When to Cool? Clinical Applications of Therapeutic Hypothermia

- Cardiac arrest with return of pulses?
- Traumatic Brain Injury?
- Stroke?
- Other brain injury?

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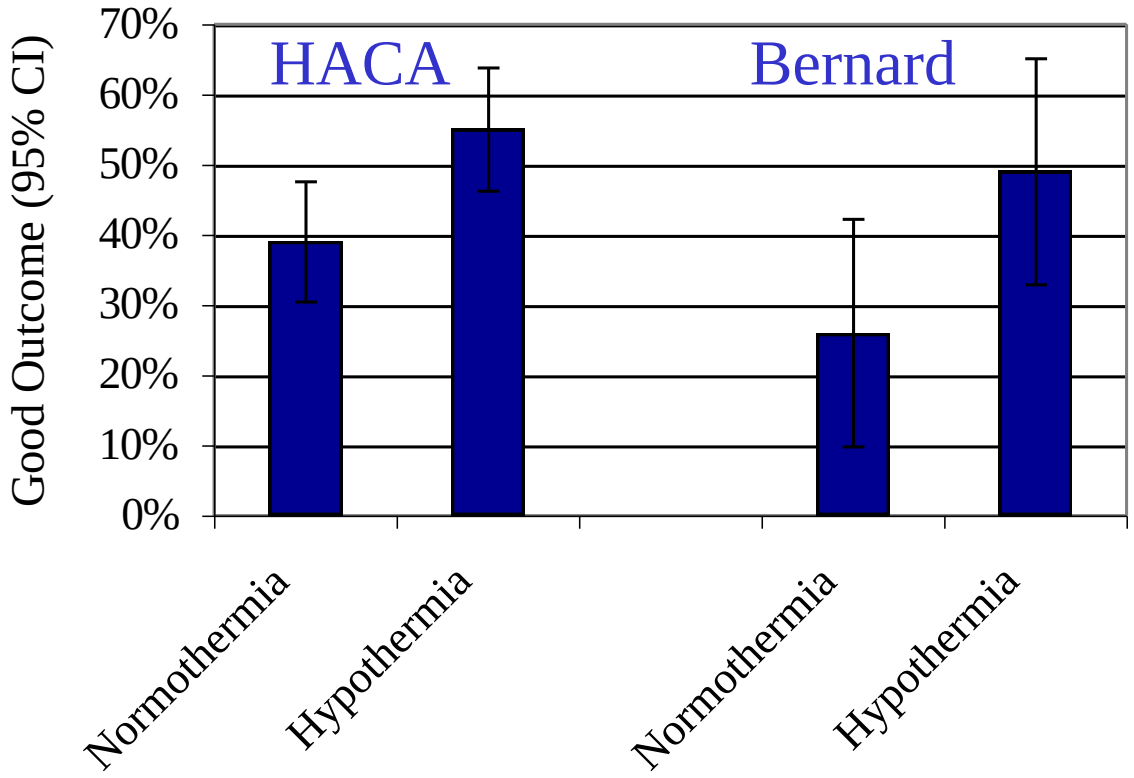
Acute Neurological Interventions after CPR

Post-CPR Care - Brain

- Animal studies have made it clear that brain damage is ongoing for 24-48 hours after reperfusion
  - Care during that time can change outcome
  - Temperature and blood pressure are particularly influential
- Clinical data have shown that certain plans of care can alter neurological outcomes



Outcome	Risk Ratio
Favorable Outcome	1.40 (1.08 - 1.81)
Death at 6 months	0.74 (0.58 - 0.95)

- NNT (Favorable Outcome) = 6.4
- NNT (Not Dead) = 7.0

- Relative Risk Reduction (Neuro) = 26%
- Relative Risk Reduction (Death) = 26%

Outcome	Odds Ratio
Good Outcome	2.65 (1.02 – 6.88)
Good Outcome	5.25 (1.47 – 18.76)

- NNT (Good Outcome) = 4.5
- NNT (Not Dead) = 6.1

- Relative Risk Reduction (Neuro) = 30%
- Relative Risk Reduction (Death) = 24%

AHA / ILCOR Guideline

- Occasional use by select physicians with interest in hypothermia

Thus, unconscious adult patients with ROSC after out-of-hospital cardiac arrest should be cooled to 32°C to 34°C (89.6°F to 93.2°F) for 12 to 24 hours when the initial rhythm was VF (Class IIa). Similar therapy may be beneficial for patients with non-VF arrest out of hospital or for in-hospital arrest (Class IIb).

AHA / ILCOR Guideline 2005

Thus, unconscious adult patients with ROSC after out-of-hospital cardiac arrest should be cooled to 32°C to 34°C (89.6°F to 93.2°F) for 12 to 24 hours when the initial rhythm was VF (Class IIa). Similar therapy may be beneficial for patients with non-VF arrest out of hospital or for in-hospital arrest (Class IIb).

Don’t be stuck in 2002

- Most animal studies were done in PEA and asystole
- Benefit for the brain has nothing to do with what stopped the heart
  - Those trials picked VF just to simplify their design
- There are newer studies extending the inclusion criteria

Not just for VF

Efficacy and Safety of Endovascular Cooling After Cardiac Arrest

Cohort Study and Bayesian Approach

Michael Holzer, MD; Marcus Müllner, MD, MSc; Fritz Sterz, MD; Oliver Robak, MD; Andreas Kliegel, MD; Heidrun Losert, MD; Gottfried Sodeck, MD; Thomas Uray, MD; Andrea Zeiner, MD; Anton N. Laggner, MD

Background and Purpose—Recently 2 randomized trials in comatose survivors of cardiac arrest documented that therapeutic hypothermia improved neurological recovery. The narrow inclusion criteria resulted in an international recommendation to cool only a restricted group of primary cardiac arrest survivors. In this retrospective cohort study we investigated the efficacy and safety of endovascular cooling in unselected survivors of cardiac arrest.

Methods—Consecutive comatose survivors of cardiac arrest, who were either cooled for 24 hours to 33°C with endovascular cooling or treated with standard postresuscitation therapy, were analyzed. Complication data were obtained by retrospective chart review.

Results—Patients in the endovascular cooling group had 2-fold increased odds of survival (67/97 patients versus 466/941 patients; odds ratio 2.28, 95% CI, 1.45 to 3.57; $P<0.001$). After adjustment for baseline imbalances the odds ratio was 1.96 (95% CI, 1.19 to 3.23; $P=0.008$). When discounting the observational data in a Bayesian analysis by using a sceptical prior the posterior odds ratio was 1.61 (95% credible interval, 1.06 to 2.44). In the endovascular cooling group, 51/97 patients (53%) survived with favorable neurology as compared with 320/941 (34%) in the control group (odds ratio 2.15, 95% CI, 1.38 to 3.35; $P=0.0003$; adjusted odds ratio 2.56, 1.57 to 4.17). There was no difference in the rate of complications except for bradycardia.

Conclusion—Endovascular cooling improved survival and short-term neurological recovery compared with standard treatment in comatose adult survivors of cardiac arrest. Temperature control was effective and safe with this device.
(*Stroke*. 2006;37:1792-1797.)

Not jus

Efficacy an

Michael Holzer, M
Andreas Kliegel, M

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treatment in comatose adult
(***Stroke***. **2006;37:1792-1797.**

TABLE 1. Demographic and Resuscitation Data of the Patients in the Endovascular Cooling and Control Group

	Endovascular Cooling (n=97)	Control (n=941)	*P*
Female, n (%)	30 (31)	329 (35)	0.426
Age, y (IQR)	52 (42–62)	60 (50–70)	<0.001
Diabetes mellitus, n (%)	9 (9)	179 (19)	0.018
New York Heart Association Class	1 (1–1)	1 (1–2)	<0.001
Out-of-hospital cardiac arrest, n (%)	89 (92)	608 (65)	<0.001
Cardiac cause of cardiac arrest, n (%)	82 (85)	600 (64)	<0.001
Ventricular fibrillation, n (%)	69 (71)	435 (46)	<0.001
BLS, n (%)	41 (42)	240 (26)	<0.001
Time to initiation of BLS (no flow), min (IQR)	5 (1–9)	0 (0–5)	<0.001
Time from initiation of BLS to ROSC (low flow), min (IQR)	15 (9–25)	13 (5–22)	0.0734
Rearrest within 24 h, n (%)	12 (12)	153 (16)	0.319
Survival at 1 mo, n (%)	67 (69)	466 (50)	<0.001
Survival and Good Neurology (CPC 1 or 2) at 1 mo, n (%)	51 (53)	320 (34)	<0.001

IQR indicates range between the 25th and 75th quartile; No flow, time interval from cardiac arrest to first resuscitation attempts; ROSC, restoration of spontaneous circulation; BLS, basic life-support.

Not just for stable patients

(Who is "stable" after cardiac arrest?)

Therapeutic hypothermia after out-of-hospital cardiac arrest: experiences with patients treated with percutaneous coronary intervention and cardiogenic shock

J. Hovdenes[1], J. H. Laake[1], L. Aaberge[2], H. Haugaa[1] and J. F. Bugge[1]
Department of [1]Anaesthesiology and Intensive Care and [2]Cardiology, Rikshospitalet, Oslo, Norway

Background: Therapeutic hypothermia has been shown to increase survival after out-of-hospital cardiac arrest (OHCA). The trials documenting such benefit excluded patients with cardiogenic shock and only a few patients were treated with percutaneous coronary intervention prior to admission to an intensive care unit (ICU). We use therapeutic hypothermia whenever cardiac arrest patients do not wake up immediately after return of spontaneous circulation.
Methods: This paper reports the outcome of 50 OHCA patients with ventricular fibrillation admitted to a tertiary referral hospital for immediate coronary angiography and percutaneous coronary intervention when indicated. Patients were treated with intra-aortic balloon counterpulsation (IABP) (23 of 50 patients) if indicated. All patients who were still comatose were treated with therapeutic hypothermia at 32–34 °C for 24 h before rewarming. The end-points were survival and cerebral performance category (CPC: 1, best; 5, dead) after 6 months.
Results: Forty-one patients (82%) survived until 6 months. Thirty-four patients (68%) were in CPC 1 or 2, and seven (14%) were in CPC 3. Of the 23 patients treated with IABP, 14 (61%) survived with CPC 1 or 2. In patients not treated with IABP, 20 patients (74%) survived with CPC 1 or 2. Forty patients (80%) developed myocardial infarction. Percutaneous coronary intervention was performed in 36 patients (72%).
Conclusion: In OHCA survivors who reached our hospital, the survival rate was high and the neurological outcome acceptable. Our results indicate that the use of therapeutic hypothermia is justified even in haemodynamically unstable patients and those treated with percutaneous coronary intervention.

Accepted for publication 22 September 2006

Key words: cardiac arrest; intra-aortic balloon counterpulsation; percutaneous coronary intervention; therapeutic hypothermia.

An integrated approach, including brain therapy, is essential

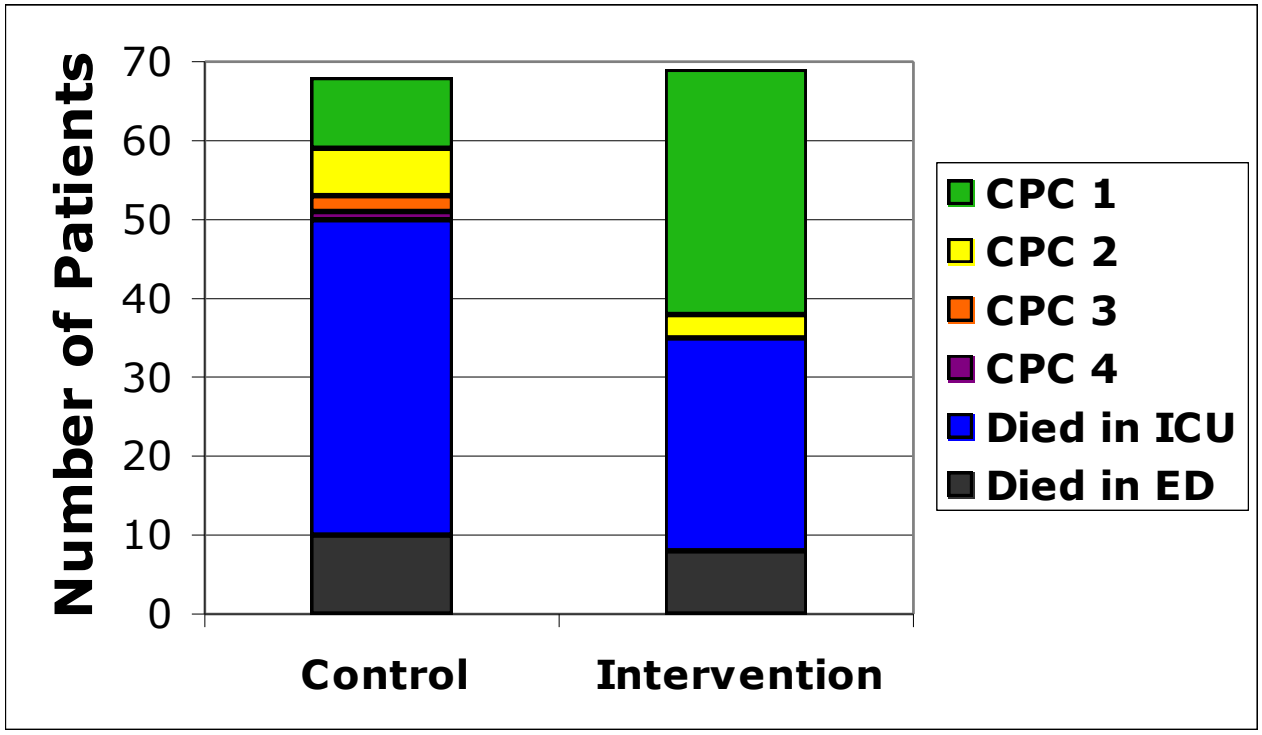
- Brain injury contributes to at least 50% of the subsequent deaths after successful resuscitation

- If we are sincerely trying to resuscitate the patient, we must address brain resuscitation:
  - perfusion, oxygenation AND temperature.

Implementation of a standard post-resuscitation protocol: Sunde (2007)

*Protocol **includes therapeutic hypothermia***

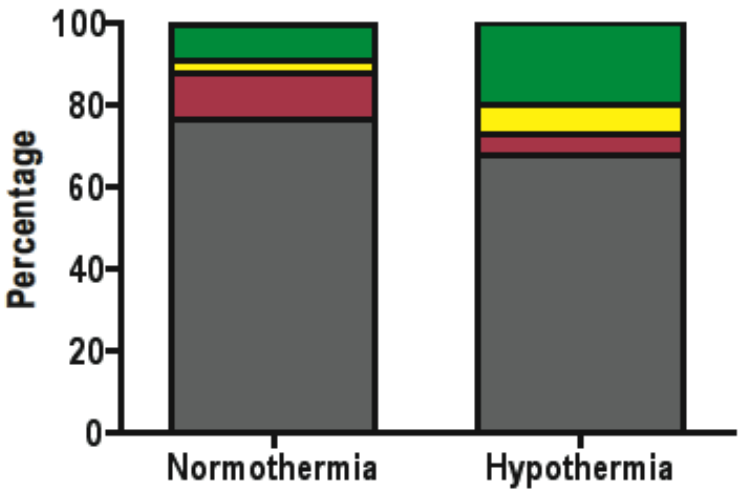
Good outcome in 34/61 = 56%



Resuscitation 2007; 73: 29-39

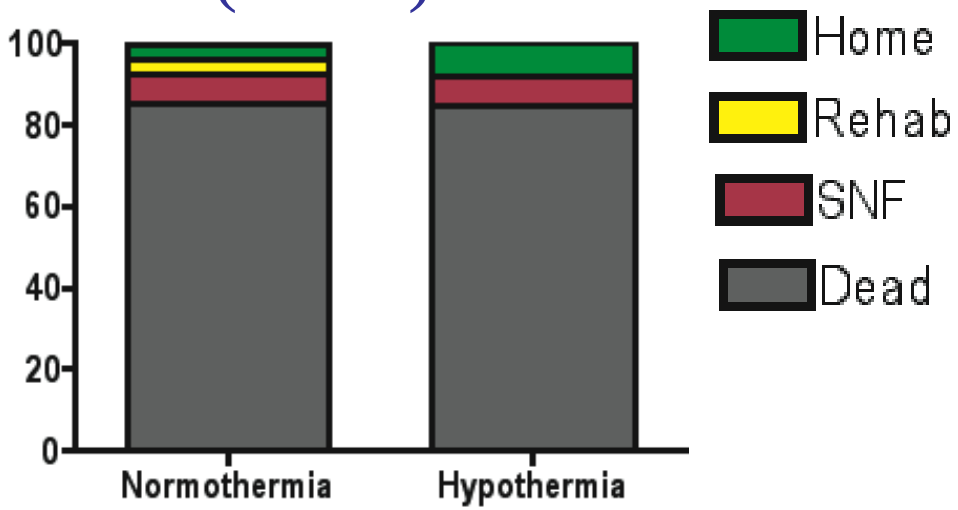
Hypothermia Benefits Differ Between Categories of Patients (2005-2007)

Out-of-Hospital Arrest (N= 90)



24% vs. 32% Alive
12% vs. 27% Good

In-Hospital Arrest (N=40)

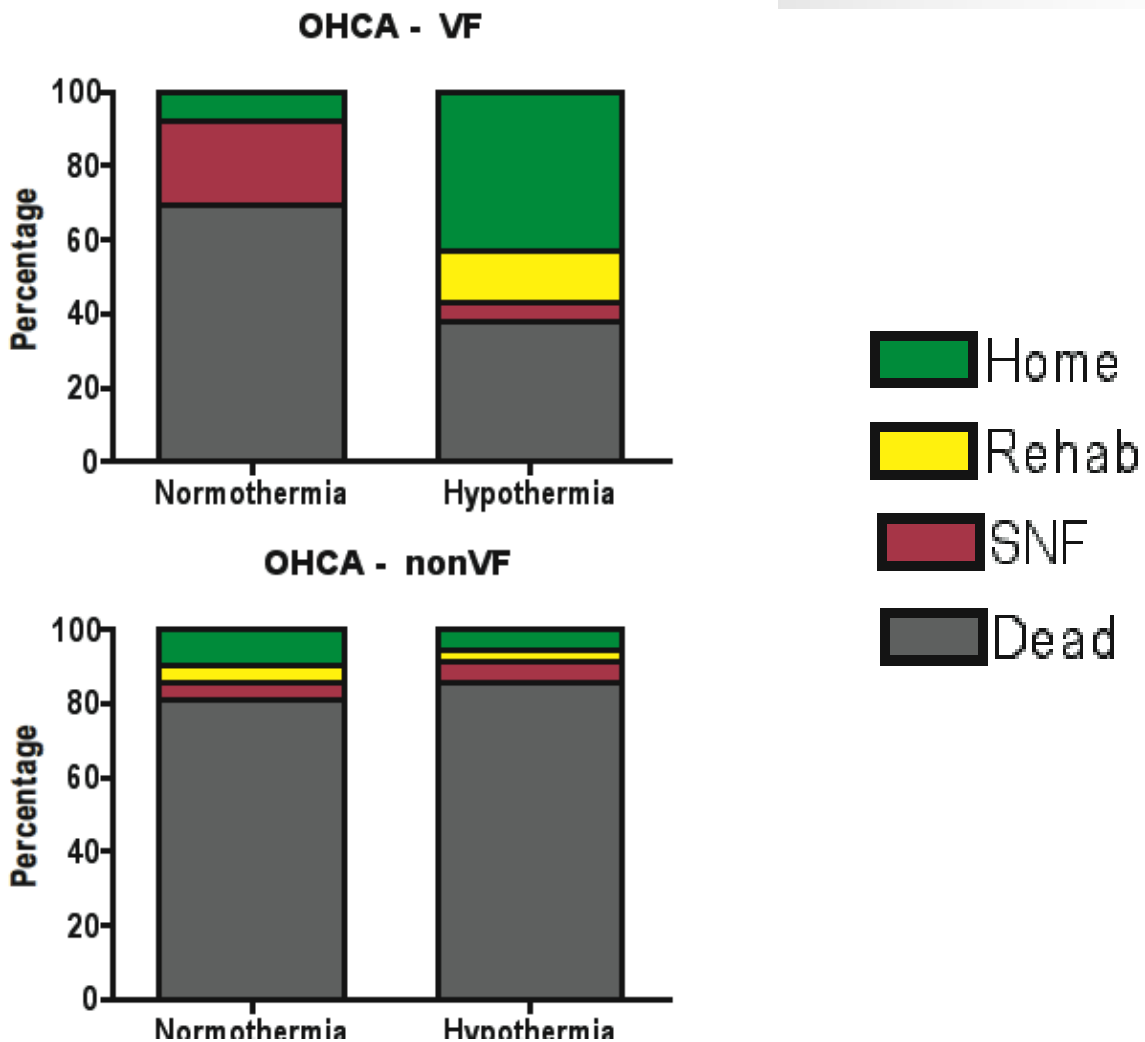


15% vs. 15% Alive
7% vs. 7% Good

Outcomes by Hypothermia or No Hypothermia - Out-of-Hospital Only (2005-2007)

VF

Non-VF



How do I cool the patient?

Temperature Monitoring Sites

- Rectal temperature can differ from core and cranial by as much as 1.5ºC, and difference is particularly great during active cooling.

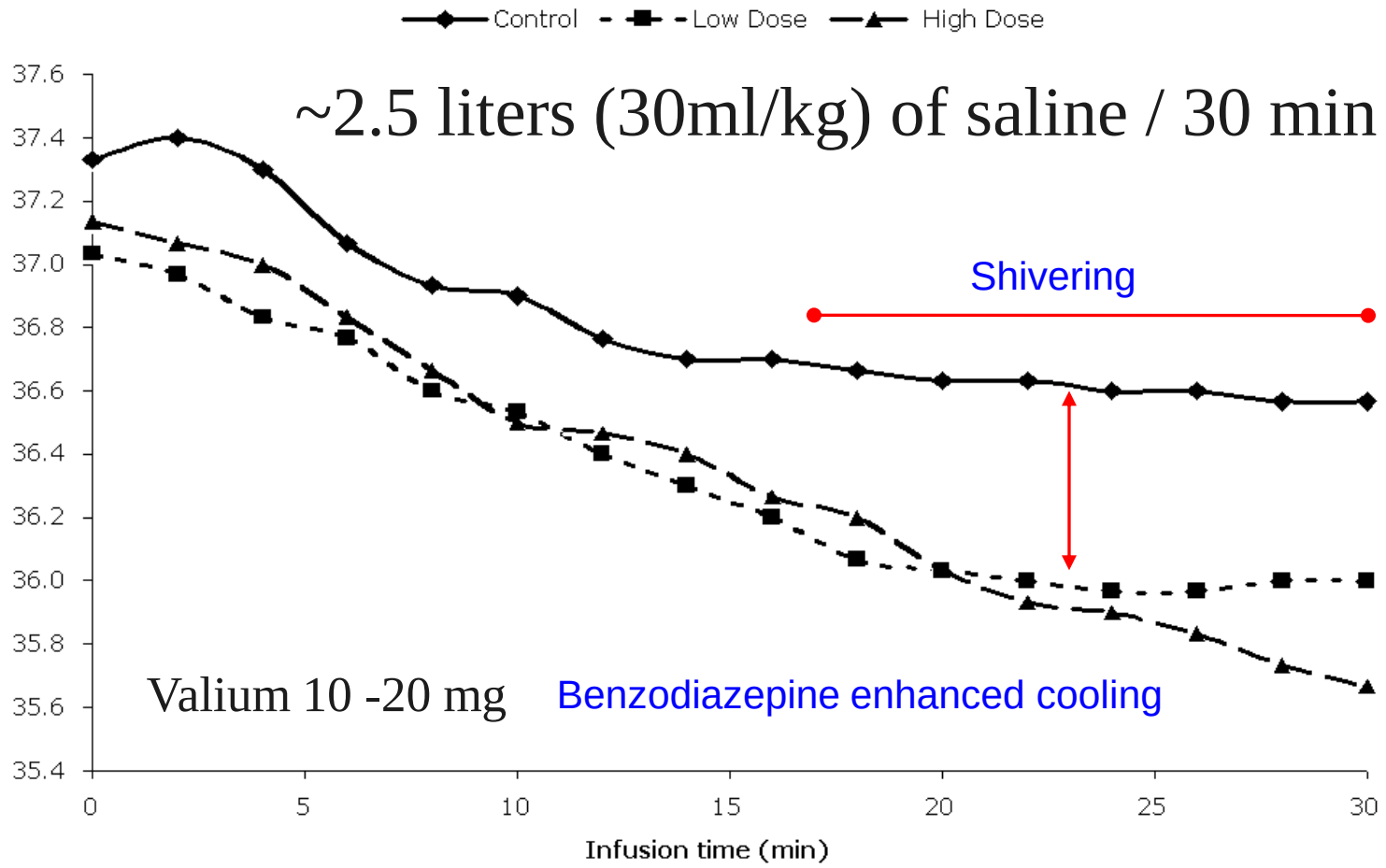
  (Stone 1995 Anesthesiol 82: 344-51; Zweifler 2004; J Neurosurg Anesthesiol 16:232-5)

- Cranial and core temperatures are best measured by PA catheter > esophageal > bladder > tympanic > rectal

Picked Esophageal Monitoring

- Tried Foley Bladder Temperature Probes
  - Special Order & More expensive (~$20 vs ~$5)
  - Nurses often place prior to getting special Foley
- Ended long tradition of rectal temperatures
  - ID had removed rectal thermometers

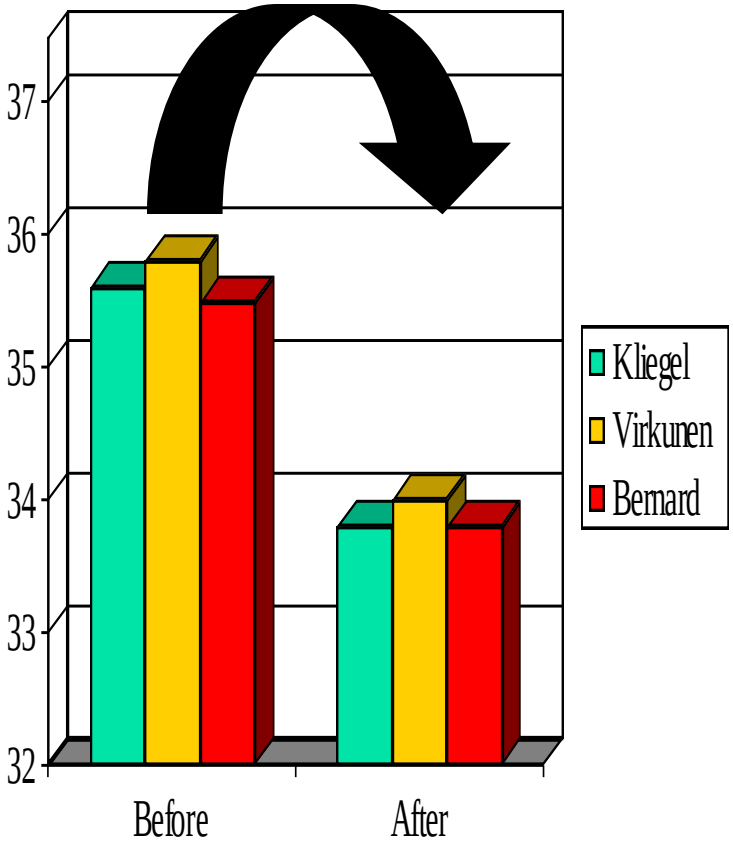
Cold IV Saline + sedation (awake volunteers) (yes- paid volunteers!)



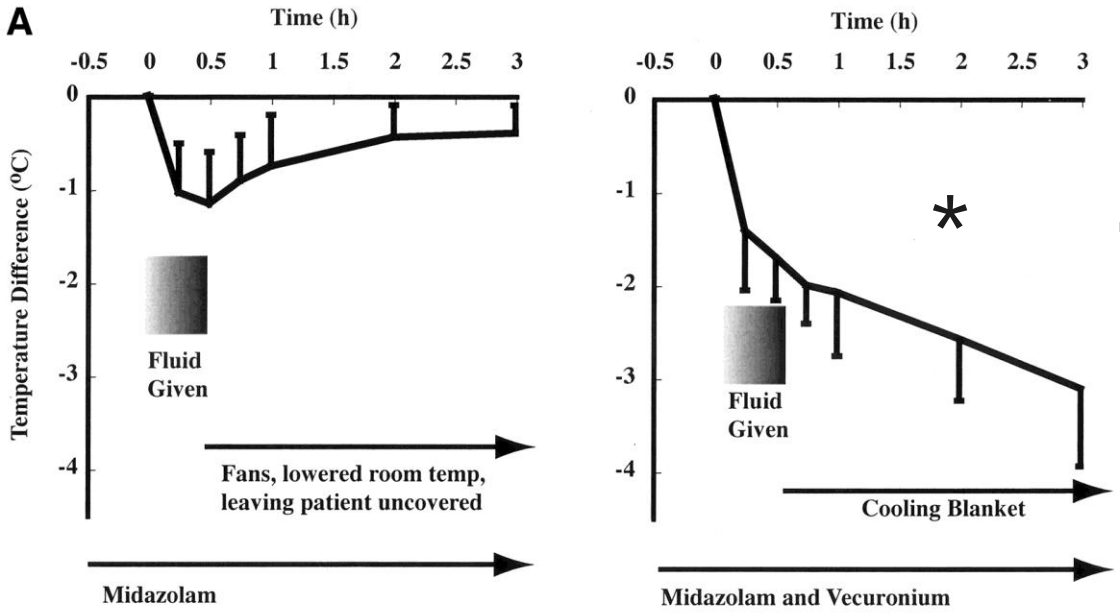
Cold (4ºC) IV Saline Induces Hypothermia

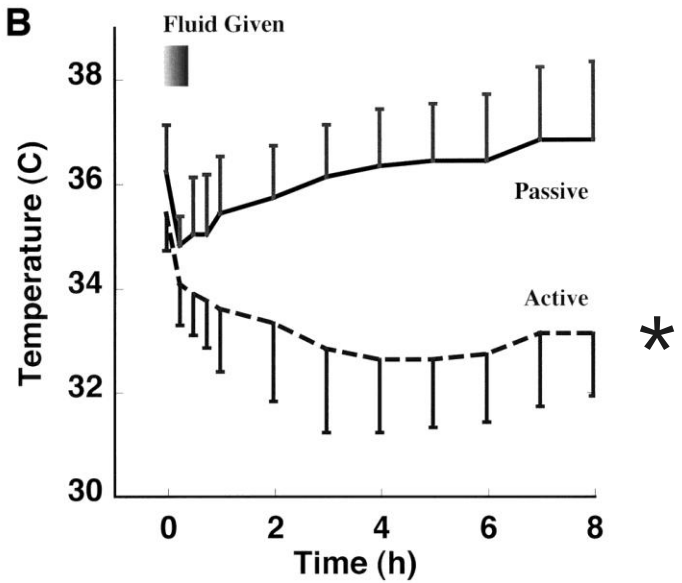
~2 liters cold saline

- Kliegel et al., 2005; Resuscitation 64: 347-351. (N= 26: 35.6ºC -> 33.8ºC)
- Virkkunen et al., 2004; Resuscitation 62: 99-302. (N=13; 35.8ºC -> 34.0 ºC)
- Bernard et al., 2003; Resuscitation 56: 9-13. (N=22: 35.5ºC -> 33.8ºC)



Seattle - Kim, F. et al. Circulation 2005;112:715-719





After initial cooling with IV saline, it is necessary to add a cooling blanket or some other maintenance device

$140
Small Fridge

$200
Box of 12 Temperature sensing Foley's

$120
Box of 24 Esophageal Temperature probes

$40
Cable from Philips monitors for these probes

Problems

- Nurse Note in CCU:
  - “Called for cooling blanket….”
  - “Blanket does not work…”
  - “Still waiting for replacement cooling blanket…”
  - “Received cooling blanket at change of shift.”

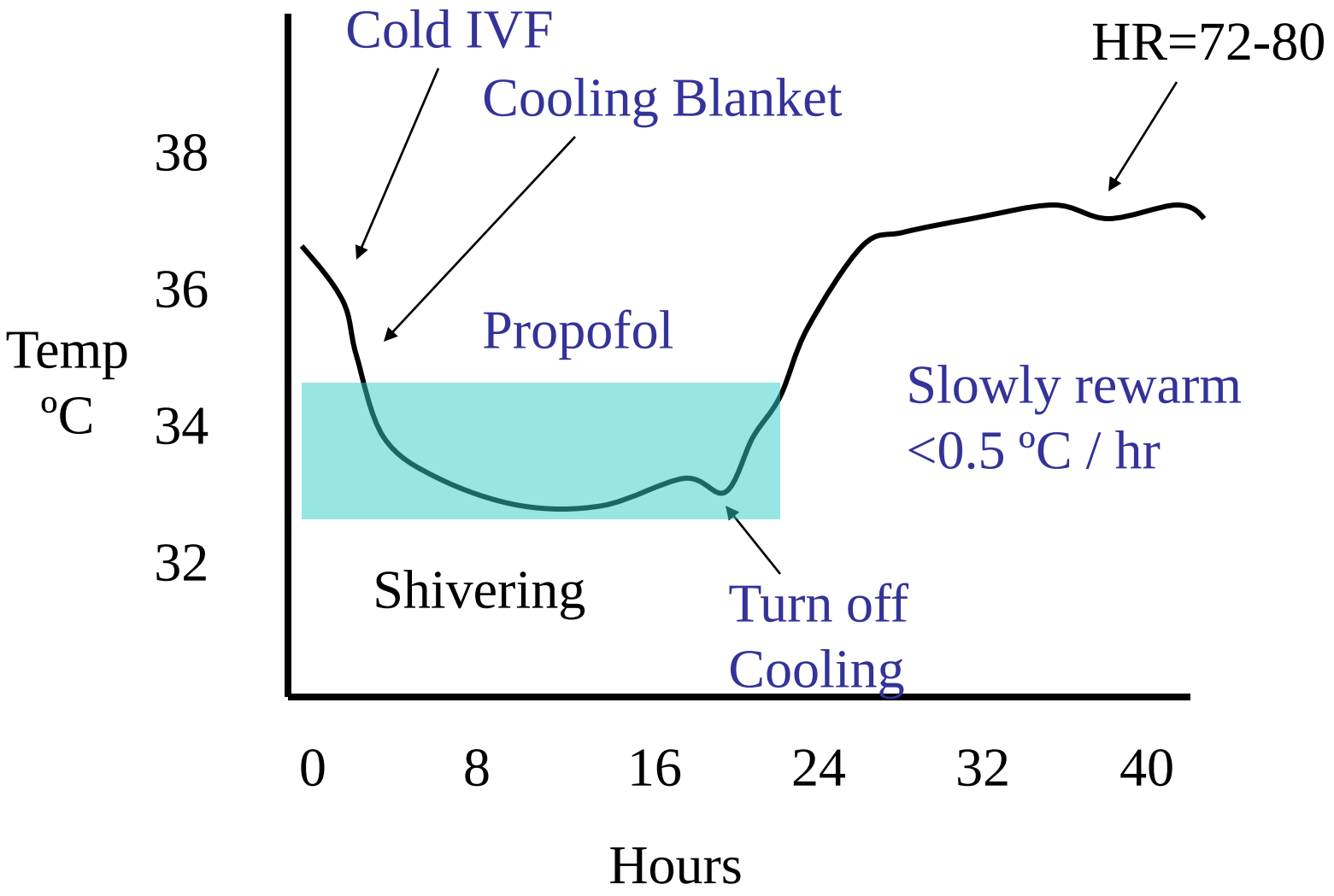
Device availability

- Central supply distributes all cooling blankets
  - Tend to accumulate in OR / PACU
- Worked with Central to make a “hypothermia pack”
  - Blanket
  - Esophageal probe
  - 2 liters of replacement saline
- Key units have dedicated cooling console

Tricks

- Adequate sedation to prevent shivering
  - Propofol if tolerated
  - If blood pressure low, fentanyl / midazolam
- Paralysis during induction
  - Watch for seizures
  - Usually no need for paralysis during maintenance
- Turn off heater on ventilator
- Cooling blanket above and below
  - Ice in bags all over head and torso

Example of Cooling



Portable Monitoring

- Uses same Esophageal / Rectal Probe and cables
- Has data logging
- Can use in ICU where cables are missing or wall monitor lacks module

Temperature Monitoring Sites

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- Cranial and core temperatures are best measured by PA catheter > esophageal > bladder > tympanic > rectal

Recommended Temperature Monitoring Sites

1. **PA catheter**
2. **Esophageal**
3. **Bladder**
4. **Cranial or Nasopharyngeal**
5. **Rectal**

(Do not use axillary with surface cooling!)

Side-effects of cooling the patient?

Cooling actually improves hemodynamics

- Mild cooling is a positive inotrope
  - Will improve the pump
- May reduce need for pressors

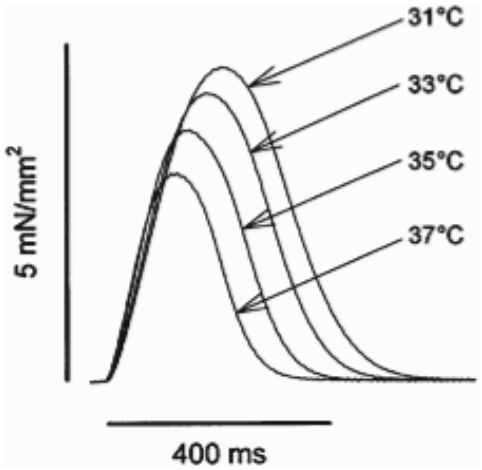
Hypothermia and the Heart

- Decreasing temperature (37º - 31ºC) increases myocardial contractility
  - ↑isometric twitch force in isolated muscle
  - ↑dP/dT, ↑stroke volume in vivo
  - ↓heart rate in vivo
  - ↑cardiac output
  - No real change in SVR, PVR in this temp range

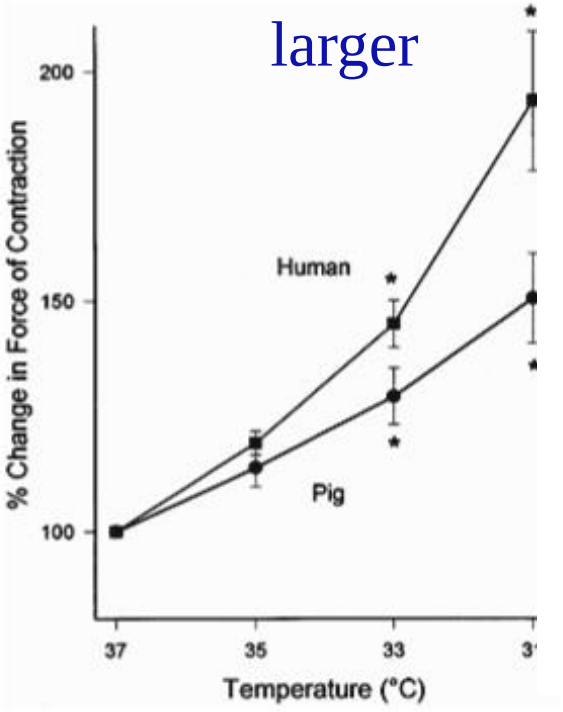
Dae et al. (2001) Am J Physiol Circ Physiol 282: H1584-1591
Weisser et al. (2001) Basic Res Cardiol 96: 198-205

Weisser (2001) Contractility and hypothermia in myocytes and swine

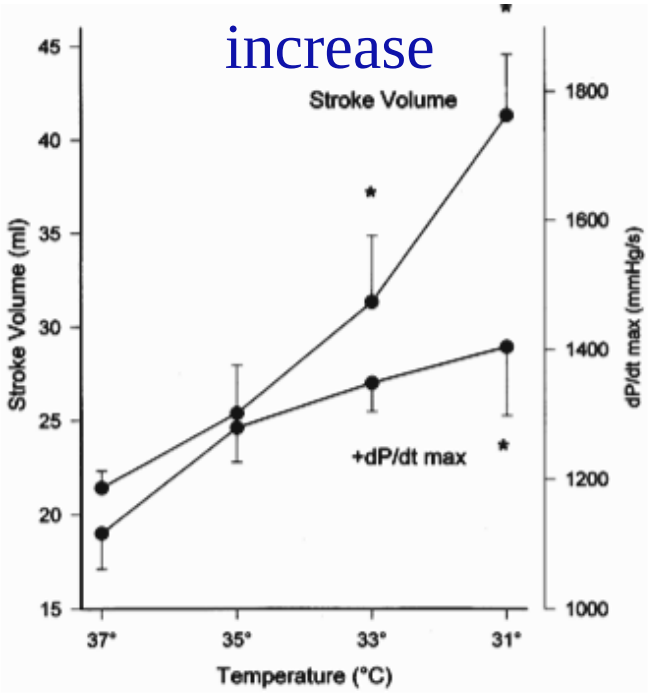
Isometric twitch increases and holds longer



Developed force of contraction is larger



Contractility and stroke volume increase

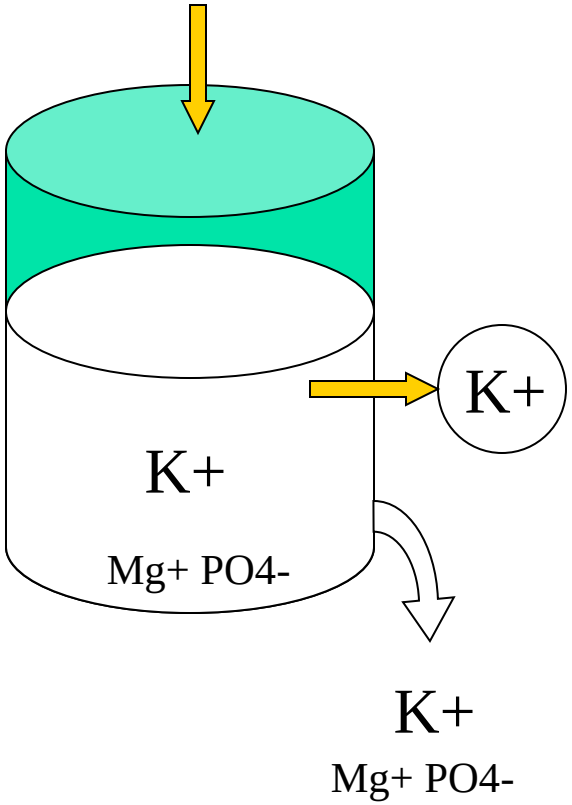


Hypothermia effects on blood

- Fever is common after cardiac arrest
  - Pneumonitis develops in 25%
  - Some infection develops in 40-50%
- Infections increase with hypothermia > 24 hours
  - Macrophage / leucocyte function is slowed
  - Effect is minimal if hypothermia < 24 hours
- Bleeding increases below ~35ºC
  - Clotting factor reactions are slowed
  - Caution if serious bleeding occurs

Electrolyte and Fluid Shifts

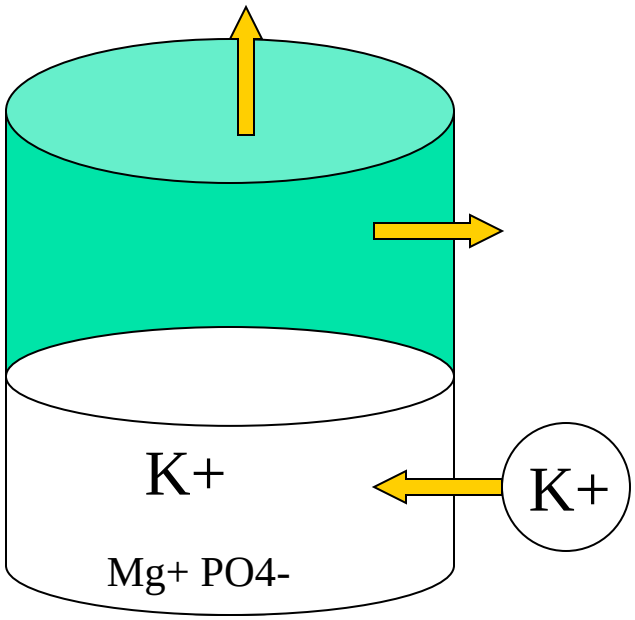
- As you cool the patient, vasoconstriction will decrease effective vascular volume.
  - Diuresis.
  - Lose potassium
  - Lose phosphate.
- Potassium shifts intracellularly



(Abiki 2001; CCM 29: 1726-30;
Zeiner 2004; Resuscitation 60: 253-61)

Electrolyte and Fluid Shifts

- As you warm up, patient intravascular space expands, and potassium shifts out of cells
  - Danger of hyperkalemia if you replaced potassium earlier
  - May appear volume depleted



HACA – Complications
(all N.S. between groups)

	Normothermia	Hypothermia
Bleeding	19%	26%
Pneumonia	29%	37%
Sepsis	7%	13%
Pulmonary Edema	4%	7%
Renal Failure / HD	10% / 4%	10% / 4%
Seizure	8%	7%
Serious Arrhythmia	32%	36%
Pancreatitis	1%	1%

Doing it

- Side effects are easily managed within scope of ICU care
  - Infection
  - Electrolyte monitoring
  - Coagulopathy
- Key is to agressively “take control” of temperature

Specialized Centers?

- Care for most diseases improves when provided by specialists who see problem often.
- Frequent use allows system improvement.
- Although CPR is a common event, most physicians care for post-CPR patients infrequently

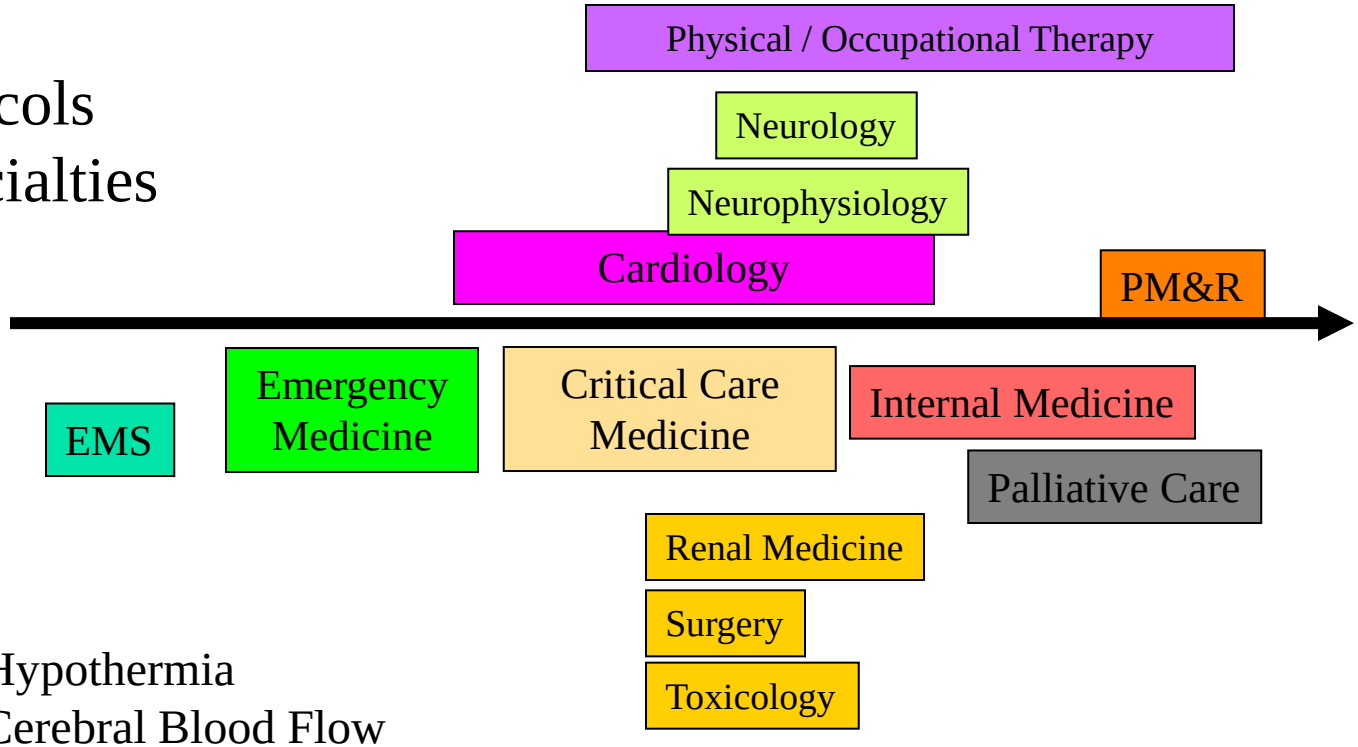
- **Trauma Centers**
  - More than just the surgeon
  - Ancillary services and subspecialties
- **Stroke Centers**
  - More than tPA
- **STEMI Centers**
  - Emergent catheterization versus diagnostic catheterization.
  - Integration of EMS, ED and cath lab.

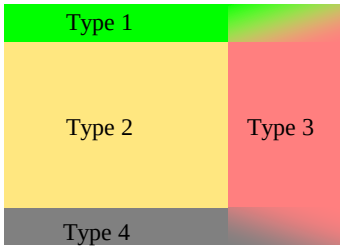
Center for Post-CPR Care

- Written protocols
  - Clinical pathways
- Multiple specialists
  - EM, Cardiology, CCM, Rehabilitation, Neurology, CT Surgery, others
- Ongoing QI programs
- Education
- Research

Center for Post-CPR Care

1. Written Protocols
2. Multiple Specialties
3. QI Programs
4. Research
5. Education

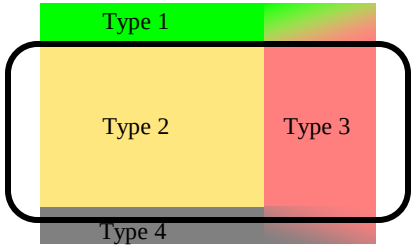




1. Hypothermia
2. Cerebral Blood Flow
3. Use Local Data to Prognosticate
4. Early Cardiac Intervention
5. Systematic Rehabilitation

Adequate Case Volume
Seen by Specialist

Monitoring and Prognosis



Published Prognostic Criteria

- No longer valid
- Would have prompted withdrawal of care for this man
- His QOL now better than most of ours

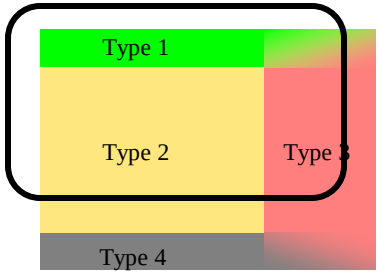
Other neurological testing?

- If clearly improving clinically
  - Not necessary
- If clearly brain dead
  - Not necessary
  - Blood flow studies, SSEP are confirmatory
- If languishing in a vegetative state
  - Some prognostic testing may help predict likelihood of awakening

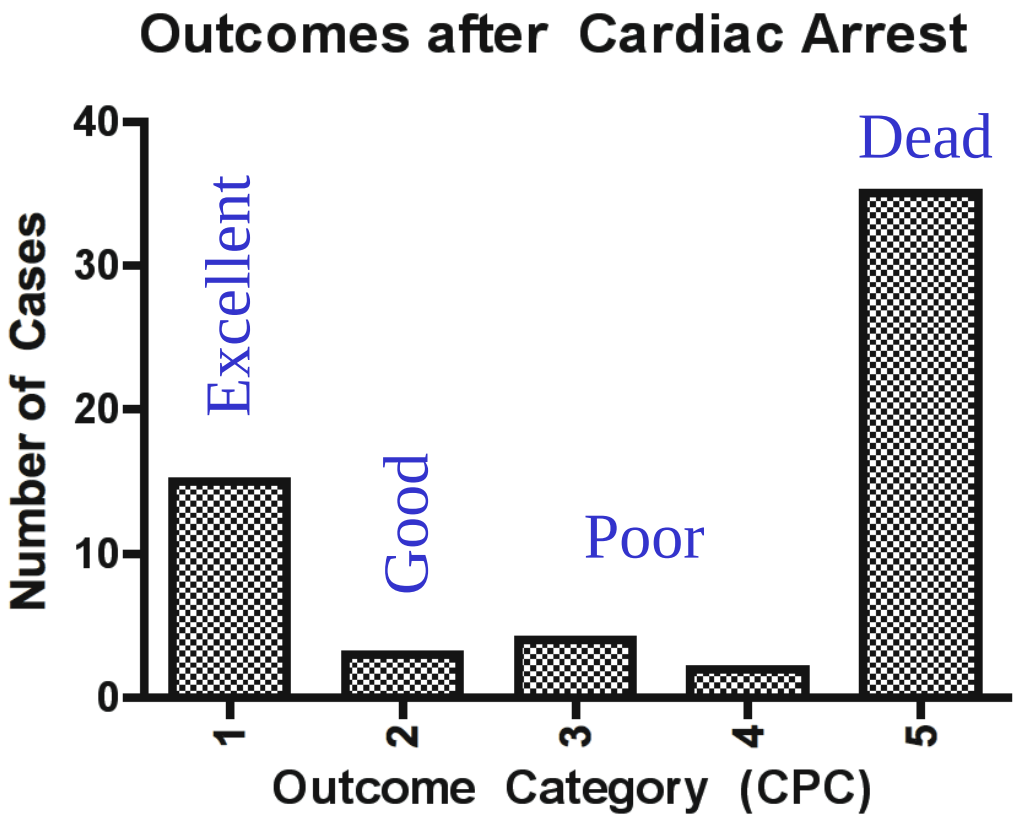
Neurophysiology Monitoring Plan for Cardiac Arrest

- Waking Up or Brain Dead (Type 1 or 4)
  - Monitoring not needed
  - Follow clinical exam
- Deep or Moderate Coma (Type 2 or 3) - not clearly awakening
  - Continuous 4-lead EEG to watch for seizures
  - SSEP at 24 and 72 hours to establish cortical responsivity
  - BER at 24 and 72 hours to exclude brainstem lesion

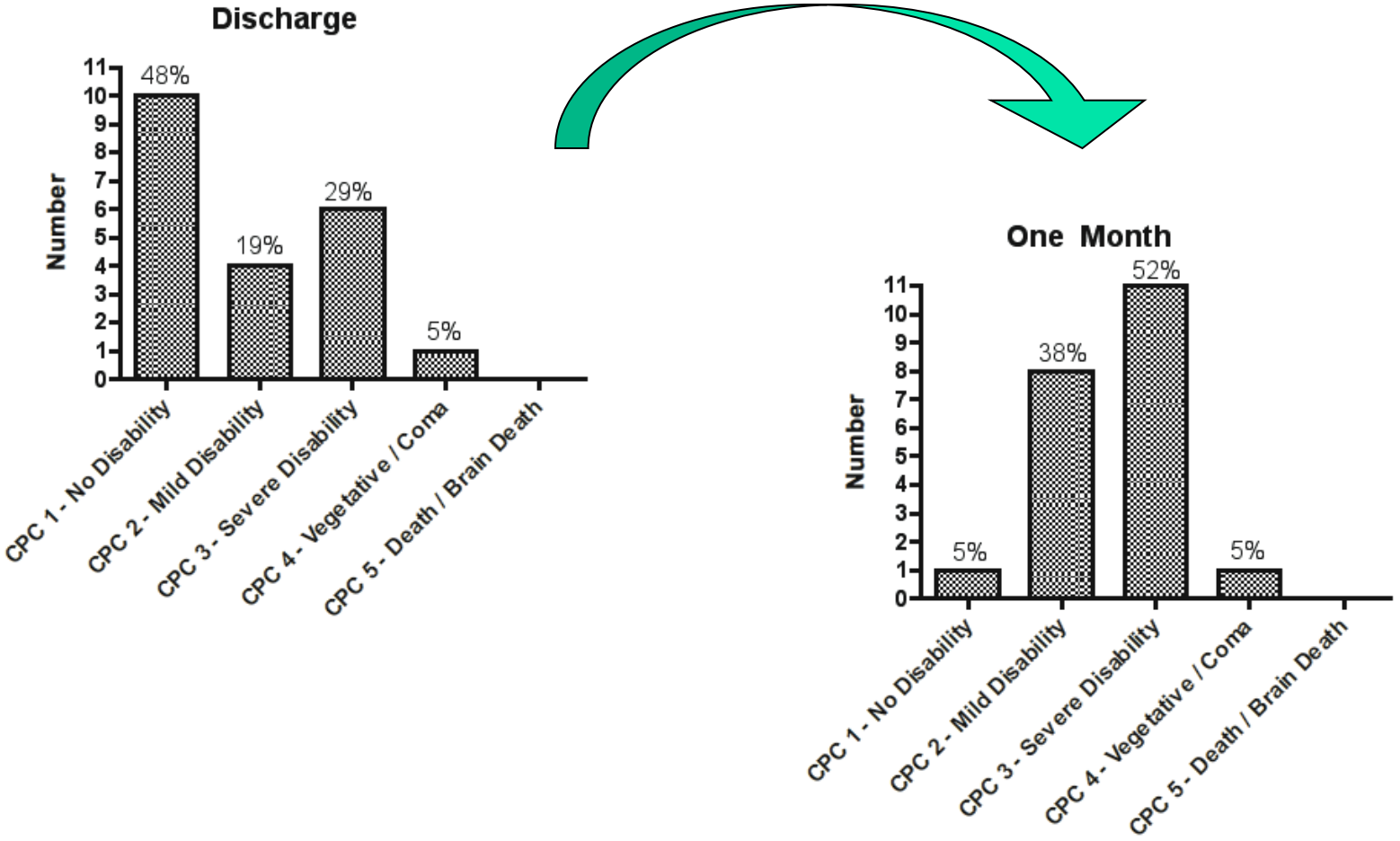
Rehabilitation after CPR



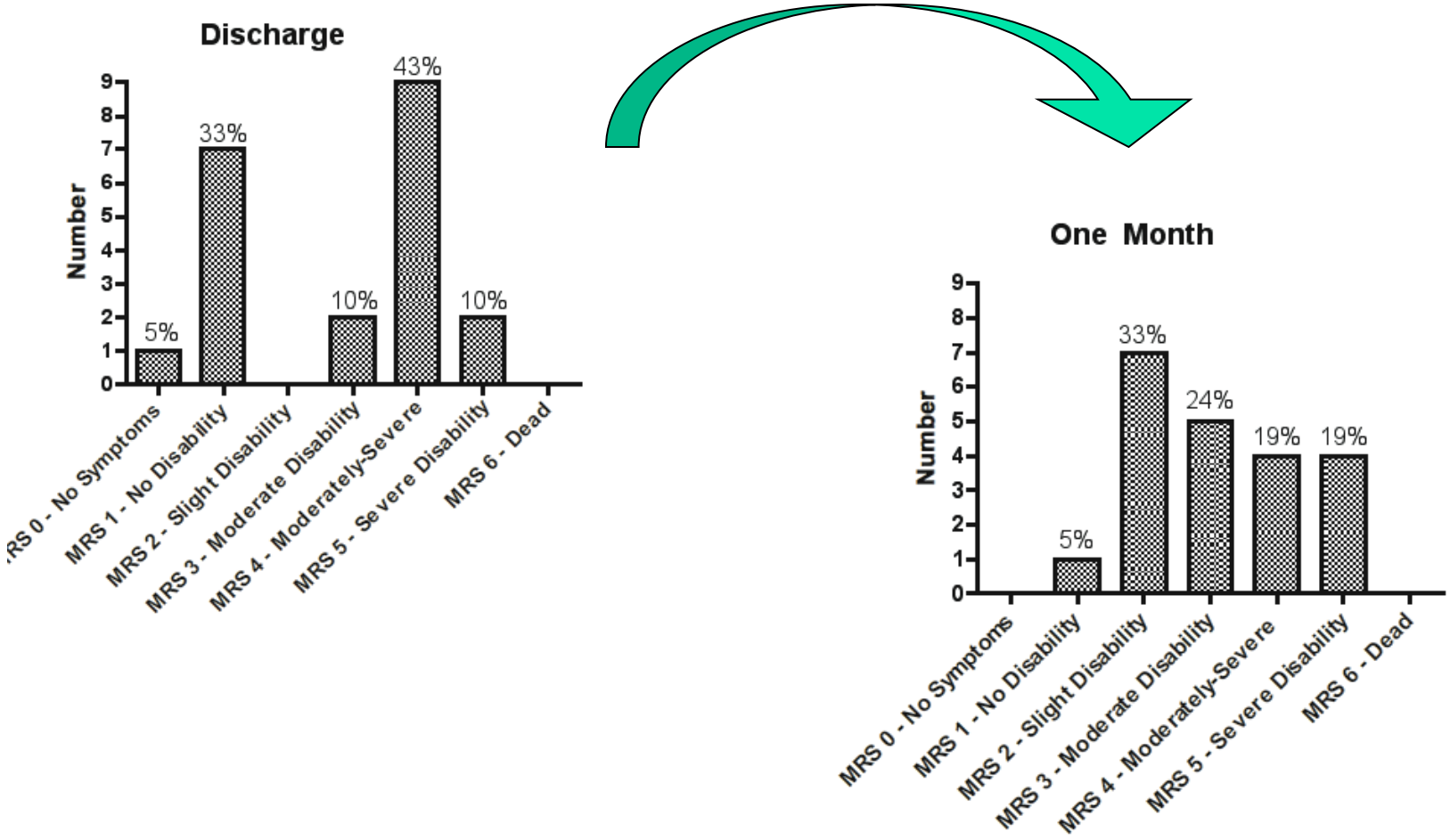
Patients at Discharge - 2007



Recovery after Discharge

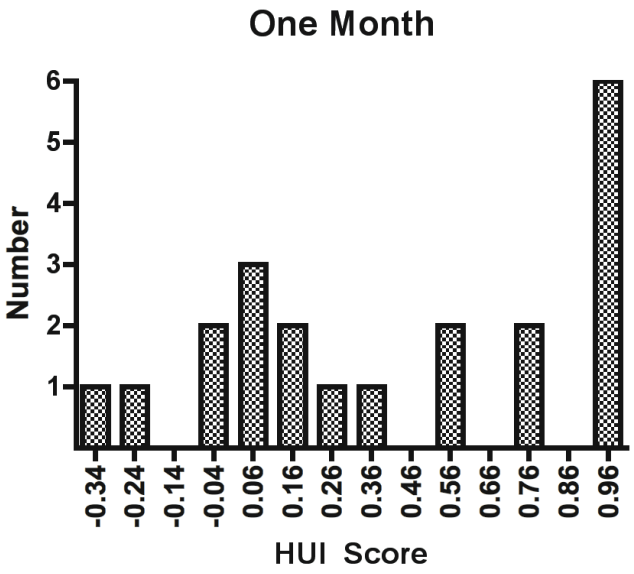


Recovery after Discharge

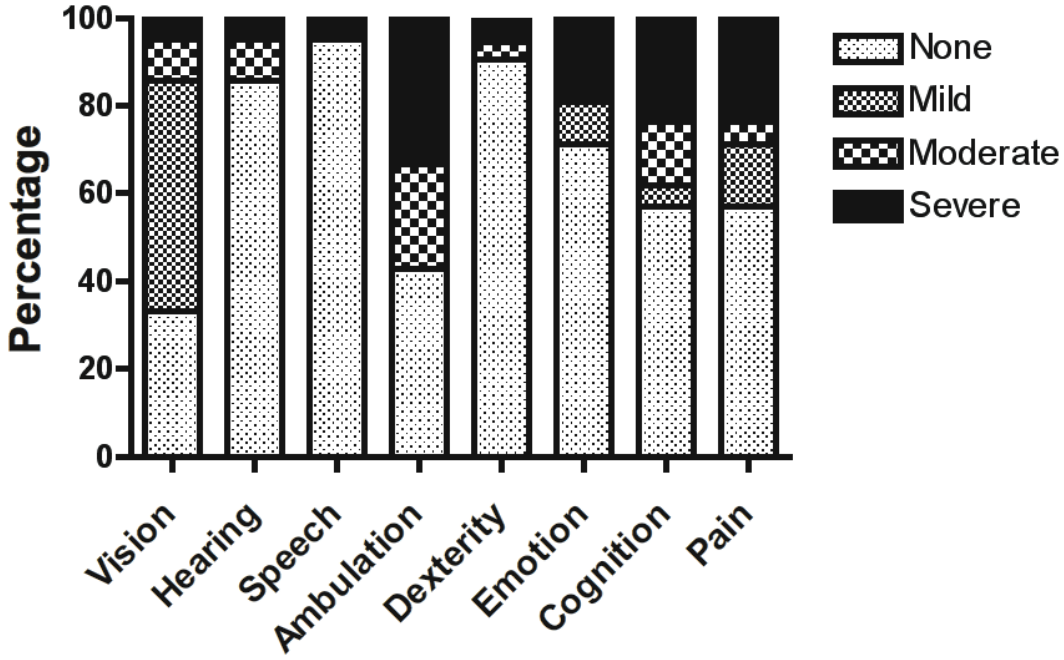


Symptoms after Discharge (Health Utilities Index)

HUI - quality of health



Subscales of Symptoms



Think Success!