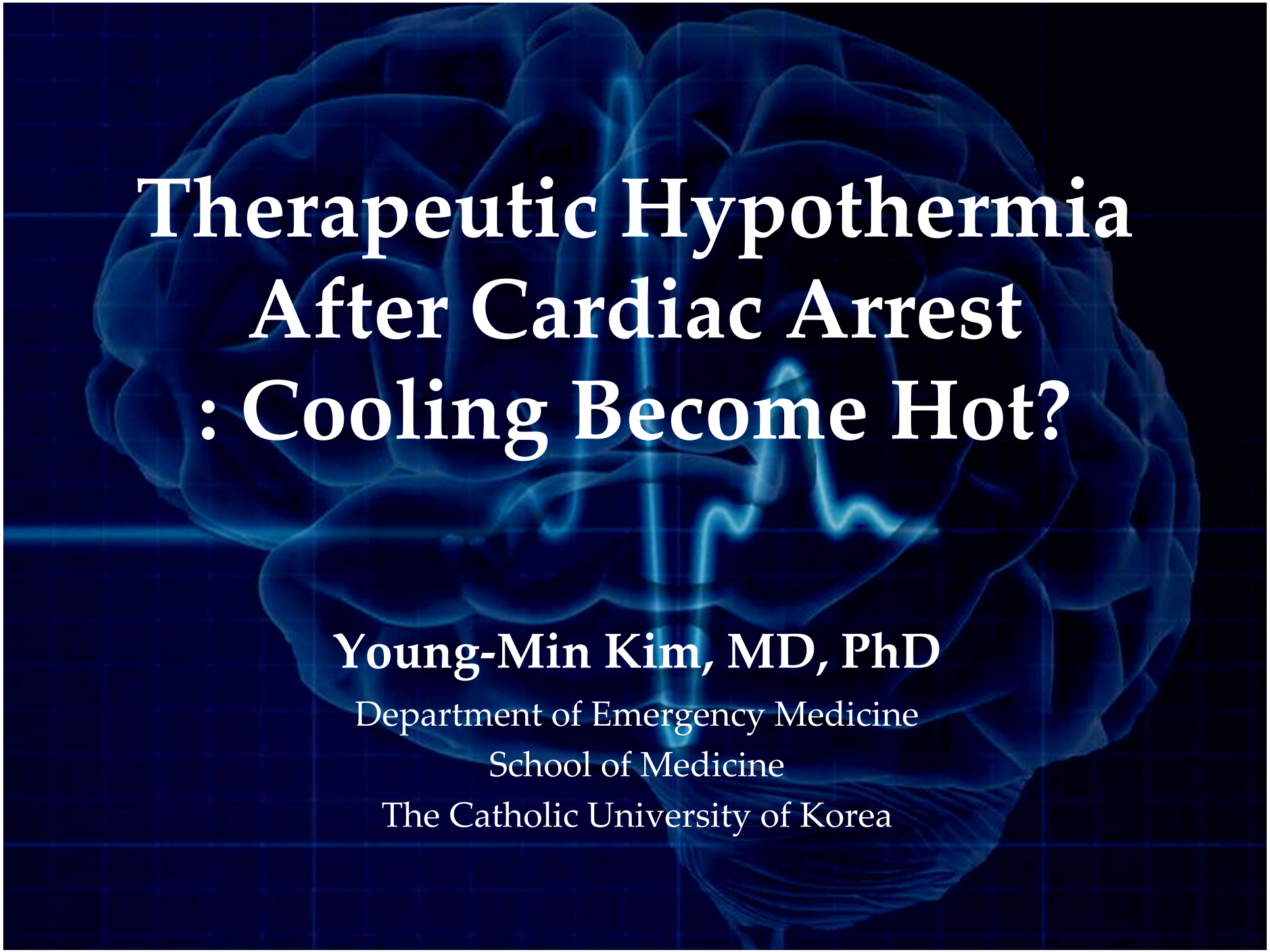


Therapeutic Hypothermia After Cardiac Arrest : Cooling Become Hot?

Young-Min Kim, MD, PhD

Department of Emergency Medicine

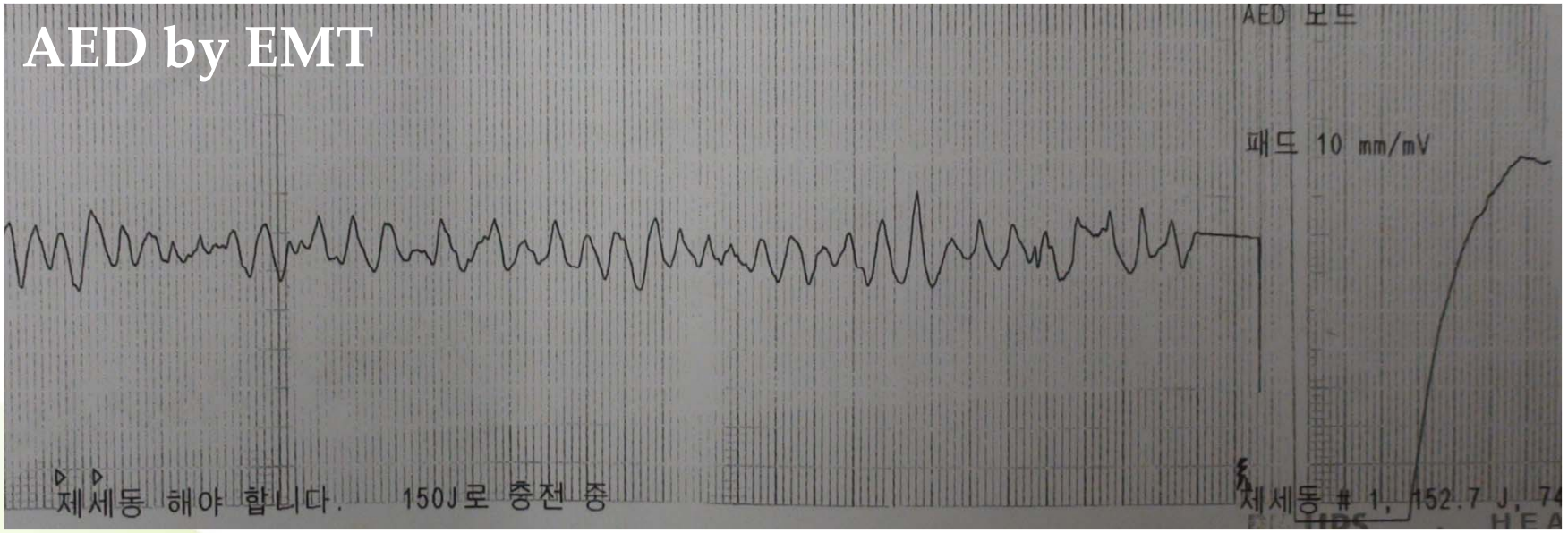
School of Medicine

The Catholic University of Korea

Outline

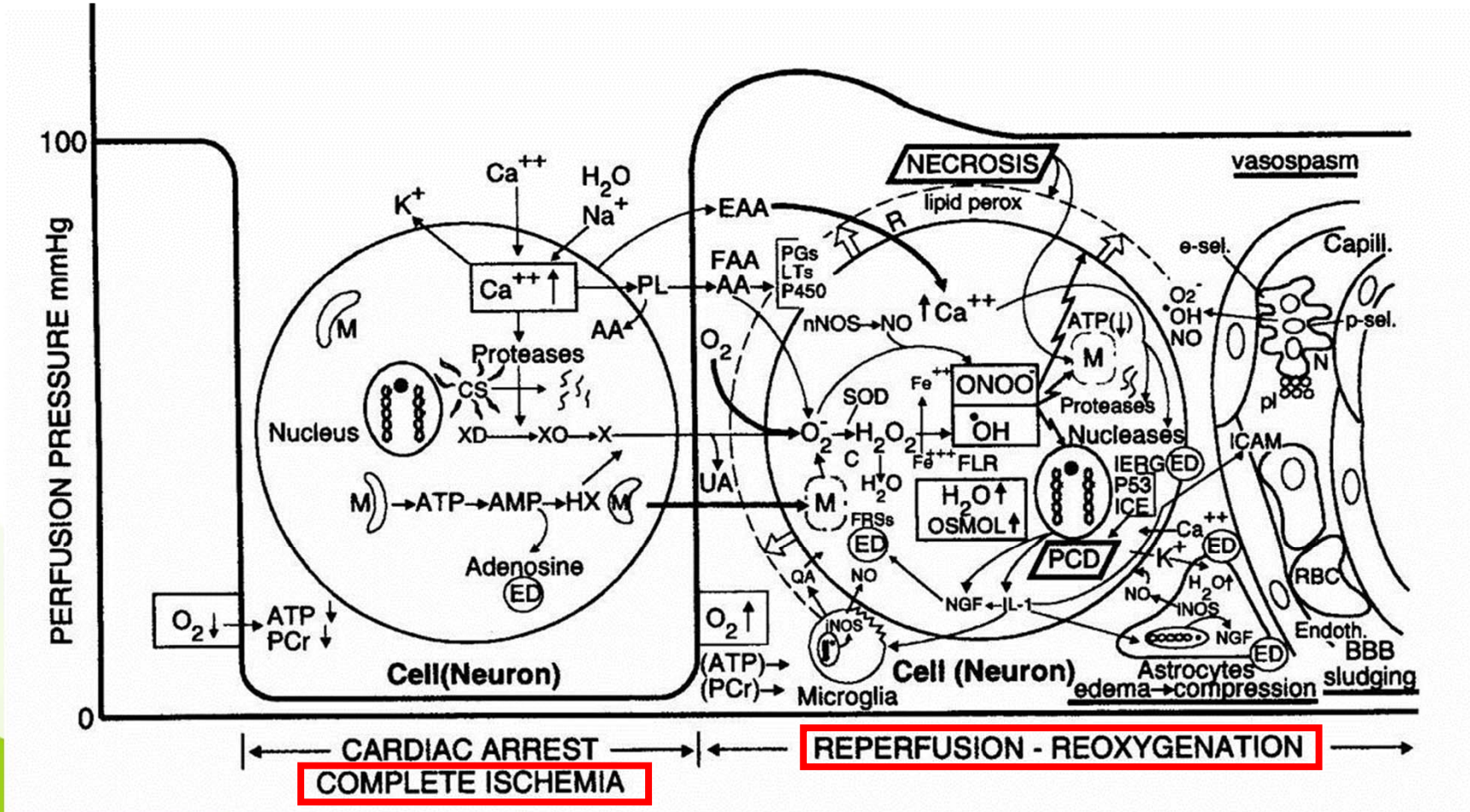
- Introduction
- Overall Trends
- Evidence-Based Update for the Practical Questions
- Conclusion

M/30, Sudden Collapse with Seizure Like Activity



→ ROSC, but Comatose

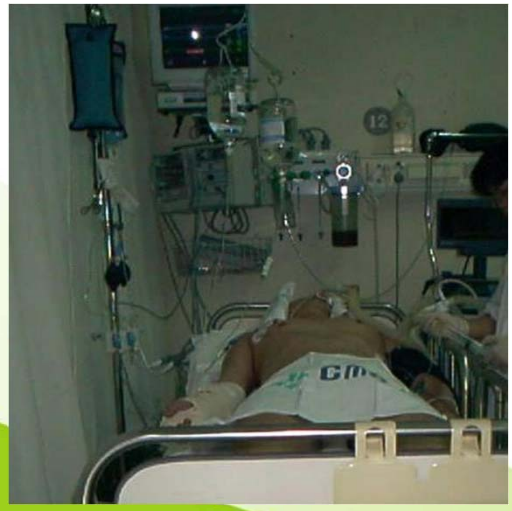
What Happened & What's Happening?

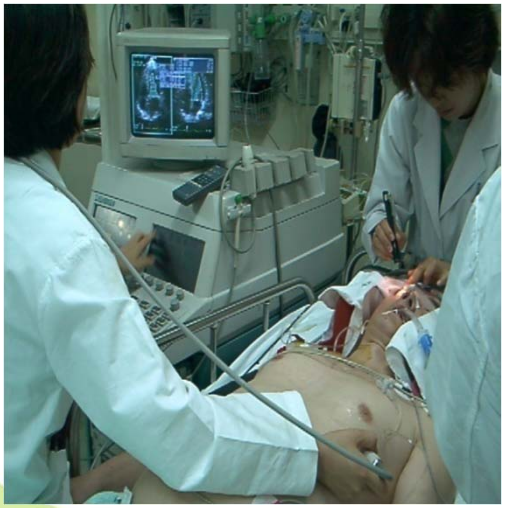


Paradis NA, et al. ***Cardiac Arrest*** **1996,Wiliams&Wilkins. p 859-87**

What Should We Do ?

Optimize ventilation and oxygenation Treat hypotension	Treat the cause	Initiate cooling





TH is Not a "New" Treatment

Case Number	3	4
Date	Sept. 1957	Nov. 1957
Age	38 C. M.	39 C. F.
Cause of arrest	tab wound	Stab wound
Duration of arrest	minutes	5 minutes
Neurologic damage	evere	Severe
Hypothermia: Range	2–33° C.	32–34° C.
Duration	8 hours	72 hours
Residual neurologic defect	None	Moderate

Baron de Larrey (1812)
Temple Fay (1937)

Russian Method of Resuscitation (1803)

Peter J. Safar (1924-2003)

Williams Junior GR, Spencer FC. *Ann Surg* 1958;148:462-6

Landmark RCTs of THACA

The New England
Journal of Medicine

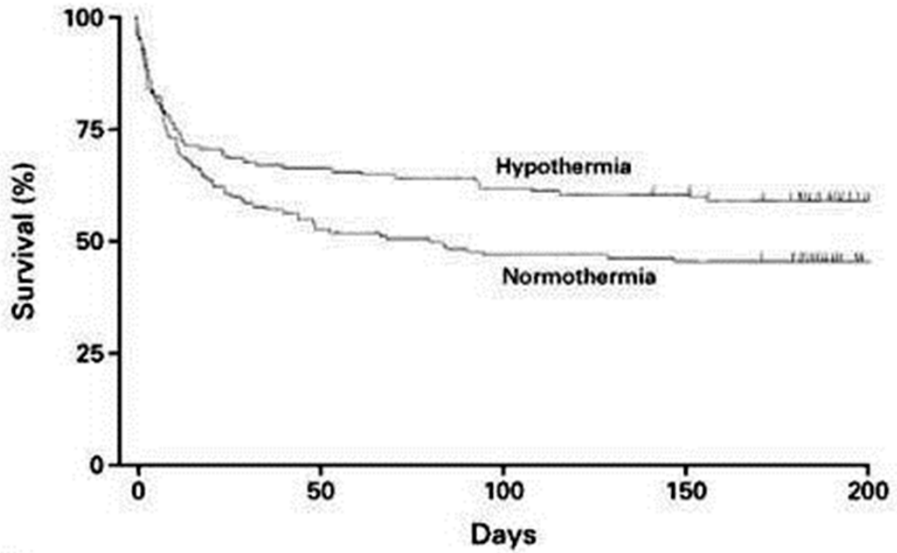
VOLUME 346 FEBRUARY 21, 2002 NUMBER 8

TREATMEN

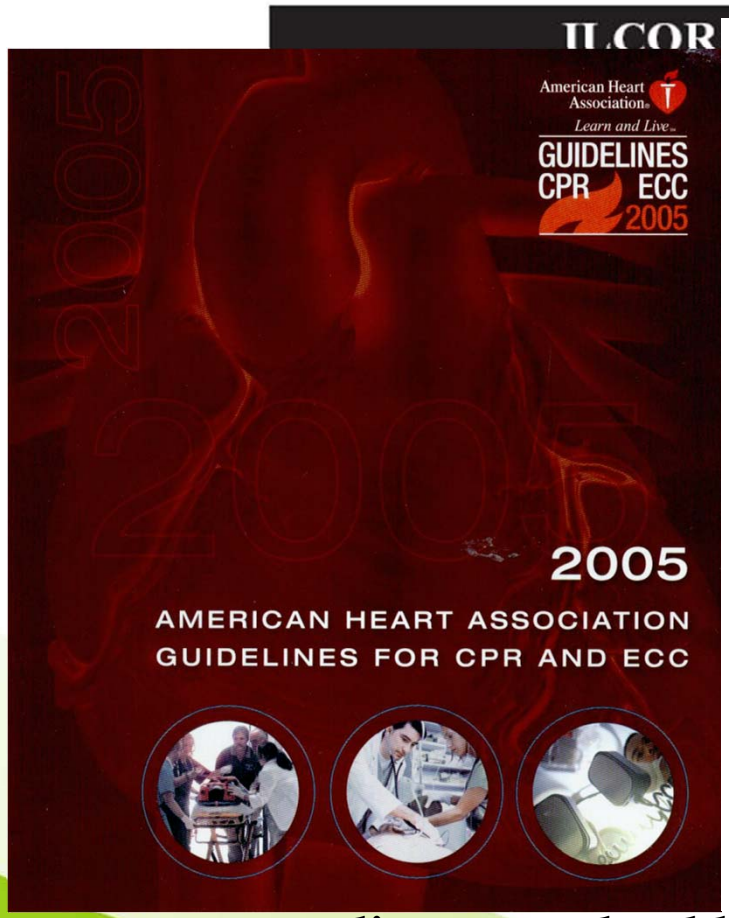
STEPHEN
BRUCE M. JONES, M

'AL CARDIAC

M.B., B.S.,
ND KAREN SMITH, B.SC.



International Recommendation

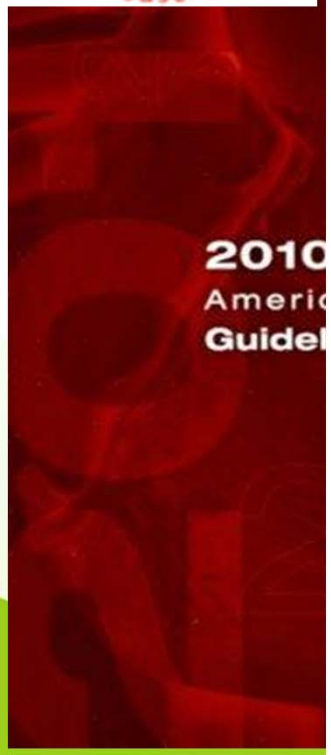


- Unconscious adult patients with ROSC after OHCA should be cooled to 32°C to 34°C for 12 to 24 hours when the initial rhythm was VF **(Class IIa)**
- With non-VF arrest out of hospital or for in-hospital arrest **(Class IIb)**

cardiac arrest should be cooled to 32-34°C for 12-24 hrs

- **Possible benefit for other rhythms or in-hospital cardiac arrest**

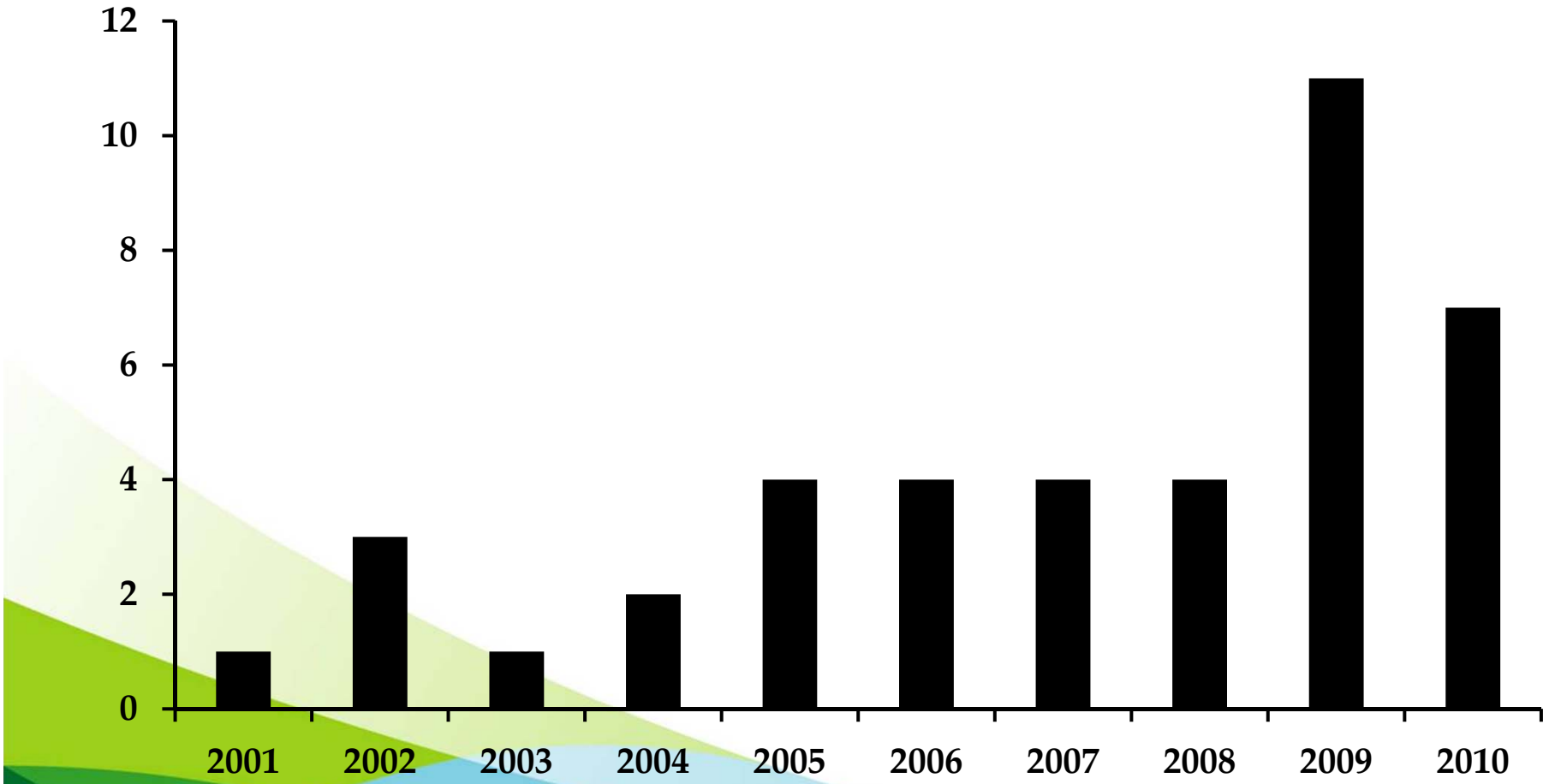
Current Recommendation



Treatment Recommendation

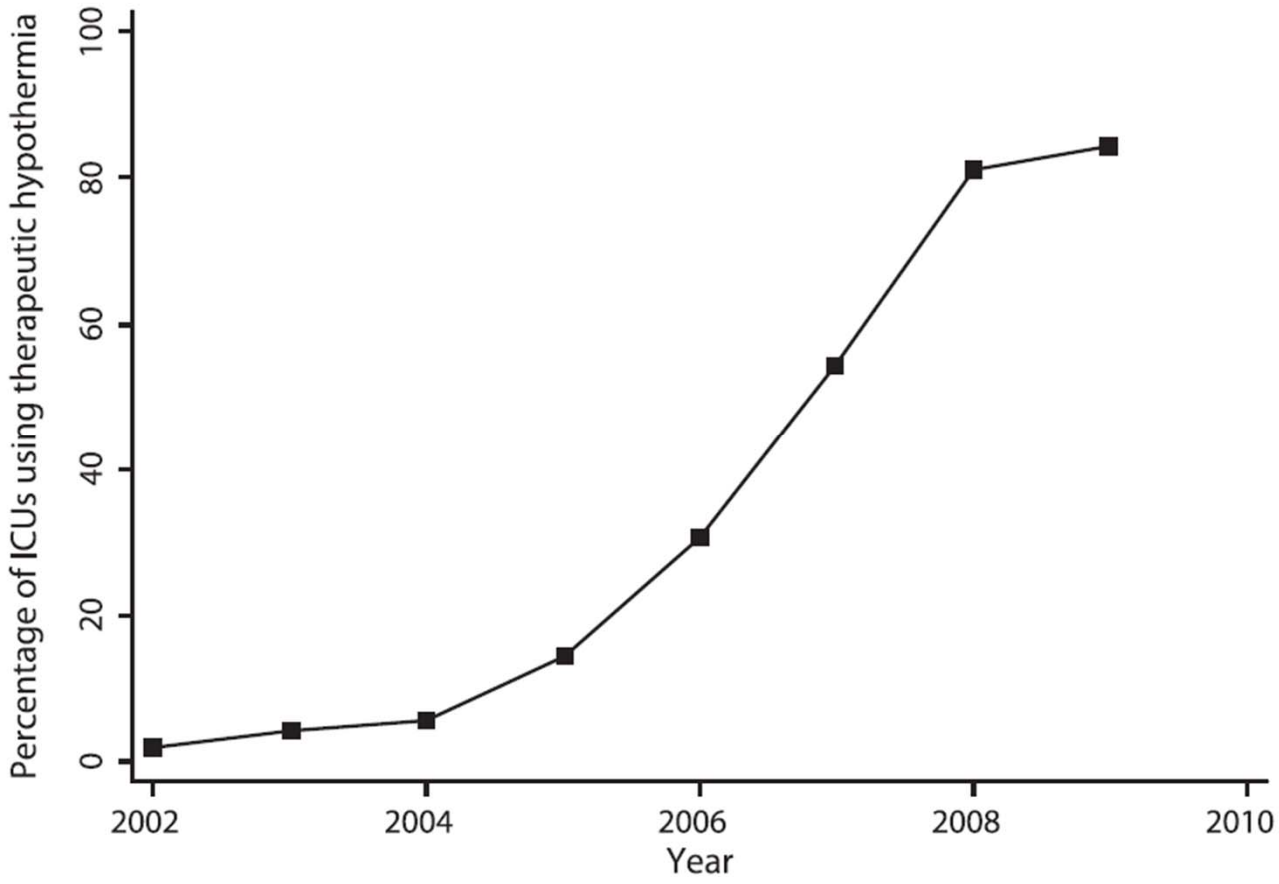
Comatose adult patients (not responding in a meaningful way to verbal commands) with spontaneous circulation after out-of-hospital VF cardiac arrest should be cooled to 32 to 34°C for 12 to 24 hours. Induced hypothermia might also benefit comatose adult patients with spontaneous circulation after out-of-hospital cardiac arrest from a nonshockable rhythm, or cardiac arrest in hospital. Rapid infusion of ice-cold IV fluid 30 mL/kg or ice packs are feasible, safe, and simple methods for initially lowering core temperature up to 1.5oC. When IV fluids are used to induce hypothermia, additional cooling strategies will be required to maintain hypothermia. Limited available evidence suggests that PCI during therapeutic hypothermia is feasible and safe and may be associated with improved outcome.

Yearly Increase in RCT for TH (Published OR Ongoing)



Yearly Increase in Implementation of TH

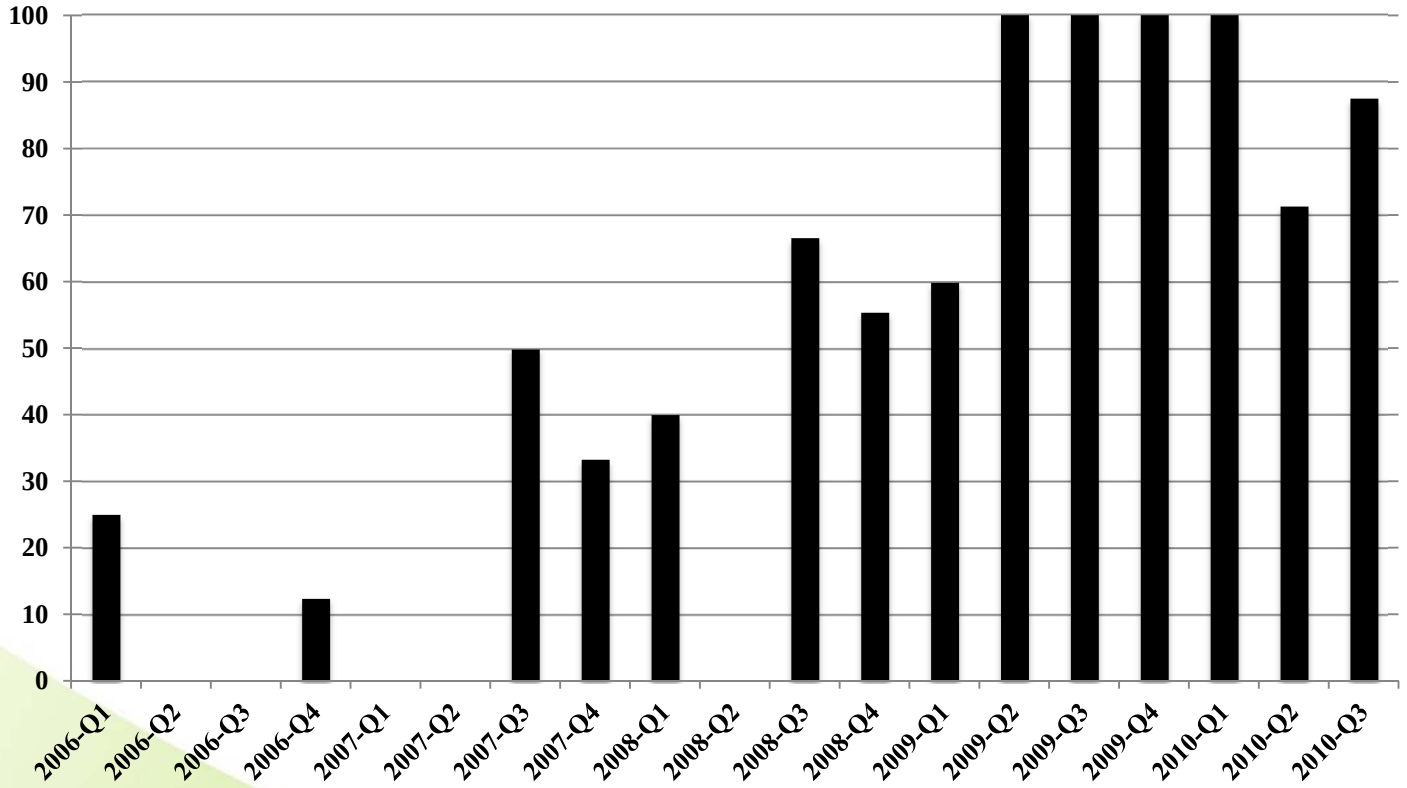
A Telephone Survey(response rate, 98.4%) , 243 UK ICUs



Binks AC, et al. *Anaesthesia* 2010;65: 260-5

Yearly Increase in Implementation of TH

Seoul St. Mary's Hospital, 2006.1.1-2010.7.31, OHCA



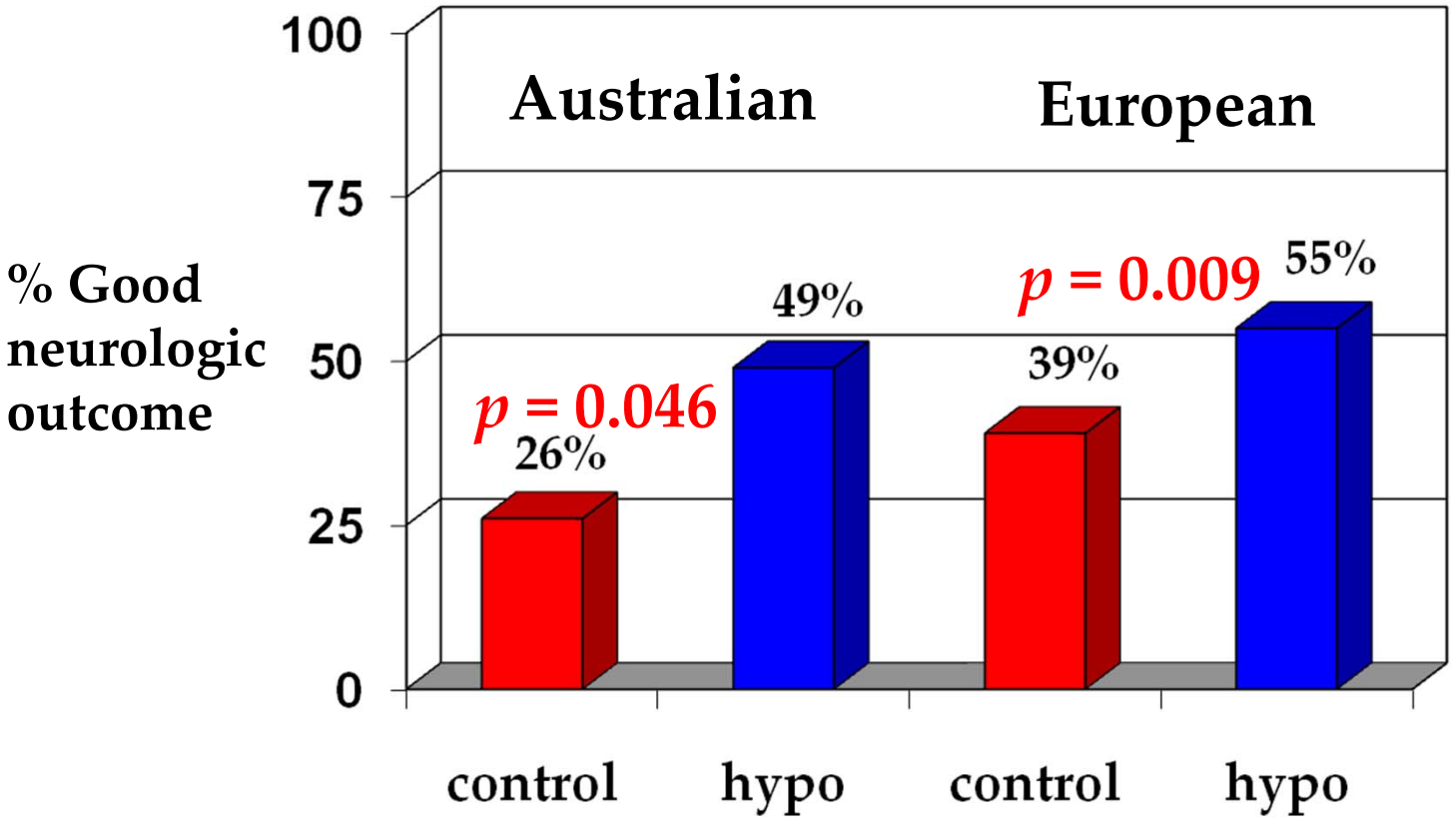
Youn CS, et al. Presented at *2010 KSEM Fall Meeting*

Practical Questions When Applying TH

- Who to cool?
- When to start cooling?
- How deep to cool?
- How long to keep cool?
- How to cool?
- What physiological changes and side effects can be developed?
- What adjunctive drugs should be given?
- Where to measure temperature?

Who to cool?

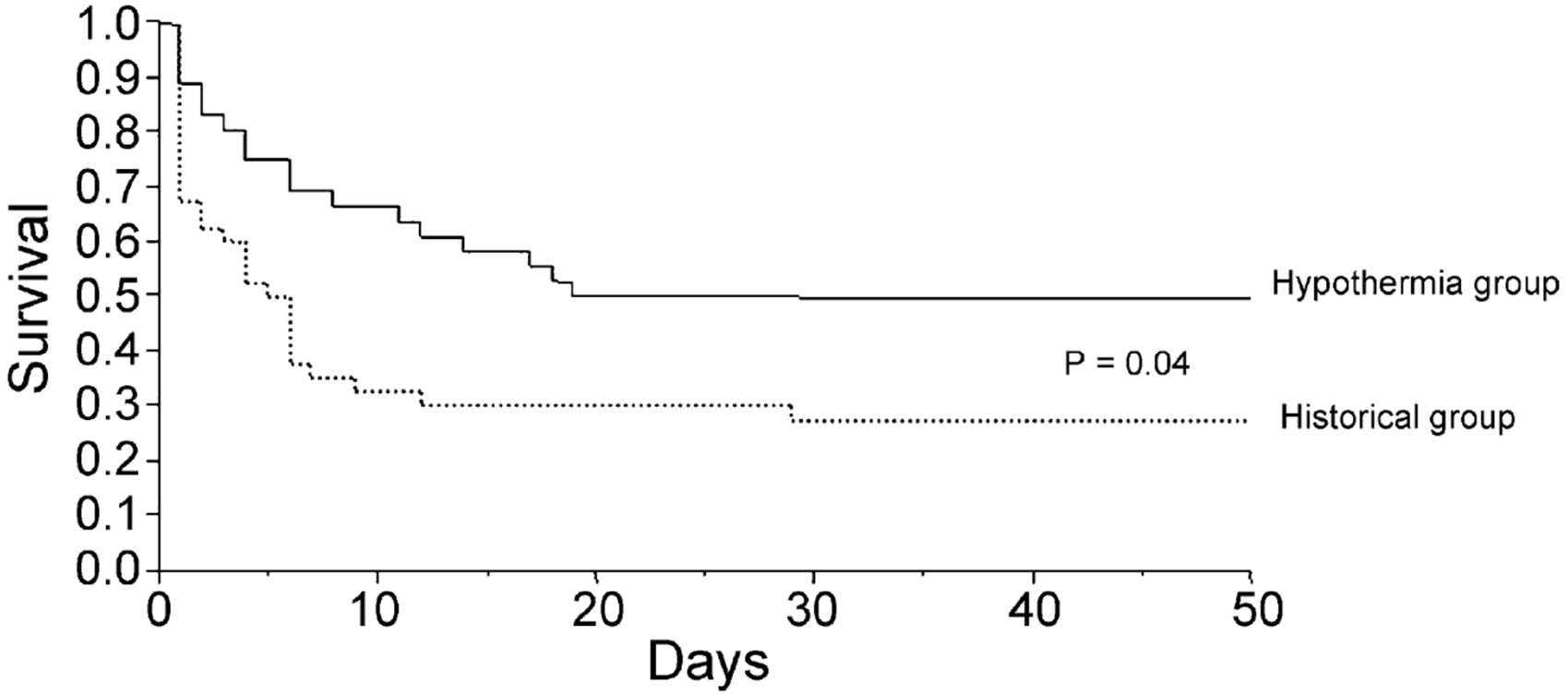
Shockable Rhythms



Bernard SA et al. (Australia) *N Engl J Med* 2002; 346: 549-56
HACA study group (Europe) *N Engl J Med* 2002; 346: 557-63

Shockable Rhythms

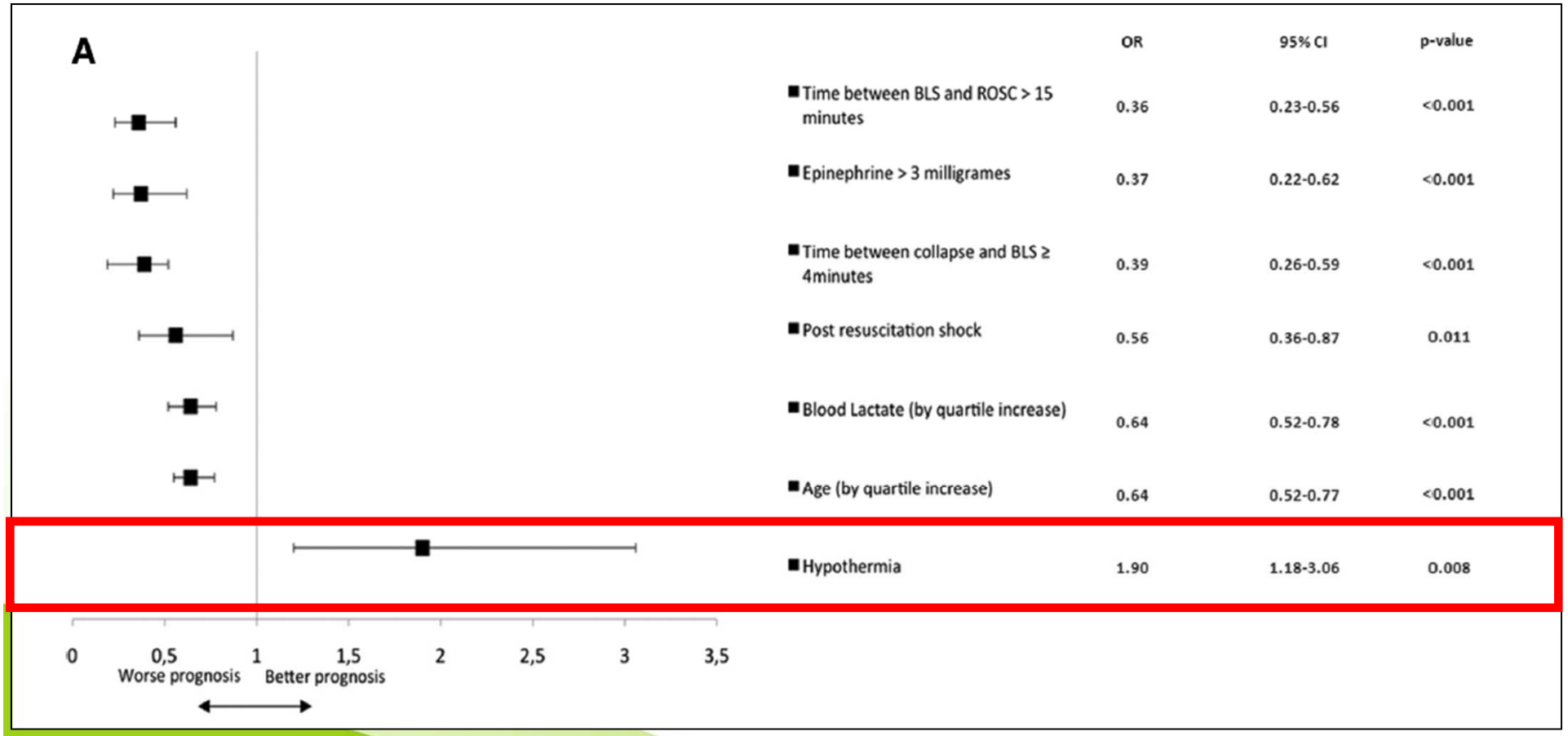
Retrospective cohort study with historical control, 68 OHCA, TH (wet cloths+ ice packs), France



Belliard G, et al. *Resuscitation* 2007;75:252–9

Shockable Rhythms

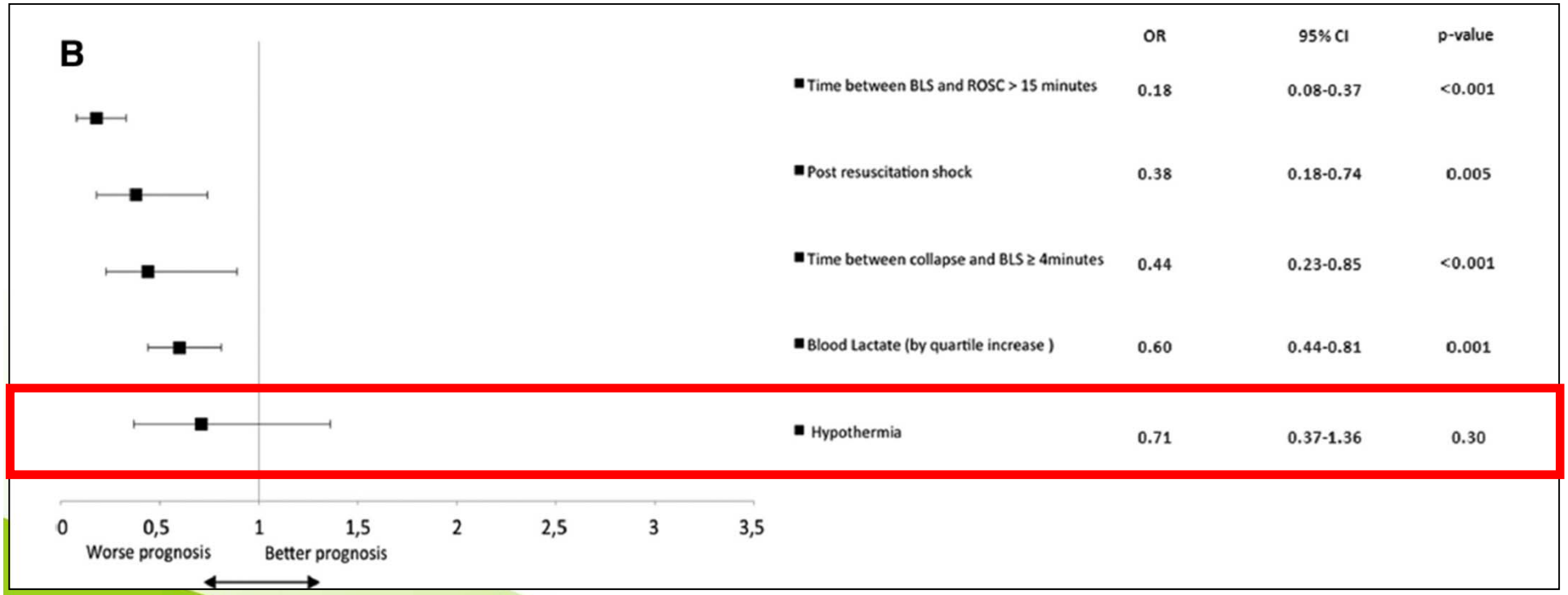
Multicenter observational study using a large registry, 1145 OHCA, France



Dumas F, et al. Circulation 2011; 123:877-86

Non-Shockable Rhythms (OHCA)

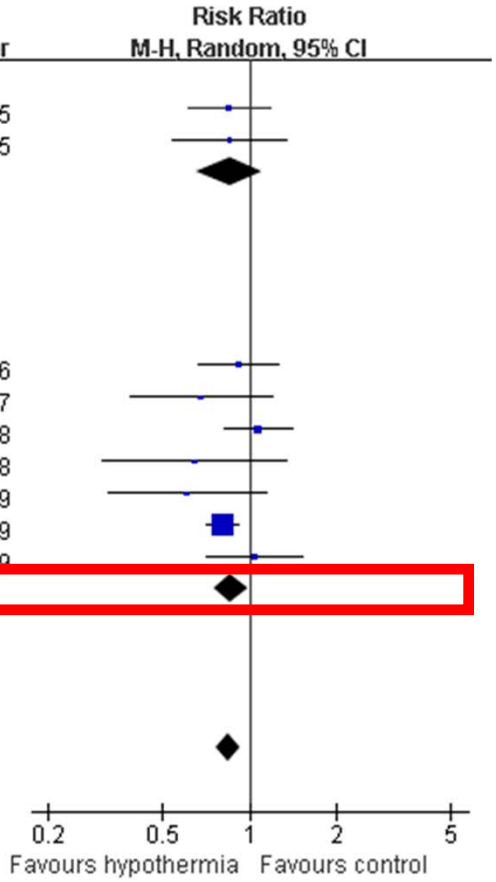
Multicenter observational study using a large registry, 1145 OHCA, France



Dumas F, et al. Circulation 2011; 123:877-86

Non-Shockable Rhythms (OHCA)

Study or Subgroup	Therapeutic hypothermia Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
2.1.1 RCTs							
Hachimi-Idrissi 2005	12	16	15	17	8.2%	0.85 [0.61, 1.18]	2005
Laurent 2005	5	6	5	5	4.3%	0.86 [0.54, 1.35]	2005
Subtotal (95% CI)		22		22	12.5%	**0.85 [0.65, 1.11]**	
Total events	17		20				
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.98); I² = 0%							
Test for overall effect: Z = 1.17 (P = 0.24)							
2.1.2 Non-RCTs							
Oddo 2006	10	12	10	11	9.1%	0.92 [0.67, 1.26]	2006
Sunde 2007	4	6	9	9	2.8%	0.68 [0.38, 1.20]	2007
Rittenberger 2008	27	31	13	16	12.2%	1.07 [0.82, 1.41]	2008
Storm 2008	6	18	16	31	1.7%	0.65 [0.31, 1.35]	2008
Bro-Jeppesen 2009	6	13	16	21	2.2%	0.61 [0.32, 1.14]	2009
Don 2009	85	122	165	191	53.5%	0.81 [0.71, 0.92]	2009
Whitfield 2009	12	15	10	13	5.9%	1.04 [0.70, 1.54]	2009
Subtotal (95% CI)		217		292	87.5%	**0.86 [0.76, 0.99]**	
Total events	150		239				
Heterogeneity: Tau² = 0.01; Chi² = 7.39, df = 6 (P = 0.29); I² = 19%							
Test for overall effect: Z = 2.12 (P = 0.03)							
Total (95% CI)		239		314	100.0%	**0.85 [0.77, 0.94]**	
Total events	167		259				
Heterogeneity: Tau² = 0.00; Chi² = 7.37, df = 8 (P = 0.50); I² = 0%							
Test for overall effect: Z = 3.33 (P = 0.0009)							



Kim YM, et al. ***Resuscitation*** **2010;81(suppl): S67**

Cardiogenic Shock

50 OHCA, VF, TH (cold fluid + surface cooling system, started in ICU)

	IABP ($n = 23$)	No IABP ($n = 27$)	*P* value
Witnessed arrest†	22 (96)	25 (93)	0.65
Ambulance arrival (min)*	6 (0–20)	10 (0–35)	0.075
ROSC (min)*	15 (4–30)	15 (5–45)	0.45
Number of defibrillations*	2 (1–20)	2 (1–12)	0.87
Start cooling (min)*	180 (60–480)	150 (30–420)	0.15
Target temperature (min)*	630 (120–1560)	400 (120–1240)	0.15
SAPS II*	52 (22–88)	58.5 (16–81)	0.38
PCI†	18 (78)	18 (67)	0.37
PCI of LAD†	15 (65)	8 (30)	0.012
PCI of CX†	3 (13)	2 (7)	0.51
PCI of RCA†	5 (22)	12 (44)	0.09
Myocardial infarction†	21 (91)	19 (70)	0.065
Max troponin-I (μg/l)*	30 (1.8–164)	5.3 (0.06–127)	0.002
Max CKMB mass (μg/l)*	382 (36–500)*	159 (7.8–500)	0.011
Alive at 6 months†	17 (74)	24 (89)	0.17
CPC 1†	12 (52)	16 (59)	0.62
CPC 2†	2 (9)	4 (15)	0.51
CPC 3†	3 (13)	4 (15)	0.86
CPC 5†	6 (26)	3 (11)	0.17
Levosimendan†	11 (48)	3 (11)	0.004
Any adrenergic drug†	20 (87)	17 (63)	0.056
Norepinephrine†	11 (48)	5 (19)	0.03
Dobutamine†	13 (57)	9 (33)	0.10
Dopamine†	3 (13)	5 (19)	0.60

Hovdenes J, et al. ***Acta Anaesthesiol Scand*** **2007;51:137-42**

Cardiogenic Shock

56 OH & IHCA, All rhythm, TH(cold fluid + surface cooling, started in CCU)

Hospitalization outcome of patients in both groups.

	Group A	Group B	*P*
APACHE II (%) (Adjusted predicted death rate)	85.7 ± 10.4	63.9 ± 17.3	<0.001
In-hospital mortality (CPC 5) [*n* (%)]	16 (57.1)	6 (21.4)	0.013
CPC 1 or 2 at discharge [*n* (%)]	11 (39.3)	20 (71.4)	0.031
CPC 3 or 4 at discharge [*n* (%)]	1 (3.5)	2 (7.4)	0.491
CPC 1 or 2 anytime during hospital stay [*n* (%)]	19 (67.9)	23 (82.1)	0.355

Comparison of treatment and mild hypothermia associated side effects in both groups.

	n (%)		*P*
	Group A	Group B	
Treatment			
Any adrenergic drug at the baseline	28 (100.0)	15 (53.6)	<0.001
Any adrenergic drug during mild hypothermia	28 (100.0)	22 (78.6)	0.023
Intra-aortic balloon pump	11 (39.3)	0 (0)	<0.001
Continuous renal replacement method	6 (21.4)	4 (14.3)	0.729
Direct percutaneous coronary intervention	11 (39.3)	18 (64.3)	0.108
Complications			
Major bleeding [*n* (%)]	6 (21.4)	3 (10.7)	0.469
Infection [*n* (%)]	13 (46.4)	12 (42.9)	1.000
Ventricular fibrillation or significant ventricular tachycardia during hypothermia [*n* (%)]	3 (10.7)	3 (10.7)	1.000
Hyperamylasaemia [*n* (%)]	5 (17.9)	2 (7.1)	0.422
Number of post-resuscitative organ dysfunctions (*n*)	2.4 ± 1.1	1.3 ± 1.21	0.001

Skulec R, et al. ***Acta Anaesthesiol Scand*** **2008;52:188-94**

Cardiogenic Shock

Multicenter observational study using a large registry, 765 OHCA, All rhythm, Europe HN

Factor	Alive at Follow-up n = 363 (48%)	Dead at Follow-up n = 391 (52%)	*p*
Inhospital factors			
Initial temperature	36.0 (35.3–36.6)	35.7 (34.8–36.4)	<.001
Shock at admission	58 (16)	70 (18)	.50
Time from arrest to initiation of hypothermia	90 (60–180)	90 (60–160)	.89
Time from arrest to core temperature <34°C	300 (200–440)	240 (145–360)	<.001
Glasgow Coma Scale at admission	3 (3–5)	3 (3–3)	<.001
Thrombolysis performed	21 (6)	18 (5)	.51
Angiography performed	237 (65)	140 (36)	<.001
Percutaneuos coronary intervention performed	149 (41)	76 (19)	<.001
Coronary artery bypass grafting performed	6 (2)	3 (1)	.32
Pacemaker used	18 (4)	11 (3)	.13
Intra-aortic balloon pump	62 (17)	53 (14)	.19
Acute myocardial infarction	229 (63)	225 (58)	.20
Inotropic/vasoactive drugs	282 (78)	315 (81)	.37
Renal replacement therapy	13 (4)	19 (5)	.47
Length of critical care unit stay	120 (73–201)	96 (48–146)	<.001

Nielson N, et al. Crit Care Med 2011; 39:57-64

Pediatric Cardiac Arrest

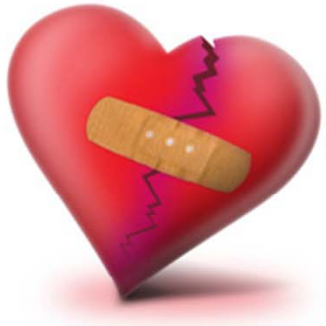
THAPCA TRIALS

Therapeutic Hypothermia After Pediatric Cardiac Arrest

- Home
- About the Study
- Clinical Centers
- Data Center
- Participating Research Networks
- Research in Children
- Publications
- Press Releases
- Contact Info

THAPCA Trials

Cardiopulmonary arrest (when the heart stops beating) is a tragic event in children that is associated with high rates of death and long term disability.



The Need

In children, this can occur in the hospital as a complication of many different medical conditions; cardiac arrest can also occur, suddenly, outside of the hospital as a result of an accident such as near drowning or a sudden illness. There is a great need for better treatments for children resuscitated after cardiac arrest in each setting to improve ultimate quality of life and to prevent long term brain injury or death.

The National Heart, Lung, and Blood Institute (NHLBI) is funding the first large scale, multi-center study to help determine the best treatment for children who are successfully resuscitated after a cardiac arrest.

Available at: http://www.thapca.org/

In-Hospital Cardiac Arrest

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

RCT, Hypothermia vs. Standard therapy, Adult IHCA, Germany
Primary outcome: All cause mortality at 6 months

Hypothermia After in-Hospital Cardiac Arrest (HACAinhospital)

The recruitment status of this study is unknown because the information has not been verified recently.
Verified on June 2008 by University of Schleswig-Holstein. Recruitment status was Recruiting

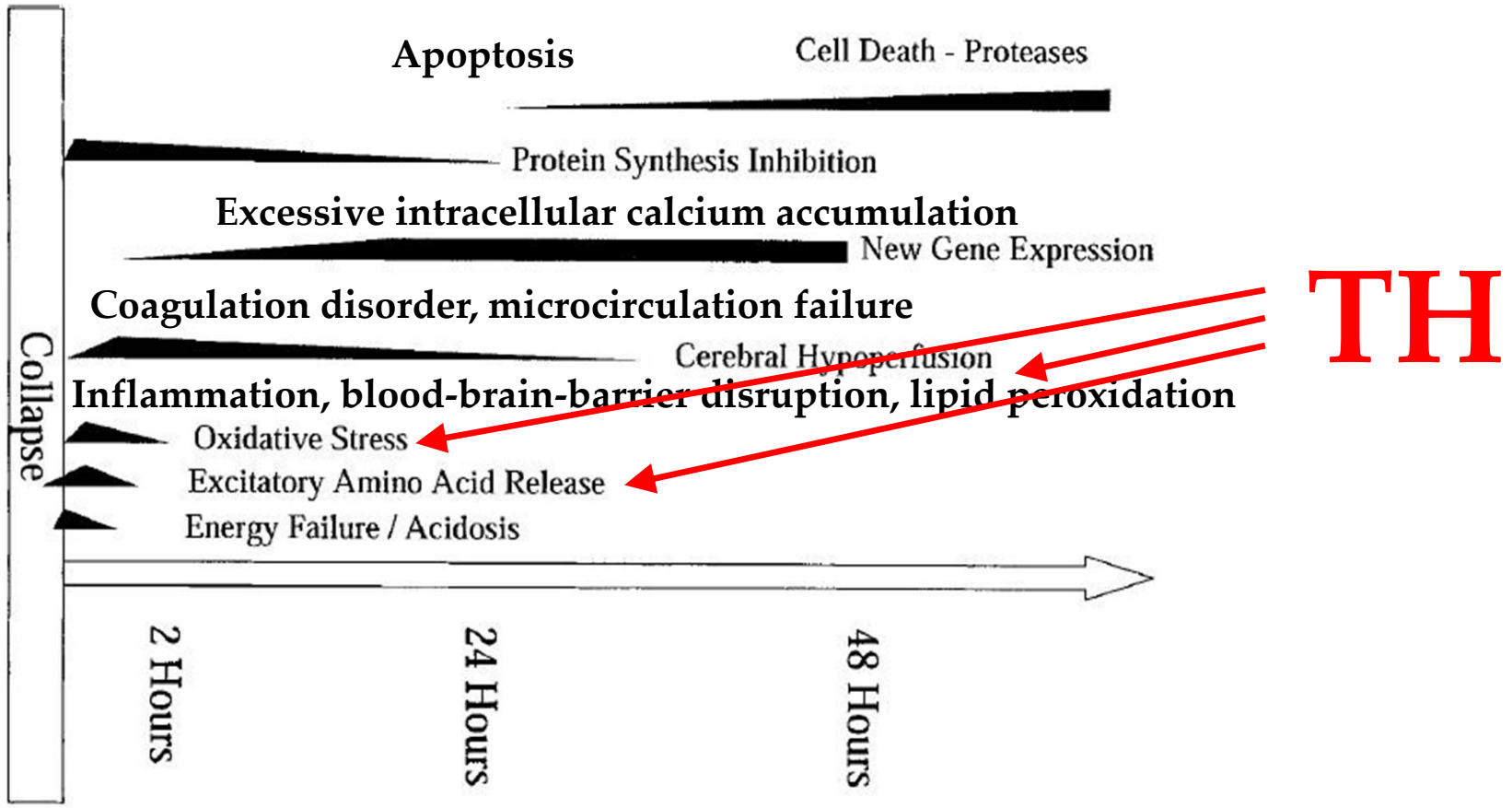
First Received on April 4, 2007. Last Updated on June 5, 2008 History of Changes

Sponsor:	University of Schleswig-Holstein
Information provided by:	University of Schleswig-Holstein
ClinicalTrials.gov Identifier:	NCT00457431

Available at: http://clinicaltrials.gov/ct2/show/study/NCT00457431

When to start cooling?

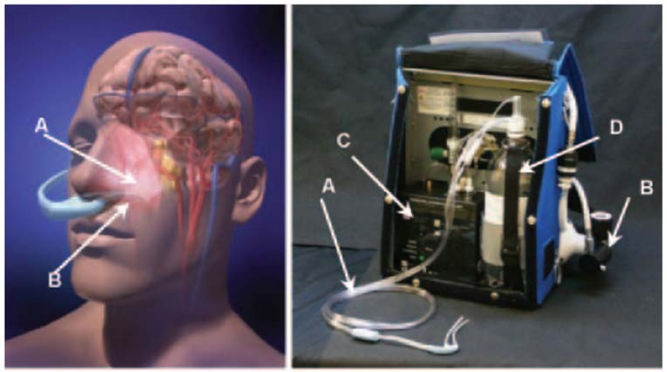
Neuroprotective Effects of TH



Angelos MG,et al. *Acad Emerg Med* 2001;8:909-24

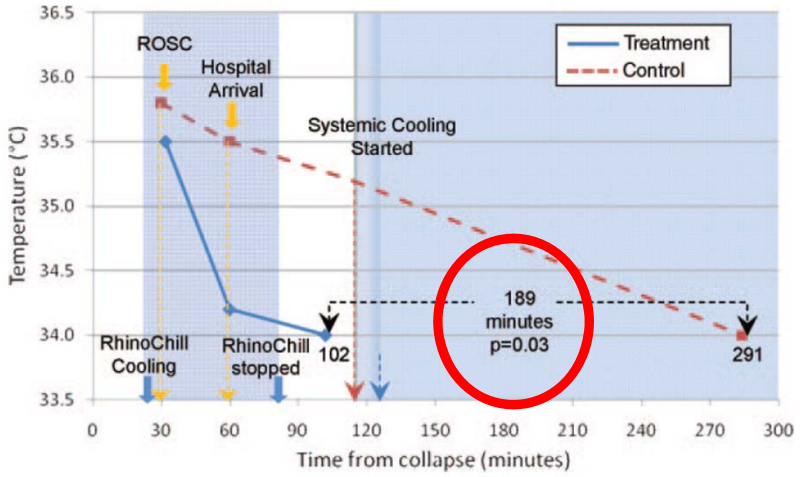
Intranasal Cooling During CPR

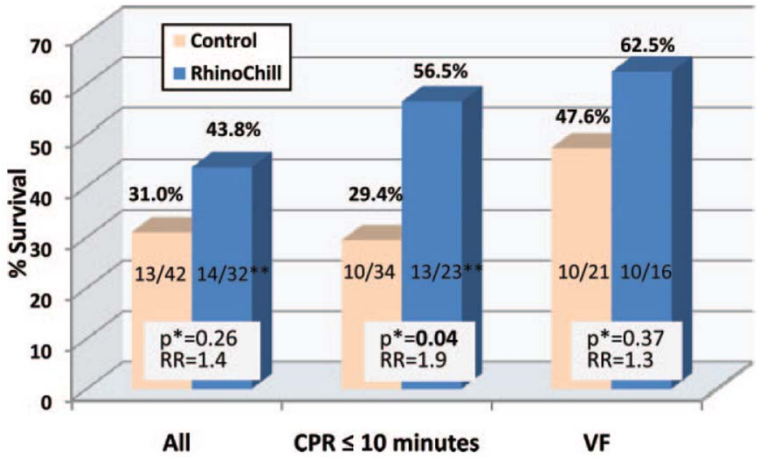
RCT, Intranasal cooling vs. Cooling after hospital admission, 194 OHCA, Europe

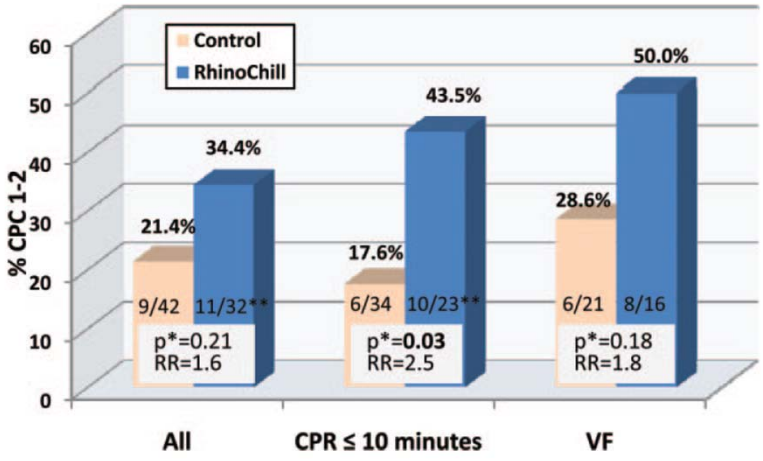


A: coolant spray
B: nasal catheter

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







Castren M, et al. *Circulation* 2010;122:729-36

Cold Fluid Infusion During CPR (Adult VF)

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

RCT, Prehospital early cooling vs. Hospital cooling, VF OHCA, Australia
Sample size n=1300, Primary outcome: Survival to hospital discharge

The RINSE Trial: The Rapid Infusion of Cold Normal Saline Trial During Cardiopulmonary Resuscitation (CPR)

This study is not yet open for participant recruitment.
Verified by Ambulance Victoria, July 2010

First Received: November 6, 2009 Last Updated: July 28, 2010 History of Changes

Sponsor:	Ambulance Victoria
Collaborator:	Monash University
Information provided by:	Ambulance Victoria
ClinicalTrials.gov Identifier:	NCT01172678

Available at: http://clinicaltrials.gov/ct2/show/NCT01172678?term=RINSE&rank=4

Cold Fluid Infusion During CPR (Adult Non-VF)

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

RCT, Prehospital early cooling vs. Hospital cooling, Non-VF OHCA, Australia
Primary outcome: Survival to hospital discharge

Rapid Infusion of Cold Normal Saline During CPR for Patients With Non-VF Out-of-hospital Cardiac Arrest (RINSE)

This study is currently recruiting participants.
Verified on July 2010 by Ambulance Victoria

First Received on July 26, 2010. Last Updated on July 29, 2010 History of Changes

Sponsor:	Ambulance Victoria
Information provided by:	Ambulance Victoria
ClinicalTrials.gov Identifier:	NCT01173393

Available at: http://clinicaltrials.gov/ct2/show/NCT01173393

Prehospital Cooling after ROSC

RCT, Prehospital cooling vs. Cooling after hospital admission ,234 OHCA, Australia

	Paramedic Cooling (n=118)	Hospital Cooling (n=116)	*P**
Favorable outcome, n (%; 95% CI)	56 (47.5; 38.2–56.9)	61 (52.6; 43.1–61.9)	0.433
Discharge to home, n (%; 95% CI)	24 (20.3; 13.5–28.7)	34 (29.3; 21.2–38.5)	…
Discharge to rehabilitation, n (%; 95% CI)	32 (27.1; 19.3–36.1)	27 (23.3; 15.9–32.0)	…
Discharge to nursing home awake, n	0	0	…
Discharge to nursing home comatose, n (%; 95% CI)	0	1 (0.9; 0.02–4.7)	…
Dead, n (%; 95% CI)	62 (52.5; 43.1–61.8)	54 (46.6; 27.2–56.0)	…

CI indicates confidence interval.
*P calculated by χ^2 test.

Bernard SA, et al. *Circulation* 2010;122:737-42.

Hypothermia Network (Europe)

Acta Anaesthesiol Scand 2009; **53**: 926–934
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ACTA ANAESTHESIOLOGICA SCANDINAVICA
doi: 10.1111/j.1399-6576.2009.02021.x

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

N. NIELSEN[1,2], J. HOVDENES[3], F. NILSSON[4], S. RUBERTSSON[5], P. STAMMET[6], K. SUNDE[7], F. VALSSON[8], M. WANSCHER[9] and H. FRIBERG[1,10], for the Hypothermia Network

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Neither time to initiation of TH ($P = 0.48$), time to achievement of target temperature ($P = 0.91$), depth of TH ($P = 0.50$), duration of TH ($P = 0.19$) nor rewarming time to normothermia ($P = 0.73$) had an association with outcome.

When to start cooling?

Landmark RCT (HACA)

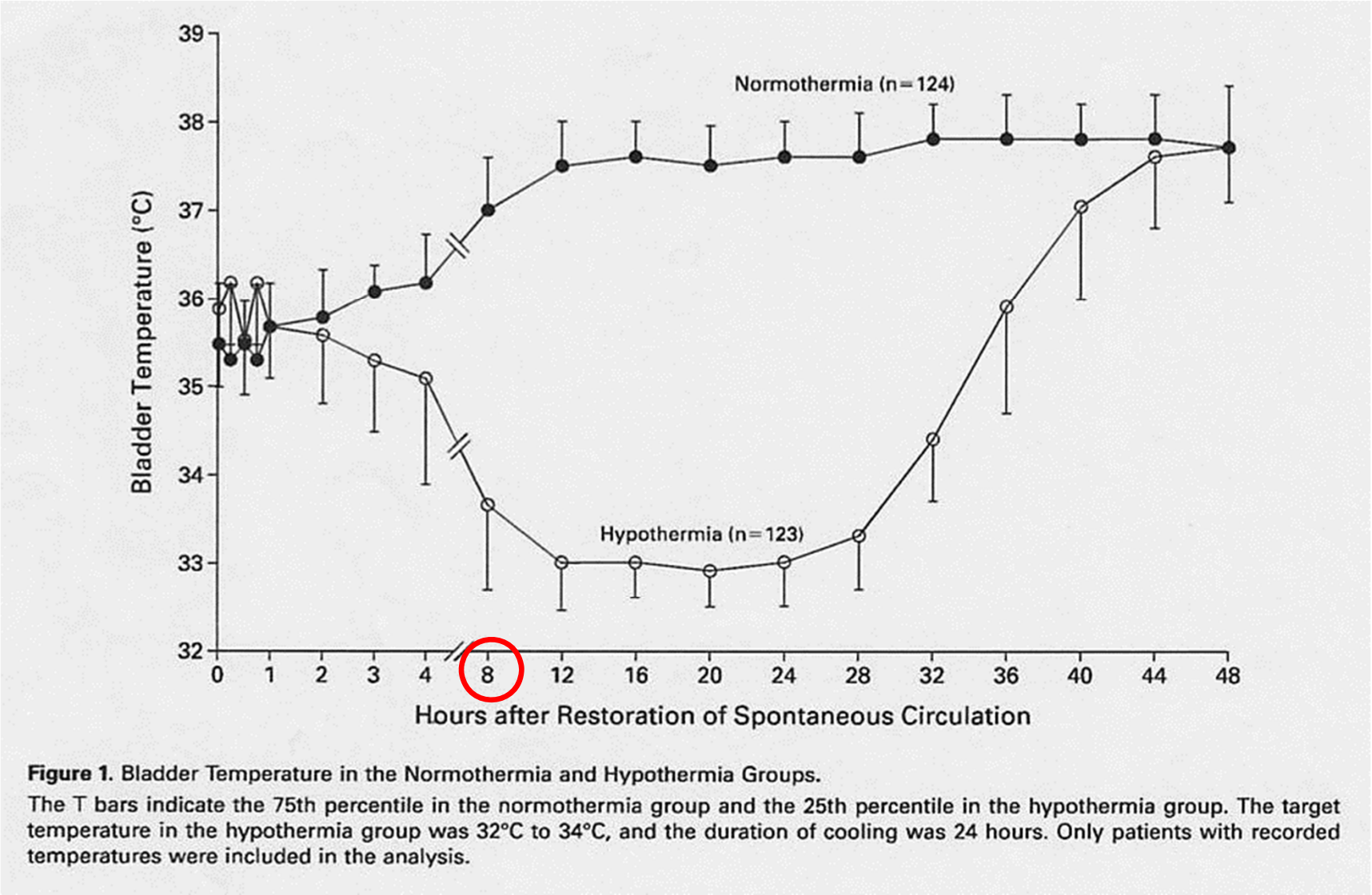


Figure 1. Bladder Temperature in the Normothermia and Hypothermia Groups.

The T bars indicate the 75th percentile in the normothermia group and the 25th percentile in the hypothermia group. The target temperature in the hypothermia group was 32°C to 34°C, and the duration of cooling was 24 hours. Only patients with recorded temperatures were included in the analysis.

HACA. *N Engl J Med* 2002; 346:549-56.

Expert Opinion

The NEW ENGLAND JOURNAL of MEDICINE

CLINICAL THERAPEUTICS

Targeted Temperature Management for Comatose Survivors of Cardiac Arrest

Michael Holzer, M.D.

hypothermia should be initiated as early as possible and not later than 10 hours after the cardiac arrest.

Holzer M. ***NEJM*** **2010;363:1256-64**

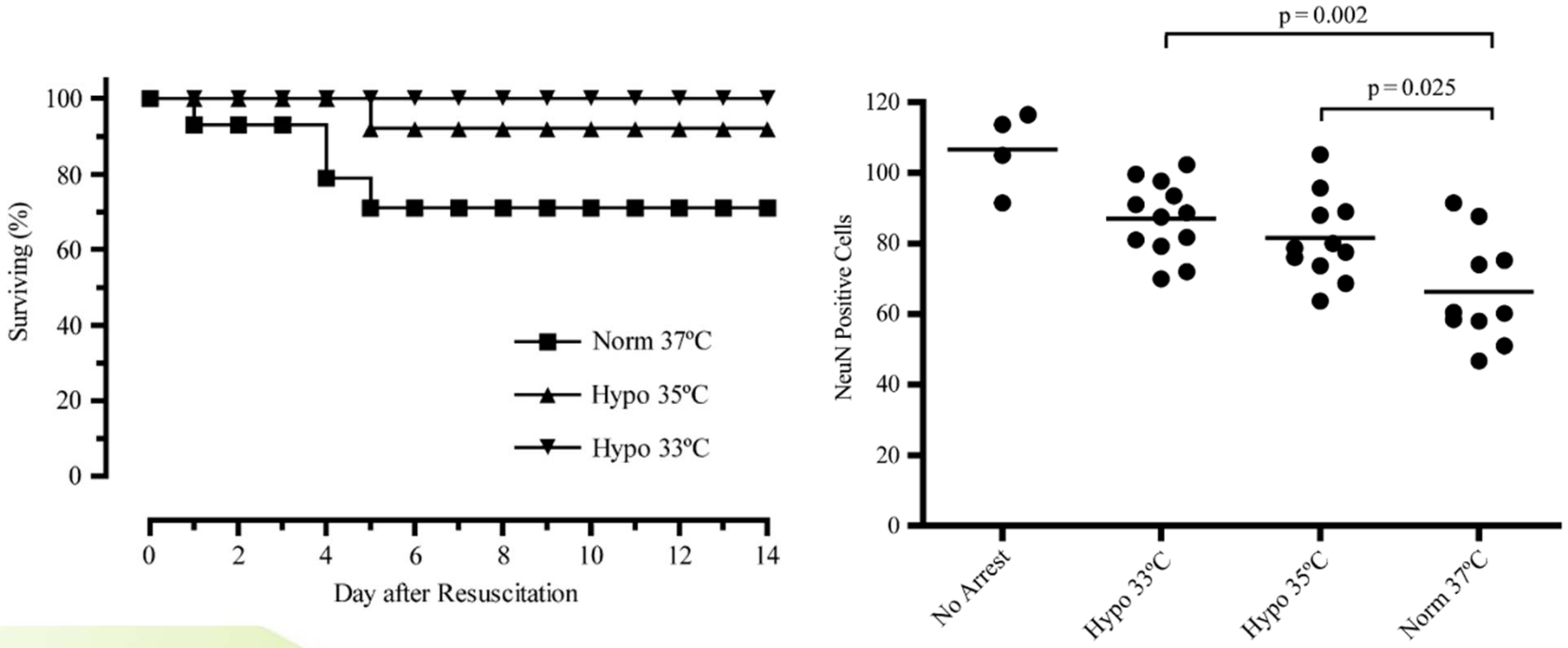
How deep to cool?

Previous Clinical Reports

Study (Year)	Method	Temp target(℃)	Time target(min)	Time cool(hr)	Time rewarm(hr)
Williams (1958)	Cooling blanket	30-34	NA	24-72	NA
Benson (1959)	Cooling blanket	31-32	NA	3-192	NA
Bernard (1997)	Ice-pack	33	74	12	6
Yanagawa (1998)	Cooling blanket	33-34	414	48	72-94
Zeiner (2000)	Cold air	32-34	276	24	7
Nagao (2000)	Cardiopulmonary bypass	34	360	72	48
Felberg (2001)	Cooling blanket	32-34	378	24	12
Hachimi-Idrissi (2001)	Helmet device	34	180 (70-240)	4	8
Holzer (2002)	Cooling catheter	32-34	95	24	8
Bernard (2002)	Ice-pack	33	120	12	6
HACA (2002)	Cold air	32-34	480 (240-960)	24	8

33 ℃ vs. 35 ℃

8 min asphyxial arrest in rats, cranial temperature 33℃, 35 ℃, or 37 ℃

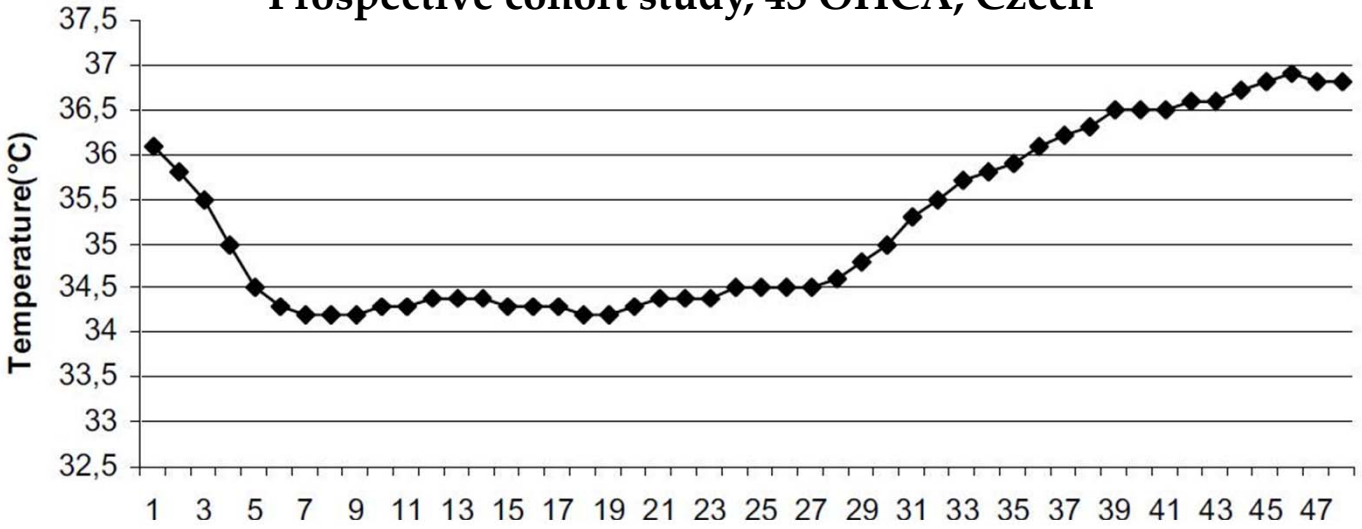


Logue ES, et al. *Acad Emerg Med* 2007;14:293-300

How deep to cool?

34-35℃

Prospective cohort study, 43 OHCA, Czech



	No/total	No/(%)
Favorable neurologic outcome	21/43	(49 %)
Death	12/43	(28 %)
– in hospital	10	
– after discharge	2	

Gal R, et al. *Bratisl Lek Listy* 2009; 110:222-5

32℃ or 34 ℃ vs. 33 ℃

Table 4 Multiple logistic regression analyses for hypotension during maintenance of target temperature (A), mortality (B), and neurologic outcome (C)

Factors	*P*	Odds ratio	95% CI
(A)			
32°C	.016	6.800	1.428-32.373
34°C	.622	1.417	0.355-5.659
(B)			
APACHE II	.023	1.139	1.018-1.275
(C)			
Sex	.031	20.067	1.325-304.027
Noncardiac	.024	16.357	1.435-186.442
Age	.019	1.100	1.016-1.192

APACHE indicates Acute Physiology and Chronic Health Evaluation.

Kim JJ, et al. *Am J Emerg Med* 2010; article in press

How deep to cool?

32 ℃ vs. 34 ℃

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

RCT, Hypothermia to 32℃ vs. Hypothermia to 34℃, OHCA, Spain
Sample size n=30, Primary outcome: Survival free from severe dependence

Trial of Different Hypothermia Temperatures in Patients Recovered From Out-of-hospital Cardiac Arrest

This study is currently recruiting participants.
Verified on June 2010 by Hospital Universitario La Paz

First Received on July 1, 2010. Last Updated on July 14, 2010 History of Changes

Sponsor:	Hospital Universitario La Paz
Information provided by:	Hospital Universitario La Paz
ClinicalTrials.gov Identifier:	NCT01155622

Available at: http://clinicaltrials.gov/ct2/show/NCT01155622

가톨릭대학교 서울성모병원
THE CATHOLIC UNIV. OF KOREA SEOUL ST. MARY'S HOSPITAL

How deep to cool?

33 ℃ vs. 36 ℃

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

RCT, Mild hypothermia (33℃) vs. Strict normothermia (36 ℃), OHCA, Europe
Sample size n=850, Primary outcome: All-cause mortality (minimum of 180 days)

Target Temperature Management After Cardiac Arrest (TTM)

This study is currently recruiting participants.
Verified by Helsingborgs Hospital, June 2010

First Received: November 25, 2009 Last Updated: December 10, 2010 History of Changes

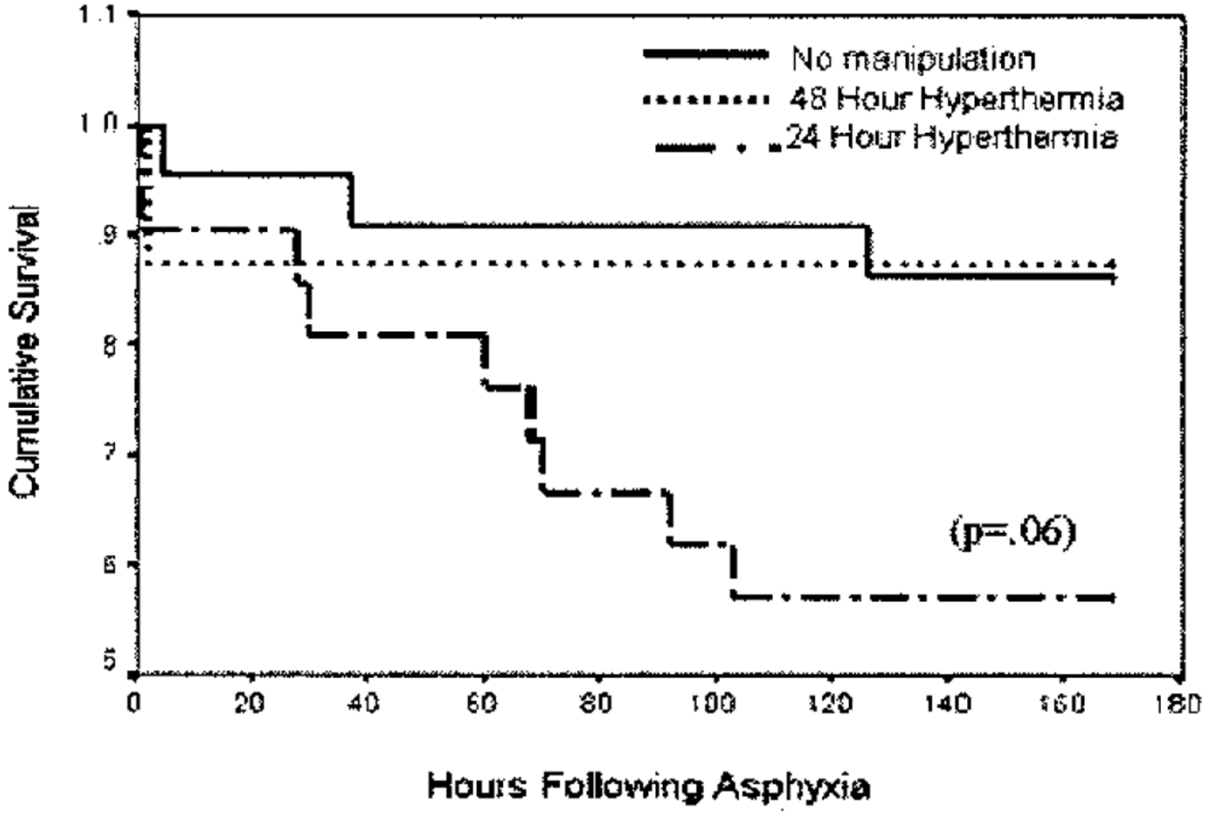
Sponsor:	Helsingborgs Hospital
Collaborators:	Scandinavian Critical Care Trials Group Copenhagen Trial Unit, Copenhagen, Denmark Lund University, Lund, Sweden
Information provided by:	Helsingborgs Hospital
ClinicalTrials.gov Identifier:	NCT01020916

Available at: http://clinicaltrials.gov/ct2/show/NCT01020916

How long to keep cool?

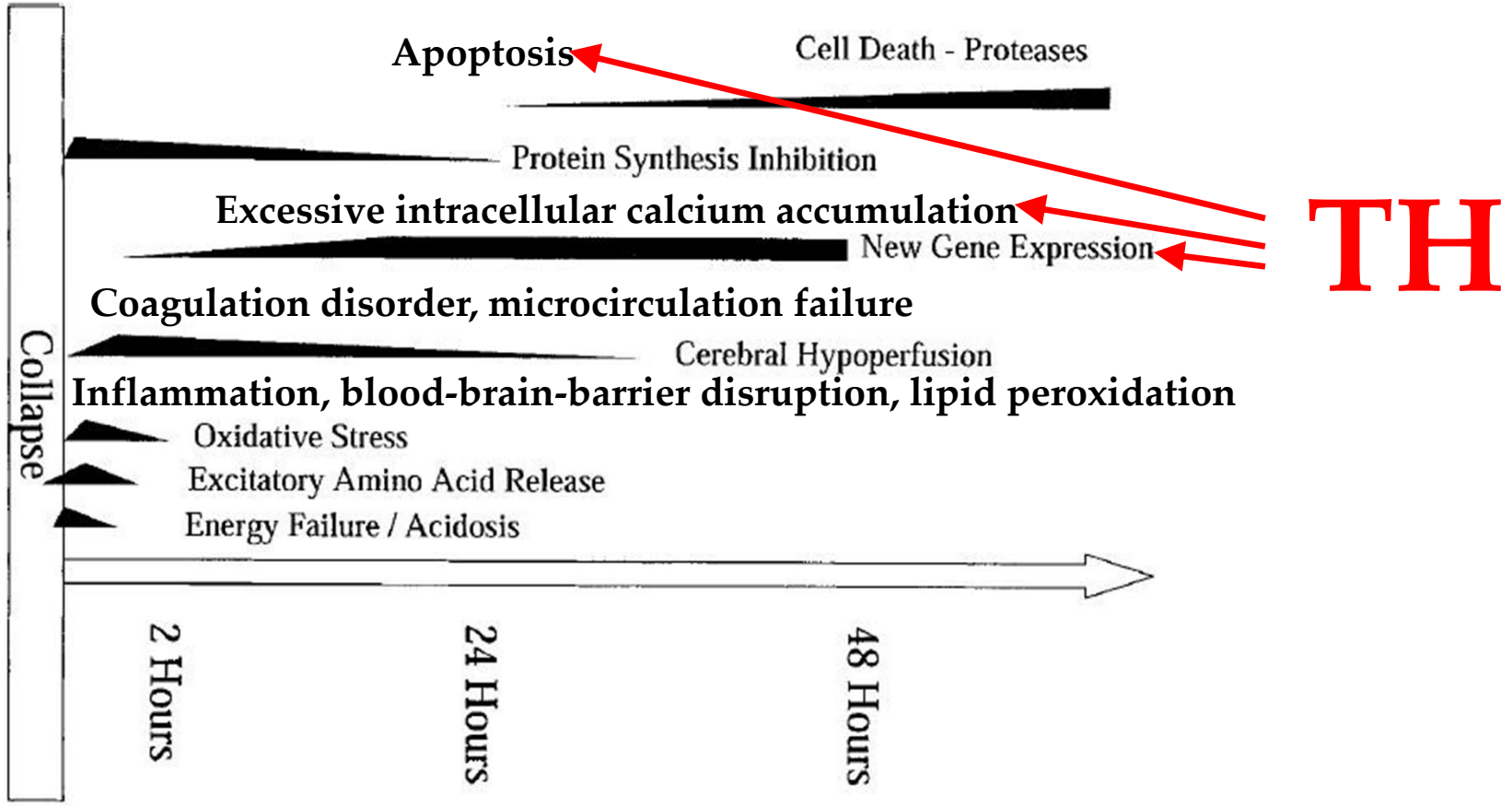
Brain is Temperature-Sensitive for 24 hours

8 min asphyxial arrest in rats, 24 hr vs. 48 hr hyperthermia



Hickey RW, et al. Crit Care Med 2003; 31:531-5

Neuroprotective Effects of TH



Angelos MG,et al. ***Acad Emerg Med*** **2001;8:909-24**

Previous Clinical Reports

Study (Year)	Method	Temp target(℃)	Time target(min)	Time cool(hr)	Time rewarm(hr)
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Bernard (2002)	Ice-pack	33	120	12	6
HACA (2002)	Cold air	32-34	480 (240-960)	24	8

24 hours vs. 72 hours (Pediatric CA)

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

RCT, 72 hr hypothermia vs. 24 hr hypothermia, Sample size n=40, USA
Primary outcome: Degree of brain injury as measured by biomarkers and MRS

Duration of Hypothermia for Neuroprotection After Pediatric Cardiac Arrest

This study is currently recruiting participants.
Verified on May 2009 by University of Pittsburgh

First Received on November 24, 2008. Last Updated on May 7, 2009 History of Changes

Sponsor:	University of Pittsburgh
Collaborators:	National Institute of Neurological Disorders and Stroke (NINDS) Laerdal Medical Children's Hospital of Pittsburgh
Information provided by:	University of Pittsburgh
ClinicalTrials.gov Identifier:	NCT00797680

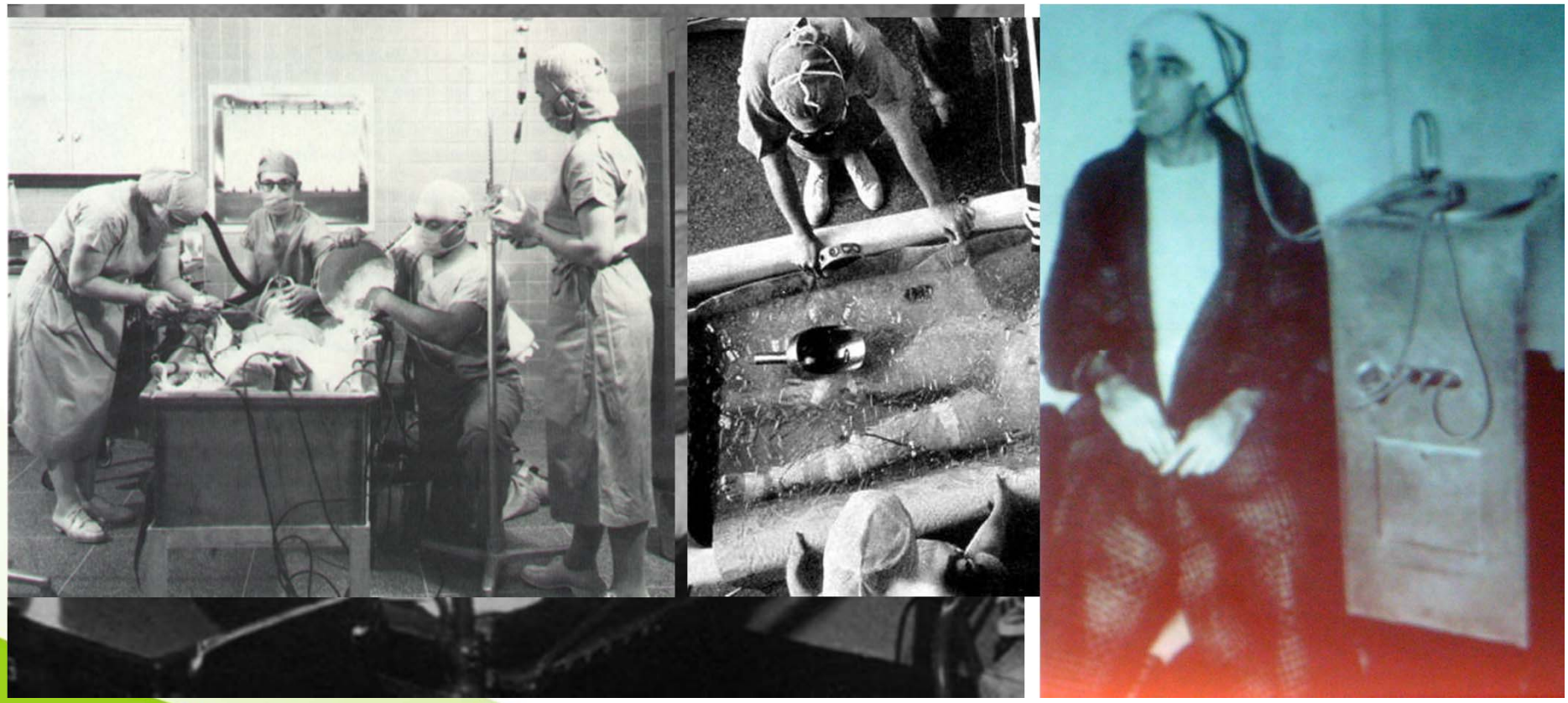
Available at: http://clinicaltrials.gov/ct2/show/NCT00797680

How to cool?

Ideal Cooling Methods and Devices

- Fast
- Easy
- Non-invasive
- Non-messy
- Cheap
- Controllable
- Short and longer term use

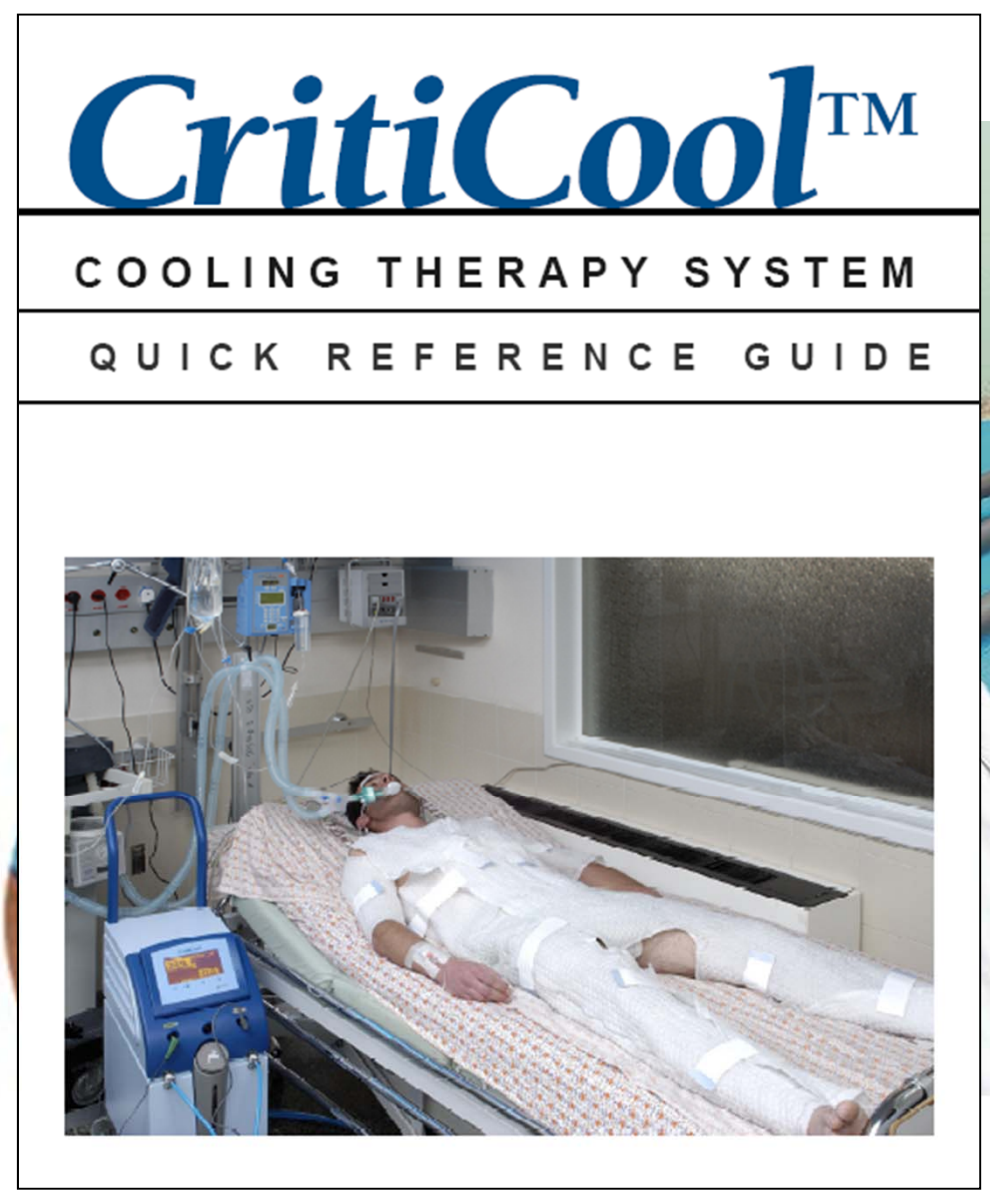
Cooling Methods and Devices



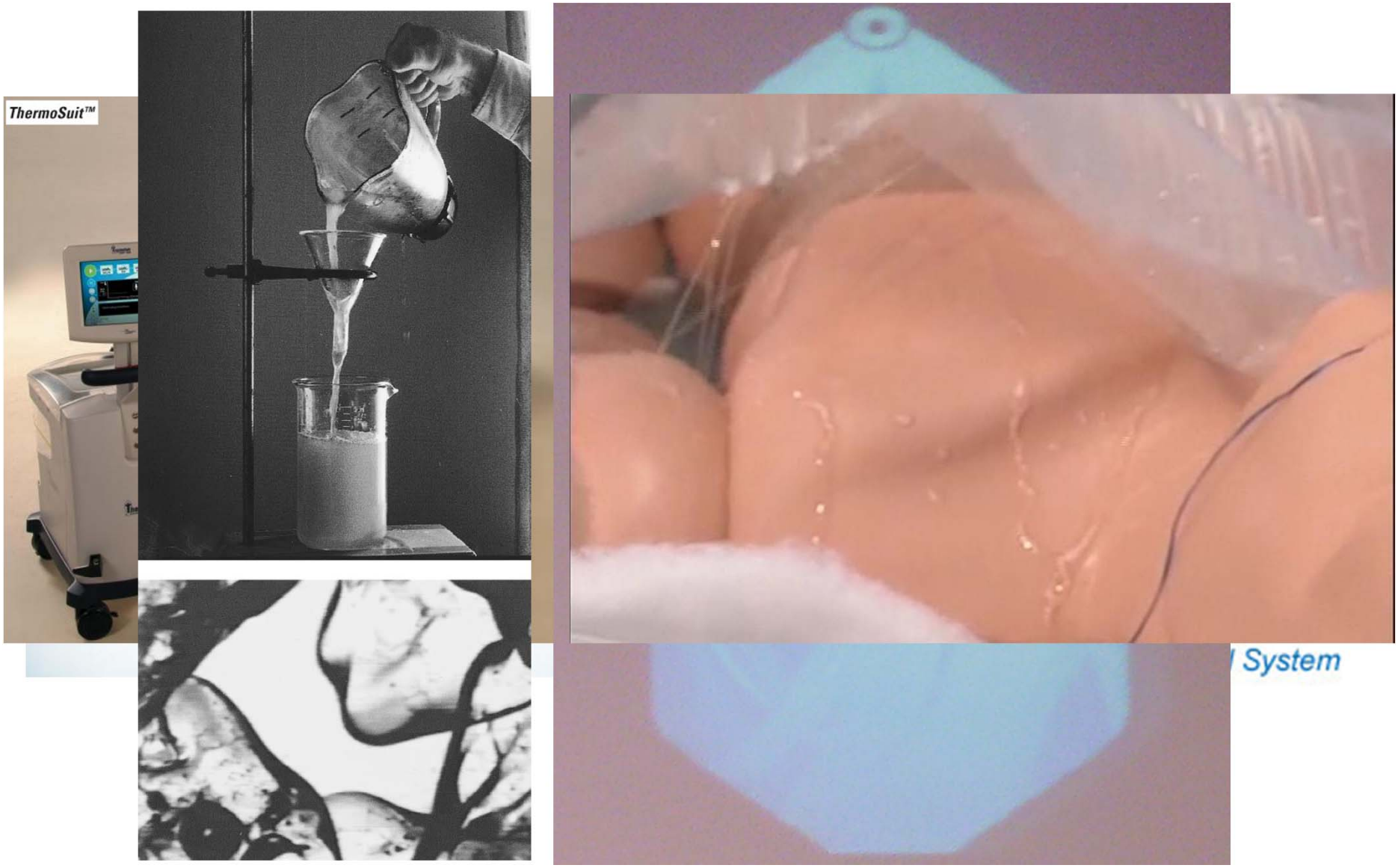
How to cool?

Cooling Methods and Devices

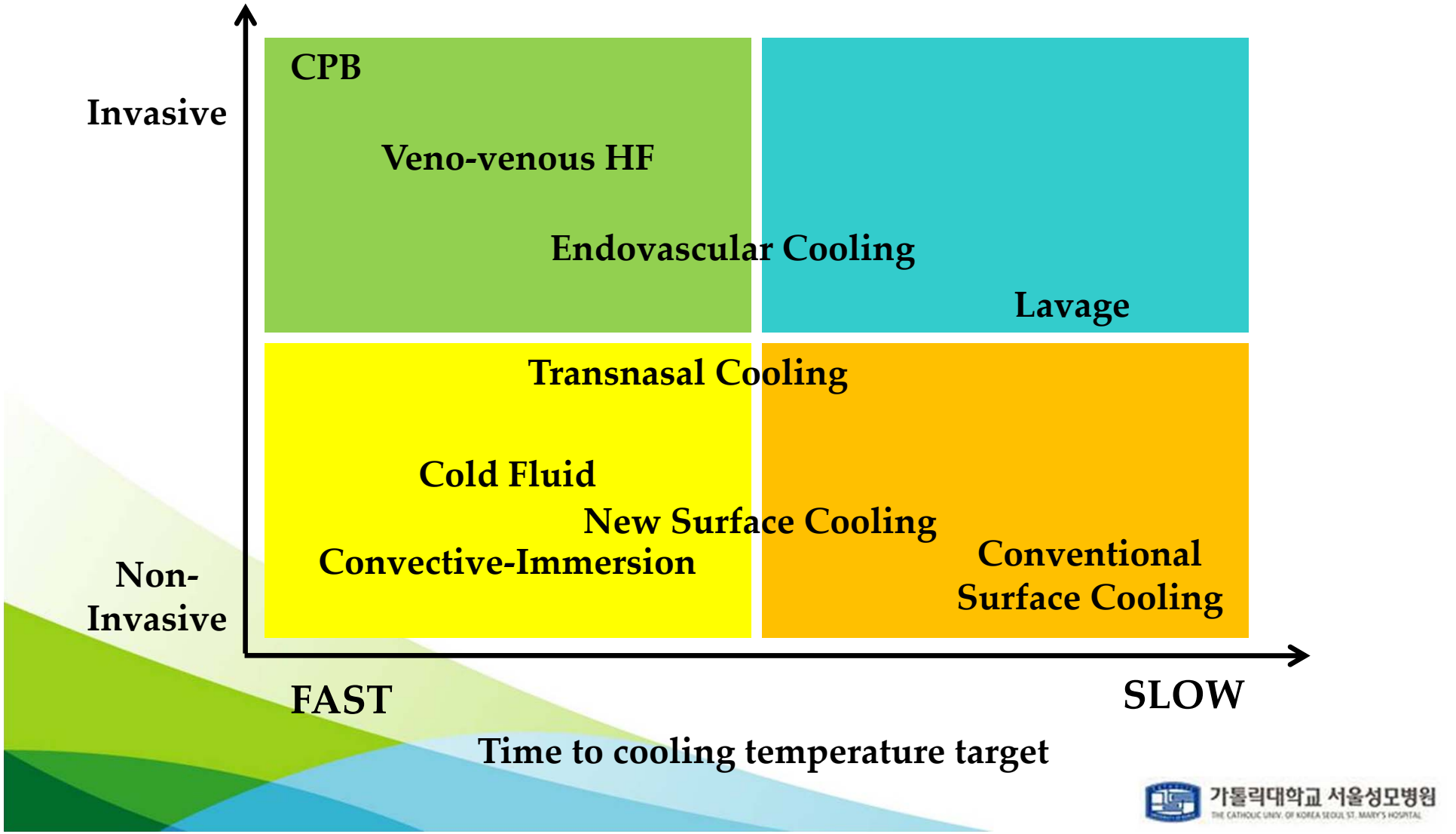
New Methods and Devices



New Methods and Devices



Efficacy and Safety of Cooling Methods

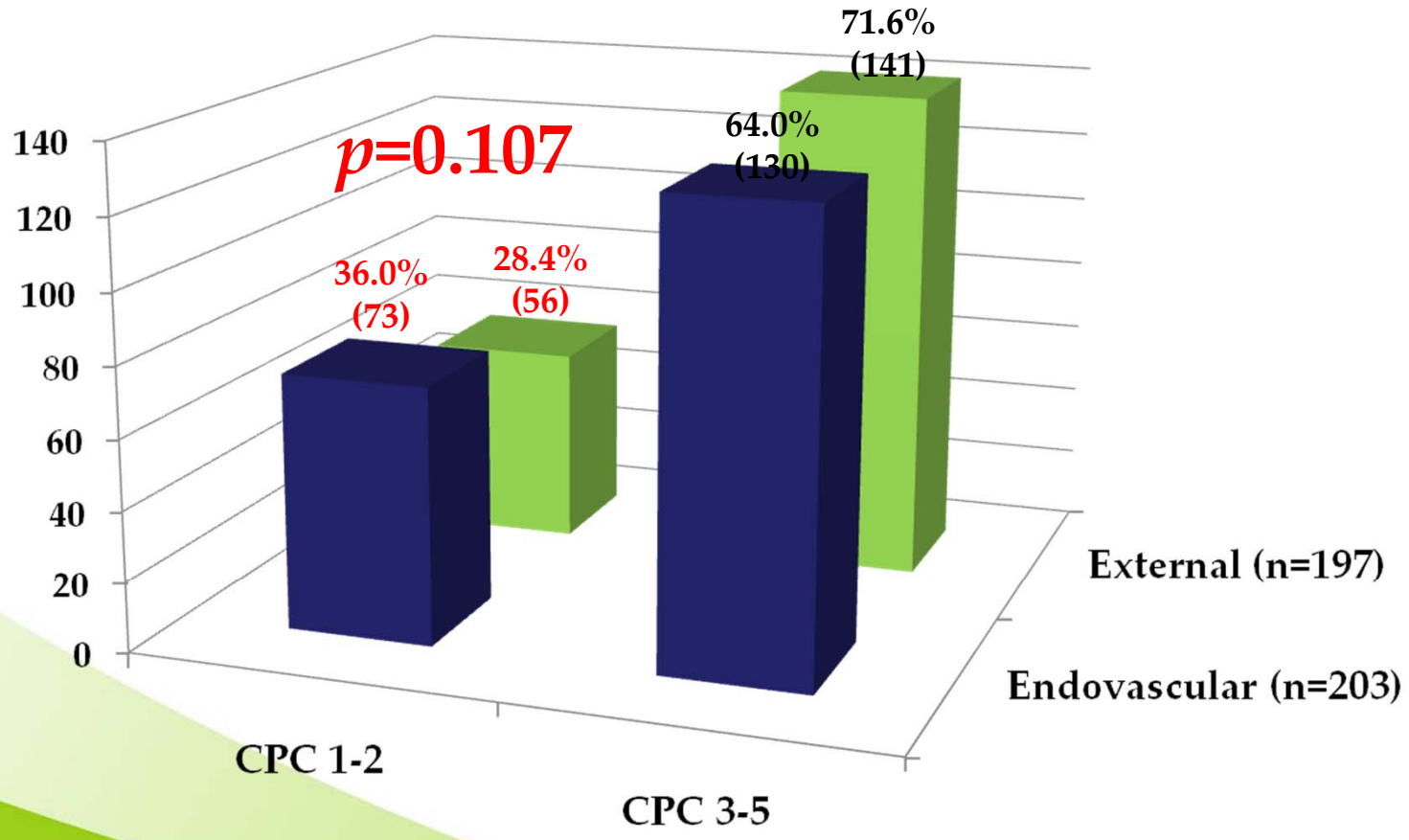


Comparison of Cooling Rate

Techniques or Methods	Rate(°C/hr)
Cold air (TheraKool®)	0.18
Ice packs (head)	0.32
Helmet with chemical cooling capabilities (Frigicap®)	0.5
Water-circulating external cooling garment (CritiCool®)	0.7
Ice packs (whole body)	0.9
Hydrogel energy transfer pads (Arctic Sun®)	1.04
Endovascular catheter (Cool Guard®)	1.46
Transnasal coolant spray (BeneChill®)	1.6
Specialized new cooling helmet	1.84
Water immersion cooling system (Thermosuit®)	3.0
Hypocarbon-filled cooling pads (EMCOOLSpad®)	3.0
Cold fluid infusion (cardiac arrest, 60ml/kg/hr)	3.4
Thermosuit® with propofol sedation	4.2
Cold fluid infusion (volunteers, 80ml/kg/hr)	5.0
Ice water immersion	6.6

Endovascular vs. External Cooling

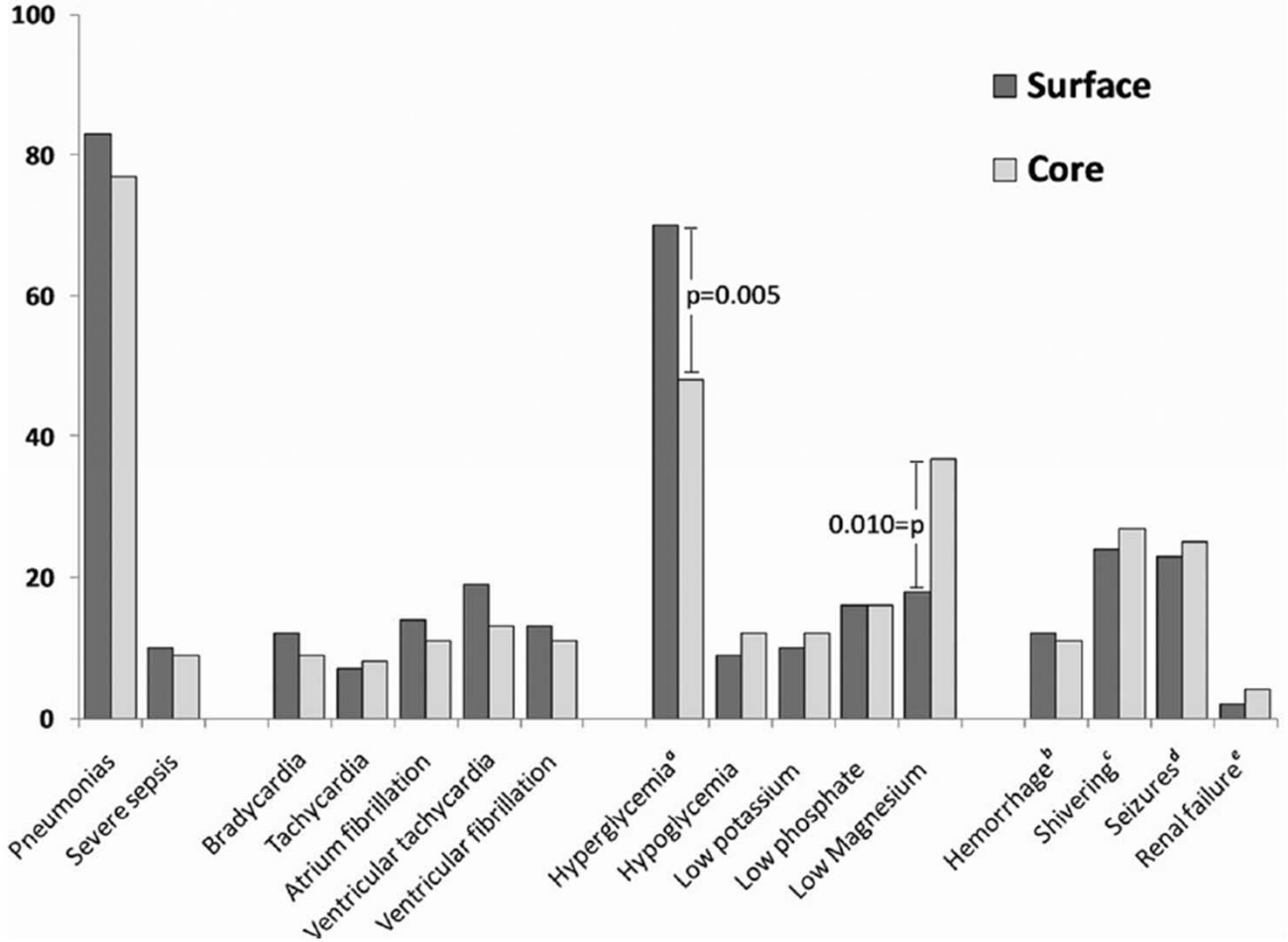
Multicenter RCT, Endovascular vs. External cooling after cardiac arrest, 400 OHCA, France



Deye N. The ICEREA Study Group. *Resuscitation* 2010;81(suppl): S3

Endovascular vs. External Cooling

Single-center observational study, Endovascular vs. Surface cooling , 167 OHCA, Norway



Tømte Ø, et al. *Crit Care Med* 2011;39: 443-9

Invasive vs. Non-Invasive

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

RCT, Coolgard vs. ActicSun, Sample size n=120, Germany
Primary outcome: Time to reach target temperature and NSE

COOL-Trial: Outcome With Invasive and Non-invasive Cooling After Cardiac Arrest

This study has been completed.

First Received on February 12, 2009. Last Updated on February 1, 2010 History of Changes

Sponsor:	University of Leipzig
Information provided by:	University of Leipzig
ClinicalTrials.gov Identifier:	NCT00843297

Available at: http://clinicaltrials.gov/ct2/show/NCT00843297

Invasive vs. Non-Invasive

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

RCT, Coolgard vs. ActicSun, Sample size n=51, Singapore
Primary outcome: Survival to hospital discharge

Comparing Therapeutic Hypothermia Using External and Internal Cooling for Post-Cardiac Arrest Patients

This study is currently recruiting participants.
Verified on June 2009 by Singapore General Hospital

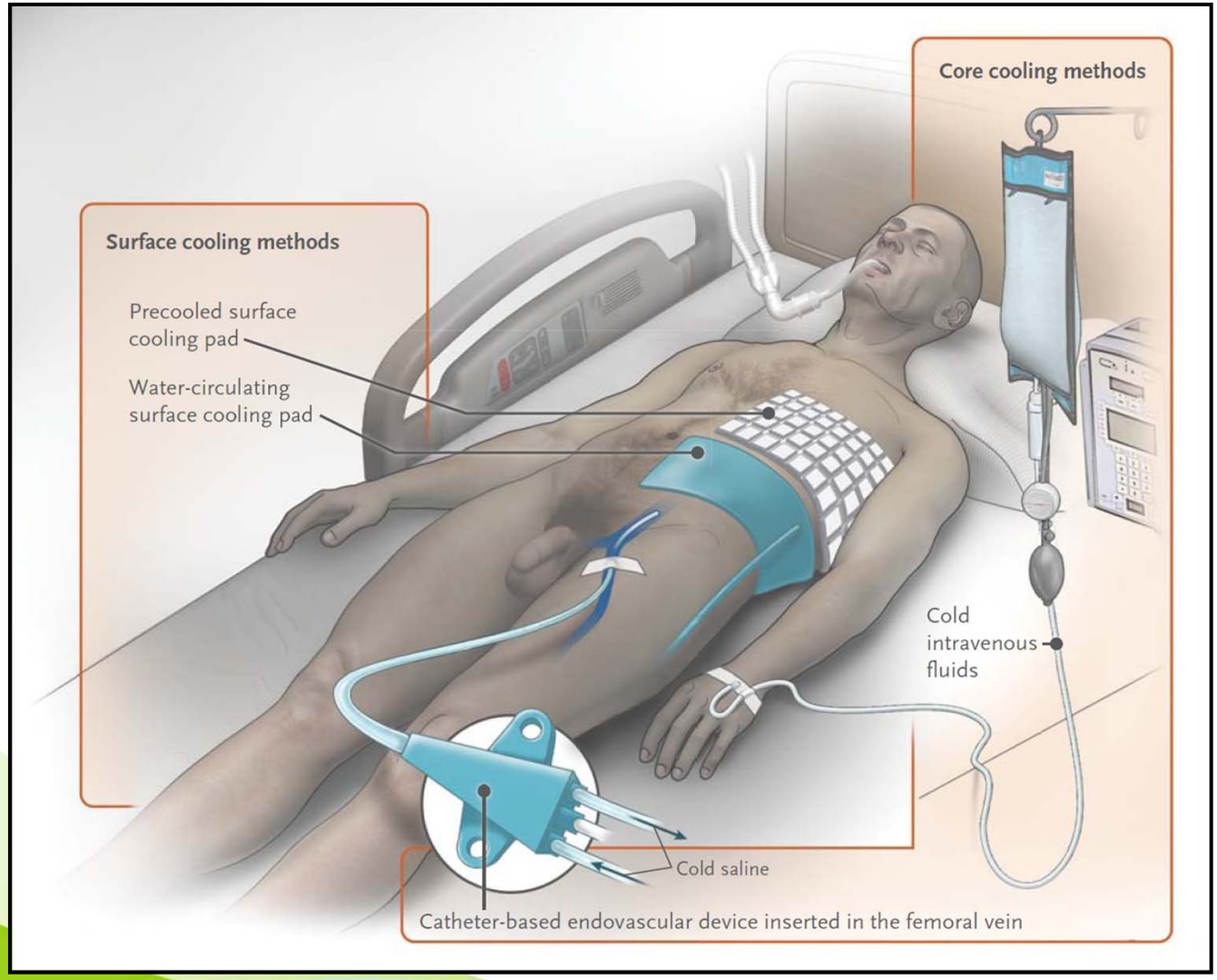
First Received on January 21, 2009. Last Updated on June 23, 2009 History of Changes

Sponsor:	Singapore General Hospital
Collaborator:	National Heart Centre of Singapore Pte Ltd
Information provided by:	Singapore General Hospital
ClinicalTrials.gov Identifier:	NCT00827957

Available at: http://clinicaltrials.gov/ct2/show/NCT00827957

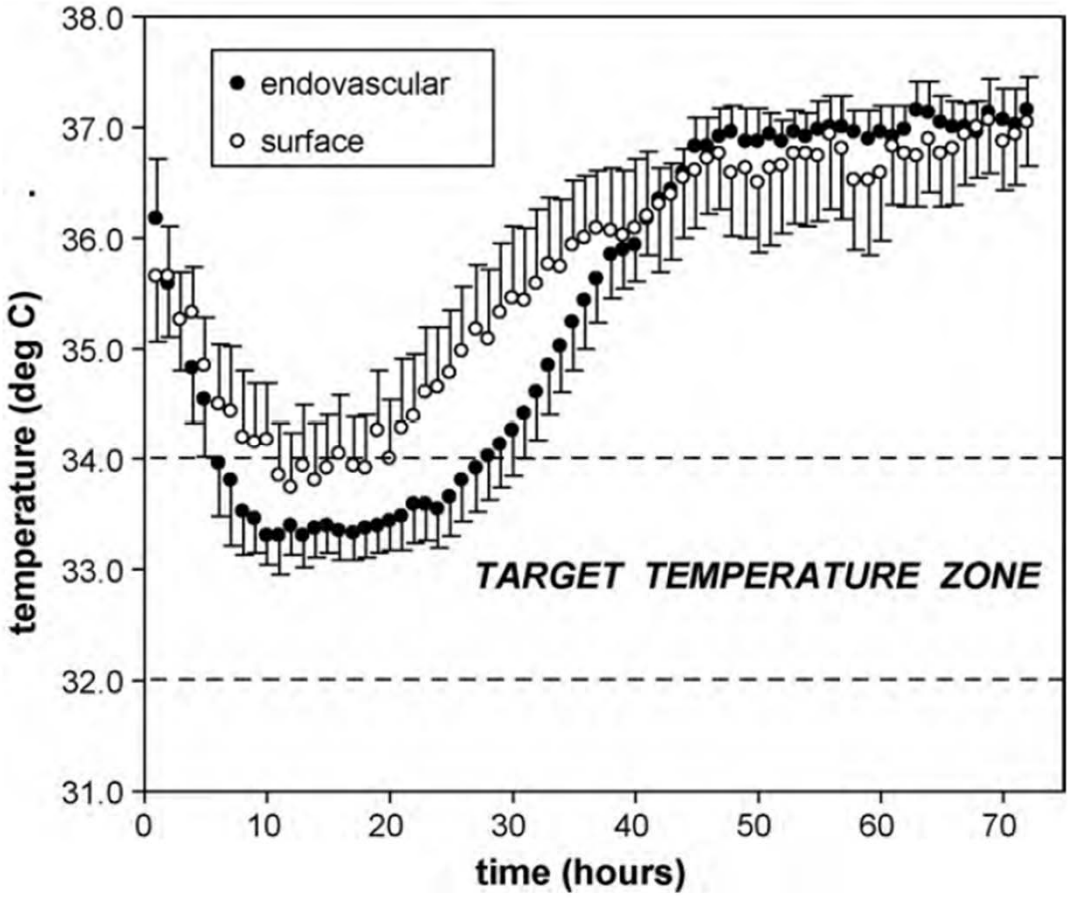
How to cool?

Combination



Holzer M. *NEJM* 2010;363:1256-64

Cold Fluid + Surface vs. Cold Fluid + Endovascular

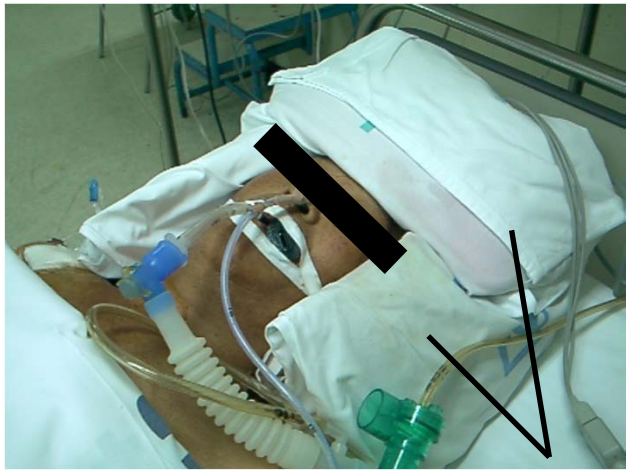


Gillies MA, et al. *Resuscitation* 2010; 81:1117-20

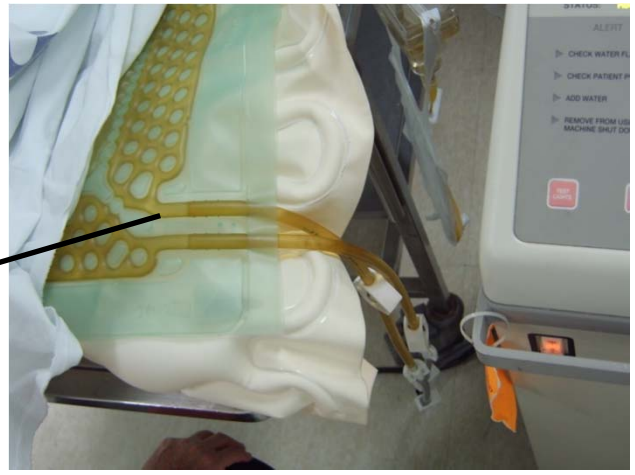
Combination I (Seoul St. Mary's)

Cold Saline Infusion (2L)

Water-Circulating Cooling Mattress

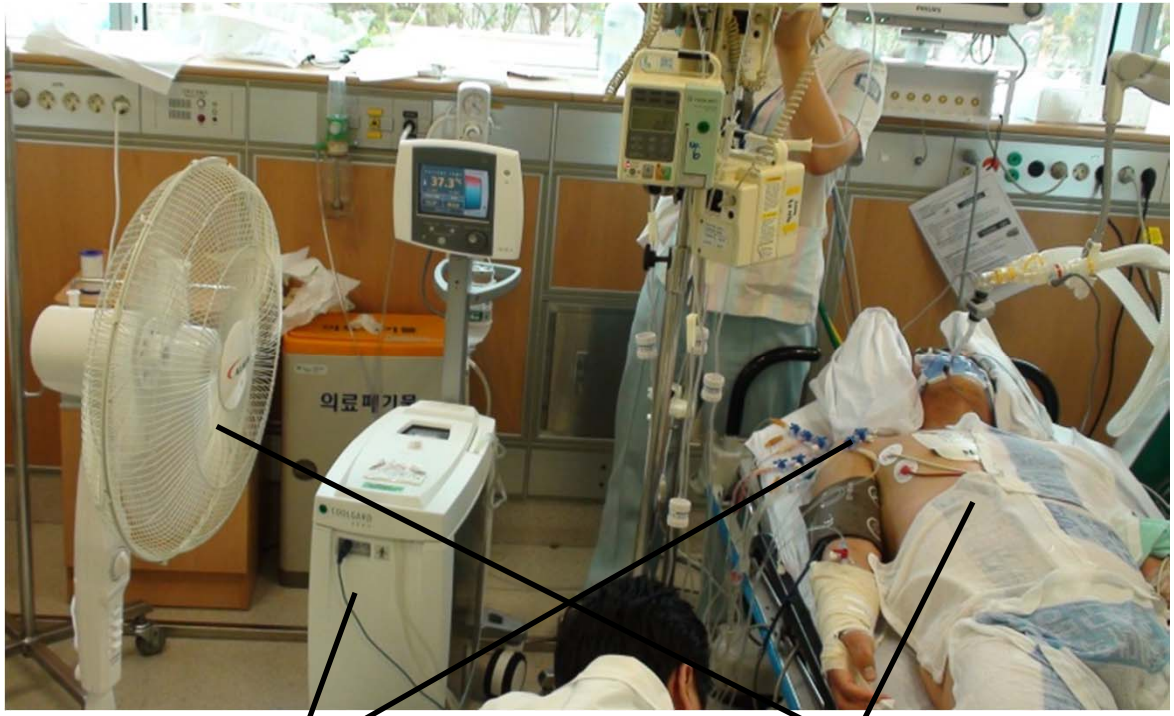


Ice Bags



Combination II (Seoul St. Mary's)

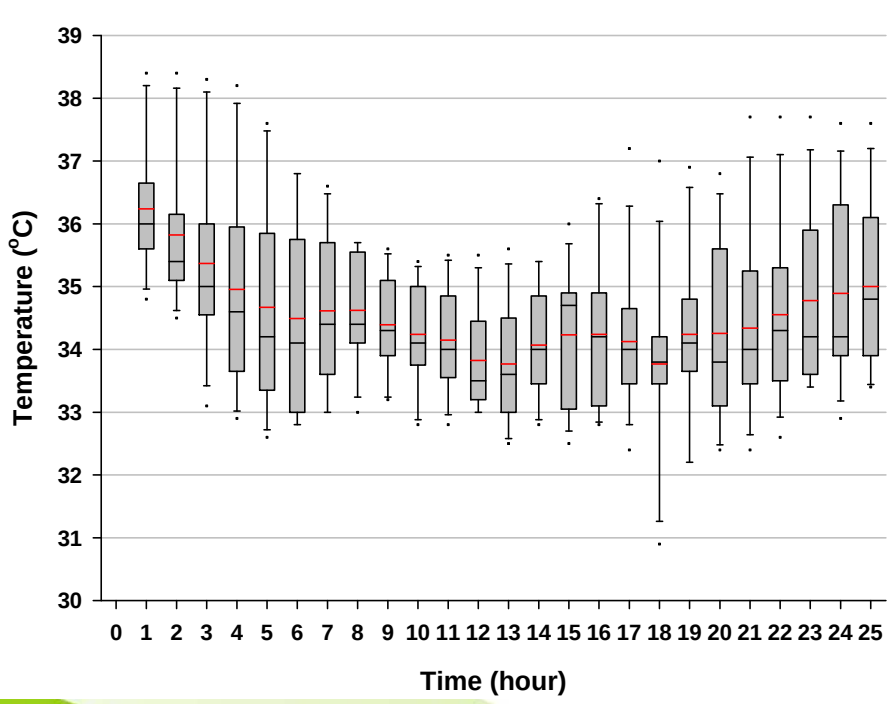
Cold Saline Infusion (2L)

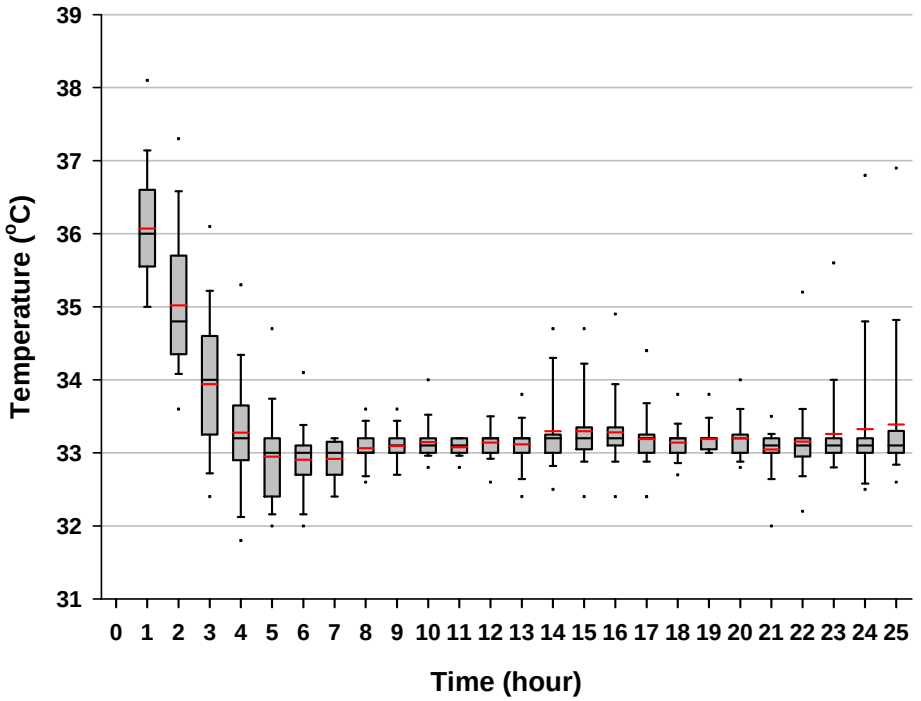


Endovascular Cooling (Cool line™ catheter)

Ice-Water Soaked Towels with Fanning

Surface only vs. Combination II





Kim YM, et al. Presented at *2010 KSEM Fall Meeting*

What physiological changes and side effects can be developed during TH?

What adjunctive drugs should be given?

Physiological changes?

Physiologic Effects of TH

Body System	Physiologic Effect	Nursing Actions
Systemic	Decreased metabolic demands	
	Decreased CO_2 production	
	Decreased O_2 consumption	Monitor pulse oximetry and P_aO_2
Neurologic	Decreased cerebral metabolic demands	
	Decreased intracranial pressure	
	Decreased level of consciousness	
Cardiovascular	Tachycardia (observed during induction)	
	Bradycardia	None, unless symptomatic
	Hypertension	Wean vasopressors, administer analgesics and sedation if appropriate
	Hypotension	Consider fluid administration and vasopressors
	Prolonged PR, QRS, and QT intervals	
	Dysrhythmias (observed ≤32°C)	Prevent overcooling
	Decreased cardiac output	None, unless hypotensive or symptomatic
	Increased central venous pressure	
	Increased mixed venous oxygenation values	
Gastrointestinal	Decreased motility	Feeding may be delayed until the rewarming phase
Genitourinary	Diuresis	Monitor urine output; replace fluids as needed
Endocrine	Insulin resistance	Administer insulin to maintain glucose within a prescribed range
Immune	Suppression of white blood cells	Institute ventilator-associated pneumonia bundles, elevated head of bed, take measures to prevent infection

Kupchik NL. *Crit Care Med* 2009;37(Suppl): S279-84

Physiologic Effects of TH

Pharmacokinetics ≤35°C

Altered clearance of various medications (data available for muscle paralyzers, propofol, fentanyl, phenytoin, pentobarbital, verapamil, propanol and volatile anesthetics (reduced clearance), but in all likelihood applies to many other types of medication)

No effect on gentamycin clearance in animal experiment

No effect on neostigmine effect or clearance in healthy volunteers

Polderman KH. ***Intensive Care Med*** **2004;30: 757-69**

Changes in Laboratory Findings

Frequency	Effect
Almost always	Mild to moderate increase in serum amylase levels (300–600 μ/l) Mild thrombocytopenia (platelet count 100–150x10^{12}) Increase in serum lactate levels (2.5–5 mmol/l)
Frequent	Moderate to severe thrombocytopenia (platelet count 30–100x10^{12}) Rise in serum glucose levels (due to decreased insulin sensitivity and decreased insulin secretion) High serum amylase levels (600–1200 μ/l) High serum lactate levels (5–7 mmol/l) Decrease in levels of potassium (K), magnesium (Mg), phosphate (P), calcium (Ca) Leukocytopenia (WBC (2–3x10^{9}/l)
Occurring regularly	Mild increase in liver enzymes (particularly SGOT and SGPT) Metabolic acidosis (due to increase in lactate levels and increased production of free fatty acids, ketones and glycerol) Slightly increased APTT and APTT
Occurring occasionally	Manifest acidosis, lactate levels ≥7 mmol/l Severe leukocytopenia (WBC <2x10^{9}) Increase in serum amylase ≥1200 μ/l Severe thrombocytopenia (platelet count ≤30x10^{12}) Manifest coagulation disorders with marked increase in APTT and PTT

Polderman KH. ***Intensive Care Med*** **2004;30: 757-69**

Immediate Side Effects in the Induction Phase

- Hypovolemia
- Electrolytes (K, Mg, P) disorders
- Hyperglycemia

Polderman KH. *Crit Care Med* 2009;37(Suppl): S186202

Adverse Events

Adverse Event	Targeted Temperature Management (N = 300)	Standard Treatment (N = 285)
	no. (%)	
Arrhythmia	55 (18)	47 (16)
Hemodynamic instability	14 (5)	15 (5)
Bleeding	26 (9)	19 (7)
Pneumonia	37 (12)	29 (10)
Sepsis	13 (4)	7 (2)
Electrolyte disorder	17 (6)	0
Renal failure	17 (6)	19 (7)
Seizures	10 (3)	11 (4)
Pancreatitis	1 (<1)	2 (1)
Pulmonary edema	33 (11)	52 (18)

Holzer M. *NEJM* 2010;363:1256-64

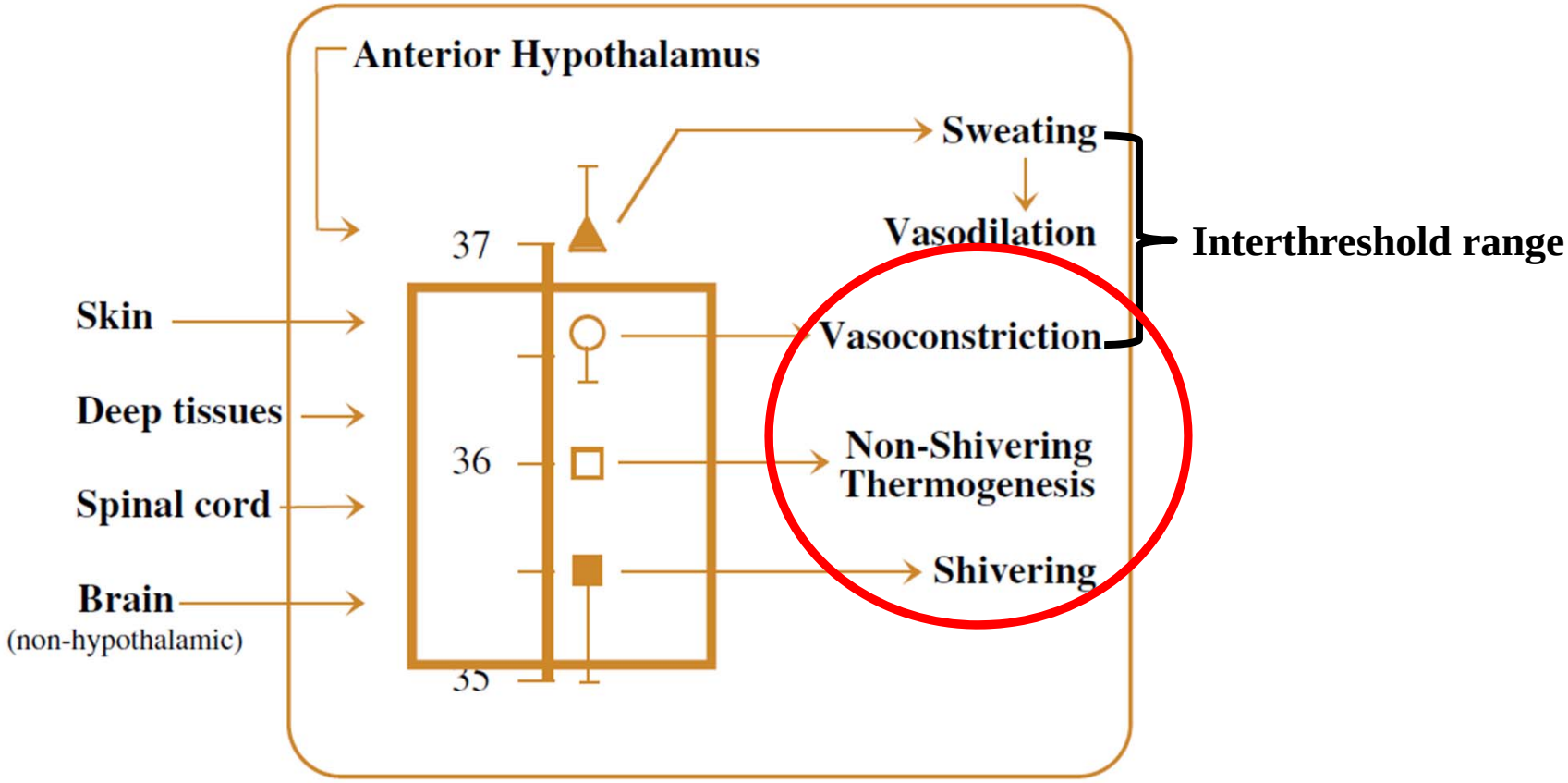
Adverse Events and Mortality

Prospective, observational, registry based study, 765 OHCA, 22 hospital in Europe and USA

Adverse Event and Concomitant Treatment	Total, n (%)	Alive, n (%)	Dead, n (%)	Univariate Odds Ratio (Lower Confidence Limit—Upper Confidence Limit)	*p*	Adjusted Odds Ratio (Lower Confidence Limit—Upper Confidence Limit)	*p*
	754 (100)	363 (48)	391 (52)				
Bleeding requiring transfusion	43 (6)	20 (6)	23 (6)	1.1 (0.57–2.2)	.76	1.0 (0.43–2.5)	.94
Pneumonia	361 (48)	208 (56)	153 (39)	0.48 (0.36–0.65)	<.001	0.88 (0.57–1.37)	.58
Sepsis	31 (4)	21 (6)	10 (3)	0.43 (0.18–0.97)	.028	0.59 (0.20–1.8)	.47
Antibiotic prophylaxis	207 (27)	94 (26)	113 (29)	1.2 (0.83–1.6)	.37	1.3 (0.80–2.0)	.31
Antibiotic therapy	414 (55)	242 (67)	172 (44)	0.39 (0.29–0.53)	<.001	.62 (0.40–0.98)	.04
Bradycardia <40 bpm	108 (14)	61 (17)	47 (12)	0.68 (0.44–1)	.062	.79 (0.42–1.5)	.47
Tachycardia >130 bpm	50 (7)	21 (6)	29 (7)	1.3 (0.70–2.5)	.38	1.7 (0.74–4.0)	.21
Atrial fibrillation	70 (9)	37 (10)	33 (8)	0.81 (0.48–1.4)	.45	1.1 (0.56–2.1)	.82
Ventricular tachycardia	76 (10)	36 (10)	40 (10)	1 (0.63–1.7)	.90	1.7 (0.87–3.3)	.12
Ventricular fibrillation	58 (8)	26 (7)	32 (8)	1.2 (0.65–2.1)	.68	2.0 (0.88–4.6)	.09
Hypoglycemia <3.0 mmol/L	40 (5)	12 (3)	28 (7)	2.3 (1.1–4.9)	.022	1.3 (0.47–3.7)	.6
Hyperglycemia >8 mmol/L >4 hrs	277 (37)	95 (26)	182 (46)	2.5 (1.8–3.4)	<.001	2.6 (1.6–4.1)	<.001
Hypokalemia <3.0 mmol/L	134 (18)	54 (15)	80 (20)	1.5 (1.0–2.2)	.046	1.3 (0.76–2.4)	.31
Hypomagnesemia <0.7 mmol/L	128 (17)	61 (17)	67 (17)	1 (0.69–1.5)	.92	1.2 (0.73–2.1)	.41
Hypophosphatemia <0.7 mmol/L	141 (19)	74 (20)	67 (17)	0.81 (0.55–1.2)	.26	0.68 (0.40–1.1)	.15
Seizures	182 (24)	44 (12)	138 (35)	4 (2.7–5.9)	<.001	1.1 (0.5–2.4)	.78
Anticonvulsants	154 (20)	32 (9)	122 (31)	4.7 (3–7.4)	<.001	5.4 (3.2–9.3)	<.001
Renal replacement therapy	32 (4)	13 (4)	19 (5)	1.4 (0.63–3.1)	.47	3.6 (1.1–12)	.04

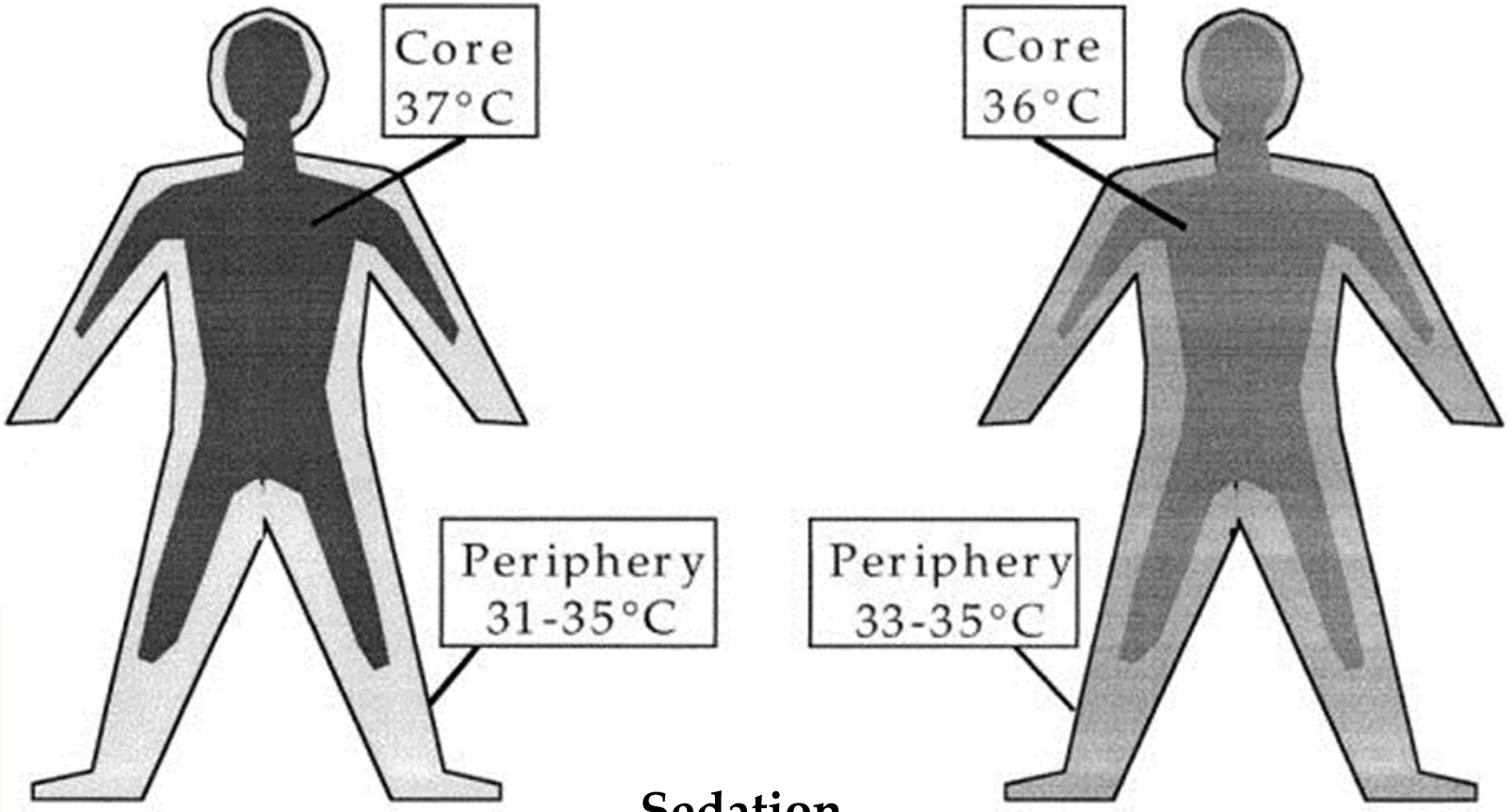
Nielsen N, et al. *Crit Care Med* 2011;39:Article in press

Normal Thermoregulation



Kurz A. *Best Pract Res Clin Anaesth* 2008;22:627-44

Sedation and/or Paralysis



Commonly Used Drugs

Drug	Efficacy	Hypotensive Effect	Sedative Effect	Advantage	Disadvantage
Midazolam	**++**	**+**	**++++**	Less hypotensive	Reduced metabolism
Propofol	**+++**	**+++**	**++++**	Brief-acting, Anti-seizure effect	More pronounced hypotension
Fentanyl	**+++**	**+**	**++**	Rapid-acting, Mild hypotensive	Reduced metabolism
Meperidine	**++++**	**+++**	**++**	Rapid-acting, Mild hypotensive	Slower metabolism
NM blockers	**+++++**	**-**	**-**	Most effective	No effect at the central level Mask insufficient sedation and/or seizure activity Risks of polyneuromyopathy

Polderman KH & Herold I. ***Crit Care Med*** **2009;37:1101-20**

Adjunctive drugs?

Remifentanil + Propofol vs. Fentanyl + Midazolam

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

RCT, Remifentanil + Propofol vs. Fentanyl + Midazolam, Norway
Sample size n=60, Primary outcome: Time from termination of sedation

Remifentanil and Propofol Versus Fentanyl and Midazolam for Sedation During Therapeutic Hypothermia. A Randomised, Controlled Trial (Cool Sedation)

This study has been completed.

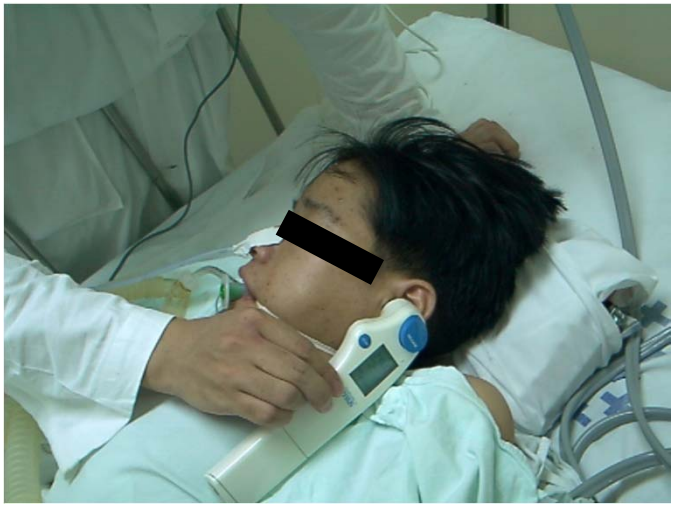
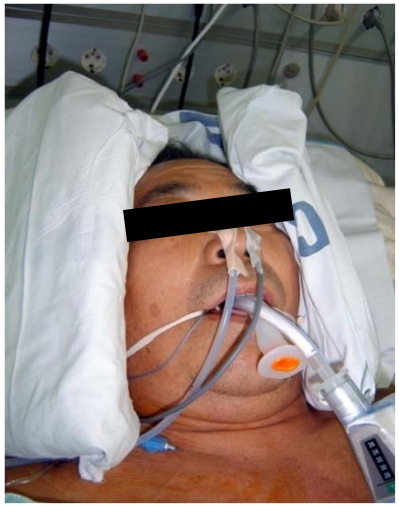
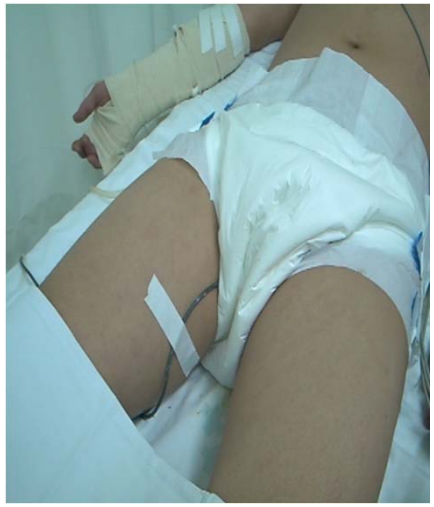
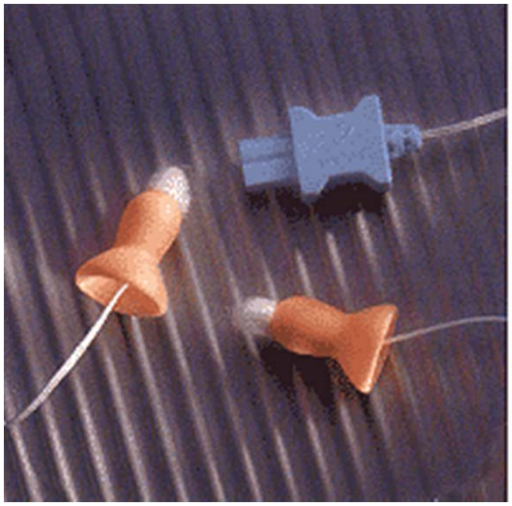
First Received on April 23, 2008. Last Updated on June 11, 2010 History of Changes

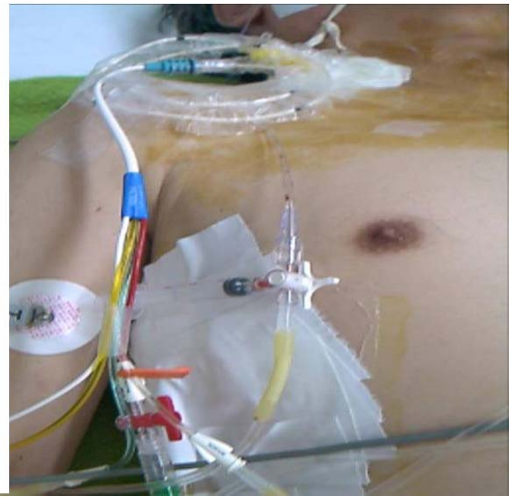
Sponsor:	Norwegian University of Science and Technology
Collaborator:	St. Olavs Hospital
Information provided by:	Norwegian University of Science and Technology
ClinicalTrials.gov Identifier:	NCT00667043

Available at: http://clinicaltrials.gov/ct2/show/NCT00667043

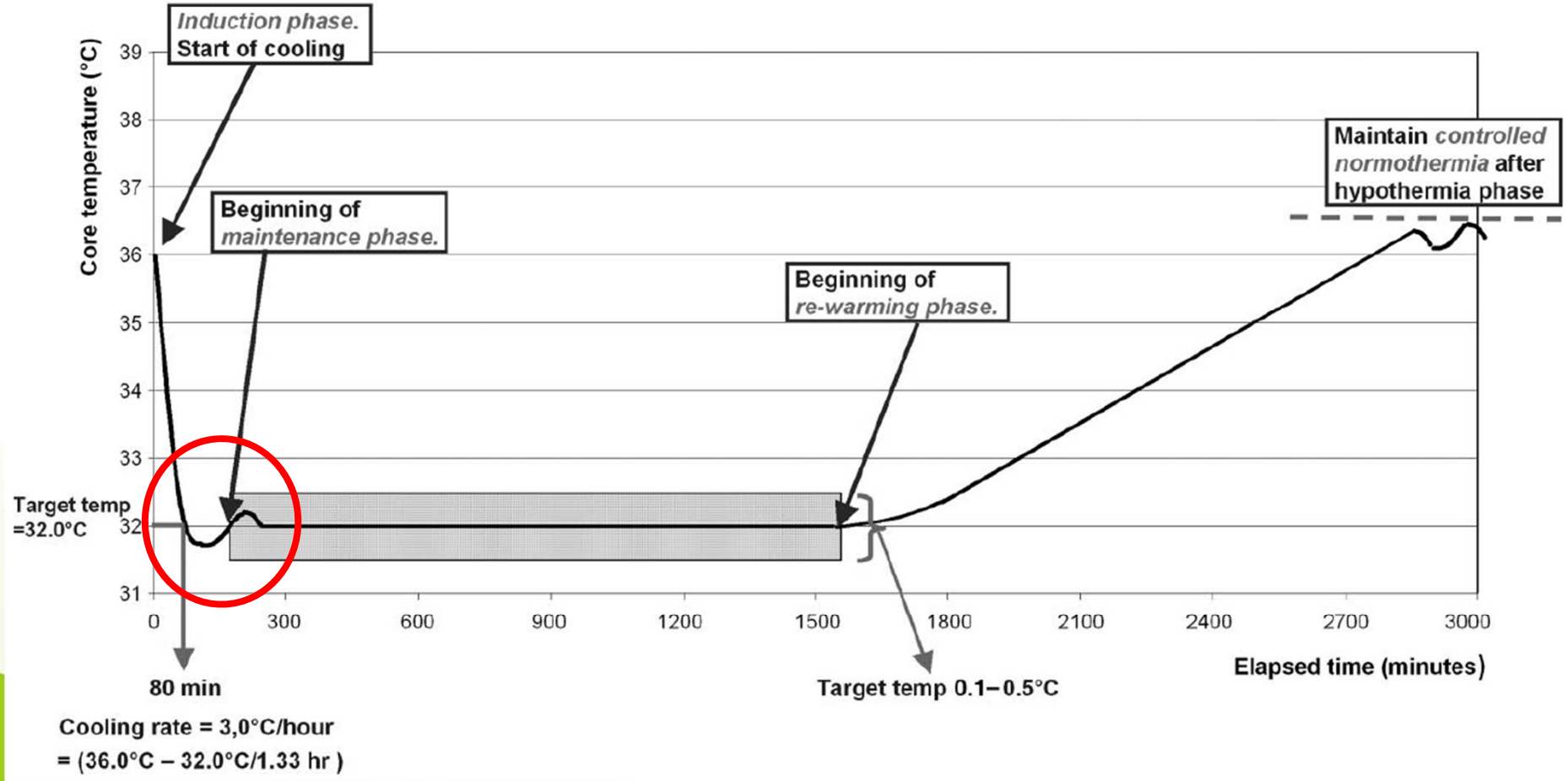
Where to measure temperature?

Temperature Monitoring



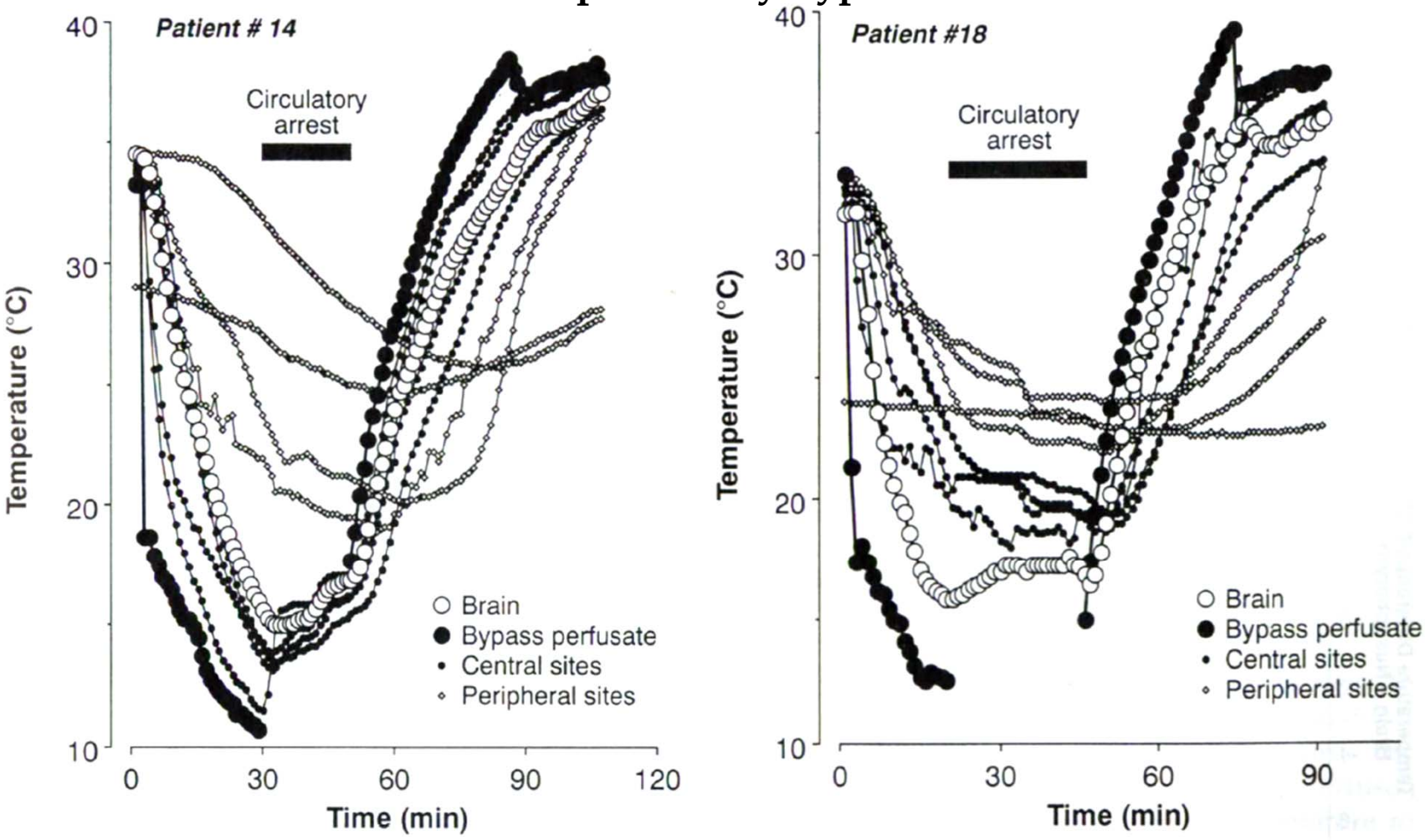
Overshoot During Rapid Induction



Polderman KH. ***Crit Care Med*** **2009;37(Suppl): S186202**

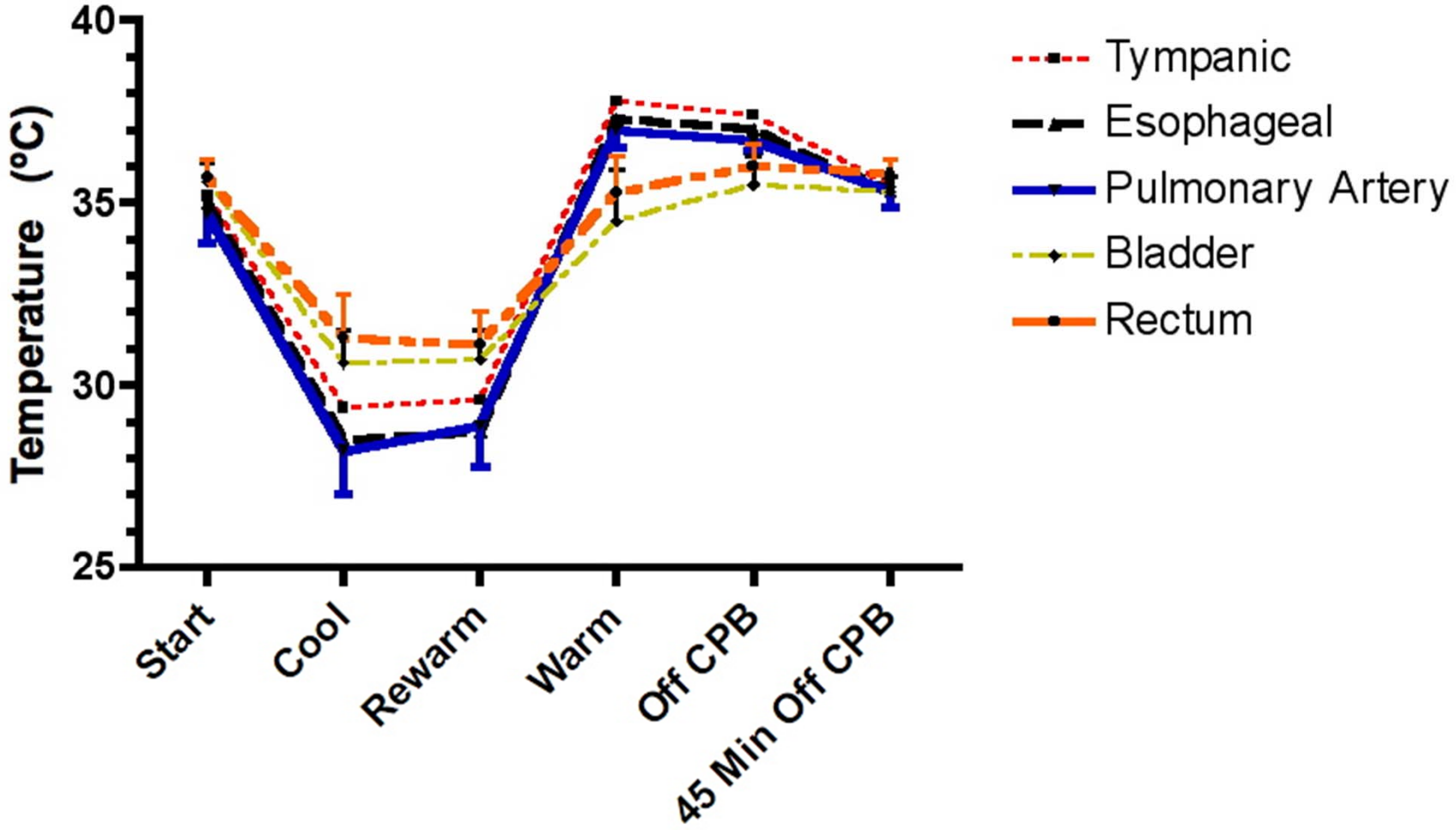
Brain vs. Central vs. Peripheral

On Cardiopulmonary Bypass (CPB)



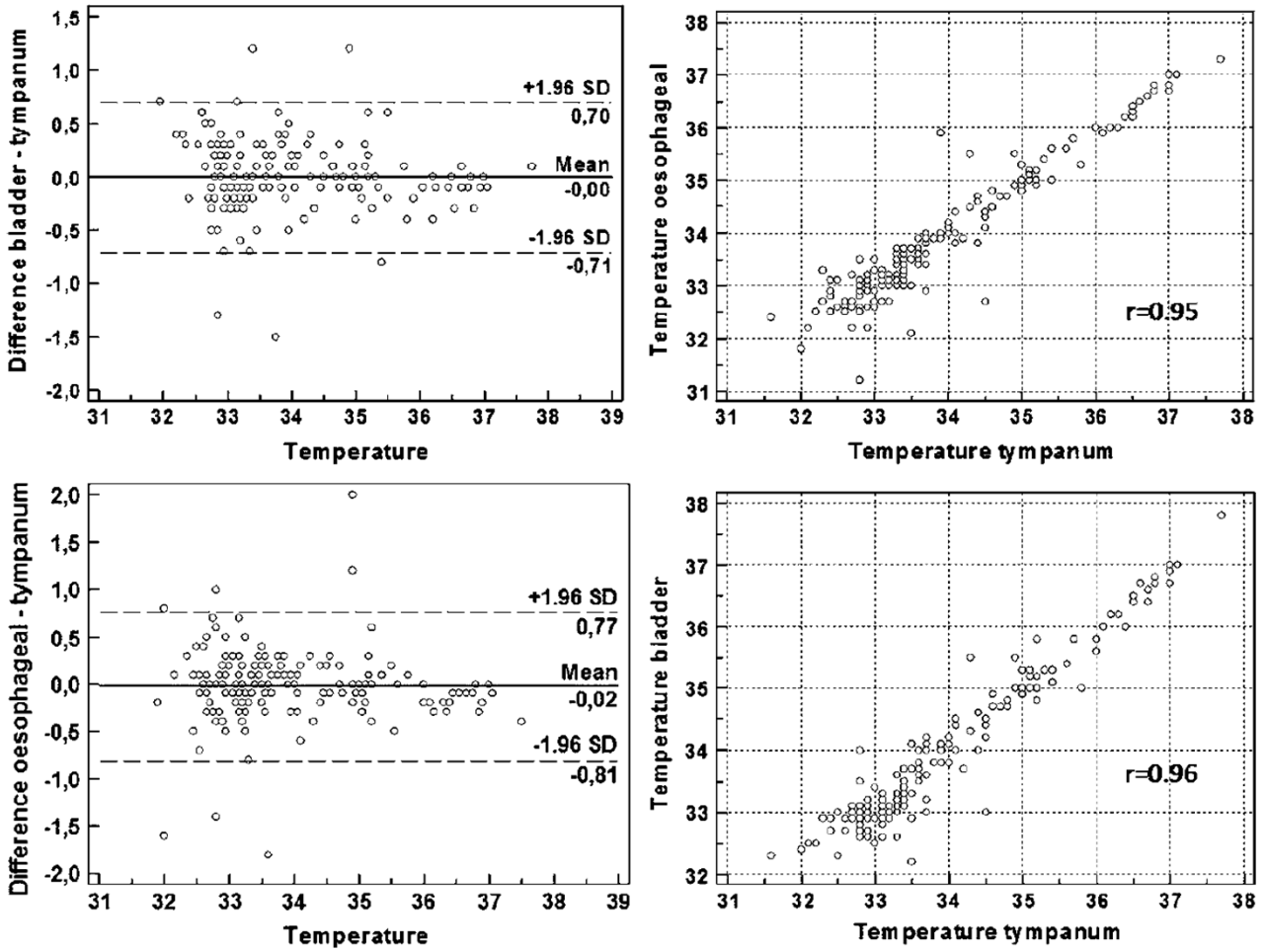
Stone JG, et al. *Anesthesiology* 1995;82:344-51

Time Lag On CPB



Pujol et al. ***J Cardiothorac Vasc Anesthesia*** **1996;10:336-43**

Tympanic Temperature during TH

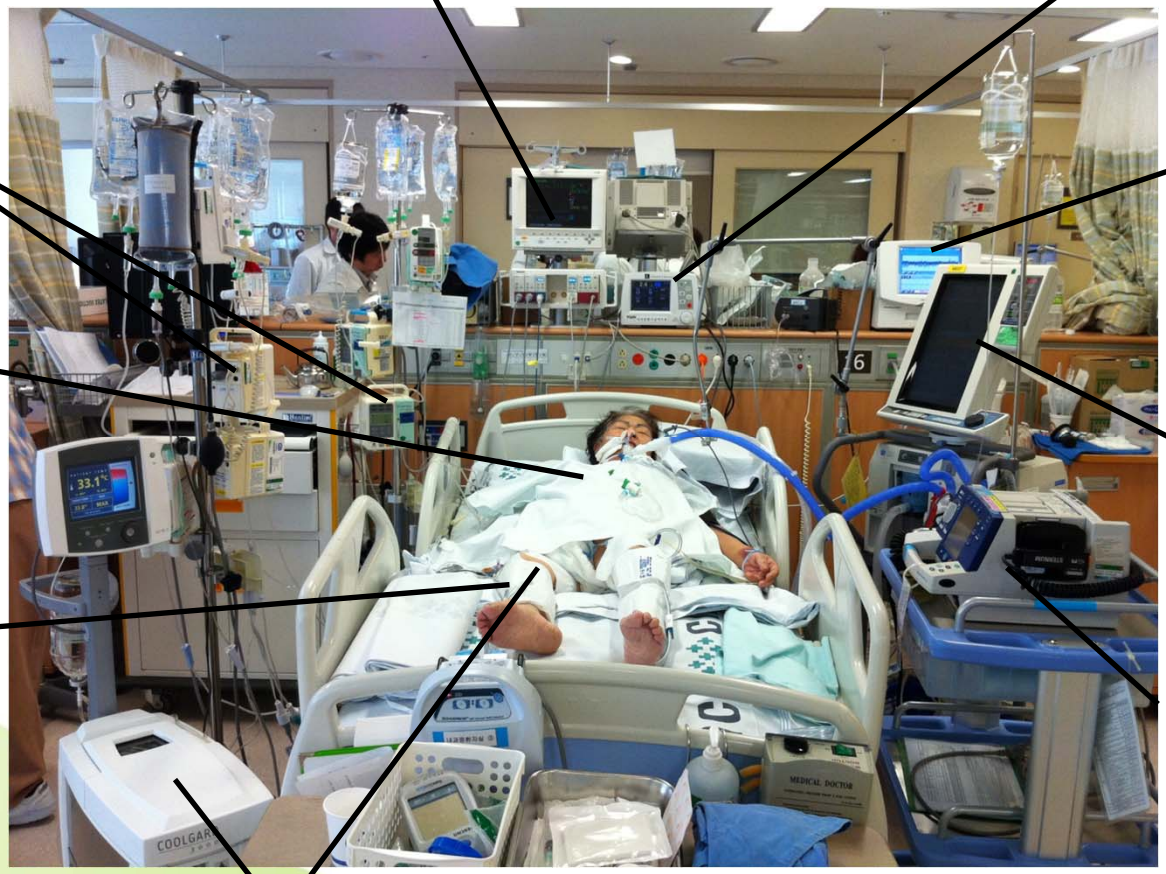


Hasper D, et al. *Emerg Med J* 2010; article in press.

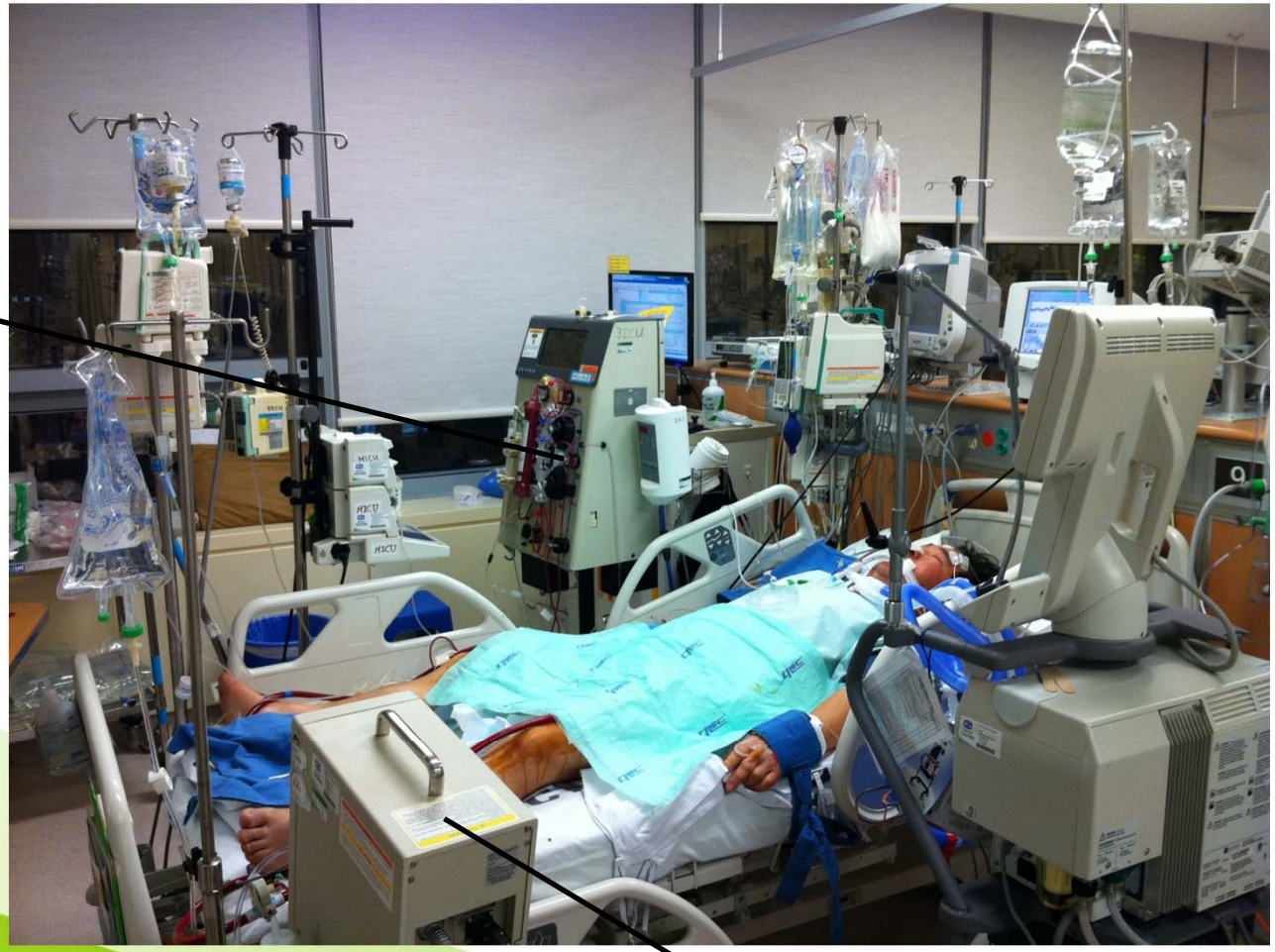
Recommended Temperature Monitoring Sites

1. PA catheter (gold standard)
2. Esophageal (lower esophagus)
3. Bladder (unless anuric)
4. TM or Nasopharyngeal (short-term use)
5. Rectal (maintenance and rewarming)

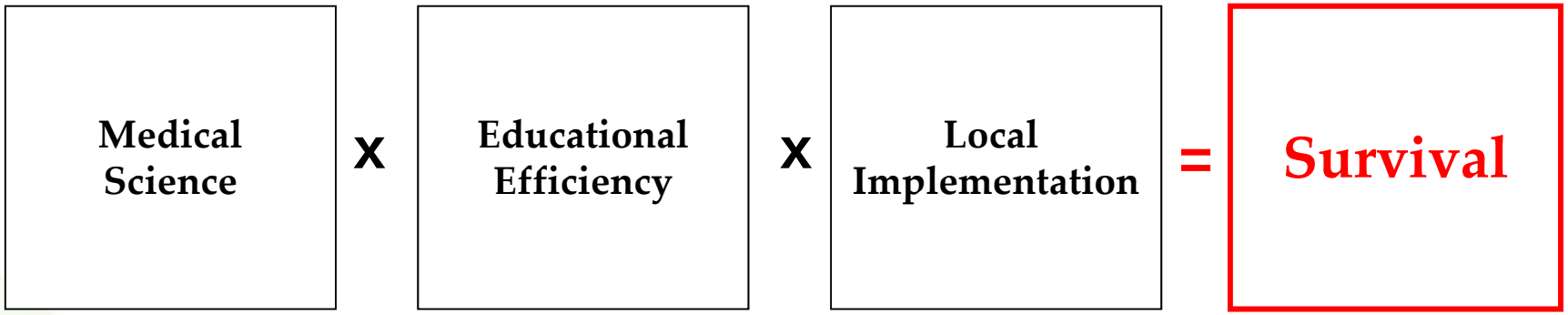
Current TH Setting (Seoul St. Mary's)



Current TH Setting (Seoul St. Mary's)

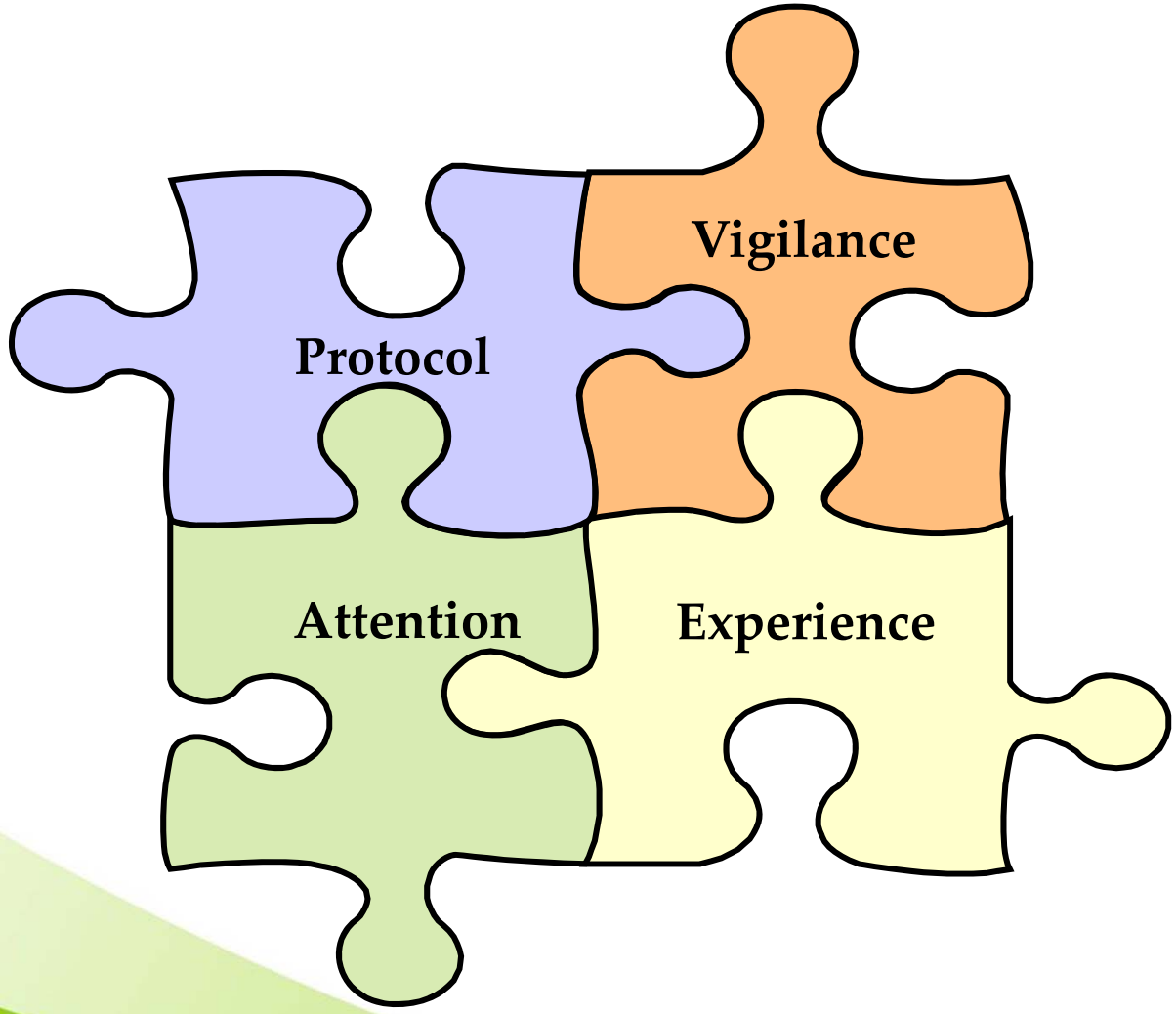


'Formula for Survival'



Resuscitation 2006-From Science to Survival,
***ERC Congress*, Stavanger, Norway (2006)**

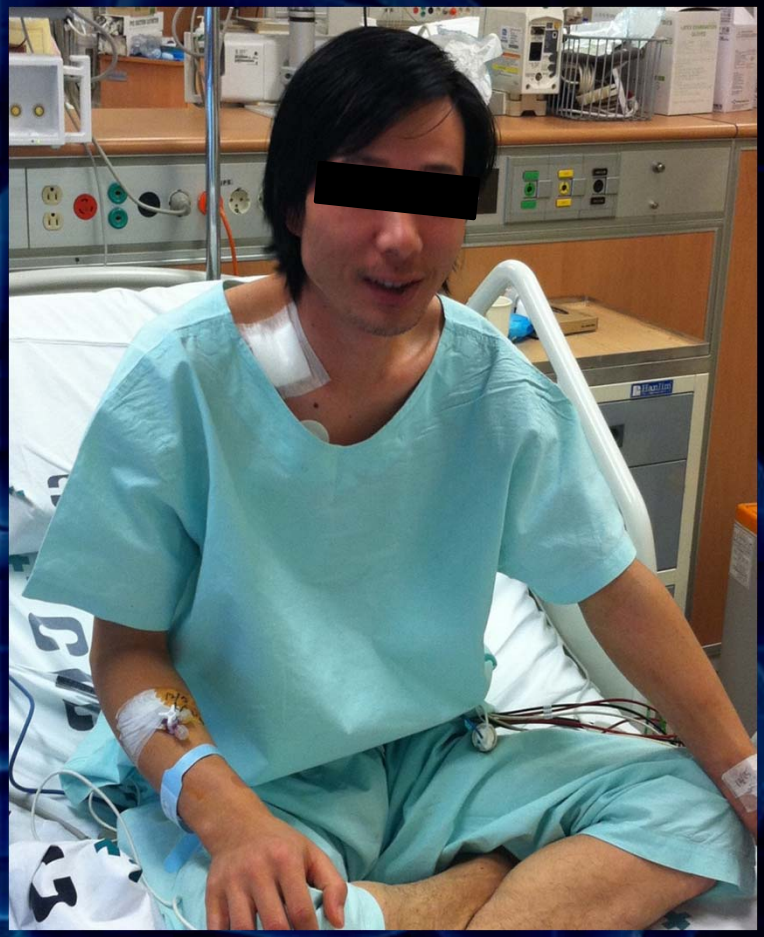
Successful Implementation of TH



Polderman KH, et al. ***Inten Care Med*** **2004;30:757-69**

Take-Home Message

- Many questions remain unanswered
- Easy to perform and lacks severe adverse effects
- Initiated as early as possible for the indicated patients
- Combine core and surface cooling methods
- Aware physiological changes and prevent potential side effects
- Carefully monitor core temperatures at central sites



Thank You !