INDUCED HYPOTHERMIA
“A Hot Topic”

R. Darrell Nelson, MD, FACEP
Emergency Medicine
Wake Forest University Health Sciences
Conflicts of Interest

• Sadly, we have no financial or industrial conflicts of interest to disclose.
• Off-label Discussion: Therapeutic hypothermia is not FDA approved
Therapeutic Hypothermia

Objectives / Discussion

items:

• Brief history
• Definition
• Who benefits?
• When to induced hypothermia?
• Methods to initiate and maintain
• Complications
• How therapeutic hypothermia fits in post-cardiac arrest care?
History of Therapeutic Hypothermia

• Ebers Papyrus ~ 3400 - 1500 BC
• Hippocrates ~ 460 – 370 BC
• Battlefield Surgeon Baron Dominique Jean Larrey 1766 – 1842
• First modern article / study in 1945 for TBI
• 1950 First application in cerebral aneurysm
What is Therapeutic Hypothermia?

• Focus is on Post Cardiac Arrest Victims
  – Protecting the Brain
  – Protecting the Heart
  – Protecting the body as a whole

• Controlled induction of MILD hypothermia by any number of means to result in a core body temperature of 32° to 34° C (89.6 – 93.2° F) for a period of usually 12 to 24 hours with passive re-warming
Who Benefits from Therapeutic Hypothermia?

- 2005 European Resuscitation Council / American Heart Association
- Unconscious adult patients with ROSC after out of hospital VF arrest
- AHA recommended therapy in non-VF arrest and in-hospital cardiac arrest
What is the Evidence?

• Bernard study (1997) Patients:
  – Mortality rate 77% to 45%
  – Good neurological outcome 14% to 50%

– RCT (2002) N=77: Mortality rate 68% to 51%
  – Good neurological outcome 26% to 49%

• European Hypothermia After Cardiac Arrest Patients RCT (2002) N=273
  – Mortality rate 55% to 41%
  – Good neurological outcome 39% to 55%
What is the Evidence?

• Bernard (RCT 2002)
  – Absolute risk reduction of 23%
  – NNT 4.5

• Hypothermia After Cardiac Arrest (RCT 2002)
  – Absolut risk reduction of 24%
  – NNT 4
What are we trying to protect?

**PATHOPHYSIOLOGY OF CARDIAC ARREST**
Pathophysiology of Cardiac Arrest

• First process is the etiology of the arrest

• Second process is the reaction of the body to the global ischemia
  – Post Cardiac Arrest Brain Injury
  – Post Cardiac Arrest Myocardial Injury
  – Systemic Ischemic / Reperfusion Response
  – Persistent Precipitating Pathology
How does Hypothermia protect?

- CMRO2
- Apoptosis
- Free Radical Production
- Mitochondrial damage
- Excitatory Amino Acid Release
- Intracellular Calcium Shifts
Sequence of neuronal cell injury following acute ischemia

- Ischemia
- Cell hypoxia
  - Glutamate
    - Open NMDA Channels (Glutamate Receptors)
  - Mitochondrial Failure
    - Mitochondrial sequestration of Calcium
      - Calcium Overload
    - ATP production
      - Calcium Pumping
  - Oxygen Free Radical Production
- Cell Death
- Reperfusion
  - Inflammatory response
How to Initiate and Maintain Therapeutic Hypothermia?

• Best Method Unknown

• Ice Packs, IV Fluids, Extra-vascular, Endovascular techniques

• Our local utilization
When to Initiate Therapeutic Hypothermia?

- Current recommendation is after ROSC in the patient which remains unconscious.
Indications / Inclusion Criteria

• Area remains controversial

• ROSC (any rhythm) where patient remains unconscious / no purposeful response

• ROSC < 30 minutes downtime

• < 6 Hours from ROSC

• MAP > 65 mmHg (includes use of vasopressor agents)
Exclusion Criteria

• ROSC with purposeful response / following commands
• No ventilator requirement
• DNR / MOST limiting scope of treatment
• Terminal illness
• Traumatic etiology leading to arrest
• Poor baseline neurological status pre-arrest
Relative Exclusion Criteria

- Pregnancy
- Active bleeding or intracranial bleeding
- Recent major surgery (Cranial / Thoracic / Abdominal)
- Severe sepsis / shock
When do we start cooling?

- Answer is unknown
- No conclusive evidence pre-hospital cooling offers a benefit
- Typically reach target temperature 1 hour faster
When do we start cooling?

- November 2013 JAMA
- Washington State: Randomized study
- 1359 patients
  - 583 VT
  - 776 some other rhythm
- No difference in survival or good neurological outcome whether EMS cooled or did not cool
How cool do we go?

- European study with 950 patients
- Randomized to target temperatures of 33 and 36°C
  - 460 died
  - Mortality similar in both groups
  - Neurological function similar in both groups
  - Serious adverse events similar in both groups
  - No difference
  - This may be we are controlling for fever

PHASES OF HYPOTHERMIA
Phases of Hypothermia

• **Induction**
  – Rapid cooling, target temp within 1 hour

• **Maintenance**
  – Precise temperature control $32^\circ$ to $34^\circ$ C

• **Rewarming**
  – Slowly, 0.1 - 0.5$^\circ$ C per hour
  – At $36^\circ$ C allow passive rewarming

• **Normothermia**
  – Maintain normothermia
Complications of Therapeutic Hypothermia

- Hemorrhage
- Hyperkalemia (clinically significant)
- Hyperglycemia
- Pharmacokinetics
- Infection including pneumonia (up to 50%)
  - Probably related to aspiration
- Sepsis (no statistical significance)
- Skin breakdown (no bathing until re-warmed)
- Seizures
- Shivering
Control of Shivering

- Hyperthermia expected and bad
- Demerol decreases shivering threshold
- Fentanyl more commonly used
- Benzodiazepines
- Anesthetics
- Magnesium
- Neuromuscular blockade
**Arrhythmia Complications**

- **EKG Changes**
  - “Normal” HR at 32°C is 40 beats per minute
  - Prolonged PR interval, widening of the QRS complex, increased QT interval, Osborn waves
  - Artificially increasing the HR is rarely necessary and can decrease myocardial contractility
  - Mixed venous or lactic acid level to determine if patient is tolerating HR
Complications of Rewarming

- Allowing too rapid warming process
- Hyperthermia
- Hyperkalemia
- Diuresis
- Shivering
Is Therapeutic Hypothermia Really Safe?

• YES
• Meta-analysis February 2013
• 63 studies
  – Mainly VT patients
  – ROSC and minimal neurological recovery
  – NNT 5 - 7
• Arrhythmia and hypokalemia most common
SUMMARY

• Should I begin therapeutic hypothermia in my EMS system?
• YES….but
  – Only if you have high-quality CPR
  – Early defibrillation
  – Team focused CPR
  – EMD aggressively instructing CPR
  – Maximized all other interventions first
Local Case Study

• 47 y/o caucasion male
• Typical Friday evening with his family
• Sudden Cardiac Arrest
• Bystander CPR by spouse
• 9 y/o daughter called 911
• First Responders / FD defibrillated with AED
• ROSC after about 15 minutes
Local Case Study

- Remained unresponsive with no respiratory effort and with fixed and dilated pupils
- Hypothermia induced with IV fluids and cold packs to neck, axilla and groin
- Arrived at FMC with Arctic Sun continued
- Therapeutic hypothermia for 24 hours
- Tuesday pupillary reaction noted with spontaneous respirations
- Wednesday awake on ventilator
Local Case Study

• Wednesday recognizing family and friends at bedside
• Thursday extubated
• Friday sitting in chair eating in CICU
• 11 days after arrest discharged home with only mild short term memory loss
• Returning to work as a High School teacher
Therapeutic Hypothermia
Whole Story in an Ice Cube

- Benefits of hypothermia known since antiquity
- Relatively cheap and easy to utilize
- Neurological outcomes improved
- Requires Multidisciplinary care
- Recommended since 2003 by AHA but continues to have poor utilization among physicians
• http://iconnect.novanthealth.org/Forsyth/POCOrderSets/POC_Documents/CriticalCareHypothermiaPostCardiacArrestOrders.pdf