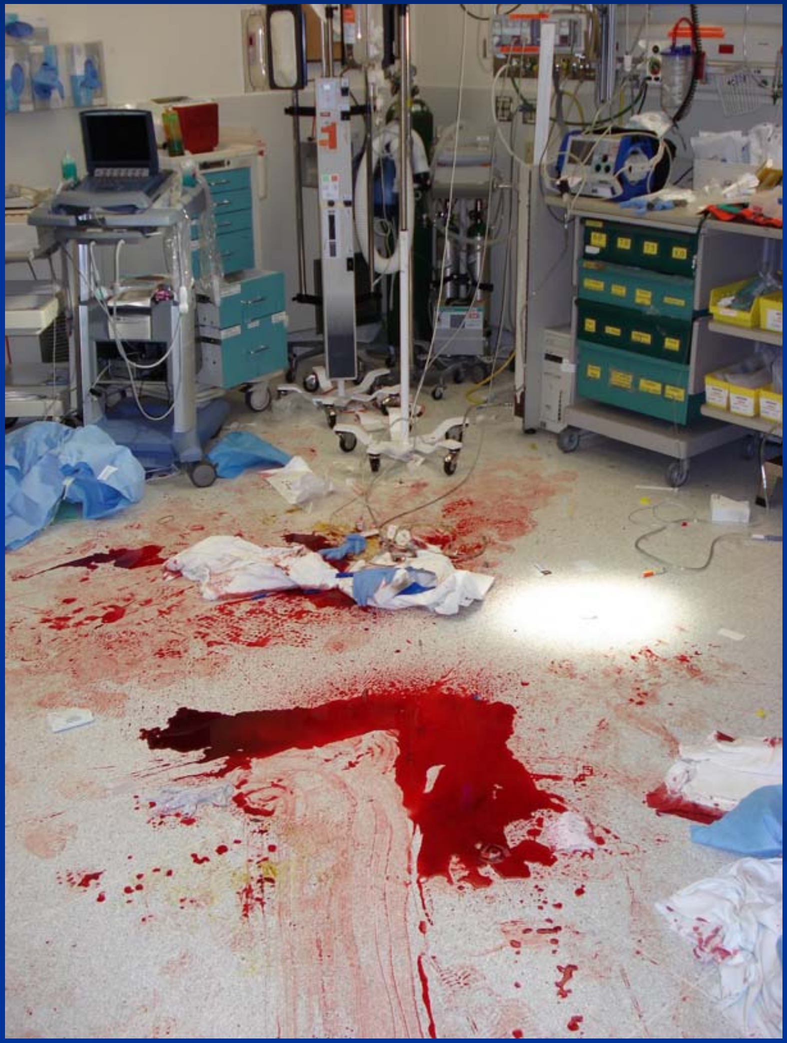
****Metabolism is reduced 5-8% for each ↓ 1° C****

Does Cold Kill?

- Gentilello LM. Ann Surg. 1997
  - N=57, randomized
  - Trauma pt with T≤35.5°C
  - Rewarming with CAVR vs standard
  - 7% vs 43% mortality
  - Pt who did not rewarm died
- ?Chicken or egg?

"All bleeding stops…eventually"

- Lethal Triad/Damage control
  - Hypothermia
  - Coagulopathy
  - Acidosis
- Marker of severity
- ? Animal models of better outcome with IH in exanguination



Rotondo M. J Trauma. 1993.
George ME. J Trauma. 2010.

Why We Warm in Trauma

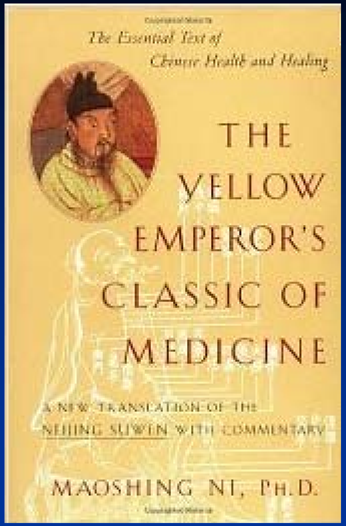
- (Spontaneous) hypothermia tripled chance of death
- ↓ 2°C increased EBL by 500cc
- 3x SSI with periop hypothermia
- Important to realize:
  - Marker of severity of injury
  - Benefits vs risk

George ME. J Trauma. 2010.
Ireland S. Resuscitation. 2010.
Wang H.E. Crit. Care Med. 2005.
Sessler. NEJM. 1997.
Kurtz. NEJM. 1996.
Jurkovich. J Trauma 1987.

How We Warm


Bair Hugger Warming Unit – Model 505
NOT STERILE
Bair Hugger Temperature Management Blanket
Model 40068
Full Body
Intraoperative Blanket
Bair Hugger
Total Temperature Management System


0 20 40 60 80 100 -20 -40



"Cold injures the body while heat injures the spirit…"

-from the *Yellow Emperor's Classic of Medicine*

History of IH Research

- Hippocrates –snow to wounds
- Baron Larrey
- 1939- Dr. Temple Fay pain control, metastatic disease
- 1954-1959- used in TBI
- 1964 – in CPR algorithm (Safar)
- 1960-1970's-↓ interest
- 1980's -animal studies with IH in cardiac arrest
  - Mild/moderate vs deep IH

Who Do We Cool?

Cardiac Arrest with Return of Spontaneous Circulation

- 350K / yr with OHCA in USA
- 25% survive to the hospital
- 70%-80% in-hospital mortality
- Overall survival 5-8% at 1yr
- Good neurologic recovery 20-30% of survivors

Neurologic Injury After Cardiac Arrest

Post-Cardiac Arrest Syndrome

- **Primary and post-arrest brain injury**
- **Post-arrest myocardial dysfunction**
- **Systemic ischemia-reperfusion response**

Don't forget the initial cause of arrest!

Circulation 2008;118:2452

Brain Injury Continues After Reperfusion

Increased:

- Oxygen free radicals
- Neutrophil infiltration
- Calcium sequestration in mitochondria
- Cellular membrane ATPase pump dysfunction
- Metabolic rate/demand
- Vascular permeability
- Loss of autoregulation / Cerebral edema

-She's only **mostly** dead.

Who We Cool

MILD THERAPEUTIC HYPOTHERMIA TO IMPROVE THE NEUROLOGIC OUTCOME AFTER CARDIAC ARREST

THE HYPOTHERMIA AFTER CARDIAC ARREST STUDY GROUP*

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.

NEJM, February 21, 2002

Neurologic Injury in Out-of-Hospital Arrest

- Multi-center, prospective, randomized
- VF/VT arrest with neuro inj
- IH 32-34° C (12hr for Bernard; 24hr for HACA)
- HACA - 6mo outcomes, screened >3500 pt

	N=pts		+Neuro (%)		p	Mortality (%)		p
	IH	C	IH	C		IH	C	
HACA	137	138	55	39	0.009	41	55	0.02
Bernard	43	34	49	26	0.046	51	68	0.145

Bernard. NEJM 2002.
HACA. NEJM 2002.

European HACA Trial

- OUTCOME MEASURE
  - Survival with min or mod disability at 6 mo
  - 55% IH; 39% C
  - Risk ratio for good outcome 1.40 (1.08-1.81)
- Number needed to treat = 6
- Sooner = better
- Complications not statistically signficant

HACA Study Group, *NEJM*

Why We Cool

Compare ICU Strategies

Treatment	NNT(mortality)
Low-dose steroid	10
ARDSnet low TV ventilation	12
Activated protein C	17
Intensive glycemic control	28
Stroke Aspirin	33
AMI Thrombolytics	37–91*
Hypothermia	**6.1-7.0**

*Depending on age

Gropper, Anesth Analg 2004: 99:566
NEJM 2002;346:549

HYPOTHERMIA: Mechanisms of Ischemic Neuroprotection

- **Improved**
  - BBB stability
  - Protection against cytoskeletal proteolysis
- **Decreased**:
  - Metabolic demand-active and basal
  - Cellular apoptosis
  - Oxygen free radical production
  - Neutrophil infiltration
  - Cytokine and leukotriene production

Lancet 2008;371:1955
Wang GJ. Neuroscience 2002.

2003 ILCOR recommendations

"Unconscious patients with spontaneous circulation after out of hospital arrest should be cooled to 32-34°C for 12-24 hours when the initial rhythm is ventricular fibrillation."

AND

"Such cooling may also be beneficial for other rhythms or in-hospital arrest."

Nolan, JP, Resuscitation, 2003

Lessons

- Animal and clinical studies
- Earlier is better
- Preservative > Resuscitative
- Resuscitative > not at all
- Fever = worse outcomes

How To Cool

- NS +/- chilled
  - Safety of chilled NS, rapid cooling
- Truncal cooling
- Localized
  - Not quite ready for prime-time
- Intravascular
- External pads

MUST CONTROL COOLING

How We Cool

VUMC

From McPherson J, MD. 2010

VUMC Induced Hypothermia Protocol

- **Induction**
  - Rapid to 32-34°C
  - Sedation, paralyze if necessary to prevent shivering
- **Maintenance**
  - Goal temperature 33°C
  - Standard 24 hr after ROSC

  *****Suppress shivering*****
- **Rewarming**
  - Most dangerous period: hypotension, brain swelling, hyperkalemia
  - Goal 37°C over 12-24h
  - Stop all sedation when normal body temperature is achieved

Cardiac Arrest Patients with STEMI: VUMC

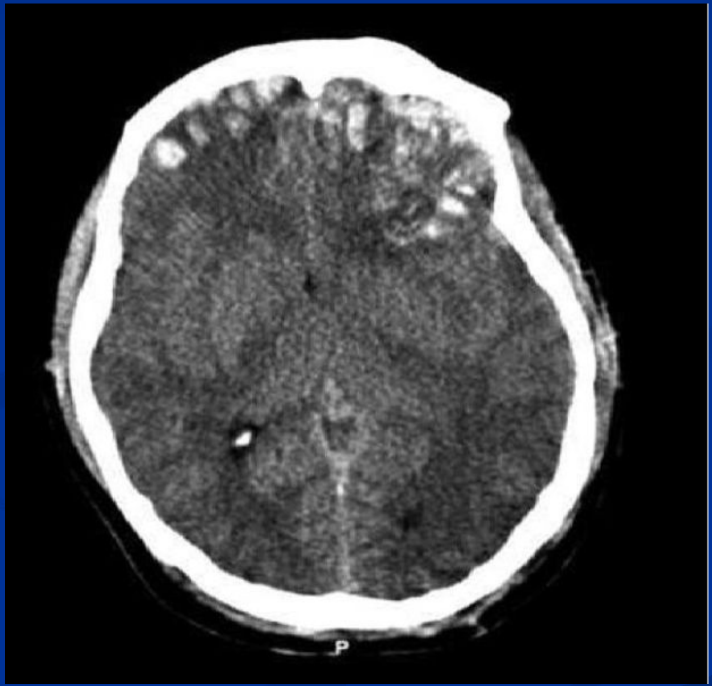
January 2007-May 2010:

- 23 pts with OHCA + STEMI
- All emergent PCI, treated with hypothermia
- 13/23 (57%) survivors
- Support with IABP or VAD required in 10 pts
  - Survival rate 2/10 in this group
- Survival 85% in pts not requiring mechanical support
- Good neurologic outcome - 92% of survivors

Information from McPherson J, MD. 2010

Traumatic Brain Injury

- TBI deaths = 50,000 pt/yr in US
- 30%-70% mortality severe TBI
- Direct neuronal inj
- Secondary inj
- Fever worsens outcome
- Hypothermia decreases ICP



Finkelstein and Alam. J Int Care Med. 2010.
Sydenham, E. Cochrane review. 2009
Park E. Canadian Medical Association Journal. 2008.
Baena RC. Neurologyl 1997.

Traumatic Brain Injury

- Mixed results of RCTs
  - Single center trials gen with positive benefit
  - Multi-center trials not replicated benefit
- Criticisms: Poor control of variables
  - ICU care, complications
  - Hydration/resuscitation
  - Hypotension and rewarming
- No increase in mortality

Fox JL. CJEM. 2010.
Finkelstein and Alam. J Int Care Med. 2010.
Sydenham, E. Cochrane review. 2009

Hypothermia in Traumatic Brain Injury

Reference	N	IH	F/U	Good Outcome (%)		p
				IH	C	
Shiozaki, 1993	33	34C/48h	6mo	38	6	NS
Clifton, 1993	46	33C/48hr	3mo	52	36	NS
Marion, 1993	82	33C/24hr	6mo	56	33	0.05
Jiang, 2000	87	34C/3-14d	1yr	47	27	<0.05
Shiozaki, 2001	91	34C/48hr	3mo	46	59	NS
Clifton, 2001	392	33C/48hr	6mo	43	43	NS
Gal, 2002	30	34C/72hr	6mo	87	47	NS
Zhi, 2003	396	33C/1-7d	6mo	62	38	<0.05
Qiu, 2005	86	34C/3-5d	2yr	65	37	<0.05
Qiu, 2007	80	34C/4d	1yr	70	48	<0.05

Traumatic Brain Injury

- Adult RCT ongoing –Japan
- Eurotherm3235 Trial
- AANS Guidelines – consider:
  - Control of refractory ↑ICP
  - Early induction
  - $\geq$48hr IH

Park E. Canadian Medical Association Journal. 2008.
Liu WG. J Int Med Res. 2006.

Traumatic Spinal Cord Injury

- September, 2007
- NFL player: incomplete cervical SCI
- Tackling player during kick-off return
- Systemic cooling en route to hospital, early decompression, successful recovery

Traumatic Spinal Cord Injury

- Animal models only, studies – 1970s-80s
  - Suggested improved outcomes
  - Mixed studies
- Suggestion of protection as prophylaxis before SC surgery/aortic repair
  - Mixed data, human studies
  - No convincing evidence of benefit
- To date, no RCTs
  - Not enough evidence to recommend for/against

Resnick, D. (2007) Position statement and evidence based recommendations from the AANS /CNs Joint section on disorders of the spine and trauma

Future

- Cold ischemia time in IH
  - Mild – 15min
  - Mod – 20min
  - Deep – 30min
  - Profound – 60min
- Preservative
- Resuscitative
- Suspended animation

Alam HB. J Surg Res. 2005.
Safar PJ. Curr Opin Anaesthesiol. 2002.

And the Future is Now…

- Trauma patient with hypotension
  - Delay vascular collapse, surgical control
  - Animal models-improved mortality, fluid limitation+mild IH

- EPR-CAT: Emergency Preservation and Resuscitation for Cardiac Arrest from Trauma - multicenter trial
- Pulseless trauma patient, exsanguinating cardiac arrest
- ED thoracotomy, aortic cannula, 10°C, repair, CPB rewarming

Kochanek P Cleveland Clinic Journal of Medicine. (2009).

Wu X. J Cereb Blood Flow Metab. 2008

Kim SH. J Trauma. 1997.

Summary

- Double-edged sword in trauma
- IH for neuro injury after OHCA
- Careful control of challenges of IH
- Possible TBI
- Risks/benefits
- Need for ongoing research
- Further areas of application