Advanced Hypothermic Life Support

Welcome!



Definition: Therapeutic Hypothermia

Definition & Terminology

History & Background

Cases & Studies

Mild Hypothermia

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How to Cool

Complications & Re-warming

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Therapeutic Hypothermia is a medical treatment method which clinically uses the advantages of a lower body temperature.



Therapeutic hypothermia can be used to treat revived (i.e. resuscitated) cardiac arrest victims. The new treatment method is able to reduce mortality of successfully resuscitated cardiac arrest victims by 35 percent and increase the chance of a good neurological outcome by 39 percent.

In addition, there exists a growing body of evidence that hypothermia increases survival chances and quality for patients with asphyxia during birth, and may be helpful from other ischemic insults such as stroke or generalized brain trauma by controlling ICP.



Hypothermia can also be used to manage fever in patients suffering neurological injuries.

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Terminology & abbreviations used in this presentation

ACLS	Advanced Cardiac Life Support		MTH	Mild Therapeutic Hypothermia
CA	Cardiac Arrest		NSE	Neuron-Specific Enolase
CCR	Cardio Cerebral Resuscitations		RCT	Randomized Controlled Trials
CNR	Complete Neurological Recovery		ROSC	Restoration of spontaneous Circulation
CNS	Central Nervous System		SCI	Spinal Cord Injury
CPR	Cardiopulmonary Resuscitation		T	True
CVA	Cerebral Vascular Accident (Stroke)		TH	Therapeutic Hypothermia
ECR	Extracorporeal Re-warming		TBI	Traumatic Brain Injury
F	False		TRP	Transient receptor potential
ICP	Intracranial Pressure		VF	Ventricular Fibrillation

Hypothermia – A short History

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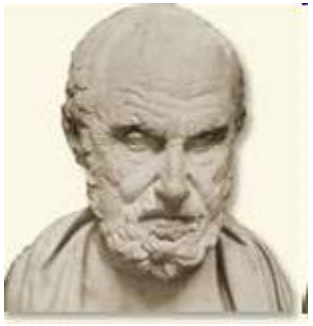
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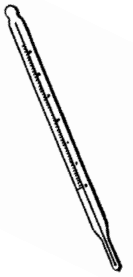
Discussion and Test



Hypothermia has been applied therapeutically since antiquity.

The Greek physician **Hippocrates**, the namesake of the Hippocratic Oath and arguably the world's first modern doctor, advocated the packing of wounded soldiers in snow and ice.

In modern times the **first medical article** concerning hypothermia was published in **1945**. In the 1950's hypothermia received its first medical application, being used in intracerebal aneurysm surgery to create a bloodless field. This period also saw sporadic investigation of more mild forms of hypothermia, with mild hypothermia being defined as a body temperature between 32-34°C (89.6-93.2°F).



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Napoleonic surgeon Baron Dominque Larrey recorded that officers, who were kept closer to the fire, survived less often than the minimally pampered infantrymen.

Who is Who in the Field?



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VIPs in the field:

Peter Safer an anesthesiologist born & trained in Vienna, who developed lifesaving cardiopulmonary resuscitation techniques that are widely used today, died in August 2003.

His students were:

Patrick M. Kochanek, MD is Professor and Vice Chairman of CCM and Director of the Safar Center for Resuscitation Research at the University of Pittsburgh.

Fritz Sterz, MD, PhD is an Associate Professor of Internal Medicine in the Department of Emergency Medicine at the Vienna General Hospital of Austria.

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Who	What	Where
Peter Andrews	Professor in the Department of Anaesthesia, Critical Care and Pain Medicine	Edinburgh, UK
Guy L. Clifton, M.D.	Professor of Neurosurgery	Houston, TX, U.S.A.
Frederick Colbourne, Ph.D	Professor of Psychology	Alberta, Canada
Prof. Dalton W. Dietrich	Professor of Neurological Surgery, Neurology and Cell Biology and Anatomy	Miami, FL, U.S.A.
Dr Ulrich Dirnagl.	Focused on stroke, cerebral blood flow regulation, and brain imaging	Charité Berlin, Germany
Nariyuki Hayashi, M.D., D.S.Sc.	Professor of Advanced Research Institute for Science and Humanities	Nihon, Japan
Janneke Horn, MD, PhD	Neurologist-intensivist on the ICU of the Academical medical Center	Amsterdam, Netherlands
Prof. Dr. Thomas Eric Jüttler	Junior Professor at the Center for Stroke Research Berlin (CSB)	Charité Berlin, Germany
Karl B. Kern, MD	Director of the Cardiac Catheterization Laboratories, and the Director of the Interventional Cardiology Fellowship	Arizona, U.S.A











Who is Who in the Field?

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Who	What	Where
Laurence Katz, MD, FACEP	Co-Director of the Carolina Resuscitation Research Group	North Carolina, U.S.A.
PD Dr. med. Rainer Kollmar	Assistant Professor for Neurology	Erlangen, Germany
Patrick D. Lyden, M.D., F.A.A.N., F.A.H.A	Chief of Neurology and Director of the Stroke Center, and Professor in the Department of Neurosciences	San Diego, CA, U.S.A.
Stephan A. Mayer, MD,	Associate Professor of Clinical Neurology and Neurological Surgery, Director of the Neurological Intensive Care Unit	New York City, NY, U.S.A.
Marko Noc, MD, PhD	Director, CICU	Ljubljana, Slovenia
Mauro Oddo, MD	Attending Physician at the Department of Critical Care Medicine	Lausanne, Switzerland
Kees Polderman	Director of adult Neurocritical care services	Pittsburgh, PA, U.S.A.
Aurel Popa-Wagner	Professor of Experimental Neurology, Director, Advances in Neuroscience Programme	Greifswald, Germany
Professor Wusi QIU	Secretary of Department of Surgery	Hangzhou, China
Dr. Seetha Shankaran	Professor of Pediatrics, Director of Neonatal Perinatal Medicine	Michigan, U.S.A.
Gary K Steinberg, MD, PhD	Professor of Neurosurgery and the Neurosciences, Director, Stanford Institute for Neuro-Innovation and Translational Neurosciences	Stanford, CA, U.S.A.









What is Happening in the Field?

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Scientific Program: 3rd International Hypothermia Symposium

- **Traumatic Brain and Spinal Cord Injury** B Romner, P Kochanek
- **Physiology of Hypothermia** P-O Grände, G Clifton
- **Neonatal Encephalopathy** M Thoresen, S Shankaran
- **Cardiac Arrest** F Sterz, H Friberg
- **Prognostication of coma after cardiac arrest** T Cronberg, M Oddo
- **Cardiac Ischemia and Resuscitation** P Johnsson, KB Kern
- **Mechanisms of Hypothermia Tissue protection** T Wieloch, D Dietrich
- **New devices and chemical hypothermia** D Erlinge, K Polderman
- **Stroke and Neurointensive Care** B Norrving, P Lyden

Currently, a growing percentage of hospitals around the world incorporate the AHA/ILCOR guidelines and include hypothermic therapies in their standard package of care for patients suffering from cardiac arrest.

What is Happening in the Field?
=> New devices and chemical hypothermia

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- **Vallionoid receptors and temperature regulation**
  Edward Högestätt
- **Long-term hypothermia using H2S acts neuroprotectively in aged rats after focal ischemia**
  Aurel Popa-Wagner
- **Hydrogen sulfide** (TBA)
- **TRP channels and temperature regulation** Peter Zygmunt
- **Neurotensin and Hibernaid, medications to induce regulated hypothermia and optimize therapeutic hypothermia**
  Laurence Katz
- **Extracorporeal cooling**
  Michael Wanscher
- **Adenosine receptors and body temperature**
  Bertil Fredholm

Hypothermic Medicine Organizations

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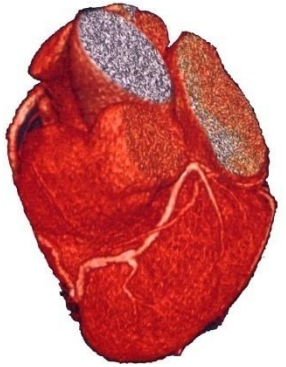
Who Else to Cool

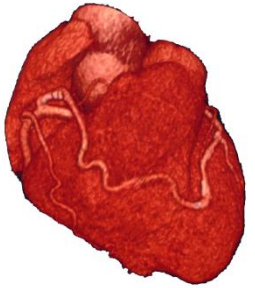
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- American Heart Association
- American College of Cardiology
- American College of Emergency Medicine
- American Association of Neurological Surgeons
- European Respiratory Society
- ILCOR Int. Liaison Committee of Resuscitation
- Society of Critical Care Medicine
- 11th International Consensus Conference (Puerto Rico, April 2009)





American Society of Hypothermic Medicine

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Journal of Hypothermic Medicine and Temperature Control, 2011



To join as a founding member:

American Society of Hypothermic Medicine
602 Audubon, Suite B
Tampa, FL 33609

Benefits of Membership:

- Professional Resources, including lecture sessions and educational material focused on hypothermic medicine
- Access to training sessions teaching evidence based knowledge of therapeutic hypothermia
- Invitation to regular ASHM national and regional meeting
- Subscription to the Journal Mary Ann Liebert Pub. Inc., edited by Dr. Dalton Dietrich

www.hypothermicmedicine.org

The Use if Extracorporeal Re-warming in a Child Submerged for 66 Minutes

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Case Study 1:

- 2.5 year old female, Salt Lake City
- At least 66 minutes submerged in cold water
- Core Temperature = 19°C
- CPR was maintained for more than two hours before initiation of extracorporeal re-warming
- First (?) successful use of ECR

JAMA.1988/; 260:377-379

Advanced Cardiac Life Support (ACLS) and Defibrillation in Severe Hypothermic Cardiac Arrest

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Case Study 2:

- 47 year old male, Connecticut
- Found unresponsive in Bathtub with cold water
- Core Temperature = 26.4°C
- Incorrect pronouncement of death by Fire Department
- Transported to Hospital more than four hours later
- Successfully resuscitated using ACLS
- Near complete neurological recovery

PMID:19145531; 2009

Accidental Hypothermia with Cardiac Arrest

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Case Study 3:

- 51 year old male, Norway
- 40 minutes immersed in sea water (6°C)
- Core Temperature 24°C
- CPR was continued for three hours
- Extracorporeal Circulation (ECR) established
- Ventricular Fibrillation (VF) at 31.5°C
- Discharged after 13 days, no evidence of permanent organ damage

ISSN: 0342-4642 (Print); 1432-1238 (Online)

Outcome of Survivors of Accidental Deep Hypothermia & Circulatory Arrest Treated with Extracorporeal Blood Warming

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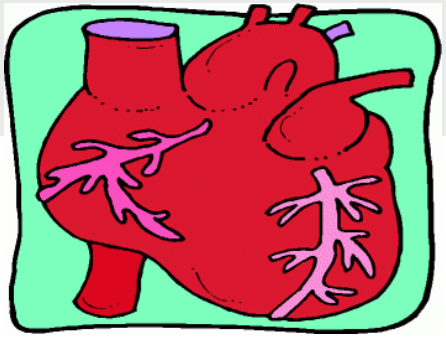
Discussion and Test

Abstract: Department of Thoracic and Cardiovascular Surgery, University of Bern, Switzerland

- Deep Hypothermia: Core Temperature , 28°C
- 15 long-term survivors out of 46
- After average of 6.7 years of follow up: No hypothermia-related sequelae were found that impaired quality of life.

New England Journal of Medicine, 1997

Open Heart Surgery Model



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- Patients have been cooled during open heart surgery prior to and after the invention of cardiopulmonary bypass.
- Slushed ice is put directly on the heart.
- Patient is re-warmed in CSU.

Mild Therapeutic Hypothermia to Improve the Neurologic Outcome after Cardiac Arrest

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Abstract: Dr. Michael Holzer M.D., Vienna, Austria

A total of 3,551 patients were assessed, 3426 did not meet the criteria, 30 were dropped, 275 were enrolled

Exclusion Criteria:

- Temperature 30°C
- Comatose state before CA
- response to verbal commands
- Pregnancy
- Blood pressure , 60 mm. Hg systolic 30 minutes after ROSC
- SAO2 , 85% for more than 15 minutes after ROSC
- Terminal illness
- coagulopathy
- EMT witnessed CA

Inclusion Criteria:

- Witnessed CA
- VF or non-perfusing VT
- Cardiac origin of the arrest
- Age 18 – 75
- 5 – 15 minutes response time
- No more than 60 minutes form collapse to ROSC

New England Journal of Medicine, Vol. 346, No 8 – February 21,2002

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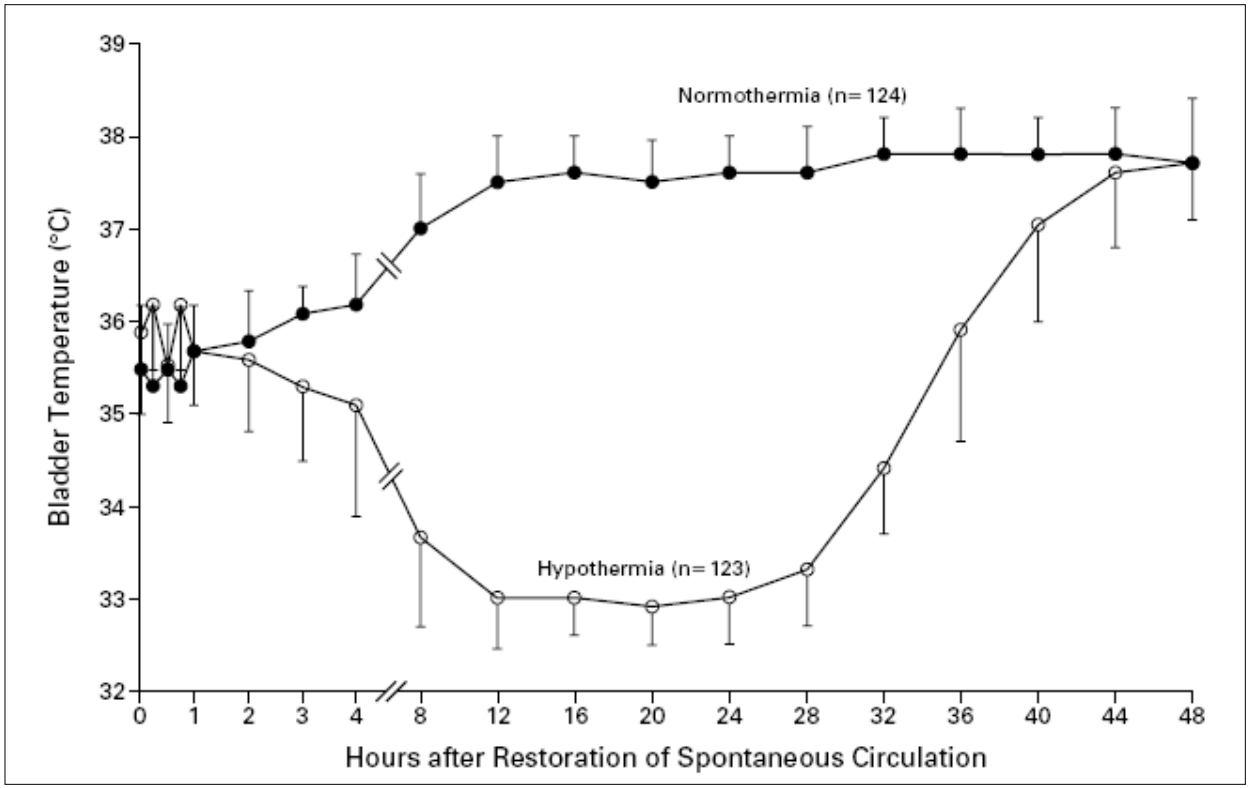
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Figure 1:

Bladder Temperature in the Normothermia and Hypothermia Groups



New England Journal of Medicine, Vol. 346, No 8 – February 21,2002

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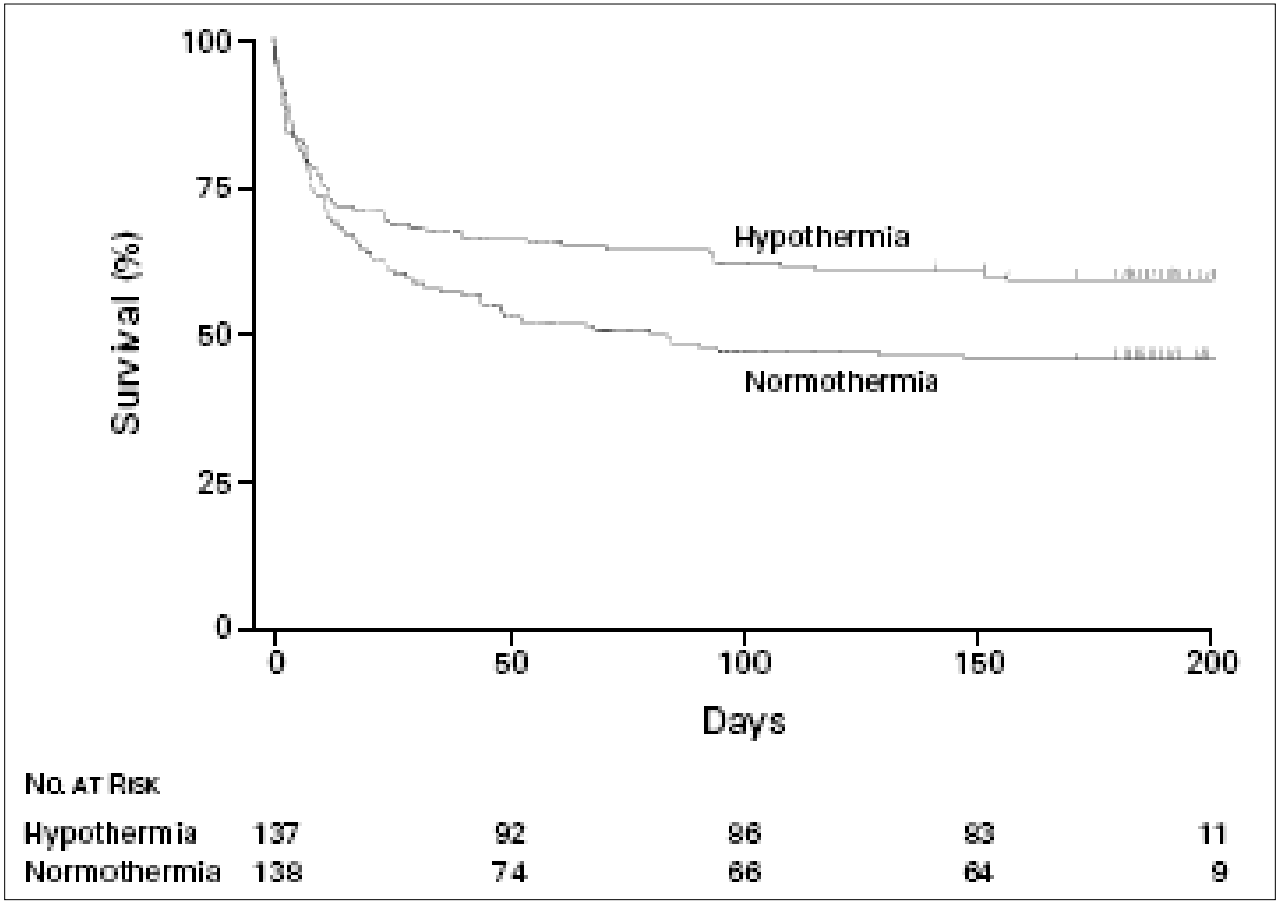
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Figure 2:

Cumulative Survival in the Normothermia and Hypothermia Groups



New England Journal of Medicine, Vol. 346, No 8 – February 21,2002

Treatment of Comatose Survivors of Out-of-Hospital Cardiac Arrest with Induced Hypothermia

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Abstract: Dr. Stephen A. Bernard, Australia

Table:

Outcome of Patients at Discharge from the Hospital

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

New England Journal of Medicine, Vol. 346, No 8 – February 21,2002

Therapeutic Hypothermia after Cardiac Arrest

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Peter J. Safer, M.D. & Patrick M. Kochanek, M.D. Pittsburgh, PA

"… we recommend the use of hypothermia in survivors of cardiac arrest – as early as possible and for at least 12 hours."



Figure 1. Cooling Device Used in the Hypothermia after Cardiac Arrest Study, Which Operates by Circulating Cool Air over the Patient.

New England Journal of Medicine, Vol. 346, No 8 – February 21,2002

Induced Hypothermia
Post Cardiac Arrest Protocols, 2002

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Admit to ICU

- □ Use external cooling blanket (Model # _____)
- □ Cool patient's temperature to 33°C (reaching target temp within 4 hours)
- □ Maintain this temp for 24 hours
- □ Ice packs may be used around the head, neck, torso & limbs
- □ Remove when core temp reached
- □ To prevent shivering, paralyze by using:

  ___ Pancuronium IV 0.1 mg/kg every 2 hours

- □ After 24 hours, passive re-warming over 8 hours

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Case 1: 9/27/2002

- 78 female (witnessed cardiac arrest)
- 5 min response time (ACLS)
- VF Cardioverted in the field
- Delivery with decerebrate posturing
- Cooled to 33°C for 24 hours
- Passive re-warming
- Extensive rehab
- total recovery with slight memory loss



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Case 2: 12/28/2002



- 81 year old female
- Overcooled
- Sentinal event
  - Cooling blanket did not warm
  - Rectal probe was not with blanket
- Patient did not recover

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Case 3: February 2005

- 71 year old white male
- CA in hospital
- From acute anterior wall STEMI
- ROSC with coma
- Cooling begun with blanket & ice bags
- Patient transferred to St. Joseph's Hospital
  - All cooling measures were stopped
  - Patient went home with significant short and long term memory deficit, post PTCA

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Case 4: 2005

- 62 year old white male
- ROSC & coma
- Found to have inferior wall STEMI
- Cooling begun with ice, blanket & cold saline
- Patient transferred to TGH for PTCA, all cooling immediately stopped

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Case 5: 2005

- T.B., 42 year old white male,
- Witnessed CA, at home
- Transport to hospital in Columbus OH
- With anterior wall STEMI / PTCA
- Patient was not cooled, severe neurological damage
- Died in Assisted Living facility three years later

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Advisory Statement by the Advanced Life Support Task Force

Summary:

"On the basis of published evidence to date (2003), the ILCOR ALS Task Force has made the following recommendations:

- Unconscious adult patients with spontaneous circulation after out-of-hospital cardiac arrest should be cooled to 32°C for 12 to 24 hours when the initial rhythm was VF.
- Such cooling may also be beneficial for other rhythms or in-hospital cardiac arrest"

Circulation. 2003; 108:118 – 2003 American Heart Association, Inc.

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Attempted development of county wide system (2002)

- Letter to all neurologists
- Letters to emergency room physicians
- Agenda item at local EMS system council

=> No interest by the community



Post Resuscitation Support 2005

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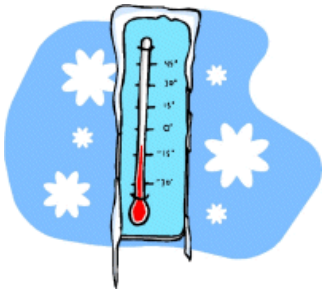
Complications & Re-warming

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=> Temperature Regulation



"Both permissive hypothermia (allowing a mild degree of hypothermia >33°C [91.5°F] that often develops spontaneously after arrest) and active induction of hypothermia may play a role in post resuscitation care."



"The postrescuscitation period is often marked by hemodynamic instability as well as laboratory abnormalities. Every organ system is at risk during this time and patients may ultimately develop multi-organ dysfunction. Promising technological interventions such as therapeutic hypothermia are being evaluated to increase the likelihood of intact neurologic survival."

Circulation. 2005;IV-84-IV-88; American Heart Association

Cardiocerebral Resuscitations (CCR)

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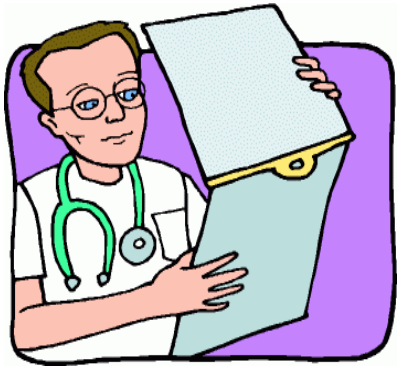
How to Cool

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Review by: Gordon A. Ewy M.D., Karl B. Kern M.D.

"Hypothermia is appropriate for patients who are comatose post-resuscitation."



Compared to conventional CPR, CCR has been shown to improve survival to hospital discharge after out-of-hospital cardiac arrest by a factor of 2.7 - 3.7

Fred Morady, M.D., F.A.C.C.

Used to be Reggae Beat, now SING:
"Staying Alive" by the Bee Gees

J Am Coll Cardiol 2009; 53:149-157

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American Heart Association

Advanced Cardiac Life Support Guidelines Manual incorporates hypothermia

- Targeted Temperature Management

1. Indicated in ROSC with lack of meaningful response to verbal commands
2. Some evidence supporting non-VF cardiac arrest cooling, IIb
3. The impact of the timing of initiating hypothermia after cardiac arrest is not completely understood
4. At least 12 to 24 hours

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American Heart Association
Learn and Live

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Definitions Hypothermia

Published Hypothermia Definitions (values in °C)

Author	Mild	Moderate	Deep
Wong (1)	32-35	26-31	20-25
Varnathan (2)	32-35	26-31	20-25
Zeiner et al (3)	34-36	28-33	17-27
Reuler (4)	34-36	28-33	17-27
Hammer and Krieger (5)	>32	28-32	20-28
Safar and Behringer (6)	33-36	28-32	11-27
Werner (7)	34-36	29-33	17-28

Signs & Symptoms of Progressive Accidental Hypothermia

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36°C: Increased activity attempting to warm up; skin pale; numb, and waxy; muscles tense; fatigue and signs of weakness.

34°-35°C: Uncontrolled intense shivering; still alert but movements uncoordinated; pain and discomfort due to coldness

31°-33°C: Skin cold; eyes dilated; extreme weakness; slurred speech; exhausted; denies problems and resists help; gradual loss of consciousness; progressive respiratory arrest.

Terminology in CNS clinical outcome trials

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Author	Pathology	Target Temperature (°C)	Term
Clifton et al (25)	Traumatic brain injury	33.0	Moderate
Bernard (20)	Cardiac arrest	33.0	Moderate
THACAS Group (21)	Cardiac arrest	32-34	Mild
Todd et al (26)	Cerebral aneurysm	32.5-33.5	Mild
Shankaran et al (22)	Neonatal asphyxia	33.5	Not defined
Gluckman et al (23)	Neonatal asphyxia	34-35	Mild

Mild Hypothermia - Thermoregulatory Responses

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- **Peripheral vasoconstrictions**
  - Pharmacological inhibition of Peripheral vasoconstrictions by medications (i.e. Propofol)

- **Shivering**
  - Threshold 35.5°C
  - Increases metabolic rate 2-4 -fold
  - Inhibition requires medications i.e. neuromuscular blockade & mechanical ventilation



Mild Hypothermia - Cardiovascular Responses

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- **Hemodynamic Function**
  - When shivering is abated with acetaminophen and meperidine, hemodynamic variables are unchanged at 35°C

- **Arrhythmias**
  - Mild cooling during CPR reduces the threshold for ventricular defibrillation
  - 30-35°C bradycardia, prolonged PR, QRS & QT intervals
  - 30°C atrial fibrillation
  - Less than 30°C VF



Mild Hypothermia - Blood



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➢ Coagulation

- In Vitro: Platelet activation thresholds are altered at 34.00°C and 36.4°C
- Patients undergoing cerebral aneurysm clipping had no greater operative blood loss at 32.5°C – 33.5°C
- Clinical studies of Hypothermia did not show problems with hemorrhage

➢ Alpha-stat/pH-stat

- Solubility of CO_2 increases as temperature decreases
- Blood gas machine measures at 37°C
- Uncorrected blood gas values = alpha-stat
- pH-stat correction of ABG $PaCO_2$ has not been well studied

Cellular and Molecular Mechanisms

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Patrick M. Kochanek, MD

Mild therapeutic hypothermia has been studied in three conditions:

- **Cardiac Arrest (CA)**
- **Traumatic Brain Injury (TBI)**
- **Stroke (CVA)**

Obviously very different conditions from which data was gathered!



Cellular and Molecular Mechanisms

Table: Clinical studies exploring the effect of mild or moderate therapeutic hypothermia vs normothermia on mechanisms involved in the evolution of secondary damage and repair in human CNS injury.

Date (Citation)	*Temperature*	*Population*	*Outcome*	*Key Finding*
1997 (25)	32-33°C vs. normothermia	TBI: Prospective single-center RCT of 82 patients	CSF glutamate and IL-1	Moderate hypothermia was associated with reductions in CSF levels of glutamate and IL-1
1998 (44)	32-33°C vs. normothermia	TBI: 39 patients with severe injury; subgroup of an RCT	CSF quinolinic acid, a macrophage marker	Hypothermia had no effect on CSF quinolinic acid levels
1999 (40)	32-33°C vs. normothermia	TBI: Prospective study of 23 patients with severe injury	Jugular venous levels of IL-6	Moderate hypothermia reduced jugular venous levels of IL-6
1999 (27)	34°C vs. normothermia	TBI: Prospective RCT of 16 patients with severe injury but ICP <20 mm Hg	CSF TNFα, IL-1β, IL-6, IL-8, IL-10	No reduction in CSF cytokines by hypothermia despite increases in levels of IL-6, IL-8, and IL-10
2000 (59)	32-33°C vs. normothermia	TBI: Prospective study of 26 patients with severe injury	Jugular venous levels of thromboxane and 6-keto-$^{15}PGF_1\alpha$	Moderate hypothermia reduced the increase in jugular venous levels of thromboxane; no effect on 6-keto-$PGF_1\alpha$

Cellular and Molecular Mechanisms

Table: Clinical studies exploring the effect of mild or moderate therapeutic hypothermia

Date (Citation)	*Temperature*	*Population*	*Outcome*	*Key Finding*
2002 (60)	34-36°C	TBI: Prospective study in 58 patients with persistent ICP >20 mm Hg treated with hypothermia	Brain interstitial levels of glutamate and lactate	Patients with spontaneous hypothermia on admission had high levels of glutamate and lactate
2003 (61)	RCT of 32°C vs. normothermia	TBI: Prospective study of 28 infants and children with severe injury	CSF levels of IL-6, IL-8	Marked increase in CSF levels of IL-6 and IL-8 after injury but no difference in hypothermia vs. normothermia
2004 (26)	32-33°C for 24 or 48 h vs normothermia	TBI: 68 adults; subset of patients from multicenter RCTs	CSF levels of glutamate, and F_2-isoprostane	Hypothermia reduced both glutamate and F_2-isoprostane
2003 (19)	RCT of mild (33 ± 1°C) vs normothermia	CA: 70 adult patients; resuscitation from VF	Serum levels of NSE and S100B	Serum levels of NSE but not S100B reduced by hypothermia
2004 (34)	32-33°C for 24 or 48 h vs normothermia	TBI: 68 adults: subset of patients from multicenter RCTs	CSF levels of F_2-isoprostane	Effect of gender on oxidative stress more dramatic than that of mild hypothermia

Cellular and Molecular Mechanisms

Date (Citation)	*Temperature*	*Population*	*Outcome*	*Key Finding*
2007 (38)	RCT of hypothermia (32-33 °C for 48 h) vs normothermia in children	TBI: 36 children , 17 treated with hypothermia	CSF levels of 21 pro- and anti-inflammatory cytokines and chemokines assessed by multiplex assay and/or ELISA	Marked increases in CSF levels of many of these inflammatory markers, but no significant effect of therapeutic hypothermia on any cytokine or chemokine
2008 (53)	Cohort of patients treated with either normothermia or hypothermia (35°C for 48-72 h)	Stroke: 30 patients, 20 treated with normothermia and 10 with hypothermia	Serum levels of MMP 9	Trend toward reduced MMP 9 levels in patients treated with hypothermia vs normothermia (p = 0.052). MMP 9 posited to represent a marker of BBB damage.
2009 (32)	RCT of 32°C vs. normothermia	TBI: Prospective study of 28 infants and children with severe injury	CSF levels of multiple markers of oxidative stress	Improvement in CSF levels of total antioxidant reserve and glutathione by hypothermia

TBI = Traumatic brain injury; CA = Cardiac arrest; CSF = Cerebrospinal fluid; IL = Interleukin; RCT = Randomized controlled trial; TNF = Tumor necrosis factor; ICP = Intracranial pressure; PGF = prostaglandin F; VF = Ventricular fibrillation; NSE = Neuron specific enolase; MMP = Matrix metalloproteinase; ELISA = Enzyme-linked immunosorbent assay; BBB = blood-brain barrier.

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Mild Hypothermia results in…

- Prevention of energy failure
- Reduces ICP
- Prevents oxidative & nitrative stress
- Attenuates neuronal death
- Affects apoptosis
- Activates cell survival pathways
- Increases brain-derived neurotrophic factor



Cellular and Molecular Mechanisms – Conclusions

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Mild Hypothermia

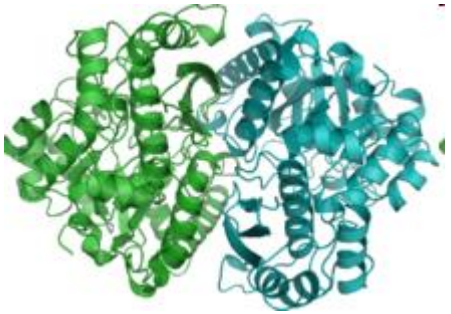
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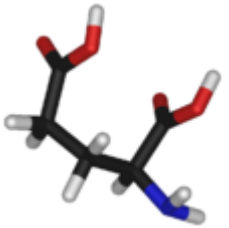
Complications & Re-warming

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Mild Hypothermia results in…



- Reduced neuron-specific enolase (NSE)
- Attenuates increases in glutamate, hyperglycolysis
- Decreases excitotoxicitiy
- Preserves antioxidant reserve
- Little evidence for attenuation for neuroinflammation
- Slows down macrophages



Cellular and Molecular Mechanisms - Conclusions

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Mild Hypothermia results in…



- Prevents blood-brain barrier damages
- Attenuates axon injury
- Attenuates Calpain-mediated proteolysis
- variable effect on S100B an astrocyte injury marker

- No singular effect that reduces all pathways
- Enhances some and reduces others.

"Evidence is largely unsupportive of effects on neuroinflammation by mild hypothermia in humans. Clinical work also suggests important gender differences on some secondary injury mechanisms such as oxidative stress." (Males affected more than females)

Studies of Mild Therapeutic Hypothermia in Ventricular Fibrillation Cardiac Arrest in Adults

Study	Outcome	Hypo-thermia	Control	RR, OR (95% CI)	Limitation	Import.	QOE
Oddo et al [22]	CPC 1,2 at discharge	24/43 (56%)	11/43 (36%)	RR 2.18 (1.23-3.88)	Comparison with historic controls, lack of multivariate analysis.	Important	Low
Bro-Jeppesen et al [53]	CPC 1,2 at discharge	33/52 (56%)	27/56 (36%)	RR 1.32 (0.94-1.85) OR 17 (1.9-155)*	Comparison with historic controls	Important	Low
European multicenter study [7]	CPC 1,2 at 6 months	75/136 (55%)	54/137 (39%)	RR 1.47 (1.09-1.82)*	Normothermia group was slightly hyperthermic (37-38°C) during the first 48 hours	Critical	Moderate
Bernard et al [8]	Discharge to home	21/43 (49%)	9/34 (25%)	OR 5.25 (1.47-18.76)*	Normothermia group was slightly hyperthermic (37.4±0.58°C) at 12 hours, no neurologic outcome	Important	Moderate
Kim et al [31]	Discharge alive	19/29 (66%)	10/22 (45%)	RR 1.44 (0.85-2.45)	Not all patients received the full dose of intravenous cooling; the continuation of cooling in-hospital was to the treating physicians' preferences	Important	Very low

RR, risk ratio; OR, odds ratio; CI, confidence interval; Import., importance of outcome (critical, important, not important); QOE, quality of evidence (high, moderate, low, very low); CPC, cerebral performance category (CPC 1 normal, CPC 2 slight disability, CPC 3 moderate disability, CPC 4 coma, CPC 5 death or brain death).
*Multivariate analysis

Paramedic Prehospital Cooling

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Kim et all:

Small trials demonstrated safety and feasibility by paramedics before hospital arrival but studies are underpowered and limited

Circulation 2010 Aug 17, 122:729

Circulation 2010 Aug 17; 122:737

Circulation 2010 Aug 17; 122:679

Paramedic Prehospital Cooling – underpowered study

AHA - Circulation 2010;122;729-736

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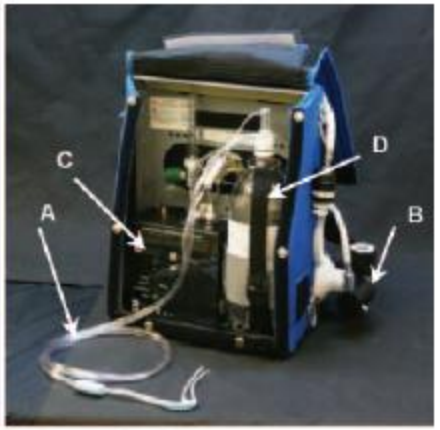
Discussion and Test

Intra-Arrest Transnasal Evaporative Cooling

A randomized, Pre-hospital, Multicenter Study (PRINCE: Pre-ROSC IntraNasal Cooling Effectiveness)



A: coolant spray
B: nasal catheter



A: nasal catheter
B: oxygen tank
C: control unit
D: coolant bottle

Baseline Characteristics:

	Treatment (n=93)	Control (n=101)	P*
VF, n (%)	27 (29.0)	32 (31.7)	0.69
PEA, n (%)	19 (20.4)	23 (22.8)	0.69
Asystole, n (%)	47 (50.5)	46 (45.5)	0.49

RX – N = 93
CON - N = 101

Pre-hospital Transnasal Evaporative Cooling is safe and feasible and improves cooling time.

Paramedic Prehospital Cooling – underpowered study

AHA - Circulation 2010; 122:737-742

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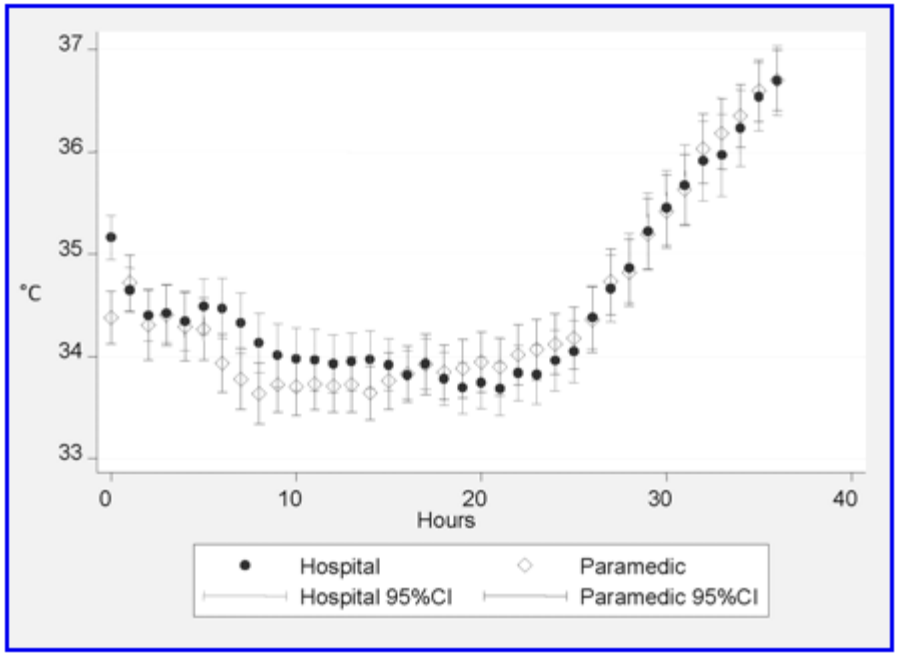
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Bernard:

Induction of Therapeutic Hypothermia by Paramedics After Resuscitation From Out-of-Hospital Ventricular Fibrillation Cardiac Arrest



RX – N = 57
CON - N = 115

Given 2000 cc of cold saline at 4C

Where is Clinical Evidence Supporting the Use of Mild Therapeutic Hypothermia in non-VF Cardiac Arrest?

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Michael Holzer, MD

"There are no studies of sufficient quality to recommend the use of mild therapeutic hypothermia as standard therapy after non-VF cardiac arrest in adults. One trial indicated a possible harm in therapeutic hypothermia, but the sample size was low and therapeutic hypothermia therapy was applied only in a small number of patients. As the pat physiologic process of cerebral damage (no flow and resuscitation) is the same as in patients with VF cardiac arrests, therapeutic hypothermia might be a useful option in those non-VF cardiac arrests."

=> Further studies are necessary to answer this question

Outcomes of Therapeutic Hypothermia With Iced Saline & Endovascular Cooling in Shockable / Nonshockable Rhythms

Vinod S. Kudagi, Nitesh Sood, Jeefrey Kluger, Joseph Taliercio, Justin Lundbye,
Hartford Hospital, Hartford, CT

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- Out of 29 patients 15 had complete neurological recovery (CNR=51.7%), 13 patients died (44.8%), and 1 patient (3%) had persistent vegetative state.
- All had STEMIs
- 10 of 17 (58.4%) with VF had CNR
- 5 of 12 (41.6%) with either PEA or asystole had CNR
- There were no Alsius catheter or hypothermia related complications in any patient.

J Am Coll Cardiol March 10, 2009; Abstracts 1050-145

Perinatal Asphyxia:
Evidence for Treatment with Hypothermia

Seetha Shankaran, MD

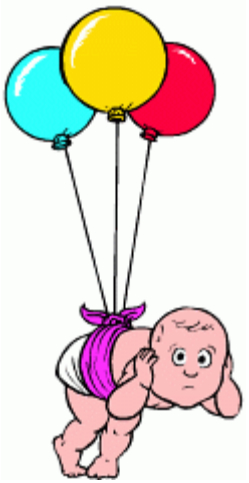
- Three Trials with Infants

- <u>Conclusion:</u>

  Disagreement on death reduction but consensus on visual Impairment reduction and CP disability reduction

  => Safe!

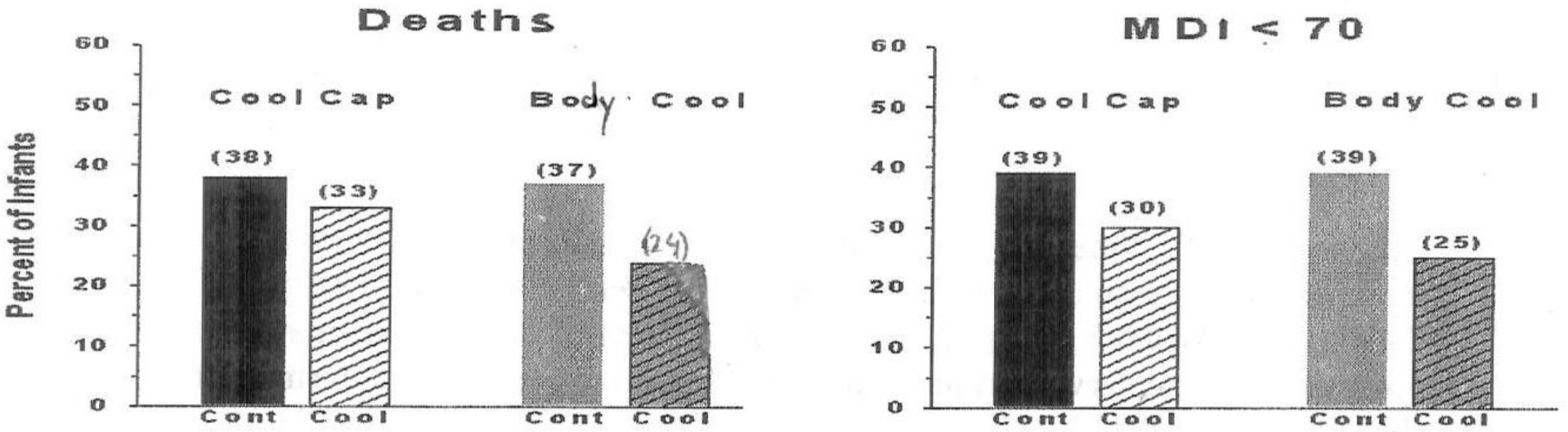




Perinatal Asphyxia:
Evidence for Treatment with Hypothermia

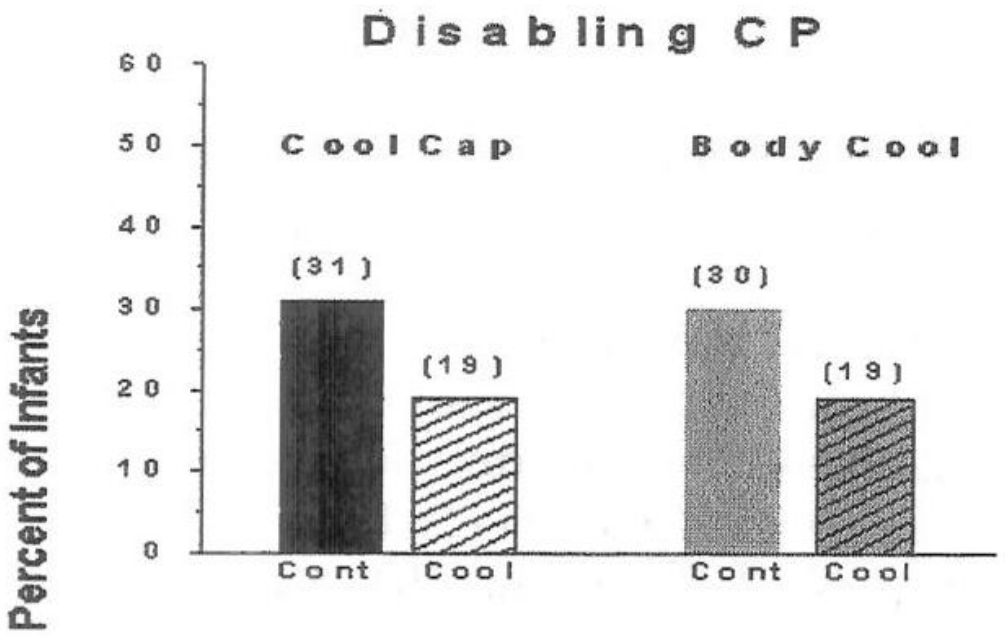
Figure 1: Mortality rate and percentage of infants with mental development index (MDI) in two hypothermia trial

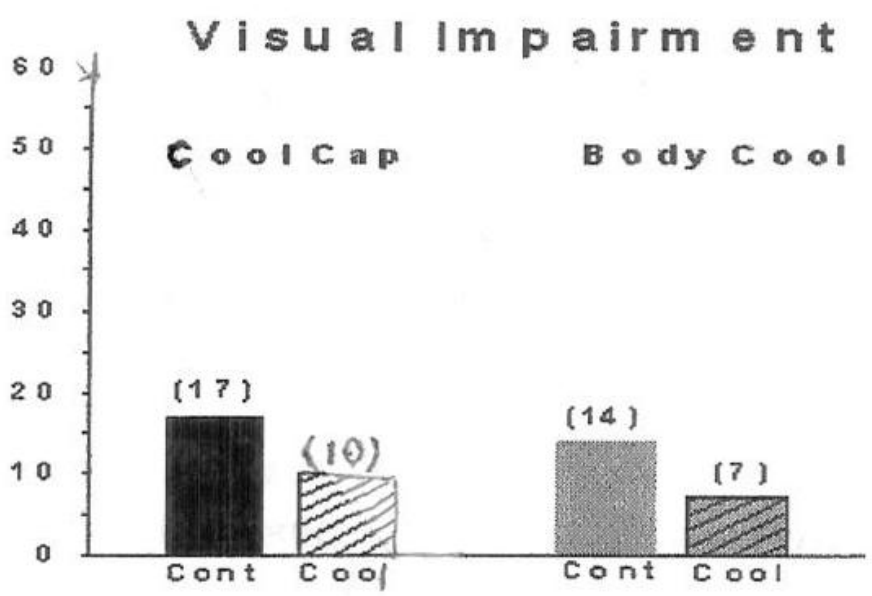
Cooling Protocol: Mild Hypothermia for 72 hours



Perinatal Asphyxia:
Evidence for Treatment with Hypothermia

Figure 2: Rate of cerebral palsy and visual impairment in two hypothermia trials





Does Hypothermia Help With Intracranial Pressure Control?

Donald W. Marion, MD, MSc

Table 1: Clinical studies of therapeutic mild to moderate hypothermia, before and after treatment effects on ICP

Study	N	During Cooling (mean ICP, mm Hg)	Before Cooling (mean ICP, mm Hg)	P value	Target T (°C)
Jiang (27)	215	≈18-20	≈28-29	<0.05	33-35
Polderman (28)#	64	14	37	<0.01	32-34
Gal (29)	30	12	18	0.0007	34.5
Lavinio (14)	24	18.3	23.1	<0.05	34
Metz (11)	10	14.5	24	<0.01	32.5-33

ICP: intracranial pressure; T: temperature.
#Subgroup of 64 patients with severe traumatic brain injury who had intracranial hypertension refractory to barbiturate coma.

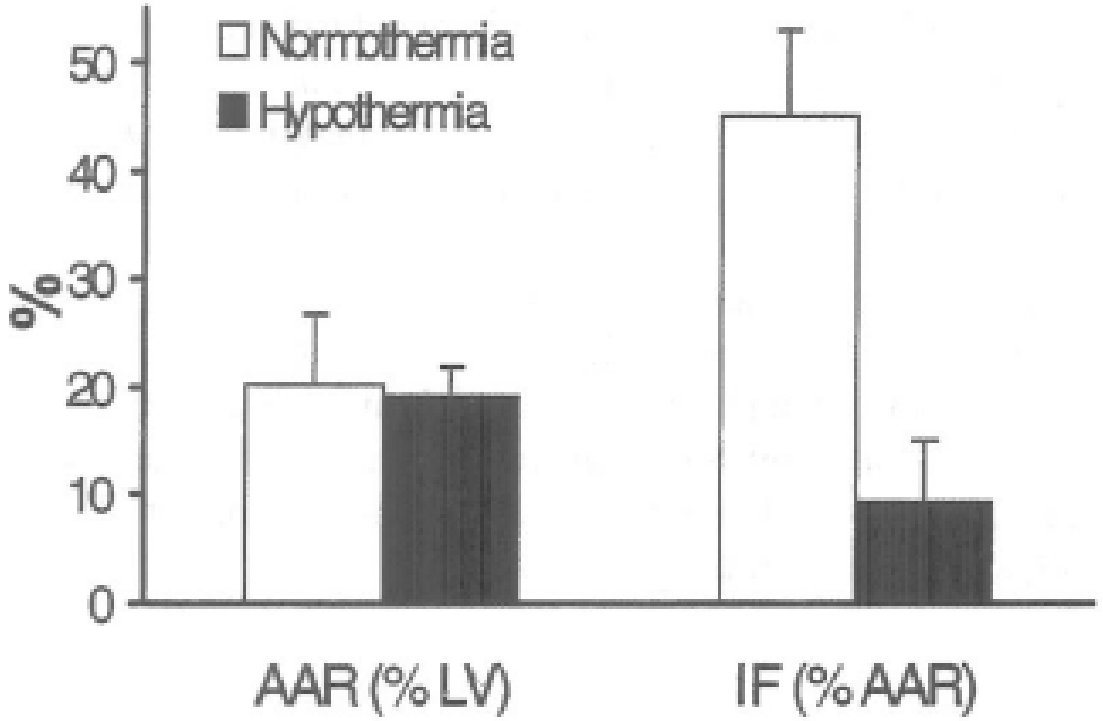
Does Hypothermia Help With Intracranial Pressure Control?

Table 2: Randomized clinical trials of therapeutic mild to moderate hypothermia with normothermia control groups

Study	N	Mean ICP: H (mm Hg)	Mean ICP: N (mm Hg)	*P* value	Target T (°C)
Adelson (P) (19)	35	14.86	17.48	<0.05	32-33
Biswas (P) (20)	21	9.5	12	NS*	32-34
Zhi (21)	396	14-21.4	20.6-25.5	<0.05	32-33
Clifton (22)	392	15.65	17.4	NS**	33
Jiang (23)	87	18.9	28.13	<0.01	33-35
Marion (9)	82	15.4	19.7	0.01	32-33
Qiu (24)	80	22.5-24.7	24.6-25.9	0.003	33-35
Liu (25)^	45	27.75	33.08	<0.05	33-35
Smrcka (26)	38	10.81	18.88	<0.0001	34
Shiozaki (13)	33	≈15	≈25.4	<0.01	34

Who else might we cool? - Myocardial Ischemia / Infarction

Figure: Infarct size in hypothermic pigs and Normothermic controls after coronary occlusion and reperfusion. The size of the area at risk (AAR) was comparable in both groups; however, infarct size (IF) was significantly reduced in the hypothermia group.



Who else might we cool? - Myocardial Ischemia / Infarction

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Figure 3. Effect of mild hypothermia (32°C or 35°C) on infarct size in rabbits after a 30-minute coronary artery occlusion. Hypothermia was commenced either before ischemia (0), or 10 or 20 minutes after occlusion. Infarct size is normalized as a percentage of the risk zone and is plotted for each group. Open and closed circles indicate individual experiments and group means, respectively. Note that the protection observed depends both on the temperature and the duration of cooling.

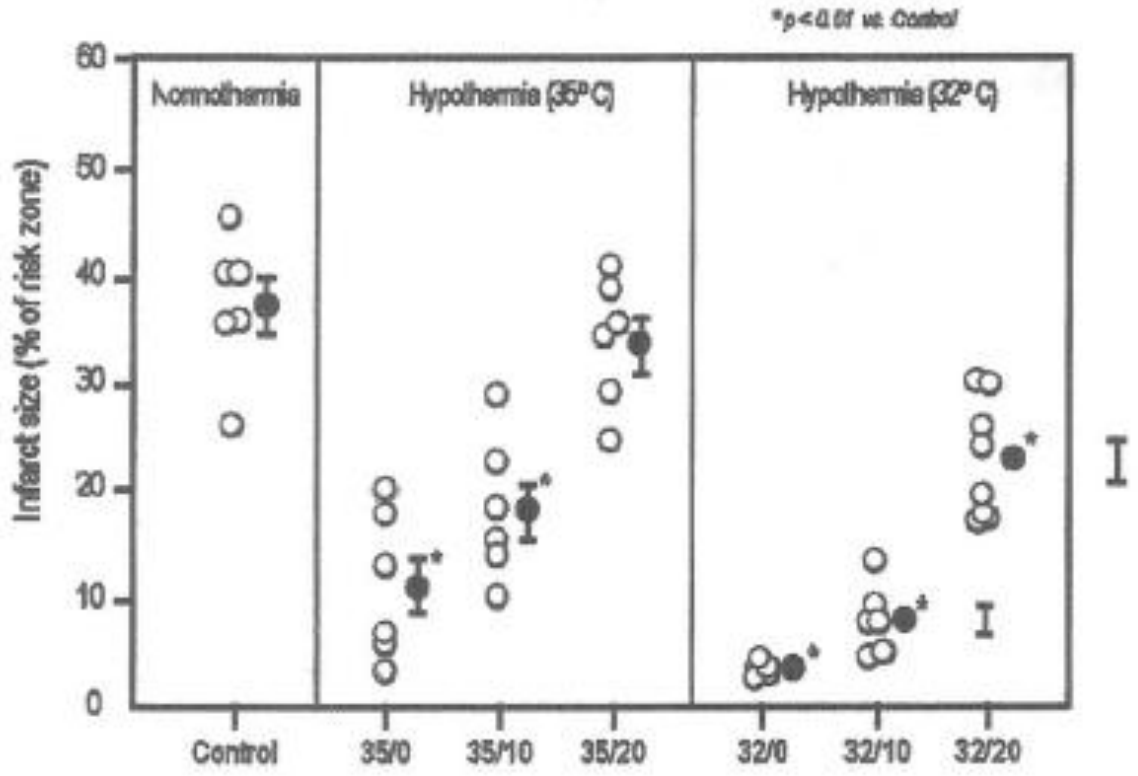


Table: Experimental Studies of mild hypothermia in acute myocardial infarctions

Author	Model	Target Temp*	Technique	Onset of Cooling	Duration of Cooling	Results
Before Coronary Occlusion						
Hale and Kloner (1997)[4]	Rabbit	35°C (3.6°C)	TRH	20 minutes before occlusion	65 minutes	↓Infarct size with cooling (16% vs. 46% of area at risk)
van den Doel et al (1998)[5]	Rat	30-31°C	Surface	Before	15-120 minutes	Hypothermia enhanced protective effect of ischemic preconditioning, but no benefit with prolonged occlusion
Dave et al (1998)[6]	Rabbit	34°C (5°C)	CCP	30 minutes before occlusion	55 minutes	↓Infarct size with cooling (16% vs. 46% of area at risk)

Table: Experimental Studies of mild hypothermia in acute myocardial infarctions

Author	Model	Target Temp*	Technique	Onset of Cooling	Duration of Cooling	Results
After Coronary Occlusion						
Boyer (1977)	Dog	32^{0}C	Surface	Not reported	Not reported	↓Myocardial O_2 consumption & LVEDP with hypothermia
Hale et al (1997)[7]	Rabbit	32^{0}C (6.3^{0}C)	TRH	10 or 25 minutes after occlusion	5 or 25 minutes	Early cooling ↓infarct size (23% vs 44%); however, no benefit with late cooling
Miki et al (1998)[8]	Rabbit	32^{0}C or 35^{0}C	Heat exchanger	5 minutes before, & 10 or 20 minutes after occlusion	35-40 minutes	Better cardioprotection at 32^{0}C then 35^{0}C and with early cooling

Table: Experimental Studies of mild hypothermia in acute myocardial infarctions

Author	Model	Target Temp*	Technique	Onset of Cooling	Duration of Cooling	Results
Hale and Kloner (1998)[9]	Rabbit	30°C (10°C)	TRH	30 minutes after occlusion	90 minutes**	At 120 minutes, ↓infarct size with cooling (59% vs. 72% of area at risk)
Dae et al (2002)[10]	Pig	34°C (4°C)	Endovascular	20 minutes after occlusion	55 minutes + gradual rewarming	↓Infarct size with hypothermia (9% vs. 45% of area at risk)
Hale et al (2003)[11]	Rabbit	32°C	Surface	10 minutes before and 2 hrs after reperfusion	2 hours	↓anatomic no-reflow and infarct size, and ↑regional myocardial flow in risk region with hypothermia

TRH=Topical regional hypothermia; CCP=Closed circuit pericardioperfusion; LVEDP=left ventricular end-diastolic pressure.
* Mean temperature reduction from baseline shown in parentheses
**Model of prolonged coronary ischemia

Simon R. Dixon, BHB, MBChB

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Patients with Myocardial Ischemia / Infarction ?

- COOL - MI Pilot

  => to gain experience in cooling MI patients who did not have CA

- LOWTEMP Pilot

  => 20 patient feasibility study, successful, no safety concerns,

- COOL-MI trial

  => well tolerated, no hemodynamic instability

- ICE-IT Trial

  => discontinued for futility after interim analysis of 20 patients revealed no difference in infarct size

- COOL-MI2 Trial

  => terminated in 2007, enrolment of only 40 patients, sponsor became insolvent

Who else might we cool? - Myocardial Ischemia / Infarction

Goran K.H. Olivecrona at all; Lund, Sweden - TCT-84, TCT 2010;
Supplement to JACC Abstracts September 2010

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RAPID MI-ICE Study

- 20 patients with STEMI
- 2 groups =>
- Rapid cooling, IV saline + endovascular cooling catheter
- Late gadolinium enhancement MRI
- target temperature

Control Group	MI-ICE group
Normal temperature DTB time 40 minutes Ischemia time 74 min.	Temp < 35C DTB time 43 minutes Ischemia time <74 min

Myocardium risk at 4 days post PTCA/STENT was reduced by 38%

Who else might we cool? - Cool MI Trial, Subset AWMI

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Figure 4. Final infarct size at 30 days for patients with anterior infarction assigned to hypothermia according to the core body temperature at reperfusion. The boxes represent the 25th and 75th interquartile ranges; the median value is shown above the horizontal line.

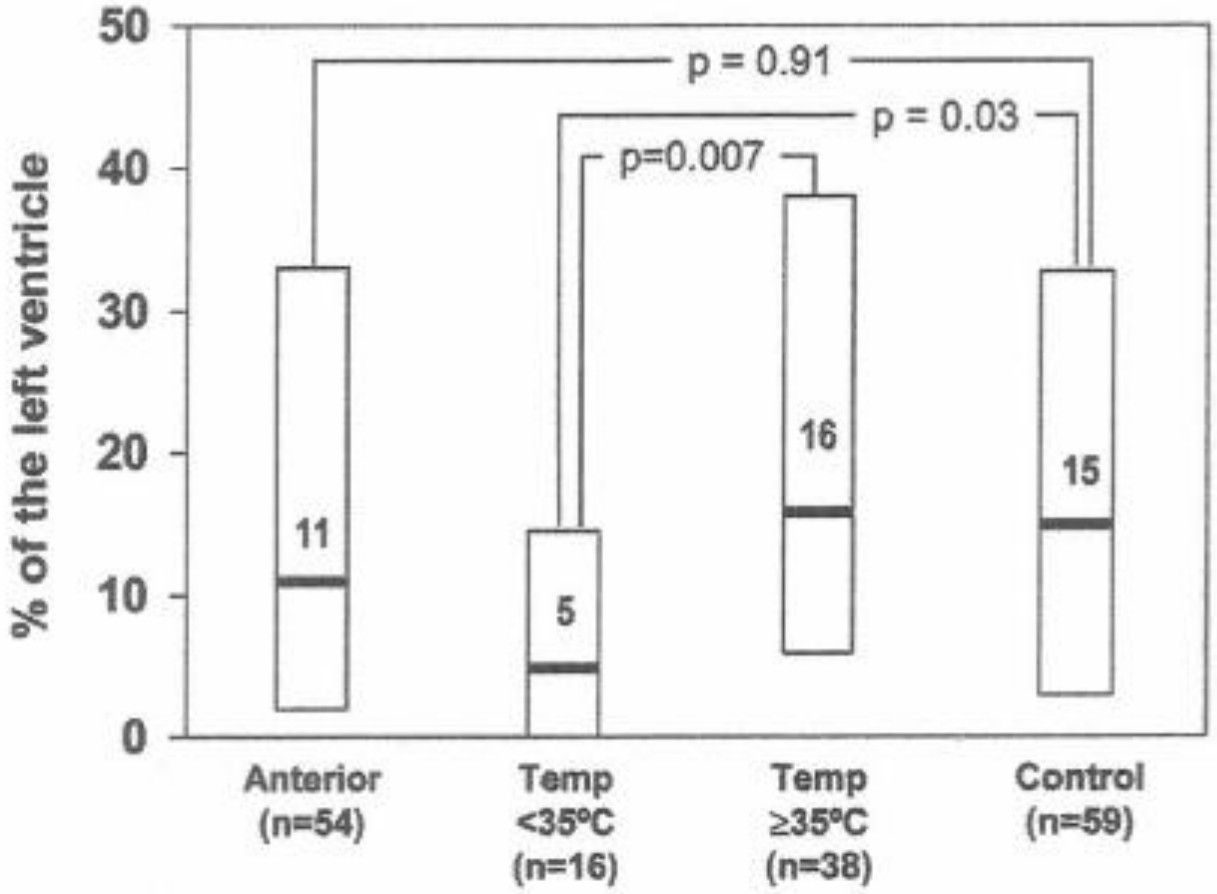


Table: Clinical trials of hypothermia for acute myocardial infarctions

Acronym	Design	Inclusion Criteria	Cooling System	Number of Patients	Target Temperature	Duration of Cooling	Primary Endpoint
Non-randomized studies							
LOW TEMP[17]	Registry	MI <6 hrs	Coolgard® Temperature Management System	20	32-34^{0}C	4 hrs	Infarct Size
NICAMI[18]	Registry	MI <6 hrs	Arctic Sun® Temperature Management System	11	34^{0}C	3 hrs	Major adverse cardiac event

Table: Clinical trials of hypothermia for acute myocardial infarctions

Randomized studies							
COOL-MI Pilot[15]	Randomized pilot study	MI <6 hrs	Reprieve™ Temperature Management System	42	33°C	3 hrs*	Major adverse cardiac event
COOL-MI[19]	Randomized, multicenter	MI <6 hrs	Reprieve™ Temperature Management System	412	33°C	3 hrs*	Infarct size
ICE-IT	Randomized, multicenter	MI <6 hrs	Celsius Control™ System	Enrolling ; Planned = 400	33°C	6 hrs	Infarct Size

*from first balloon inflation

Trial discontinued after no difference in infarct size in 200 patients.

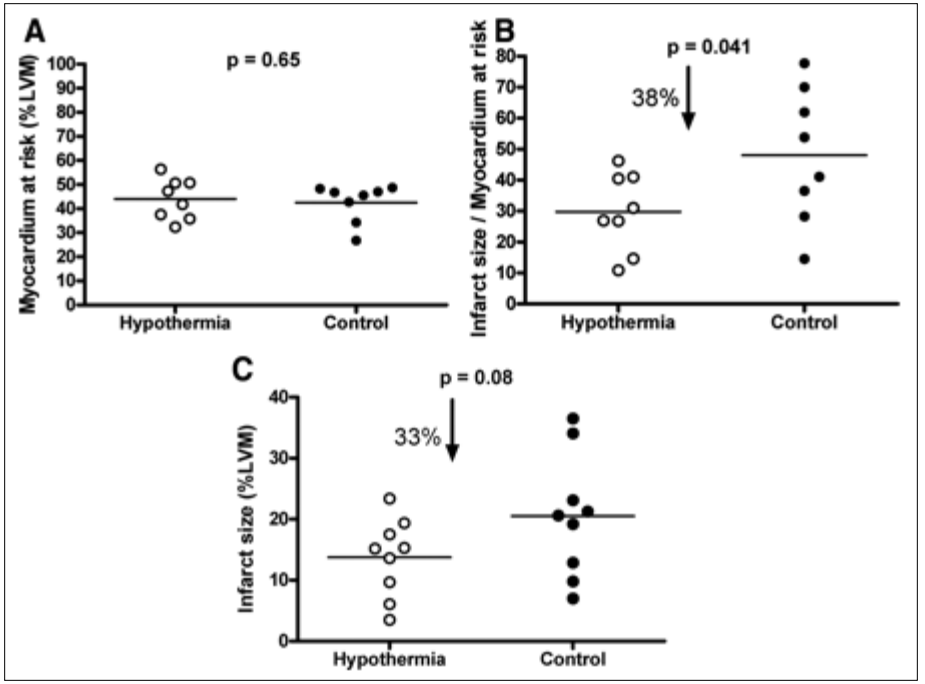
Underpowered Study: Hypothermia in acute MI – did not delay PTCA

AHA – Circulation Interventions Oct 2010

Lund – Sweden (Matthias Goetberg et all)

Pilot Study of Rapid Cooling by Cold Saline and Endovascular Cooling before Reperfusion in Patients with ST-Elevation Myocardial Infarction

Only 20 patients



Who else might we cool? - Stroke

Stefan Schwab, MD, PhD, BHB

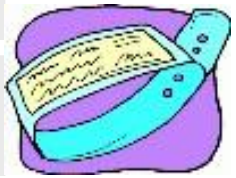


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Patients with Stroke?

"So far, the limited data of non-randomized trials in malignant stroke are not sufficient to recommend it."

- Studies show that mild hypothermia at 35C is safe in MCA stroke
- Useful to control levels of ICP re-warming resolves in rebounding of ICP
- Less lesion growths than in normal IC patients
- Short periods of hypothermia might be useful before or during thrombolysis
- Pneumonia was the only severe side effect



=> Large clinical trials with early, more rapid cooling are needed

Who else might we cool? – TBI

James S. Hutchison, MD

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Patients with Traumatic Brain Injury?



Conclusions:

- effective treatment for increased ICP
- no conclusive data on morbidity or mortality

Recommendation:

"Hypothermia therapy is an effective therapy for refractory intracranial hypertension in patients with traumatic brain injury.

… Hypothermia therapy improves outcome in adults with VF or VT induced cardiac arrest.

… Further studies are necessary in children."

Who else might we cool? - TBI – Table of Cases

Cases Table

1st Author	Design	Patient Population Sample Size (N)	Intervention	Co-interventions	Outcome	Quality
Pediatric randomized controlled trials						
Hutchison, et al. 2008(10)	RCT Blinded for evaluation	Children < 18, GCS ≤ 8, N=225	**(1) Te=32-33°C** (2) Te=36.5-37.5°C Duration 24 hrs Rewarm over 12-18 hrs		No significant difference in unfavorable outcome (PCPC 4-6). Hypothermia: Non-significant trend towards ↑ in mortality.	**Excellent**

Who else might we cool? - TBI – Table of Cases

1st Author	Design	Patient Population Sample Size (N)	Intervention	Co-interventions	Outcome	Quality
Adelson, 2005(11)	RCT	Hypo (A): Children Age<13, GCS≤8, N=48; enrolled within 6 hrs of injury. Hypo (B): Children Age<18 yrs , GCS≤8, N=27 Enrolled 6-24 hrs after injury.	(1) Tr=32-33°C (2) Tr =36.5-37.5°C Duration 48 hrs Rewarming over 12-18 hrs.		Hypo: ↓ ICP Non-significant trend to ↓ mortality and to improvement for 3 and 6 month GOS-E. Non-significant ↑ arrhythmias (but easily remedied).	Good

Who else might we cool? - TBI – Table of Cases

1st Author	Design	Patient Population Sample Size (N)	Intervention	Co-interventions	Outcome	Quality
Randomized controlled trials - mixed children and adults						
Smrcka et al, 2005(30)	RCT	Adults & children, age≤60, GCS≤8, N=72 Cooled within 15 hrs after injury	(1)Tbl =34°C (2)Tbl =normal Duration: 72hrs		Hypo: Significant improvement in outcome in patients with extra-cerebral hematomas. No significant improvement in patients primary brain lesions. Hypo. significantly ↓ ICP and ↑ CPP with both types of brain injury.	Good

Review Article

Jess Arcure BS, MSC & Eric E. Harrison, MD

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Use of Early Hypothermia in the Treatment of Traumatic Brain Injuries

- Reviewed all literature and found trends with no significant difference in outcome
- We suggest further studies with more rapid onset and achievement of hypothermia
- i.e. suggest use of Thermo-Suit, EM-Cools

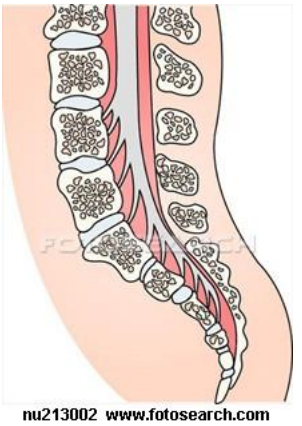
Journal of Special Operations Medicine, Summer Edition 2009

Who else might we cool? - SCI

W. Dalton Dietrich III, PhD

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Patients with Spinal Cord Injury?



- Techniques of local cooling utilizing the irrigation of the spinal cord with cold saline were shown to be feasible for acute SCI, because the practice of surgical decompression allowed exposure to the injured spinal cord segment.
- Results of the first safety (phase I clinical) trial and outcome of the use of endovascular hypothermia treatment show an **encouraging trend** for improvement in abbreviated injury scale scores. The studies of moderate hypothermia let the procedure appear **relatively safe**.
- Recent studies by Dalton Dietrich show reduction in neurological improvement when cooling spinal cord injuries
- <u>Recommendation:</u>

  => multi-center trial to evaluate larger numbers of patients.

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Kevin Everett's Recovery from Spinal Cord Injury

- paralyzed during a football game
- suffered direct compression, between the C-3 and C-4 vertebrae
- Patient was hyperthermic
- IV cold saline given in ambulance
- Hypothermia during surgery with decompression
- Started recovering motor functions
- Intravascular catheter cooling
- Continues to recover



Who else might we cool? – Other Conditions

Samual A. Tisherman, MD

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➢ Hemorrhagic shock



– Multiple laboratory studies have demonstrated that mild to moderate hypothermia (30-34°C) during and after hemorrhagic shock can **improve survival** in various models

– A prospective, randomized, controlled clinical trial is needed

➢ Exsanguination Cardiac Arrest

– Large animal studies have demonstrated the feasibility of inducing EPR for 2 hours, and possibly up to **3 hours, of circulatory arrest** with some **good outcomes** utilizing the aortic flush to achieve profound hypothermia (tympanic membrane **temperature <10°C**)

Who else might we cool? – ARDS & Sepsis

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	Control Group	Hypothermic Group
19 Patients	10 patients	9 patients
Treatment	Conventional treatment	Conventional treatment + mild hypothermia (~34°C) for an average of 70 hours
		20% reduction of heart rate, significant improvement in oxygenation and intrapulmonary shunt, increase in blood pressure
Survival	**0**	**3**

Who else might we cool? – Other Conditions

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- **Acute Liver failure**
  - Severe complications; associated with increased ICP
  - 13 of 14 transplant candidates were successfully transplanted after ~32 hours of cooling
  - Study suggests that hypothermia decrease ICP by restoring normal cerebral blood flow autoregulation and carbon dioxide reactivity.



Who else might we cool?
=> Patients with Fever in ICU?

Michael N. Diringer, MD



Patients with heat stroke

=> 35 year old Chinese merchant marine with temperature of 107°F

<u>Recommendation:</u>

"Early control of fever of a limited duration in patients with acute neurologic insult who do not have signs of infection is recommended, if it can be accomplished within minimum risk."

How should we cool? - The Use of Cold IV Fluid

Francis Kim, MD



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- Rapid infusion of 2 liters of normal saline solution in hospital lowers temp by 1.7 - 1.8 C
- Protocols should include paralytic agents and sedatives
- Infusions are well tolerated
- Problem: No randomized hospital studies
- All studies have been efficacy trials
- Study in process, in Seattle

Conclusions:

"The safety and efficacy of using cold fluid to rapidly induce mild hypothermia in resuscitated cardiac arrest patients in the pre-hospital settings have been demonstrated. The main promise of the technique is use in the pre-hospital setting by paramedics or EMS providers. Whether pre-hospital cooling using cold fluid improves survival and outcomes is yet to be determined."

How should we cool? – Endovascular Cooling

Ken Nagao, MD

Study	N	Additional Cooling Methods	Target temp. (Place of measurement)	Time interval between initiation of cooling and attainment of target temp.	Favorable neurological outcome
Cardiac arrest					
Al-Senani (13)	13	None	33°C (bladder)	210 min (IQR 80-315), 0.8°C/h (IQR 0.2 to 1.1)	38%
Kiegel (14)	26	Cold fluid	33°C (bladder)	135 ± 112 min	50%
Holzer (15)	97	Cold fluid	33°C (bladder)	158 min, 1.2°C/h (IQR 0.7 to 1.5)	53%
Pichon (16)	40	None	33°C (bladder)	187 ± 119 min	33%
Hoedemaeckers (17)	5	None	33°C (rectum)	1.45 ± 0.42°C/h	
Intracranial disease or brain injury					
Georgiadis (18)	6	None	33°C (bladder)	180 ± 60 min, 1.4 ± 0.6°C/h	
Keller (19)	10	None	33-34°C (bladder)	190 ± 110 min	
Sahuguillo (20)	24	None	32.5°C (bladder)	3.0 h (range 1.0 to 16 h)	
Acute myocardial infarction					
Dixon (21)	21	None	33°C (esophagus)	34.7 ± 0.9°C at the time of first PCI	
Kandzari (22)	18	None	33°C (bladder)	35.4°C (IQR 35.2 to 35.8) at the time of first PCI	

How should we cool? – Surface Cooling Methods

Kjetil Sunde, MD, PhD

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METHOD	COOLING RATE
Extensive application of **ice packs**/cold wet blankets to the head, neck, and torso	0.9°C per hour
Cold Air (TheraCool, Kinetic Concepts, Wareham, UK)	0.3°C per hour
Combination of **alcohol and cooling cover** filled with water	0.25°C per hour
Large, **adhesive cooling pads** applied around trunk and limbs, combined with an automatic **feedback control system** (Artic Sun, Medi-Therm)	1.2°C per hour
Total body suits filled with **water** circulating system (Blanketrol, Maxi-Therm Cooling System, Thermowrap)	1.3°C per hour

How should we cool? – Surface Cooling Methods

Kjetil Sunde, MD, PhD

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METHOD	COOLING RATE
Cold Air total body tent (recirculation of air with automatic feedback control) (Delta-Therm)	1.25°C per hour
Complete patient immersion in a specially designed cold water-filled bed (Thermosuit System)	**Cools to 33°C in 20 minutes**
Pre-cooled mattress system (latex wrapping incorporating a mixture of water/graphite), glued to the skin (Emcoolspad)	3.3°C per hour
Cooling helmet (Frigicap), faster head cooling, but very slow total body cooling	0.5°C per hour

Conclusion:

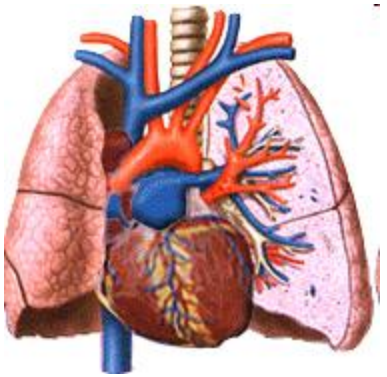
"Surface cooling is feasible, safe and has various degrees of efficacy depending on the system used."

What Temperature Should We Monitor?

Fritz R. Sterz, MD

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Invasive Techniques



- **Pulmonary** => most accurate & gold standard
- **Brain** => not practical
- **Jugular bulb** => reasonable approximation
- **Nasopharynx** => unreliable
- **Tracheal** => via temperature tube: accurate
- **Esophageal** => good alternative to pulmonary artery catheter
- **Urinary bladder** => unreliable, unpredictable
- **Rectal** => unreliable
- **Blood** =>little data available

What Temperature Should We Monitor?

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Noninvasive Techniques

- **Temporal** artery => unreliable
- **Tympanic** => unreliable
- **Oral** => rarely used in critical ill patients
- **Skin** => unreliable



Conclusion:

"Temperature monitoring in critical care provides important data required to guide delivery of care, but measurement of core temperature requires the placement of pulmonary artery catheter."

BUT…

The esophageal temperature monitoring is a good alternative to pulmonary artery catheter. The esophageal probe can be easily placed though an endotracheal tube placed in the esophagus.

When to Cool and for How Long?

Nicolas Deye, MD

- Multiple animal studies documented the importance of initiating cooling as soon as possible.
- Although human data support cooling at 32-34°C, the optimal temperature level has not yet been determined.
- No randomized human studies have examined the outcomes of earliest possible therapeutic hypothermia.
- According to guidelines, multiple external or internal cooling techniques can be used to initiate cooling within minutes to hours after CA.

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Birger Wolff and others; "Early Achievement of TH and the neurologic outcome after CA"; published in the **International Journal of Cardiology (2008)**

Conclusion:

"According to our data, early achievement of MTH is determinant of the final neurologic outcome. Thus, measures to speed up the initiation of cooling therapy after CA appear warranted."

Leah A. Swanson and others; "Cool It: TH for CA in Patients With ST-Elevation Myocardial Infarction and Unique Benefits With Combined Treatment"; published in the **Journal of the American College of Cardiology, March 10, 2009**

Results:

"For each hour TH was delayed, the relative risk of death increased by 20%."

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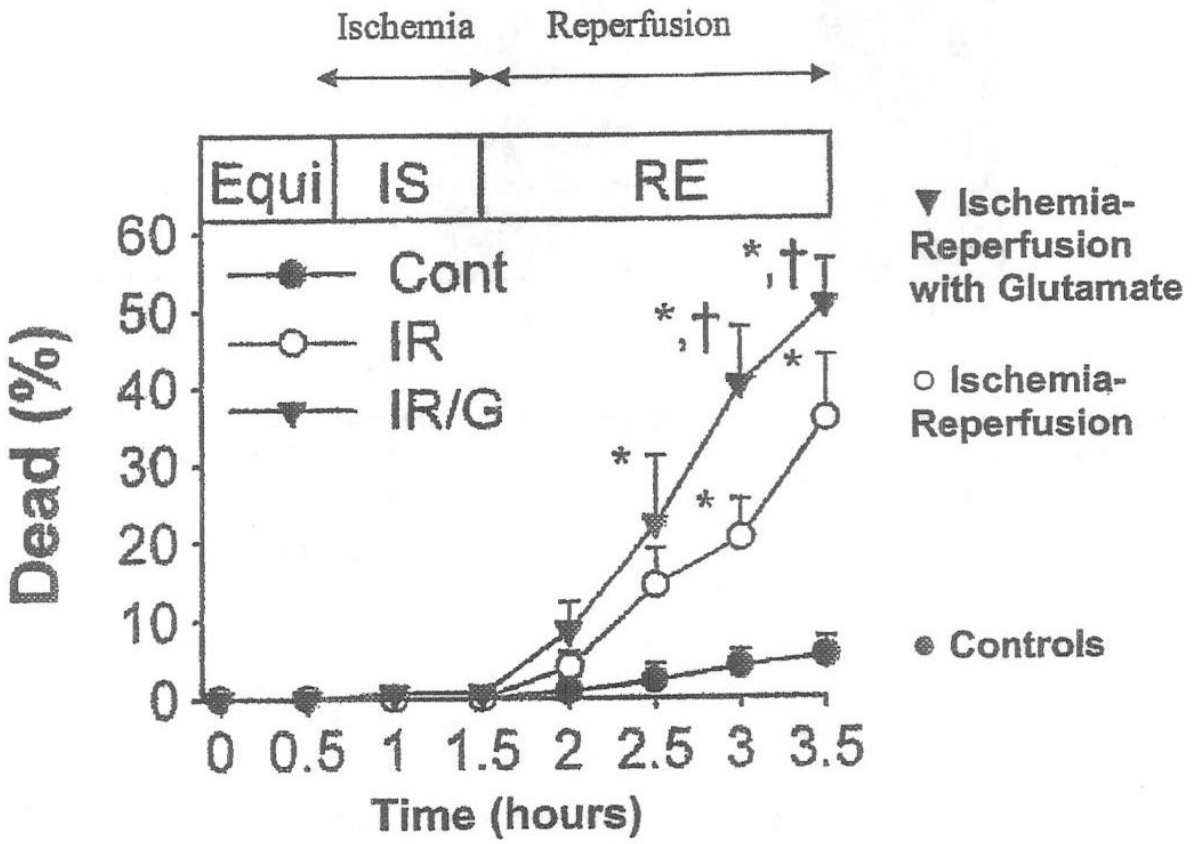
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William J. Ohley, PhD

Figure 1: Neuronal Cell Death vs. Time (1-hour ischemia / reperfusion model)



University of Rhode Island, June 23, 2008

Some frogs freeze solid



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The Eastern wood frog is found even north of the Arctic Circle, where they not only survive freezing but do so every winter

- Freezes over several hours
- Uses glucose and urea as antifreeze
- Stops breathing, heart stops
- Stays like that for three months
- Temperature -5°C or 23°F
- 67% of frog is frozen
- Blood sugar rises 100-times normal

April Holladay, science correspondent, July 11, 2001
http://www.wonderquest.com/FrogsPolar.htm

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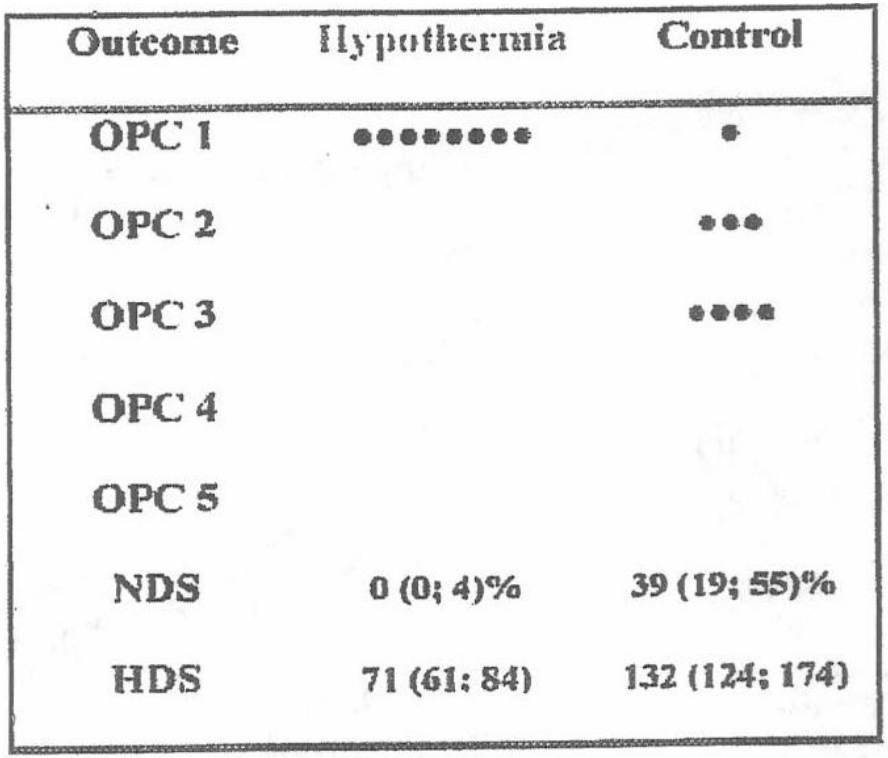
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Figure 2: Outcomes in Swine Following 10 Minutes Cardiac Arrest and 8 Minutes CPR



Outcome	Hypothermia	Control
OPC 1	●●●●●●●●	●
OPC 2		●●●
OPC 3		●●●●
OPC 4		
OPC 5		
NDS	0 (0; 4)%	39 (19; 55)%
HDS	71 (61; 84)	132 (124; 174)

*Outcomes in terms of final overall performance categories (*OPC 1-5*) on day 9. Each *dot* represents one swine. Neurologic deficit scores (*NDS*) and histologic damage scores (*HDS*) are given as median (interquartile range). *Hypothermia*, hypothermia group (n = 8); *Control*, control group (n = 8); *ROSC*, restoration of spontaneous circulation. OPC at 9 days, $p = .002$; NDS at 9 days, $p = .001$; HDS at 9 days, $p < .001$.

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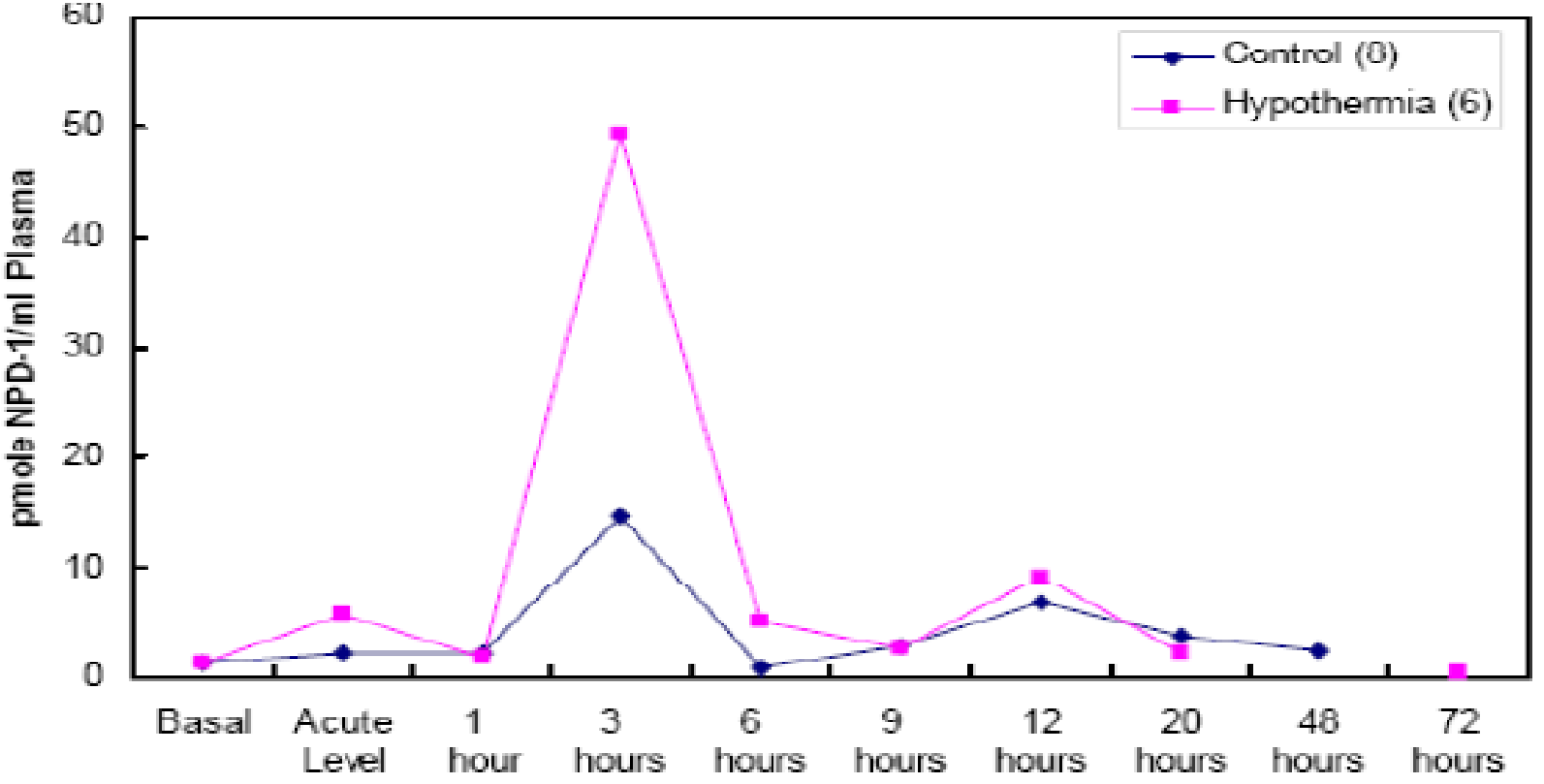
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Figure 3: Augmentation of Neuroprotectin D-1 following CA and resuscitation in the swine model. The primary release of NPD-1 was three hours after resuscitation. Rapid hypothermia therapy delivered with the TSS increased NPD-1 release by a factor of five



Possible Complications of Hypothermia

Larry M. Gentilello, MD

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Coagulation & Infection

- Increase incidence of Pneumonia
- Reduced platelet counts
- May side-track medical personal from their main ABCs of resuscitation
- Overshoot in either direction
- May delay other critical procedures



Possible Complications of Hypothermia

Samual M. Poloyac, PharmD, PhD

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Implications on Drug Metabolism

- A study performed in critically injured children found that moderate hypothermia decreases the metabolism of phenobarbital.
- Target remifentalin concentrations may be obtained by decreasing the infusion rate ~30% per 5°C decrease in temperature
- Currently no dosing guidelines exist for critically ill patients receiving >12 hours of mild to moderate hypothermia.
- There is strong evidence that the metabolism of several neuromuscular blockers is altered during TH
- Pancuronium: there is no change in receptor affinity or sensitivity with hypothermia



Recommendation:

Drug concentration monitoring.

How to Re-Warm – Clinical Considerations

Patrick M. Kochanek, MD; Ericka Fink, MD; Michael Bell, MD

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- Do NOT overshoot!
- Most studies before 2000 used a re-warming rate of 1°C per hour, while more recent studies have generally used a rate of 1°C every 4 hours.



Table: Randomized Controlled Trials of Mild Hypothermia Across Central Nervous System Injury – Details of Re-Warming

Author	Condition	Age	Result	Re-warming rate	Other remarks
(1) Shiozake et al 1993	TBI	Adult	Beneficial	"Slowly"	Re-cooled if ICP rebounded; refractory rebound ICP in one patient, sustained hypovolemic shock in another during re-warming
(2) Marion et al 1997	TBI	Adult	Beneficial	No greater than 1°C per hour	Some rebound in ICP and reduction in CPP during, but CPP > 70 mm Hg

How to Re-Warm

Author	Condition	Age	Result	Re-warming rate	Other remarks
(3) Shiozake et al 1999	TBI without intracranial hypertension	Adult	No benefit	1°C per day	No comment on re-warming complications
(4) Jiang et al 2000	TBI	Adult	Beneficial	No greater than 1°C per hour	No comment on re-warming complications
(5) Clifton et al 2001	TBI	Adult	No benefit	1°C every 4 hours	Therapy intensity level (TIL) greater in hypothermia group during re-warming; greater duration of vasopressor therapy in hypothermia group.
(6) Zhi et al 2003	TBI	Adult	Beneficial	1°C every 4 hours	No comment on re-warming complications
(7) Jiang et al 2006	TBI	Adult	Beneficial	No greater than 1°C per hour	Comparison of 2 days vs 5 days of cooling—ICP rebounded during re-warming in 2 day group only

How to Re-Warm

Author	Condition	Age	Result	Re-warming rate	Other remarks
(8) Lavinio et al 2007	TBI	Adult	Not an outcome study	1°C every 4 hours	Temperature >37°C in 70.1% of patients during re-warming; when it occurred, it was associated with disturbed blood flow auto-regulation
(9) Biswas et al 2002	TBI	Pediatric	Beneficial	No greater than 1°C per hour	Reduced CPP with re-warming
(10) Adelson et al 2005	TBI	Pediatric	Not an outcome study	1°C every 3-4 hours	Rebound increase in ICP with re-warming
(11) Hutchison 2008	TBI	Pediatric	No benefit; trend towards increased mortality	1°C every 4 hours	Hypotension, reduced CPP, and increased pressor requirement with re-warming

How to Re-Warm

Author	Condition	Age	Result	Re-warming rate	Other remarks
(12) Bernard et al, 2002	Cardiac arrest	Adult	Benefit	~1°C per 1.4 hours	No adverse hemodynamic effects observed during re-warming despite careful monitoring of hemodynamic effects including cardiac output
(13) HACA trial 2002	Cardiac arrest	Adult	Benefit	Passive re-warming ~1.0°C per 2 hours	No comment on re-warming complications
(14) Busch et al 2006	Cardiac arrest	Adult	Benefit	Passive re-warming ~1.0 °C per 2.5 hours	Occasional "too quick" re-warming with rebound hyperthermia
(15) Arrich et al 2007	Cardiac arrest	Adult	Not an outcome study	~1.0 °C per 3.3 hours	Re-warming time ~8.5 hours with endovascular device while ~10 hours with other approaches; no comment on re-warming complications with either approach

How to Re-Warm

Author	Condition	Age	Result	Re-warming rate	Other remarks
(16) Pichon et al 2007	Cardiac Arrest	Adult	Not an outcome study	~1.0 °C per 3.3 hours	Post re-warming rebound hyperthermia observed in 74% of patients using endovascular approach
(17) Steiner et al 2001	Stroke	Adult	Benefit	"Slow, controlled re-warming" at ~1°C per ~10-40 hours	Herniation in two patients during re-warming
(18) Georgiadis et al 2002	Stroke	Adult	Less efficacious than craniectomy	~1°C per 8.0 hours	A fixed re-warming time and rate were not feasible because of a variety of ICP behaviors; 50 episodes of raised ICP during re-warming

How to Re-Warm

Author	Condition	Age	Result	Re-warming rate	Other remarks
(19) Shankaran et al 2005	Perinatal asphyxia	Neonate	Benefit	~1.0°C per 2 hours	No comment on re-warming complications
(20) Gebauer et al 2006	Perinatal asphyxia	Neonate	Not an outcome study	Passive re-warming	No hypotension observed during re-warming and none of the infants required additional pressors or volume during re-warming

TBI, traumatic brain injury; ICP, intracranial pressure; CPP, cerebral perfusion pressure.

Arctic Ground Squirrel

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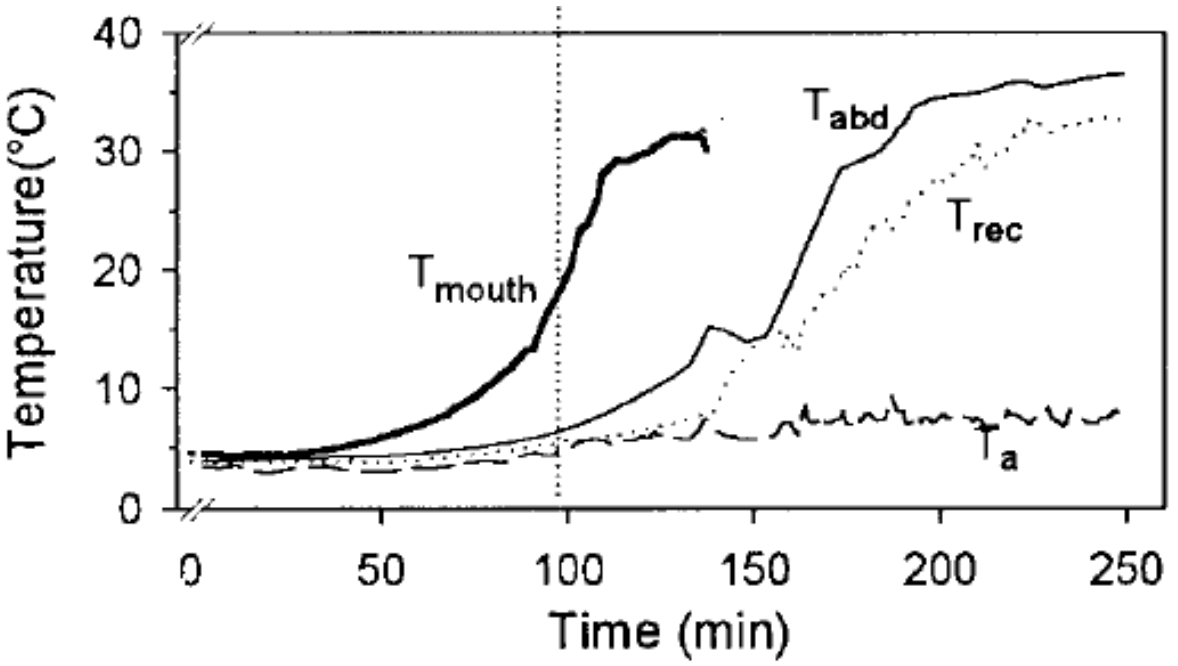
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- body temperature of the arctic ground squirrel drops from 98.6°F to 26.4°F - that's below the freezing point of water and is the lowest known body temperature of any living mammal
- have developed a unique mechanism that allows their body fluids to become supercooled - to fall below the freezing point without crystallizing into ice and damaging cell tissue.





ADF&G Wildlife Conservation
www.wildlife.alaska.gov

Living Will

I,_____, am of sound mind, and I voluntarily make this declaration.

If I become terminally ill or permanently unconscious as determined by my doctor and at least one other doctor, and if I am unable to participate in decisions regarding my medical care, I intend this declaration to be honored as the expression of my legal right to consent to or refuse medical treatment.

My desires concerning medical treatment are …

It is my desire that if in the event of cardiac arrest and resuscitation, and I am unconscious, begin therapeutic hypothermia for 24 hours according to Advanced Hypothermic Life Support Guidelines and after re-warming, reassess my chance of recovery after 72 hours have elapsed and if at that time it appears that I will be in a vegetative state, then do not proceed further with heroic measures.

My family, the medical facility, and any doctors, nurses and other medical personnel involved in my care shall have no civil or criminal liability for following my wishes as expressed in this declaration.

Quiz

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1. What is the most comparable site to the PA for measuring core body temperature?

a) esophageal

b) bladder

c) rectal

d) tympanic

2. When body temperature is reduced below 30°C, substantial risk emerges for cardiac arrhythmias and respiratory arrest as well as VF and AF

a) T

b) F

Quiz

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3. A frequently cited threshold for shivering is 33°C.

a) T

b) F

Correct answer: 35.5°C

4. EKG abnormality(-ies) associated with temperature in the range of 30 - 35°C are

a) bradycardias

b) prolonged PR interval

c) prolonged QRS

d) prolonged QT

e) all of the above

f) none of the above

Quiz

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5. Patients undergoing cerebral aneurysm clipping had no greater operative blood loss at 32.5-33.5°C than those maintained at 36-37°C.

a) T

b) F

6. $PaCO_2$ values obtained from the blood gas machine directly reflect PCO_2 during hypothermia.

a) T

b) F

Correct answer: Use alpha-stat

7. Evidence is largely unsupportive of mild hypothermia effects on neuroinflammation.

a) T

b) F

Quiz

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8. The beneficial effects of therapeutic hypothermia on ICP have been repeatedly shown in clinical TBI and CVA.

a) T

b) F

9. The two major randomized studies of hypothermic treatment of VF cardiac arrest have shown

a) 10-14% better outcomes

b) 15-24% better outcomes

c) 25-34% better outcomes

d) 35-44% better outcomes

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10. The quality of evidence supporting therapeutic hypothermia in non VF cardiac arrest is very high.

a) T

b) F

11. Therapeutic hypothermia significantly reduces disability in perinatal encephalopathy.

a) T

b) F

12. The limited data of non-randomized trials in malignant stroke are not sufficient to recommend therapeutic hypothermia.

a) T

b) F

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13. Large clinical randomized studies have conclusively demonstrated that therapeutic hypothermia before PTCA limits all types of myocardial infarct size.

a) T

b) F

Only with AWMI

14. Shivering stops at

a) 35°C

b) 34°C

c) 36°C

15. Which should you use to adjust ventilation?

a) alpha-stat

b) PH-stat which adjusts for temperature

Quiz

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16. Overcooling is detrimental in cardiac arrest patients.

a) T

b) F

17. Hyperthermic overshoot is not deleterious in TBI and CVA patients.

a) T

b) F **Correct answer: causes rebound ICP**

18. Which of the following re-warming strategies are recommended?

a) re-warming at a rate no faster than 1°C per 2 hours in CA

b) re-warming at a rate no faster than 1°C per 4 hours in TBI

c) re-warming at a rate even slower in severe CVA

d) not A, B, and C

e) all A, B, and C

Quiz

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19. There are no significant coagulation or clotting problems at 34° or 33°C in Trauma patients in the therapeutic hypothermia literature.

a) T

b) F

20. Cooling during CPR reduces the threshold for ventricular defibrillation.

a) T

b) F

21. 2L IV 4°C Saline does the following

a) requires pancuronium

b) requires sedation

c) lowers temperature (core) up to 1.7°C

d) all of the above

e) none of the above

Quiz

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22. There have been no prospective randomized clinical trails of therapeutic controlled hypothermia in Trauma patients (TBI) with hemorrhagic shock.

a) T
b) F

23. There are adequate studies of hypothermic use in acute spinal cord injury to support systemic therapeutic hypothermia as an option.

a) T
b) F

24. Urinary bladder probe temperature is

a) more reliable than rectal
b) accuracy is ± 0.4
c) 2-4°C lower than brain temp
d) all of the above
e) none of the above

Quiz

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25. Rectal temperature probe

a) is unreliable
b) may have variable position
c) can perforate
d) is equal to PA
e) all of the above
f) A,B, and C only
g) none of the above

26. PA temperature probe or esophageal probe

a) is the gold standard
b) is best measured in the distal ¼ of the esophagus
c) frequently inserted in an esophageal ET tube to prevent coiling
d) all of the above
e) none of the above

Quiz

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27. There is no reduction in cytochrome P450 drug metabolism during hypothermia.

a) T

b) F

28. Hypertension appears to be a very common complication of re-warming in children with TBI.

a) T

b) F

Correct answer: hypotension

29. Hypothermia has been found to be therapeutic in all but one of these:

a) VF

b) hyperthermic CVA

c) perinatal asphyxia

d) TBI

e) OHS

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30. There are specific drug dosage adjustments available for each °C of hypothermia.

a) T

b) F

31. Pancuronuim does not have a receptor effect in humans.

a) T

b) F

32. Serum neuron-specific enolase (NSE) is a biochemical marker that can be measured to reflect brain damage.

a) T

b) F

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33. A landmark paper by Woolf .et.al. supports cooling as soon as possible and quickest to target temperature.

a) T

b) F

34. Cooling method rate of cooling (°C/hr)

a) ice packs to groin **0.3°C / hr**

b) cool air **0.3°C / hr**

c) alcohol + cover **0.25°C / hr**

d) water circulating blanket **0.3°C / hr**

e) Medevance adhesive pads **1 – 1.2°C / hr**

f) total body suit MTRF, Akina **0.9°C / hr**

g) Total Body Blanketrol Cincinnati Subzero **1.3°C / hr**

h) KCl cold air total body tent **0.7°C / hr**

i) Complete patient immersion ThermoSuit **3°C / hr**

j) Emcools Pre-refrigerated graphite/H2O cube pads with adhesive **3.3°C / hr**

k) Cap Fricap **0.5°C / hr**

l) IV Saline 2L over 30 minutes 4°C **1.7°C / hr**

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Questions?

Upcoming Events about Therapeutic Hypothermia

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Upcoming Events:



4th International Hypothermic Symposium

Shanghai in 2011

Thank you very much

for your time!