TEMPERATURE CONTROL AFTER CARDIAC ARREST

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Allina Health

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OBJECTIVES

Upon completion of this lecture, participants should be able to:

Explain:

- Indications for temperature control
- Outcomes for survivors of cardiac arrest
- Side effects and practical implementation of temperature control
- Current understanding of temperature targets
- General prognostication process

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Terminology

- 2000s — Therapeutic Hypothermia
- 2010s — Targeted Temperature Management
- 2020s — **Temperature Control**

Normothermia or fever avoidance – maintain < 37.7 C

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Epidemiology

In the United States[1,2]:

- Cardiac arrest is responsible for 436,000 deaths per year
- Nearly 350,000 out-of-hospital arrests occur
- 290,000 in-hospital arrests occur in adults

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Epidemiology

Worldwide, survival for OHCA only 1 in 12 (8%)[1-4]

Slightly higher in the United States:
- 9-10% overall
- Significant variation by region
- Up to 20-27% range for VFib

1 in 4 survive to get to hospital in the US

In Hospital arrest:

1 in 4 survive to discharge

Up to 60-80% good neuro outcome in survivors who discharge

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Minnesota Statistics

Data from 2021[4]

- 21% shockable rhythm
- 37% bystander CPR
- Survival with good neurological outcome (CPC 1-2) was 9%

MN Performance Compared to CARES national registry (2017)[5]

- Generally less likely to receive bystander CPR (33% vs 39%)
- Better survival with good neuro outcome 12% vs 8%

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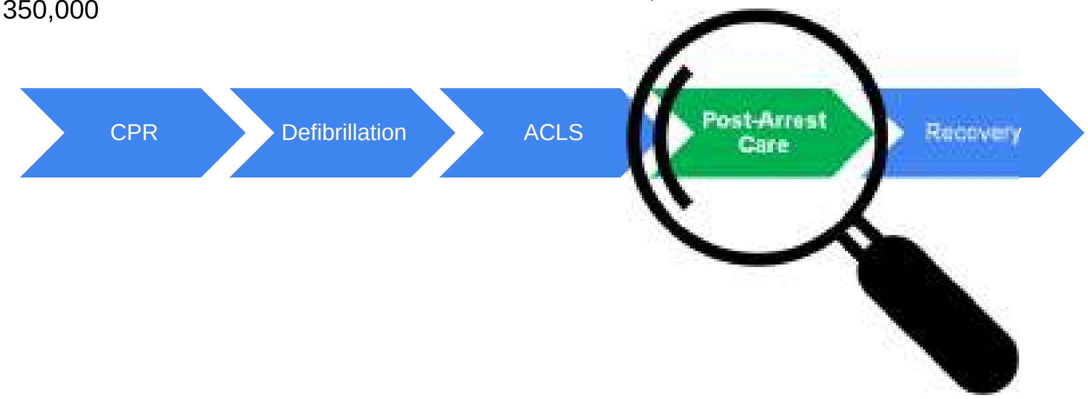
Post-Arrest Care

OHCA

350,000

1 in 4
Survive to
Hospital[6]



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Post-Arrest Care

OHCA

1 in 4
Survive to
Hospital

1 in 5
survive to
discharge

1 in 2
with good
neuro
outcome

IHCA

1 in 4
survive to
discharge

>1 in 2 with
good neuro
outcome

6, 7, 8

8

Outcomes from major trials

TTM2	45% survival with good neuro outcome
CAPITAL CHILL	51-55% survival with good neuro outcome
TTH48	65-69% good neuro outcome at 6 mo
TTM	46-48% good neuro outcome
HACA	45-61% good neuro outcome
Bernard	51-74% good neuro outcome

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OHCA Survivors

Of shockable arrest patients that survive to the hospital to receive good ICU care and temperature control:

~50% can achieve survival *with* good neurologic outcome

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What is a "good outcome" ?

Modified Rankin Scale (mRS)

0	No symptoms
1	No significant disability, able to carry out all usual activities
2	Slight disability. Able to manage on affairs without assistance
3	Moderate disability. Requires some help
4	Moderate to severe disability. Unable to manage own bodily needs without assistance
5	Severe disability. Requires constant nursing care
6	Dead

Cerebral Performance Scale (CPC)

CPC 1	Alert, able to work, might have mild neurologic or psychologic deficit
CPC 2	Moderate cerebral disability: independent in ADLs. Able to work with monitoring
CPC 3	Severe disability, dependent on others
CPC 4	Coma or vegetative state
CPC 5	Brain death

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Long-Term Outcomes

Patients discharged alive from the hospital:

- 2022 Systematic Review of 33 studies (nearly 17,000 patients)[8]
- Only 15% had poor cerebral performance score (CPC 3-4)
- Average survival was 5 years with 10 yr survival rates of 62%

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How does temperature management help?

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Hypoxia-Ischemia

- ↓ ATP, ↓ Glucose, Energy failure
- ↑ Intracellular calcium
- Programmed cell death (apoptosis)
- Endothelial dysfunction, capillary leak
- Cerebral edema, microthrombi
- ↑ Excitatory neurotransmitters (glutamate)
- Free radical formation, oxidative damage

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Induced Hypothermia

- ↓ Cerebral metabolism (7% per 1ºC)
- ↑ Cerebral vasoconstriction, ↓ permeability and edema, ↓ ICP
- Inhibits enzymes responsible for programmed cell death (caspase)
- ↓ Cytokine production
- ↓ Glutamate and ↓ intracellular calcium
- ↓ Free radical formation

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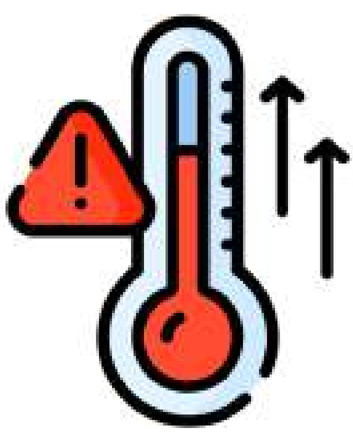
Fever Avoidance

Fever associated with worse outcomes after cardiac arrest[12,13,14]

Accelerates the mechanisms mentioned earlier (especially cerebral metabolic rate and energy demand)



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Post-Resuscitation Shock

Response to whole body ischemia-reperfusion[10]

- Myocardial dysfunction
- Cytokine release
- Vasodilation
- Capillary leak/third spacing
- Relative adrenal insufficiency?
- Bowel ischemia/translocation?

Sounds a lot like sepsis…

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Side Effects of Hypothermia

Cardiovascular - Rhythm

Primarily bradycardia, can cause PR or QRS prolongation

Problematic arrhythmia (VF)

- Rarely happens above 32C
- More common in accidental hypothermia <28C

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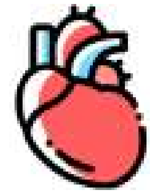
Side Effects of Hypothermia



Cardiovascular - Hemodynamics

↑ Peripheral vascular resistance

↓ Cardiac output (Although: ↓ myocardial oxygen demand)

Relative hypovolemia, diuresis + capillary leak

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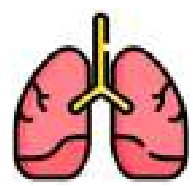
Side Effects of Hypothermia



Respiratory

↓ Metabolism, ↓ pCO_2, ↓ O_2 demand

Modest ↓ pO_2 and ↓ pCO_2 measurements for each 1ºC < 37

(usually corrected on modern blood gas analyzers)

Avoid hyperoxia – associated with worse outcomes

Generally, normalize CO_2, aim for SpO_2 94-98%

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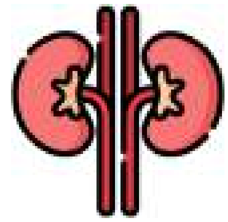
Side Effects of Hypothermia



Renal

↓ K (shifts potassium into cells)

- Replace to prevent arrhythmia
- Avoid over-replacement during rewarming
- Gradual rewarming helps prevent high K

↓ Mg and Phos

Cold Diuresis

- Vasoconstriction -> increased glomerular blood flow
- ↓ antidiuretic hormone (ADH)
- ↑ atrial natriuretic peptide (ANP)

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Side Effects of Hypothermia

Endocrine

↓ Insulin production by the pancreas

↑ Insulin resistance in peripheral tissues

Typically requires insulin infusion

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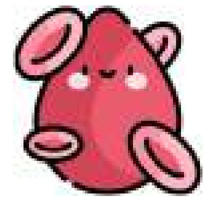
Side Effects of Hypothermia



Hematologic

↓ WBC count and function

(usually starts a bit high then decreases to normal)

↓ Platelet count and function

↑ Clotting time

Bleeding requiring transfusion is rare

No ↑ bleeding, sepsis, or pneumonia in major trials

Hypothermia has even been used in patients with ICH

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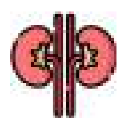
37 36 35 34 33 32 31 30

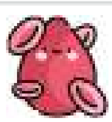
↓ Cardiac output
↓ HR
↑ Vasoconstriction



↑ UOP
↑ Electrolyte wasting
↑ Intracellular shifts
↓ Mg, Phos, K

↓ Insulin secretion
↓ Insulin resistance
↑ Glucose

↓ Hepatic Drug Metabolism



↓ Platelet aggregation

↑ Arrhythmias

↓ Immune function
↑ Infection

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Side Effects of Hypothermia

All the side effects are worse lower temperature

Much of the info extrapolated from experience with accidental hypothermia or deep hypothermia during circulatory arrest

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Temperature Management

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Cooling devices

Simple/available:

- Ice packs/fans
- Iced saline infusion - out of favor
- Standard cooling blanket

Feedback controlled devices:

(preferred per guidelines)

- Surface cooling adhesive pads
- Intravascular cooling catheter
- Intranasal device
- Helmet

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Shivering Threshold

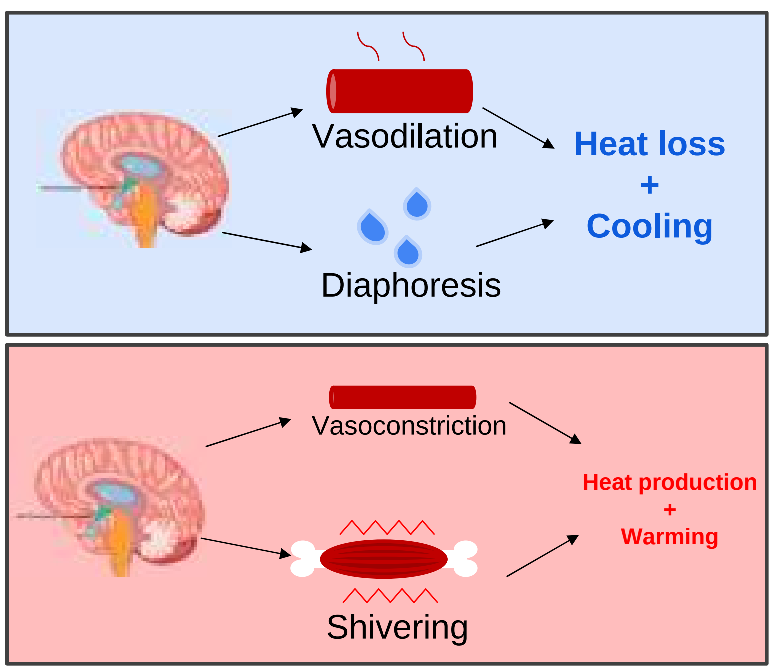
Strong response to difference between core temp and hypothalamus set temp

Heat loss: vasodilation and diaphoresis

Heat production: shivering

Heat retention: vasoconstriction

Strongest shiver response 35-36C and tends to subside by ↓34C



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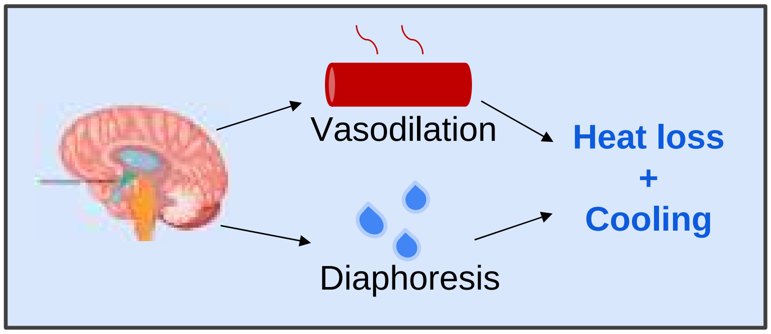

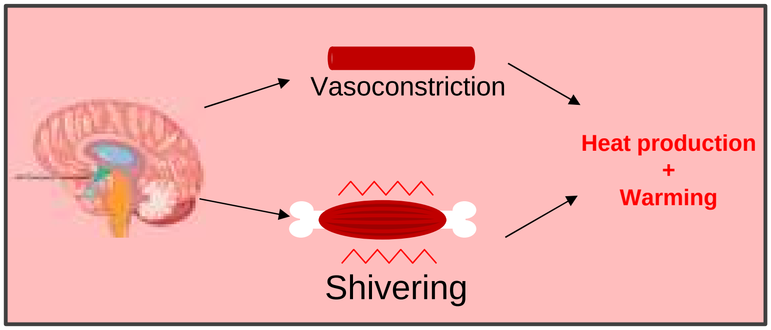

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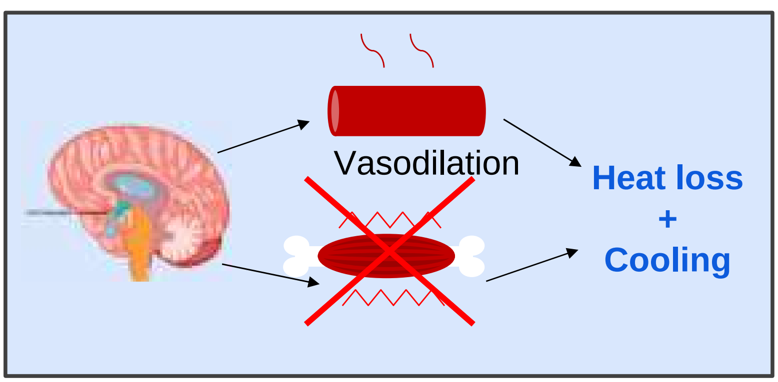
Shivering Threshold

Counterwarming

- Skin temperature contributes 20% to stimulus for shivering
- Wrap hands, face: ↑ concentration cutaneous temp sensors
- One group showed:
- ↑ shiver control + ↓ metabolic demand (=control of microshivering) by adding forced air warming blanket



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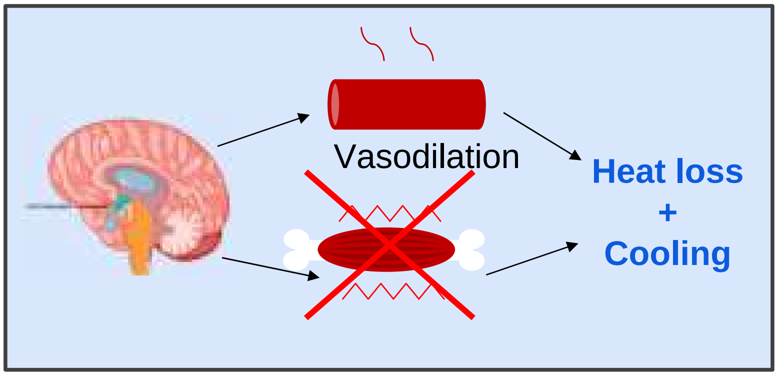
Shivering Threshold

Medications to ↓ shiver threshold

- Meperidine
- Buspirone
- Dexmedetomidine
- Magnesium
- Fentanyl
- Propofol



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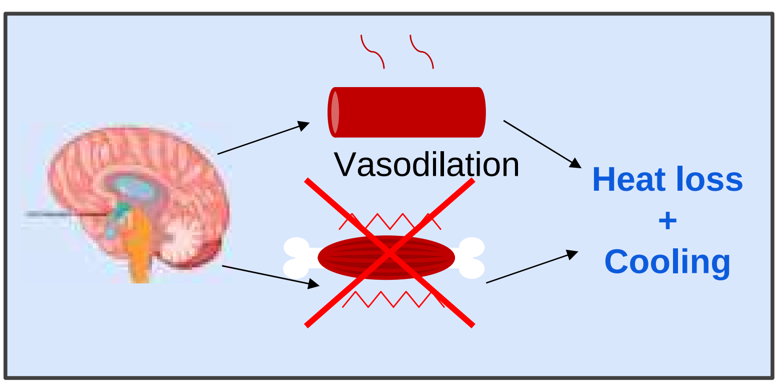
Shivering Threshold

Neuromuscular blockade

- Cisatracurium
- Rocuronium
- Vecuronium



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Criteria

Inclusion Criteria:

Guideline Recommended[2]:

Cardiac arrest regardless of location (In Hospital or Out of Hospital)

Shockable or non-shockable rhythm

Unresponsive/Comatose as defined by **not following commands**

- This was the definition used in the major trials

Exclusion Criteria:

Responsive (following commands or GCS >8)

Severe active bleeding, especially intracranial

Arrest due to trauma

Relative:

- >60 minutes from arrest to ROSC
- >12 hours since ROSC
- Unwitnessed arrest/unknown down time
- Terminal illness (life expectancy < 6 months)
- Recent surgery with unacceptable bleed risk (neuro or spine)

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Special populations

Thrombolysis or anticoagulation is not a contraindication

- TTM can be used after arrest due to PE

Pregnancy is not a strict contraindication

- Pregnant patients excluded from the major trials
- Temperature control used successfully in pregnant patients[15,16]
- Usually done in consultation with Maternal Fetal Medicine

Intracranial bleeding (ICH or SAH) not a strict contraindication[17,18]

- Normothermia already in use for neurogenic fever in the setting of ICH SAH, or acute ischemic stroke

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Current AHA Guideline Recommendations (Dec 2023)[2]

Key recommendations regarding temperature control

We recommend that all adults who do not follow commands after return of spontaneous circulation, regardless of arrest location or presenting rhythm, receive treatment that includes a deliberate strategy for temperature control

We recommend selecting and maintaining a constant temperature between 32°C and 37.5°C during post arrest temperature control

There is insufficient evidence to recommend a specific therapeutic temperature for different sub-groups of patients with cardiac arrest

Patients with spontaneous hypothermia after return of spontaneous circulation who do not follow commands should not be routinely actively or passively rewarmed faster than 0.5° C per hour

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Timing

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Rate of cooling

Faster rate of cooling (shorter time to target temp) is theoretically better

Intravascular device is faster than surface (7 hrs vs 10 hrs to reach 33C)

Difference in outcomes only found in animal studies,

No proven difference in humans[20,21]

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Timing of initiation

Some studies investigated pre-hospital initiation of hypothermia

- Iced saline infusion
- Intranasal device – can be placed during CPR

No improvement in survival or neurologic outcome

Iced saline led to ↓chance of ROSC and ↑pulmonary edema[26]

→ Pre-hospital cooling (especially with saline) not recommended

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Timing of initiation

May still be beneficial to initiate several hours after arrest[27]

Up to 8 hours to reach goal temp in major trials (for low temp 33C)

Potential logistical benefit of choosing higher goal temp 36 or 37.5?

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Duration of cooling

No identifiable difference in outcome 24 vs 48 hrs

Current trial ICECAP (Influence of Cooling duration on Efficacy in Cardiac Arrest Patients) examining 12 vs 24 vs 48 hrs

Most current recommendations are:

- ≥24 hrs if 33-36 is chosen
- Then followed active fever prevention to < 37.7 for 72 hrs after rewarming
- OR if 37.5 is chosen, maintain 72 hrs of < 37.7 following ROSC

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Historical perspective

Hypothermia After Cardiac Arrest (HACA)

- 32 vs 34 C
- Witnessed VT or VF OOHCA
- Within 4 hrs ROSC
- 24 hrs cooling

- 55% vs 39% favorable neuro
- 41% vs 55% mortality

Bernard, et al

- 33C v normothermia

- Within 2 hrs ROSC
- 12 hrs cooling

- 49% vs 26% survival w good neuro

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Historical perspective

2002

HACA
- Shockable OHCA
- 33 vs 37
- Survival and Neuro outcome

Bernard et al
- Vfib OHCA
- 33 vs 37
- Survival and Neuro outcome

- Small sample size
- Fever in non TH group
- Unblinded

- Very few non shockable

2010

TTM
- Presumed Cardiac OHCA
- 33 vs 36
- No difference

2013

HYPERION
- IHCA and OHCA
- Non-shockable
- 33 vs 37
- No survival benefit
- Improved neuro

- Does include IHCA
- Best non-shockable data

2014

Kim et al
- OHCA VF or Non-shockable
- Pre hospital cooling v std care
- No difference

2017

Kirkegaard
- Witnessed OHCA
- Presumed cardiac
- 33 for 24 vs 48 hrs
- No difference

2018

FROST-I
- Witnessed OHCA
- Presumed cardiac
- 32 v 33 v 34
- No neuro difference

2021

TTM2
- OHCA presumed cardiac cause
- 33 vs 37.5
- No survival benefit
- No improved neuro

- >90% witness
- 80% bystander CPR
- Time to CPR 1 min
- Mostly shockable
- No IHCA

- **Active cooling and NMB were needed for many 37.5 pts**

2023

AHA Guideline Update:

32-37.5

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Doing nothing is not the answer

- After TTM trial there was a shift in goal temperature in ICUs
- More lenient temperature control and increase in early fever
- Seemingly more difficult to maintain goal 36 than 33
- **Associated with worse survival and neurologic outcomes**[28,29,30]

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Some major remaining questions

- Is just <u>normo</u>thermia/fever prevention enough?
- Do different patients benefit from different temperatures?
  - In Hospital vs Out of Hospital
  - Shockable vs Non-shockable
  - Long vs short time to ROSC
- Is ultra fast cooling beneficial?
- How long to cool?

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Neuroprognostication

- Standardized method should be used
- No single test accurate enough on its own to predict outcome
- Strong recommendation: wait 72 hrs after ROSC or rewarming
- Sedation clearance prolonged with hypothermia, shock liver, AKI. Needs time to clear
- EEG is helpful

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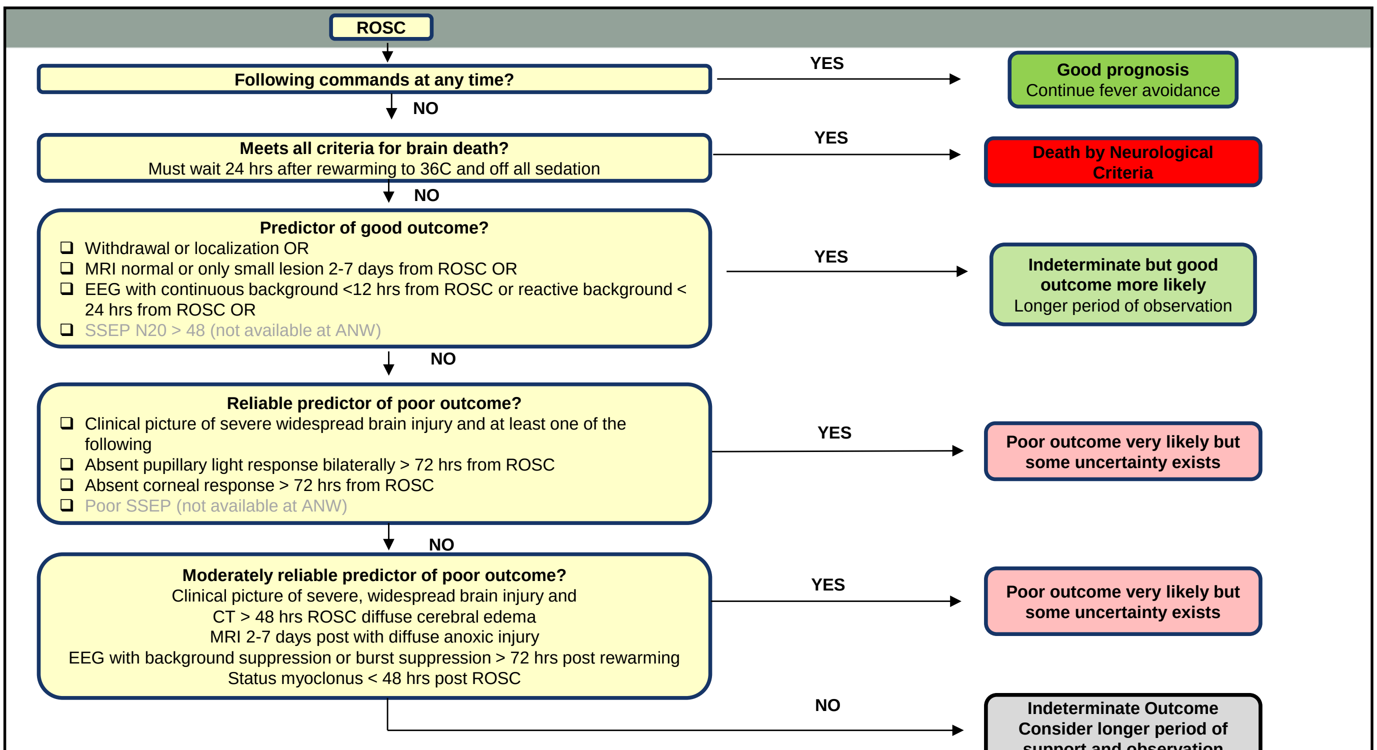

*Adapted from Guidelines for Neuroprognostication by NCS and from the ERC-ESICM algorithm

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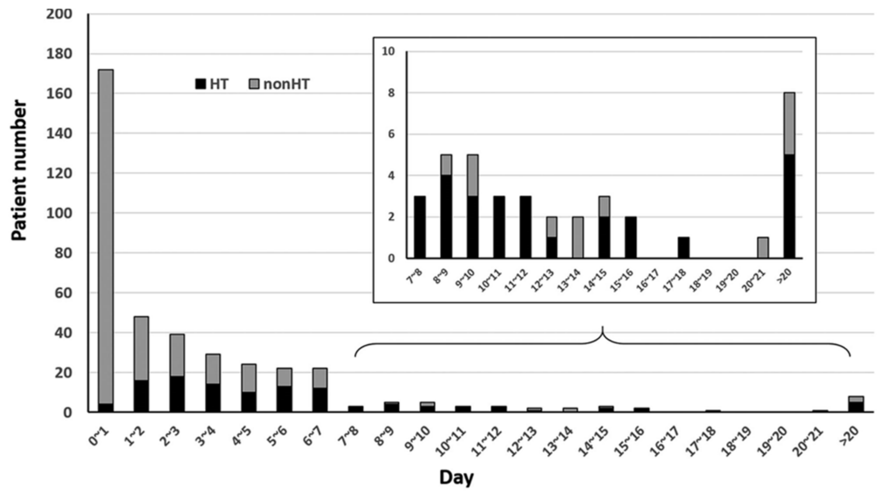
Time Until Awakening

- 80% who had good outcome awakened by 7 days[9]
- Some required 20+ days
- 38% of pts in the TTM trial awakened after 5 days[19]



	0~1	1~2	2~3	3~4	4~5	5~6	6~7	7~8	8~9	9~10	10~11
Total(N=395)	173	48	39	29	24	22	22	3	5	5	3
HT(N=144)	4	16	18	14	10	13	12	3	4	3	3
nonHT(N=281)	169	32	21	15	14	9	10	0	1	2	0

	11~12	12~13	13~14	14~15	15~16	16~17	17~18	18~19	19~20	20~21	>20
Total(N=395)	3	2	2	3	2	0	1	0	0	1	8
HT(N=144)	3	1	0	2	2	0	1	0	0	0	5
nonHT(N=281)	0	1	2	1	0	0	0	0	0	1	3

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Post discharge improvement

- Neurological improvement can continue for 6 months post discharge[23]
- Half of patients improved mRS by 1-3 points
- 20% improved from a poor to a good score

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Key Points/Takeaways

- Ideal target temperature not yet determined but standardized strategy recommended
- If a hypothermia method is not chosen, fever avoidance still critical
- Temp control recommended for all adult cardiac arrest pts with ROSC regardless of initial rhythm or location of arrest
- If patient presents below goal temp do not warm actively to goal unless <32C
- Neuroprognostication should be standardized and wait for 72 hrs post ROSC or rewarming
- Neuro improvement can happen after discharge up to 6 months

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BIBLIOGRAPHY/LECTURE REFERENCES

1. American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics-2023 Update: A Report From the American Heart Association. *Circulation*. 2023 Feb 21;147(8):e93-e621. Epub 2023 Jan 25.

2. Sarah M. Perman, et al. 2023 American Heart Association Focused Update on Adult Advanced Cardiovascular Life Support: An Update to the American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*. 2024;149:e254–e273

3. Girotra S, Nallamothu BK, Spertus JA, Li Y, Krumholz HM, Chan PS; American Heart Association Get with the Guidelines–Resuscitation Investigators. Trends in survival after in-hospital cardiac arrest. *N Engl J Med*. 2012 Nov 15;367(20):1912-20

4. Gaisendrees C. The Minnesota first-responder AED project: Aiming to increase survival in out-of-hospital cardiac arrest. *Resusc Plus*. 2023 Aug 2;15:100437. doi: 10.1016/j.resplu.2023.100437

5. Adabag S. Outcomes of sudden cardiac arrest in a state-wide integrated resuscitation program: Results from the Minnesota Resuscitation Consortium. *Resuscitation*. 2017 Jan;110:95-100. doi: 10.1016/j.resuscitation.2016.10.029. Epub 2016 Nov 16

6. Chan PS, McNally B, Tang F, Kellermann A; CARES Surveillance Group. Recent trends in survival from out-of-hospital cardiac arrest in the United States. *Circulation*. 2014 Nov 18;130(21):1876-82

7. Niemann, James T. MD. Is There Life After Hospital Discharge for Resuscitated Cardiac Arrest Patients?*. *Critical Care Medicine* 41(5):p 1372-1373, May 2013.

8. Amacher SA, Bohren C, Blatter R, et al. Long-term Survival After Out-of-Hospital Cardiac Arrest: A Systematic Review and Meta-analysis. *JAMA Cardiol.* 2022;7(6):633–643

9. Tsai MS, Chen WJ, Chen WT, Tien YT, Chang WT, Ong HN, Huang CH. Should We Prolong the Observation Period for Neurological Recovery After Cardiac Arrest? *Crit Care Med*. 2022 Mar 1;50(3):389-397.

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BIBLIOGRAPHY/LECTURE REFERENCES

10. Jozwiak M, Bougouin W, Geri G, Grimaldi D, Cariou A. Post-resuscitation shock: recent advances in pathophysiology and treatment. *Ann Intensive Care*. 2020 Dec 14;10(1):170

11. Roberts BW, Kilgannon JH, Hunter BR, Puskarich MA, Pierce L, Donnino M, Leary M, Kline JA, Jones AE, Shapiro NI, Abella BS, Trzeciak S. Association Between Early Hyperoxia Exposure After Resuscitation From Cardiac Arrest and Neurological Disability: Prospective Multicenter Protocol-Directed Cohort Study. *Circulation*. 2018 May 15;137(20):2114-2124

12. Zeiner A, Holzer M, Sterz F, Schörkhuber W, Eisenburger P, Havel C, et al. Hyperthermia after cardiac arrest is associated with an unfavorable neurologic outcome. *Arch Intern Med*. 2001;161:2007–12.

13. Leary M, Grossestreuer AV, Iannacone S, Gonzalez M, Shofer FS, Povey C, et al. Pyrexia and neurologic outcomes after therapeutic hypothermia for cardiac arrest. *Resuscitation*. 2013;84:1056–61.

14. Bro-Jeppesen J, Hassager C, Wanscher M, Søholm H, Thomsen JH, Lippert FK, et al. Post-hypothermia fever is associated with increased mortality after out-of-hospital cardiac arrest. *Resuscitation*. 2013;84:1734–40.

15. Hogg JP 3rd, Temming LA, Pollack R. Therapeutic hypothermia and cardiac intervention after cardiac arrest in pregnancy with underlying maternal arrhythmia: A case report. *Case Rep Womens Health*. 2020 Oct 6;28:e00259

16. Oguayo KN, et al. Successful Use of Therapeutic Hypothermia in a Pregnant Patient. *Tex Heart Inst J*. 2015 Aug 1;42(4):367-71

17. Fischer M, et al. Targeted Temperature Management in Spontaneous Intracerebral Hemorrhage: A Systematic Review. *Curr Drug Targets*. 2017;18(12):1430-1440

18. Lavinio A, et al. Targeted temperature management in patients with intracerebral haemorrhage, subarachnoid haemorrhage, or acute ischaemic stroke: updated consensus guideline recommendations by the Neuroprotective Therapy Consensus Review (NTCR) group. *Br J Anaesth*. 2023 Aug;131(2):294-301.

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BIBLIOGRAPHY/LECTURE REFERENCES

19. Lybeck A, Cronberg T, Aneman A, Hassager C, Horn J, Hovdenes J, Kjærgaard J, Kuiper M, Wanscher M, Stammet P, Wise MP, Nielsen N, Ullén S, Friberg H; TTM-trial investigators. Time to awakening after cardiac arrest and the association with target temperature management. Resuscitation. 2018 May;126:166-171. doi: 10.1016/j.resuscitation.2018.01.027. PMID: 29371115.

20. Kazutoshi K, Safar P, Radovsky A, Tisherman SA, Stezoski SW, Alexander H: Delay in cooling negates the beneficial effect of mild resuscitative cerebral hypothermia after cardiac arrest in dogs: a prospective, randomized study. *Crit Care Med* 1993, 21: 1348-1358

21. Noguchi K, Matsumoto N, Shiozaki T, Tasaki O, Ogura H, Kuwagata Y, Sugimoto H, Seiyama A: Effects of timing and duration of hypothermia on survival in an experimental gerbil model of global ischemia. *Resuscitation* 2011, 82: 481-486.

22. Rajajee, V., Muehlschlegel, S., Wartenberg, K.E. *et al.* Guidelines for Neuroprognostication in Comatose Adult Survivors of Cardiac Arrest. *Neurocrit Care* 38, 533–563 (2023).

23. Tong JT, Eyngorn I, Mlynash M, Albers GW, Hirsch KG. Functional Neurologic Outcomes Change Over the First 6 Months After Cardiac Arrest. Crit Care Med. 2016 Dec;44(12):e1202-e1207

24. Bradley SM, Liu W, McNally B, et al. Temporal Trends in the Use of Therapeutic Hypothermia for Out-of-Hospital Cardiac Arrest. *JAMA Netw Open.* 2018;1(7):e184511.

25. Janet E. Bray, Dion Stub, Jason E. Bloom, Louise Segan, Biswadev Mitra, Karen Smith, Judith Finn, Stephen Bernard, Changing target temperature from 33°C to 36°C in the ICU management of out-of-hospital cardiac arrest: A before and after study,Resuscitation, Volume 113, 2017, Pages 39-43

26. Bernard SA, Smith K, Finn J, Hein C, Grantham H, Bray JE, Deasy C, Stephenson M, Williams TA, Straney LD, Brink D, Larsen R, Cotton C, Cameron P. Induction of Therapeutic Hypothermia During Out-of-Hospital Cardiac Arrest Using a Rapid Infusion of Cold Saline: The RINSE Trial (Rapid Infusion of Cold Normal Saline). Circulation. 2016 Sep 13;134(11):797-805. doi: 10.1161/CIRCULATIONAHA.116.021989. Epub 2016 Aug 25. PMID: 27562972.

27. Laptook AR, Shankaran S, Tyson JE, et al. Effect of Therapeutic Hypothermia Initiated After 6 Hours of Age on Death or Disability Among Newborns With Hypoxic-Ischemic Encephalopathy: A Randomized Clinical Trial. *JAMA.* 2017;318(16):1550–1560.

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BIBLIOGRAPHY/LECTURE REFERENCES

28. Bradley SM, Liu W, McNally B, et al. Temporal Trends in the Use of Therapeutic Hypothermia for Out-of-Hospital Cardiac Arrest. *JAMA Netw Open.* 2018;1(7):e184511.

29. Nolan JP, Orzechowska I, Harrison DA, Soar J, Perkins GD, Shankar-Hari M. Changes in temperature management and outcome after out-of-hospital cardiac arrest in United Kingdom intensive care units following publication of the targeted temperature management trial. Resuscitation. 2021 May;162:304-311. doi: 10.1016/j.resuscitation.2021.03.027. Epub 2021 Apr 2. PMID: 33819502.

30. Bray JE, Stub D, Bloom JE, Segan L, Mitra B, Smith K, Finn J, Bernard S. Changing target temperature from 33°C to 36°C in the ICU management of out-of-hospital cardiac arrest: A before and after study. Resuscitation. 2017 Apr;113:39-43. doi: 10.1016/j.resuscitation.2017.01.016. Epub 2017 Jan 31. PMID: 28159575.

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