Targeted Temperature Management: An Evolving Therapy for Cardiac Arrest

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NP Forum
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Objectives

To understand:

- What Therapeutic Temperature Management (TTM) is
- The goals of TTM
- How we apply the treatment in CCU
- Prognostication
- Long term implications
History

- Hippocrates recommended packing of severe wounds in snow to stop bleeding.
- In Napoleonic wars of 1800s, noted that injured soldiers who were farther from the fire fared better than officers who were re-warmed.
- Used to treat Typhoid Fever.
History

- **1938** – generalized refrigeration of the human brain.
- **1945-1964** – first studies on induced hypothermia for traumatic brain injury.
- **1950s** – induced hypothermia used intraoperatively during cardiac surgery.
- **2002** – landmark studies published on hypothermia after cardiac arrest.
What is Targeted Temperature Management (TTM)?

- Also known as Therapeutic Hypothermia, Induced Hypothermia, or “Brain Cooling”
- Therapeutic treatment where a patient’s body temperature is lowered in a controlled manner for a predetermined amount of time
- Helps reduce the risk of ischemic injury to tissue following a period of insufficient blood flow
Insufficient Blood Flow

May be due to:

- Cardiac arrest
- The occlusion of an artery by an embolism, as occurs in the case of strokes
- Neonates suffering from hypoxic-ischemic encephalopathy
- Traumatic brain or spinal cord injury without fever
- Neurogenic fever following brain trauma
Cardiac Arrest

- 40,000 people arrest annually in Canada
- 85% of arrests occur out of hospital,
  - 5% survival to hospital admission
- Many remain comatose after arrest
- Poor survival rate with intact neurologic function
  - Dysfunction ranges from mild cognitive impairment through to vegetative state
Neuro - Mechanism

Mechanism of neurological injury associated with cardiac arrest:

- ischemic injury to tissue following a period of insufficient blood flow
- reperfusion injury following re-establishment of blood flow
Neuro - Mechanism

- Cardiac arrest presents global ischemic insult to the brain, largely influenced by duration of interrupted cerebral blood flow.
- Cerebral hyperemia, followed by vasospasm and multifocal and global hypoperfusion.
- Cerebral O2 stores gone in 20 seconds, glucose and ATP in 5 minutes.
- Leads to neuronal death.
How Cooling Helps

- Counteracts neuroexcitation of brain cells, reducing the degree of cell death.
- Stabilizes blood-brain barrier.
- Suppresses inflammatory process.
- Decreases cerebral metabolism (6-10% for every degree Celsius the body temperature drops).
Decreases death and neurological damage!!
American Heart Association 2015 guidelines for post cardiac arrest care includes class 1 (strong) recommendations for TTM.

- For all patients remaining comatose following resuscitation from cardiac arrest
- Shockable, out-of-hospital arrest (LOE B)
- Non-shockable, in-hospital arrest (LOE C)
- Target temperature 32-36°C (LOE B)

2015 Canadian Guidelines for the use of TTM: target temperature 32-34°C
Inclusion Considerations

- Initial rhythm
  - Witnessed vs. unwitnessed
- Downtime
- Glasgow Coma Scale
- Pre-arrest quality of life
Temperature Management

- Induction
  - Getting to desired goal

- Maintenance
  - Keeping the patient at the desired temp for a predefined period of time

- Rewarming
  - Returning to normothermia
Induction Phase

- Sedation
- Paralytics
- Ventilator
  - Assist Control
- Iced IV fluids
  - Normal Saline or Ringer’s Lactate
- Target 32-34°C (36°C?)
<table>
<thead>
<tr>
<th>Method</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surface Cooling (blankets, gel pads, ice packs and fans)</td>
<td>Non-invasive, Cheap, Minimal training.</td>
<td>Slow, Less thermal control, Messy.</td>
</tr>
<tr>
<td>Intra-vascular Cooling (ICY catheter)</td>
<td>More thermal control, No skin issues.</td>
<td>Invasive, More expensive, Requires special training to insert.</td>
</tr>
</tbody>
</table>
Temperature Monitoring

- PA catheter
- Esophageal
- Bladder
  - If patient has adequate U/O 0 – 30 cc/hr – varies per manufacturer
- Rectal/skin/tympanic less accurate
Maintenance Phase

- Sedation and Paralytics continue
- Rhythm and Blood Pressure control
  - Amiodarone, Inotropes, Vasopressors, Fluid
- Continuous Monitoring
  - End Tidal CO2, Temperature
  - Hourly pupil assessments
- Laboratory
  - ABG, electrolytes, PT/PTT, cultures, blood glucose
Sedation

- Reduces oxygen consumption
- Can prevent shivering
- More rapid cooling
- May delay prognostication
- May contribute to hypotension
Paralysis

- Eliminates shivering
  - Decrease MVO2
- MUST sedate prior to paralyzing
- Seizures may be concealed
Ventilator Management

- Avoid high FiO2 (PO2>300)
  - Titrate FiO2 to keep PaO2 85-100mmhg
- Adjust vent for normal acid-base balance
  - Hyperventilation may produce cerebral ischemia
  - Hypoventilation may increase ICP
  - Target *normocarbia*
- Vigilance for early signs of pneumonia!
Fluid and Electrolytes

- Cold diuresis
  - Venoconstriction,
- If uncorrected
  - Hypovolemia → hypoperfusion
  - Hemoconcentration → hyperviscosity
- Rewarming may unmask hypovolemia
Fluid and Electrolytes

- Decreased electrolytes
  - K+, Mg, Phos
- Diuresis induced renal excretion
- Intracellular electrolyte shifts
  - Shift extracellular with rewarming
  - Prevented with slow controlled rewarming
- Replace to low normal during cooling
  - If increased, treat before rewarming
Infection

- Must be vigilant
  - Signs/symptoms not available
- Inspect lines/tubes, skin, routine CXRs
- Suspect if sudden increase in work of cooling device (↓ water temp)
  - Indicates increased heat production
- Have low threshold to start antibiotics
Many medications are required during TH sedatives, analgesia, anti-epileptics, paralytics, etc. None have specific dose recommendations during TH. Majority of pts require decreased doses during TH or at standard doses experience prolonged effects.
Rewarming Phase

- Stop all active cooling
- Rewarm *slowly* (0.1-0.5°C/hr)
- Discontinue Neuromuscular Blocking Agents
- Titrate sedation
- Monitor for rebound *hyperthermia*
Central Nervous System

- **Decision-making is not as easy as it sounds**
  - Don’t neuroprognosticate during TH
  - Wait until TH reversed *at least* 72 hours
- Deeply sedate and paralyze during cooling
- Use of NSE as a biomarker
Seizures

- Seizures may be concealed by NMBA
  - Occur in 5 – 15% who achieve ROSC
  - 10 – 40% of those who remain comatose
  - Increase cerebral metabolism 3-fold
  - *EEG monitoring

- Good neuro outcomes reported in patients initially with status epilepticus
Tips and Tricks for Shivering

- Decrease pt temperature by 1°C
- Apply warm blankets to hands and feet
  - this may trick pt brain, although pt core temp remains cool
- Keep Mg over 1.0
Adverse Effects

- 3 most frequent Adverse Effects
  - Arrhythmia
  - Pneumonia
  - Bleeding

- Adverse effects in TH pts (74%)

- Adverse effects in standard care (71%)

- No significant difference in any AE measured!

Holzer, NEJM 2010 Combined results from 4 comparative clinical trials
Therapeutic Hypothermia and PCI

- Immediate 12 lead ECG to determine cath or not
  - do not delay cath for cooling.
  - May do in conjunction

- Timing:
  - STEMI: minimize delay to cath lab
Therapeutic Hypothermia and PCI

- Initiate moderate hypothermia with ice packs, cool infusions, add cooling device if time
- Cooling devices can be used during angiography
- Continue cooling post cath/PCI per protocol
- Standard medications (ASA, heparin, IIb/IIIa inhibitors, clopidogrel) can be used
- No apparent increased risks of bleeding
Post-Resuscitation Care Bundle

- STEMI
  - Early PCI
- Therapeutic Hypothermia
- Early Hemodynamic Optimization
- Hyperglycemia
  - Glucose Management – b.g.<10
- ALI/ARDS
- Antibiotic, GI, DVT Prophylaxis
Evidence to date:

- HACA 2002 - RCT
- Bernard 2002 - RCT
- Arrich 2016 – Systematic Review

Support the use of TTM for cardiac arrest
‘Cool’ Registry

- Enrolled patients resuscitated from cardiac arrest March 2014 to August 2015 who:
  - Were admitted to the CCU (n=65) or ICU (n=45) at the Royal Alexandra Hospital
  - remained unresponsive
<table>
<thead>
<tr>
<th></th>
<th>TH (n=56)</th>
<th>No TH (n=44)</th>
<th>TTM (n=10)</th>
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<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Male</td>
<td>40 (71.43)</td>
<td>30 (68.18)</td>
<td>7 (70.00)</td>
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<tr>
<td>Female</td>
<td>16 (28.57)</td>
<td>14 (31.82)</td>
<td>3 (30.00)</td>
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<tr>
<td><strong>Age Mean(SD)</strong></td>
<td>61.23214</td>
<td>57.97727</td>
<td>48.1</td>
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<tr>
<td></td>
<td>(SD=12.84734)</td>
<td>(SD=15.7384)</td>
<td>(SD=18.788)</td>
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<td><strong>Location of arrest</strong></td>
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<tr>
<td>IHCA</td>
<td>4 (7.14)</td>
<td>12 (27.27)</td>
<td>2 (20.00)</td>
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<td>OHCA</td>
<td>52 (92.86)</td>
<td>32 (72.73)</td>
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<td><strong>Initial Rhythm</strong></td>
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<td>Shockable</td>
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<tr>
<td>Vfib</td>
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<td><strong>Witnessed</strong></td>
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<td>Unwitnessed</td>
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<td><strong>Bystander CPR</strong></td>
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<td>Yes</td>
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<td><strong>MI Cause of Arrest</strong></td>
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<td></td>
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<td>3 (30.00)</td>
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<tr>
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<td>20 (35.71)</td>
<td>39 (88.64)</td>
<td>7 (70.00)</td>
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<td>Deceased</td>
<td>31 (55.36)</td>
<td>38 (86.36)</td>
<td>9 (90.00)</td>
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</table>
‘Cool’ Registry: Results

- TH was associated with continuing improvements in neurological functioning

Primary Outcome

- MoCA-3 months: mean improvement of 3.3 points (SD 2.60) for TH patients (n=8)
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Ross Tsuyuki, 2/21/2016
‘Cool’ Registry: Results

Secondary Outcomes:

- **MoCA** - 6 months: mean improvement of 4.3 points (SD 4.72) for TH patients (n=7)
- **CPC** - 3 & 6 months: mean improvement of 0.7 points (SD .72) and 0.7 points (SD 0.8) for TH patients (n=15)
- **mRS** - 3 & 6 months: mean improvement of 1.5 points (SD 1.13) and 1.9 points (SD 1.36) for TH patients (n=15)
‘Cool’ Registry: Results

Secondary Outcomes cont’d:

- **Survival**: TH patients (n=56) also had a decreased hazard of death compared to the no TH group (n=44), HR 0.39 (95% CI 0.24, 0.64; p=0.0006).
‘Cool’ Registry: Conclusions

- Supports the use of TH in the treatment of patients resuscitated from cardiac arrest.
Overall Conclusions

- Confirmed efficacy of TH for on mortality and neurological function
- Neurological improvement continues over time
- Cannot accurately assess outcomes at short follow-up times
- Variety of tools should be used to assess neurological outcomes in future studies
References

References

