Management of the Post Cardiac Arrest Patient

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Disclosures

• Employer: University of Pittsburgh/ UPMC

• Expert Witness

• Grants:
  • Neurologic Emergencies Treatment Trials Networks (NETT)
  • Scaife Foundation
  • Laerdal Foundation
Objectives

- Review of literature using TTM in medical patients
- Review post-arrest care bundle
- Review common implementation barriers
- Illustrate how to implement these changes and incorporate updates

Out of Hospital Cardiac Arrest - A Common Disease

- 600-1000 Americans will suffer OOHCA today
- 300,000 Americans suffer OOHCA yearly
- 25+ will suffer OOHCA during this talk
- High morbidity and mortality
  - ~50% never make it to the hospital
Multiple Ways to Die

How Can We Improve Outcomes?

Saving “hearts and brains too young to die”
Different systems = different outcomes

![Bar chart showing survival rates from OOHCA (all rhythms) for various cities.]

- Vancouver: 5.5, 9.7%
- Toronto: 16.3%
- Seattle: 7%
- Portland: 10.6%
- Pittsburgh: 5.3, 9.7%
- Ottawa: 4.5, 11%
- Milwaukee: 5.5, 9.7%
- Iowa: 4.5, 11%
- Dallas: 4.5, 11%
- Alabama: 5.5, 9.7%

Nichol, 2008

Systems of Care for Post–Cardiac Arrest Patients

Establish a comprehensive, structured, multidisciplinary system that treats post–cardiac arrest patients in a consistent manner.

- therapeutic hypothermia
- optimize cerebral blood flow
- optimization of hemodynamics and gas exchange
- immediate coronary reperfusion when indicated
- neurological diagnosis, management, and prognostication
Effects of Hypothermia
Mechanism of Hypothermia

- Decrease in cerebral metabolism
  - 6% reduction for every 1°C drop in temperature

- Suppression of reperfusion injury
  - Decreased free radical production
  - Reduction in excitatory neurotransmitters
  - Suppression of Ca^{2+} mediated cell death
  - Anti-inflammatory effects

  Nolan et al. (2003) Circulation

Hypothermia and the Injured Heart

- Mild hypothermia reduces ultimate infarct size.
- LAD occlusions in 60-80 kg swine for 60 minutes
- Endovascular cooling to 34°C from 20-75 minutes.

Why?

- Decreasing temperature increases myocardial contractility
  - ↑isometric twitch force in isolated muscle
  - ↑dP/dT, ↑stroke volume in vivo
  - ↓heart rate in vivo (like B-blockade)
  - ↑cardiac output
  - No real change in SVR, PVR in this temp range

- Decreasing temperature may save myocardium

Animal studies of mild-moderate hypothermia (32-34°C).

Immediate, brief hypothermia has benefit
Benefit of brief hypothermia not long-lasting
Longer duration has lasting benefit
Any delay negates benefit of brief hypothermia
Longer duration has benefit after delay
Brief delay negates benefit of brief or 3-hour hypothermia
Longer duration has benefit after even long delay
No duration has benefit after 8-12 hour delay
RCT’s on TTM (OHCA VF/VT)

Therapeutic Hypothermia

The New England Journal of Medicine

MILD THERAPEUTIC HYPOTHERMIA TO IMPROVE THE NEUROLOGIC OUTCOME AFTER CARDIAC ARREST

TREATMENT OF COMATOSE SURVIVORS OF OUT-OF-HOSPITAL CARDIAC ARREST WITH INDUCED HYPOTHERMIA

Stephan A. Bernard, M.B., B.S., Timothy W. Gray, M.B., B.S., Michael D. Brist, M.B., B.S.,
### Outcome Risk Ratio

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Risk Ratio</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable Outcome</td>
<td>1.40 (1.08 - 1.81)</td>
<td>2.65 (1.02 - 6.88)</td>
</tr>
<tr>
<td>Death at 6 months</td>
<td>0.74 (0.58 - 0.95)</td>
<td>5.25 (1.47 - 18.76)</td>
</tr>
</tbody>
</table>

**HACA**

- **NNT (Favorable Outcome)** = 6.4
- **NNT (Not Dead)** = 7.0
- **Relative Risk Reduction (Neuro)** = 26%
- **Relative Risk Reduction (Death)** = 26%

**Bernard**

- **NNT (Good Outcome)** = 4.5
- **NNT (Not Dead)** = 6.1
- **Relative Risk Reduction (Neuro)** = 30%
- **Relative Risk Reduction (Death)** = 24%

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**Laurent, 2005**

- RCT of 42 subjects to Hemofiltration @37°C vs Hemofiltration @32°C
- OHCA with shockable or asystole
- Primary outcome was mortality at 6 months
- Survival was 32% in 32°C and 45% in 37°C (p=0.28)
Zhang 2005

- RCT of 16 patients to 33°C (for 72 hours) or no temp management
- GCS at 3 days was 13 in TH and 10 in no TH (p<0.05)
- Secondary endpoint: Barthel index 86 vs. 52 (p<0.01)

32° vs 34°C

Hypothermia in Comatose Survivors From Out-of-Hospital Cardiac Arrest: Pilot Trial Comparing 2 Levels of Target Temperature
Esteban Lopez-de-Sa, Juan R. Rey, Eduardo Armada, Pablo Salinas, Ana Viana-Tejedor, Sandra Espinosa-Garcia, Mercedes Martinez-Moreno, Ervigio Corral and Jose Lopez-Sendon

_Circulation_. 2012;126:2826-2833; originally published online November 6, 2012;
Methods

- Randomized 36 subjects to 32° or 34°C
- Primary outcome: avoidance of severe dependence at 6 months (Barthel Index>60)
- 32°C group: 61.4% without severe dependence
- 34°C group: 15.4% without severe dependence

Targeted Temperature Management at 33°C versus 36°C after Cardiac Arrest

- 952 comatose post-arrest patients randomized
  - Larger than the last 2 trials combined
- Maintained for 24 hours, rewarmed for 12
- No withdrawal until 72 hours after rewarming
- Blinded neurologist and standard algorithm for prognostication
Outcomes

- Survival 50% in 33°C group
- 52% in 36°C group

OHCA VF/VT arrest

Diagram showing data for different interventions.
The details...

| Bystander witnessed cardiac arrest — no. (%) | 420 (99) | 418 (99) |
| Bystander performed CPR — no. (%) | 344 (73) | 339 (73) |

| First monitored rhythm — no. (%) |   |   |
| Shockable rhythm | 375 (79) | 377 (83) |
| Ventricular fibrillation | 349 (74) | 356 (77) |
| Nonshockable ventricular tachycardia | 12 (3) | 12 (3) |

| Unknown rhythm but responsive to shock | 5 (1) | 5 (1) |
| Perishing rhythm after bystander-initiated defibrillation | 9 (2) | 4 (1) |
| Asystole | 59 (12) | 54 (12) |
| Pulseless electrical activity | 37 (8) | 28 (6) |
| Unknown first rhythm, not responsive to shock or not shocked | 2 (<0.5) | 6 (1) |

Time from cardiac arrest to event — min:

| Start of first life support |   |   |
| Median | 1 | 1 |
| Interquartile range | 0–2 | 0–2 |

Questions

- Screened 1431 to enroll 950, what happened to those other 481?
- 189 did not meet inclusion criteria
- 160 lost due to no consent: wasn’t this EFIC?
What is my system like?

- VF/VT 30-40%
- Bystander CPR 30%

- ROC data: ~25%
  - Nichol 2008 JAMA

Observational Studies
(OHCA Non-VF/VT)
Testori, 2011

- Registry of 374 OHCA, witnessed, non-shockable
- Intervention: 32-34°C for 24 hours vs. no management
- CPC 1-2 was 35% in TH group, 23% in no management (p<0.05; OR 1.84 95% CI 1.08, 3.13)

Dumas, 2011

- Registry of 437 OHCA, non-shockable
- Intervention: 32-34°C vs no temp management
- CPC 1-2 in 15% in TH vs 17% in no temp management (OR 0.83; 95% CI 0.49, 1.4)
Nichol, 2013

- GWTG registry of 8316 IHCA arrest, regardless of rhythm
- Compared survival between those coded as receiving TH and not (only 2.6% received TH)
- Survival 27% for TH and 31% for no TH (OR 0.90; 95% CI 0.65, 1.23)
Can We Return to Pre-2002 Care?

- Fever is common (41%) even after TH
  - Leary 2013 Resuscitation
- Early fever (onset median: 15 hours after arrest) without TH remains associated with mortality: 69% vs 31% (p=0.003)
  - Gebhardt 2013 Resuscitation
- Answer: NO

Evidence on Targeted Temperature Management

- RCTs suggest that controlling of temperature (33-36°C) is better than not controlling temperature (37°C or higher)
  - Moderate Quality Evidence
- RCTs suggests that outcomes with 32°C-34°C, 33°C and 36°C are similar.
  - High Quality Evidence
Is “Coma” a Binary Variable?

- GCS 3 ≠ GCS 7
- GCS 3 with brainstem ≠ GCS without brainstem

FOUR Score

- NCS Guru, Elco Wijdicks
Combine initial FOUR score and SOFA score to define four “Categories of illness severity”

Category 1 - No coma
Category 2 - Coma, stable
Category 3 - Coma, cardiopulmonary failure
Category 4 – Coma, w/ brainstem dysfunction

Shock

None | Moderate | Severe
--- | --- | ---
Type 1 | Type 2 | Type 3

Neurological Injury

None | Some | Complete
--- | --- | ---
Type 1 | Type 2 | Type 4

Category: SOFA vs. FOUR

Category 1 - No coma
Category 2 - Coma, stable
Category 3 - Coma, cardiopulmonary failure
Category 4 – Coma, w/ brainstem dysfunction
Category Associated with Primary Rhythm

Think Cerebral Blood Flow
Cerebral perfusion varies over time

**Transient cerebral ischemia**
- Hyperemia 20-30 minutes
- Hypoperfusion 2-24 hours

Blood Pressure and Ventilation

- **Auto-regulation**
  - Impaired / right-shifted
- **CO2-reactivity**
  - Preserved
Blood Pressure and Ventilation

Auto-regulation
- Impaired / right-shifted

CO2-reactivity
- Preserved

CBF

MAP

pCO2

Infused norepinephrine to increase CBF

Autoregulation of Cerebral Blood Flow in Patients Resuscitated From Cardiac Arrest

Claas Sandgreen, MD; Finn Stolze Larsen, MD; Tina Maria Herrøg, MD; Gitte Moos Knudsen, MD; Søren Boesgaard, MD; Jan Aldershvile, MD
Blood Pressure and Ventilation

This is scenario for first several hours after CPR

Brain Tissue Hypoxia

- TH decreases metabolic demand
- Brain tissue hypoxia is common
- Will TH help?
- Who will benefit?
EEG Monitoring

- HACA (2002) reported 8% incidence of seizures in cohort of patients in original hypothermia trial.

- Tomte (2011) reported 24% incidence of seizures in a less selected cohort of patients.

EEG monitored continuously if possible during hypothermia or until clear improvement or until clear endpoint (e.g., brain death).

Use of Continuous EEG - Pittsburgh

103 /331 subjects (31%) have malignant EEG (NCSE, SE, GPED, MSE)
EEG, Category and Survival (n=327)

Survival (%)

<table>
<thead>
<tr>
<th>Category</th>
<th>No Malignant EEG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category 1</td>
<td>100</td>
</tr>
<tr>
<td>Category 2</td>
<td>69</td>
</tr>
<tr>
<td>Category 3</td>
<td>50</td>
</tr>
<tr>
<td>Category 4</td>
<td>16</td>
</tr>
</tbody>
</table>

Odds Ratio for Survival:
- PCAC 0.37 (0.27-0.49); EEG 0.39 (0.21-0.74)

EEG, Category and Good Outcome (n=327)

Good Outcome (%)

<table>
<thead>
<tr>
<th>Category</th>
<th>No Malignant EEG</th>
<th>Malignant EEG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category 1</td>
<td>50</td>
<td>0</td>
</tr>
<tr>
<td>Category 2</td>
<td>47</td>
<td>15</td>
</tr>
<tr>
<td>Category 3</td>
<td>23</td>
<td>20</td>
</tr>
<tr>
<td>Category 4</td>
<td>9</td>
<td>2</td>
</tr>
</tbody>
</table>

Odds Ratio for Good Outcome:
- PCAC 0.35 (0.25-0.51); EEG 0.24 (0.10-0.62)
Seizures and Temperature

When induced hypothermia (33-34°C for 72 hours) is used for neonatal hypoxic-ischemic encephalopathy, the frequency of seizures is reduced (Low 2012; Arch Dis Child Fetal Neonatal Ed 2012; 97: F267-72).

In the neonatal HIE population, seizures may be more common than after adult cardiac arrest (Azzopardi 2009; Arch Dis Child Fetal Neonatal Ed 2009; 94: F260-4).
Hypothermia?

- Lower temperatures will reduce cerebral edema
- Lower temperatures may improve tolerance to transient tissue hypoxia
- Lower temperatures will reduce incidence of seizures

Acute coronary syndrome

- Most common cause of Out-of-hospital Cardiac Arrest
  - 70% - 85% of cases (when a diagnosis is made)
  - STEMI in 12-40% (a lot of “ascertainment bias”)

- Other causes more common for In-hospital Cardiac Arrest
  - Respiratory failure / airway misadventure
  - Progression of shock
Catheterization of Consecutive CA Patients (Spaulding 1997 - Paris)

- 85 consecutive patients have coronary angiography
  - 36 STEMI (42%)
  - 18 LBBB (21%)
  - 28 Chest pain before arrest (25%)

- One or more vessels with >50% stenosis identified in (60/85) 71% of cases

Acute Coronary Syndrome is most cause of out-of-hospital cardiac arrest

Coronary Angiography Predicts Improved Outcome Following Cardiac Arrest: Propensity-adjusted Analysis

Joshua C. Reynolds, MD, Clinton W. Callaway, MD, PhD,
Samir R. Khoury, PhD, MPH, Charity G. Moore, PhD, MSPH,
Rene J. Alvarez, MD, and Jon C. Rittenberger, MD, MS

- Good outcome for
  - 52 / 96 (54%) cases with CATH versus
  - 36 / 145 (28%) of cases with no CATH

- CATH has **2.16 [1.12, 4.19]** odds ratio of good outcome
  - adjusting for Coma, Hypothermia, STEMI, Age, Sex, In-hospital or Out-of-Hospital, and Initial Rhythm
Dumas (2010) – Multivariable Regression

- Time BLS-ROSC > 15 min
- Time Collapse-BLS > 5 min
- Diabetes Mellitus
- Age > 59 years
- Asystole / PEA
- Blood Lactate (quartile)
- STEMI
- Successful PCI

Circ Cardiovasc Interv 2010;3;200-207
• Largest survival difference among 203 hospitals was that between hospitals with (n=117) and without (n=86) cardiac catheterization capabilities

• Association with volume of cases (>40 per year was better)

OR 1.46, 95% CI 1.26-1.61
Implanted Cardioverter Defibrillators

Symptoms after Discharge (Health Utilities Index)

HUI - quality of health  Subscales of Symptoms

One Month

Number

0 1 2 3 4

HUI Score

100

80

60

40

20

0

None  Mild  Moderate  Severe

Percentage

0 20 40 60 80 100

Vision  Hearing  Speech  Ambulation  Dexterity  Emotion  Cognition  Pain
Take Home

- Managing temperature is required
- Unclear what is best temperature or duration
  - 32-36°C is reasonable
  - 12-24 hours is reasonable
- We need to phenotype neurologic injury in a standardized fashion
  - Unlikely that one size fits all