

# **Targeted Temperature Management in Post Cardiac Arrest Patients**

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**Continuing Education Presentation  
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## Objectives

- Explain the rationale behind the process of post cardiac arrest Targeted Temperature Management (TTM)
- Explain the evidence-based recommendations for the use of medications during the TTM process
- List the major side effects of each medication recommended for use in post cardiac arrest TTM





# Post Cardiac Arrest Care

## American Heart Association:

- All comatose adult patients who attain return of spontaneous circulation (ROSC) undergo targeted temperature management (TTM)
- Cerebral perfusion scores significantly improved in patients who underwent TTM





# Post Cardiac Arrest Care

## 2015 Recommendations- Highlights

- Comatose adult patients with ROSC after out-of-hospital ventricular fibrillation (*VF*) or ventricular tachycardia (*VT*) cardiac arrest should be cooled to 32°C to 36°C
  - Class I, (LOE B-R)
  
- Comatose adult patients with ROSC after out-of-hospital *with non VF/VT (non shockable)* cardiac arrest or in hospital cardiac arrest should be cooled to 32°C to 36°C
  - Class I, (LOE C-EO)

LOE= Level of evidence

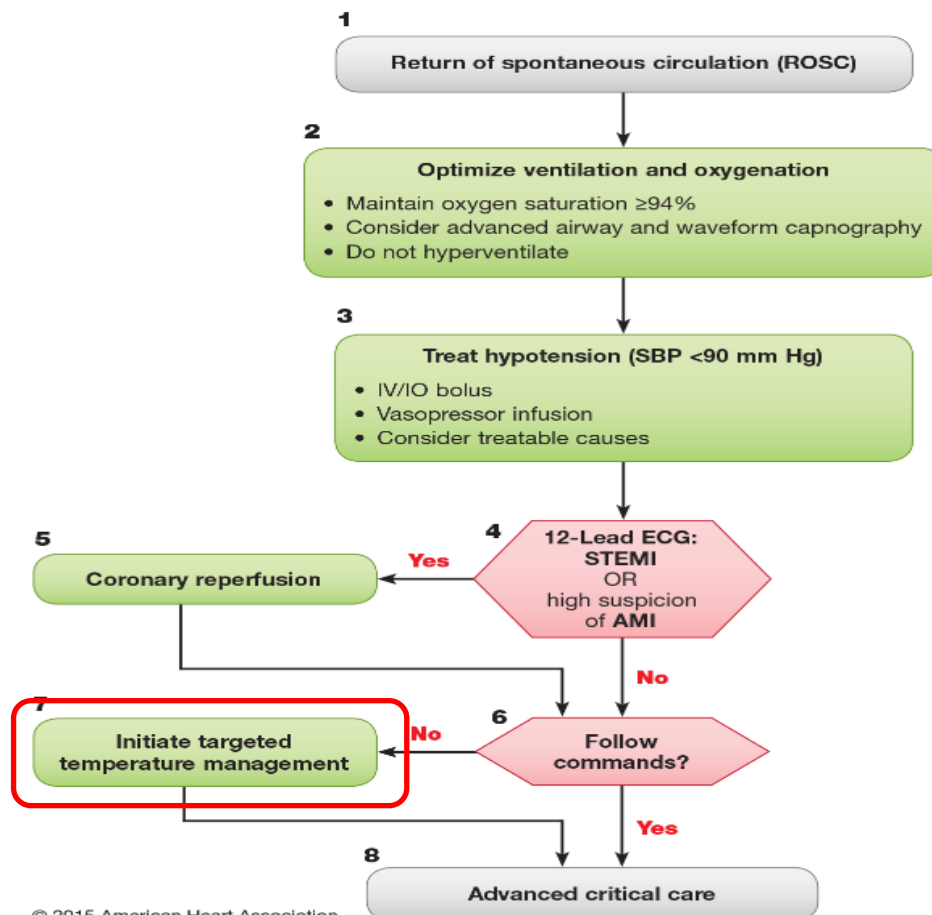
R= based on randomized studies

EO= based on consensus of expert opinions



# Overview

## Adult Immediate Post-Cardiac Arrest Care Algorithm—2015 Update



### Doses/Details

**Ventilation/oxygenation:**  
Avoid excessive ventilation. Start at 10 breaths/min and titrate to target PETCO<sub>2</sub> of 35-40 mm Hg. When feasible, titrate FIO<sub>2</sub> to minimum necessary to achieve SpO<sub>2</sub> ≥94%.

**IV bolus:**  
Approximately 1-2 L normal saline or lactated Ringer's

**Epinephrine IV infusion:**  
0.1-0.5 mcg/kg per minute (in 70-kg adult: 7-35 mcg per minute)

**Dopamine IV infusion:**  
5-10 mcg/kg per minute

**Norepinephrine IV infusion:**  
0.1-0.5 mcg/kg per minute (in 70-kg adult: 7-35 mcg per minute)

### Reversible Causes

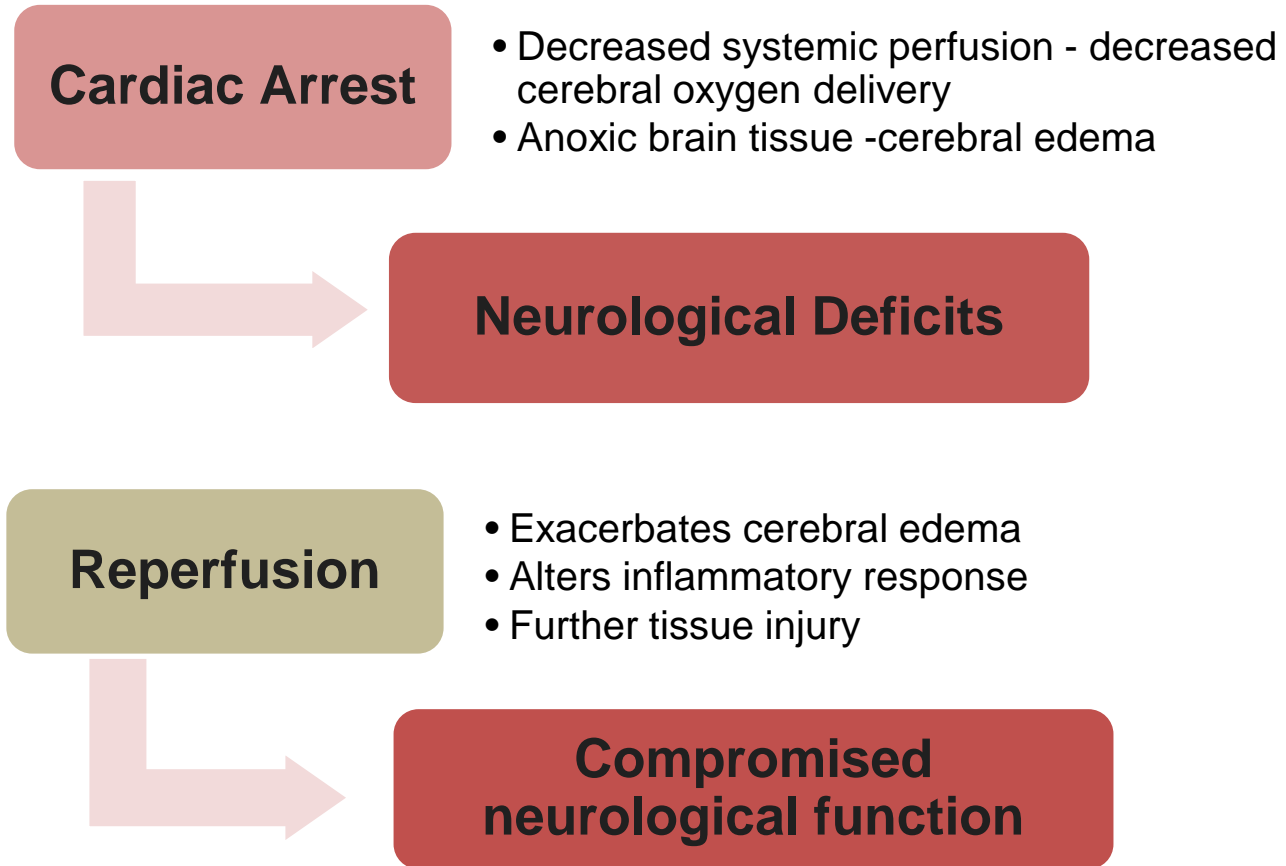
- Hypovolemia
- Hypoxia
- Hydrogen ion (acidosis)
- Hypo-/hyperkalemia
- Hypothermia
- Tension pneumothorax
- Tamponade, cardiac
- Toxins
- Thrombosis, pulmonary
- Thrombosis, coronary

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# Post Cardiac Arrest Care





# Targeted Temperature Management (TTM)

**Targeted temperature management** previously known as *therapeutic hypothermia*

- Active treatment to achieve and maintain a specific temperature (between 32°C and 36°C)
- Goal to preserve neurological function



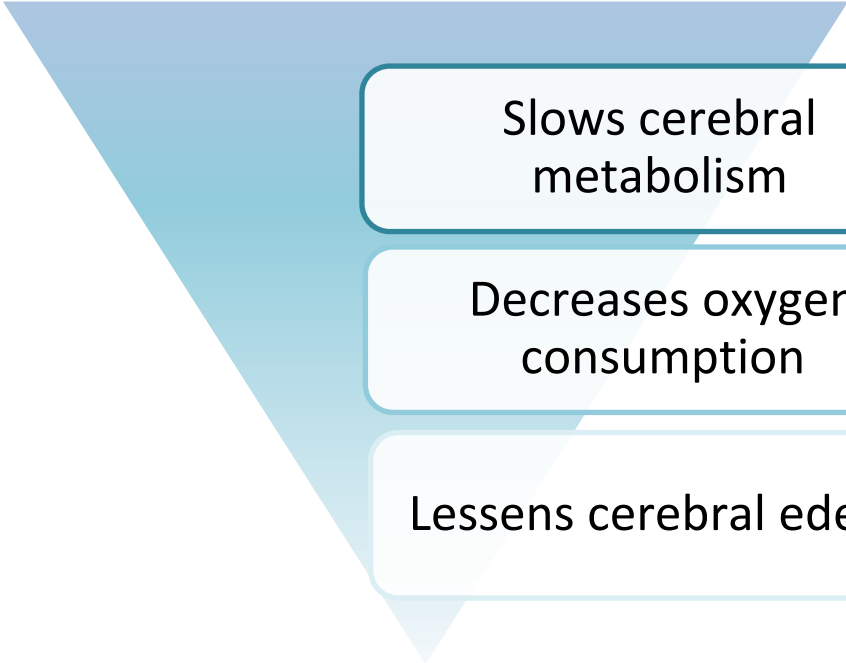
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# Mechanism of TTM

## Targeted Temperature Management



Slows cerebral metabolism

Decreases oxygen consumption

Lessens cerebral edema







## Landmark Trials

- Improved neurological outcomes and mortality in comatose patients with out-of-hospital cardiac arrest

Trial	Design	Outcome	Summary
Bernard S et al 2002	n=77; RCT, un-blinded trial	Survival to discharge with good neurological outcome 49% vs 26% (p=0.046, NNT=4)	Improved the incidence of favorable discharge disposition
Holzer M et al (HACA Trial) 2002	n=136; RCT, multicenter	Favorable neurologic outcome within 6 months 55% vs. 39% (RR 1.40; 95% CI 1.08-1.81; p=0.009)	Therapeutic mild hypothermia increased rate of favorable outcome.

RCT=Randomized Controlled Trial

NNT=Number needed to treat

CI=Confidence Interval

RR=Relative Risk

- 9 Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. N Engl J Med. 2002;346:557-63..  
Holzer M, et al. "Mild Therapeutic Hypothermia to Improve the Neurologic Outcome After Cardiac Arrest". The New England Journal of Medicine. 2002. 346(8):549-556.



## Landmark Trials

Nielsen N et al (*TTM trial*) 2013

- TTM at 33°C vs 36°C for 24 hours

Outcome	33°C Group	36°C Group	Hazard Ratio or Risk Ratio (95% CI)*	P Value
	no./total no. (%)			
Primary outcome: deaths at end of trial	235/473 (50)	225/466 (48)	1.06 (0.89–1.28)	0.51
Secondary outcomes				
Neurologic function at follow-up†				
CPC of 3–5	251/469 (54)	242/464 (52)	1.02 (0.88–1.16)	0.78
Modified Rankin scale score of 4–6	245/469 (52)	239/464 (52)	1.01 (0.89–1.14)	0.87
Deaths at 180 days	226/473 (48)	220/466 (47)	1.01 (0.87–1.15)	0.92

- Cooling to 33°C vs 36°C did not provide any additional benefit





# Landmark Trials

## Common misconception

- *'TTM trial showed no benefit with TTM'*

## TTM trial

- Both groups received active cooling
- Comparison between two target temperatures (33°C vs 36°C)
- High bystander CPR (shorter “no flow” time)





## Pop Quiz!

- ❖ Patients undergoing targeted temperature management post cardiac arrest are recommended to be cooled to:
  - a. 30°C
  - b. 32°C - 36°C
  - c. 25°C - 30°C
  - d. All of the above
  - e. None of the above



## Pop Quiz!

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  - a. 30°C
  - b. 32°C - 36°C**
  - c. 25°C - 30°C
  - d. All of the above
  - e. None of the above





# Ideal Temperature Target

Nielsen et al

- 33°C vs 36°C offered no additional benefit
  - Did not show any additional adverse effects when cooled to 33°C
    - Any adverse events (93% vs 90%;  $p=0.86$ )
  - No clinical or statistically significant differences in patient outcomes
- ***Due to lack of significant data, either temperature goal (33°C or 36°C) seem reasonable.***
- ***Patient specific temperature targets***





## Initiation of TTM: Optimal time

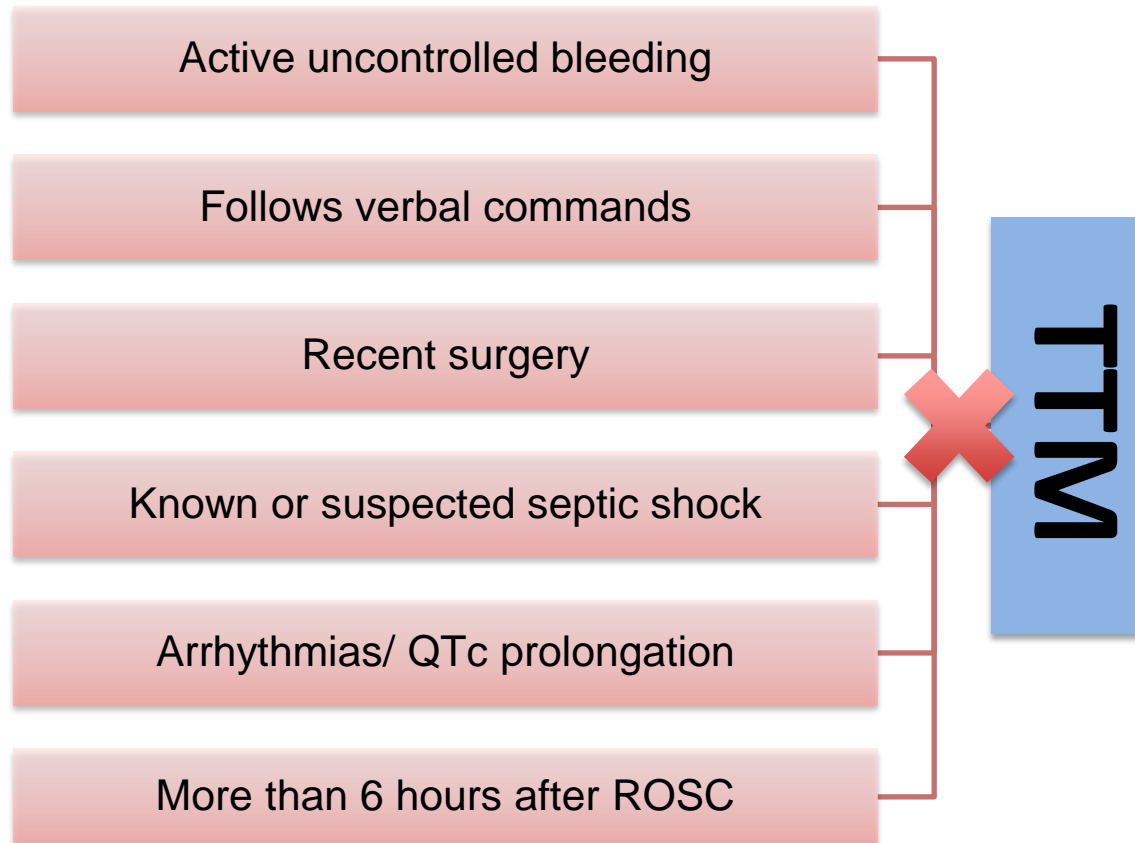
Trial	Design	Outcome	Summary
Mooney et al 2011	n=140; case review, multicenter	Survival to elapsed time from ROSC to initiation of cooling <i>Relative hazard estimate: 1.20 (95% CI 1.04-1.39)</i>	For every hour delay in cooling risk of death increases by 20%

- ***TTM is a medical emergency!***



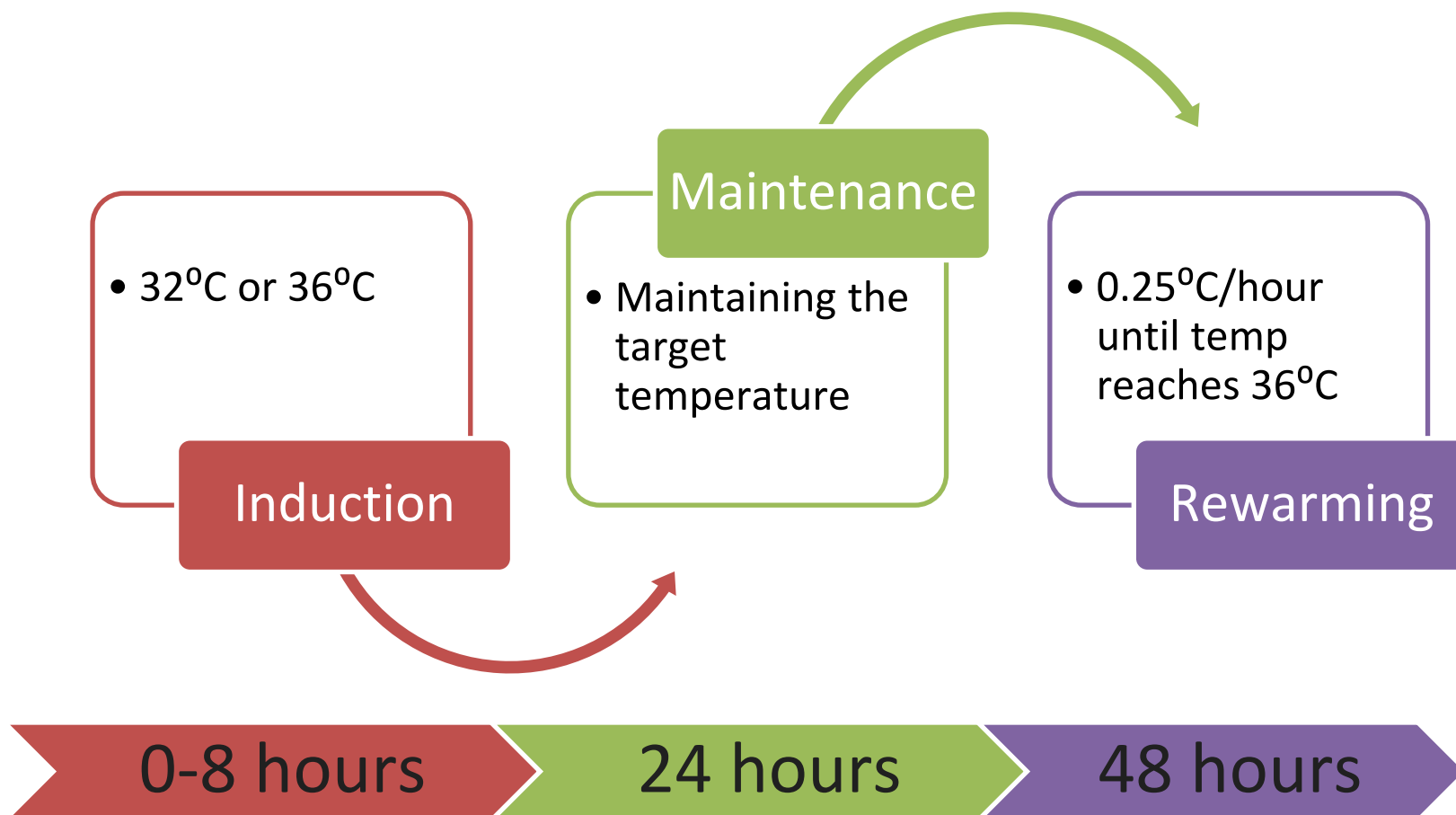


## Relative Contraindications of TTM





## Temperature Management Overview





## Pop Quiz!

- ❖ Targeted temperature is achieved by which of the following ways
  - a. Cooling blanket
  - b. Infusing cold 0.9% sodium chloride
  - c. Keeping the patient in a refrigerator
  - d. A & B
  - e. All of the above





## Pop Quiz!

- ❖ Targeted temperature is achieved by which of the following ways
  - a. Cooling blanket
  - b. Infusing cold 0.9% sodium chloride
  - c. Keeping the patient in a refrigerator
  - d. **A & B**
  - e. All of the above





# Methods to Institute TTM

## Conventional cooling techniques

- Cold saline, crushed ice or ice bags

## Surface cooling systems

- Moving cold fluid or cold air through blanket of pads wrapped around the patient.
- Cooling blankets and surface pads

## Intravascular cooling systems

- Circulating cool or warm saline in a closed loop through a catheter's balloon
- Catheter balloons: Femoral, jugular, subclavian

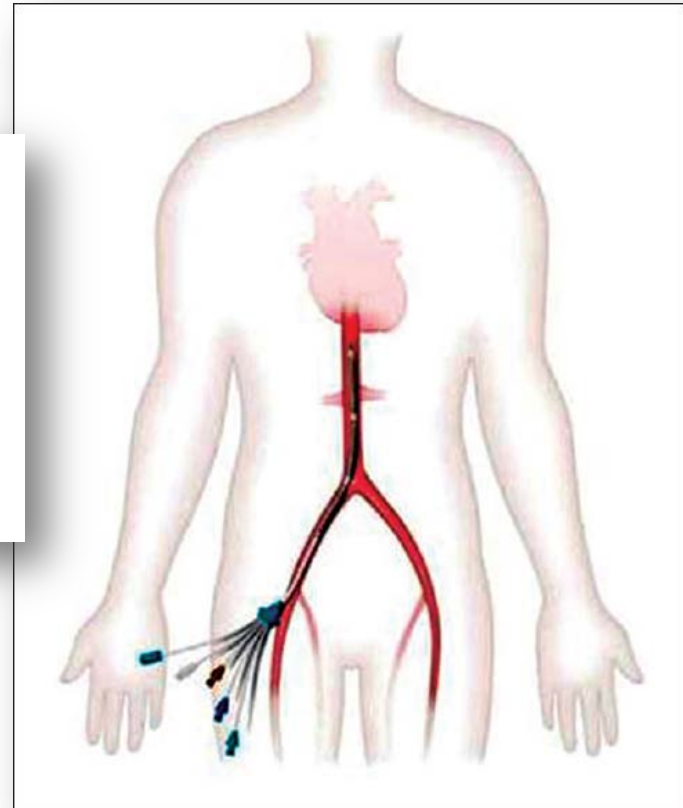


# Methods to Institute TTM

## Surface vs Intravascular cooling



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## Methods to Institute TTM

Gillies M et al.

- *Objective:* Surface vs Endovascular cooling
- *Study design:* Retrospective cohort study, n= 83
- *Outcomes:*
  - Less temperature variation in endovascular group
    - Between 10 hour and 20 hour of cooling (1.0 vs 1.7; p=0.003)
  - No difference in outcomes:
    - Hospital mortality (54.2% vs 50.0%; p=0.51)
    - Poor neurological outcomes (59% vs 57.1%; p=0.82)



# Induction Phase



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# Induction Phase

## Hemodynamic Stability

- No specific MAP or SBP targets
  - Published protocols recommend to maintain MAP at 65 mmHg or SBP above 80 mmHg
  - SBP <80 mmHg
    - Norepinephrine
      - 0.1–0.5 mcg/kg/min (In a 70 kg adult, 7–35 mcg/min)
  - Symptomatic Bradycardia
    - Dopamine
      - 5–10 mcg/kg/min
    - May tolerate HR 30-40 bpm!!!
    - Overstimulation of heart rate can decrease myocardial contractility

SBP: Systolic blood pressure

MAP: Mean arterial pressure







# Induction Phase

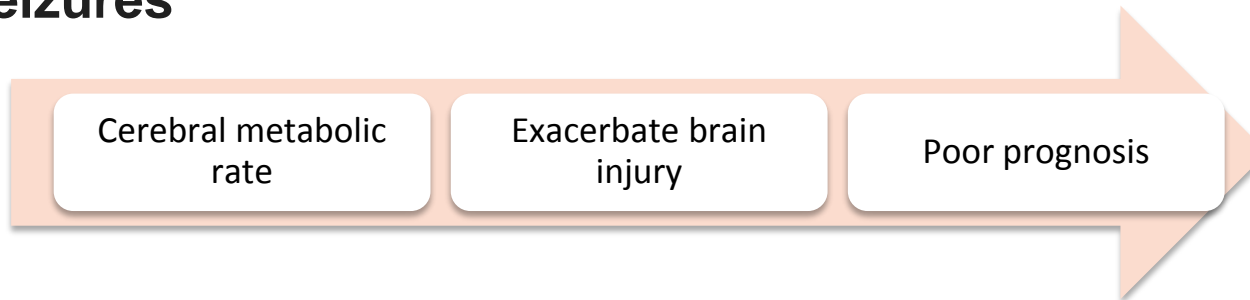
## Goals

- Monitor for seizures
- Optimize analgosedation
- Minimize metabolic demand
  - Paralytics
  - Shivering prevention



# Induction Phase

## Seizures



- Common, occurs in one-third of the patients post cardiac arrest
- Routine seizure prophylaxis in post cardiac arrest patients
  - Not recommended
  - Increased risk of side effects
- *Monitoring may include continuous/intermittent Electroencephalography(EEG) or Bispectral Index (BIS)*





# Sedation and Analgesia

Animal studies have shown:

- Inadequate sedation leads to partial or complete loss of protective effects of TTM

Goals:

- Optimize analgosedation
  - Prior to initiation of pharmacologic paralytic
- Minimize doses of sedatives and analgesia
  - Hypothermia reduces clearance
- Select agents with short half-life
  - Enables early prognostication





# Sedation and Analgesia

## Fentanyl IV

- Opioid analgesic; provides sedation and analgesia
- 100 x potent than morphine, fast onset of action (0-2 seconds)
- Metabolized by liver; decrease in hepatic blood flow
- Adverse effects
  - Respiratory depression
  - Chest wall rigidity with bolus administration
  - Ileus

## Fritz H et al & Zhou et al

- Hypothermia decreases systemic clearance





# Sedation and Analgesia

## Propofol

- Sedative
- Fast onset (10 seconds) and offset of action (3-10 minutes)
- Decreases
  - Cerebral metabolic oxygen demand
  - Shivering threshold
- Adverse effects: Hypotension, bradycardia, propofol infusion syndrome, hypertriglyceridemia

## Zhou et al

- Clearance of propofol decreased by 25% compared to normothermia conditions
  - 0.59 (95% CI: 0.24–1.38) L/min vs 0.79 (0.58–1.08) L/min



# Sedation and Analgesia

## Midazolam

- Benzodiazepine; provides sedation and amnesia
  - Sedative impact on brain provides shiver control
  - Onset of action (15 minutes); duration of action (<2 hours)
  - Active metabolite: 1-hydroxymidazolam
- Adverse effects: Respiratory depression, bradypnea
- Accumulation of active metabolite in renal impairment; prolonged sedation





## Pop Quiz!

- ❖ A 50 year old post cardiac arrest patient is ordered cisatracurium while being started on external cooling pads to attain a temperature of 33°C. What sedative would you recommend in this hemodynamically stable patient based on pharmacokinetic data available in patients undergoing TTM?
  - a. Propofol
  - b. Pentobarbital
  - c. Dexmedetomidine
  - d. Midazolam
  - e. None of the above





## Pop Quiz!

- ❖ A 50 year old post cardiac arrest patient is ordered cisatracurium while being started on external cooling pads to attain a temperature of 33°C. What sedative would you recommend in this hemodynamically stable patient based on pharmacokinetic data available in patients undergoing TTM?
  - a. **Propofol**
  - b. Pentobarbital
  - c. Dexmedetomidine
  - d. Midazolam
  - e. None of the above







## Neuromuscular blockers (NMB)

- Achieve target temperature quicker
- Quickest method to cease shivering
  - Useful in hemodynamically unstable patients

### Caveats to Use

- Train-of-four (TOF) unreliable
  - Decreased peripheral nerve conduction
- Mask seizures
  - Continuous EEG monitoring is recommended





## Neuromuscular blockers (NMB)

2016 Critical care guideline recommendations:

- No recommendation for routine use in TTM
- Suggest NMBs can be used to manage overt shivering during TTM

Task force good practice statement:

- Assessment of degree of blockade
  - Peripheral nerve stimulation + clinical assessment (ventilator triggering, degree of shivering)
- Protocol guided NMB use in patients undergoing therapeutic hypothermia
- Adequate analgesia and sedation prior to and during neuromuscular blockade.





## Neuromuscular blockers (NMB)

- Saliccioli et al
  - *Objective:* Continuous NMB for 24 hours and outcomes in OHCA
  - *Study design:* n=111, A post hoc analysis, prospective observation study
  - *Outcomes:*
    - Increase in crude survival rate with continuous NMB use
      - 78% vs 41%;  $p = 0.004$
    - Post multivariate adjustment
      - OR: 7.23, 95% CI: 1.56-33.38
    - Showed improved lactate clearance

OR: Odds ratio

CI: Confidence interval

OHCA: Out of hospital cardiac arrest





## Neuromuscular blockers (NMB)

- Lascarrou et al.
  - *Objective:* Effect of NMB on neurological outcomes and incidence of pneumonia
  - *Study design:* Observational retrospective study, n= 144
  - *Outcomes:*
    - No statistically significant difference in neurological outcomes after 3 months in NMB group
      - 42% vs. 36%,  $p = 0.26$
    - Early-onset pneumonia higher in NMB group
      - 64% vs. 33%;  $p = 0.005$ ; *after adjustment for propensity scores; no difference*





# Neuromuscular blockers (NMB)

## Cisatracurium

- Neuromuscular blocker; given only after sedation
- Eliminated through urine
  - Accumulation with renal impairment

### Adverse effects:

- May mask insufficient sedation and/or seizures
- Neuropathy and prolonged weakness

### *Alternative Agent:*

## Vecuronium

- Active metabolite: 3-desacetyl vecuronium
- Rate of elimination decreased in hepatic dysfunction
  - Significant increase in duration of action



# Maintenance Phase



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# Post Cardiac Arrest Care

## 2015 Recommendations- Highlights

- Hypothermia (TTM) post cardiac arrest *should be maintained* for at least 24 hours after achieving target temperature.
  - Class IIa, (LOE C-EO)
- Reasonable to actively prevent fever in comatose patients after TTM.
  - (Class IIb, LOE C-LD)

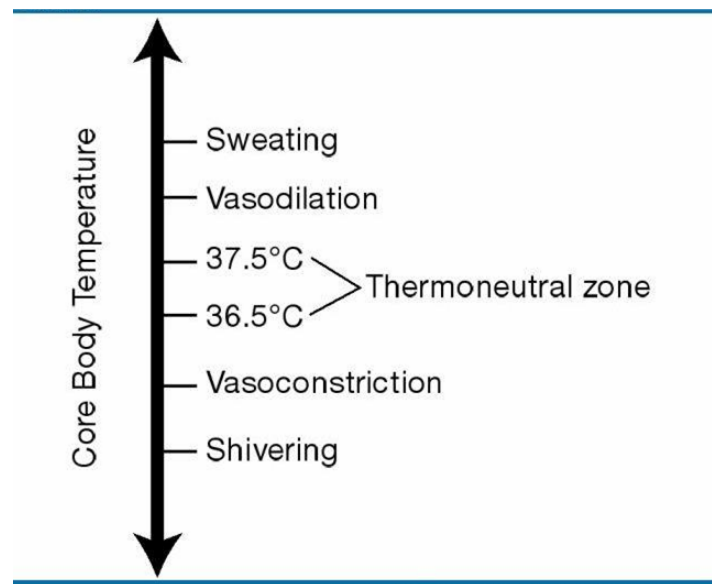
LOE= Level of evidence

EO= based on consensus of expert opinions



# Shivering Pathophysiology

- Human body maintains a core temperature:  $36.4^{\circ}\text{C} \pm 0.4^{\circ}\text{C}$
- Shivering:
  - Involuntary response to enhance heat production
  - Resulting in an increase in oxygen consumption







# Bedside Shivering Assessment Scale

- Bedside Shivering Assessment Scale (BSAS)
  - Quick assessment to identify shivering in patients

**Table** Bedside Shivering Assessment Scale<sup>a</sup>

Score	Type of shivering	Location
0	None	No shivering is detected on palpation of the masseter, neck, or chest muscles
1	Mild	Shivering localized to the neck and thorax only
2	Moderate	Shivering involves gross movement of the upper extremities (in addition to neck and thorax)
3	Severe	Shivering involves gross movements of the trunk and upper and lower extremities

<sup>a</sup> Data from Badjatia et al.<sup>16</sup>

- Frequent shivering assessment is required in the induction phase

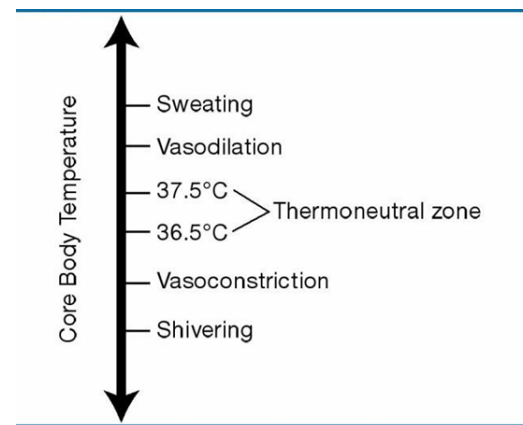
41 Badjatia N, Strongilis E, Gordon E, et al. Metabolic impact of shivering during therapeutic temperature modulation: the Bedside Shivering Assessment Scale. Stroke. 2008; 39(12):3232–3247.



# Pharmacologic Management

Widen interthreshold range

- Lowering vasoconstriction and shivering threshold
  - Raising vasodilation and sweating thresholds
- 
- Pharmacologic agents:
    - Acetaminophen
    - Buspirone
    - Dexmedetomidine
    - Meperidine
    - Magnesium





# Pharmacologic Management

## Acetaminophen

- Inhibition of cyclooxygenase-mediated prostaglandin synthesis
- Lowers hypothalamic set-point
- Provides analgesia

Studies showed high dose acetaminophen (4-6 g /day) decreased body temperature by 0.3°C – 0.4°C

Adverse effects: Liver toxicity

Note: Dose reduction or discontinuation in hepatic impairment patients



# Pharmacologic Management

## Buspirone

- Acts centrally as 5 HT1 receptor agonist to decrease shivering threshold

Mokhtarani et al showed that combination of buspirone and meperidine caused little sedation or respiratory adverse effects

- Shivering thresholds:

Buspirone 60mg	Buspirone 30mg + low dose Meperidine (serum conc 0.4mcg/mL)	High dose Meperidine (Serum conc 0.8mcg/mL)
35°C +/- 0.8°C	33.4°C +/- 0.7°C	33.4°C +/- 0.7°C

Adverse effects: Hypotension, nausea





# Pharmacologic Management

## Buspirone and Dexmedetomidine

- Buspirone (5 HT1 receptor agonist), Dexmedetomidine ( $\alpha$ 2-agonist)

Lenhardt R et al showed buspirone and dexmedetomidine synergistically reduced shivering threshold.

- Shivering thresholds: ( $p < 0.01$ )
  - Control:  $36.4^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$
  - Buspirone only:  $34.9^{\circ}\text{C} \pm 0.6^{\circ}\text{C}$
  - Dexmedetomidine only:  $36.1^{\circ}\text{C} \pm 0.6^{\circ}\text{C}$
  - Combination:  $34.2^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$



# Pharmacologic Management

## Meperidine IV

- K-opioid receptors and  $\alpha_2$  adrenergic receptors

Kurz A et al showed

- Reduced shivering threshold nearly twice as much as the vasoconstriction threshold
  - ( $6.1^{\circ}\text{C} \pm 3.0^{\circ}\text{C}$  and  $3.3^{\circ}\text{C} \pm 1.5^{\circ}\text{C}$ ,  $p = 0.001$ )

Adverse effects: Somnolence, seizures, hypotension, seizures





# Pharmacologic Management

## Magnesium Sulfate

- Peripheral vasodilation – decrease time to goal temperature

### Zwelfler et al

- Magnesium + Meperidine vs Meperidine containing other regimens in healthy patients cooled to 31°C
- Showed that the magnesium group
  - » Higher comfort scores ( $p < 0.001$ )
  - » No adverse events associated with addition of magnesium
  - » Vasodilation: 88% vs 29% ( $p = 0.02$ )

Adverse effects : Hypotension, heart block, CNS depression





## Pop Quiz!

- ❖ What is the major side effect we need to monitor for a patient receiving meperidine during TTM?
  - a. Seizure
  - b. Shivering
  - c. Hypertension
  - d. None of the above







## Pop Quiz!

- ❖ What is the major side effect we need to monitor for a patient receiving meperidine during TTM?
  - a. **Seizure**
  - b. Shivering
  - c. Hypertension
  - d. None of the above



# Rewarming Phase



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# Post Cardiac Arrest Care

## 2015 Recommendations- Highlights

- Reasonable to actively prevent fever in comatose patients after TTM
  - (Class IIb, LOE C-LD)

### 24 hours after TTM start time

- Goal:
  - Rewarm to 36.5°C at a rate of 0.25°C/hour
  - Actively maintain temperature at 36.5°C for 24 hours
  - Passively maintain normothermia for next 48 hours

LOE=Level of evidence

EO= based on consensus of expert opinions





# Rewarming Phase

## Post-cooling Fever

Bro-Jeppesen et al

- *Objective:* 30 day mortality in patients with post-cooling fever vs no fever
- *Study design:* Prospective, observational, cohort study, n = 270
- *Outcomes:*
  - 30 day mortality
    - Adjusted hazard rate (HR):1.8 (95% CI: 1.1-2.7,  $p=0.02$ )
  - Good neurological outcomes
    - (61% vs 75%,  $p=0.02$ )





# ICU Management

## Electrolyte management

- Monitor levels:
  - Magnesium, potassium, calcium and phosphorus
- During TTM:
  - Dysrhythmias: low magnesium and potassium
  - Replace potassium:  $<3.5\text{mEq/L}$
- Post TTM:
  - Elevation in electrolyte levels due to shifting of electrolytes
  - Increased hyperkalemia risk





# ICU Management

## Hyperglycemia

- Decreased insulin sensitivity and secretion
- Negative neurological outcomes seen with hyperglycemia
- Management: Initiate continuous intravenous insulin
  - Monitor glucose levels closely

## Venous Thromboembolism (VTE) Prophylaxis

- Assess patients coagulation need appropriately
- Avoid SUBQ administration

## Stress Ulcer Prophylaxis

- Follow institutional policy





## Pop Quiz!

- ❖ The rationale for cooling patients post cardiac arrest is:
  - a. To preserve neurologic function
  - b. To allow heart to rest and recover
  - c. To allow patients body to recover from shock
  - d. None of the above





## Pop Quiz!

- ❖ The rationale for cooling patients post cardiac arrest is:
  - a. **To preserve neurologic function**
  - b. To allow heart to rest and recover
  - c. To allow patients body to recover from shock
  - d. None of the above







## Pharmacist Impact

- High risk medication classes
- Potentially uncommon medications
- Reduce delay in medication administration
- Medication education

**Be competent and proactive!**



# Targeted Temperature Management in Post Cardiac Arrest Patients

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Continuing Education Presentation  
June 15<sup>th</sup>, 2017



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