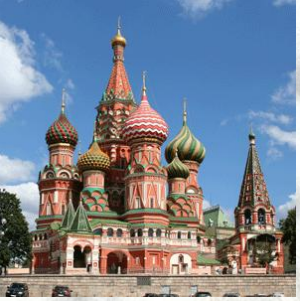
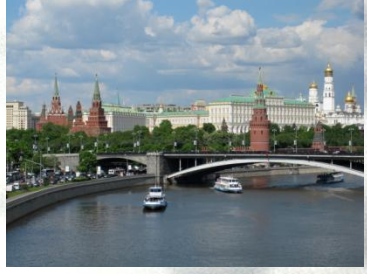


Moskow, May 25TH 2012



Can we cool awake and non-intubated patients?

Kees H. Polderman

University of Pittsburgh Medical Center

Pittsburgh, United States

UPMC | University of Pittsburgh Medical Center

WHY would we even want to do this???

Potential indications for induced hypothermia

- Acute disseminated encephalomyelitis — Level IV
- Cardiac arrest due to non-coronary causes — Level IV
- Intracranial haemorrhage — Level IV
- Sepsis/septic encephalopathy — Level IV
- Preventing/delaying cardiac arrest in severe hypovolemic shock — Level IV
- Perioperative (vascular, cardiac and neurosurgery) — Level III
- Perinatal asphyxia — Level I
- Post-anoxic encephalopathy VT/VF — Level I
- Post-anoxic encephalopathy Asystole/PEA — Level III
- Traumatic brain injury – improving outcome — Level IIA
- Mitigating myocardial injury during Ischemia/reperfusion — Level III
- Traumatic brain injury - reducing ICP — Level I
- Reversing cardiac shock following cardiac surgery — Level III
- Delayed Spinal ischemia — Level IV
- Subarachnoid haemorrhage — Level IV
- Stroke – improving outcome — Level III
- Stroke - reducing ICP — Level III
- Preventing cardiac injury during cardiac surgery — Level III
- Prevent radiocontrast nephropathy — Level IV
- Hepatic encephalopathy (reducing ICP) — Level III
- Bacterial meningitis — Level IV
- Spinal cord contusion — Level IV
- ARDS Inprove oxygenation — Level IV
- Grand mal seizures — Level IV
- Symptomatic treatment of Fever in the presence of neurological injury: Level IIB

Polderman KH. Induced hypothermia and fever control for prevention and treatment of neurological injuries. Lancet 2008; 371:1955-69.

Acute disseminated encephalomyelitis
Level IV

Cardiac arrest due to non-coronary causes
Level IV

Intracranial haemorrhage
Level IV

Sepsis/septic encephalopathy
Level IV

Preventing/delaying cardiac arrest in severe hypovolemic shock
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Perioperative (vascular, cardiac and neurosurgery)
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Perinatal asphyxia
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Traumatic brain injury – improving outcome
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Mitigating myocardial injury during Ischemia/reperfusion
Level III

The strongest evidence.....

Traumatic brain injury - reducing ICP
Level I

Reversing cardiac shock following cardiac surgery
Level III

Delayed Spinal ischemia
Level IV

Subarachnoid haemorrhage
Level IV

Stroke – improving outcome
Level III

Stroke - reducing ICP
Level III

Preventing cardiac injury during cardiac surgery
Level III

Prevent radiocontrast nephropathy
Level IV

Hepatic encephalopathy (reducing ICP)
Level III

Bacterial meningitis
Level IV

Spinal cord contusion
Level IV

ARDS
Inprove oxygenation
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Grand mal seizures
Level IV

Symptomatic treatment of Fever in the presence of neurological injury: Level IIB

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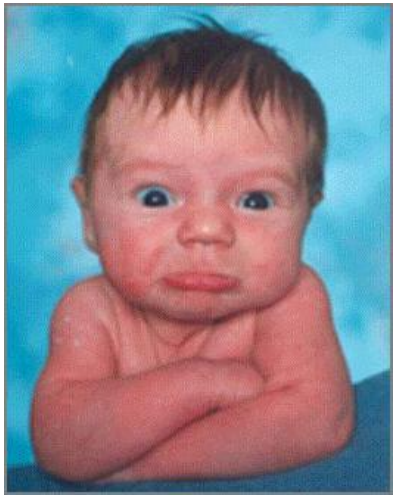
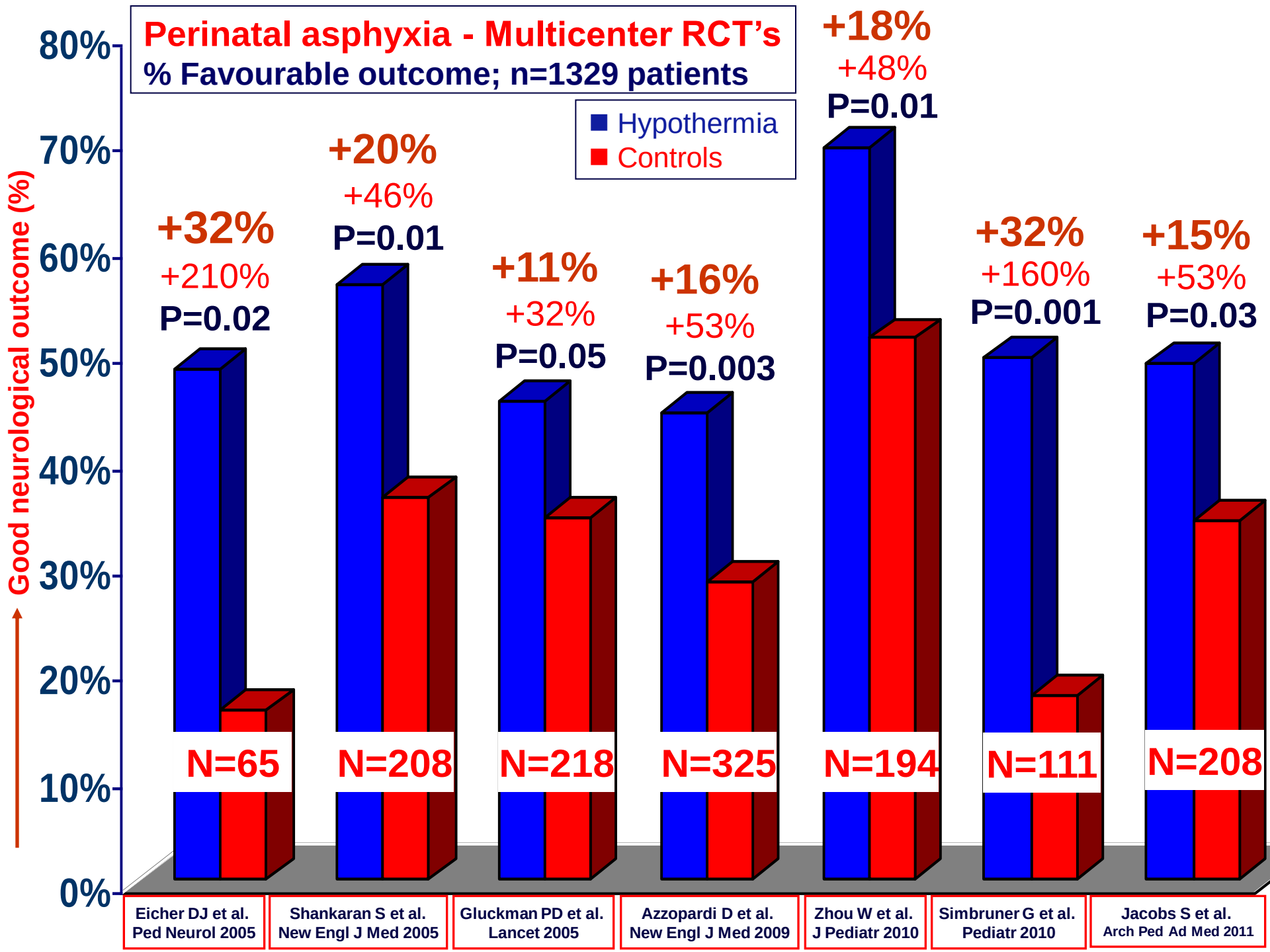
The strongest evidence that cooling can prevent post-hypoxic brain injury:



Cooling for neonatal asphyxia.


Perinatal asphyxia - Multicenter RCT's
% Favourable outcome; n=1329 patients
Hypothermia
Controls
Good neurological outcome (%)
80%
70%
60%
50%
40%
30%
20%
10%
0%
+32%
+210%
P=0.02
N=65
+20%
+46%
P=0.01
N=208
+11%
+32%
P=0.05
N=218
+16%
+53%
P=0.003
N=325
+18%
+48%
P=0.01
N=194
+32%
+160%
P=0.001
N=111
+15%
+53%
P=0.03
N=208
Eicher DJ et al. Ped Neurol 2005
Shankaran S et al. New Engl J Med 2005
Gluckman PD et al. Lancet 2005
Azzopardi D et al. New Engl J Med 2009
Zhou W et al. J Pediatr 2010
Simbruner G et al. Pediatr 2010
Jacobs S et al. Arch Ped Ad Med 2011

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Novel indications……(?)

Traumatic brain injury - reducing ICP
Level I

Reversing cardiac shock following cardiac surgery
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Potential indications were patients might not be intubated..

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Level I

Reversing cardiac shock following cardiac surgery
Level III

Delayed Spinal ischemia
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Subarachnoid haemorrhage
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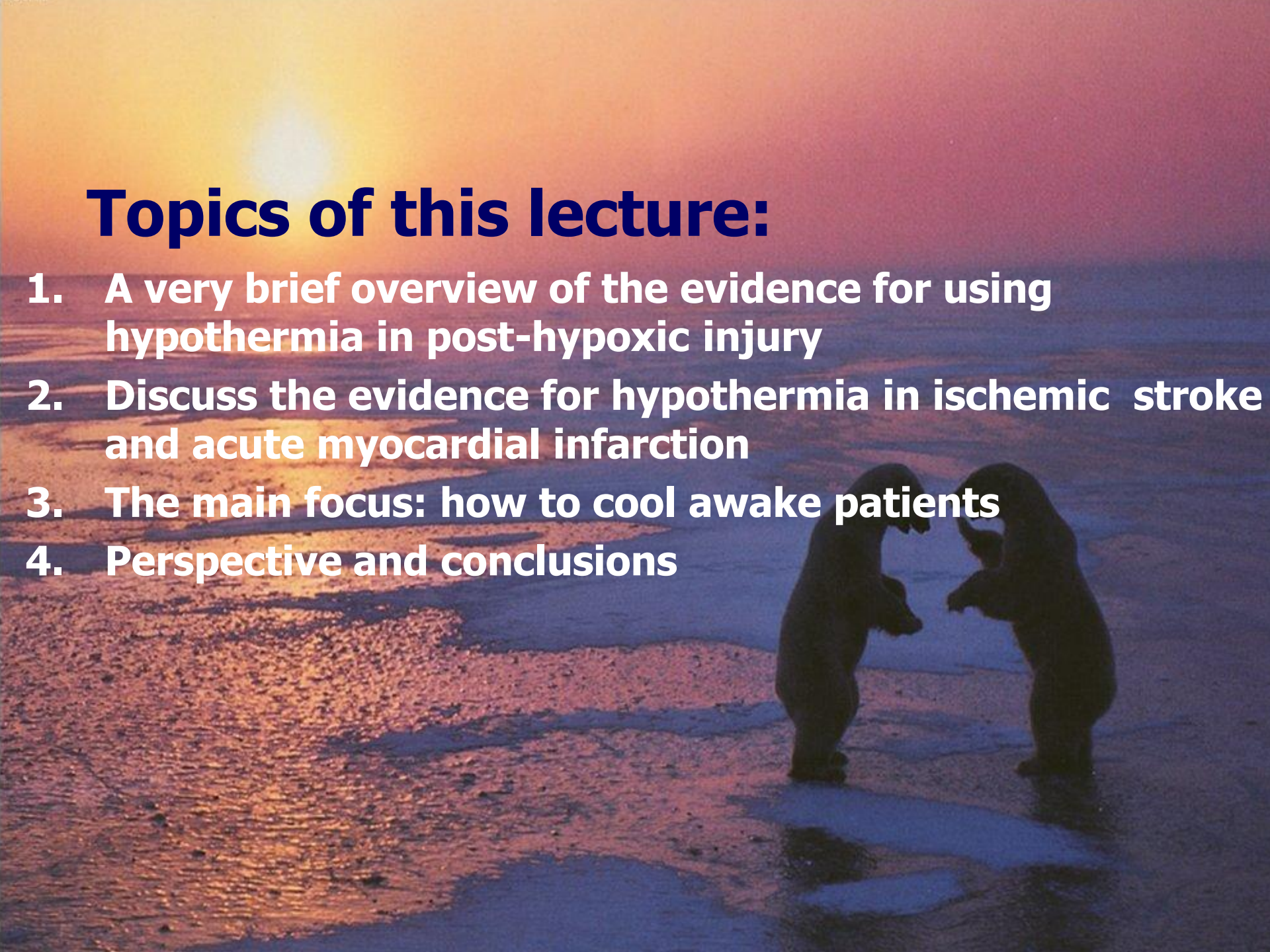


Topics of this lecture:

1. A very brief overview of the evidence for using hypothermia in post-hypoxic injury
2. Discuss the evidence for hypothermia in ischemic stroke and acute myocardial infarction
3. The main focus: how to cool awake patients
4. Perspective and conclusions

BMJ

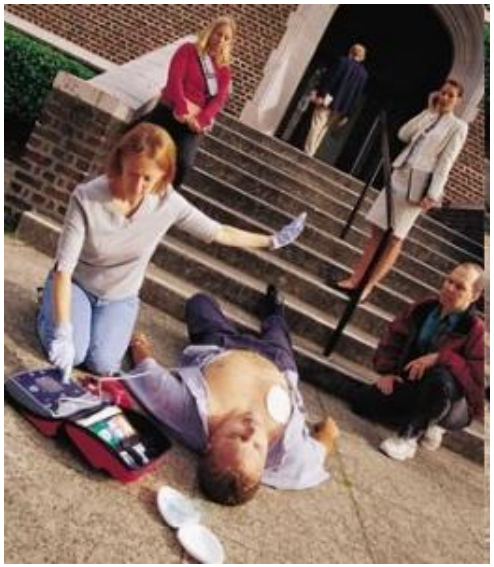
BMJ 2011;343:d5889 doi: 10.1136/bmj.d5889

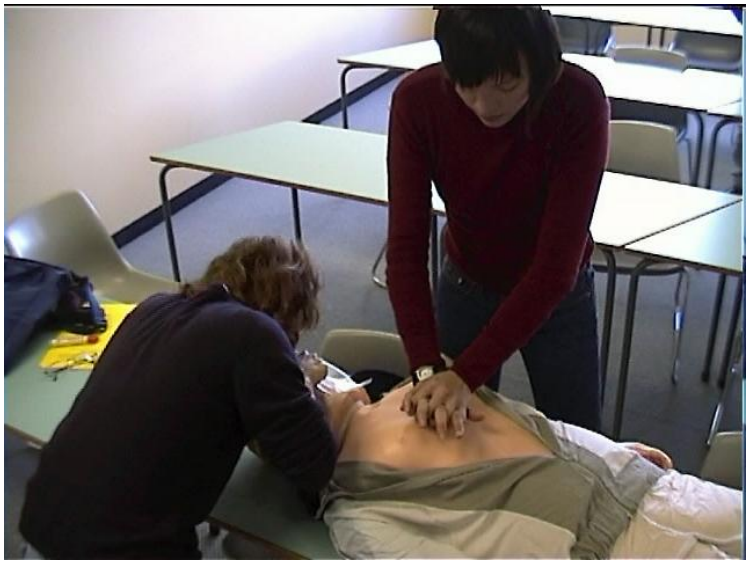
HEAD TO HEAD

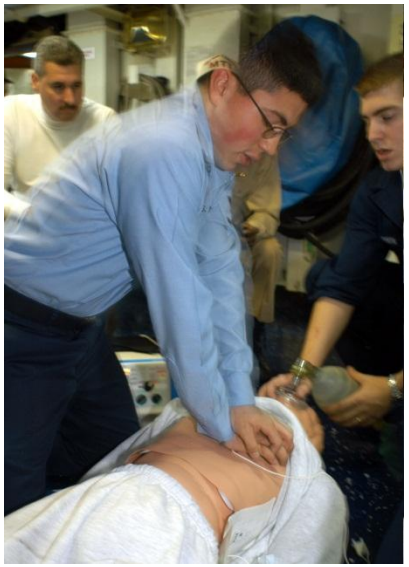
Does the evidence support the use of mild hypothermia after cardiac arrest? No

Several guidelines recommend hypothermia for comatose patients who have had a cardiac arrest outside hospital. **Jerry Nolan** and **Jasmeet Soar** (doi:10.1136/bmj.d5830) believe the data support this advice, but **Andrew Walden**, **Niklas Nielsen**, and **Matt Wise** question the quality of the evidence

Cooling for cardiac arrest…

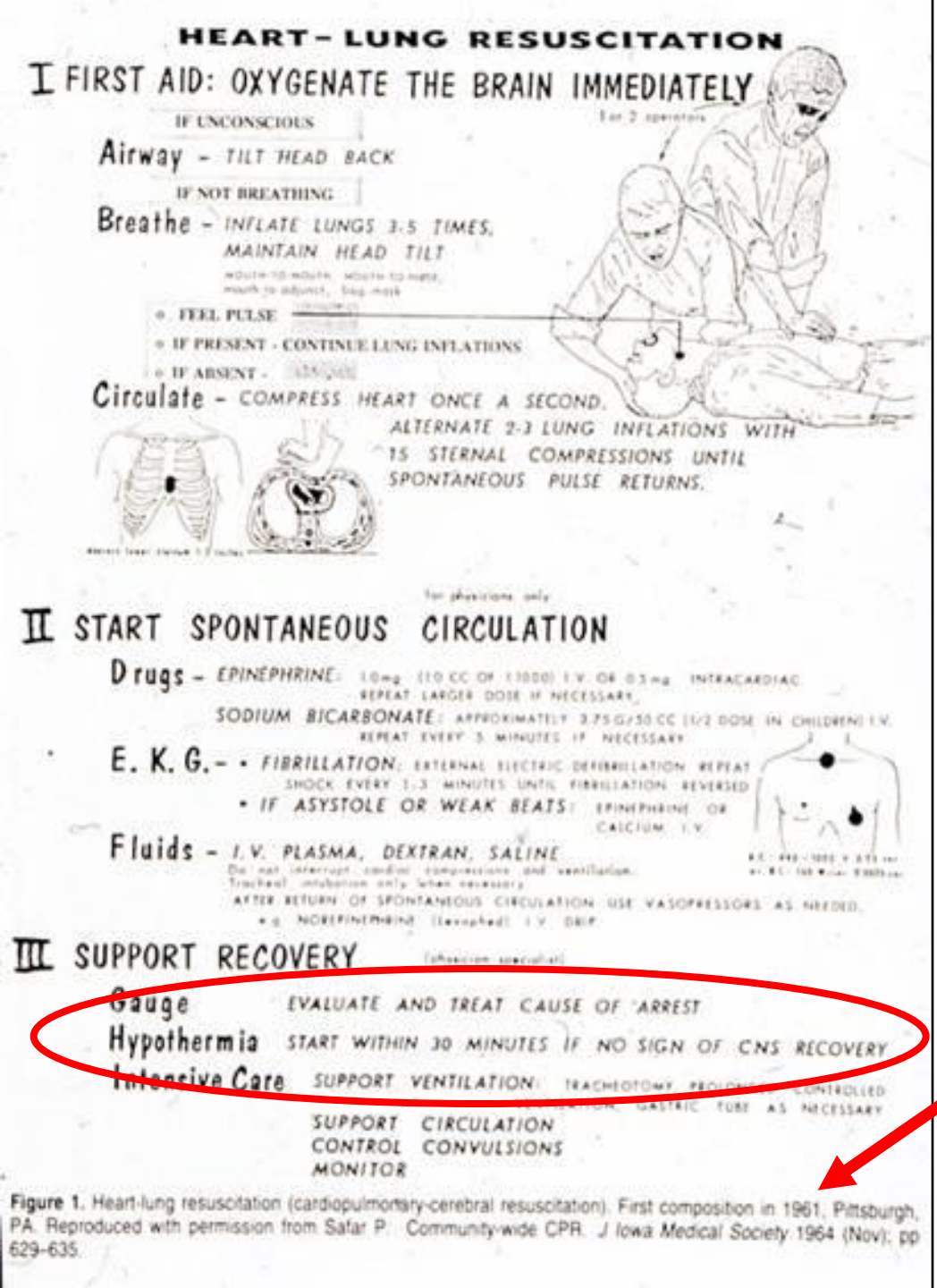






It is NOT just about cooling....

- **Promote awareness, use of bystander CPR, availability of defibrillators;**
- **New emphasis on the importance of chest compressions, at the expense of breaths, especially in BLS;**
- **Prevent hypotension, [additional] hypoxia, hyper/hypocapnia, hypovolemia, and electrolyte disorders in the ER and ICU;**
- **Immediate cardiac revascularisation (at least in witnessed arrest patients);**
- **Etc. etc.**
- **And of course, use induced hypothermia!**



HEART-LUNG RESUSCITATION

I FIRST AID: OXYGENATE THE BRAIN IMMEDIATELY

IF UNCONSCIOUS

Airway - TILT HEAD BACK

IF NOT BREATHING

Breathe - INFLATE LUNGS 3-5 TIMES. MAINTAIN HEAD TILT

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

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

II START SPONTANEOUS CIRCULATION

Drugs - EPINEPHRINE:

SODIUM BICARBONATE:

E. K. G. - • FIBRILLATION:

• IF ASYSTOLE OR WEAK BEATS:

Fluids - I.V. PLASMA, DEXTRAN, SALINE

AFTER RETURN OF SPONTANEOUS CIRCULATION USE VASOPRESSORS AS NEEDED.

III SUPPORT RECOVERY

Gauge EVALUATE AND TREAT CAUSE OF ARREST

Hypothermia START WITHIN 30 MINUTES IF NO SIGN OF CNS RECOVERY

Intensive Care SUPPORT VENTILATION:

SUPPORT CIRCULATION
CONTROL CONVULSIONS
MONITOR

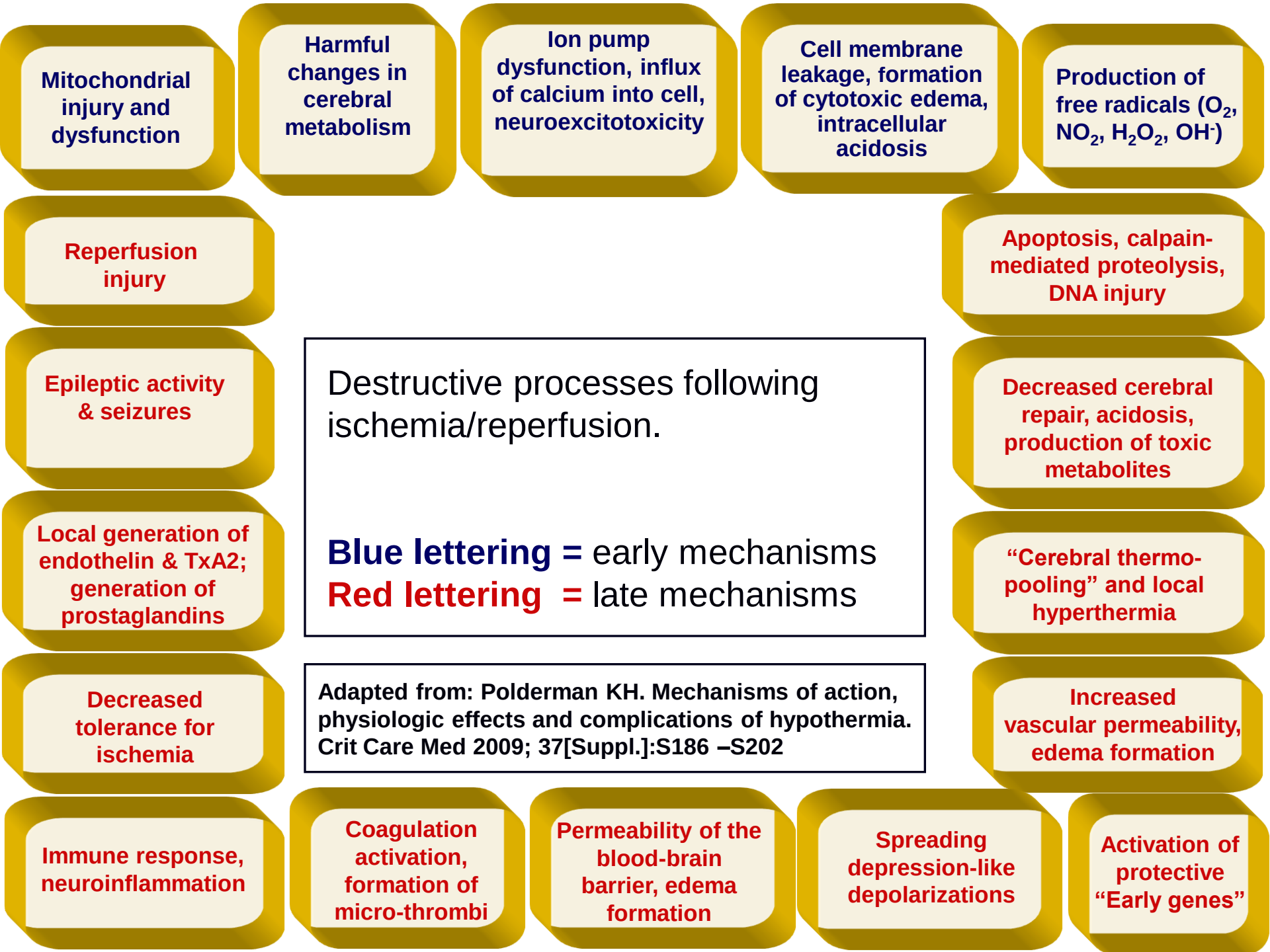
Figure 1. Heart-lung resuscitation (cardiopulmonary-cerebral resuscitation). First composition in 1961, Pittsburgh, PA. Reproduced with permission from Safar P. Community-wide CPR. *J Iowa Medical Society* 1964 (Nov); pp 629-635.

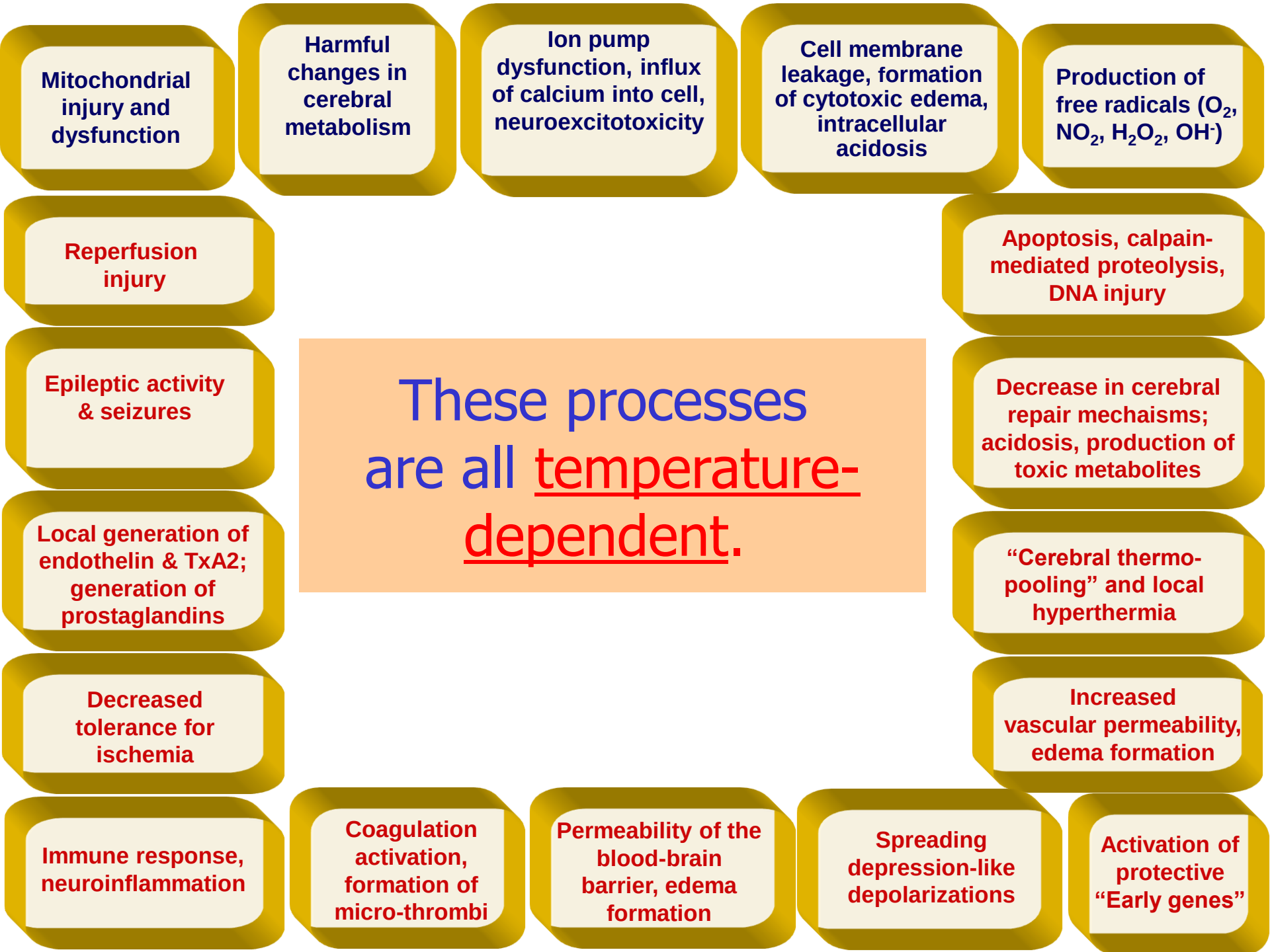
51 years ago…

RCT's: published 41 years (!!!) after these first results.....

What have we learned in this period?

- **Reducing metabolic rate is NOT the main mechanism for how this works.**


Mitochondrial injury and dysfunction
Harmful changes in cerebral metabolism
Ion pump dysfunction, influx of calcium into cell, neuroexcitotoxicity
Cell membrane leakage, formation of cytotoxic edema, intracellular acidosis
Production of free radicals (O_2, NO_2, H_2O_2, OH^-)
Reperfusion injury
Apoptosis, calpain-mediated proteolysis, DNA injury
Epileptic activity & seizures
Decreased cerebral repair, acidosis, production of toxic metabolites
Local generation of endothelin & TxA2; generation of prostaglandins
"Cerebral thermo-pooling" and local hyperthermia
Decreased tolerance for ischemia
Increased vascular permeability, edema formation
Immune response, neuroinflammation
Coagulation activation, formation of micro-thrombi
Permeability of the blood-brain barrier, edema formation
Spreading depression-like depolarizations
Activation of protective "Early genes"
Destructive processes following ischemia/reperfusion.
Blue lettering = early mechanisms
Red lettering = late mechanisms
Adapted from: Polderman KH. Mechanisms of action, physiologic effects and complications of hypothermia. Crit Care Med 2009; 37[Suppl.]:S186 –S202


Mitochondrial injury and dysfunction
Harmful changes in cerebral metabolism
Ion pump dysfunction, influx of calcium into cell, neuroexcitotoxicity
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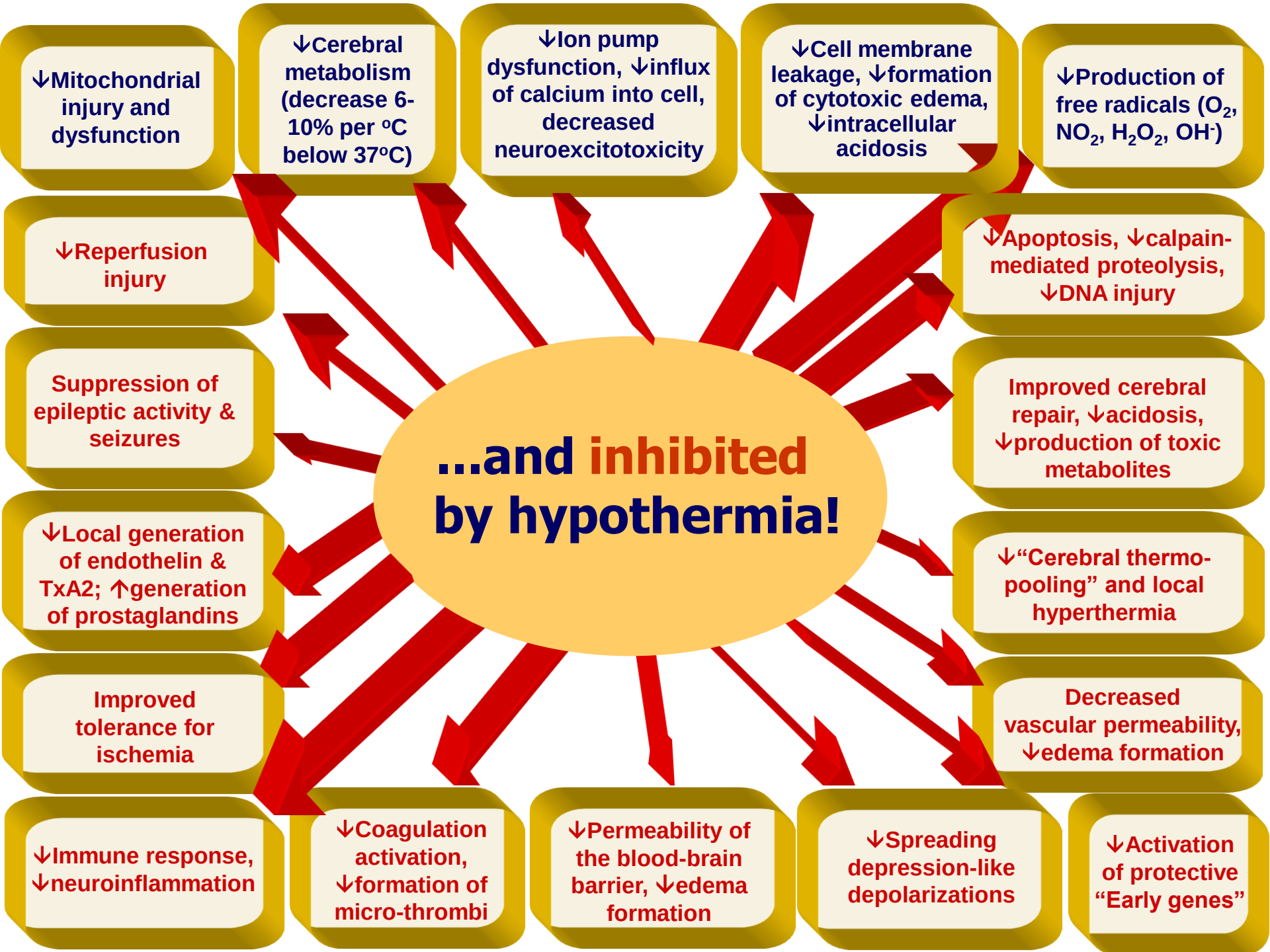
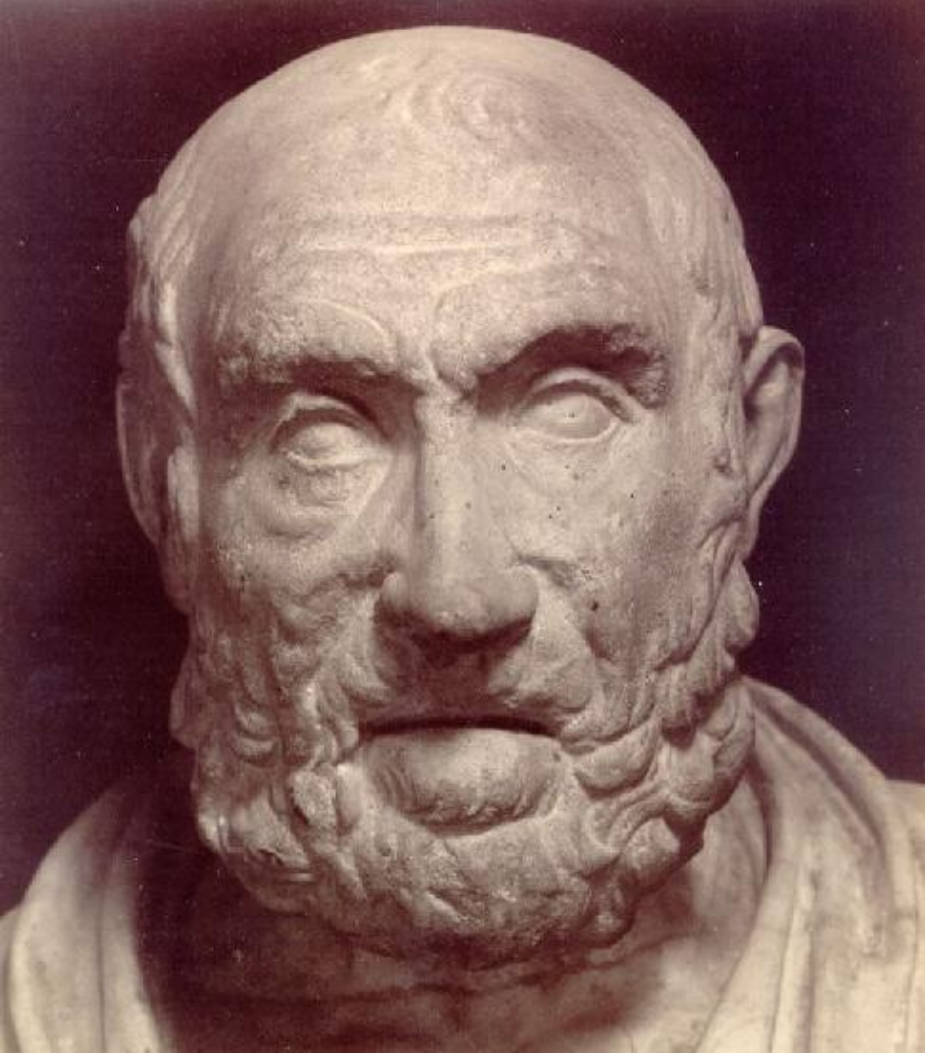
Production of free radicals (O_2, NO_2, H_2O_2, OH^-)
Reperfusion injury
Apoptosis, calpain-mediated proteolysis, DNA injury
Epileptic activity & seizures
These processes are all temperature-dependent.
Decrease in cerebral repair mechaisms; acidosis, production of toxic metabolites
Local generation of endothelin & TxA2; generation of prostaglandins
"Cerebral thermo-pooling" and local hyperthermia
Decreased tolerance for ischemia
Increased vascular permeability, edema formation
Immune response, neuroinflammation
Coagulation activation, formation of micro-thrombi
Permeability of the blood-brain barrier, edema formation
Spreading depression-like depolarizations
Activation of protective "Early genes"

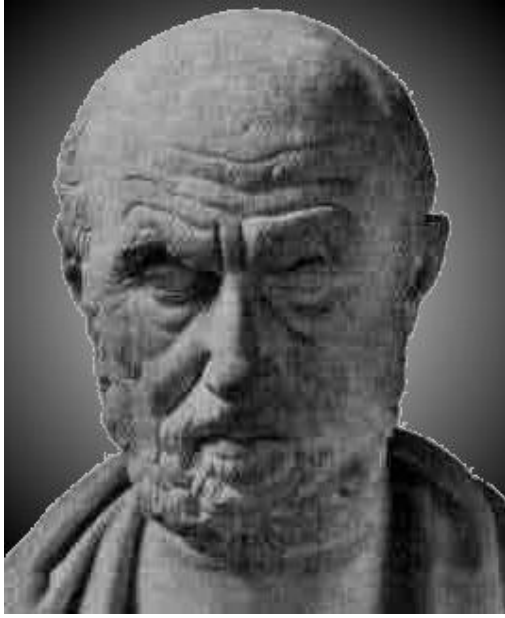

↑Mitochondrial injury and dysfunction
↑Cerebral metabolism (increase 6-10% per ºC below 37ºC)
↑Ion pump dysfunction, ↑influx of calcium into cell, decreased neuroexcitotoxicity
↑Cell membrane leakage, ↑formation of cytotoxic edema, ↑intracellular acidosis
↑Production of free radicals (O_2, NO_2, H_2O_2, OH^-)
↑Reperfusion injury
↑Apoptosis, ↑calpain-mediated proteolysis, ↑DNA injury
Increase of epileptic activity & seizures
More depressed cerebral repair, ↑acidosis, ↑production of toxic metabolites
↑Local generation of endothelin & TxA2; ↓generation of prostaglandins
↑"Cerebral thermo-pooling" and local hyperthermia
Decreased tolerance for ischemia
Decreased vascular permeability, ↑edema formation
They are all stimulated by fever…
↑Immune response, ↑neuroinflammation
↑Coagulation activation, ↑formation of micro-thrombi
↑Permeability of the blood-brain barrier, ↑edema formation
↑Spreading depression-like depolarizations
↑Activation of protective "Early genes"


↓Mitochondrial injury and dysfunction
↓Cerebral metabolism (decrease 6-10% per °C below 37°C)
↓Ion pump dysfunction, ↓influx of calcium into cell, decreased neuroexcitotoxicity
↓Cell membrane leakage, ↓formation of cytotoxic edema, ↓intracellular acidosis
↓Production of free radicals (O_2, NO_2, H_2O_2, OH^-)
↓Reperfusion injury
↓Apoptosis, ↓calpain-mediated proteolysis, ↓DNA injury
Suppression of epileptic activity & seizures
Improved cerebral repair, ↓acidosis, ↓production of toxic metabolites
...and inhibited by hypothermia!
↓Local generation of endothelin & TxA2; ↑generation of prostaglandins
↓"Cerebral thermo-pooling" and local hyperthermia
Improved tolerance for ischemia
Decreased vascular permeability, ↓edema formation
↓Immune response, ↓neuroinflammation
↓Coagulation activation, ↓formation of micro-thrombi
↓Permeability of the blood-brain barrier, ↓edema formation
↓Spreading depression-like depolarizations
↓Activation of protective "Early genes"

What have we learned in this period?

- **Reducing metabolic rate is NOT the main mechanism for how this works.**
- **SO, we need "only" to cool to around 32^{o}C degrees (not to 24-28 degrees as was done in the 1950's)**
- **In recent years, we have learnt much on how to effectively control shivering….**





"In whatever part of the body excess of heat or cold is felt, the disease is there to be discovered."

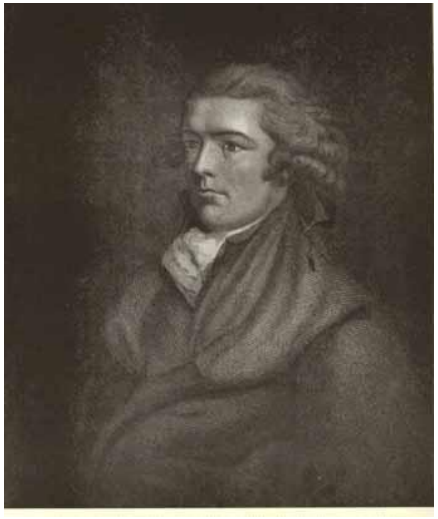
The ancient Greeks immersed the body in wet mud. The area that dried more quickly indicated a warmer region, and was considered the diseased tissue.

The history of hypothermia..

Hua To (±110 A.D. - ±207 A.D.): Chinese physician. As a treatment for fever he forcibly immersed his naked and febrile patient in a stone trough in his garden until the vapour rose several feet above the trough.

The history of hypothermia..

Robert Boyle (1672) and, later on James Currie (1798) and William Osler attempted to use hypothermia in the treatment of thypoid fever by immersing patients in ice-cold brine or sea-water.



Boyle R. New Experiments and Observations upon Cold (1665); Currie J. Medical Reports on the Effects of Water, Cold and Warm, as a Remedy in Fevers and Febrile Diseases whether applied to the Surface of the Body, or used as a Drink, with observations on the Nature of Fever and on the Effects of Opium, Alcohol and Inanition (1797)

The history of hypothermia..

In 1814, Napoleon's surgeon-general Baron Larrey described that during the Napoleonic wars, wounded soldiers who were put close to a campfire died earlier than those who were not re-warmed

Larrey IJ: Memoirs of military service and campaigns of the French armies, vol 2. Baltimore, J Cushing, 1814, pp 156-164

The history of hypothermia..

William Osler (1849-1919), after initial skepticism, began using hypothermia for the treatment of typhoid fever; he reported a 17% absolute decrease in rates of mortality in his patients at Johns Hopkins Hospital after he implemented this procedure.

Osler W. The Cold-Bath Treatment of Typhoid Fever. Medical News Philadelphia 1892.

THE COLD-BATH TREATMENT OF TYPHOID FEVER.[1]

By WILLIAM OSLER, M. D.,

Professor of Medicine in the Johns Hopkins University.

GENTLEMEN: While no one can bring a railing accusation against us as a profession for neglecting the things that pertain to the cure of disease by drugs, we must bear meekly the rebuke of those who claim that non-medicinal agents, such as systematic exercise, fresh air, and the use of water scarcely receive the attention which their virtues demand. Particularly is this the case with water as a means of controlling the severer symptoms of fever. For centuries it was one of the great hygienic measures, and the use of baths in disease is recommended by writers in every age since Hippocrates. You will find, indeed, in the writings of the Father of Medicine an admirable account of the indications and uses of the bath, to some of which I shall refer again.

During the first half of this century hydrotherapy was largely in the hands of the hydropaths, by which term may be distinguished the large class of hermaphrodite practitioners who look upon water as a cure-all; but under the guidance of von Ziemssen, Liebermeister, Winternitz, Brand, and others, the use of compresses, douches, and the various forms of baths has been introduced largely into rational practice. More than thirty years ago Brand, of Stettin, urged the systematic treatment of typhoid fever by cold baths. The method has been successfully carried out on a

[1]A Clinical Lecture delivered to the Graduate Class of the Johns Hopkins Hospital, Baltimore, November 9, 1892.

Reprint from the *Medical News*, Philadelphia, December 3, 1892.

Osler W. Medical News, Dec 3D 1892.

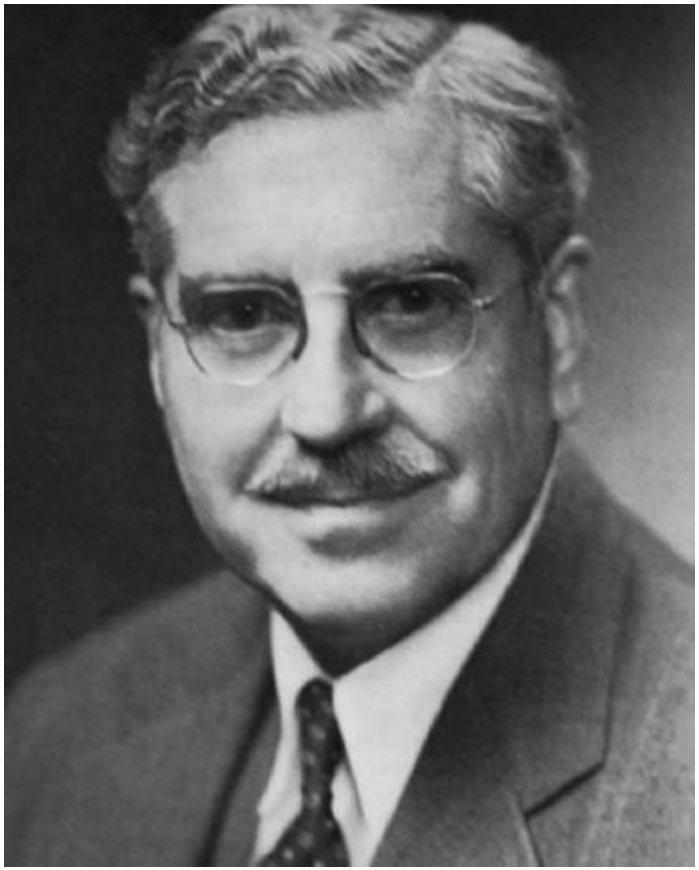
yet reached the daily lives of the doctors in this country. Practically, the mortality under the cold-bath treatment in hospitals has been reduced from 15 and 20 or 25 per cent., to an average of 6 or 7 per cent., taking all cases, or even very much lower if the cases are seen early. Indeed, Brand has figures that show an absence of mortality in some 1,200 cases in which the treatment began before the fifth day. But in hospital practice we can never expect to see our patients before the end of the first week. At the German Hospital in Philadelphia, where the method has been followed most accurately by Dr. J. C. Wilson and his colleagues, there were ninety-four consecutive cases treated without a death; but I understand from Dr. Wilson that this remarkable good fortune has not continued, though the mortality has been kept at a very low rate. Our own more limited experience is also strikingly in favor of the method, and a report is in course of publication dealing with the first hundred cases so treated. In the first year of the opening of the hospital there were thirty-two cases treated on the symptomatic and expectant plan, of which eight died, a mortality of 25 per cent., a rate unusually high even for a general hospital. The cases, however, were of unusual severity; one had acute hemorrhagic nephritis, with profuse hematuria; one case, admitted at the beginning of the third week, had extensive double pneumonia. Two cases died of perforation, while another case died of profuse hemorrhage from the bowels. On the other hand, in the first hundred cases treated by the cold baths, the mortality has been only 7 per cent., a reduction so striking and remarkable that it must be attributed to the good results of the bath. Even this rate of mortality, which is about the average for hospitals in which the rigid Brand system is carried out, would be considered by the proposer of the method far too high. In the report referred to I have given full details of the fatal cases, and it will be noticed that one of the seven, an old man of seventy, was admitted late in the disease with extensive lobar pneumonia, and as the disease was not recognized as typhoid he was not bathed. Two cases were admitted in relapse.

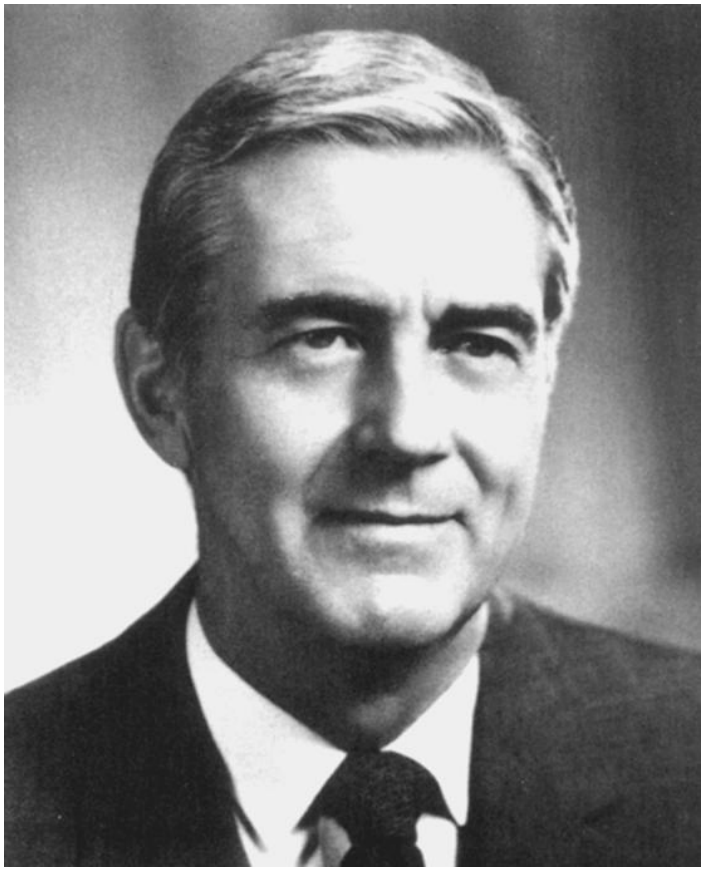
You will be pleased to learn that in the cases treated this year we are still gratified with the results of the method. We are at about the seventieth case in our second series of a hundred cases, and only six of these have died.

Osler W. Medical News, Dec 3D 1892.

The history of hypothermia..

- First clinical reports on use of hypothermia published in the 1940's and 1950's





Fay T Assoc Res Nerv Ment Dis Proc 24:611-619; Bigelow WG et al, Ann Surg 1950;132:531-537

EARLY EXPERIENCES WITH LOCAL AND GENERALIZED REFRIGERATION OF THE HUMAN BRAIN*

TEMPLE FAY, M.D.†

Philadelphia, Pennsylvania

Lessons from history...

The first attempt at general refrigeration was made on November 28, 1938, which was welcomed as a cool crisp day in Philadelphia. Cool enough so that when I moved the other patients out of a small four-bed ward, shut off the heat, closed the door to the hall, and opened the windows, Nature herself supplied the cold air that aided the cracked ice, 150 pounds of which was begged from the hospital kitchen.

Fay T. Observations on prolonged human refrigeration. N Y St J Med 1940;40:1351-54;
Fay T. Observations on refrigeration in cases of severe cerebral trauma. Res Publ Ass Nerv Ment Dis 1945;24:611-19

EARLY EXPERIENCES WITH LOCAL AND GENERALIZED REFRIGERATION OF THE HUMAN BRAIN*

TEMPLE FAY, M.D.†

Local and generalized refrigeration of the human brain appears to be such a simple thing today.

For many reasons, chiefly because of prejudice on the part of the nurses, we had not dared submerge the entire patient in a bed of cracked ice. As it was, the Superintendent of the hospital was more concerned about the wet mattress from the melting ice than a scientific principle. The nurses' home, internes' quarters and many members of the staff of other services, were alive with dubious comment and conjecture regarding the idea of human refrigeration.

The first attempt at general refrigeration was made on November 28, 1938, which was welcomed as a cool crisp day in Philadelphia. Cool enough so that when I moved the other patients out of a small four-bed ward, shut off the heat, closed the door to the hall, and opened the windows, Nature herself supplied the cold air that aided the cracked ice, 150 pounds of which was begged from the hospital kitchen.

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Lessons from history...

It is well to remember that this was more than 20 years ago, when all of our clinical thermometers were calibrated down to only 94°F., as the lowest temperature compatible with survival of the human being. Below this level, we were then assured that human life could not be long sustained.

This "thermal barrier" was so deeply ingrained into medical techniques at that time that "subnormal temperatures" were to be combated at all cost, and "shock cabinets" with electrical heating devices or hot water bottles and warm blankets were considered as necessary emergency equipment in every hospital.

Fay T. Early experiences with local and generalized refrigeration of the human brain. J Neurosurg 1959; 239-59.

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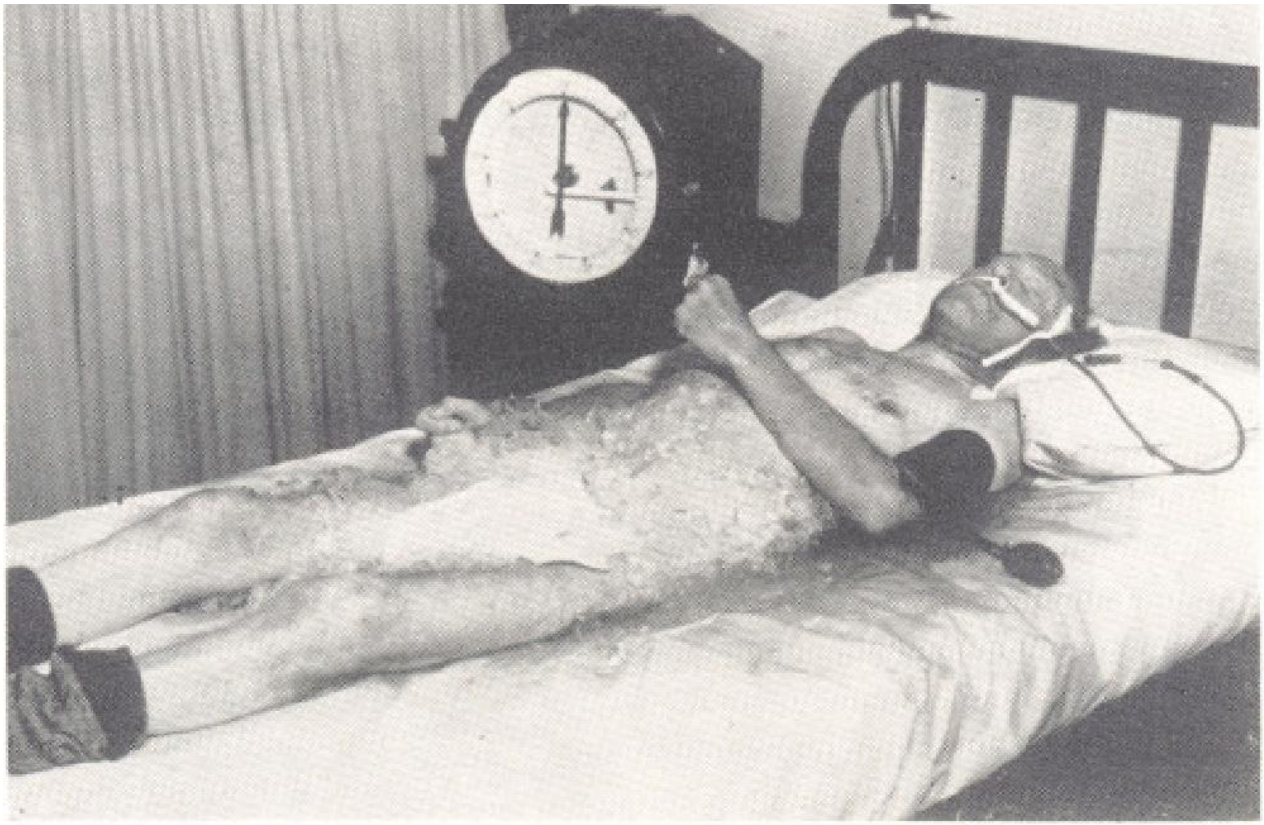

FIG. 5. Early method of total refrigeration with recording thermocouple (89.5°F. rectal). Patient was under Amytal Sodium, chloral hydrate and paraldehyde anesthesia. This patient (a physician) insisted upon keeping socks on.

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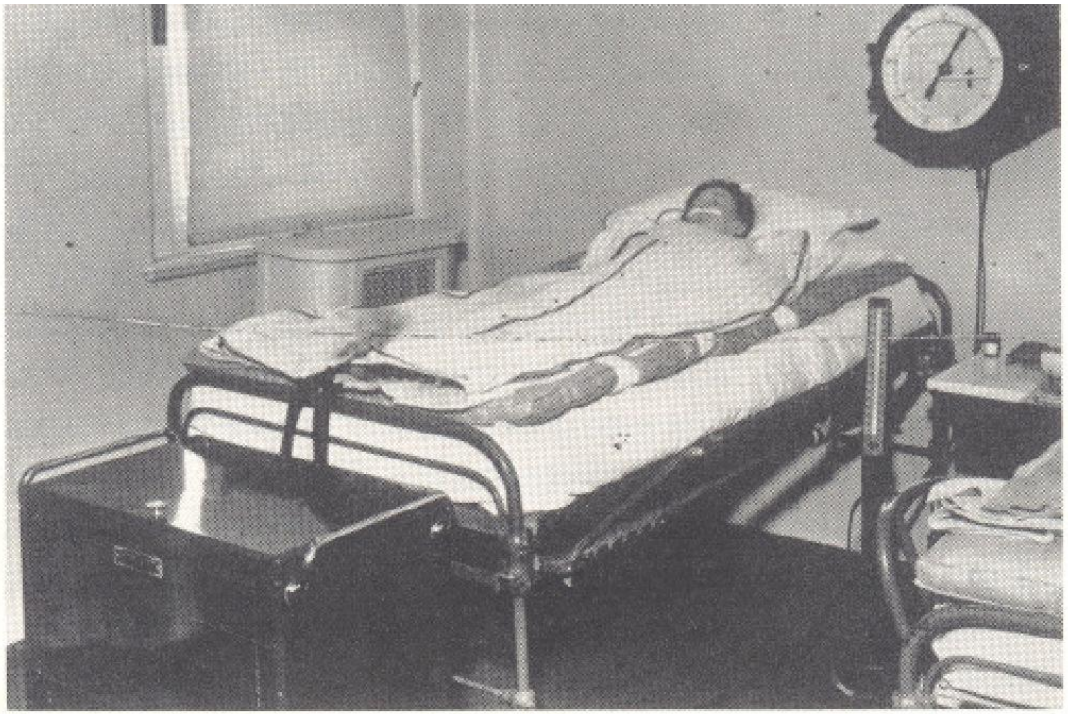

FIG. 6. Showing detail of apparatus and equipment in use on Dec. 27, 1939. Special insulated mattress is between bed and "zipper" blanket containing rubber tubing, so that continuous circulation of brine-chilled solution could be directed toward either half of the blanket. Refrigeration apparatus, designed by the author and Mr. Brenner of the Therm-O-Rite Company of Buffalo, was quiet, with automatic temperature control. Rectal electrothermocouple designed by Dr. George Henny, and constantly registering dial thermometer, supplied by Leeds and Northrup Co., showed this patient's temperature to be 89.5°F. rectal. This large-face type of dial thermometer was calibrated from 70°F. to 110°F. and could be constantly observed by the nurse at the ward station 40 feet away.

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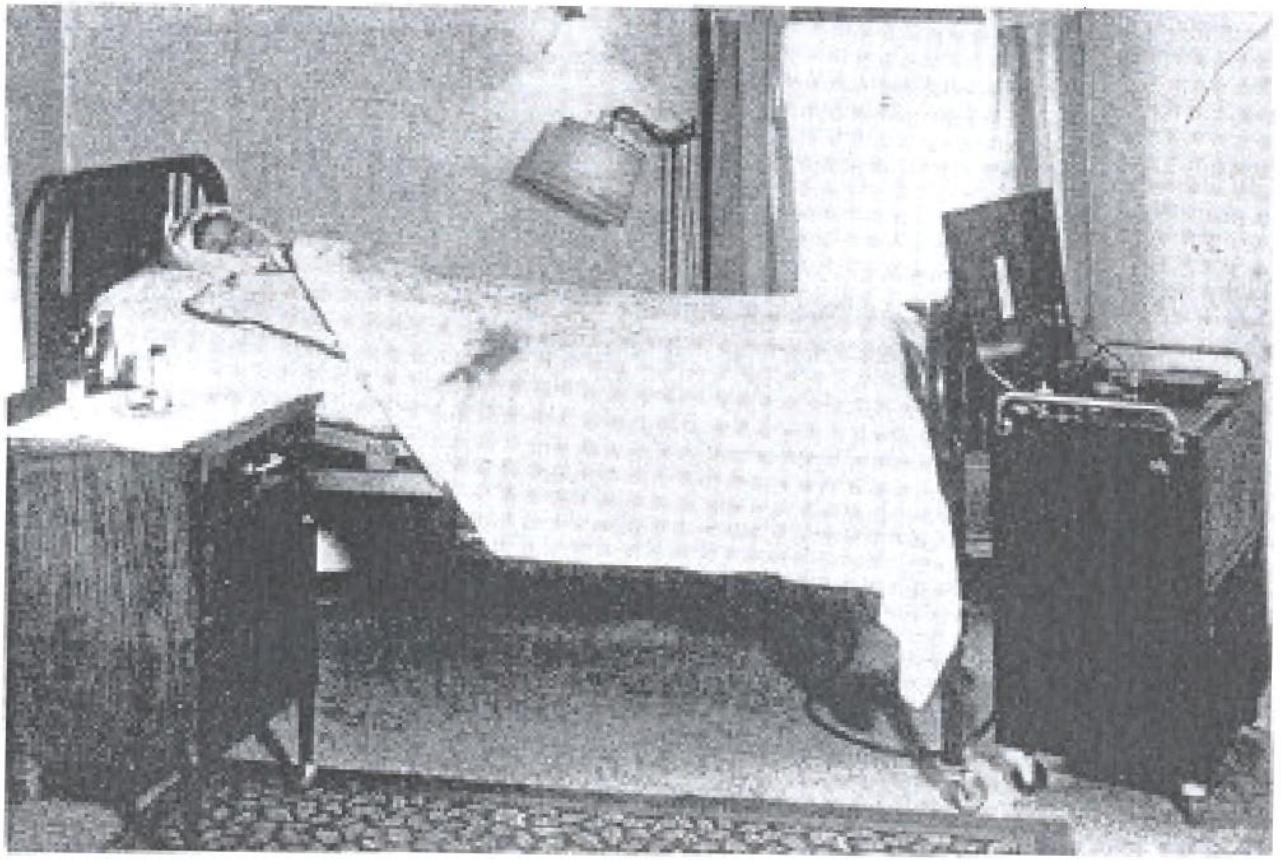

FIG. 7. Final modern equipment used for general refrigeration. Note addition of hood to the blanket, for full application of cold to the head (donated by Therm-O-Rite Products Co.).

EARLY EXPERIENCES WITH LOCAL AND GENERALIZED REFRIGERATION OF THE HUMAN BRAIN*

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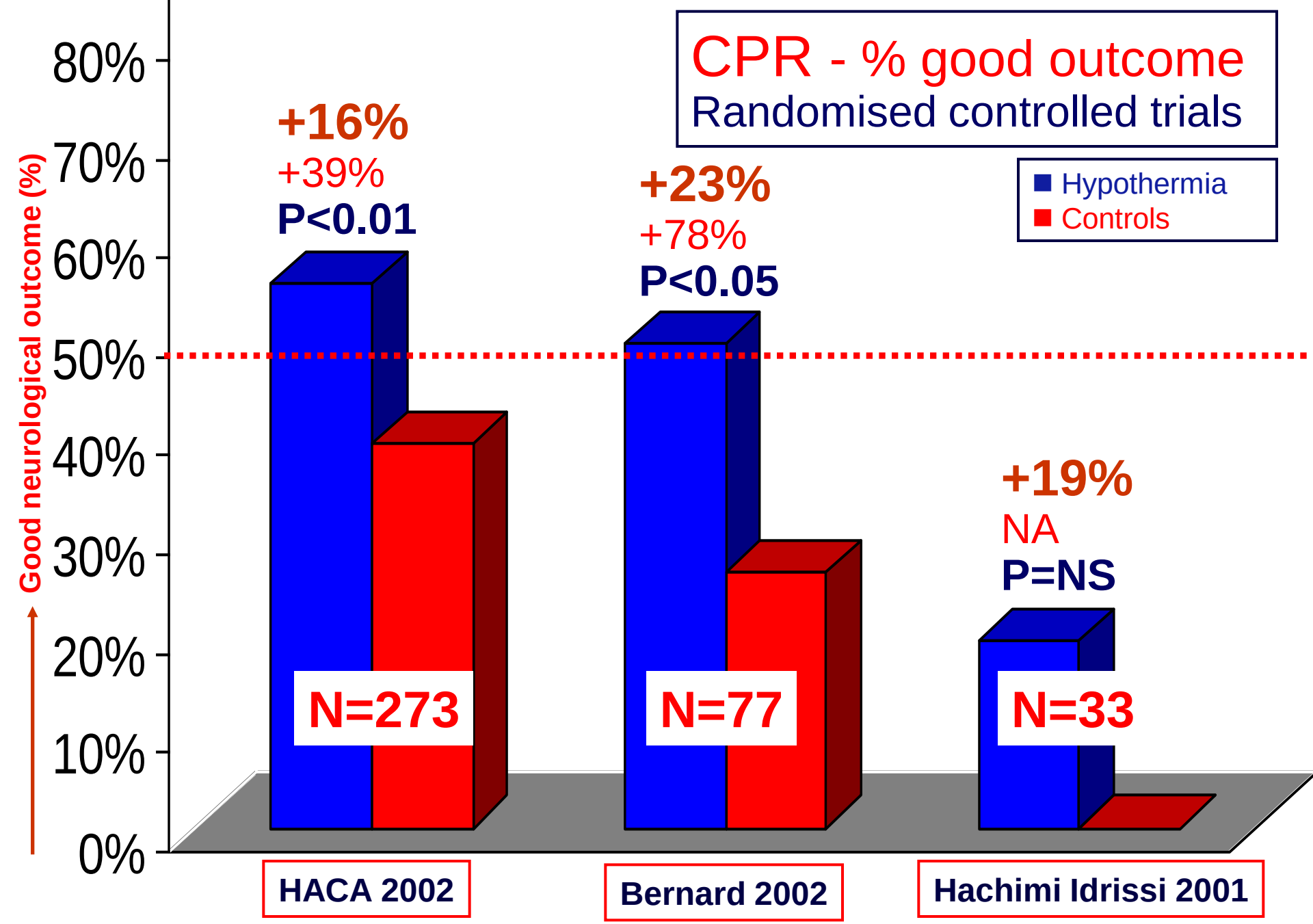
FIG. 8. With this mobile refrigeration apparatus, G.M. (April 9, 1940) was able to enjoy a fair degree of activity in the ward during the weeks of local refrigeration of the brain through an implanted capsule (Fig. 3) in the cavity of an evacuated glioma.

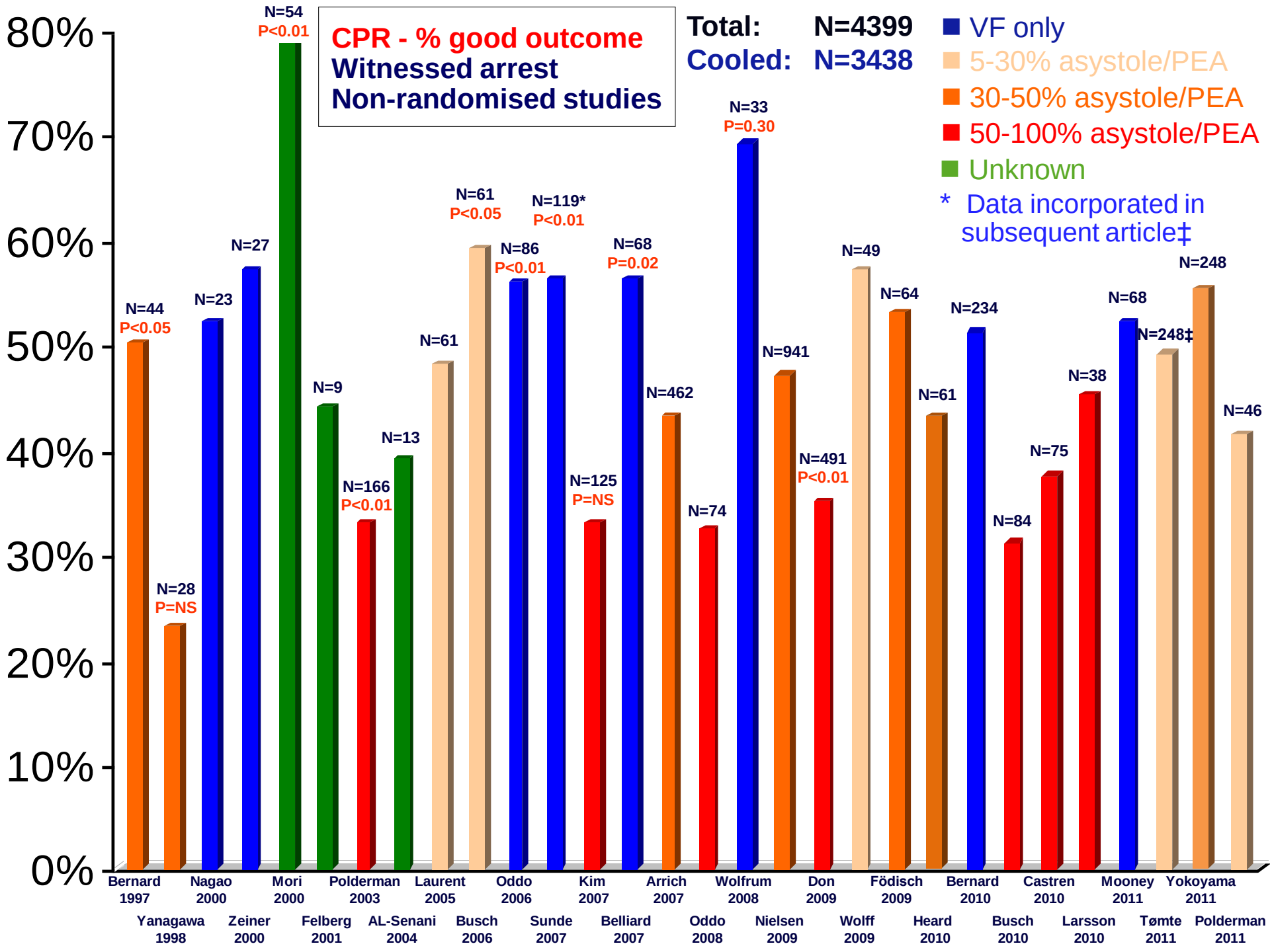
The New England Journal of Medicine

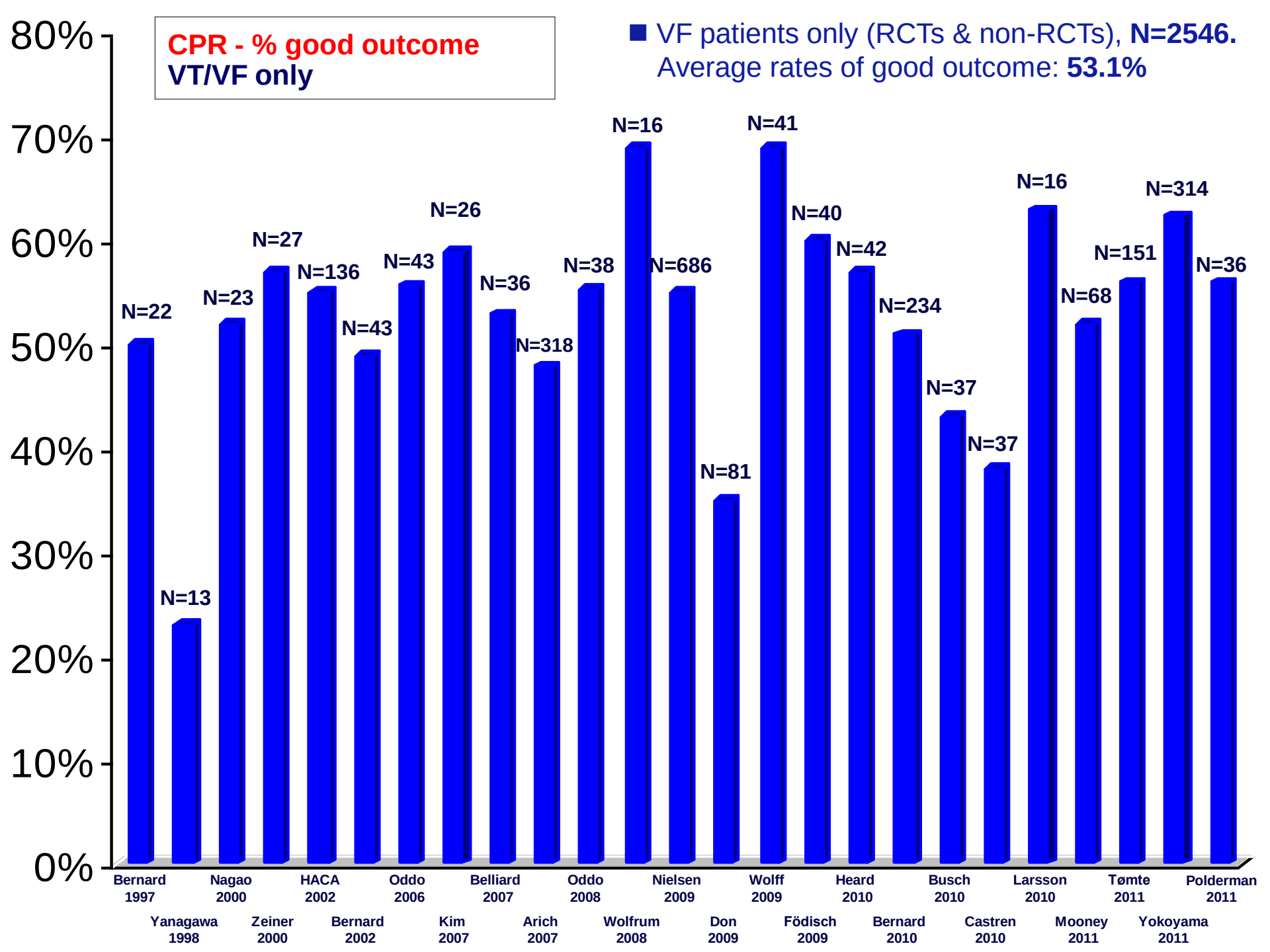
Established in 1812 as THE NEW ENGLAND JOURNAL OF MEDICINE AND SURGERY

VOLUME 346 FEBRUARY 21, 2002 NUMBER 8



Polderman KH. Lancet 2008;371:1955-1969.


CPR - % good outcome
Witnessed arrest
Non-randomised studies
Total: N=4399
Cooled: N=3438
VF only
5-30% asystole/PEA
30-50% asystole/PEA
50-100% asystole/PEA
Unknown
* Data incorporated in subsequent article‡
80%
70%
60%
50%
40%
30%
20%
10%
0%
N=44 P<0.05
N=28 P=NS
N=23
N=27
N=54 P<0.01
N=9
N=166 P<0.01
N=13
N=61
N=61 P<0.05
N=86 P<0.01
N=119* P<0.01
N=125 P=NS
N=68 P=0.02
N=462
N=74
N=33 P=0.30
N=941
N=491 P<0.01
N=49
N=64
N=61
N=234
N=84
N=75
N=38
N=68
N=248‡
N=248
N=46
Bernard 1997
Yanagawa 1998
Nagao 2000
Zeiner 2000
Mori 2000
Felberg 2001
Polderman 2003
AL-Senani 2004
Laurent 2005
Busch 2006
Oddo 2006
Sunde 2007
Kim 2007
Belliard 2007
Arrich 2007
Oddo 2008
Wolfrum 2008
Nielsen 2009
Don 2009
Wolff 2009
Födisch 2009
Heard 2010
Bernard 2010
Busch 2010
Castren 2010
Larsson 2010
Mooney 2011
Tømte 2011
Yokoyama 2011
Polderman 2011


CPR - % good outcome
VT/VF only
VF patients only (RCTs & non-RCTs), N=2546.
Average rates of good outcome: 53.1%
80%
70%
60%
50%
40%
30%
20%
10%
0%
N=22
N=13
N=23
N=27
N=136
N=43
N=43
N=26
N=36
N=318
N=38
N=16
N=686
N=81
N=41
N=40
N=42
N=234
N=37
N=37
N=16
N=68
N=151
N=314
N=36
Bernard 1997
Yanagawa 1998
Nagao 2000
Zeiner 2000
HACA 2002
Bernard 2002
Oddo 2006
Kim 2007
Belliard 2007
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Wolfrum 2008
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Bernard 2010
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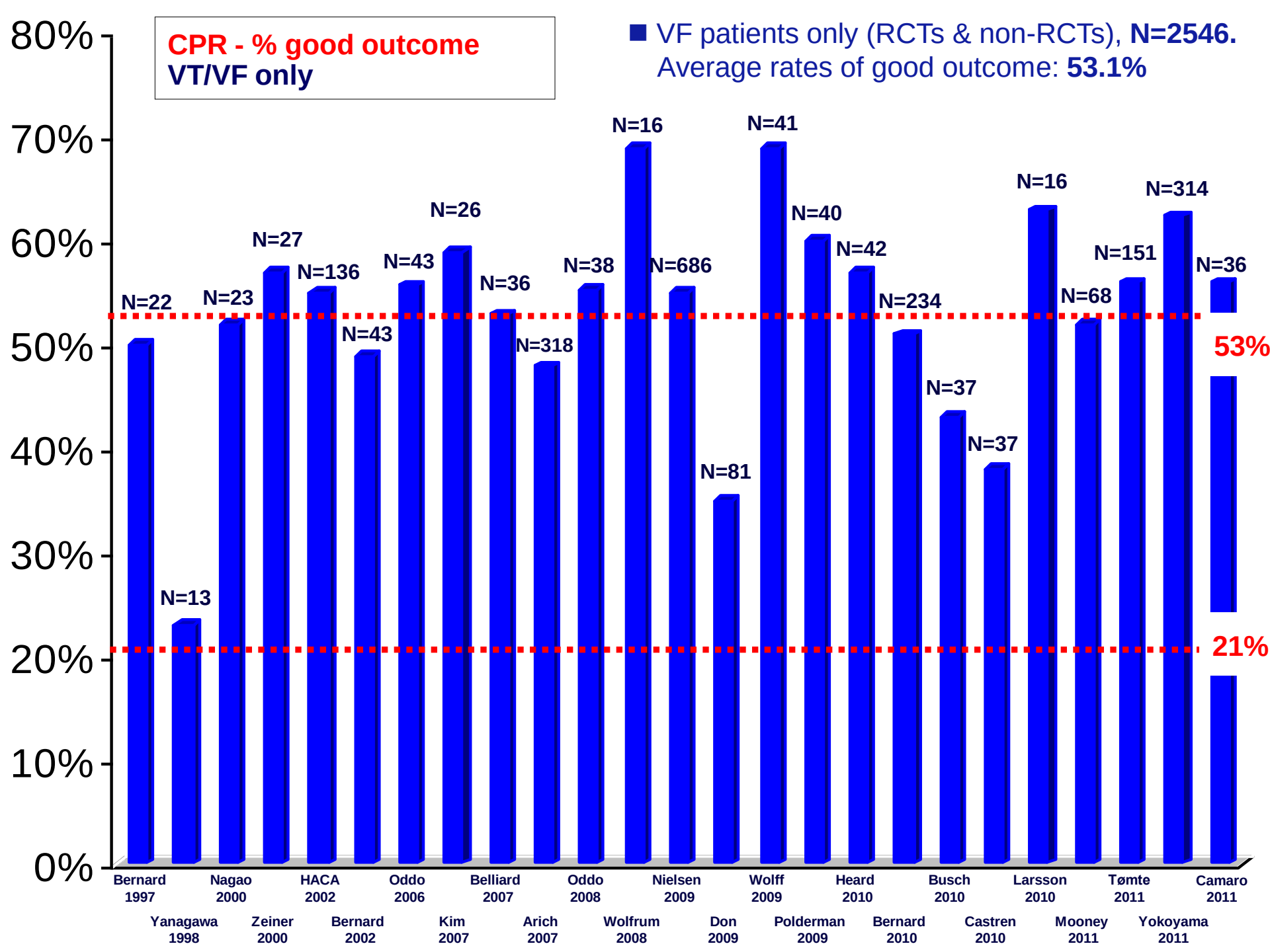
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Castren 2010
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Mooney 2011
Tømte 2011
Yokoyama 2011
Camaro 2011

Influence of mild therapeutic hypothermia after cardiac arrest on hospital mortality

Greetje van der Wal, MD; Sylvia Brinkman, MSc; Laurens L. A. Bisschops, MD; Cornelia W. Hoedemaekers, MD, PhD; Johannes G. van der Hoeven, MD, PhD; Dylan W. de Lange, MD, PhD; Nicolette F. de Keizer, PhD; Peter Pickkers, MD, PhD

Table 3. Intensive care unit and in-hospital length of stay (days) of patients before and after introduction of mild therapeutic hypothermia

Median (25% to 75%) Length of Stay (Days)	Total		Survivors		Nonsurvivors	
	Before MTH	After MTH	Before MTH	After MTH	Before MTH	After MTH
Intensive care unit	2.6* (0.9–5.3)	3.0 (1.3–5.8)	3.7* (1.6–7.0)	4.8 (2.7–7.9)	2.2 (0.6–4.5)	2.4 (0.8–4.5)
Hospital	5.0* (2.2–15.0)	6.0 (2.4–17.0)	18.0 (9.0–35.5)	19.0 (10.0–33.0)	3.8 (1.7–7.7)	3.5 (1.7–7.0)

*Significant difference between before and after implementation of mild therapeutic hypothermia (MTH) with a p value of $<.001$.

N=5317 patients

N=1547 before implementation of hypothermia

N=3770 after implementation hypothermia

Influence of mild therapeutic hypothermia after cardiac arrest on hospital mortality

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Table 1. Characteristics of patients after cardiac arrest with a reduced consciousness level (Glasgow Coma Scale score of ≤8) admitted to an intensive care unit that responded to the survey and meeting the Simplified Acute Physiology Score II inclusion criteria from January 1, 1999 until January 1, 2009

Characteristic	All Patients	Before Introduction of Mild Therapeutic Hypothermia	After Introduction of Mild Therapeutic Hypothermia
Number of patients	5317	1547	3770
Mortality (%)	67.3	72.0	65.4
Male (%)	64.1	64.1	64.1
Age (mean ± standard deviation) (yrs)	64.1 ± 15.2	63.6 ± 15.4	64.3 ± 15.1
Vasopressor (%)			
Median (25% to 75%) Glasgow Coma Scale score at admission			
Simplified Acute Physiology Score II score (mean ± standard deviation)	70.3 ± 15.2	69.8 ± 15.7	70.5 ± 15.0
Median (25% to 75%) minimal temperature (°C)	34.0 (32.2–35.9)	35.5 (34.3–36.5)	33.0 (32.0–35.4)
Median (25% to 75%) maximal temperature(°C)	36.9 (35.5–38.0)	37.8 (36.8–38.5)	36.4 (35.1–37.6)
Type of admission			
Medical (%)	92.7	92.6	92.7
Surgical, acute (%)	5.0	5.5	4.8
Surgical, elective (%)	2.3	1.9	2.5

Absolute mortality reduction 6.6%

Hypothermia….

- Works for cardiac arrest.
- Works for neonatal asphyxia.
- SO, what about stroke? After all, this is also an ischemic injury..

Differences…

- Longer duration of ischemia;
- Often little or no reperfusion, unless there is rapid spontaneous clot lysis, or if the patient receives TPA (success rate 30-50%), or undergoes clot removal….
- If there is no reperfusion, cooling can still be used to control ICP and to mitigate damage in a relatively small penumbra, but results are likely to be more modest.

Use of hypothermia in *ischemic stroke:*

Authors	No of pts (H/C)	Target temp	Time from injury to start of cooling	Time to target temp	Duration	Re-warming rate
Severe stroke, mostly sedated patients in ICU setting						
Naritomi H et al. 1996	4 (4 / 0)	33°C	< 5 hrs		72-96 hrs	
Schwab et al. 1998	20 (20 / 0)	Patient data included in subsequent study (Schwab et al. 1998, see below).				
Schwab et al. 1998	25 (25 / 0)	33°C	14±7 hrs, range 4-24	3.5-6.2 hrs	48-72 hrs	7-24 hrs median 18
Steiner T et al. 2001	15 (15 / 0)	32-33°C	4-84 hrs, median 17	2-7 hrs	72 hrs	26-88 hrs
Schwab et al. 2001	50 (50 / 0)	33°C	22 ± 9 hrs	3.5-11 hrs	48-72 hrs	Passive 17 hrs
Jian S et al. 2003	50 (50 / 0)	Patient data included in subsequent study (Schwab et al. 2001, see above).				
Georgiadis et al. 2001	6 (6 / 0)	33°C	28 ± 17 hrs	3±1 hrs, range 2-4.5	48-72 hrs	0.12-0.2°C/hr
Georgiadis et al. 2002	36 (19 / 17)	33°C	24 (range 18-24)	4 ± 1 hrs, range 2-6	48-72 hrs	Not stated
De Georgia et al. 2004*	40 (18 / 22)	33°C	8'59'' ± 2'52''	Variable;	24 hrs.	0.2°C/hr
Moderate Stroke (awake patients)						
Kammersgaard et al. 2000	73 (17 / 56)	35.5°C	3.25 ± 4.5 hrs	6 hrs	6 hrs	4 hrs
Krieger et al. 2001*	19 (10 / 9)	32±1°C	6.2 ± 1.3 hrs	3.5 ± 1.5	48 (range 24-96) hrs	0.25-0.5°Ch
Knoll et al. 2002	18 (18 / 0)	36-37°C		3.3 hrs	24 hrs	N/A
Els et al. 2006	25 (12 / 13)	35°C	15 ± 6 hrs	2±1 (range 1.5-3.5) hrs	48 hrs	Not stated
Lyden et al. 2006*	18 (18 / 0)	33°C	7.7 ± 3.1 hrs	7 hrs	12-24 hrs	12 hrs
Guluma et al. 2006	10 (10 / 0)	33°C	<6 hrs	1.7±0.7 hrs	24 hrs	0.3°C/hr
Hemmen et al. 2010 ICTuS-L*	58 (28 / 30)	33°C	<6 hrs	1.1 hrs (median)	24 hrs	0.33°C/hr

*Cooling combined with thrombolytics/reperfusion.

Total number of cooled patients reported so far: 270.
Malignant MCA infarction: 157. Less severe/moderate stroke: 113.

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Intravenous Thrombolysis Plus Hypothermia for Acute Treatment of Ischemic Stroke (ICTuS-L)

Final Results

Thomas M. Hemmen, MD, PhD; Rema Raman, PhD; Kama Z. Guluma, MD; Brett C. Meyer, MD; Joao A. Gomes, MD; Salvador Cruz-Flores, MD; Christine A. Wijman, MD, PhD; Karen S. Rapp, RN; James C. Grotta, MD; Patrick D. Lyden, MD; for the ICTuS-L Investigators

Table 1. Patient Group Randomization by Time of tPA Treatment From Stroke Onset

Hours From Stroke	Group	Patients (No.)	tPA	HY
0–3	1	22	+	–
	2	22	+	+
3–6	3	6	–	–
	4	2	+	–
	5	4	–	+
	6	2	+	+
total		58		

Hemmen TM et al. Stroke 2010; 41(10):2265-70

Table 3. Outcome Measures Between HY and NT Patients

	HY (Groups 2, 5, 6; n=28)	NT (Groups 1, 3, 4; n=30)	Fisher Exact Test *P*
mRS 0–1 at 90 days	5	7	0.747
NIHSS at 90 day (mean±SD)	6.3 (±6.6)	3.8 (±3.0)	0.355
At least one SAE (%)	75	43.3	0.018
Pneumonia (%)	50	10	0.001
All ICH (%)	28.6	20	0.752
Symptomatic ICH (%)	3.6	10	0.609
Mortality by 90 days (%)	21.4%	16.7	0.744

SAE indicates serious adverse event; ICH, intracerebral hemorrhage.

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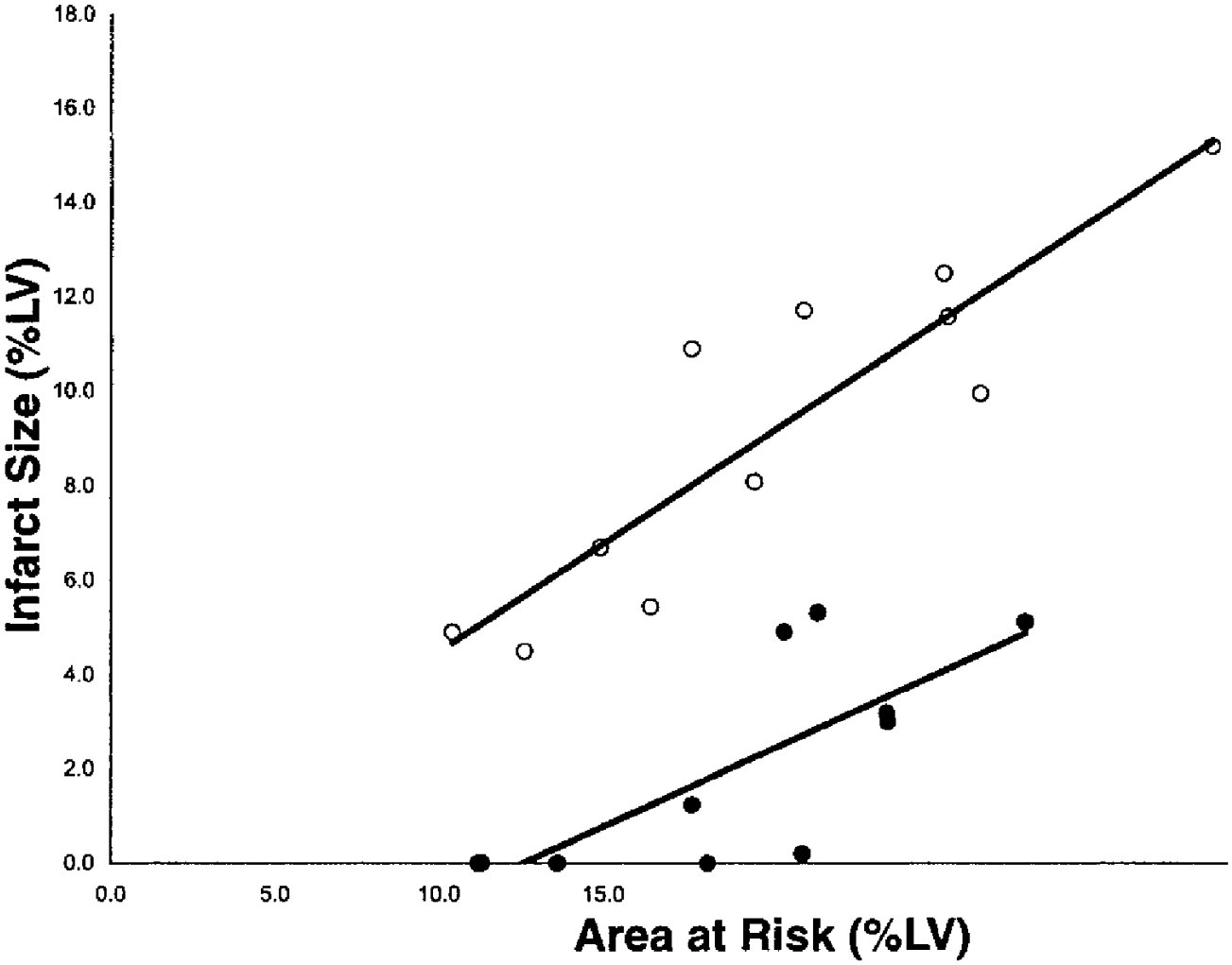
SAE indicates serious adverse event; ICH, intracerebral hemorrhage.

Hemmen TM et al. Stroke 2010; 41(10):2265-70

Cooling may protect the heart as well as the brain…

- **Animal studies have reported reductions in infarct size of 30-90% (!) of area at risk, depending on region of the heart and the timing of cooling.**



Normothermia

Hypothermia

Fig. 3. Scattergram of infarct size (% of LV) plotted against AAR (% of LV) in normothermic controls (○; $n = 11$) and hypothermia (●; $n = 11$) groups.

Dae MW et al. Am J Physiol Heart Circ Physiol 2002; 282: H1584–H1591

Resuscitation Science

Intra–Cardiopulmonary Resuscitation Hypothermia With and Without Volume Loading in an Ischemic Model of Cardiac Arrest

Demetris Yannopoulos, MD; Menekhem Zviman, PhD; Valeria Castro, BSc; Aravindan Kolandaivelu, MD, PhD; Ravi Ranjan, MD, PhD; Robert F. Wilson, MD; Henry R. Halperin, MD, MA

Yannopoulos D et al. Circulation 2009; 120:1426-35

1 **A: controls**

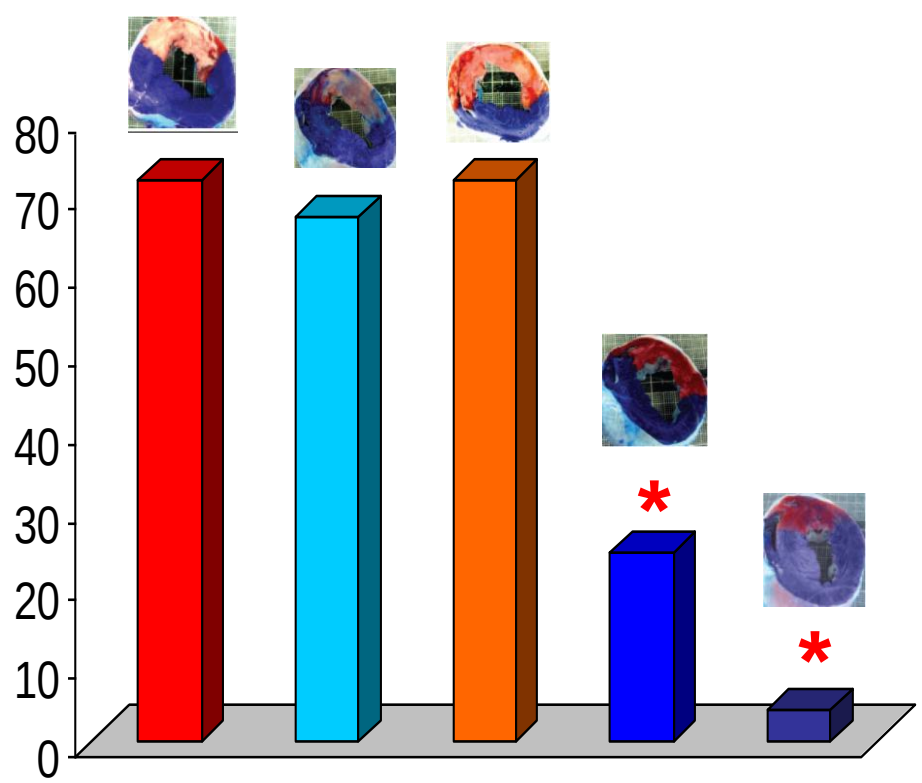
2 **B: Surface cooling after ROSC**

3 **C: Warm saline during CPR**

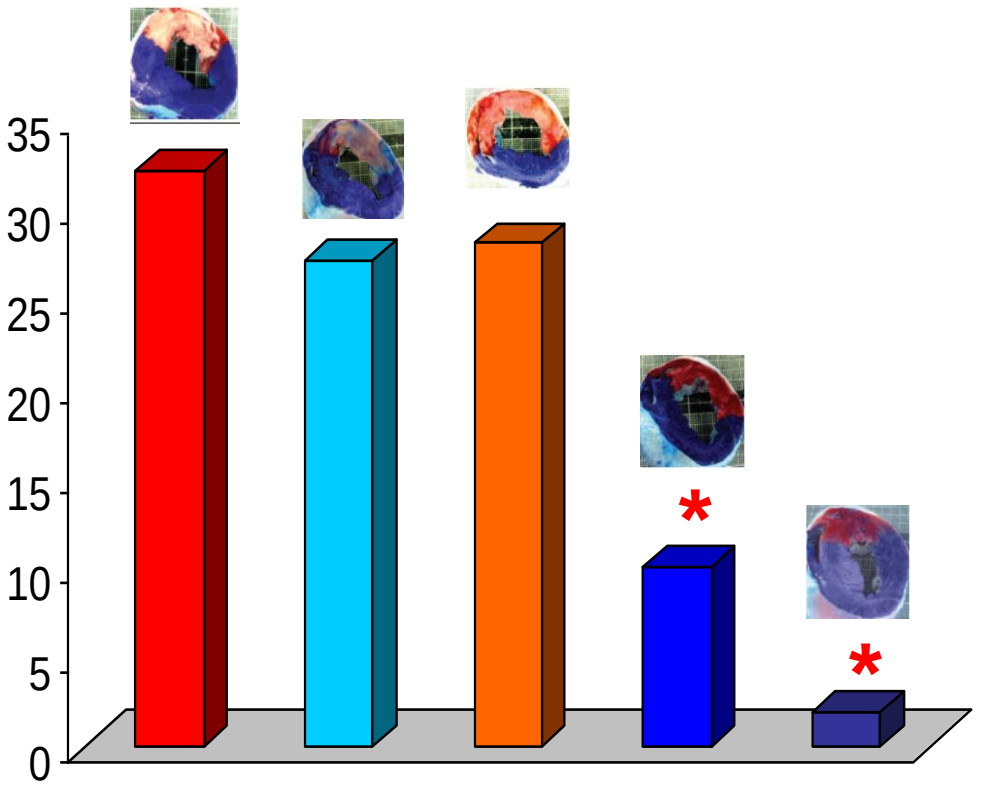
4 **D: Cold saline during CPR + surface cooling**

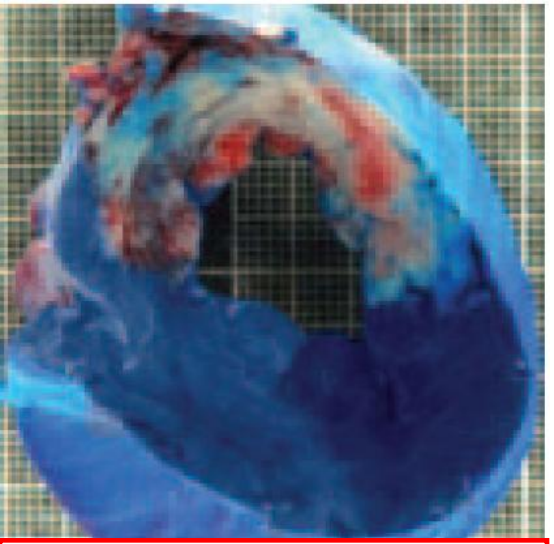
5 **E: Right atrial cooling with IV device**

Infarct size (% of area at risk)

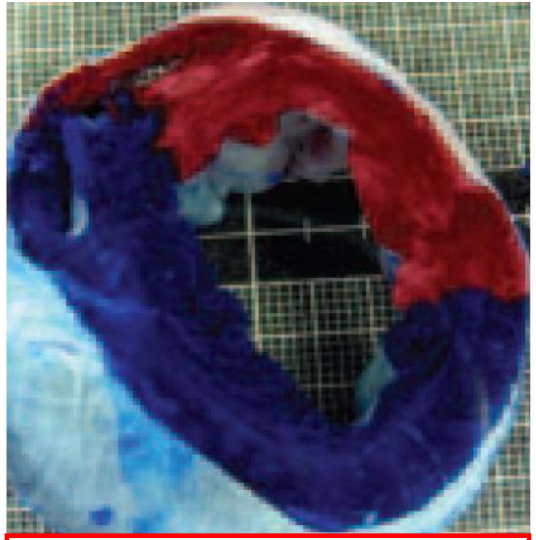


Infarct size (% of total LV)



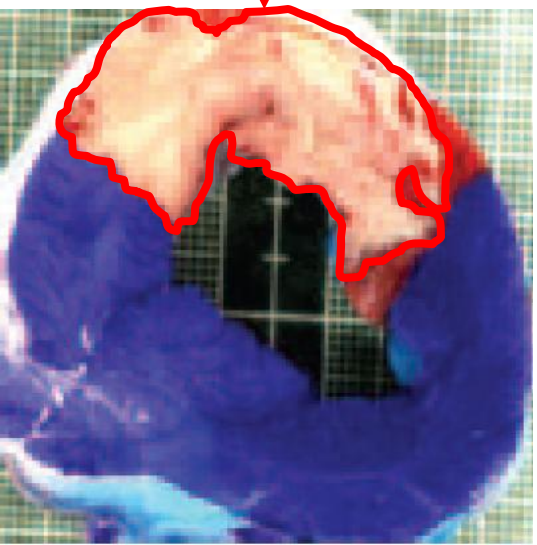


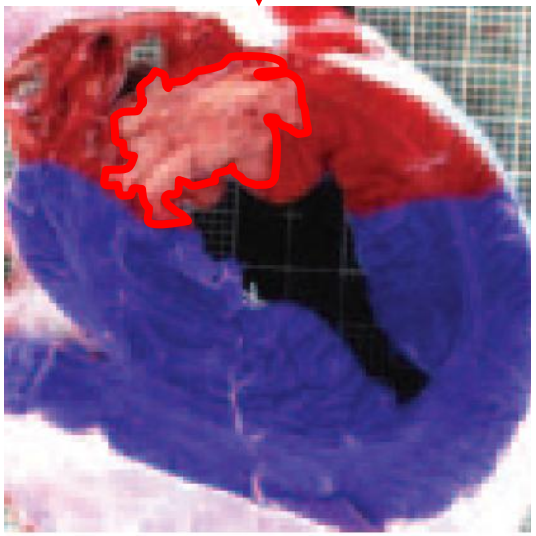
Group A (controls);

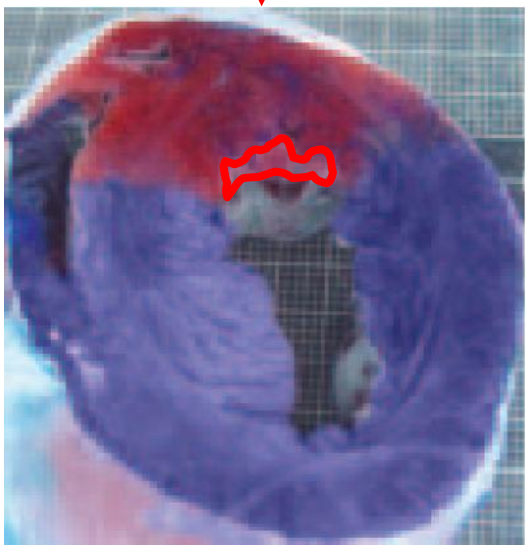


Group D (cold fluids & surface cooling)

Group E (rapid cooling with cardiac device)





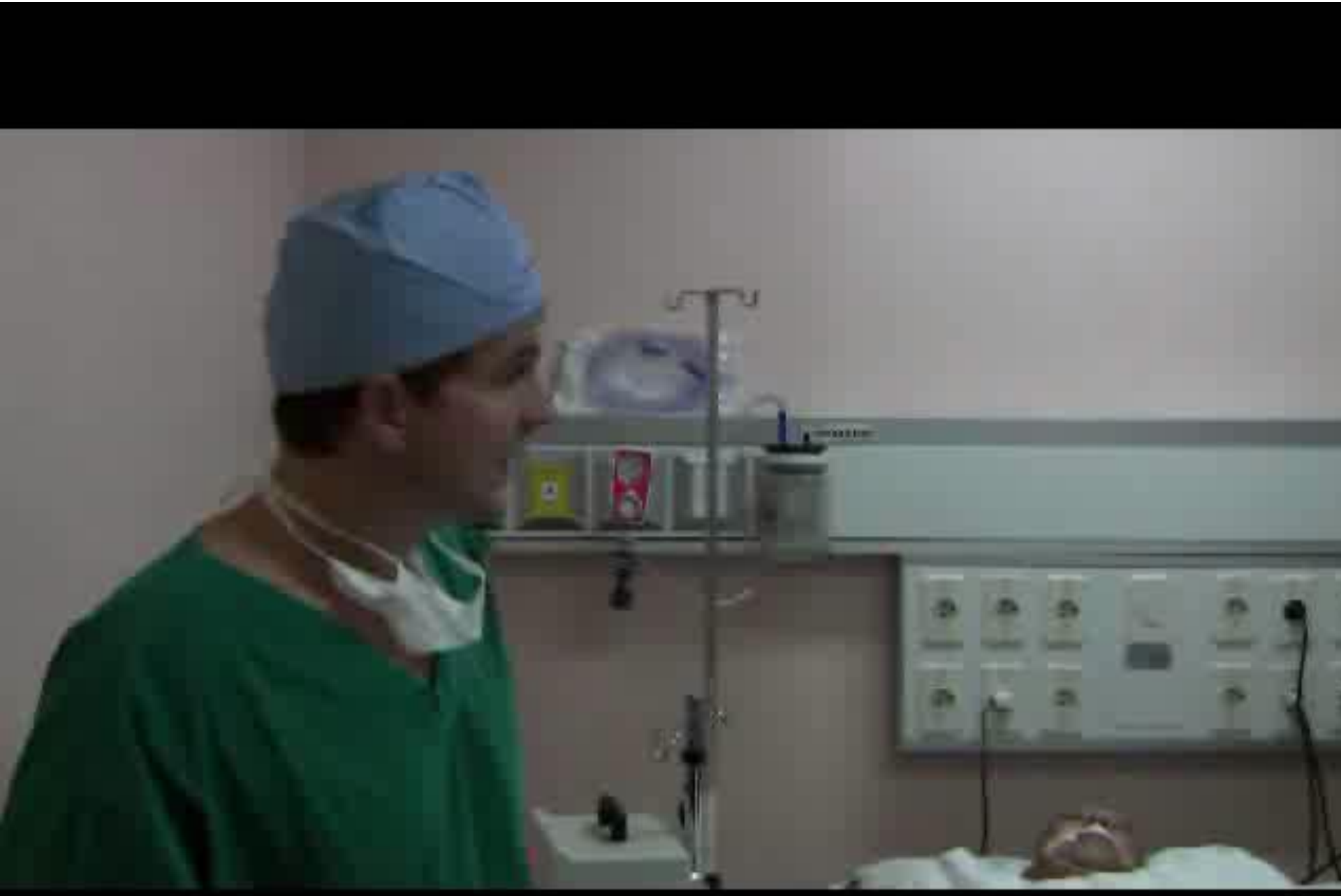


So, this means cooling awake patients…

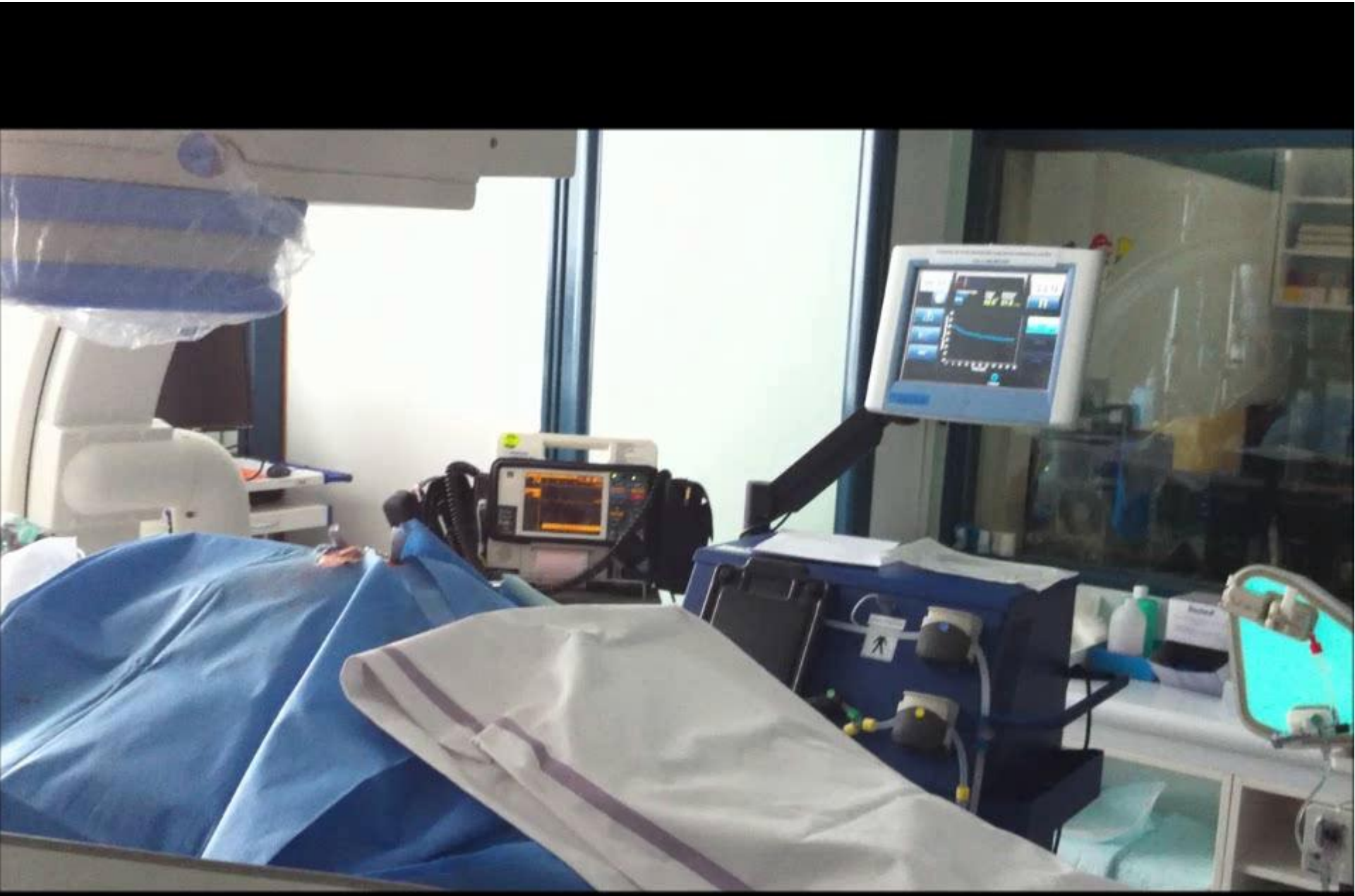
- **SO….. can this be done??**
- **Or do we need to sedate & intubate them for this treatment???**

Cooling awake patients…..

Cooling awake patients…..



Cooling awake patients…..

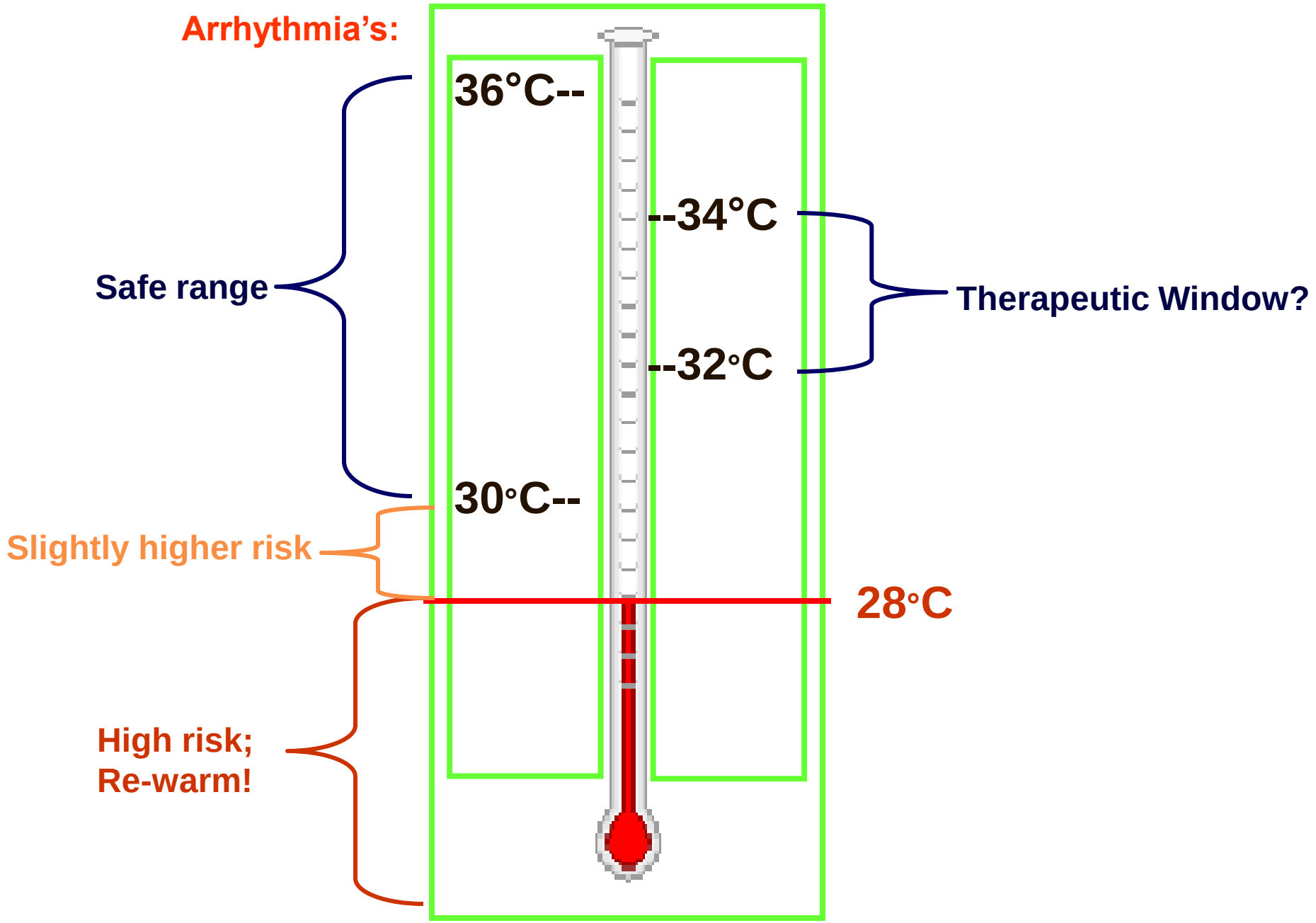


So, HOW can we achieve this?

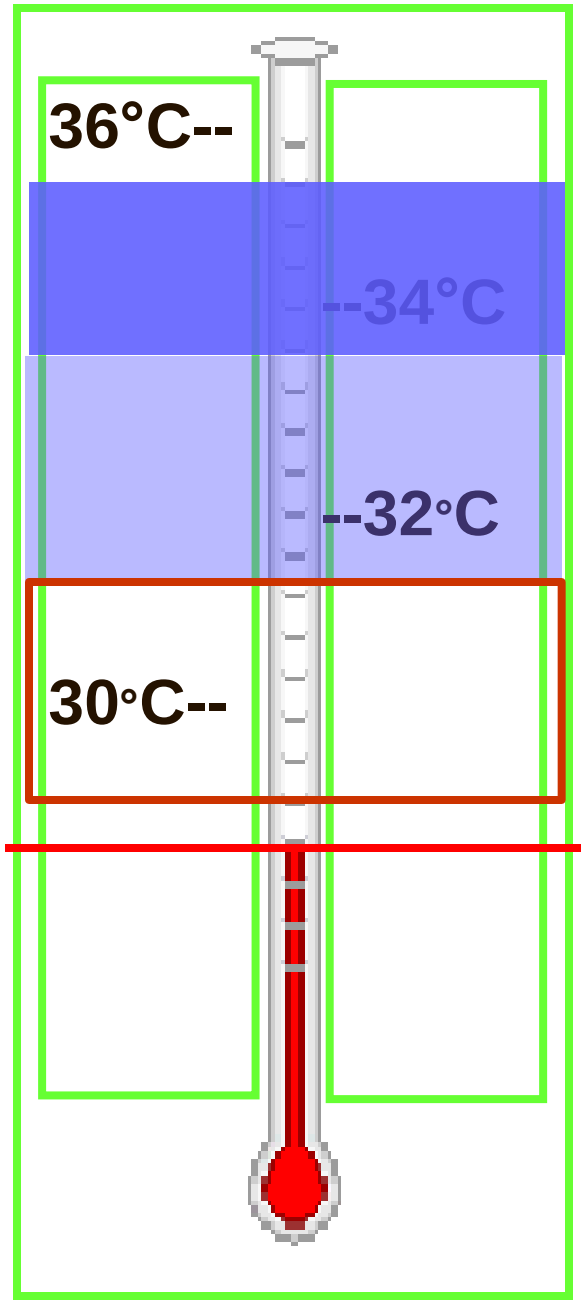
Myths vs. reality...

- Mild hypothermia (not<30^{o}C) does NOT cause arrhythmia's (in fact it decreases risk of arrhythmia's).
- Cooling does NOT cause hypotension, and is safe to use in patients with cardiac shock (it will stabilize these patients).
- Cooling *does* increase infection risk.
- Cooling *can* cause metabolic changes (hypovolemia, hypocapnia, electrolyte loss, decreased drug clearance, shivering etc.) that need to be properly managed.

Which target temperature?



Which target temperature?



Maximum shivering (±35.9-±33.5°C; peak at ±35.5°C

Much decreased shivering response (±31.0-±33.5°C;

Shivering stops completely

28°C

The three phases of hypothermia:

1. Induction phase: get below 34^{o}C and to target temperature as quickly as possible. Small overshoot acceptable provided temperature remains >30^{o}C.
2. Maintenance phase: should be reliable, with no or minor fluctuations (maximum 0.2-0.5^{o}C).
3. Re-warming phase: slow and controlled (0.2-0.5^{o}C/hr)

Physiology of temperature control…

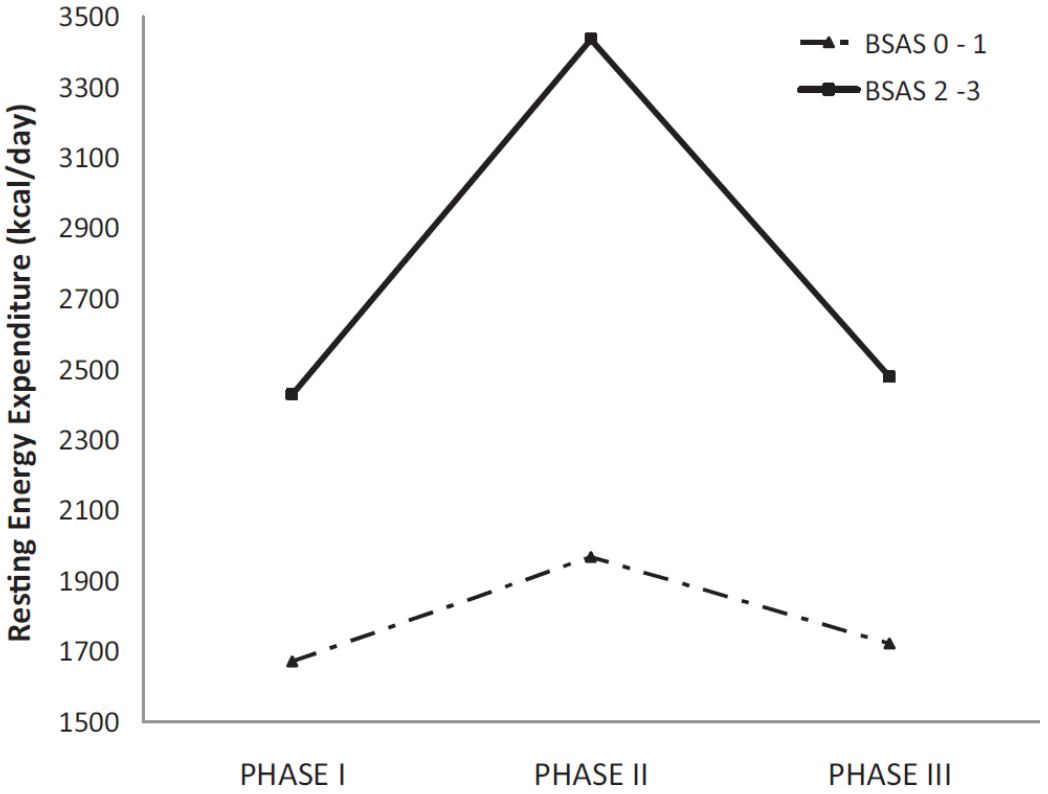
- About 90% of information regarding temperature comes from the skin; 10% comes from the core
- SO….. In theory (and, as the evidence suggests, in practice) we can FOOL the body and circumvent it's thermoregulatory defense mechanisms.

SKIN COUNTERWARMING can be a highly effective anti-shivering strategy.

Metabolic benefits of surface counter warming during therapeutic temperature modulation*

Neeraj Badjatia, MD, MSc; Evangelia Strongilis, RD; Mary Prescutti, RN; Luis Fernandez, MD; Andres Fernandez, MD; Manuel Buitrago, MD, PhD; J. Michael Schmidt, PhD; Stephan A. Mayer, MD, FCCM

Conclusions: **Surface CW provides beneficial control of shivering and improves the metabolic profile during TTM. (Crit Care Med 2009; 37:1893–1897)**



Badjadia N et al., Crit Care Med 2009; 37:1893-7.

Also, SKIN COUNTERWARMING can be a highly effective anti-shivering strategy.

Blowing hot and cold? Skin counter warming to prevent shivering during therapeutic cooling*

Arthur R. H. van Zanten, MD, PhD
Department of Intensive Care
Gelderse Vallei Hospital
Ede, The Netherlands
Kees H. Polderman, MD, PhD
Department of Intensive Care
Utrecht University Medical Center
Utrecht, The Netherlands

van Zanten AR et al., Crit Care Med 2009; 37:2106-2108; Polderman KH et al. Crit Care Med 2009; 37:1101-20; Badjadia N et al., Crit Care Med 2009; 37:1893-7.

Cooling awake patients…..

We will likely still need some drugs, especially in the induction and re-warming phase….

Table 4. Drugs that can be used to control shivering

Drug	Efficacy	Hypotensive Effect	Sedative Effect[a]	Additional Comments, Advantages, and Disadvantages
Magnesium (2–3 g)[b]	++	+	−	Advantages: some evidence for direct neuroprotective effects of Mg. "Pre-emptive" correction of hypothermia-induced Mg depletion
Propofol (20–150 mg)[b]	+++	+++	++++	Advantages: brief-acting. Anti-seizure effect. Disadvantage: more pronounced hypotension
Benzodiazepines (dose depending on type of drug; e.g. Midazolam 2.5–10 mg)[b]	++	+	++++	Advantages: less hypotension. Disadvantages: Complicates neurological evaluation. Reduced metabolism during cooling can lead to drug accumulation with persistent sedative effect after rewarming
Meperidine 10–25 mg	++++	+	++	Advantages: rapid (1–5 mins) effect. Effect lasts longer than with quick-acting opoids. Effect more pronounced than other opoids because of activity at Kappa–receptors. Relatively mild hypotensive effect. Disadvantages: complicates neurological evaluation. Slower metabolism during cooling.
Quick-acting opiates: Fentanyl 50–100 μg,[b] Alfentanyl 100–250 μg	+++	+	++	Advantages: rapid (1–5 mins) effect. Relatively mild hypotensive effect. Disadvantages: complicates neurological evaluation. Decreased drug metabolism during cooling
Morphine 2.5–5 mg[b]	+++	+++	++	Advantage: low costs; additional sedative effect. Disadvantages: delayed (20 mins) effect. Greater hypotensive effect compared with fentanyl
Dexmedetomidine 50–100 μg[b]	++	+	++	Advantages: brief-acting; only mild hypotension. Disadvantages: only moderately effective; expensive. Currently not available in Europe
Clonidine 75–200 μg[b]	+++	++++	+	Effect in 4–7 mins. Disadvantages: Hypotension, additional bradycardia
Ketanserin 10 mg[b]	++	++	−	Effect in 4–7 mins. Advantages: increases cooling rate. Disadvantage: moderate hypotensive effect
Tramadol 50–100 mg	++	++	++	More rapid effect than morphine (±5 mins). Relatively mild hypotensive effect. Disadvantages: complicates neurological evaluation. Metabolism decreases during hypothermia. Can cause seizures
Urapidil 10–20 mg	+++?	+++	−	Conflicting results of studies on efficacy. Disadvantage: pronounced hypotensive effect
Doxapram 100 mg	+++	−	−	Advantages: rapid action (1–5 mins). Can increase heart rate and blood pressure. Disadvantages: can cause laryngeal spasms
Physostigmine 2 mg	++	++	−	Can cause additional bradycardia and hypotension
Flumazenil 0.25–0.5 mg	++	−	−	Few data available. Efficacy may be lower outside the peri-operative setting
Nefopam 10–20 mg	+++	−	+	Can induce convulsions and anaphylactic reactions Currently not available in the United States
Metamizol	+	−	−	Low efficacy
Ondansetron	+	−	±	Low efficacy
Other options: Lidocaine, Nalbuphine, Pentazocine, Methylphenidate	−/±	−	−	Questionable or no efficacy
Muscle paralyzers	+++++	−	−	Advantage: 100% effective. Disadvantages: does not affect neurological triggers for shivering; may mask insufficient sedation and/or seizure activity; long-term risks of critical illness neuropathy

Polderman KH et al. Critical Care Med 2009;37:1101-20

List of alternatives to combat shivering:

- Magnesium ($MgSO_4$, MgCl, et.)
- Buspirone
- Meperidine/pethidine
- Quick-acting opiates (fentanyl, remi-fentanyl) (or slow-acting opoids such as Morphine)
- Propofol
- Benzodiazepines (midazolam, temazepam, diazepam, etc. etc.)
- Clonidine
- Ketanserin
- Tramadol
- Dexmedetomidine
- Others: Doxapram, Urapidil, Physostigmine, etc.

Polderman KH et al. Critical Care Med 2009; 37:1101-20

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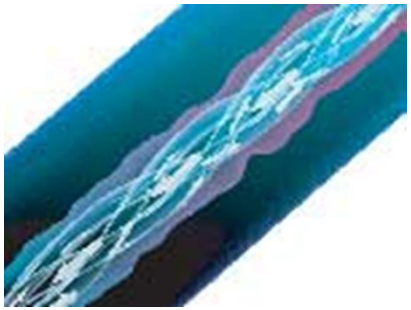
Polderman KH et al. Critical Care Med 2009; 37:1101-20

The cooling methods….



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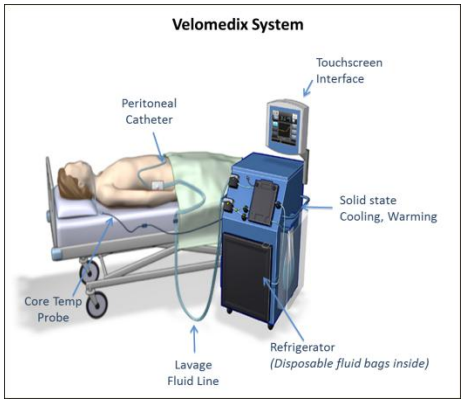

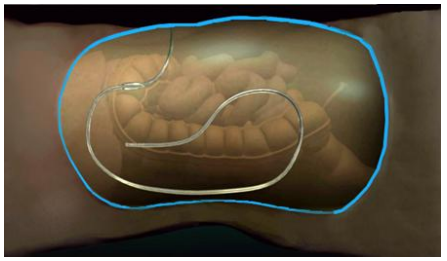

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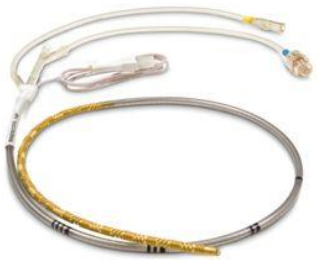

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Conclusions

- Cooling awake patients? **Yes, we can!**
- Methods: probably invasive (core) cooling combined with maximum skin counterwarming (one feasibility study using the Arctic Sun adhesive pads in awake patients is ongoing, perhaps this also combines sufficiently well with skin counterwarming – this remains to be determined).
- First line drugs: Magnesium drip (serum level 2-2.5 mmol/l); perhaps Buspirone
- Second line drugs: meperidine, fentanyl, clonidine

Conclusions

- This can (and I personally believe this *will*), cause a paradigm shift for this field; it would significantly expand the number of patients with indications for therapeutic temperature management, and fundamentally change the way we view and apply temperature manipulation.

If you are interested and want to learn more about this topic...

Chilling at the beach in Europe, June 7 - 9 2012 in Portoroz, Slovenia
http://chilling-at-the-beach.eu/

Thank you for your attention!


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