MULTICENTER TRIALS IN TTM

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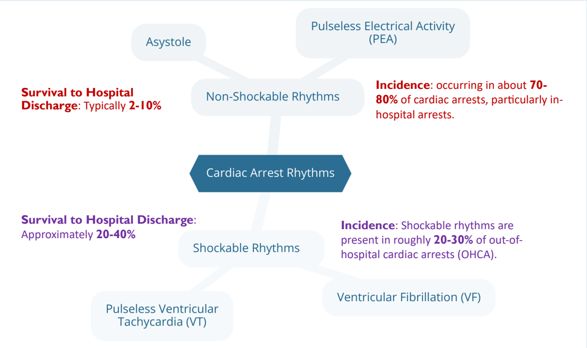
Research fellow at University of Pittsburgh PA, USA

CARDIAC ARREST RHYTHMS



DEFINITION

- **Definition**:
  Cardiac arrest is the sudden cessation of heart function, resulting in the loss of blood flow to the body.
- **Characteristics**:
  - Loss of consciousness
  - Absence of pulse
  - Lack of breathing or abnormal gasping
- **Distinction**:
  Cardiac arrest differs from a heart attack (myocardial infarction), which is due to blocked blood flow, whereas cardiac arrest is an electrical malfunction.

PATHOPHYSIOLOGY OF CARDIAC ARREST

- **Underlying Mechanism**:
  - Disruption in the electrical system of the heart, leading to abnormal heart rhythms.
- **Types of Dysfunction**:
  - **Shockable rhythms** (ventricular fibrillation, pulseless ventricular tachycardia)
  - **Non-shockable rhythms** (asystole, pulseless electrical activity)
- **Effects on Body**:
  - No circulation → Cellular hypoxia → Rapid cell death, particularly in the brain and heart
- **Time Sensitivity**:
  - Brain damage can occur within 4-6 minutes; irreversible damage within 10 minutes if untreated.

CAUSES OF CARDIAC ARREST

- **Shockable Rhythms**:
  - **Ventricular Fibrillation (VF)**: Chaotic, irregular electrical activity
  - **Pulseless Ventricular Tachycardia (VT)**: Fast, ineffective contraction rhythm
  - **Causes**: Often linked to ischemic heart disease, electrolyte imbalances, drugs, and cardiomyopathy.
- **Non-Shockable Rhythms**:
  - **Asystole**: Complete lack of electrical activity ("flatline")
  - **Pulseless Electrical Activity (PEA)**: Electrical impulses present, but no effective contraction
  - **Causes**: Severe hypoxia, acidosis, hypovolemia, tension pneumothorax, or trauma.

5H'S AND 5T'S

- **5 H's**

1. **Hypoxia** - Insufficient oxygen levels in the blood, preventing effective tissue oxygenation.
2. **Hypovolemia** - Loss of blood or fluid volume, often from trauma or dehydration.
3. **Hydrogen ions (Acidosis)** - pH imbalance, often metabolic or respiratory acidosis.
4. **Hyperkalemia / Hypokalemia** - Abnormal potassium levels affecting cardiac function.
5. **Hypothermia** - Low body temperature that slows metabolic and cardiac function.

5H'S AND 5T'S

- **5 T's**

1. **Tension pneumothorax** - Collapsed lung due to trapped air in the chest cavity, causing pressure on the heart.
2. **Tamponade (cardiac)** - Fluid accumulation in the pericardium, compressing the heart and impeding function.
3. **Toxins** - Poisoning from drugs or chemicals that interfere with heart rhythm.
4. **Thrombosis (pulmonary)** - Pulmonary embolism blocking blood flow in the lungs.
5. **Thrombosis (coronary)** - Myocardial infarction from blocked coronary arteries, leading to cardiac arrest.

TREATMENT OF CARDIAC ARREST

- **Immediate Steps**:
  - **Bystander CPR**: Emphasis on chest compressions and rapid intervention
  - **Defibrillation**: For shockable rhythms (VF/VT), ideally within 3-5 minutes of collapse
- **Advanced Cardiac Life Support (ACLS)**:
  - Airway management, IV access, medication administration (e.g., epinephrine)
  - Continuous monitoring and pulse checks
  - Targeted temperature management post-ROSC (Return of Spontaneous Circulation)
- **Post-Resuscitation Care**:
  - Neurological assessment, stabilization, and intensive care monitoring

PROGNOSIS AND OUTCOMES

- **Factors Influencing Prognosis**:
  - Time to CPR and defibrillation
  - Initial rhythm (shockable rhythms have better outcomes)
  - Underlying health and cause of arrest
- **Neurological Outcomes**:
  - Rapid ROSC and temperature management critical for brain health
  - Many survivors of IHCA experience favorable neurological recovery

ACLS PROTOCOL AFTER CARDIAC ARREST

- **Maintain Airway and Breathing:**
  - Use advanced airway if needed (endotracheal intubation).
  - Provide 100% oxygen initially, then adjust to keep oxygen saturation >94%.
  - Continuous waveform capnography to confirm and monitor placement.
- **Optimize Circulation:**
  - Monitor blood pressure; target a systolic BP ≥90 mmHg.
  - Administer IV fluids and vasopressors (e.g., norepinephrine or epinephrine) as needed.

- **Monitor for Return of Spontaneous Circulation (ROSC)**
- **Confirm ROSC**:
  - Pulse and blood pressure present
  - Abrupt increase in end-tidal CO_2 ($EtCO_2$)
  - Spike in arterial pressure if an arterial line is in place
- **Targeted Temperature Management (TTM)**
- **Temperature Goal**:
  - Maintain a core temperature between 32-36°C for 24 hours.
  - Helps reduce brain injury risk and improve neurological outcomes.

CONTINUOUS MONITORING AND SUPPORT

- **Hemodynamic Support**:
  - Keep MAP (mean arterial pressure) >65 mmHg to ensure adequate organ perfusion.
- **Glucose Control**:
  - Maintain blood glucose levels between 140-180 mg/dL.
- **Assess Reversible Causes**:
  - Re-evaluate **5H and 5T** causes to prevent recurrence.

A CLOSER LOOK

Out-of-Hospital Cardiac Arrest (OHCA)

•Global incidence: ~55 per 100,000 person-years
•Survival to discharge: ~8.8% | 1-year survival: ~7.7%
•Key factors for better survival: Bystander CPR, EMS-witnessed arrest

In-Hospital Cardiac Arrest (IHCA)

•Incidence: 1-1.5 per 1,000 admissions
•ROSC in ~53% | Discharge survival: ~23.6%
•Favorable neurological outcome in ~83% of survivors

Regional Variations

•**Europe**: Third leading cause of death; ongoing cross-country analysis
•**United States**: ~326,000 OHCA and 209,000 IHCA cases annually
•**China**: Incidence of sudden cardiac death at 41.8 per 100,000
•**South India**: Incidence at 39.7 per 100,000

European Sudden Cardiac Arrest network: towards Prevention, Education and New Effective Treatments (ESCAPE-NET): A major European Horizon 2020 project focused on cardiac arrest

Hanno L Tan, Nikolaos Dagres, Bernd W Böttiger, Peter J Schwartz, ESCAPE-NET Investigators Author Notes

European Heart Journal, Volume 39, Issue 2, 07 January 2018, Pages 86–88, https://doi.org/10.1093/eurheartj/ehx758

GLOBAL DISPARITIES

- Survival and incidence vary by healthcare infrastructure, socioeconomic factors, bystander CPR availability, and access to defibrillators
- Higher incidence and lower survival rates in economically deprived areas

Higher Survival Rates:

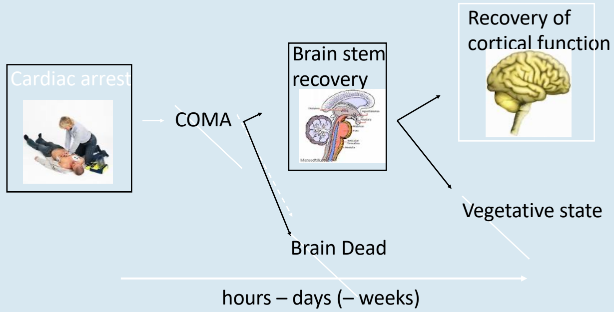
- **Norway:** Reports a survival rate of approximately 25% for out-of-hospital cardiac arrests (OHCA).
- **Netherlands:** Achieves a survival rate of around 21% for OHCA.

Lower Survival Rates:

- **Spain:** Records a survival rate of about 6% for OHCA.
- **Italy:** Exhibits a survival rate of approximately 5% for OHCA.

NATURAL COURSE OF NEUROLOGICAL RECOVERY FOLLOWING CARDIAC ARREST

PATIL KD ET AL. CIRC RES. 2015 JUN 5;116(12):2041-9



THE CHAIN OF SURVIVAL

American Heart Association (AHA) in the early 1990s.
It was based on the work of **Mary M. Newman**

Co-Founder, President & CEO

Sudden Cardiac Arrest Foundation

Pittsburgh, Pennsylvania

THE PIONEERS

Pioneering Cardiopulmonary Resuscitation (CPR)

In the 1950s, Safar collaborated with James Elam

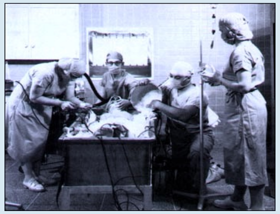
- mouth-to-mouth resuscitation
- combined with external chest compressions
- the establishment of the ABCs (Airway, Breathing, Circulation

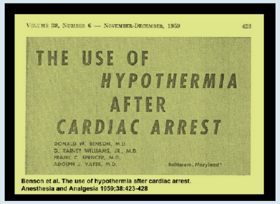
This protocol became the foundation of modern CPR

Advancements in Critical Care

- Create one of the first intensive care units in the USA
- Establish paramedic emergency services.

Background

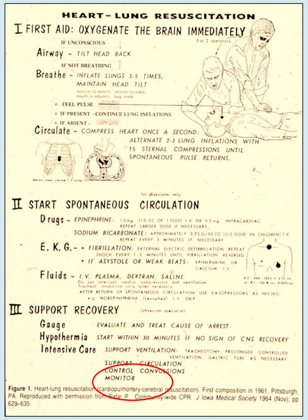



Volume 38, Number 6 — November-December, 1959 423

THE USE OF HYPOTHERMIA AFTER CARDIAC ARREST

Donald W. Benson, M.D.
G. Rainey Williams, Jr., M.D.
Frank C. Spencer, M.D.
Adolph J. Yates, M.D.
Baltimore, Maryland*

Benson et al. The use of hypothermia after cardiac arrest.
Anesthesia and Analgesia 1959;38:423-428


HEART-LUNG RESUSCITATION

I FIRST AID: OXYGENATE THE BRAIN IMMEDIATELY
1 or 2 operators
IF UNCONSCIOUS
Airway - TILT HEAD BACK
IF NOT BREATHING
Breathe - INFLATE LUNGS 3-5 TIMES, MAINTAIN HEAD TILT
mouth-to-mouth, mouth-to-nose, mouth to adjunct, bag-mask
o FEEL PULSE
o IF PRESENT - CONTINUE LUNG INFLATIONS
o IF ABSENT -
Circulate - COMPRESS HEART ONCE A SECOND. ALTERNATE 2-3 LUNG INFLATIONS WITH 15 STERNAL COMPRESSIONS UNTIL SPONTANEOUS PULSE RETURNS.

for physicians only
II START SPONTANEOUS CIRCULATION
Drugs - EPINEPHRINE: 1.0mg (1.0 CC OF 1:1000) I.V. OR 0.5 mg INTRACARDIAC REPEAT LARGER DOSE IF NECESSARY
SODIUM BICARBONATE: APPROXIMATELY 3.75 G/50 CC (1/2 DOSE IN CHILDREN) I.V. REPEAT EVERY 5 MINUTES IF NECESSARY
E. K. G. - • FIBRILLATION: EXTERNAL ELECTRIC DEFIBRILLATION REPEAT SHOCK EVERY 1-3 MINUTES UNTIL FIBRILLATION REVERSED
• IF ASYSTOLE OR WEAK BEATS: EPINEPHRINE OR CALCIUM I.V.
Fluids - I.V. PLASMA, DEXTRAN, SALINE
Do not interrupt cardiac compressions and ventilation. Tracheal intubation only when necessary.
AFTER RETURN OF SPONTANEOUS CIRCULATION USE VASOPRESSORS AS NEEDED, e.g. NOREPINEPHRINE (Levophed) I.V. DRIP

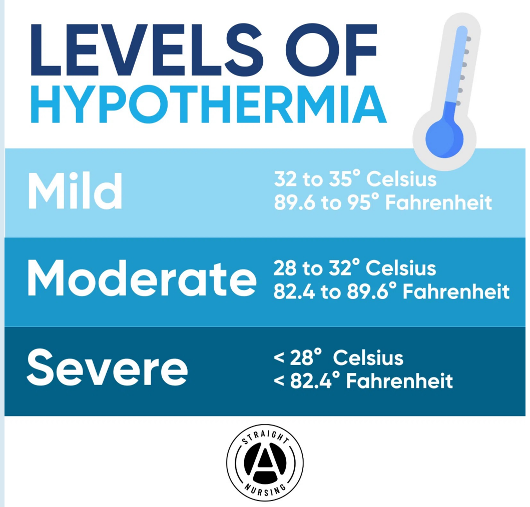
III SUPPORT RECOVERY (physician-specialist)
Gauge EVALUATE AND TREAT CAUSE OF ARREST
Hypothermia START WITHIN 30 MINUTES IF NO SIGN OF CNS RECOVERY
Intensive Care SUPPORT VENTILATION: TRACHEOTOMY, PROLONGED CONTROLLED VENTILATION, GASTRIC TUBE AS NECESSARY
SUPPORT CIRCULATION
CONTROL CONVULSIONS
MONITOR

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.

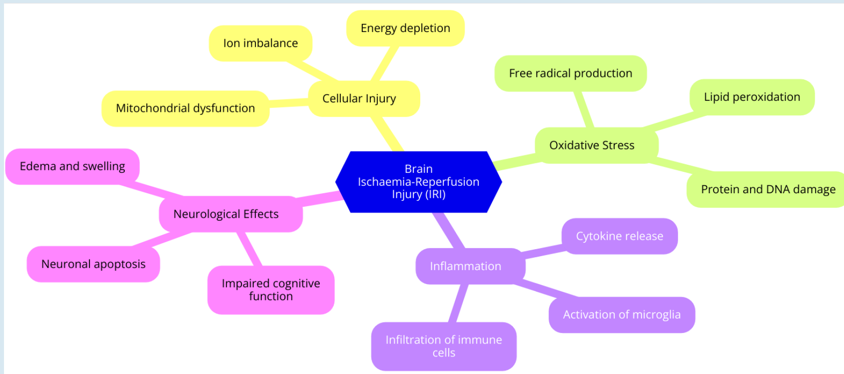
THE CURRENT CHALLENGES OF CARDIAC ARREST

Out of hospital and Post cardiac arrest management

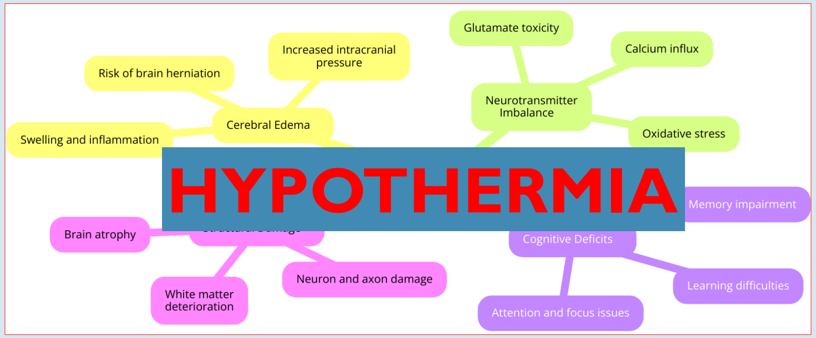
MILD HYPOTHERMIA IN OHCA PATIENTS



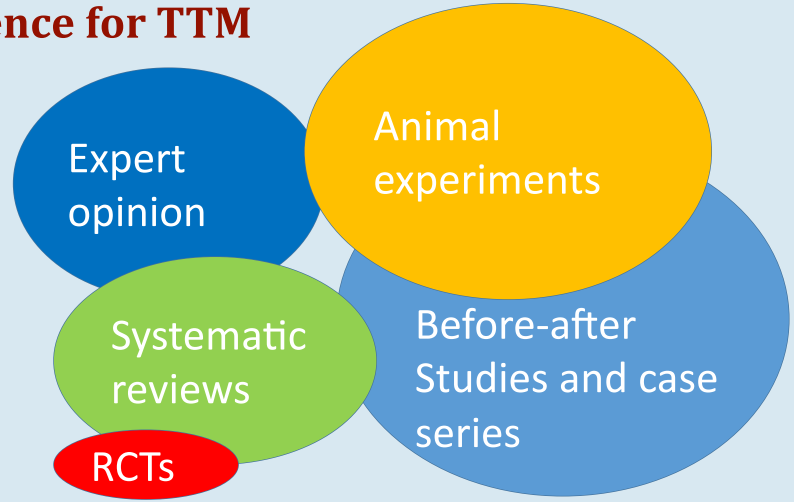
ISCHAEMIA-REPERFUSION SYNDROME



POST ANOXIC BRAIN INJURY



Evidence for TTM



BACKGROUND

ORIGINAL ARTICLE

Treatment of Comatose Survivors of Out-of-Hospital Cardiac Arrest with Induced Hypothermia

Stephen A. Bernard, M.B., B.S., Timothy W. Gray, M.B., B.S., Michael D. Buist, M.B., B.S., Bruce M. Jones, M.B., B.S., William Silvester, M.B., B.S., Geoff Gutteridge, M.B., B.S., and Karen Smith, B.Sc.
N Engl J Med 2002; 346:557-563 | February 21, 2002

Mild Therapeutic Hypothermia to Improve the Neurologic Outcome after Cardiac Arrest

The Hypothermia after Cardiac Arrest Study Group
N Engl J Med 2002; 346:549-556 | February 21, 2002

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Treatment of Comatose Survivors of Out-of-Hospital Cardiac Arrest with Induced Hypothermia

Authors: Stephen A. Bernard, M.B., B.S., Timothy W. Gray, M.B., B.S., Michael D. Buist, M.B., B.S., Bruce M. Jones, M.B., B.S., William Silvester, M.B., B.S., Geoff Gutteridge, M.B., B.S., and Karen Smith, B.Sc. Author Info & Affiliations

Published February 21, 2002 | N Engl J Med 2002;346:557-563 | DOI: 10.1056/NEJMoa003289 | VOL. 346 NO. 8

- Quasi-randomised, odd and even days
- 84 eligible patients, 77 included
- Unscheduled interim analysis after 62 patients
- All rythms included
- Unusual outcome measure: *survival to hospital discharge with sufficiently good neurologic function to be discharged to home or to a rehabilitation facility.*
- Uneven groups (43 vs 34 patients)
- Temperature in control group (37.1 -37.3 °C)

TABLE 5. OUTCOME OF PATIENTS AT DISCHARGE FROM THE HOSPITAL.

OUTCOME*	HYPOTHERMIA (N=43)	NORMOTHERMIA (N=34)
	number of patients	
Normal or minimal disability (able to care for self, discharged directly to home)	15	7
Moderate disability (discharged to a rehabilitation facility)	6	2
Severe disability, awake but completely dependent (discharged to a long-term nursing facility)	0	1
Severe disability, unconscious (discharged to a long-term nursing facility)	0	1
Death	22	23

ORIGINAL ARTICLE

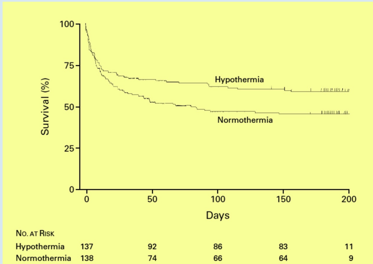
Mild Therapeutic Hypothermia to Improve the Neurologic Outcome after Cardiac Arrest

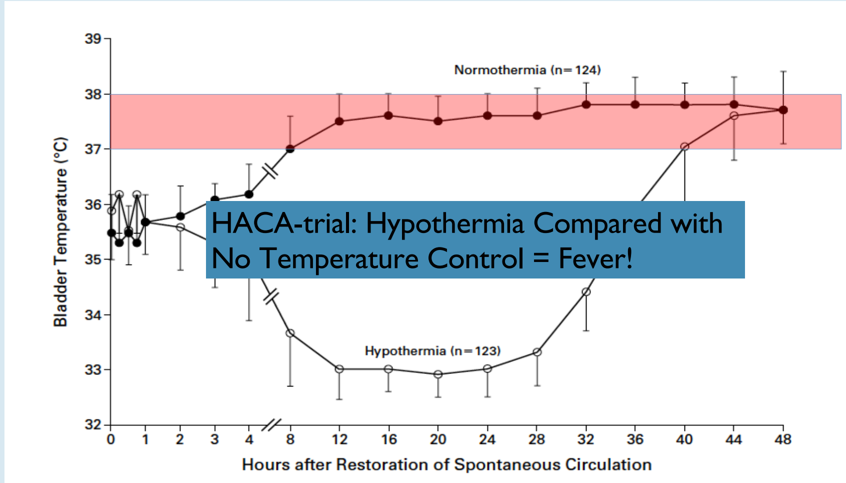
This article has been corrected. VIEW THE CORRECTION

Author: The Hypothermia after Cardiac Arrest Study Group* Author Info & Affiliations

Published February 21, 2002 | N Engl J Med 2002;346:549-556 | DOI: 10.1056/NEJMoa012689 | VOL. 346 NO. 8

- ✓ Less risk of bias/systematic errors!
- ✓ Patients after ventricular fibrillation
- ✓ Included only 8 % of patients with ROSC





ILCOR Recommandations

Resuscitation 57 (2003) 231–235

RESUSCITATION

www.elsevier.com/locate/resuscitation

Therapeutic hypothermia after cardiac arrest.
An advisory statement by the Advanced Life Support Task Force of the International Liaison Committee on Resuscitation☆

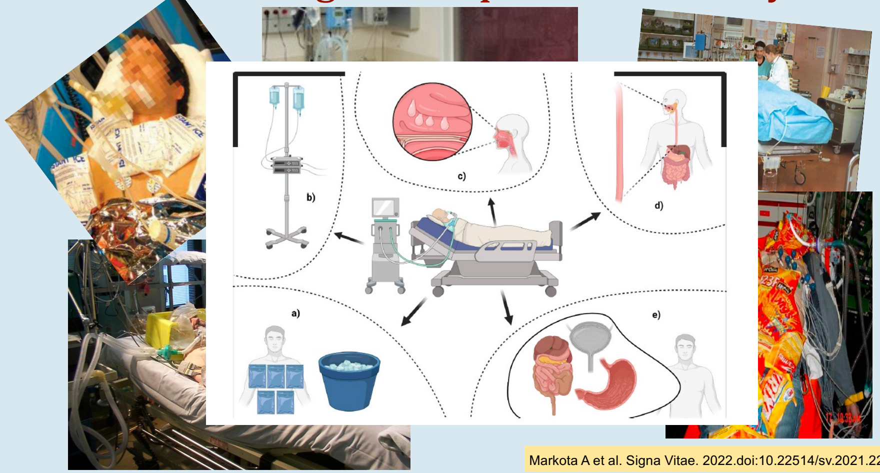
Jerry P. Nolan[a,*], Peter T. Morley[b], Terry L. Vanden Hoek[c], Robert W. Hickey[d,1], ALS Task Force[2]

ILCOR Recommendations

On the basis of the published evidence to date, the Advanced Life Support (ALS) Task Force of the International Liaison Committee on Resuscitation (ILCOR) made the following recommendations in October 2002:

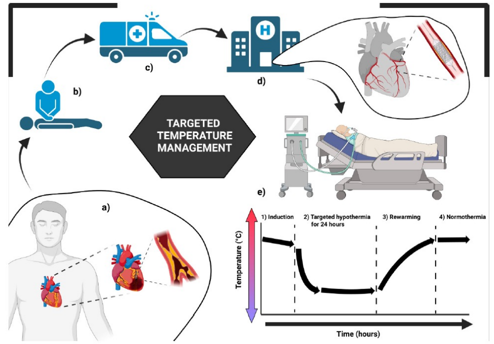
- Unconscious adult patients with spontaneous circulation after out-of-hospital cardiac arrest should be cooled to 32°C to 34°C for 12 to 24 hours when the initial rhythm was ventricular fibrillation (VF).
- Such cooling may also be beneficial for other rhythms or in-hospital cardiac arrest.

Different cooling techniques … too many ?



Markota A et al. Signa Vitae. 2022.doi:10.22514/sv.2021.227

It went viral



INCREASED RISK OF:

- Infection
- Arrhythmia
- Hemodinamic failure
- Seizures
- Major bleeding
- Delayed weaning

A Meta-Analysis


Contents lists available at ScienceDirect

International Journal of Cardiology

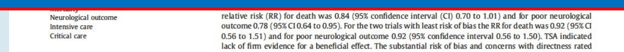
journal homepage: www.elsevier.com/locate/ijcard

ELSEVIER

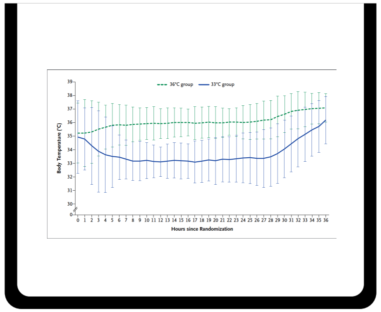
CARDIOLOGY

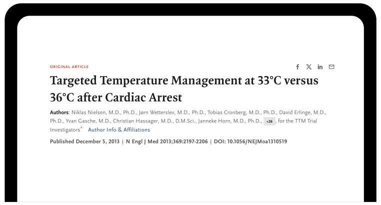
Earlier trials

- Possible risk of systematic errors
- Possible risk of being underpowered
- Investigated a selected group


Neurological outcome
Intensive care
Critical care

relative risk (RR) for death was 0.84 (95% confidence interval (CI) 0.70 to 1.01) and for poor neurological outcome 0.78 (95% CI 0.64 to 0.95). For the two trials with least risk of bias the RR for death was 0.92 (95% CI 0.56 to 1.51) and for poor neurological outcome 0.92 (95% confidence interval 0.56 to 1.50). TSA indicated lack of firm evidence for a beneficial effect. The substantial risk of bias and concerns with directness rated

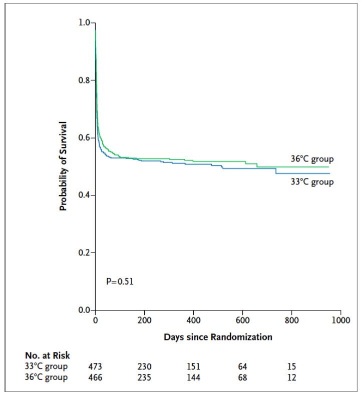


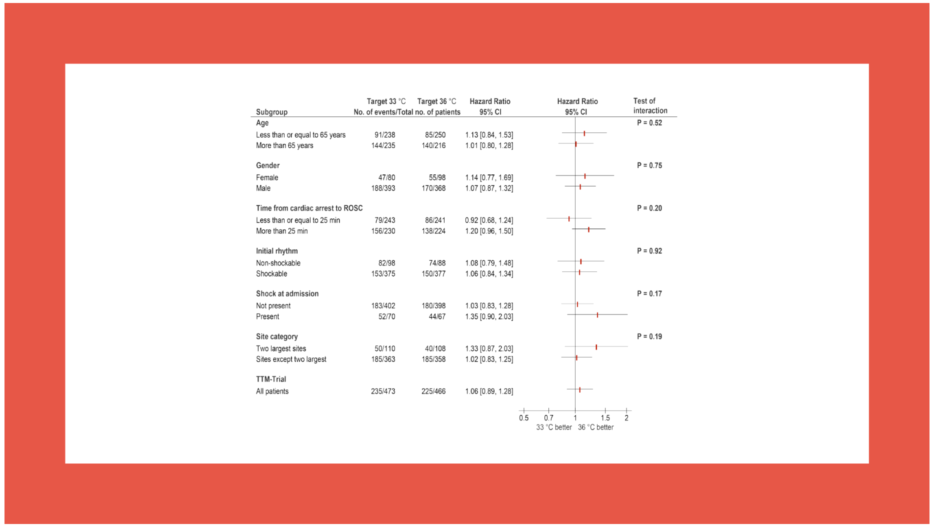

ORIGINAL ARTICLE

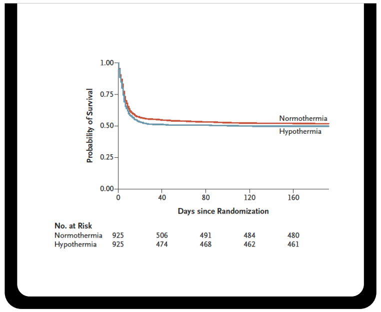
Targeted Temperature Management at 33°C versus 36°C after Cardiac Arrest

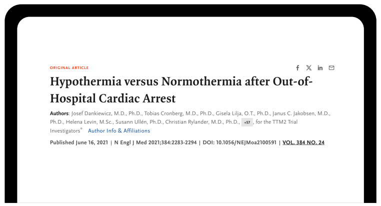
Authors: Niklas Nielsen, M.D., Ph.D., Jørn Wetterslev, M.D., Ph.D., Tobias Cronberg, M.D., Ph.D., David Erlinge, M.D., Ph.D., Yvan Gasche, M.D., Christian Hassager, M.D., D.M.Sci., Janneke Horn, M.D., Ph.D., +26, for the TTM Trial Investigators* Author Info & Affiliations

Published December 5, 2013 | N Engl J Med 2013;369:2197-2206 | DOI: 10.1056/NEJMoa1310519





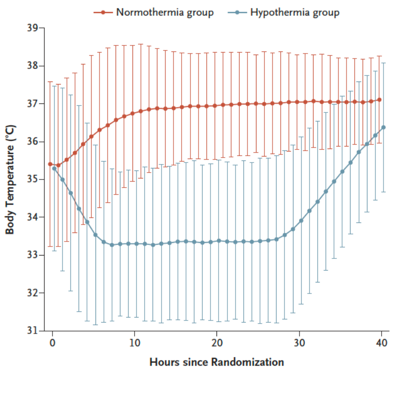


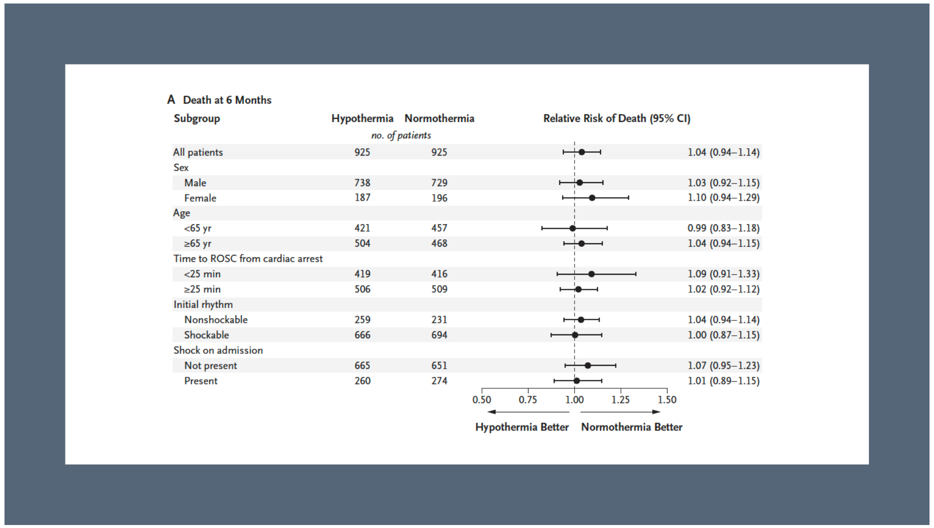

ORIGINAL ARTICLE

Hypothermia versus Normothermia after Out-of-Hospital Cardiac Arrest

Authors: Josef Dankiewicz, M.D., Ph.D., Tobias Cronberg, M.D., Ph.D., Gisela Lilja, O.T., Ph.D., Janus C. Jakobsen, M.D., Ph.D., Helena Levin, M.Sc., Susann Ullén, Ph.D., Christian Rylander, M.D., Ph.D., +57, for the TTM2 Trial Investigators* Author Info & Affiliations

Published June 16, 2021 | N Engl J Med 2021;384:2283-2294 | DOI: 10.1056/NEJMoa2100591 | VOL. 384 NO. 24





TTM1 + TTM2

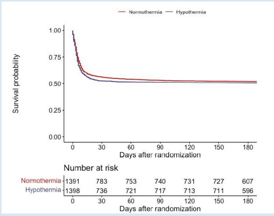
ORIGINAL ARTICLE

Hypothermic versus Normothermic Temperature Control after Cardiac Arrest

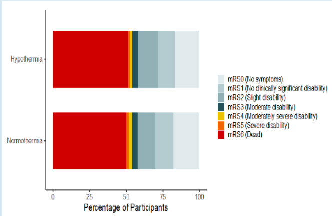
Authors: Johan Holgersson, M.D., Martin Abild Stengaard Meyer, M.D., Josef Dankiewicz, M.D., Ph.D., Gisela Lilja, O.T., Ph.D., Susann Ullén, Ph.D., Christian Hassager, M.D., D.M.Sc., Tobias Cronberg, M.D., Ph.D., +37 , and Janus Christian Jakobsen, M.D., Ph.D. Author Info & Affiliations

Published June 15, 2022 | NEJM Evid 2022;1(11) | DOI: 10.1056/EVIDoa2200137 | VOL. 1 NO. 11

Effects on survival



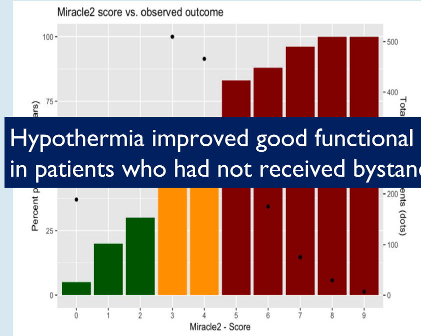
mRS at 180 d

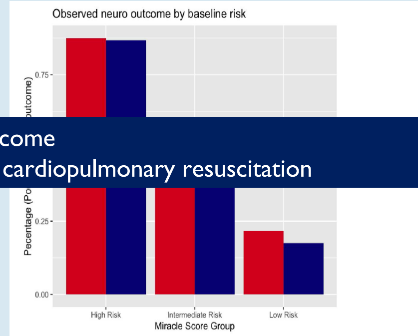


MIRACLE2

Severity & survival

TTM & survival





Hypothermia improved good functional outcome
in patients who had not received bystander cardiopulmonary resuscitation

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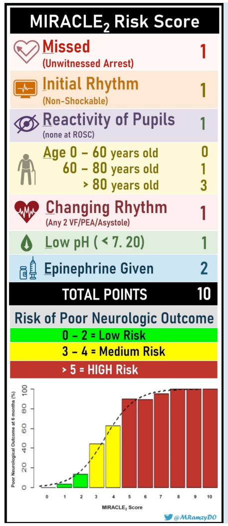


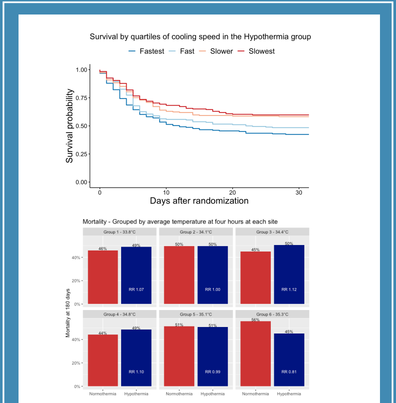
Seven predictor variables resulting in a final score ranging from 0 to 10 were used in the final model and it was named MIRACLE2

SPEED OF COOLING

RESEARCH Open Access

Speed of cooling after cardiac arrest in relation to the intervention effect: a sub-study from the TTM2-trial

Rupert F. G. Simpson, Josef Dankiewicz, Grigoris V. Karamasis, Paolo Pelosi, Matthias Haenggi, Paul J. Young, Janus Christian Jakobsen, Jonathan Bannard-Smith, Pedro D. Wendel-Garcia, Fabio Silvio Taccone, Per Nordberg, Matt P. Wise, Anders M. Grejs, Gisela Lilja, Roy Bjørkholt Olsen, Alain Cariou, Jean Baptiste Lascarrou, Manoj Saxena, Jan Hovdenes, Matthew Thomas, Hans Friberg, John R. Davies, Niklas Nielsen and Thomas R. Keeble



What TTM 1 & TTM2 trials did show ?

- Strictly controlled TTM regiments (32 °C vs 36 °C & 33 °C vs 36.5-37.7 °C) do not give different results
- Target temperature management works and it is necessary (with data available)
- The importance of avoiding fever in cardiac arrest

Limitations of TTM 1 & TTM 2 trials

❖ OHCA patients (generazibility to in hospital?)

❖ High patients' heterogeneity
✓ shockable and non-shockable rhythms
✓ no age limit

❖ Very short no-flow time and a large number of bystander-initiated resuscitation (implying a limited brain injury)

COMMENTARY Open Access

Targeted temperature management and cardiac arrest after the TTM-2 study

Fabio Silvio Taccone[1*], Jean-Baptiste Lascarrou[2] and Markus B. Skrifvars[3]

	Bernard et al. [1]	HACA group [2]	Nielsen et al. [7]	Dankiewicz et al. [5]	Lascarrou et al. [4]
Design	Single-Centre	Multicentric	Multicentric	Multicentric	Multicentric
N (HT group)	79 (43)**	275 (138)*	939 (473)	1861 (930)	584 (284)
Age, years	67 (49–89)	59 (49–67)	64 ± 12	64 ± 13	67 (57–76)
Male gender	58%	77%	83%	80%	65%
OHCA	100%	100%	100%	100%	74%
Shock on Admission	NR	49*	15%	28%	56%
STEMI on Admission	NR	NR	40%	41%	16%
Lactate, mmol/L	8.3 (2.2–14.9)	NR	6.7 ± 4.5	5.9 ± 4.4	5.8 (3.2–9.0)
Outcome Assessment	Hospital Discharge	6 months	6 months	6 months	3 months
Mortality, %*	51%	41%	50%	50%	81%
UO Assessment Scale	CPC 3–5	CPC 3–5	CPC 3–5	mRS 4–6	CPC 3–5
UO, %	51	45	54	55	90
Prognostication Rules	Absent	Absent	Present	Present	Present
Generalisability/Bias	Low/high	Low/high	High/low	High/low	High/moderate

All the randomized studies on TTM after cardiac arrest are not entirely comparable !

A Systematic Review & Meta-Analysis

Journal of Clinical Medicine MDPI

Review

Targeted Temperature Management after Cardiac Arrest: A Systematic Review and Meta-Analysis with Trial Sequential Analysis

Filippo Sanfilippo [1,*,†], Luigi La Via [1,2,†], Bruno Lanzafame [1,2], Veronica Dezio [1,2], Diana Busalacchi [2], Antonio Messina [3,4], Giuseppe Ristagno [5], Paolo Pelosi [6,7] and Marinella Astuto [1,2]

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2 School of Anaesthesia and Intensive Care, University Hospital "G. Rodolico", University of Catania, 95123 Catania, Italy; diana.busalacchi@gmail.com
3 Department of Biomedical Sciences, Humanitas University, Via Rita Levi Montalcini 4, 20090 Milan, Italy; mess81rc@gmail.com
4 IRCCS Humanitas Research Hospital, 20089 Milan, Italy

PICOS CRITERIA

Population	Patients experiencing CA both in and out-of-hospital, independently from the initially detected rhythm (shockable or not), with TTM performed after hospital arrival
Intervention	TTM with temperature range set at 32–34 °C
Comparison	TTM with either actively controlled or uncontrolled normothermia
Outcome(s)	Survival and neurological outcome at longest follow-up (primary); adverse effects (secondary)
Study design	Randomized controlled trial only

CA: cardiac arrest; TTM: target temperature management.

❖ **Effects on survival & neurologic outcome**

➢ **TTM (Temperature range of 32-34 °C)**
➢ **Controls:**
- "actively" controlled (avoiding fever)
- "uncontrolled" normothermia (may hesitate in hyperthermia/fever)

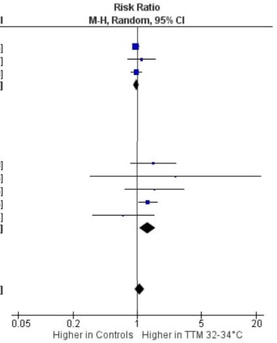
❖ **Serious adverse events**

Sanfilippo F et al. J. Clin. Med. 2021, 10, 3943

First Author Year	Location of Arrest	First Rhythm Detected	Treatment in the Intervention Group / Treatment in the Control Group	Longest Follow Up GNO Assessment
Dankiewicz 2021 *N* = 1861	OHCA	Shockable 74% Non-shockable 26%	TTM (surface/ iv, 33 °C, 28 h) + active RW (12 h) / Normothermia (≤37.5 °C + surface/iv if ≥37.8 °C)	6-months mRS
Nielsen 2013 *N* = 939	OHCA	Shockable 80% Non-shockable 20%	TTM (any method, 33 °C, 28 h) + active RW (8 h) / TTM (any method, 36 °C, 28 h) + active RW (2 h)	6-months—End trial CPC—mRS
Lascarrou 2019 *N* = 548	Mixed (73% OHCA)	Non-shockable 100%	TTM (any method, 33 °C, 24 h) + active RW (8–16 h, 36 °C, 24 h) / TTM (any method, 37 °C, 48 h)	90-days CPC
Holzer 2002 *N* = 136	OHCA	Shockable 96% Other 4%	TTM (mattress, 32–34 °C, 24 h) + passive RW / Normothermia (no target)	6-months CPC
Bernard 2002 *N* = 77	OHCA	Shockable 100%	TTM (ice-packs, 33 °C, 12 h) + active RW (6 h) / Normothermia (37 °C)	Hospital discharge Home/short term rehab
Hachimi-idrissi 2005 *N* = 61	OHCA	Non-shockable 54% / Shockable 46%	TTM (Helmet, 33 °C, brief *) + passive RW / Normothermia (37 °C) / TTM (mattress, 33 °C, 24 h) + passive RW / Normothermia (37 °C)	6-months CPC
Laurent 2005 * *N* = 42	OHCA	Shockable 74% Non-shockable 26%	TTM (HF + ice-packs, 32 °C, 24 h) + passive RW / Normothermia + HF 8 h (37 °C)	6-months CPC
Hachimi-idrissi 2001 *N* = 30	OHCA	Non-shockable 100%	TTM (Helmet, 34 °C, brief *) + passive RW / Normothermia + treatment of fever (38 °C)	2-weeks CPC

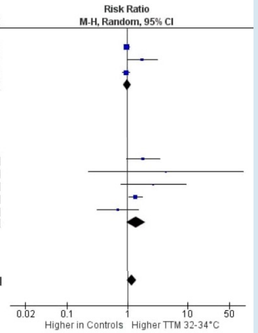
Effects on survival

Study or Subgroup	TTM 32-34°C Events	TTM 32-34°C Total	Controls Events	Controls Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Actively controlled normothermia						
Dankiewicz, New Engl J Med 2021	460	925	479	925	34.8%	0.96 [0.88, 1.05]
Lascarrou, New Engl J Med 2019	53	284	50	297	9.5%	1.11 [0.78, 1.57]
Nielsen, New Engl J Med 2013	238	473	241	466	29.5%	0.97 [0.86, 1.10]
Subtotal (95% CI)		**1682**		**1688**	**73.8%**	**0.97 [0.90, 1.04]**
Total events	751		770			
Heterogeneity: Tau² = 0.00; Chi² = 0.62, df = 2 (P = 0.73); I² = 0%						
Test for overall effect: Z = 0.83 (P = 0.41)						
1.1.2 Passively controlled normothermia						
Bernard, New Engl J Med 2002	21	43	11	34	4.1%	1.51 [0.85, 2.68]
Hachimi-idrissi, Resuscitation 2001	3	16	1	14	0.3%	2.63 [0.31, 22.46]
Hachimi-idrissi, Resuscitation 2005	12	30	8	31	2.6%	1.55 [0.74, 3.25]
Holzer, New Engl J Med 2002	81	137	62	138	16.9%	1.32 [1.04, 1.66]
Laurent, JACC 2005	7	22	9	20	2.3%	0.71 [0.32, 1.54]
Subtotal (95% CI)		**248**		**237**	**26.2%**	**1.31 [1.07, 1.59]**
Total events	124		91			
Heterogeneity: Tau² = 0.00; Chi² = 3.24, df = 4 (P = 0.52); I² = 0%						
Test for overall effect: Z = 2.65 (P = 0.008)						
Total (95% CI)		**1930**		**1925**	**100.0%**	**1.06 [0.94, 1.20]**
Total events	875		861			
Heterogeneity: Tau² = 0.01; Chi² = 11.58, df = 7 (P = 0.12); I² = 40%						
Test for overall effect: Z = 0.92 (P = 0.36)						
Test for subgroup differences: Chi² = 7.71, df = 1 (P = 0.005), I² = 87.0%						



Effects on neurologic outcome

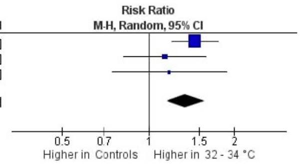
Study or Subgroup	TTM 32-34°C Events	TTM 32-34°C Total	TTM 36°C or SoC Events	TTM 36°C or SoC Total	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Actively controlled normothermia						
Dankiewicz, New Engl J Med 2021	393	881	387	866	29.8%	1.00 [0.90, 1.11]
Lascarrou, New Engl J Med 2019	29	284	17	297	7.9%	1.78 [1.00, 3.17]
Nielsen, New Engl J Med 2013	218	469	222	464	28.0%	0.97 [0.85, 1.11]
Subtotal (95% CI)		**1634**		**1627**	**65.7%**	**1.02 [0.88, 1.18]**
Total events	640		626			
Heterogeneity: Tau² = 0.01; Chi² = 4.10, df = 2 (P = 0.13); I² = 51%						
Test for overall effect: Z = 0.27 (P = 0.79)						
1.2.2 Passively controlled normothermia						
Bernard, New Engl J Med 2002	21	43	9	34	6.7%	1.84 [0.97, 3.49]
Hachimi-idrissi, Resuscitation 2001	2	16	0	14	0.4%	4.41 [0.23, 84.79]
Hachimi-idrissi, Resuscitation 2005	8	30	3	31	2.1%	2.76 [0.81, 9.41]
Holzer, New Engl J Med 2002	75	136	54	137	20.2%	1.40 [1.08, 1.81]
Laurent, JACC 2005	7	22	9	20	4.8%	0.71 [0.32, 1.54]
Subtotal (95% CI)		**247**		**236**	**34.3%**	**1.42 [0.99, 2.04]**
Total events	113		75			
Heterogeneity: Tau² = 0.05; Chi² = 5.46, df = 4 (P = 0.24); I² = 27%						
Test for overall effect: Z = 1.93 (P = 0.05)						
Total (95% CI)		**1881**		**1863**	**100.0%**	**1.17 [0.97, 1.41]**
Total events	753		701			
Heterogeneity: Tau² = 0.03; Chi² = 17.55, df = 7 (P = 0.01); I² = 60%						
Test for overall effect: Z = 1.66 (P = 0.10)						
Test for subgroup differences: Chi² = 2.87, df = 1 (P = 0.09), I² = 65.1%						



Adverse events

Arrhythmias

Study or Subgroup	TTM 32 - 34 °C Events	TTM 32 - 34 °C Total	TTM Controls Events	TTM Controls Total	Weight	Risk Ratio M-H, Random, 95% CI
Dankiewicz, New Engl J Med 2021	222	927	152	921	67.6%	1.45 [1.21, 1.75]
Holzer, New Engl J Med 2002	49	135	44	138	21.2%	1.14 [0.82, 1.58]
Lascarrou, New Engl J Med 2019	35	284	31	297	11.2%	1.18 [0.75, 1.86]
Total (95% CI)		**1346**		**1356**	**100.0%**	**1.35 [1.16, 1.57]**
Total events	306		227			
Heterogeneity: Tau² = 0.00; Chi² = 1.94, df = 2 (P = 0.38); I² = 0%						
Test for overall effect: Z = 3.83 (P = 0.0001)						



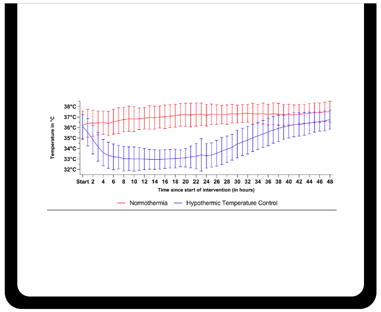
No differences in the incidence of:
✓ bleeding (RR 1.10 (95%CI 0.83, 1.44))
✓ pneumonia (RR 1.11 (95%CI 0.96, 1.29))

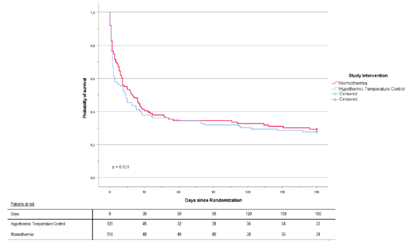
CONCLUSIONS

- ❖ In CA survivors admitted to hospital, the implementation of TTM with a target temperature of 32 - 34 °C:
- ✓ does not improve survival nor neurological outcome
- ✓ it increases the risk of arrhythmias

- ❖ For survival, robust evidence and no more studies are needed.
- ❖ For neurological outcome current evidence is not robust enough - thus new research is needed.

- ❖ Approaching temperature management with“uncontrolled” normothermia may be associated with worse outcomes and this should not be considered an option nowadays.






ORIGINAL RESEARCH ARTICLE

Temperature Control After In-Hospital Cardiac Arrest: A Randomized Clinical Trial

Sebastian Wolfrum, MD*; Kevin Roedl, MD*; Alexia Hanebutte, MD; Rüdiger Pfeifer, MD; Volkhard Kurowski, MD; Reimer Riessen, MD; Anne Daubmann, MSc; Stephan Braune, MD; Gerold Söffker, MD; Eric Bibiza-Freiwald, MSc; Karl Wegscheider, PhD; Heribert Schunkert, MD; Holger Thiele, MD*; Stefan Kluge, MD*; for the Hypothermia After In-Hospital Cardiac Arrest Study Group

The STEPCARE trial

The STEPCARE trial is an international, multicenter, parallel group, noncommercial, randomized, factorial, superiority trial to include 3100 patients

1. Continuous sedation for 36 h or minimal sedation (SEDCARE)
2. Fever management with or without a TTM device for 72 h (TEMPCARE)
3. A mean arterial pressure target of > 85mmHg or > 65mmHg for 36 hours (MAPCARE)

Follow-up will be performed at 30 days and 6 months after cardiac arrest including mortality, functional outcome and quality of life

1. Detailed cognitive outcome with focus on patients and caregivers
2. Prognostication to identify and validate early and accurate instruments and algorithm
3. Biobank with blood samples at 0, 24, 48, and 72 hours after the cardiac arrest

NEUROPROTEZIONE:
IMPLICAZIONI CLINICHE
DELL’IPERTERMIA,
EVIDENZE SCIENTIFICHE SPERIMENTALI
E CLINICHE

Learning outcome

- Definition of fever
- What is normothermia?
- Mechanism of cellular damage
- Fever in injured brain
- Recommendations
- Neuro-protection after cardiac arrest
- Limitation and a sneak peek of future

What's fever?

Carl Reinhold August Wunderlich's Study (1868) - Wunderlich's large-scale study in the 19th century established **37°C (98.6°F)** as the average normal body temperature, a standard that has been widely referenced since. However, the study's methodology and tools have been re-evaluated in modern contexts.

Recent Studies - More recent studies suggest that the average body temperature might be slightly lower than 37°C:

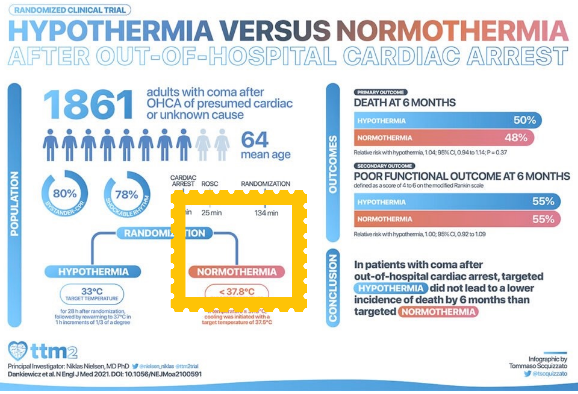
•**Mackowiak et al. (1992)**: In a study published in *JAMA*, Mackowiak and colleagues found that the average oral temperature is closer to **36.8°C (98.2°F)** and varies across individuals.

•**Protsiv et al. (2020)**: A study in *eLife* analyzed historical and contemporary temperature data and found a trend suggesting that the average human body temperature has decreased over the last century, now closer to **36.6°C (97.9°F)**.

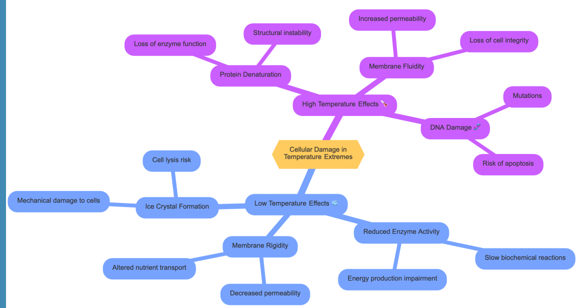
DEFINITION

Fever, also known as pyrexia , is defined as having a temperature above the normal range due to an increase in the body's temperature set point. There is not a single agreed-upon upper limit for normal temperature with sources using values between 37.5 and 38.3 °C (99.5 and 100.9 °F).

What's normothermia?



WHY CAN WE GET MUCH COOLER THAN WE GET HOT?



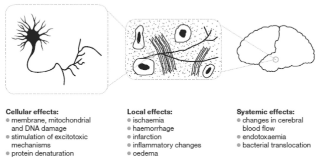
MECHANISM OF CEREBRAL DAMAGE

Mechanisms of Injury

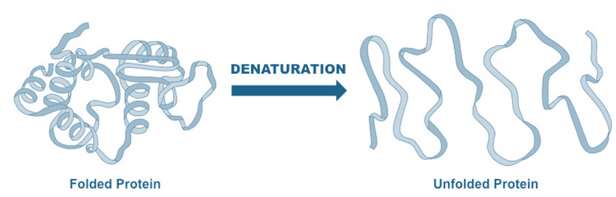
Excitotoxicity: Hyperthermia promotes release of excitatory neurotransmitters, leading to cellular damage.

Oxidative Stress: Elevated temperatures increase reactive oxygen species, causing neuronal injury.

Inflammatory Response: Hyperthermia triggers neuroinflammation, worsening cognitive outcomes.



Cellular effects of hyperthermia



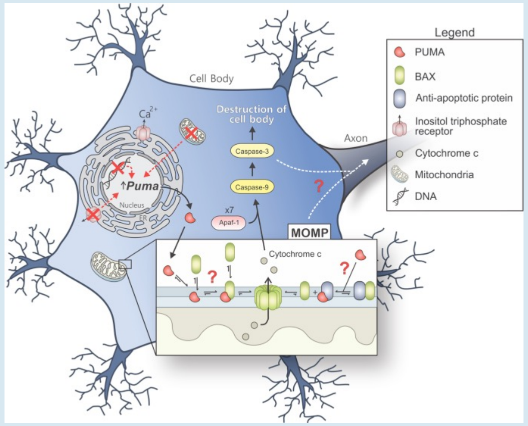
Cellular denaturing

⬆ ionic flux
mitocondrial dysfunction

>40°C Aggregates

HT potentiates damage caused by toxic insults like hypoxia and ischaemia

Neuronal death



Caspase
Apoptosi

Cell death ⬆
glutamate e glycine

Heat shock proteins

AD, SM, TBI

Fever in injured brain

Clinical paper
Post-hypothermia fever is associated with increased mortality after out-of-hospital cardiac arrest☆
John Bro-Jeppesen[a,*], Christian Hassager[a], Michael Wanscher[b], Helle Søholm[a], Jakob H. Thomsen[a], Freddy K. Lippert[c], Jacob E. Møller[a], Lars Køber[a], Jesper Kjaergaard[a]

Similar PFC vs No fever

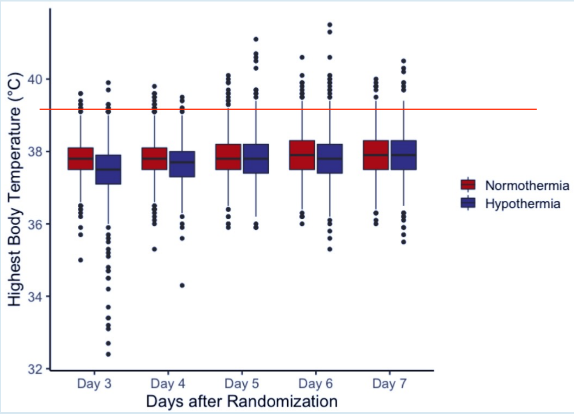
>39°C for >7h

Marker or secondary injury?

Should we actively treat or prevent PCF?

Protocols include a post cooling TH period..
is this improving the neurological outcome?

TTM2 trial fever



ERC-ESICM Recommendations

GOOD PRACTICE — We **recommend** continuous monitoring of core temperature in patients who remain comatose

LOW — We **recommend** actively preventing fever (defined as a temperature > 37.7°C) in post-cardiac arrest patients who remain comatose.

GOOD PRACTICE — We **recommend** actively preventing fever for at least 72 hours in post-cardiac arrest patients who remain comatose.

GOOD PRACTICE — this is insufficient, by using a cooling device with a target temperature of 37.5°C.

GOOD PRACTICE — There is currently insufficient evidence to recommend for or against temperature control at 32-36°C in sub-populations of cardiac arrest patients or using early cooling, and future research may help elucidate this. We **recommend not** actively rewarming comatose patients with mild hypothermia after ROSC to achieve normothermia.

MODERATE — We **recommend not** using prehospital cooling with rapid infusion of large volumes of cold IV fluid immediately after ROSC.

Hyperthermia after brain damage

CLINICAL STUDIES

Michael M. Todd, M.D.
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William R. Clarke, Ph.D.

PERIOPERATIVE FEVER AND OUTCOME IN SURGICAL PATIENTS WITH ANEURYSMAL SUBARACHNOID HEMORRHAGE

70%
1/3 non infctive

Stroke
Volume 26, Issue 11, November 1995; Pages 2040-2043
https://doi.org/10.1161/01.STR.26.11.2040

American Heart Association.

ARTICLE

Fever in Acute Stroke Worsens Prognosis
A Prospective Study

Incidence

•Hyperthermia is common post-brain injury, occurring in **up to 50%** of patients.

•Often arises within the **first 72 hours** after the injury.

Risk for Mortality

•**Hyperthermia (≥ 38°C)** is associated with a **significantly increased mortality risk**.

•**20-30% rise in mortality** in hyperthermic brain-injured patients versus normothermic.

Neurocognitive disorders

> Intensive Care Med. 2009 Aug;35(8):1454-8. doi: 10.1007/s00134-009-1500-x. Epub 2009 Apr 29.

Early organ dysfunction course, cooling time and outcome in classic heatstroke

Sebastian Pease [1], Lila Bouadma, Nathalie Kermarrec, Frédérique Schortgen, Bernard Régnier,

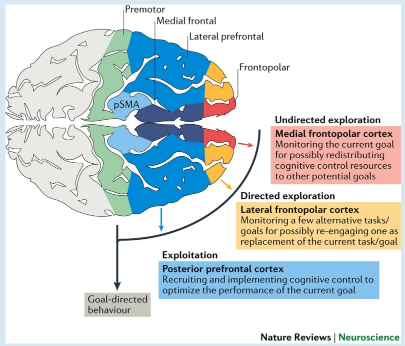
Controlled Clinical Trial > Int J Hyperthermia. 2012;28(7):621-6. doi: 10.3109/02656736.2012.705217. Epub 2012 Sep 4.

Hyperthermia impairs the executive function using the Attention Network Test

Gang Sun [1], Xiao Yang, Qingjun Jiang, Kai Liu, Bo Li, Li Li, Lun Zhao, Min Li

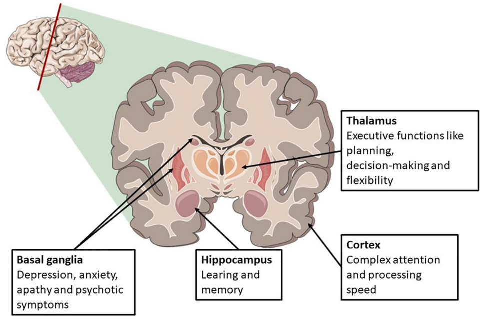
Common Neurocognitive Disorders

•**Memory Impairment:** Difficulty with short-term memory retention and recall.
•**Attention Deficits:** Reduced ability to sustain attention and concentrate.
•**Executive Dysfunction:** Impairments in planning, organizing, and problem-solving.
•**Language Difficulties:** Challenges in word-finding, fluency, and comprehension.
•**Emotional Dysregulation:** Increased irritability, mood swings, or depression.



NEURO COGNITIVE DISORDERS

Limbic system: memory and learning ability
Prefrontal cortex: executive functions
Intraparietal sulcus: processing and memory



Systemic effects of Hyperthermia

> Neuroscience. 2009 Jul 7;161(3):926-39. doi: 10.1016/j.neuroscience.2009.04.004. Epub 2009 Apr 9.

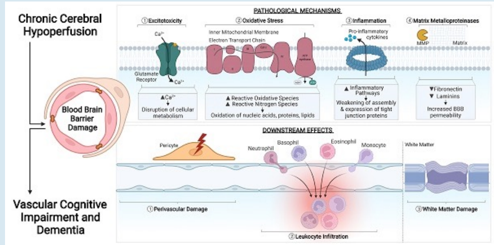
Permeability of the blood-brain barrier depends on brain temperature

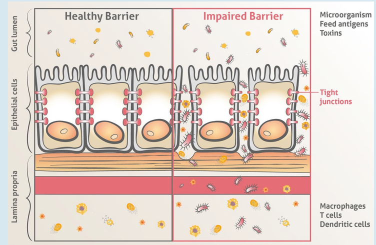
E A Kiyatkin [1], H S Sharma

Review > Prog Brain Res. 2007;162:153-69. doi: 10.1016/S0079-6123(06)62009-8.

Cerebral pathophysiology and clinical neurology of hyperthermia in humans

Olaf L Cremer [1], Cor J Kalkman





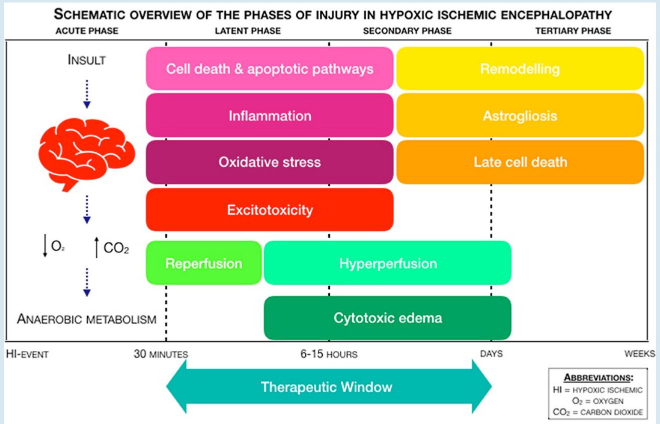
What if outcome is unclear?

conservative vs pessimistic

Learning outcome

1. Pathophysiology of brain injury
2. Treatment of BI
3. Targeted temperature management (TTM)
4. Neuroprotective agents
5. Outcomes
6. Awakening from coma
7. Neuroprognostication
   - Bias in neuroprognostication
   - Clinical examination
   - Blood biomarkers
   - Neurophysiology
   - Imaging
8. Recap

Pathophysiology of brain injury



primary injury

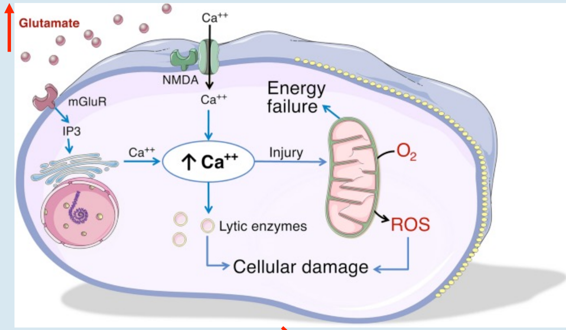
Brain receives 15-20% CO viability depends on oxygen and glucose

CBF stop

consciousness 4- 10 s
EEG 10-30 s isoelectric

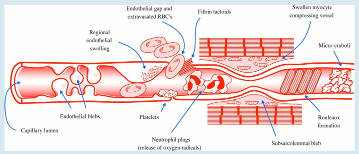
Pathophysiology of brain injury

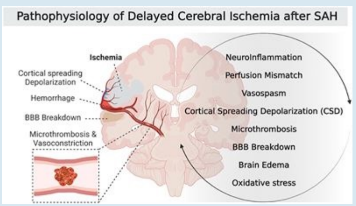
primary injury



secondary injury

Pathophysiology of brain injury





No reflow phenomenon

Cerebral disregulation

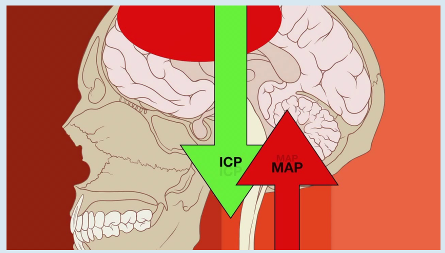
Delayed hypoperfusion

Relationship Between CBF and CPP

•**Cerebral Blood Flow (CBF)** refers to the blood volume passing through 100g of brain tissue per minute. Adequate CBF is essential to supply the brain with oxygen and nutrients.

•**Cerebral Perfusion Pressure (CPP)** is the pressure driving blood flow to the brain, calculated as:

CPP=MAP−ICP



Relationship Between CBF and CPP

Key Points of the Relationship

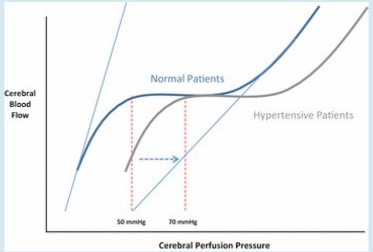
1.Direct Influence: CPP directly influences CBF. When CPP falls too low, CBF decreases, risking ischemia, while high CPP may lead to hyperemia and potentially raise ICP.

2.Autoregulation:

1. **Autoregulation** is the brain's ability to maintain consistent CBF despite changes in CPP, usually within a CPP range of **50-150 mmHg**.
2. Outside this range, autoregulation fails, and CBF becomes linearly dependent on CPP:
   1. **Low CPP (<50 mmHg)** can cause hypoperfusion, risking ischemia.
   2. **High CPP (>150 mmHg)** may overwhelm autoregulatory mechanisms, increasing ICP and the risk of edema.

3.Conditions Affecting CBF and CPP:

1. **Brain injury** can disrupt autoregulation, making CBF highly dependent on CPP.
2. **Hyperthermia, hypotension, or elevated ICP** can reduce CPP, compromising CBF and increasing the risk of ischemic damage.



Awakening from coma

Delayed awakening after cardiac arrest: prevalence and risk factors in the Parisian registry

Marine Paul, Wulfran Bougouin, Guillaume Geri, Florence Dumas, Benoit Champigneulle, Stéphane Legriel, Julien Charpentier, Jean-Paul Mira, Claudio Sandroni & Alain Cariou

Intensive Care Medicine **42**, 1128–1136 (2016) | Cite this article

Late Awakening in Survivors of Postanoxic Coma: Early Neurophysiologic Predictors and Association With ICU and Long-Term Neurologic Recovery

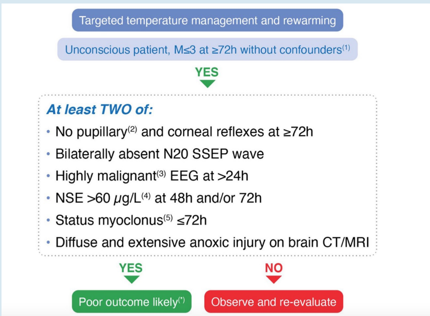
Rey, Arnaud MD[1]; Rossetti, Andrea O. MD[2]; Miroz, John-Paul RN[1]; Eckert, Philippe MD[1]; Oddo, Mauro MD[1]

70% within 48h

latest 25 days after

Late awakening (>5 gg) associated to severe neurological disability

Neuroprognostication



Bias in prognostication

False positive rate (FPR) should be zero
(high accuracy)
Narrow confidence intervals
(high precision)

Self fulfilling prophecy

Blinding test results

Investigate prognostication in countries where WLST is not performed

Sedation

A patient's health outcome can sometimes align with the expectations and beliefs of their care team, influencing the recovery process.

Predictors of Neurological Outcome After Cardiac Arrest

1. Initial Rhythm

•**Shockable Rhythms** (e.g., Ventricular Fibrillation or Ventricular Tachycardia): Higher chance of favorable neurological outcomes.
•**Non-shockable Rhythms** (e.g., Asystole or Pulseless Electrical Activity): Associated with poorer outcomes.

2. Time to Return of Spontaneous Circulation (ROSC)

•**Shorter Duration to ROSC**: Linked to better neurological recovery.
•**Longer Duration (>20 minutes)**: Associated with higher risk of poor neurological outcomes.

3. Duration and Quality of CPR

•**Short, Effective CPR**: High-quality CPR, with minimal interruptions, improves cerebral perfusion and outcome.
•**Prolonged CPR (>30 minutes)**: Generally indicates a poorer prognosis.

Predictors of Neurological Outcome After Cardiac Arrest

4. Post-Cardiac Arrest Hypothermia Management

•**Therapeutic Hypothermia** (Targeted Temperature Management): Cooling to 32-36°C has shown to improve neurological outcomes by reducing brain injury.

5. Neurological Examination at 72 Hours

•**Pupillary Reaction**: Non-reactive pupils at 72 hours post-arrest is a strong indicator of poor outcome.
•**Motor Response**: Lack of motor response or absent brainstem reflexes can signal worse outcomes.

6. Biomarkers

•**Serum Neuron-Specific Enolase (NSE)**: Elevated levels are associated with greater brain injury and poorer prognosis.
•**S100B Protein**: Another marker that, when elevated, can indicate worse neurological outcomes.

7. EEG Patterns

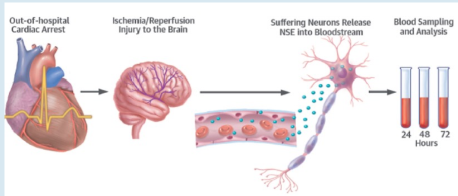
•**Early EEG after ROSC**: Patterns such as burst suppression or status epilepticus are associated with poor neurological recovery.
•**Continuous and Normal EEG Patterns**: More favorable for recovery.

Predictors of neurological outcome

Clinical examination

motor response	response to pain (GCS-M≤3) at≥72 h after ROSC
ocular reflexes	At≥72 h after ROSC, bilaterally absent pupillary or corneal reflexes
myoclonus	early (<48 h), a generalised distribution, a synchronous stereotyped pattern, and prolonged (>30 min) duration

Predictors of neurological outcome



NSE

NSE-levels increase and peak at 48–72

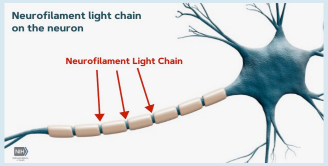
cut-off for reliable prediction of poor outcome is 60 mg L^{-1} at 48–72 h

levels <17 mg L^{-1} predict good outcome

ORIGINAL

Serum markers of brain injury can predict good neurological outcome after out-of-hospital cardiac arrest

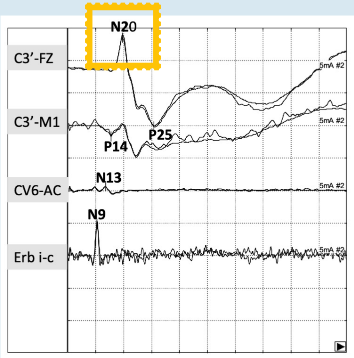
Marion Moseby-Knappe[1*], Niklas Mattsson-Carlgren[1,2,3], Pascal Stammet[4], Sofia Backman[5], Kaj Blennow[6,7],



Electrophysiology

Predictors of neurological outcome

activation of primary sensory cortex



Key SSEP Waves

1.N9 Wave (Peripheral Response)

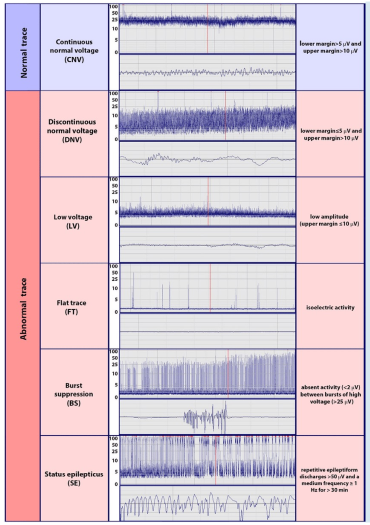
1. **Location**: Brachial plexus (near the shoulder, recorded from the arm).
2. **Meaning**: Indicates intact peripheral nerve conduction from the stimulation site to the brachial plexus.
3. **Interpretation**: Absence of the N9 wave suggests an issue with peripheral nerves.

2.N13 Wave (Cervical Response)

1. **Location**: Cervical spinal cord (neck region).
2. **Meaning**: Reflects conduction from the brachial plexus to the cervical spinal cord.
3. **Interpretation**: Absence or delay in N13 suggests issues within the cervical spine or spinal cord pathways.

3.N20 Wave (Cortical Response)

1. **Location**: Somatosensory cortex (top of the head, recorded from the scalp).
2. **Meaning**: This is the most important wave in SSEP for brain assessment. It represents the cortical response to sensory input and reflects intact sensory conduction to the brain.
3. **Interpretation**:
   1. **Present N20 Wave**: Suggests functional sensory pathways to the brain, generally associated with a better prognosis in comatose patients.
   2. **Absent N20 Wave**: Strongly predicts poor neurological outcome after events like cardiac arrest, as it indicates a lack of cortical response to sensory input.



Electrophysiology

American Clinical Neurophysiology Society's Standardized Critical Care EEG Terminology: 2021 Version

Lawrence J. Hirsch,* Michael W.K. Fong,† Markus Leitinger,‡ Suzette M. LaRoche,§ Sandor Beniczky,||

Background EEG Patterns

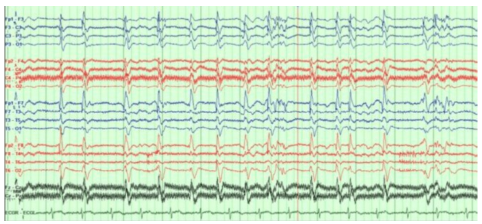
•**Continuous EEG**: Generally associated with a better prognosis if the background is continuous and reactive.
•**Discontinuous or Burst-Suppression Patterns**: Often indicate a poorer prognosis, especially if they persist without improvement.
•**Suppression**: Background EEG with very low amplitude (<10 μV) or isoelectric tracing indicates severe brain injury and poor prognosis.

Reactivity and Responsiveness
•**Reactivity**: The EEG's response to external stimuli (such as noise or touch).
- **Prognostic Value**: EEG that shows reactivity to stimuli is a positive prognostic indicator. Non-reactive EEG suggests severe brain dysfunction and is associated with poor outcomes.

Summary of Prognostic Indicators by ACNS 2021
•**Good Prognosis**: Continuous, reactive EEG without burst suppression or epileptiform activity.
•**Poor Prognosis**: Suppressed, isoelectric EEG, burst suppression without improvement, or persistent unresponsive status epilepticus.

EPILEPTIFORM PATTERNS

- **Generalized Periodic Discharges (GPDs)**:
  - **Prognostic Value**: GPDs, especially if combined with a suppressed or burst-suppression background, are associated with poor prognosis. Their presence is often indicative of widespread cortical damage.
- **Status Epilepticus**:
  - **Pattern**: Continuous seizure activity or EEG patterns meeting status epilepticus criteria.
  - **Prognostic Value**: Prolonged, unresponsive status epilepticus is strongly associated with poor outcomes, although short-lived, treatable seizures may not necessarily predict a negative outcome.



PREDICTING NEUROLOGICAL OUTCOME AFTER CARDIAC ARREST: ROLE OF NEUROIMAGING

Key Imaging Modalities

CT Scan

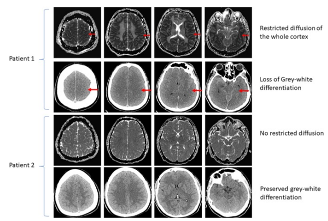
Cerebral Edema: Severe brain swelling and loss of gray-white differentiation are associated with poor outcomes.

Early Hypodensities: Visible hypodense areas indicate significant injury and a likely poor prognosis.

MRI (Diffusion-Weighted Imaging - DWI)

Hypoxic-Ischemic Injury: Presence of diffuse restricted diffusion areas, especially in the cortex, basal ganglia, or cerebellum, strongly predicts poor outcomes.

Early DWI Changes: DWI is highly sensitive and specific for early ischemic changes post-arrest, aiding in rapid assessment.



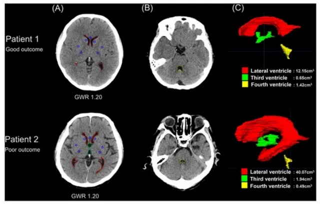
ROLE OF GWR IN PROGNOSTICATION

Normal GWR: Gray matter (higher density) typically appears brighter than white matter on a CT scan.

Decreased GWR: After cardiac arrest, hypoxic brain injury can cause cerebral edema, leading to a loss of distinction between gray and white matter due to decreased gray matter density.

Predictive Value:

- **Low GWR (<1.2)** is associated with poor neurological outcomes, often indicating severe brain injury and a high likelihood of non-recovery.
- **High GWR** is generally more favorable, indicating less edema and higher potential for neurological recovery.



Recap

1. Primary (ischaemic) and secondary (reperfusion) injury occur sequentially during cardiac arrest, resuscitation, and the acute post-resuscitation phase.
2. TTM is a strategy to achieve and maintain a specified body temperature, typically from 33 to 37.5 °C.
3. Difficult to define the optimal timing, dosing (temperature level) and duration of treatment.
4. Neuroprognostication: clinical, electrophysiology, biomarkers and imaging
5. Clinical: motor response, ocular reflexes and myoclonus
6. Biomarkers: NSE is standard practice while NFL is most reliable biomarker but still needs confirmation
7. EEG is complex and prone to subjectivity. Recently ACNS standardize the interpretation.
8. Still no definite consensus on the optimal timing of imaging. Generally TC as a first step than MRI.
9. Predicting good neurological outcome is challenging, needs more investigation.

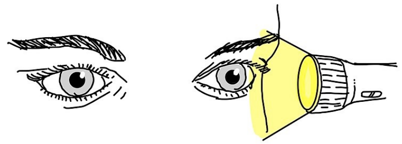
- Erik Roman-Pognuz MD, PhD
- Department of Medical Science - University

- Anatomy of the pupillary light reflex. What are we assessing?
- Why we do assess pupils?
- Standard vs automated
- Clinical use of automated pupillometry
- Prognostication of patient prognosis
- Pupillometry in anesthesia
- Limitation and a sneak peek of future

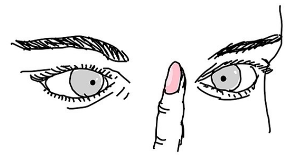
who's first?

Sir Robertson, Douglas Argyll

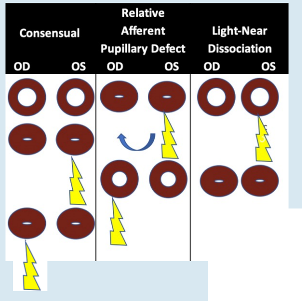
(Edimb 1837 - Gondal, India, 1909)

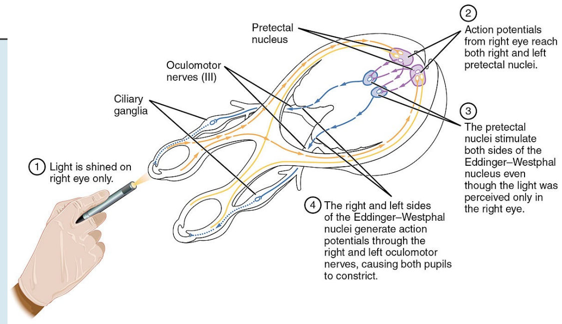


Pupils DO **NOT** constrict when exposed to bright light. ("light reflex")



Pupils DO constrict on a near object. ("accommodation reflex")

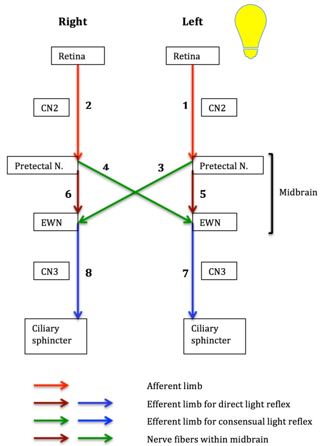




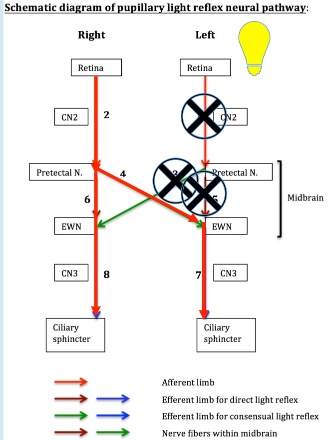
- Left direct light reflex involves neural segments 1, 5, and 7.
- Left consensual light reflex involves neural segments 2, 4, and 7.
- Right direct light reflex involves neural segments 2, 6, and 8.
- Right consensual light reflex involves neural segments 1, 3, and 8.

Diagnostic tool for sensory and motor function for the eye and brain stem

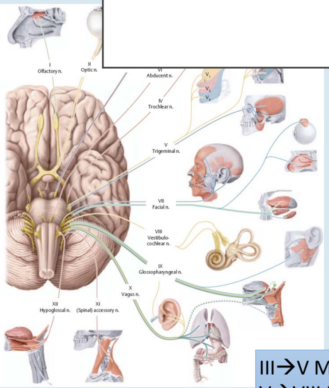
Schematic diagram of pupillary light reflex neural pathway:



Schematic diagram of pupillary light reflex neural pathway:



- Left consensual reflex is normal
- Right direct reflex is normal

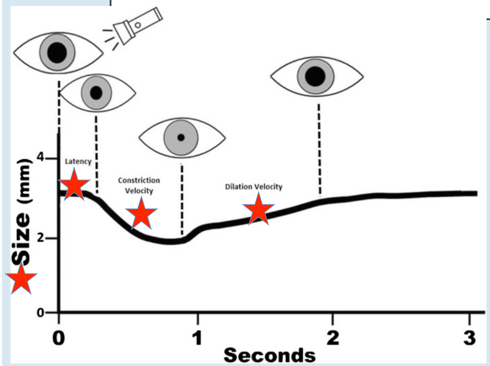


III→V Midbrain
V→VIII Pons
V, VII→XII Medulla

Pros easy and inexpensive
Cons qualitative, Inter examiner variabilit and lack of reliability

Pros standardise the intensity, distance from the eye and duration of stimulus.Displays a quantitative and reproducible measures.
Cons cost

AUTOMATED PUPILLOMETRY TECHNIQUE



Infrared visible light source coupled with a camera

A infrared light measure the pupil baseline

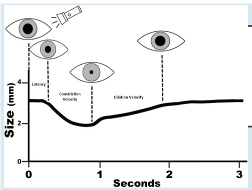
After 3'' a visible light delivered

The pupillary response recorded with camera

Other parameters

- pupillogram
- data trending

Non invasive neuromonitoring bedside tool



AUTOMATED PUPILLOMETRY TECHNIQUE

Pupillary function	Pupillometry derived variable
Pupil constriction to light stimulation	• Size (mm) • Asymmetry (mm) • Constriction change to light stimulation (% PLR) • Latency (sec) • Constriction velocity (mm/s) • Dilation velocity (mm/s) • Neurologic Pupillary Index: NPi*, a computed value derived from a mathematic algorithm including several of the above variables
Pupil dilation to painful stimulation	• Pupillary reflex dilation: PRD (%)** • Pupillary Pain Index: PPI**

*Calculated only by the Neuroptics® NPi-200 pupillometer; **available only on the NeuroLight-Algiscan® pupillometer.

Measured Value*	Assessment
3.0 – 4.9	Normal/"Brisk"
< 3.0	Abnormal/"Sluggish"
0	Non-Reactive, Immeasurable, or Atypical Response

DEVICES

Neurolight Algiscan

No comparable data on available devices
Possible that Information with both devices is not the same

No comparable studies that examine accuracy

cubical nerve stimulator (10-60 mA)

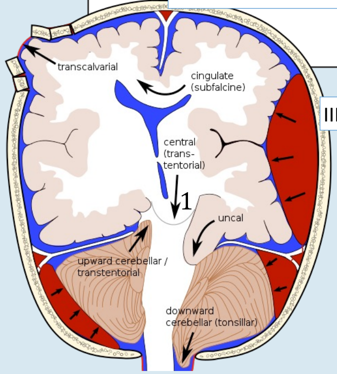
- PRD
- PPI

NPi index algorithm derived value
NPi>= 3 normal reactivity

Neuroptics NPi

Severe TBI ICTH may cause TTH (1)

CLINICAL USE OF AP
NEUROLOGICAL ASSESSMENT



III oculomotor compression or distortion of midbrain

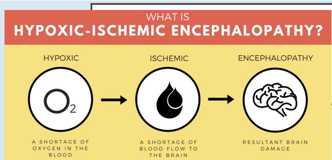
Automated Pupillometry and Detection of Clinical Transtentorial Brain Herniation: A Case Series

Alexander Papangelou, MD; Elizabeth K. Zink, MS, RN†; Wan-Tsu W. Chang, MD‡§;*

Quantitative pupillometry for the monitoring of intracranial hypertension in patients with severe traumatic brain injury

Fritz-Patrick Jahns[1], John Paul Miroz[2], Mahmoud Messerer[3], Roy T. Daniel[3], Fabio Silvio Taccone[4],

In comatose with BI deterioration of AP parameters (
may predict ICHT and suggest investigation or treatm



CLINICAL USE OF AP
NEUROLOGICAL PROGNOSTICATION

HIBI after CA

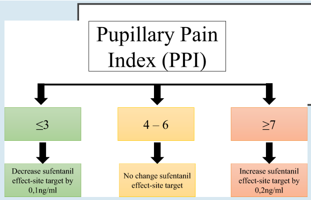
Clinical paper Resuscitation 83 (2012) 1223–1228

Infrared pupillometry to detect the light reflex during cardiopulmonary

BMJ Open

Outcome Prognostication of Acute Brain Injury using the Neurological Pupil Index (ORANGE) study: protocol for a prospective, observational, multicentre, international cohort study

Mauro Oddo,[1,2] Fabio Taccone,[3] Stefania Galimberti,[4,5] Paola Rebora,[4,6]



CLINICAL USE OF AP
MONITORING ANALGESIA

Perioperative Medicine | August 2017

Pupillometry-guided Intraoperative Remifentanil Administration *versus* Standard Practice Influences Opioid Use: A Randomized Study FREE

Nada Sabourdin, M.D.; Jérôme Barrois, M.D.; Nicolas Louvet, M.D.; Agnès Rigouzzo, M.D.;

Objective Assessment of the Immediate Postoperative Analgesia Using Pupillary Reflex Measurement

A Prospective and Observational Study

Mourad Aissou, M.D.,* Aurelie Snauwaert, M.D.,† Claire Dupuis, M.D.,† Arthur Atchabahian, M.D.

CRITICAL CARE, TRAUMA, AND RESUSCITATION: BRIEF REPORT

The Relevance of Pupillometry for Evaluation of Analgesia Before Noxious Procedures in the Intensive Care Unit

Lukaszewicz, Anne-Claire MD, PhD; Dereu, Domitille MD; Gayat, Etienne MD, PhD; Payen, Didier MD, PhD

- like s-PLR requires afferent and efferent pathways are intact
- inter individual variability in pupil size and reactivity
- anesthetic and opioids that affect s-PLR may alter AP (NPi unaffected)
- AP requires equipments and consumables, unsuitable for low resource setti

Original Research Article

Pupillometry via smartphone for low-resource settings

Davide Piaggio [a], Georgy Namm [a], Paolo Melillo [b], Francesca Simonelli [b], Ernesto Iadanza [c],