The Physiologic Effects of Mild Hypothermia

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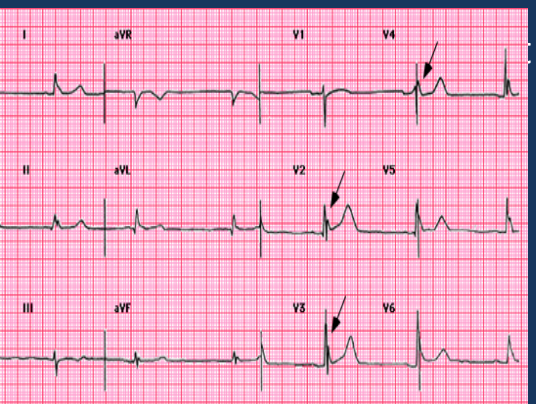

Disclosure

- Gaymar Industries
- Inverness Medical
- NIH-NHLBI co-PI ALI in severe sepsis
- Beatrice Wind Gift Fund

Outline

- Accidental Hypothermia
- Historic Perspective
- Physiologic Effects versus Adverse Effects
  - Organ Systems Approach
  - Experience in Randomized Clinical Trials
  - Experience From Hypothermia Registry
- Conclusions

Accidental Hypothermia

Accidental Hypothermia: Unintentional decline in core temperature below 35°C

Severity Based on Body Temperature on Arrival:

Mild	90.0-95° F	32.2-35° C
Moderate	82.4-90° F	28-32.2° C
Severe	< 82.4° F	< 28° C

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

Physiologic Changes Associated with Hypothermia

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

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Early Translation Failure

- 1950's Hypothesis
- Lower Temp→ Lower Metabolism
- Temp Dependent Metabolic Processes
- Decreased O_2 Demand
- Decreased Glucose Demand by Brain
- Therefore, Lower = Better

Polderman, KH. CCM 2009; 37: S186-202

The Clinical Use of Hypothemia Following Cardiac Arrest *

G. Rainey Williams, Jr., M.D., Frank C. Spencer, M.D.

From the Department of Surgery, The Johns Hopkins University School of Medicine and Hospital, Baltimore, Maryland

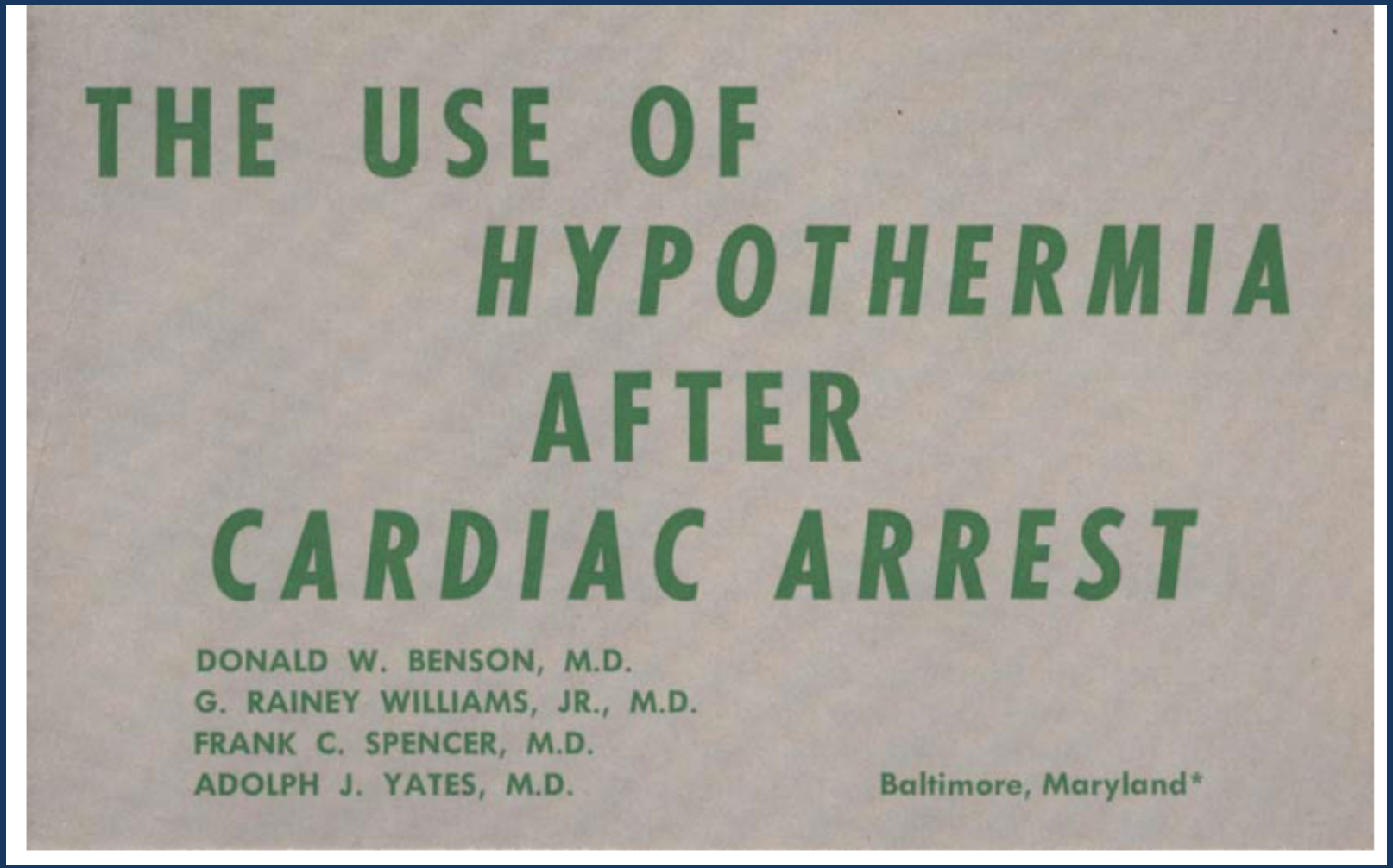
- "It has been repeatedly demonstrated that hypothermia will *protect* the brain against anoxic injury. This protection appears related to the demonstrable reduction in cerebral oxygen consumption and cerebral blood flow present in hypothermic individuals."

Williams GR, Annals of Surgery. 1958; 148: 462-466

TABLE 1

Case Number	1	2	3	4
Date	Jan. 1957	Aug. 1957	Sept. 1957	Nov. 1957
Age	5 yr. C. M.	9 yr. C. F.	38 C. M.	39 C. F.
Cause of arrest	Bronchogram	Asthma	Stab wound	Stab wound
Duration of arrest	5 minutes	5 minutes	5 minutes	5 minutes
Neurologic damage	Severe	Severe	Severe	Severe
Hypothermia: Range	32–34° C.	30–32° C.	32–33° C.	32–34° C.
Duration	72 hours	24 hours	48 hours	72 hours
Residual neurologic defect	None	None	None	Moderate

Williams GR, Annals of Surgery. 1958; 148: 462-466



THE USE OF HYPOTHERMIA AFTER CARDIAC ARREST

DONALD W. BENSON, M.D.
G. RAINEY WILLIAMS, JR., M.D.
FRANK C. SPENCER, M.D.
ADOLPH J. YATES, M.D.

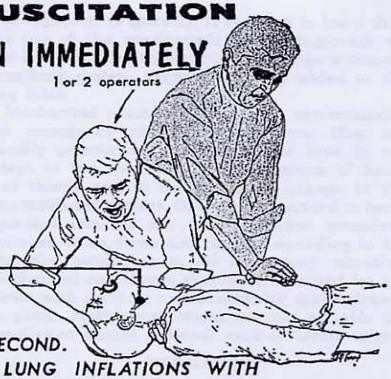
Baltimore, Maryland*

"Hypothermia has been shown to protect the brain against anoxia. There is a reduction in the cerebral oxygen consumption and cerebral blood flow with body cooling."

Benson DW et al. Anesthesia and Analgesia 1959; 38: 423-428

HEART–LUNG RESUSCITATION

I FIRST AID: OXYGENATE THE BRAIN IMMEDIATELY



IF UNCONSCIOUS

Airway – *TILT HEAD BACK*

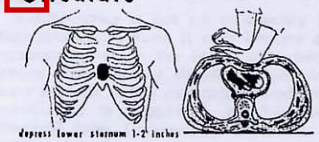
IF NOT BREATHING

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

MOUTH-TO-MOUTH, MOUTH-TO-NOSE, mouth-to-adjunct, bag-mask

- FEEL PULSE
- IF PRESENT – CONTINUE LUNG INFLATIONS
- IF ABSENT –

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



for physicians only

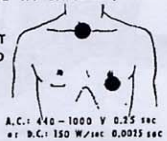
II START SPONTANEOUS CIRCULATION

Drugs – *EPINEPHRINE:* 1.0 mg (1.0 CC OF 1:1000) I.V. OR 0.5 mg INTRACARDIAC. REPEAT LARGER DOSE IF NECESSARY

SODIUM BICARBONATE: APPROXIMATELY 3.75 G/50 CC (1/2 DOSE IN CHILDREN) I.V. REPEAT EVERY 5 MINUTES IF NECESSARY

E. K. G. – • *FIBRILLATION:* EXTERNAL ELECTRIC DEFIBRILLATION. REPEAT SHOCK EVERY 1-3 MINUTES UNTIL FIBRILLATION REVERSED

• *IF ASYSTOLE OR WEAK BEATS:* EPINEPHRINE OR CALCIUM I.V.



Fluids – *I.V. PLASMA, DEXTRAN, SALINE*
Do not interrupt cardiac compressions and ventilation.
Tracheal intubation only when necessary.

AFTER RETURN OF SPONTANEOUS CIRCULATION USE VASOPRESSORS AS NEEDED,
e.g. NOREPINEPHRINE (Levophed) I.V. DRIP

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

Figure 1. The A, B, C of emergency resuscitation. These instructions have been arranged for the front and back of a billfold card or for a poster which may be obtained from the Pennsylvania Heart Association or the Pennsylvania Department of Health, Harrisburg.

Peter Safar:

Journal of the Iowa Medical Society, November, 1964

ABC…DEF

Post-Arrest Care:

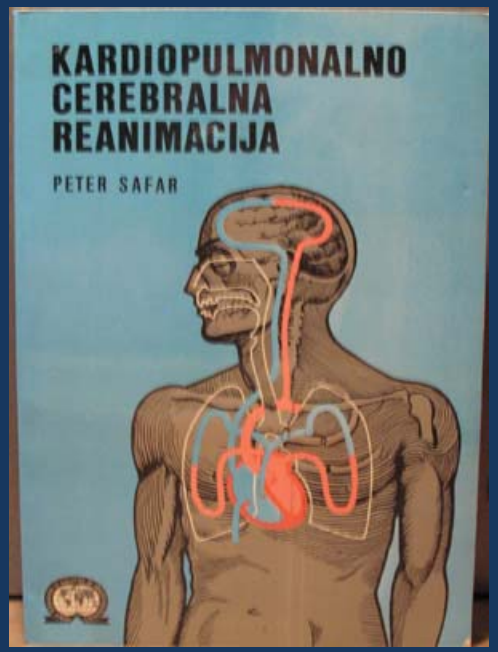
Gauge

Hypothermia

Intensive Care

Problems Leading to Abandonment of Hypothermia

- Clinical application at Pittsburgh in the 60s
- Complications:
  - Bleeding
  - Arrhythmias, including bradycardia
  - Hypotension
- But…
  - Cooling to 30°C (moderate)
  - Overshoot (into severe range)
  - Labor Intensive
  - Applied to heterogeneous patient population
- 1980s, 1990s: Focused on cardiac arrest; animal studies; pilot studies; randomized trials



Insights from Animal Experiments

- Mild versus Moderate Hypothermia
- Protective Effects not primarily result of decreased metabolism (O_2 and glucose consumption)
- Ischemia and Reperfusion are complex cascades of injury and repair
- Negovsky coins phrase “Post-Resuscitation Disease”

The second step in resuscitation—the treatment of the 'post-resuscitation disease'

V. A. NEGOVSKY

Laboratory of Experimental Resuscitation, Academy of Medical Sciences of the U.S.S.R., 9, *October 25th Street, Moscow, U.S.S.R.*

In the first stages of the development of the science of resuscitation, 'reanimatology', research workers have been limited mainly to the study of the pathology of death, and to the elaboration of a series of techniques of resuscitation. We now have at our disposal some knowledge of the process of disintegration of physiological functions during the dying of an organism, and of their restoration during resuscitation. We also have at our disposal a number of methods available to a large circle of practising doctors. Extensive experimental studies and clinical findings have clearly proved that after the first step in resuscitation when heart function and respiration have been restored, the second step in resuscitation arises—the more complicated problems of treating the after-effects of a general hypoxia. There are characteristic disturbances in the functions of the central nervous system and internal organs, in metabolism and in homeostasis among other systems.

There is much evidence that the organism experiences a specific pathological condition after resuscitation. We are inclined to call this condition 'the post-resuscitation disease', and to examine it as an independent nosological form. Indeed, irreversible changes occur during clinical death and after resuscitation.

Negovsky VA. Resuscitation 1972; 1: 1-7

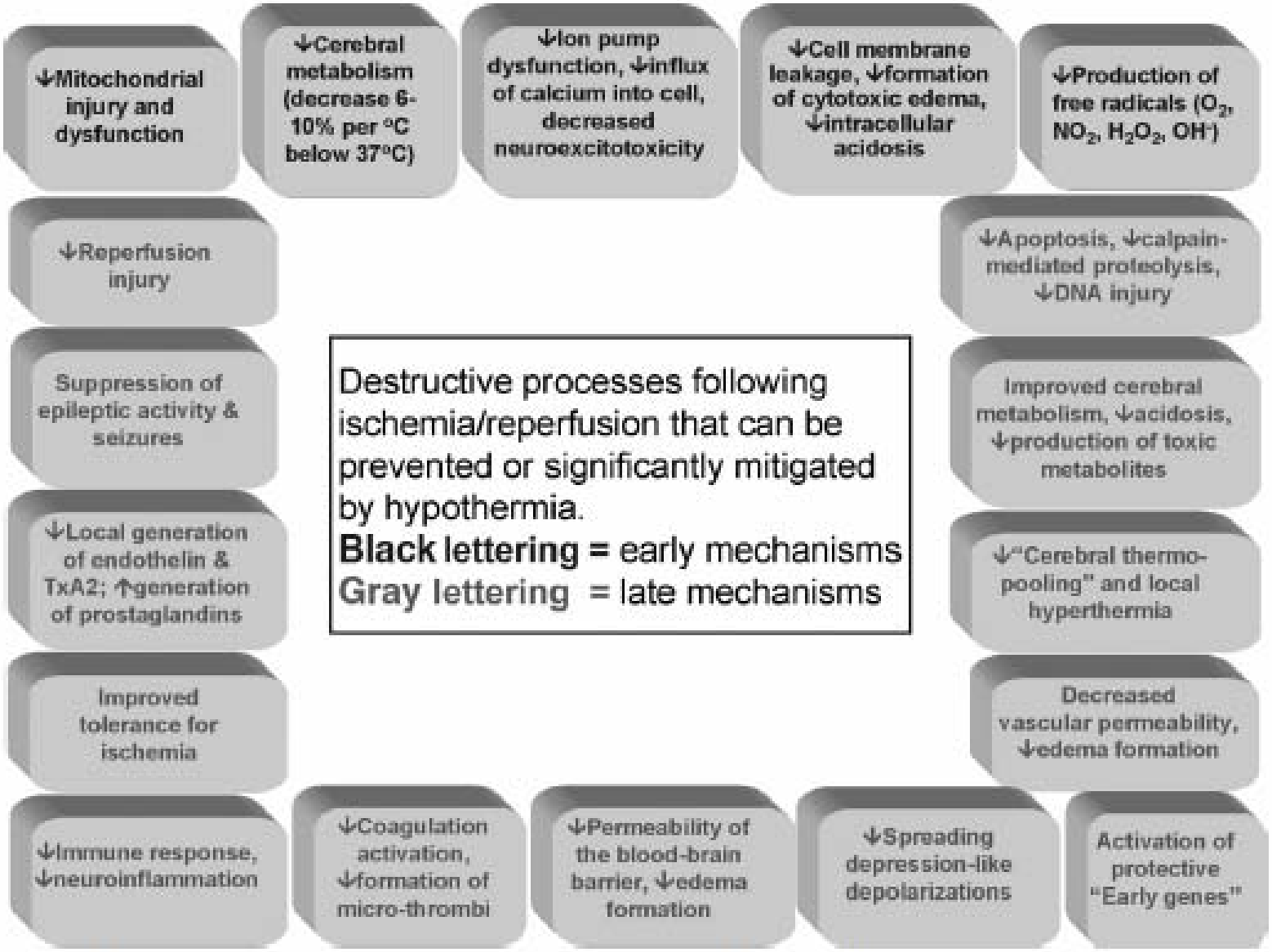


Figure 1. Schematic depiction of the mechanisms underlying the protective effects of mild to moderate hypothermia. *TxA2*, thromboxane A2.

Polderman, KH. CCM 2009; 37: S186-202

Destructive Processes

- Cellular Injury
  - Necrosis
  - Full or Partial Recovery
  - Apoptosis (programmed cell death):
    - 7 Day Window
    - Membrane Dysfunction → ↑ LA, ↑ Ca into cells
    - Dysfunction of ATP-dependent ion pumps
    - Caspase activation
    - Increased glutamate

Polderman, KH. CCM 2009; 37: S186-202
Xu, L. J Cereb Blood Flow Metab 2002; 22: 21-28
Ning, XH. J Appl Physiol 2002; 92: 2200-2207

Destructive Processes

- Free radical generation
  - Release of oxygen free radicals by ischemia, amplified by reperfusion
    - Superoxide (O2-)
    - Peroxynitrite (NO2-)
    - Hydrogen Peroxide (H2O2)
    - Hydroxyl Radicals (OH-)
  - Produce oxidation, irreversible injury to cell membranes, mitochondria, endothelium, lipids, proteins, nucleic acids

Globus, MY-T. J Neurochem 1995; 65: 1250-1256
Novack, TA. J Clin Exp Neuropsychol 1996; 18: 685-706

Destructive Processes

- Blood Brain Barrier:
  - Ischemia/Reperfusion increases permeability
- Vasoactive Mediators:
  - Ischemia → ↑ Thromboxane A2 (TxA2)
    - Vasoactive
    - ↑ increased platelet aggregation
  - Local vasoconstriction, hypoperfusion, microthrombi

Huang, ZC. Can J Neurol Sci 1999; 26: 298-304

Aibiki, M. Crit Care Med 2000; 28: 3902-3906

Hypothermia's Role

- All of these processes are temperature dependent
- Hypothermia can blunt, reverse, or prevent these destructive processes
- For example, hypothermia blunts early apoptosis
- Hypothermia decreases permeability of BBB

Huang, ZC. Can J Neurol Sci 1999; 26: 298-304

Polderman, KH. CCM 2009; 37: S186-202

Safar: Dog model of VF arrest

- Normothermic VF of 11 minutes
- Defibrillation and controlled reperfusion
- Controlled ventilation for 20 hrs; ICU to 96 hrs
- Control group (n=8)
  - Normothermic (37.5°C), Normotensive, Hypocapnic
- Experimental group (n=8)
  - Mild hypothermia (34°C) from 10 minutes to 12 hours
  - Cerebral blood flow promotion w/ induced moderate HTN
  - Mild hemodilution, Normocapnia

Safar, P. Stroke 1996; 27:105-113

Dog model of VF arrest: Results

- All 16 dogs in the protocol survived
- Control group (n=8):
  - All OPC 3 (severe disability) or 4 (coma)
- Experimental group (n=8):
  - 6/8 (75%) dogs OPC 1 (normal)
  - 1/8 (12.5%) OPC 2 (moderate disability)
  - 1/8 (12.5%) OPC 3

($P<.001$)

Safar, P. Stroke 1996; 27:105-113

Physiologic Effects

- Decreased Metabolic Rate
- CNS
- Cardiovascular
- Respiratory
- Renal/Electrolytes
- Musculoskeletal
- Endocrine/Metabolic
- Gastrointestinal
- Infectious Disease
- Hematologic

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

Myths About Adverse Effects of Mild Therapeutic Hypothermia

- Hypotension
- Decreased myocardial contractility
- Reason: Misinterpretations of “cold diuresis”, myocardial stunning, and “sepsis-like syndrome”
- Corollary: Can’t use in patients with cardiogenic shock
- Marked coagulopathy
- Increased arrhythmias

Decreased Metabolic Rate

- Cerebral metabolism decreases 6-10%/°C decrease in core T°
- At core T of 33°C, metabolic rate drops by 25-40%
- O_2 consumption and CO_2 production decrease by same amount
- This is an important protective effect but only one of dozens

Polderman, KH. Crit Care Med 2009; 37: S186-202

Aoki M. Ann Thorac Surg 1993; 55: 1093-1103

Central Nervous System

- Confusion/Delirium
- Slurred speech
- Impaired judgment
- Amnesia
- Apathy

Not applicable in comatose, sedated, sometimes paralyzed post-arrest patients

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 CO 25-40%
- Arrhythmias very rare at Temp > 30°C
  - At 32-34°C, ↑ rate of conversion of VF (in swine)

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 accidental hypothermia
  - tachypnea, then progressive ↓ in MV
- In TH after OHCA, ventilation controlled
- ↑Solubility of O_2 & CO_2 ->↓PaO_2, $PaCO_2$
- Bronchorrhea, bronchospasm
- Left shift of Oxy-HgB dis curve→↓DO_2
- Ventilator settings require frequent changes during induction

Renal/Electrolytes

- Cold diuresis
  - Increased venous return 2/2 venoconstriction
  - ↑ANP, ↓ADH, & tubular dysfunction
  - If uncorrected, causes hypovolemia, hemoconcentration
- ↓ electrolytes (K, Mg, Phos) due to
  - diuresis-induced ↑ renal excretion
  - intracellular electrolyte shifts

Polderman, KH. Crit Care Med 2009; 37: S186-202
Polderman, KH. J Neurosurg 2001; 94: 697-705

Musculoskeletal

- Induction of hypothermia → activation of counter-regulatory mechanisms
  - Vasoconstriction begins @ ≈ 36.5°C
  - Shivering begins @ ≈ 35.5°C
  - In awake patients
    - increased VO2 (40-100%); ↑ MyocardialVO_2
    - 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 2/2 ↓ speed of enzymatic reactions
  - ↓ blood flow, bile excretion
  - Affected drugs: pressors, sedatives, analgesics, NRB, etc
- Hyperglycemia
  - Decreased insulin sensitivity
  - Decreased insulin secretion by pancreatic islet cells
  - Hyperglycemia is damaging to the injured brain
- ↑ lactate, ketones, free fatty acids

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

Gastrointestinal

- Ileus: impaired bowel function
- Delayed gastric emptying
- Gastric stress ulcers
- Hepatic dysfunction – LFT's (transaminitis)
- Pancreatic dysfunction – ↑amylase, but no clinical pancreatitis

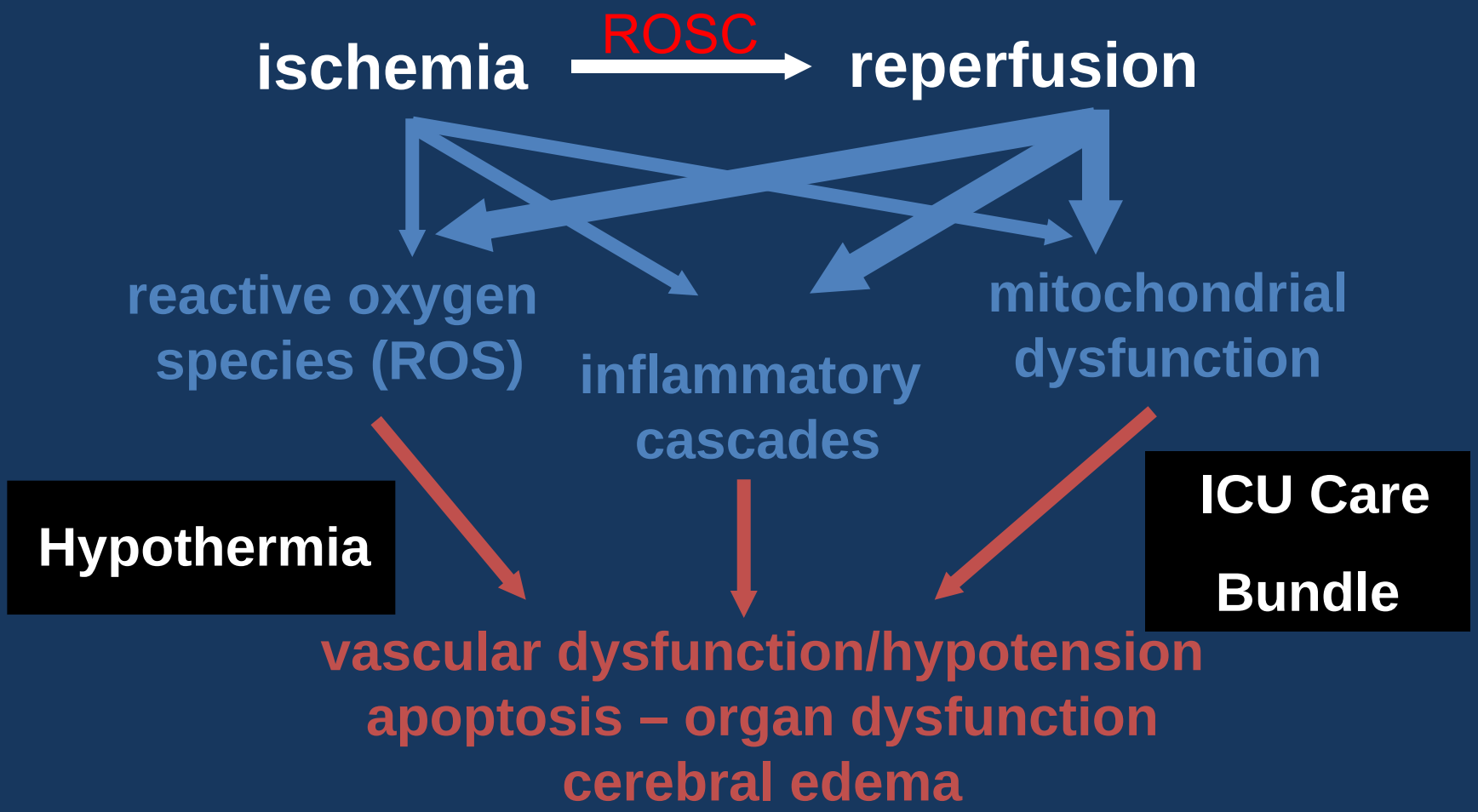
Infectious Disease

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

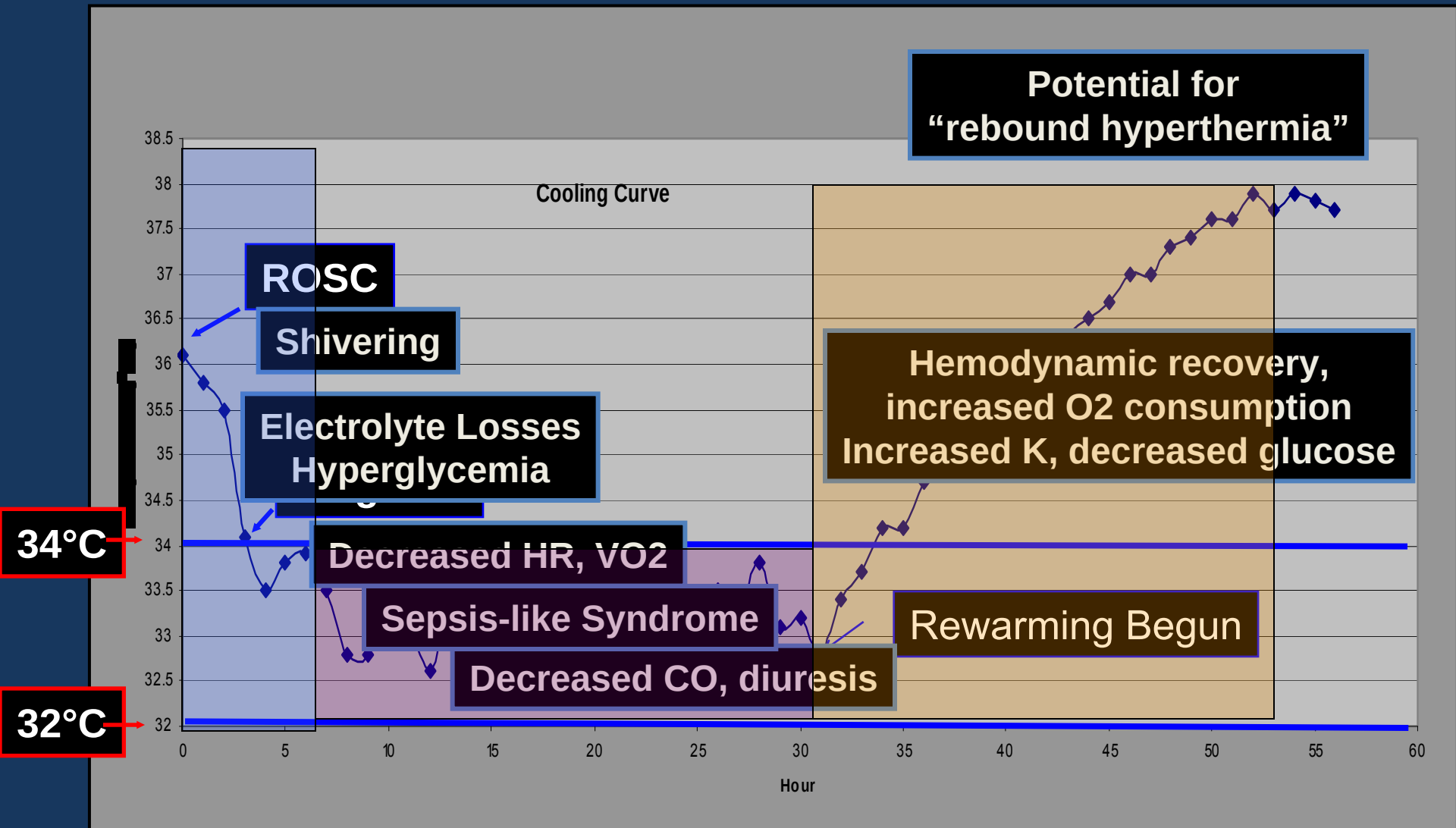
Hematologic

- ↑ HgB
- ↓ 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

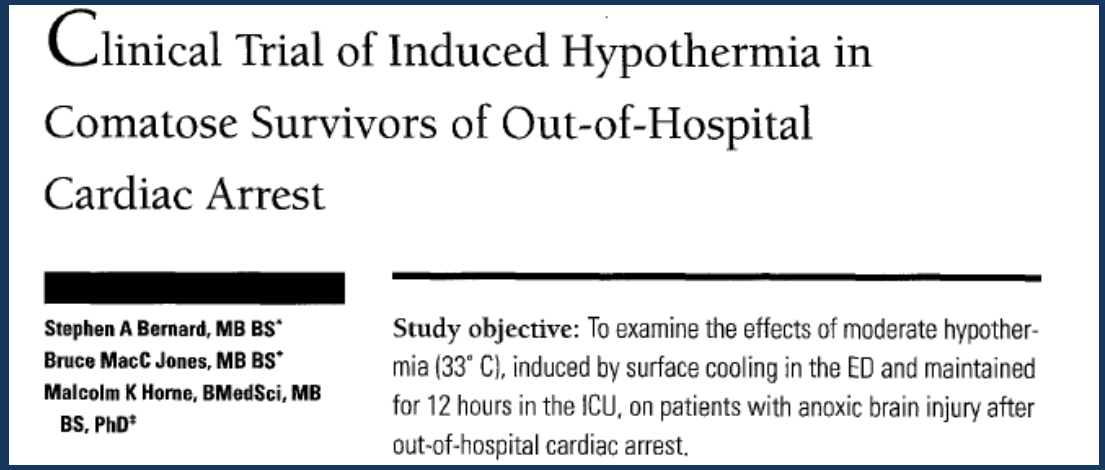
Etiology and Exacerbation of the Metabolic Phase



Hypothermia-induced Physiologic Changes



33 years pass…



Clinical Trial of Induced Hypothermia in Comatose Survivors of Out-of-Hospital Cardiac Arrest

[redacted]

Stephen A Bernard, MB BS*
Bruce MacC Jones, MB BS*
Malcolm K Horne, BMedSci, MB BS, PhD‡

Study objective: To examine the effects of moderate hypothermia (33° C), induced by surface cooling in the ED and maintained for 12 hours in the ICU, on patients with anoxic brain injury after out-of-hospital cardiac arrest.

- 22 OHCA, comatose, prospectively treated w/ mild TH to 33°C for 12 hours
- 22 OHCA, comatose, from historic chart review treated with normothermia

Bernard, SA. Annals Emerg Med 1997; 30: 146-153

Table 2.

Results of analyses obtained in hypothermic (IH) and normothermic (control) patients during the 24 hours after arrival at the ED.

Parameters (Mean±SD)	Time Since Arrival in ED (Hours) 0	6	12	18	24
Temp (°C)					
Control	35.6±1.2	36.5±.7	37.3±.8*	37.6±.8*	37.5±.6*
IH	35.3±1.0	32.6±.7*†	33.0±.6*†	35.8±1.1	37.5±.6
MAP (mm Hg)					
Control	83±38	87±14	87±19	90±11	91±20
IH	79±41	98±15	90±12	83±13	81±7
Pulse					
Control	91±39	99±23	103±23	104±22	104±18
IH	88±43	75±19*†	77±23†	79±16†	92±25
pH					
Control	7.23±.16	7.39±.11	7.41±.10	7.42±.06	7.44±.03
IH	7.20±.17	7.35±.11	7.35±.08	7.33±.07†	7.39±.07
Potassium (mmol/L)					
Control	3.8±.8	3.7±.5	3.8±.5	4.0±.6	4.1±.8
IH	3.6±.6	3.7±.5	4.1±.6	4.4±.8*†	4.7±1.0
Total leukocyte count (×1,000/mm³)					
Control	13.5±6.2	—	—	—	16.6±7.4
IH	15.1±7.2	—	—	—	16.9±7.5
Platelet count (×1,000/mm³)					
Control	270±85	—	—	—	241±84
IH	266±76	—	—	—	239±82

*$P < .05$, comparison within treatments against arrival.
†$P < .05$, comparison between treatments at comparative times.

Bernard, SA. Annals Emerg Med 1997; 30: 146-153

Results

- Good Outcome:
  - IH: 11/22
  - Control: 3/22 $p < 0.05$
- Mortality:
  - IH: 10/22
  - Control: 17/22 $p < 0.05$

Bernard, SA. Annals Emerg Med 1997; 30: 146-153

Experience From RCT's

NEJM, 2002

- **HACA and Bernard et al:**
  - **Different cooling techniques**
  - **Different durations of hypothermia**
  - **Different degrees of invasive monitoring**
  - **Different outcome measures for adverse events**
  - **Many lessons to learn OTHER THAN TH**

HACA

TABLE 4. COMPLICATIONS DURING THE FIRST SEVEN DAYS AFTER CARDIAC ARREST.*

COMPLICATION	NORMOTHERMIA	HYPOTHERMIA	
	no./total no. (%)		
Bleeding of any severity†	26/138 (19)	35/135 (26)	NS
Need for platelet transfusion	0/138	2/135 (1)	
Pneumonia	40/137 (29)	50/135 (37)	NS
Sepsis	9/138 (7)	17/135 (13)	NS
Pancreatitis	2/138 (1)	1/135 (1)	NS
Renal failure	14/138 (10)	13/135 (10)	
Hemodialysis	6/138 (4)	6/135 (4)	
Pulmonary edema	5/133 (4)	9/136 (7)	
Seizures	11/133 (8)	10/136 (7)	
Lethal or long-lasting arrhythmia	44/138 (32)	49/135 (36)	
Pressure sores	0/133	0/136	

Hypothermia:

- No differences in complications
- Trend towards more infectious complications (pneumonia, sepsis)
- Trend toward more bleeding, but not statistically significant

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TABLE 2. PHYSIOLOGICAL AND HEMODYNAMIC VALUES.*

VARIABLE	TREATMENT GROUP	ADMISSION TO ICU	6 HR	12 HR	18 HR	24 HR
Number of patients	Hypothermia	39	39	39	39	38
	Normothermia	33	32	32	32	31
Temperature (°C)	Hypothermia	33.3±0.98†	32.7±1.19†	33.1±0.89†	36.0±1.24†	37.4±0.85†
	Normothermia	36.0±0.76†	37.1±0.75	37.4±0.58†	37.3±0.56†	37.3±0.59†
	P value‡	<0.001	<0.001	<0.001	<0.001	0.60
Mean arterial blood pressure (mm Hg)	Hypothermia	108.7±20.89†	97.0±14.92	89.5±13.16	88.8±9.17	89.1±12.9
	Normothermia	94.4±18.80	92.2±13.00	90.8±14.16	91.3±12.96	92.1±11.76
	P value‡	0.02	0.16	0.82§	0.38	0.24
Pulse (per minute)	Hypothermia	82±21.6§	72±17.1§	70±17.6	80±18.2§	89±17.9†
	Normothermia	100±17.0	100±21.9	94±17.9	97±16.8	99±15.5
	P value‡	0.001	<0.001	<0.001	<0.001	0.02
Cardiac index (liters/min/m² of body-surface area)¶	Hypothermia	2.0	2.1	2.4	2.9	3.4
		(1.2–4.4)	(0.9–4.2)	(0.8–4.9)	(1.5–7.3)§	(1.6–6.8)§
	Normothermia	2.6	2.7	3.2	3.3	3.0
		(1.4–5.5)	(1.4–6.1)	(1.2–6.1)	(1.5–5.8)	(1.8–5.7)
	P value‡	0.01	0.16	0.10	0.12	0.54
Systemic vascular resistance (dyn-sec·cm⁻⁵)¶	Hypothermia	2213	1808	1564	1198	987
		(599–4645)	(836–4531)	(439–4280)	(402–2833)§	(551–2500)§
	Normothermia	1356	1278.5	1056	964	1072
		(481–2545)	(346–2841)	(340–3163)	(479–2204)†	(591–1998)
	P value‡	0.02	<0.001	0.002	0.23	0.50

Hypothermia: ↓ HR, ↑ SVR, trend toward ↓CO, no significant arrhythmias

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TABLE 3. BIOCHEMICAL VALUES.*

VARIABLE	TREATMENT GROUP	ADMISSION TO ED	ADMISSION TO ICU	6 Hr	12 Hr	24 Hr
Number of patients	Hypothermia	43	39	39	39	38
	Normothermia	34	33	32	32	31
Potassium (mmol/liter)	Hypothermia	3.8 (2.5–7.8)	3.6 (2.6–6.9)	3.6 (2.7–6.3)	4.1 (2.6–7.6)	4.5 (2.9–7.1)‡
	Normothermia	3.9 (2.2–6.4)	3.9 (2.5–5.1)	4.0 (2.7–5.7)	4.2 (3.3–5.7)	3.9 (3.9–4.6)
	P value§	0.84	0.98	0.06	0.52	<0.001
Lactate (mmol/liter)	Hypothermia	8.3 (2.2–14.9)	2.7 (0.9–11.6)‡	3.7 (1.2–11.8)‡	4.4 (1–11.1)‡	2.5 (0.7–11.4)‡
	Normothermia	7.5 (2–14)	2.6 (0.9–8.4)‡	3.3 (1.1–9.3)‡	3.5 (1–12.4)‡	1.6 (0.6–11)‡
	P value§	0.75	0.46	0.79	0.67	0.08
Glucose (mmol/liter)¶	Hypothermia	13.3 (9.0–33.0)	16.2 (7.4–26.8)	16.0 (7.1–36.7)	16.1 (4.2–28)	8.0 (1.6–27.8)‡
	Normothermia	12.6 (4.8–22.7)	10.5 (6.6–17.9)	12.1 (5.8–25)	11.6 (6.2–28)	7.5 (3.5–15.1)‡
	P value§	0.13	0.002	0.02	0.14	0.92

Hypothermia Effects:

- K ↓ initially, then ↑ significantly w/ rewarming
- Trend toward ↑ LA
- Significant ↑ Glucose

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TABLE 4. HEMATOLOGIC VALUES.*

VARIABLE	TREATMENT GROUP	ADMISSION TO ED	12 HR	24 HR
Number of patients	Hypothermia	43	39	38
	Normothermia	34	32	31
Platelet count ($\times 10^{-3}$/mm^3)	Hypothermia	209±65.7	193±60.2†	190±63.3†
	Normothermia	221±63.4	217±63.0	199±54.2†
	P value‡	0.46	0.24	0.82
White-cell count ($\times 10^{-3}$/mm^3)	Hypothermia	10.9 (5.7–21.5)	14.5 (5.5–30.4)§	14.6 (7.1–35.3)§
	Normothermia	11.1 (6.3–25.3)	14.6 (8.5–29)§	15.8 (9.8–25.3)§
	P value‡	0.46	0.12	0.34

Hypothermia:

- No impact on platelet or WBC counts
- ”No clinically significant infections were noted”

Experience from Individual Centers

Table 8. Rate of infections and arrhythmias

	Therapeutic Hypothermia	Standard Resuscitation	*p* Value
Infection[a]	19/55 (34.5)	23/54 (42.6)	.38
Arrhythmia[b]	20/55 (36.4)	23/54 (42.6)	.51

[a]Therapeutic hypothermia: pneumonia n = 16, sepsis n = 2, urinary tract infection n = 1. Standard resuscitation: pneumonia n = 19, central venous catheter infections n = 2, sepsis n = 2; [b]unsustained ventricular tachycardia or atrial fibrillation. Data are presented as number of patients/ total with complications according to treatment group (%).

Tabl ods

	Control period ($n = 58$)	Intervention period ($n = 61$)	OR (95% CI)	*p*-Value
General complications	37 (64)	44 (72)	1.47 (0.68–3.19)	0.44
Pneumonia	33 (57)	29 (48)	1.28 (0.69–2.40)	0.43
Sepsis	1 (1)	2 (3)	2.33 (0.21–26.21)	0.60
Severe arrhythmias	9 (16)	15 (25)	1.90 (0.80–4.53)	0.14
Brady-arrhythmias	0	3		
Tachy-arrhythmias	9	12		
Seizures	16 (28)	11 (18)	0.63 (0.28–1.39)	0.34
Status epilepticus	3 (5)	5 (8)	1.98 (0.46–8.56)	0.47

Pulse rate >120 min or <40 min lasting for > 5 min was defined as severe arrhythmias.

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Outcome, timing and adverse events in therapeutic hypothermia after out-of-hospital cardiac arrest

- Hypothermia Network Registry
- Oct 2004-Oct 2008
- 986 OHCA pts > 18 yo; 34 centers, 7 countries
- OHC to ROSC:
  - 20 (14–30) minutes
- OHCA to initiation of hypothermia:
  - 90 (60–165) minutes
- OHCA to goal temperature (≤34°C):
  - 260 (178–400) minutes

Nielsen *et al.* Acta Anaesthesiol Scanda 2009; 53: 926-934

Table 6

(a) Adverse events: all 34 centres and (b) adverse events: 22 reporting centers.

	n = 986
(a)	
Bradycardia < 40 beats/min	127 (13)
Tachycardia > 130 beats/min	57 (6)
Atrial fibrillation	88 (9)
VT	89 (9)
VF	71 (7)
Any combination of arrhythmia	325 (33)
Pneumonia	407(41)
Sepsis	35 (4)
Other infection	41 (4)
Bleeding requiring transfusion	44 (4)
Intracerebral bleeding	2 (0.2)
Seizures	233 (24)
	n = 760
(b)	
Hypoglycaemia < 3 mmol/l	42 (6)
Sustained hyperglycaemia > 8 mmol/l > 4 h	278 (37)
Hypokalaemia (< 3.0 mmol/l)	133 (18)
Hypomagnesaemia (< 0.7 mmol/l)	132 (18)
Hypophosphataemia (< 0.7 mmol/l)	143 (19)

Data presented as absolute numbers and percentages.TH, therapeutic hypothermia; VT, ventricular tachycardia; VF, ventricular fibrillation.

Summary

- Hypothermia is associated with numerous adverse physiologic effects in the setting of accidental hypothermia
- Therapeutic hypothermia produces numerous side effects, some advantageous, some disadvantageous
- However, the incidence of significant adverse events is low from clinical trials and institutional experience
- Be vigilant for hypokalemia, hypovolemia, hyperglycemia, shivering, and infection

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PATH

- Penn Alliance for Therapeutic Hypothermia
- A Post-Arrest Therapeutic Hypothermia Registry
- A quality assurance and research tool
- Secure on-line, web-accessible database of post-arrest patients treated with therapeutic hypothermia
- Scheduled to go live 2/15/10
- For questions contact:
  - gaieskid@uphs.upenn.edu
  - *www.med.upenn.edu/resuscitation/hypothermia/*