Therapeutic Hypothermia for Cardiac Arrest:
What are we waiting for?

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Objectives:

- Review Initial Trials
- Pathophysiology / Side Effects
- Cooling Methods
- Barriers to Implementation
- Furthur Studies
- Future Directions

Some Stats…

- US: 240,000 out-of hosp CA/yr
- 20-38% VF/VT
- Europe: 375,000 CA/yr
- In-tact Neurologic survival rate = 1.4%!!!

Cobb LA, FahrenhruchCE, Olsufka M, Copass MK. Changing incidence of out-of- hospital ventricular fibrillation, 1980-200. JAMA 2002;288:3008-13.

Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med 2002;346(8):549-56.

Froehler MT, Geocadin RG. Hypothermia for neuroprotection after cardiac arrest: Mechanisms, clinical trials and patient care. J of the Neurological Sciences 2007;261;118-126.

First rhythm and survival

	First Rhythm	Survival	Discharge
Asystole	36%	35%	10%
PEA	30%	39%	10%
VF/VT	25%	VF 34% VT 35%	34% 35%

Peberdy MA, Kaye w, Ornato JP, Larkin G, and the NRCPR Investigators. Cardiopulmonary resuscitation of adults in the hospital: A report of 14 720 cardiac arrests from the National Registry of Cardiopulmonary Resuscitation. Resuscitation 2003;58:297-308.

UMMS Data

	2002	2003	NRCPR
Reported Arrests	191	182	
Code team activated	35%	37%	
Expired	59%	58%	
ROSC	37%	37%	**44%**
Discharged	**17%**	**18%**	**17%**
Discharged (from ROSC)	46%	48%	
Duration of arrest	25.6 min	24.6 min	

Mild Therapeutic Hypothermia to Improve the Neurologic Outcome after Cardiac Arrest

Out of Hospital arrests (10 in hosp)

VT or pulseless VT

- 275 patients with ROSC
  - 137 in hypothermia group
  - 138 in normothermia group

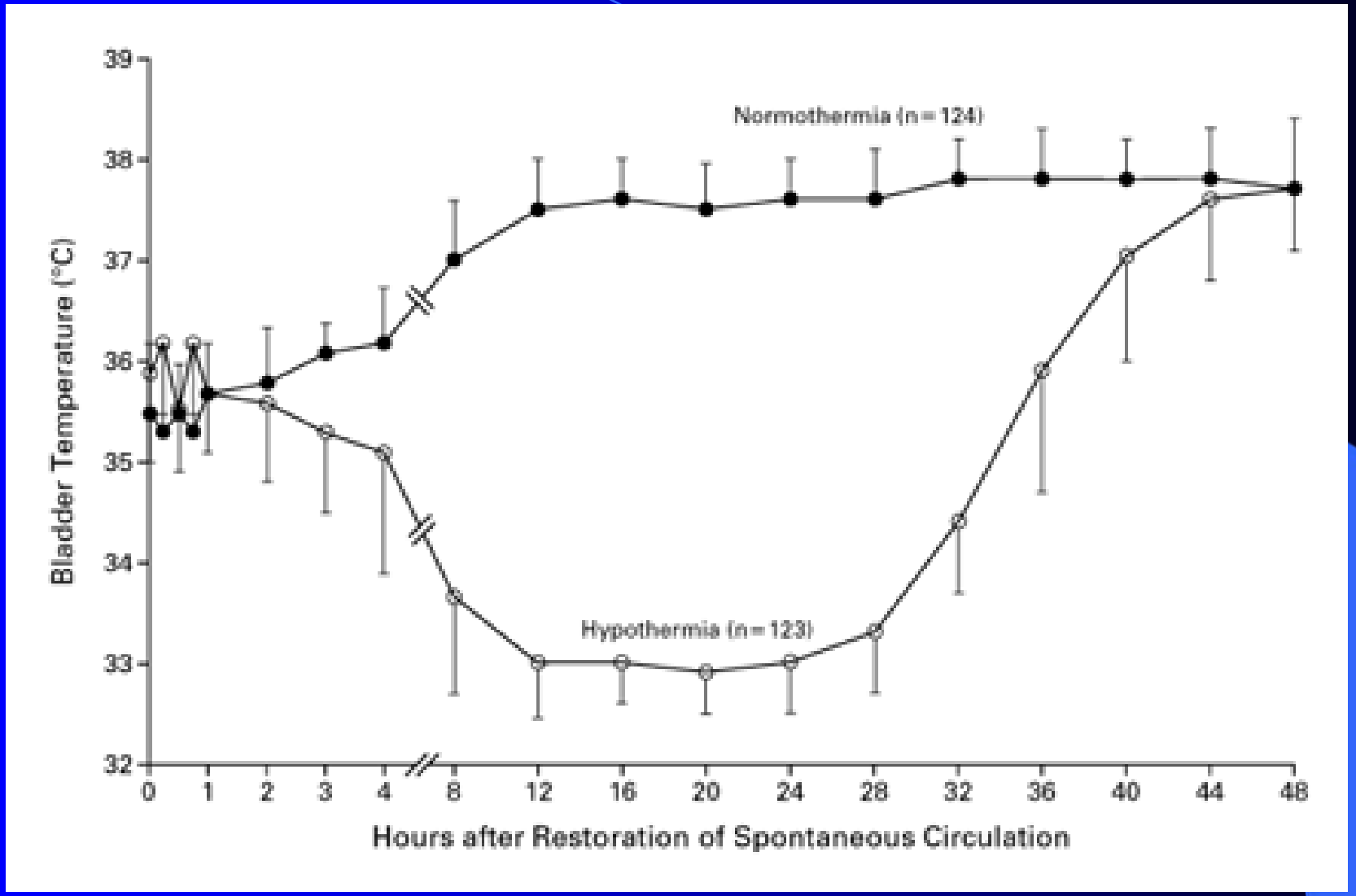
Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med 2002;346(8):549-56.

How did they that!?!?

- Goal of 32-34° C
- Temp sensing foley
- Cold air Mattress
- Ice Packs PRN (93 of 132)
- Target Temp in 4 hours
- Neuromuscular blockade
- Passively re-warmed over 8 hours

Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med 2002;346(8):549-56.

Figure 1. Bladder Temperature in the Normothermia and Hypothermia Groups.



The Hypothermia after Cardiac Arrest Study Group. N Engl J Med 2002;346:549-556

TABLE 2. NEUROLOGIC OUTCOME AND MORTALITY AT SIX MONTHS.

OUTCOME	NORMOTHERMIA	HYPOTHERMIA	RISK RATIO (95% CI)*	P VALUE†
	no./total no. (%)			
Favorable neurologic outcome‡	54/137 (39)	75/136 (55)	1.40 (1.08–1.81)	0.009
Death	76/138 (55)	56/137 (41)	0.74 (0.58–0.95)	0.02

- Neurologic Outcome NNT = 6
- Mortality Outcome NNT = 7

Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med 2002;346(8):549-56.

Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia

1996-1999 4 ED in Melbourne

77 patients

VF, ROSC with persistent coma

Excluded men<18, women<50

43 in Hypothermia, 34 in Normothermia

Bernard S. Treatment of Comatose Survivors of Out-of-Hospital Cardiac Arrest with Induced Hypothermia. NEJM. Vol 346 No8. Feb 21, 2002.

How did they do it !?!?!

- Goal of 33° C in 2 hr
- Ice packs
- Temp by TM or foley until Swan placed
- Maintained for 12 hours
- *Active* rewarming at 18 hrs

Bernard S. Treatment of Comatose Survivors of Out-of-Hospital Cardiac Arrest with Induced Hypothermia. NEJM. Vol 346 No8. Feb 21, 2002.

Results

- Neurolgic:
  - 21/43 (49%) Good = Home or Rehab
  - 9/34 (26%) BAD = USH or Dead
  - P= 0.046

- 30 day mortality
  - Hypothermia 51%
  - Normothermia 68%
  - P= 0.145 NOT SIGNIFICANT

Bernard S. Treatment of Comatose Survivors of Out-of-Hospital Cardiac Arrest with Induced Hypothermia. NEJM. Vol 346 No8. Feb 21, 2002.

Advanced Life Support Task Force of the International Liason Committee on Resuscitation (ILCOR)

- Oct ’02

1. Unconscious adult patients with spontaneous circulation after out-of-hospital cardiac arrest should be cooled to 32-34° C for 12-24 hrs when the initial rhythm was VF

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

Nolan J.P. et al. Therapeutic hypothermia after cardiac arrest. An advisory statement by the Advanced Life support Task Force of the International Liaison Committee on Resuscitation. *Resuscitation* 57 (2003) 231-235.

Protecting the Brain

- 1° C = 6-7% decrease in Cerebral Metabolic rate
- Chemotaxis
- Inflammation
- Free radicals
- Blood-brain barrier
- Edema

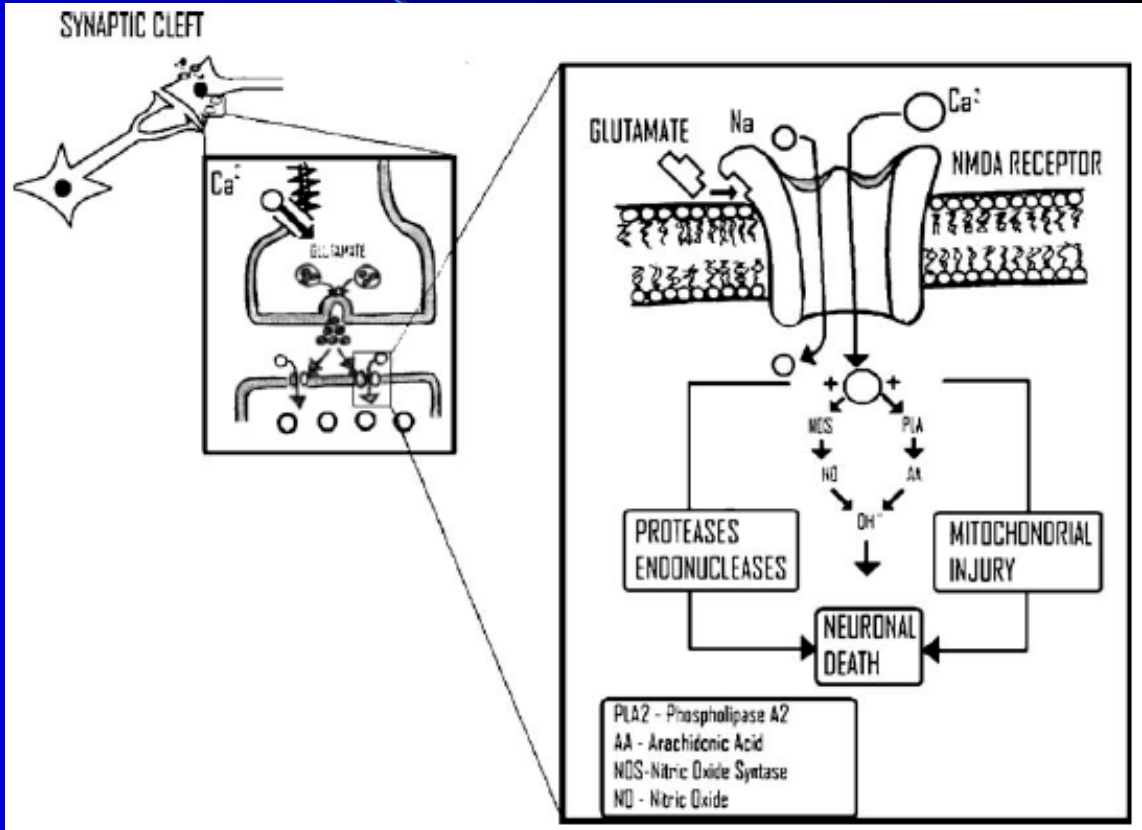
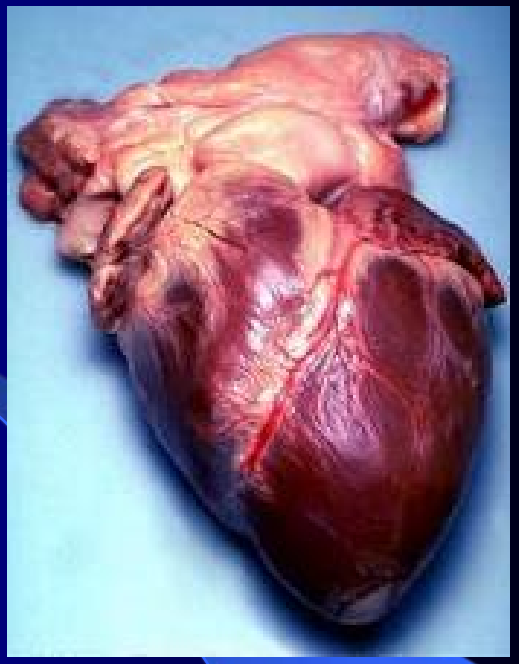


Figure 1 Pathophysiology of brain injury at the cellular level.

Froehler MT, Geocadin RG. Hypothermia for neuroprotection after cardiac arrest: Mechanisms, clinical trials and patient care. J of the Neurological Sciences 2007;261;118-126.

Side Effects

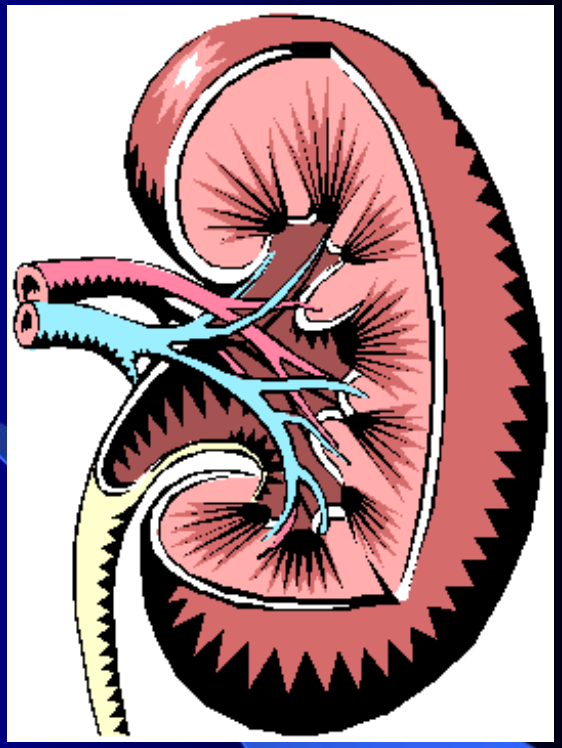


- **Cardiovascular**
  - **Increased SVR**
  - **Decreased HR**
  - **Arrhythmia not statistically sig**
- **Respiratory**
  - **Adjust ventilator for decreased Metabolic Rate**
  - **Solubility of ABGs**

Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. N Engl J Med 2002;346(8):557-63.

Bernard SA, Buist M. Induced hypothermia in critical care medicine: A review. Crit Care Med 2003;31(7):2041-2051.

- Renal/Electrolytes
  - Diuresis
  - K Shifts
  - PO4 Shifts
- Heme
  - Platelet dysfunction
  - Coagulopathy?
  - No bleeding on ASA, Plavix, Abciximab
- Endocrine
  - Hyperglycemia



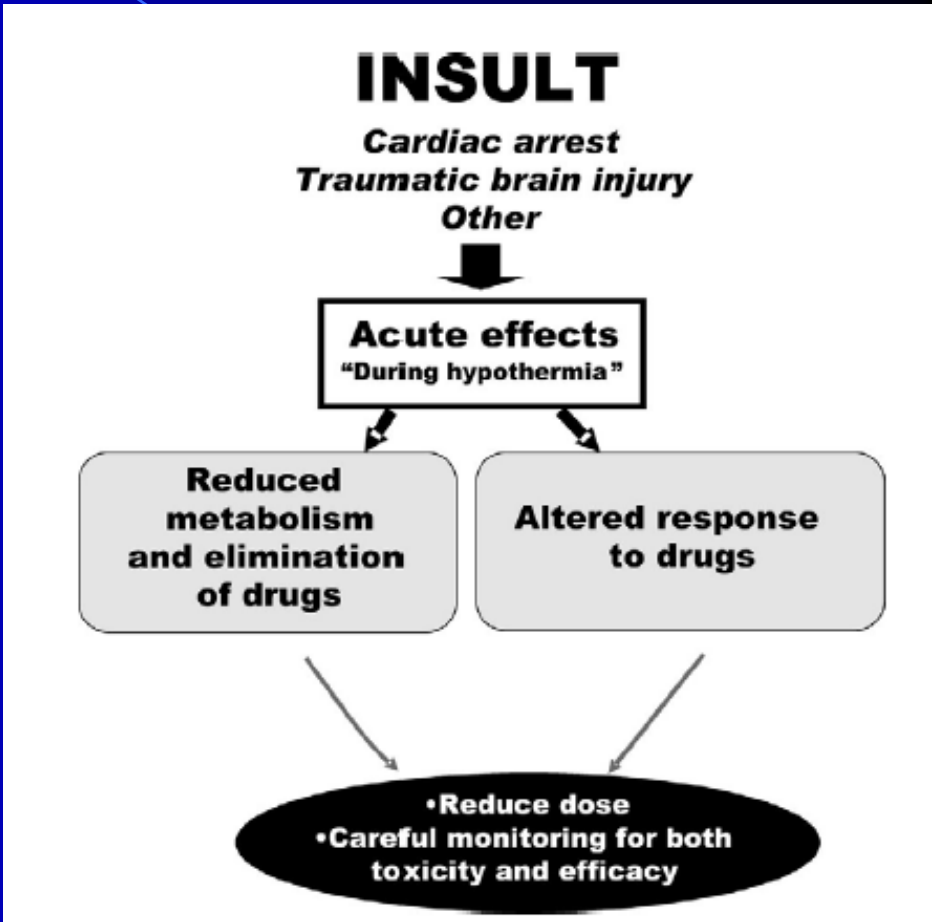
Hovdenes J, Laake JH, Aaberge L, et al. Therapeutic hypothermia after out-of-hospital cardiac arrest: experiences with patients treated with percutaneous coronary intervention and cardiogenic shock. Acta Anaesthesiol Scand 2007;51:137-142.

Bernard SA, Buist M. Induced hypothermia in critical care medicine: A review. Crit Care Med 2003;31(7):2041-2051.

Drug Metabolism:

- Cytochrome P450
- Decreased 7-22% per deg C
  - Steroids
  - Neuromuscular blockers
  - Antibiotics

  - So… decrease doses if necessary



Tortorici MA, Kochanek PM, Poloyac SM. Effects of hypothermia on drug disposition, metabolism, and response: A focus on hypothermia-mediated alterations on the cytochrome P450 enzyme system. Crit.Care Med 2007;35(9):2196-2204.

But, does it matter???

Table 4 Side effects of mild therapeutic hypothermia after cardiac arrest

Side effect	[No. of ICUs/MTH-users]	(%)	Therapeutic consequences (%)
Infection	60/93	64.5	21.5
Hypotension	58/93	62.4	22.6
Bleeding	45/93	48.4	10.8
Electrolyte disarrangements	8/93	8.6	62.5
Arrhythmias	6/93	6.5	33.3
Changes in glucose levels	2/93	2.1	50.0

Results of a nationwide survey on the use of mild therapeutic hypothermia (MTH) after cardiac arrest. Side effects and therapeutic relevance are listed as reported by the MTH-users.

Wolfrum S, Radke PW, Pischon T. Mild therapeutic hypothermia after cardiac arrest – A nationwide survey on the implementation of the ILCOR guidelines in German intensive care units. Resuscitation 2007;72:207-213.

Cooling Methods

Non-Invasive

- Ice Packs
  - 0.9°C/hr, goal in 2hr
- Cool Air Mattress
  - Unsuccessful in HACA
  - 93/137 ice added
- Cooling Caps
- Hydrogel Pads

Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. N Engl J Med 2002;346(8):557-63.

Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med 2002;346(8):549-56.

Cooling Cap

- 180min to reach 34°C
- More success with infants
- Body Surface Area

Alzaga AG, Cerdan M, Varon J. Therapeutic hypothermia. Resuscitation 2006;70:369-380.

Hydrogel Pads

- 1.2°C/hr
- 137 min to target
- Skin examined Q8
- No adverse effects

Haugk M, Sterz F, Grassberger M et al. Feasibility and efficacy of a new non-invasive surface cooling device in post-resuscitation intensive care medicine. Resuscitation 2007 75:76-81.

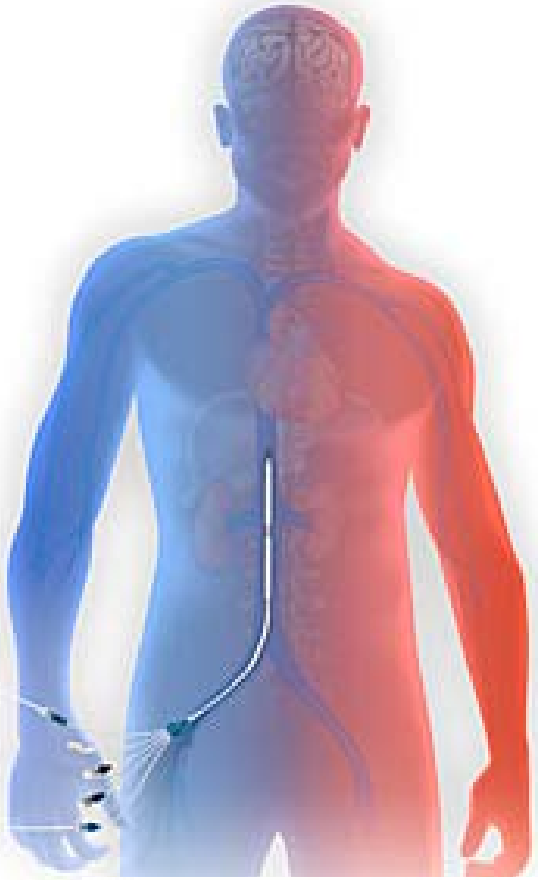
Invasive

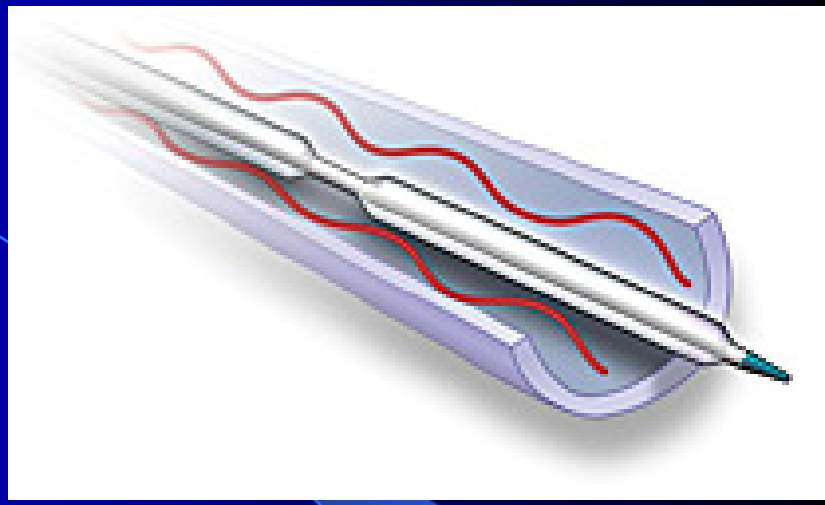
- 4°C IV fluids
- 1.2-1.6°C
- Unsuccessful as Maintenance Therapy

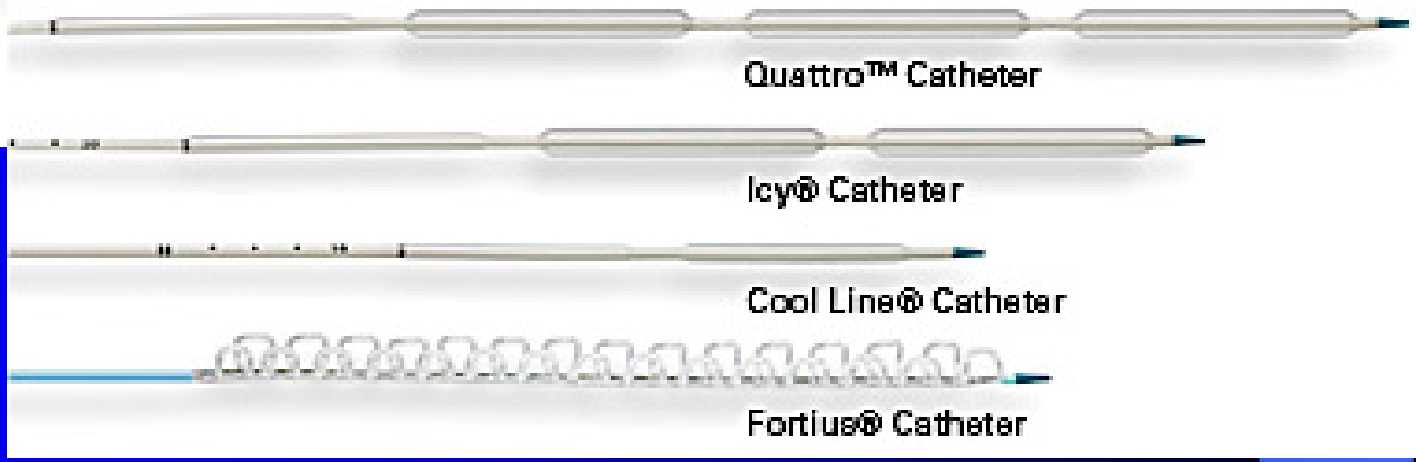
- Endovascular Cooling Catheter
- 0.8°C/hour
- 3hr 39min to goal!
- Increased Arrhythmia
  - 7.2% vs 0.9%, p=0.01
- Femoral Line

Al-Senani FM, GraffaginoC, Grotta JC, et al. A prospective, multicenter pilot study to evaluate the feasibility and safety of using the CoolGard System and Icy catheter following cardiac arrest. Resuscitation 2004;62(2):143-50.

Arrich J, The European Resuscitation Council Hypothermia After Cardiac Arrest Registry Study Group. Clinical application of mild therapeutic hypothermia after cardiac arrest. Crit Care Med 2007;35(4):1041-1047.





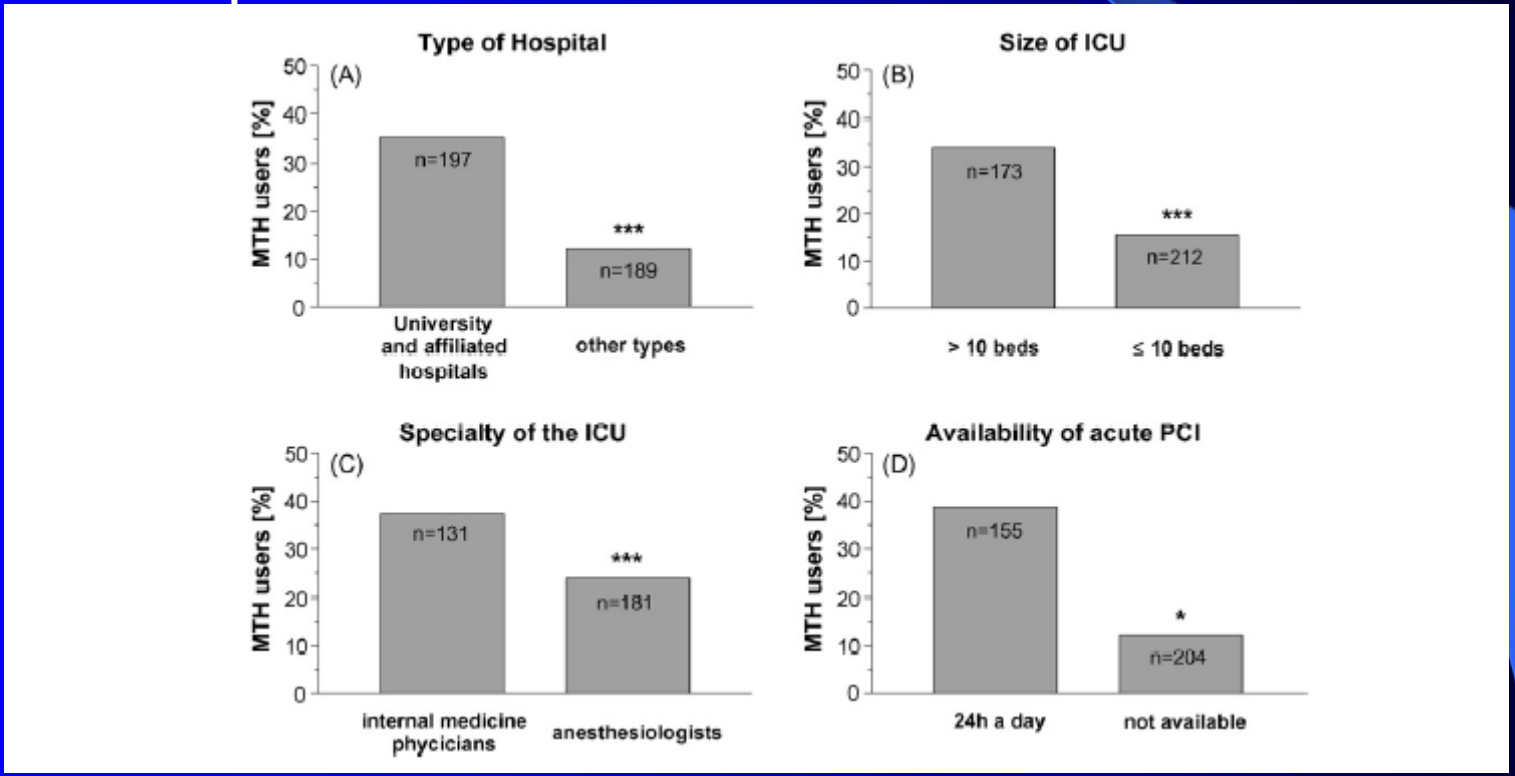

Quattro™ Catheter
Icy® Catheter
Cool Line® Catheter
Fortius® Catheter

Lets Review…

- TH improves Neurologic Outcome and Mortality in VT/pulseless VT
- Physiologic Concerns
- Noninvasive and Invasive Cooling Methods
  - Combo of cold fluids + surface cooling

Utilization of TH: Germany

- 2007: 23.5% of German ICUs
- 7.5% prior to ’03, 51% started in ‘05
- >1650 patients treated so far



Wolfrum S, Radke PW, Pischon T. Mild therapeutic hypothermia after cardiac arrest – A nationwide survey on the implementation of the ILCOR guidelines in German intensive care units. Resuscitation 2007;72:207-213

Utilization of TH: Finland

- TH in 19/20 ICUs
- 407/1555 SCA pts got TH
- 20 pts with in-hosp SCA
- 55.3% alive at 6 mo!
- Survival to d/c assoc with younger age

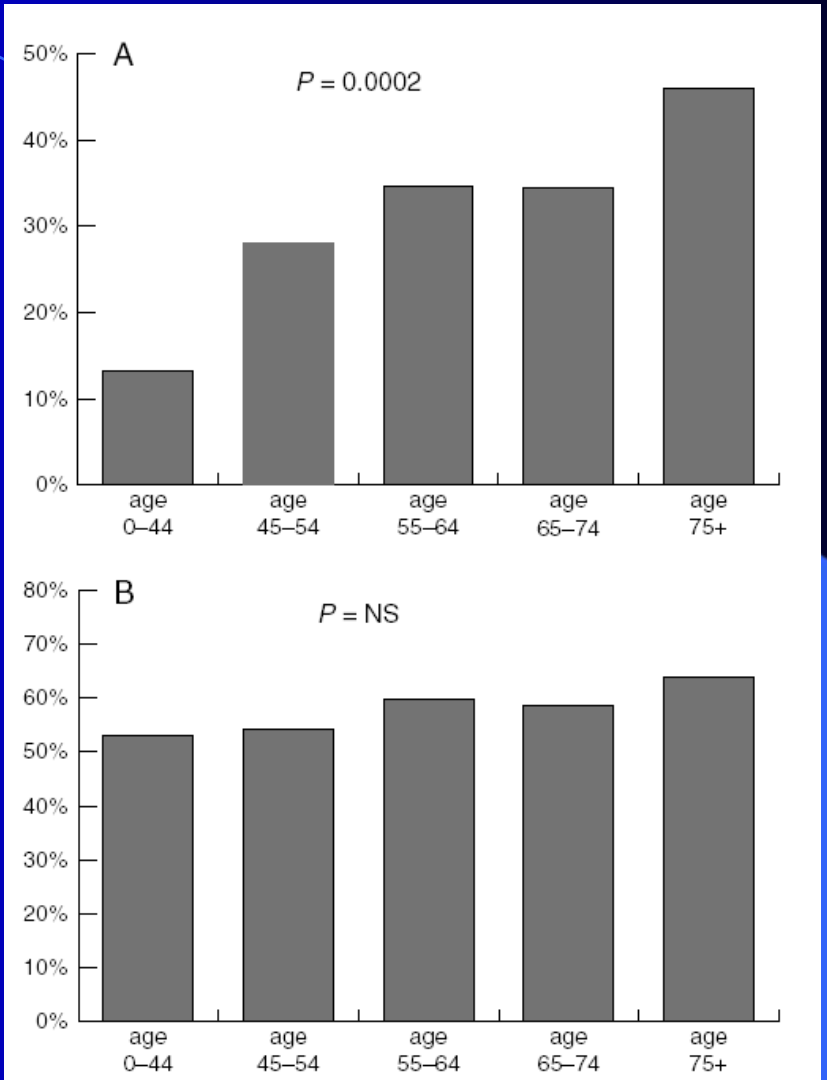


Fig. 2. In-hospital mortality (%) in the different age groups. (A) Patients who received hypothermia treatment (n = 407), (B) patients who received standard treatment (n = 1148).

Oksanen T, Pettila V, Hynen M, Varpula. Therapeutic hypothermia after cardiac arrest: implementation and outcome in Finnish intensive care units. Acta Anaesthesiol Scand 2007;51:866-871.

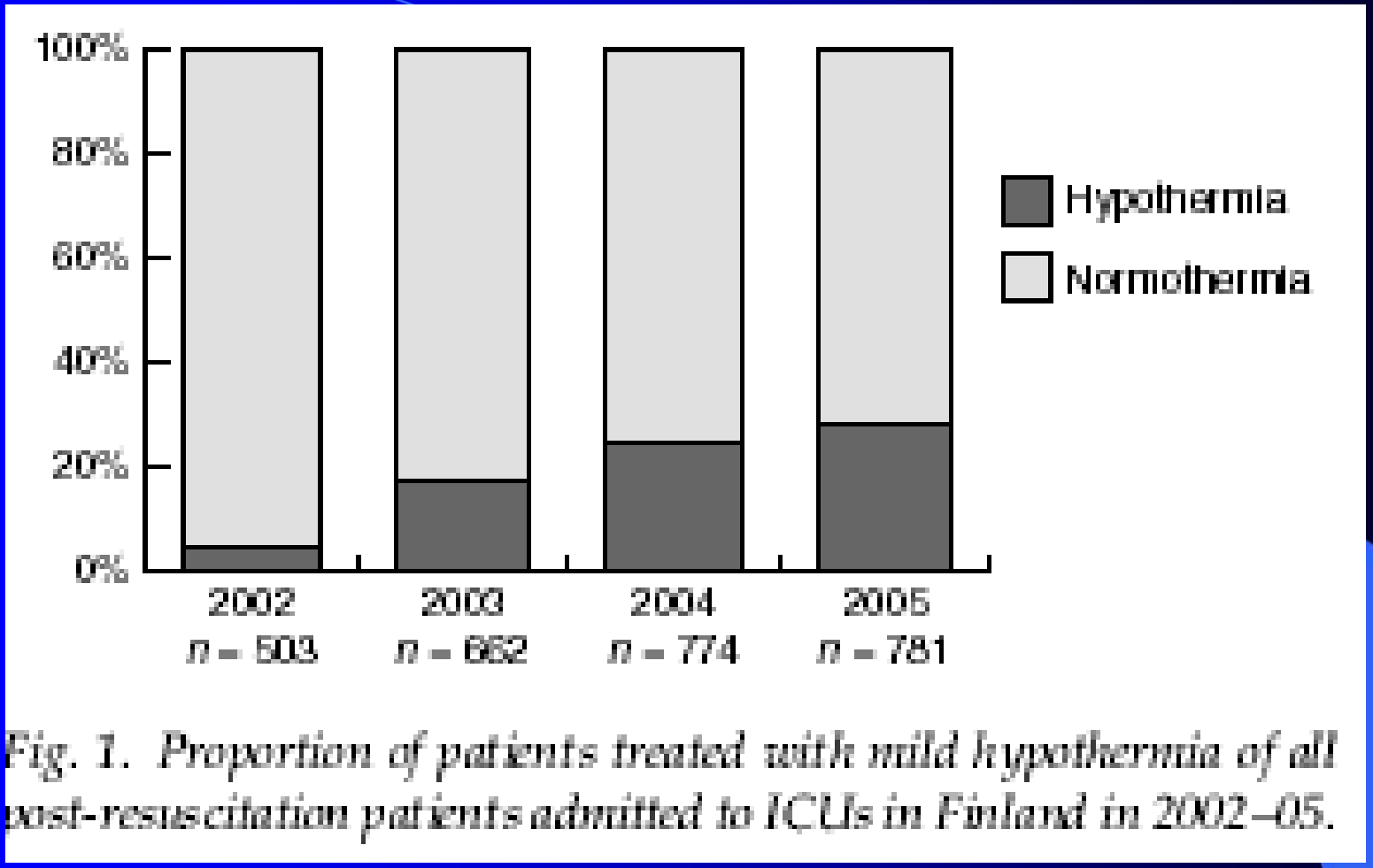


Fig. 1. Proportion of patients treated with mild hypothermia of all post-resuscitation patients admitted to ICUs in Finland in 2002–05.

Oksanen T, Pettila V, Hynen M, Varpula. Therapeutic hypothermia after cardiac arrest: implementation and outcome in Finnish intensive care units. Acta Anaesthesiol Scand 2007;51:866-871.

Utilization: USA

- Survey of Critical Care, Cards, EM Docs
- 79% academic docs
- 74% US never used
- 69% non-US never used

- 34% thought unethical to randomize to normothermia

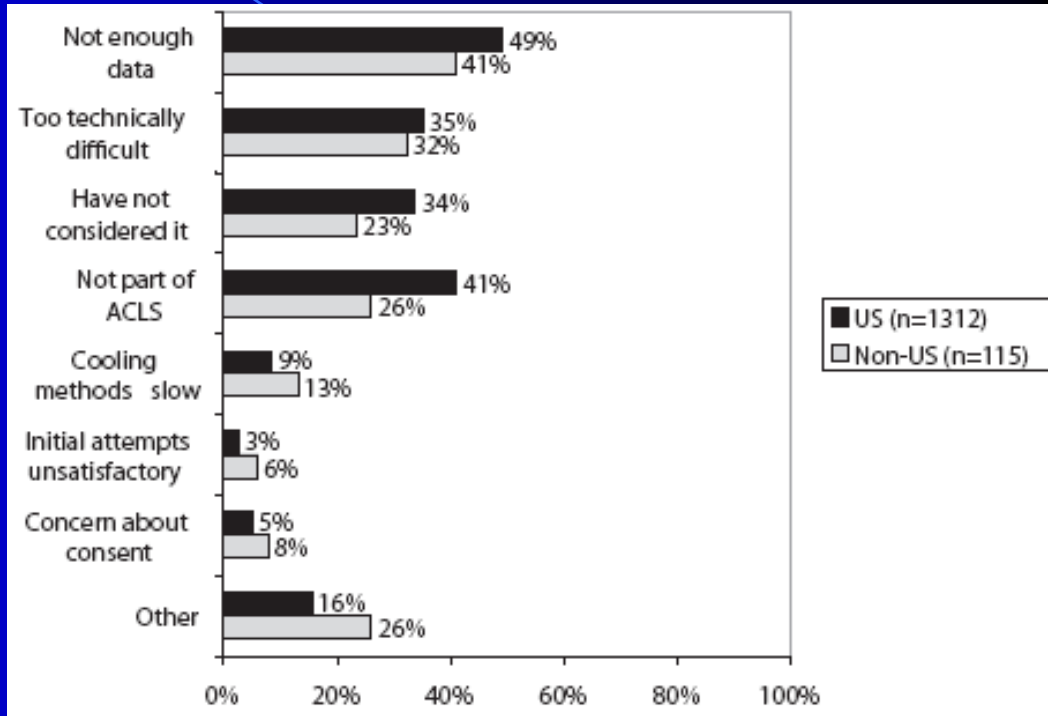


Figure 3. Responses to the question, "Which of the following issues have prevented you from using hypothermia as a therapeutic tool?" Note that respondents were allowed to choose multiple answers; thus, the total percentages add up to >100%. *ACLS*, Advanced Cardiac Life Support; *US*, United States.

Merchant RM, Soar J, Skirifvars MB, et al. Therapeutic hypothermia utilization among physicians after resuscitation from cardiac arrest. Crit Care Med 2006;34:1935-1940.

Conclusion…

We Are Behind!

Clinical Application of Mild Therapeutic Hypothermia After Cardiac Arrest

- 19 sites in Europe, 2 years
- 462 of 587 patients who met criteria for TH
- 43 in-hospital arrests

Table 1. Descriptive analysis of collected data (n = 587)

	All Patients (n = 587)	Hypothermia (n = 462)	Normothermia (n = 123)	*p* Value
Outcome				
Unfavorable outcome, n (%)	334 (57)	250 (55)	84 (68)	.02
Died during hospital stay, n (%)	279 (48)	195 (43)	84 (68)	<.001

Arrich J, The European Resuscitation Council Hypothermia After Cardiac Arrest Registry Study Group. Clinical application of mild therapeutic hypothermia after cardiac arrest. Crit Care Med 2007;35(4):1041-1047.

Benefit in PEA / Asystole

Table 5. Outcome and temperature profiles of patients with pulseless electrical activity/ electromechanical dissociation or asystole as first rhythm (n = 197)

	Hypothermia (n = 124)	Normothermia (n = 73)	*p* Value
Outcome			
Unfavorable outcome, n (%)	89 (81)	59 (81)	.977
Died during hospital stay, n (%)	79 (65)	59 (81)	.023

Arrich J, The European Resuscitation Council Hypothermia After Cardiac Arrest Registry Study Group. Clinical application of mild therapeutic hypothermia after cardiac arrest. Crit Care Med 2007;35(4):1041-1047.

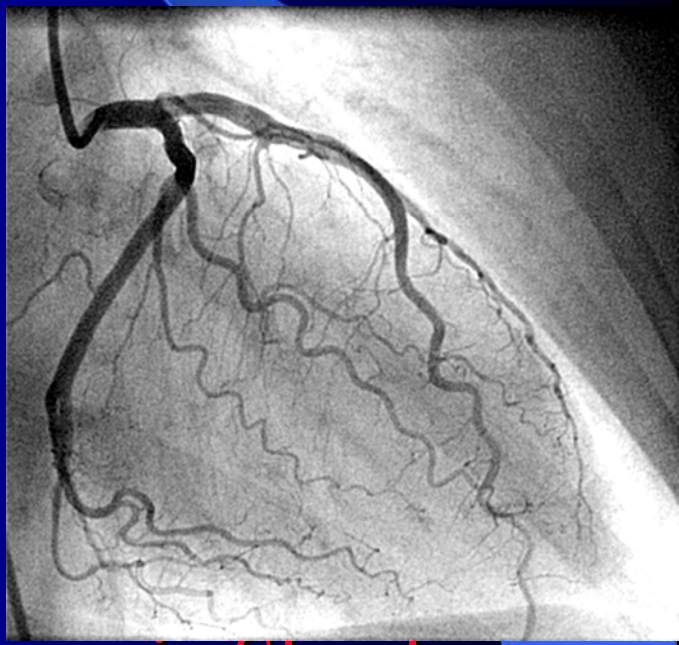
Adverse Events

- 15 pts Hemorrhage (3%)
- 28 pts Arrhythmia (16%)
  - Endovascular Device: 7.2%
  - Other method: 0.9% p=0.01

Arrich J, The European Resuscitation Council Hypothermia After Cardiac Arrest Registry Study Group. Clinical application of mild therapeutic hypothermia after cardiac arrest. Crit Care Med 2007;35(4):1041-1047.

Cardiac Questions

- 50 consecutive VF/VT pts
  - All TH: start in Ambo, Cath lab, or ICU
  - 98% cath
  - 72% PCI
  - 23pts with IABP
  - No significant bleeding
  - 82% survival Rate



Benefit from TH + Cath in Cardiogenic Shock

Hovdenes J, Laake JH, Aaberge L, et al. Therapeutic hypothermia after out-of-hospital cardiac arrest: experiences with patients treated with percutaneous coronary intervention and cardiogenic shock. Acta Anaesthesiol Scand 2007;51:137-142.

TH Prior to Cath

- 62 patients with out of hosp CA
  - 40/52 comatose pts got TH
  - 47 cathed
  - 30 stented
  - No statistically Significant Difference in Complicaitons

Sunde K, Pytte M, Jacobsen D, et al. Implementation of a standardized treatment protocol for post resuscitation care after out-of-hospital cardiac arrest. Resuscitation 2007;73:29-39.

Future Directions
Time to onset of TH

Animal Studies

- Dogs:
  - TH at time of ROSC vs 15 minutes after
  - No benefit in 15 minute group
- Mice
  - TH during CA vs. at time of ROSC
  - Better 72hr survival in CA group

Kuboyama K, Safar P, Radovsky A, Tisherman SA, Stezoski SW, Alexander H. Delay in cooling negates the beneficial effect of mild resuscitative cerebral hypothermia after cardiac arrest in dogs: a prospective, randomized study. Crit Care Med 1993;21:1348-58.

Abella BS, Zhao D, Alvarado J, et al. Intra-Arrest Cooling Improves Outcomes in a Murine Cardiac Arrest Model. Circulation 2004;109:2786-2791.

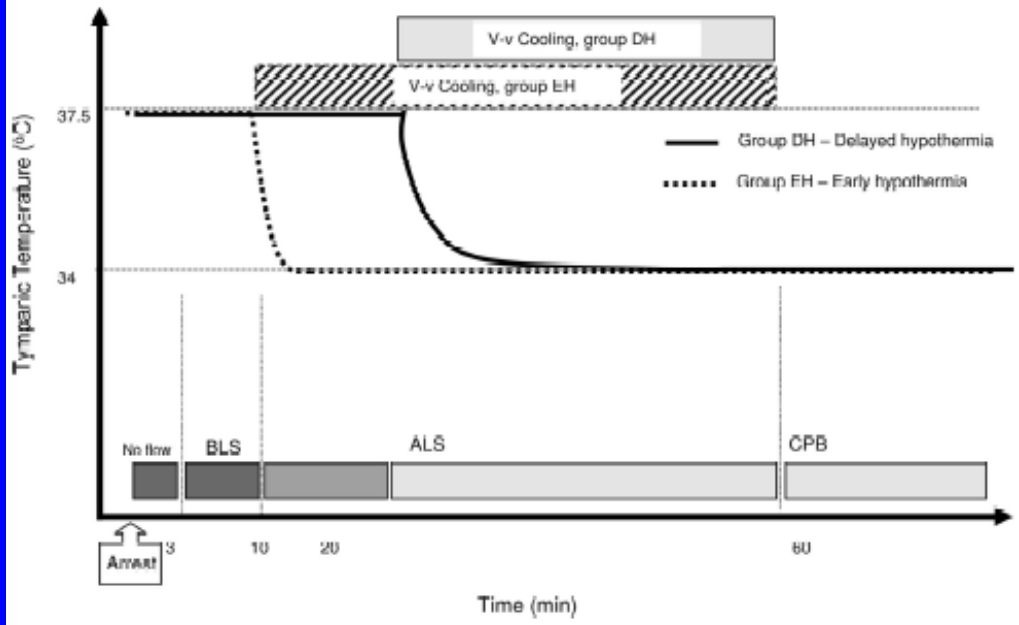


Figure 1. Study protocol. Three minutes of normovolemic VF was followed by 7 minutes of BLS and 50 minutes of ALS. V-v indicates venovenous.

-Cold Saline to 34C after 10 or 20 minutes of VF

-ACLS at 20 minutes

- 7/9 survive in TH vs 1/8 in delayed group

. Nozari A, Safar P, Stezoski SW, et al. Critical Time Window for Intra-Arrest Cooling With Cold Saline Flush in a Dog Model of Cardiopulmonary Resuscitation. Circulation 2006;113:2690-2696.

Better than CPR!!!

- 5/6 pigs survive vs. 4/7 who got CPR
- Improved Neurologic Performance

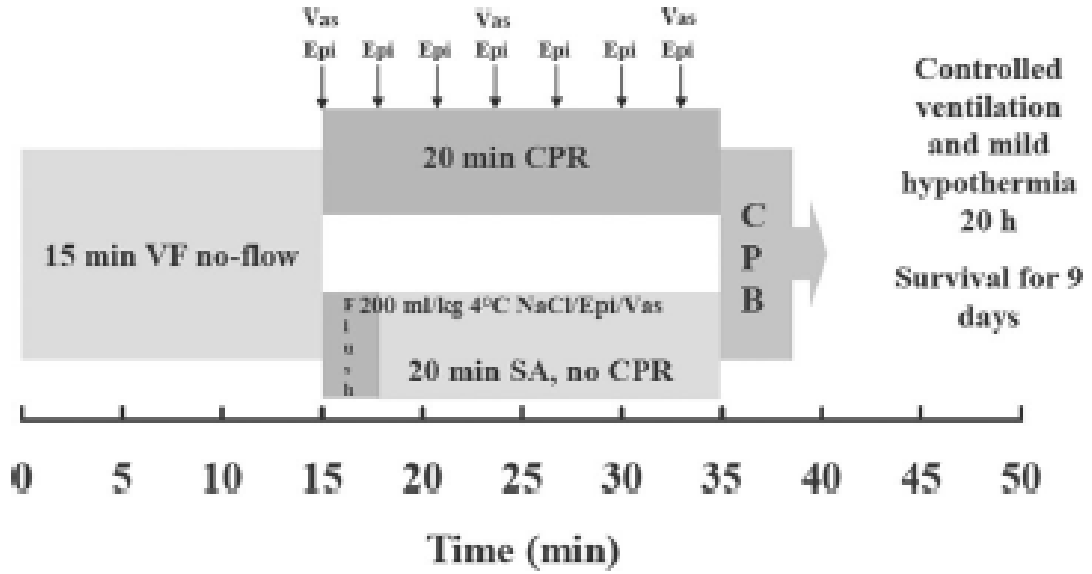


Figure 1. Experimental protocol. *VF*, ventricular fibrillation; *Vas*, vasopressin 0.4 IU/kg; *Epi*, epinephrine 0.04 mg/kg; *CPR*, cardiopulmonary resuscitation; *CPB*, cardiopulmonary bypass.

Janta A, Bayegan K, Weihs W, et al. Emergency preservation and resuscitation improve survival after 15 minutes of normovolemic cardiac arrest in pigs. Crit Care Med 2007;35(12):2785-2791.

Early Induction in Humans

- 30ml/kg 4°C LR in ED
  - 1.6°C drop, no Pulmonary edema
- 2L 4°C in ED
  - 1.7°C in patients who received neuromuscular blockers and 1.1°C in those who did not
  - Pre and Post TTE, no Pulmonary Edema

Bernard S, Buist M, Monteiro O, Smith K. Induced hypothermia using large volume, ice-cold intravenous fluid in comatose survivors of out-of-hospital cardiac arrest: a preliminary report. Resuscitation 2003;53(1):9-13.

Kim f, Olsufka M, Carlbom D, et al. Pilot study of rapid infusion of 2L of 4 degrees C normal saline for induction of mild hypothermia in hospitalized, comatose survivors of out-of-hospital cardiac arrest. Circulation 2005;112(5):715-9.

Induction in the Ambulance

- 2L of 4°C NS and neuromuscular blockers
- Decrease in Temp of 1.24°C
- Trend towards increased survival in VF
  - TH not continued in-house at all hospitals

Kim F, Olsufka M, Longstreth WT, et al. Pilot Randomized Clinical Trial of Prehospital Induction od Mild Hypothermia in Out-of-Hospital Cardiac Arrest Patients With a Rapid Infusion of 4°C Normal Saline. Circulation 2007;115:3064-3070.

TH: Conclusions

- Neurologic and Mortality Benefit
- Possible Benefit in-hospital
- Benefit in PEA/Asystole
- Be Aware of Physiologic Changes
- Earlier Cooling may provide added Benefit

This is Standard of Care

- University of Washington
- University of Chicago
- Mass General
- University of Texas
- St. Luke's
- UCSF
- San Fransisco General
- Maine Med Ctr
- University of Pittsburgh
- BWMC

What are We Waiting For?