

# induced Effects of hypothermia

**Prof. dr. Armand R.J. Girbes**  
Chairman department of Intensive Care  
Amsterdam, NL



**Presentation available at:  
[www.ArmandGirbes.com](http://www.ArmandGirbes.com)**

# Effects of hypothermia

## Which effects?

- On a cellular level
- Clinical effects
- EBM / RCT



# Effects of hypothermia

- **Important subject**
  - Application in the ICU – prevention of (additional):
    - Brain injury
      - trauma
      - hypoxia
    - Myocardial injury
  - New recent data & trials



# Effects of hypothermia

- **Induced hypothermia**
  - Nothing new
    - Baron Larrey (1800's)
    - Fay, T – cerebral trauma (1945)
    - Bigelow WG – cardiac surgery (1950)
    - Rosomoff HL – (1965)
  - Stopped
  - Lack of “dose finding studies”
    - Ideal temperature
    - Ideal duration
  - Re-invented 1980's



# Effects of hypothermia

- **Classical problem**
  - especially in doctors:
  - Something is good →
  - **MORE IS BETTER**  
(inotropes, fluids, mechanical ventilation)
  - Cold is good →
  - **COLDER IS BETTER**



# Effects of hypothermia

- **Potential beneficial effects by hypothermia**
  - Reduction of glucose & oxygen consumption (7% per Centigrade)
  - Inhibition of Caspase activation (~ apoptosis)
  - Prevention of mitochondrial dysfunction
  - Lowers excitatory AA & lactate during ischemia/reperfusion
  - Improves ion homeostasis during ischemia/reperfusion
  - Suppression of
    - pro-inflammatory cytokine release
    - reperfusion related DNA injury
    - lipid peroxidation
    - leucotriene production
    - NO production



# Effects of hypothermia

- **Potential beneficial effects of hypothermia (2)**
  - Decrease of Free-radical production
  - Reduction of Blood-Brain Barrier disruption
    - → less edema
  - Cell membrane preservation
  - Prevention of local (intracerebral) hyperthermia



# Effects of hypothermia

- **Potential harmful effects in the ICU patient**
  - General
    - Peripheral vasoconstriction
    - Shivering
      - increase O<sub>2</sub> consumption, muscle tone ↑
    - Insulin secretion & sensitivity ↓ → hyperglycemia
    - Drug pharmacokinetics altered / clearance ↓
  - Cardiovascular
    - ECG changes
    - Tachycardia >> Bradycardia >> Dysrhythmias >> VF
    - Cardiodepression
  - Respiratory
    - Risk pneumonia ↑
    - MV ↓



# Effects of hypothermia

- **Potential harmful effects in the ICU patient**
  - Renal
    - “Cold” diuresis
    - Potassium shifts into cells (CAVE rewarming)
    - Tubular dysfunction
      - Loss of Phosphate & Magnesium

J Neurosurg 94:697–705, 2001

Hypophosphatemia and hypomagnesemia induced by cooling in patients with severe head injury

KEES H. POLDERMAN, M.D., PH.D., SASKIA M. PEERDEMAN, M.D.,  
AND ARMAND R. J. GIRBES, M.D., PH.D.

*Surgical Intensive Care Unit and Department of Neurosurgery, University Hospital Vrije Universiteit,  
Amsterdam, The Netherlands*



# Effects of hypothermia

- **Potential harmful effects in the ICU patient**
  - Acid-base:  
CO<sub>2</sub> better solubility  
→ Temp corrected BGA: resp. alkalosis
    - alpha stat: no Temp correction for CO<sub>2</sub>
    - pH stat: Temp correction for CO<sub>2</sub>



# Effects of hypothermia

- **Potential harmful effects in the ICU patient**
  - Gastrointestinal
    - Impaired bowel function & motility
    - (Mild) pancreatitis
  - Hematological
    - Immunosuppression, WBC count ↓ → risk sepsis ↑
    - Platelet function & count ↓
    - Clotting times ↑



# Effects of hypothermia

- **Potential indications**
  - CPR
  - TBI
  - Stroke
  - Fever in patients with neurological injury
  - SAB
  - Intra-operative hypothermia
    - Neurosurgery (aneurysm)
    - Vascular surgery – spinal cord protection
    - Cardiac surgery



# Effects of hypothermia

## The Evidence

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Level I:	Supported by at least two sufficiently large randomized controlled clinical trials (RCCTs) of good quality <sup>a</sup> , and/or supported by a meta-analysis of RCCTs
Level IIa:	Supported by at least one RCCT meeting the abovementioned criteria, supported by data from other sources (animal experiments, case control studies, etc.)
Level IIb:	Supported by one RCCT without supporting evidence from other sources
Level III:	Supported by at least one clinical non-randomized trial (cohort studies, case control studies, etc.)
Level IV:	Recommendations and opinions by experts and guideline committees, based on clinical experience, descriptive studies, case reports, etc.

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# Effects of hypothermia

## The evidence

- **Cardiopulmonary resuscitation**
  - Many studies with historical controls
  - RCT
    - NEJM 2002;326:549-556
    - NEJM 2002;326:557-563



# Effects of hypothermia

## The evidence

- Bernard S et al. NEJM, Australia
  - N=77 witnessed arrest VT/VF
    - Cooling started early: < 2 hr ROSC – in ambulance
    - 33° C for 12 hr
    - Results:
      - Good outcome: 49% vs 26% (p=0.046)
      - Survival: 49% vs 32% (NS)



# Effects of hypothermia

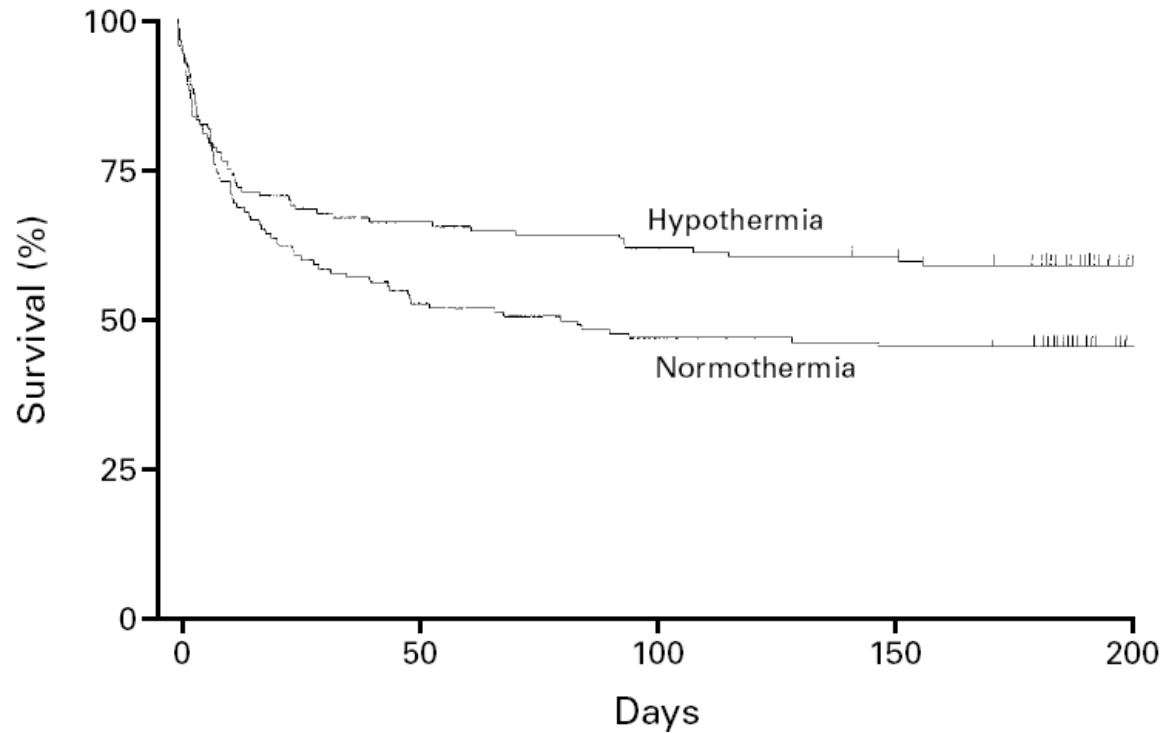
## The evidence

- Holzer et al. NEJM, Europe
  - N=273 witnessed arrest, VF/VT
    - NB 3551 patients evaluated for eligibility
  - Target: 32° - 34°C for 24 hr
  - Results (at 6 months):
    - Good neurologic outcome: 55% vs 39%
    - Survival: 59% vs 45%



# Effects of hypothermia

## The evidence



No. AT RISK

Hypothermia	137	92	86	83	11
Normothermia	138	74	66	64	9



# Effects of hypothermia

## The evidence

### Level of evidence

- CPR                      Class I
- TBI
- Stroke
- Fever
- SAB
- Intraoperative



# Effects of hypothermia

## The evidence

- **TBI**

- Many studies with historical controls

- RCT

- Clifton et al. NEJM 2001;344:556-563

- N=392 coma after closed TBI

- Target 33°C – achieved after  $8.4 \pm 3.0$  hrs

- Hypothermia for 48 hrs

- Results:

- » Mortality 28% vs 27%

- » Poor neurological outcome 57% vs 57%



# Effects of hypothermia

## The evidence

- **TBI**

RCT – hypothermia reduced ICP

**TABLE 3.** MEAN DAILY ARTERIAL PRESSURE, INTRACRANIAL PRESSURE, AND CEREBRAL PERFUSION PRESSURE IN PATIENTS WITH BRAIN INJURY ASSIGNED TO INDUCTION OF HYPOTHERMIA OR TO NORMOTHERMIA.\*

VARIABLE	DAY 1			DAY 2			DAY 3			DAY 4			DAYS 1-4		
	HYPO-THERMIA	NORMO-THERMIA	P VALUE	HYPO-THERMIA	NORMO-THERMIA	P VALUE	HYPO-THERMIA	NORMO-THERMIA	P VALUE	HYPO-THERMIA	NORMO-THERMIA	P VALUE	HYPO-THERMIA	NORMO-THERMIA	P VALUE
Mean arterial pressure															
Mean (mm Hg)	95.5	92.6	0.003	93.4	95.2	0.05	92.4	95.8	<0.001	92.4	96.2	<0.001	93.1	94.6	0.05
Patients in whom pressure was ever <70 mm Hg (%)	31	40	0.08	18	11	0.06	15	8	0.07	18	8	0.006	53	51	0.75
Intracranial pressure															
Mean (mm Hg)	15.7	17.1	0.20	15.6	17.7	0.19	16.2	16.1	0.91	16.3	16.5	0.83	18.1	17.9	0.85
Patients in whom pressure was ever >30 mm Hg (%)	23	32	0.06	14	28	0.002	16	26	0.03	21	29	0.06	41	59	0.02
Therapy Intensity Level†	4.9	5.3	0.21	5.2	5.0	0.80	5.3	4.3	0.005	4.5	3.8	0.06	5.0	4.6	0.21
Cerebral perfusion pressure‡															
Mean (mm Hg)	79.9	74.8	0.003	78.0	78.0	1.00	76.3	79.7	0.003	76.1	79.8	0.01	75.2	76.6	0.37
Patients in whom pressure was ever <50 mm Hg (%)	22	31	0.06	18	13	0.20	11	9	0.73	15	8	0.07	44	42	0.75

\*Induction and maintenance of hypothermia occurred on days 1 and 2, rewarming occurred on day 3, and post-rewarming treatment occurred on day 4.

†The Therapy Intensity Level was designed to quantify the effects of therapy on the analysis of levels of intracranial pressure — for example, to distinguish between levels of intracranial pressure maintained with sedation alone and the same levels achieved with barbiturate coma. It is a 16-point scale with values ranging from 0 to 15, with higher values indicating more treatment. This score was calculated every 24 hours according to the therapies used during that period.



# Effects of hypothermia

## The evidence

- TBI

### HYPOTHERMIA FOR TRAUMATIC BRAIN INJURY — A GOOD IDEA PROVED INEFFECTIVE



The NEW ENGLAND  
JOURNAL of MEDICINE

RAJ K. NARAYAN, M.D.  
Temple University School of Medicine  
Philadelphia, PA 19140



# Effects of hypothermia

## The evidence

- **TBI comments on RCT**
  - Different outcome in different centers
  - Centers participated with little experience
  - Slow induction of hypothermia
  - Glucose control unknown
  - More hypotensive periods in hypothermia group (10% vs 3%)
  - Hypovolemia? Electrolyte/Magnesium disorders?
  - Still: Benefits in patients with hypothermia at admission



# Effects of hypothermia

## Level of evidence

- CPR Class I
- TBI Class I for ICP lowering  
Class IIa for fever
- Stroke Class III
- Fever Class IIb
- SAB Class IV
- Intraoperative Class III



# Effects of hypothermia

- **Treatment effect**  
balance of Beneficial ↔ Detrimental effects



# Effects of hypothermia

- **Problems with RCT**
  - No previous dose finding studies
  - Different outcome in specialized high volume centers vs small low-volume hospitals (unpublished data)
  - No control for sufficient treatment of side-effects
    - e.g. Magnesium supply, CPP, infection control (SDD).



# Effects of hypothermia

- **Conclusion**

- Post CPR should be treated with Hypothermia
  - only after witnessed arrest with VF (??)
  - ideal time window & temperature still not known
- Fever should be treated in case of neurological injury
- Other indications:
  - not certain, but should be considered !!
- Hypothermia only in experienced centers

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