The Evolution of Therapeutic Hypothermia
Changes and Challenges for Managing the Post-Resuscitation Patient

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Disclosures

• Mike Mooney
  – I have no financial relationships or other conflict of interests to disclose, and I will not discuss off label use and/or investigational use in my presentation

• Matt Pavlovec
  – I have no financial relationships or other conflict of interests to disclose, and I will not discuss off label use and/or investigational use in my presentation
Objectives

• Incidence & Epidemiology of SCA/OHCA
• Resuscitation Centers of Excellence
• History of Targeted Temperature Management & Cool It
• Science of Targeted Temperature Management
• Targeted Temperature Management from Arrest to Discharge
  – EMS & ED focus
  – ICU focus
  – Post-ICU focus
• Trends & Controversies in Targeted Temperature Management
Cardiac Arrest is COMMON!

- The incidence of EMS-assessed OHCA in the U.S. is **326,200**
- Approximately **60% of OHCA** are treated by EMS personnel
- **No symptoms** prior to the arrest in **25%** of EMS treated OHCA
- Among EMS-treated OHCA, **23%** have an initial rhythm of **VF/VT**
- Cardiac arrest is **witnessed by a bystander** in **38.7%** of cases, by an **EMS provider** in **10.9%** of cases, and **unwitnessed** in **50.4%**
- The majority of OHCA, **69.5%,** occur at a home or residence
- The median age for OHCA is **66** years

Heart Disease and Stroke Statistics – 2015 Update; *Circulation*; Jan. 2015
• Survival of all heart rhythms – 11%
• Survival of witnessed, shockable heart rhythms – 31%
Cardiac Arrest Registry to Enhance Survival (CARES)

• For Out-of-Hospital Cardiac Arrest
  – Survival to hospital discharge with any first recorded rhythm was 10.8%
    • In Minnesota it was 13.9%
  – Survival with good neurologic function was 8.9%
    • In Minnesota it was 12.7%
  – Survival after bystander-witnessed VF was 33.9%
    • In Minnesota it was 40.9%

• For Non-Traumatic Cardiac Arrest
  – Survival to hospital discharge was 15.9%
    • In Minnesota it was 24.1%
  – Survival with good neurologic function was 13.3%
    • In Minnesota it was 20%
Epidemiology of Cardiac Arrest

• The incidence of OHCA per 10,000 adults is 10.1 among blacks, 6.5 among Hispanics, and 5.8 among whites
• Males constituted 61.6% of CA victims
• Prior heart disease is a major risk factor for cardiac arrest, as is smoking, diet, and weight
• Average post-arrest care is > $100,000 per individual
  – Total aggregate cost in the U.S. was $33 billion per year


• Per the AHA, 25.5% of all-cause in-hospital CA survived to discharge
  – Despite 95% being witnessed or monitored
Resuscitation Centers of Excellence – in real practice

- Maintains standard triage and treatment protocols for CA
  - Comprehensive CV Emergencies protocols
- Initiates hypothermia as soon as possible when indicated
  - Cool It Program
- Initiates cardiology consult as soon as possible
  - Cardiology in-house, 24/7 and Level 1 STEMI Program
- Has ability to treat simultaneous CA patients
  - Large, capable ED, CV Lab, and CV ICU
- Has ability to treat re-arrest, including mechanical circulatory support
  - VA ECMO, Impella, RVAD
Resuscitation Centers of Excellence – in real practice

• Capable of ICD placement and providing appropriate follow up
  – Electrophysiology Department
• Defers prognostication and withdrawal of care for at least 72 hours
  – EEG monitoring, Epilepsy, and Neurology Departments
• Works with EMS medical direction and CA referral center
  – Professional outreach
• Provides CPR training for community, with goal of achieving bystander CPR rates > 50%
  – Community outreach
• Participates in national QI program to improve CA outcomes
  – CARES, INTCAR, GWTG-R
The Chain of Survival ends in Centers of Excellence

Resuscitation Centers of Excellence
- 24/7 Revascularization
- ECMO
- Hypothermia
- CT and Vascular Surgery
- Neurology and EEG
- EP and ICDs
- Research: CARES, INTCAR
Case Study

- 60 year old male
  - No significant past medical history
  - Was at the casino when he developed CP
  - He waited 15 minutes, became diaphoretic, and walked to his car to get some fresh air – no change
  - Called 911 and EMS arrived
  - Alert/oriented, substernal CP 10/10
  - EKG completed; STEMI
  - Hypotensive and nauseated
    - IV, ASA, Zofran; unable to give NTG due to pressure
  - Transported to local hospital
Case Study

- Arrived at referring hospital 30 miles from ANW
- Awake, minimally verbal, complaining of 10/10 CP
- Level One STEMI activated after consult with MHI cardiologist
- Received Ticagrelor and Heparin
- Had two episodes of Wide Complex Tachycardia
- Received Lidocaine and Amiodarone
- Went into VF, was defibrillated, and had immediate ROSC
  - Occurred 3 times before decision to intubate
• Developed VF again, this time unable to convert so LUCAS applied
• Intermittent pulses but immediately back into VF; “What do we do?”
  – Palpable pulse with LUCAS, good EtCO2
• **KEPT THE LUCAS ON AND TRANSPORTED!**
  – Heavy snow storm made for slow travel
• Neck, axilla and groin packed in ice
Case Study

• Level One STEMI and SHOCK teams already activated
• On arrival at ANW, EMS reports continuous CPR needed and several doses of Epi given en route
• Patient immediately prepped and placed on ECMO
• At this point, 106 minutes of CPR!!
• Angiography performed and stents placed after patient placed on pump
• Cooling catheters placed at the same time
Case Study

• Admitted to CV ICU with consults to Advanced Heart Failure, Intensivists, Vascular surgery, Neurology and Epileptologist
• Day 1 – EF 15%; ECMO and Targeted Temperature Management initiated
• Day 4 – EF 25%; ECMO decannulated; sedation vacation attempted; delirium, agitation, febrile; developed Streptococcal endocarditis and septic shock
• Day 14 – Unable to wean sedation; labile blood pressures; continued agitation; elevated peak pressures on vent; palliative care consulted
• Day 21 – Started squeezing hands intermittently on command. Reflex?
• Day 29 – Woke up; communicating by writing
• Day 41 – Discharged to rehab unit
• Rehab Day 14 – Trach decannulated; full neuro recovery; discharged to home on LIFEVEST and eventually had ICD placed

• COMPLETELY INDEPENDENT AT HOME!
The History of Therapeutic Hypothermia

• Described by ancient Egyptians in the Ebers Papyrus (~2500 BC)
• Hippocrates surrounded badly wounded patients with ice and snow to reduce blood loss (~400 BC)
• Galen also described treatments with hypothermia (Rome ~170 AD)
• Hua To forcibly immersed febrile patients in a stone trough until the vapor rose several feet in the air (China ~170 AD)
• Napoleon’s surgeon-general, Baron Larrey, described wounded soldiers who were put close to a campfire dying earlier than those who were not re-warmed (France ~1800 AD)

Therapeutic Hypothermia in the Modern Era

• Case reports in the 1930’s and 40’s of drowning victims surviving after prolonged asphyxia

• Fay, Bigelow and Williams experimented with TH for surgical and TBI patients in the 1950’s – no RCT’s, uncertain benefits, and difficult implementation

• In 1958 Benson et al. use ‘deep’ TH specifically for cardiac arrest – good results but unmanageable side effects

• Interest in TH was low until the 1980’s when several animal trials showed good neurological outcomes – and manageable side effects – with ‘mild’ hypothermia

• Current paradigm shift happens in 2002 when the HACA group and Bernard et al. publish their findings
# 2002 Hypothermia Trials - Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Hypothermia (%)</th>
<th>Normothermia (%)</th>
<th>RR (95% CI)</th>
<th>P value</th>
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<tbody>
<tr>
<td><strong>Alive at hospital discharge with favourable neurological recovery</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HACA</td>
<td>72/137 (53%)</td>
<td>50/138 (36%)</td>
<td>1.51 (1.14-1.89)</td>
<td>0.006</td>
</tr>
<tr>
<td>Bernard</td>
<td>21/43 (49%)</td>
<td>9/34 (26%)</td>
<td>2.65 (1.0-6.88)</td>
<td>0.046</td>
</tr>
<tr>
<td><strong>Alive at 6 months with favourable neurological recovery</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HACA</td>
<td>71/136 (55%)</td>
<td>50/137 (39%)</td>
<td>1.44 (1.11-1.76)</td>
<td>0.009</td>
</tr>
</tbody>
</table>
In 2002 trials from Austria, Australia, and Japan show the efficacy of Therapeutic Hypothermia.

In 2005 MHI shows the potential of a standardized referral system with Level One Heart.

In 2006 these factors were combined to bring world class post-CA care to greater Minnesota.

Conducted significant education with referring ED and EMS agency staff.

Contributing to the greater understanding of post-CA care while increasing survivability:

- International Cardiac Arrest Registry (INTCAR)
- Cardiac Arrest Registry to Enhance Survival (CARES)
Cool It Program Evolution

• Through multi-disciplinary efforts, pioneering research, and continuous process improvement
  – Partnership between Cardiologists, Intensivists, Nursing, and many more
  – Participation with INTCAR and CARES, and publications in *Circulation* and other leading peer reviewed journals
  – Process improvement resulting in changes to sedation and paralysis, shivering management, neuroprognostication, and more

Contributions to the literature have led to ECC recommendations from the AHA and ILCOR
Therapeutic Hypothermia incorporated into Emergency Cardiac Care

• 31st Bethesda Conference in 1999
  – First mention of cooling in ECC – no recommendations though
• In 2003 ILCOR published the following Advisory Statement …
  – Unconscious adult patients with spontaneous circulation after OHCA should be cooled to 32°C – 34°C for 12 – 24 hrs when the initial rhythm was VF
  – Such cooling may also be beneficial for other rhythms or IHCA
• In 2010 the AHA publishes a Policy Statement on regional systems of care for OHCA
• Updates to ECC Guidelines from 2005 through 2015 continue to emphasize TTM with refinements based on the current literature

We’re getting better with every patient!
Ischemic Hypoxia & Reperfusion Injury

- Ischemia
  - Glutamate release
  - Calcium shifts
  - Mitochondrial dysfunction
  - Oxygen-free radicals
  - Excitotoxicity
  - Inflammatory cascades
  - Cell death
  - Blood brain barrier disruption & cerebral edema

- Reperfusion

- Hypothermia
  - Lower metabolic rate
  - Less oxygen consumption

Overview of the Cool It Program

Preserving neurological function in post cardiac arrest patients!

It’s all about the brain!!!
Does the patient meet TTM criteria?

Inclusion Criteria
• ROSC within 60 minutes
• Non-traumatic arrest
• Unable to follow simple commands

Exclusion Criteria
• Active Bleeding
• DNR/DNI
• Chronic coma/vegetative state prior to arrest
• Persistent hypotension despite pressors
In the Field

• Continue ACLS and place on LUCAS
• Early information will be limited, but if the patient meets criteria ...
• Initiate TTM as soon as practical
  – Intra-arrest or immediately after ROSC
  – Ice packs to the neck, groin, and axilla
  – Note the time cooling was initiated
• Transport to the nearest ED or to a Resuscitation Center of Excellence, depending on distance and local protocol
In the ED

• Prior to ROSC, same direction as In the Field
  – Continue ACLS and place on LUCAS
  – Determine if patient meets TTM criteria
  – Initiate cooling if appropriate

• If patient meets TTM criteria ...
  – Expose the patient
  – Obtain 12 lead EKG
  – Obtain core temp
    • Record initial temp and time cooling was initiated
    • If < 34°C, continue temp checks q 10 min
    • If > 34°C, continue to cool with ice packs to the neck, groin, and axilla
Transferring out of the ED

• Contact the Resuscitation Center of Excellence early
• Arrange for transport at the same time ... air if possible
• What did the EKG reveal?
  – Follow STEMI protocol if appropriate
    • Patient goes directly to CV Lab
    • NO thrombolytics – assume chest trauma from CPR
• Prep for transport with sedation and paralytics
• If time allows consider CT of head and/or a central line
Admitting to the ICU

- Mechanical Cooling
- Oral Gastric Tube
- Esophageal temp probe
- Vent settings
- Maintenance IV’s
- Bolus paralytic, sedation and analgesia
- Initial labs
- 12-Lead EKG

- Vital signs – maintenance and rewarming
- Cardiac monitor and defibrillator
- EtCO2 and BIS monitors
- Consults stat – Intensivist, Cardiology and Epilepsy
- Imaging: Head CT, CXR
- Lines: Arterial, Central, PA
- Video EEG

- IABP, Impella, or ECMO?
Physiological Considerations

• Risk for bradycardia
  – Slowed electrical conduction – be conscious of what sedation you’re using; consider TPM
• Risk for arrhythmias
  – Should be connected to a defibrillator with defib pads on at all times!
• Risk for hypotension
  – Vasodilation from post resuscitation inflammatory cascade and cardiac dysfunction (low EF)
  – Once cool usually normotensive or hypertensive due to vasoconstriction and increased SVR
  – Rewarming causes hypotension due to vasodilation – anticipate need for fluids and pressors
• Risk for bleeding
  – Altered coagulation – avoid any IV or peripheral sticks
• Risk for shivering
  – Increases O2 consumption dramatically – major reason for paralytic
• Risk for seizures
  – Anoxic brain injury causes cerebral edema and encephalopathy – should be monitored through EEG; may need anticonvulsants
• Risk for infection
  – Artificially immunocompromised – watch white count; consider prophylactic antibiotics
Nursing Considerations

• Paralyzed patient
  – Ensure adequate sedation
  – BIS monitor and Train of Four
• No finger stick glucose
  – Coagulation negatively affected
• Skin care
  – Skin checks at least q 2 hrs
• Eye care
  – Paralyzed patient
• Prevent shivering
  – Socks on hands and feet; warm blankets or forced air (Bair Hugger)
• Often will be 2:1 nursing care for the first few hours
Temperature Source

• Use two sources – a primary and a secondary
  – Oral is good for double checking ... but not quite accurate enough as the primary source
  – PA catheter is the most accurate ... but not everyone needs a PAC
  – Bladder is also very accurate ... if the patient is producing enough urine – typically our secondary source
  – Esophageal is nearly as accurate as a PAC or bladder temp ... and has no significant draw backs – typically our primary source

• Confirm placement with CXR
Common Infusions

- **Crystalloids**
  - Normal Saline

- **Electrolytes**
  - Magnesium

- **Vasopressors**
  - Norepinephrine
  - Vasopressin

- **Inotropes**
  - DOBUTamine
  - DOPamine

- **Analgesics**
  - Fentanyl

- **Sedation**
  - Midazolam
  - Propofol

- **Paralytics**
  - Cisatracurium

- **Heparin**

- **Insulin**

- **Antibiotics**
Lab Work

• ABG’s
• Lactate
• Electrolytes
  – Expect K and Phos to decrease with intracellular shifts
  – Replace K up until 8 hours prior to rewarming unless < 3
• CBC, Coags, Plts
• Amylase, Liver function, Lipase
• Cardiac Enzymes
• Cultures

Neuron Specific Enolase (NSE)

• Biomarker of brain damage which may be useful in predicting neurological outcome
• Must be used in context with other clinical tests and physical exam, neurological outcome cannot be predicted by NSE alone
Analgesia, Sedation & Paralysis

Analgesia & Sedation

• Rationale
  – Facilitate mechanical ventilation
  – Avoid pain – CPR, cold
  – Assure amnesia

• Continuous infusions
  – As low as possible if not paralyzed
  – use repeat boluses if necessary

• Agents
  – Fentanyl
  – Versed
  – Propofol
  – Precedex

Paralysis

• Rationale
  – Facilitate mechanical ventilation
  – Abolish shivering

• Sedate prior to paralysis!!!

• Monitor with BIS
  – Target 40 – 80

• Agents
  – Atracurium
  – Cisatracurium

Wean as soon as able to prevent delirium and Post-ICU Syndrome!
Hemodynamic Support

• Target MAP of 80-100 – consider lower if ACS presentation
• Maintain CVP 8-15
• Monitor lactates to assess cellular perfusion
• Vasoactive Medications
  – Unknown EF or EF < 40 – DOBUTamine
    • Add DOPamine or Epi
  – Normal EF – Norepinephrine
    • Add Vasopressin
  – NTG for hypertension
• Mechanical Circulatory Support
  – VA ECMO in severe hypotension
  – IABP
Shivering Prevention

• We USED to paralyze everyone until they rewarmed to 36° C
  – Extended use of paralytics correlates with higher doses of sedation and longer LOS
• The NEW(er) thinking is to use paralytics to quickly cool patients and then as a last resort for vent compliance and to stop shivering
• There are many things to try first
  – Wrap hands, feet and head
  – Use Bair Hugger set at 43° C
  – Keep cooling catheter away from direct contact with skin
  – Magnesium drip (increases the shivering threshold)
  – Tylenol per order – for neurologic fevers
  – Buspar and Demerol per order
Rewarming

• Begin active rewarming 24 hours after reaching goal temp
  – No more than 0.25° C/hr – target normothermia within 16 hrs
  – Volume loading – target high normal CVP or PAW
  – Stop K replacement prior to rewarming if greater than 3 mmol/L – expect K to shift to the extracellular space
  – If paralyzed, shut off at 36° C
• If not following commands and not trying to extubate, maintain normothermia for an additional 24-48 hrs
  – Prevent shivering with surface warmers
Neuro Consult & Neuroprognostication

- Neurology & Epilepsy consulted immediately
  - EEG monitoring throughout cooling and rewarming, *but* ...
  - No neuroprognostication until 72 hours after cooling was initiated, *and* ...
  - No neuroprognostication until paralytics have been off for > 24 hours
  - If patient is not making purposeful movement or following simple commands after rewarming a CT or MRI may be ordered
  - Can take up to 5 days or more for sedation and paralytics to clear
    - Shock liver, AKI, and slowed metabolism from cooling can all be confounding factors
Family Considerations

• Most families are in a state of shock
• Remind them that this is the time to take care of themselves
  – Many need to know it is okay to go home
• It could be a few days to a week until we know what kind of a neurological outcome their loved one will have
• Use the “Long, Dark Tunnel” analogy
  – We all have to wait till we come out the other side to know what to expect
• There will often come a time for a family meeting to consider the patient’s wishes ... and whether or not comfort cares should be considered
Other Consults while in the ICU

• Social Worker
  – Will follow patients from admission to discharge
  – Will coordinate Discharge Planning meeting

• Care Coordinator RN
  – Will actively follow patients at time of transfer
  – Will coordinate required After Discharge appointments

• Spiritual care

• Smoking cessation (if appropriate)

• Hospitalist
  – Takes over for the Intensivist after the patient comes off the vent
  – Manages non-cardiac issues
Transfer out of the ICU

• Always transfer to a Telemetry floor
  – Consults defaulted for ...
    • Physical therapy
    • Occupational therapy
    • Speech and language pathology
    • Neuropsychology
    • Physical medicine and rehab
    • Cardiac rehab
  – Additional, as needed, consults for ...
    • Electrophysiology
Patient Consults & Assessments

• Physical Therapy
  – Safety in moving, ambulation, strength
  – Home environment
• Occupational Therapy
  – Self care
  – Managing money
  – Driving
  – Work responsibilities
• Speech/Language Pathology
  – Thinking skills
  – Memory
  – Problem solving
• Cardiac Rehab
  – If patient has CAD, will treat per protocol
  – In all cases, will teach family CPR

• Neuropsychology
  – Baseline of cognitive function as inpatient
  – Follow up in 4-6 weeks for further cognitive therapy
• Physical Medicine and Rehab
  – Determine next organized rehab program
  – Will confirm or modify, and reinforce, recommendations of physical, occupational, and speech therapies
• Electrophysiology
  – ICD placement considered for all VF/VT arrests
Discharge Planning

• Social Worker
  – Coordinates patient/family Discharge Planning meeting

• Attendees include:
  – Family
  – Social Worker
  – Care Coordinator
  – Attending Physician
  – OT, if able (otherwise will leave activity recommendations for after discharge)
  – Others as able

• After Discharge Planning meeting
  – 4-6 week post-discharge appointments for:
    • Occupational therapy
    • Neuropsychology
    • Cardiac MRI (or TTE for patients with devices)
    • Cardiology appointment
  – Orders for patient activity at home
Extensive management while hospitalized!
- Sedation / Analgesia / Therapeutic Paralysis
- Mechanical Ventilation / Aspiration / ARDS / Respiratory Failure
- Seizures / Cerebral Hemorrhage
- Acute Renal Failure / Acidosis
- Leukocytosis / Coagulopathy / Hyperglycemia
- ACS / Ventricular Arrhythmia / Cardiogenic Shock

Extensive rehab and follow up needed!

Necessitates a large group of experts to manage successfully!!
Outcomes of the Cool It Program

• Over 650 post cardiac arrest patients have been cooled
• Significantly increased survivability and quality of life
  – All cause CA, ~40% achieve ROSC, and only ~25% of those will survive to hospital DC
  – With cooling ~44% survive to DC, but if they’re cooled at ANW ~51% survive to DC
  – 89% of CA survivors at ANW go home with a CPC score of 1 or 2: No neuro deficits!

Currently researching better forms of neuroprognostication, led by Drs. Jim White and Max Mulder
1. Success starts with a committed team who are focused on improving outcomes.
2. Developing a regional network of partners,
3. Developing evidence based protocols,
4. Educating all players,
5. Conducting research and continuously improving processes

... Works!
Targeted Temperature Management Controversies and Trends

What’s the best time to initiate?
• AHA recommendations in the 2015 ECC update say no chilled saline in the field, but it’s okay to start cooling
• No trials are currently looking at the best time to initiate
• The Cool It protocol has always said ice packs, not chilled saline, and to start cooling as quickly as able
  – New products to help cool in the field
    • Cryothermic Cooling System

What’s the best target temp?
• TTM trial in 2013
  – 33⁰ or 36⁰ C have virtually the same outcomes
• 2015 AHA recommendation – anywhere in that range
• MHI recommendation – 33⁰ C unless contraindicated (bleeding, hypotension despite pressors/MCS)
  – Starting to use 36⁰ C more often for cooling our ECMO patients
    • Need to be anticoagulated, limited venous access
Should we cool ALL arrests?

- PEA/Asystole arrests have higher mortality compared to VF/VT arrests
- True whether patients are cooled or not
  - Trials that have cooled both still find better outcomes for PEA/Asystole arrests compared to no cooling
  - This is what we have found with the Cool It Program as well
    - Survivability for VF/VT, all cause, 69%
    - Survivability for PEA/Asystole, all cause, 31%
- AHA recommends cooling for all VF/VT, and suggests cooling for all PEA/Asystole

Should we cool in-house arrests?

- 2016 report from Chan et al. in JAMA, and using the AHA GWTG-Resuscitation registry, found worse outcomes for in-hospital arrests that were cooled
  - Retrospective analysis, no RCTs asking this question
  - Not what we’ve found in the Cool It DB
    - In-house arrests at ANW that were cooled had > 60% survivability
Targeted Temperature Management
Controversies and Trends

How much is too much oxygen?
• Several retrospective studies show worse outcomes in cardiac arrest patients, as well as many other etiologies, that are hyper-oxygenated (> 300 PaO2)
• Contributes to the creation of free radicals and reperfusion injury
• AHA/ILCOR recommends targeting SpO2 of 94-96% post ROSC
  – Equates to a PaO2 WNL

How accurate is neuroprognostication?
• Application of American Academy of Neurology guidelines to assess prognosis in post TTM pts will likely be overly pessimistic
  – EEG early and continuous
  – Clinical exam 72 hrs after normothermia
  – SSEP 48 hrs after normothermia
  – Biomarkers, i.e. NSE, at 48 and 72 hrs after normothermia – but utility is unclear
  – Imaging, i.e. CT, 24 – 48 hrs after normothermia – but again, utility is unclear
• Strong need for continued research and refinement
  – Current work being done at ANW through our DB and the INTCAR DB

Blondin, NA & Greer, DM; Neurologic prognosis in cardiac arrest patients treated with therapeutic hypothermia; *The Neurologist*; 2011; 17:241-248
Thank You!