When to stop after cardiac arrest?

Eyal Golan, MD PhD(c)
Clinical Associate, Critical Care Medicine & Neurocritical Care Medicine
Interdepartmental Division of Critical Care and Department of Medicine
University of Toronto
Conflicts of interest

Financial: None

? Academic: Research focus
Guideline development
(ILCOR, AHA-ECC, CCCTG-CNCS)
Cardiac arrest is both devastating and common

213 out of hospital arrests / 100,000 adults

Overall survival about 8%

But survival rates among those admitted to hospital are much higher...

13,263 Patients Health-Person Oriented Information Database

Redpath Am Heart J 2010

38% survival

In-hospital survival rates in patients admitted after OHCA stratified by year ($P = .30$).
The most likely outcome in adult out-of-hospital cardiac arrest patients that survive to hospital discharge

1. Minimal disability
2. Moderate disability
3. Severe disability
4. Vegetative state
The most likely outcome in adult out-of-hospital cardiac arrest patients that survive to hospital discharge

1. Minimal disability
2. Moderate disability
3. Severe disability
4. Vegetative state
But survival rates among those admitted to hospital are much higher...

38% survival

More than two thirds have minimal to no disability

13,263 Patients Health-Person Oriented Information Database

Redpath Am Heart J 2010

In-hospital survival rates in patients admitted after OHCA stratified by year (P = .30).

Aufderheide T et al. NEJM 2011;365:798-806
Predicting good neurological outcome in adult cardiac arrest survivors that receive targeted temperature management

Golan E, Scales DC, Morrison LM 2014 (data not yet published)
Predicting good neurological outcome in adult cardiac arrest survivors that receive targeted temperature management

78% of patients that survived to hospital discharge experienced a very good neurological outcome as defined by a CPC 1 (431/550 patients)
Cognitive outcomes of patients undergoing therapeutic hypothermia after cardiac arrest

ABSTRACT

Objective: We aimed to study the long-term cognitive abilities of patients surviving out-of-hospital cardiac arrest who were treated with therapeutic hypothermia (TH).

Methods: We prospectively identified and examined consecutive survivors of out-of-hospital cardiac arrest who underwent TH at our institution from June 2006 to May 2011. The results of brain imaging, serum neuron-specific enolase (NSE) measurements, and EEGs were recorded. We assessed cognitive domains using the modified Telephone Interview for Cognitive Status. An education-adjusted score of ≥32 was considered normal.

Results: Of 133 total patients, 77 (58%) were alive at a median follow-up of 20 months (interquartile range 14–24 months). We interviewed 56 patients (73% of those alive). Median age was 67 years (range 24–88 years). Fifty-one patients (91%) were living independently. Modified Telephone Interview for Cognitive Status scores ranged from 18 to 41. Thirty-three (60%) were considered cognitively normal and 22 (40%) were cognitively impaired. The time to assessment did not differ among the cognitive outcomes (p = 0.557). The median duration of coma was 2 days, possibly indicating that patients with severe anoxic injury were not included. Eighteen patients were not working at the time of their cardiac arrest (17 were retired and 1 was unemployed). Of the 38 patients who were working up to the time of the cardiac arrest, 30 (79%) returned to work. Cognitive outcome was not associated with age, time to return of spontaneous circulation, brain atrophy, or leukoaraiosis.

Conclusions: The majority of surviving patients who underwent TH after cardiac arrest in this series had preserved cognitive function and were able to return to work. Neurology 2013 811–8

GLOSSARY

CPC = Cerebral Performance Category; IQR = Interquartile range; NSE = neuron-specific enolase; OHCA = out-of-hospital cardiac arrest; ROSC = return of spontaneous circulation; TH = therapeutic hypothermia; TICS = Telephone Interview for Cognitive Status, modified.

Out-of-hospital cardiac arrest (OHCA) strikes suddenly and is frequently fatal. Over the past decade, people who undergo cardiac arrest and cardiopulmonary resuscitation are increasingly surviving.1–3 During a cardiac arrest, neuronal injury begins to occur because blood flow to the brain ceases. For the first few minutes of cardiac arrest, neurons are still viable, but they are rapidly depleting of oxygen and energy; after this point, irreversible neuronal injury occurs. The subsequent cognitive outcomes of these patients are poorly understood.
“The majority (79%) of surviving patients who underwent TH after cardiac arrest in this series had preserved cognitive function and were able to return to work.”
The Chain of Survival
The most common mechanism of death during ICU

1. Brain death
2. A decision to withdrawal life support
3. Sepsis
4. Acute respiratory distress syndrome
The most common mechanism of death during ICU

1. Brain death
2. A decision to withdrawal life support
3. Sepsis
4. Acute respiratory distress syndrome
Our predictions are important!

Termination of life support is the most common way that patients die during ICU

Physician prediction of poor outcome is the strongest predictor of termination of life support
Avoid prematurely terminating life support in patients who will survive
Avoid continuing life support in patients who will have poor outcomes
Clinicians are generally poor at subjectively predicting survival, functional outcome and quality after critical illness.

Physicians tend to over-estimate poor outcomes and under-estimate good outcomes.
Factors to consider

1. Our predictions are important
2. Self-fulfilling prophecies
3. Dichotomous outcomes
4. Targeted temperature management
5. Selective memory
6. Diagnostic test accuracy
Factors to consider

1. Our predictions are important
2. Self-fulfilling prophecies
3. Dichotomous outcomes
4. Targeted temperature management
5. Selective memory
6. Diagnostic test accuracy
Factors to consider

1. Our predictions are important
2. Self-fulfilling prophecies
3. Dichotomous outcomes
4. Targeted temperature management
5. Selective memory
6. Diagnostic test accuracy
Self-fulfilling prophecies

Problems clinically
Physicians become falsely reassured

Problems for research
Most studies do not prevent physicians from stopping life support in response to clinical predictors

Newer trials aim to prevent “early” withdrawal

Geocadin et al. Neurology 2006; 67:105
Factors to consider

1. Our predictions are important
2. Self-fulfilling prophecies
3. Dichotomous outcomes
4. Targeted temperature management
5. Selective memory
6. Diagnostic test accuracy
Emphasis is on predicting poor, not good outcomes

Patients may still wish to base decisions to withdraw life support on intermediate outcomes

Spectrum of outcomes between disability and complete neurological recovery
Factors to consider

1. Our predictions are important
2. Self-fulfilling prophecies
3. Dichotomous outcomes
4. Targeted temperature management
5. Selective memory
6. Diagnostic test accuracy
Mild therapeutic hypothermia for Cardiac Arrest Survivors

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


MILD THERAPEUTIC HYPOTHERMIA TO IMPROVE THE NEUROLOGIC OUTCOME AFTER CARDIAC ARREST

The Hypothermia after Cardiac Arrest Study Group*

The New England Journal of Medicine
Hypothermia improved survival with good neurological outcome

[1] Holzer et al, NEJM 2002; 0.3C/hr cooling with cold air and ice packs
[2] Bernard et al, NEJM 2002; 0.9C/hr cooling with ice packs
Hypothermia improved survival with good neurological outcome

Number needed to treat to have one more patient survive with good neurological outcome (NNT) = 5

[2] Bernard et al, NEJM 2002; 0.9°C/hr cooling with ice packs
Part 8: Advanced Life Support

2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations

Laurie J. Morrison, Co-Chair*; Charles D. Deakin, Co-Chair*; Peter T. Morley; Clifton W. Callaway; Richard E. Kerber; Steven L. Kronick; Eric J. Lavonas; Mark S. Link; Robert W. Neumar; Charles W. Otto; Michael Parr; Michael Shuster; Kjetil Sunde; Mary Ann Peberdy; Wanchun Tang; Terry L. Vanden Hoek; Bernd W. Böttiger; Saul Drajer; Swee Han Lim; Jerry P. Nolan; on behalf of the Advanced Life Support Chapter Collaborators
Part 8: Advanced Life Support
2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations

Laurie J. Morrison, Co-Chair*; Charles D. Deakin, Co-Chair*; Peter T. Morley; Clifton W. Callaway; Richard E. Kerber; Steven L. Kronick; Eric J. Lavonas; Mark S. Link; Robert W. Neumar; Charles W. Otto; Michael Parr; Michael Shuster; Kjetil Sundt; Mary Ann Peberdy; Wanchun Tang; Terry L. Vanden Hoek; Bernad W. Böttiger; Saul Dzraj; Swee Han Lim; Jerry P. Nokes; on behalf of the Advanced Life Support Chapter Collaborators

- no clinical neurologic signs reliably predict poor outcome 24 hours

- In patients not treated with hypothermia and have no confounding factors, the absence of both pupillary light and corneal reflex at 72 hours reliably predicts poor outcome

- Absence of vestibulo-ocular reflexes at 24 hours and a GCS motor score of 2 or less at 72 hours are less reliable

- Other clinical signs, including myoclonus, are not recommended for predicting poor outcome.
The Targeted Temperature Management (TTM) Trial

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

Niklas Nielsen, M.D., Ph.D., Jørn Wetterslev, M.D., Ph.D., Tobias Cronberg, M.D., Ph.D.,
The Targeted Temperature Management (TTM) Trial

Box A: 4 h
Achievement of target temperature

Box B: 24 h
Maintenance of target temperature

Box C: 8 h
Rewarming to normothermia.

CT of neck/head, coronary angiography, PCI, and other diagnostics and interventions when indicated

Start of intervention as soon as possible after sustained ROSC

Sedation mandatory
The Targeted Temperature Management (TTM) Trial
TTM changes the accuracy of our clinical predictors

- Confounding due to sedating/paralyzing medications used to induce and maintain hypothermia

- May change accuracy of predictors used for neuroprognostication by attenuating degree of brain injury

- We have all seen examples
Factors to consider

1. Our predictions are important
2. Self-fulfilling prophecies
3. Dichotomous outcomes
4. Targeted temperature management
5. Selective memory
6. Diagnostic test accuracy
Reversible brain death after cardiopulmonary arrest and induced hypothermia*

- “A 55-yr-old man presented with cardiac arrest… spontaneous perfusion restored, and therapeutic hypothermia provided”
- “Death was pronounced and the family consented to organ donation.”

Webb and Samuels, CCM 2011.
Reversible brain death after cardiopulmonary arrest and induced hypothermia

“24 hrs after brain death, on arrival to the operating room for organ procurement, the patient was found to have regained corneal reflexes, cough reflex, and spontaneous respirations.”

Webb and Samuels, CCM 2011.
Factors to consider

1. Our predictions are important
2. Self-fulfilling prophecies
3. Dichotomous outcomes
4. Targeted temperature management
5. Selective memory
6. Diagnostic test accuracy
The confidence problem

No consensus on the **PRECISION** that should be obtained for predicting poor outcomes

How wide should confidence intervals around **ZERO** be?
Prognostication after Cardiac Arrest and Hypothermia
A Prospective Study

Andrea O. Rossetti, MD,¹ Mauro Oddo, MD,² Giancarlo Logroscino, MD, PhD,³ and Peter W. Kaplan, MBBS, FRCP¹,⁴

• 111 cardiac arrests treated with hypothermia
• Neurological examination 36-72 HOURS
  – EEG
  – SSEP
  – All measurements during normothermia and off sedation
• CPC assessed at 3 to 6 months
<table>
<thead>
<tr>
<th>Variable</th>
<th>FPR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-VF CA (asystole or PEA)</td>
<td>0.15 (0.06–0.29)</td>
</tr>
<tr>
<td>ROSC &gt;25 minutes</td>
<td>0.24 (0.13–0.40)</td>
</tr>
<tr>
<td>≥1 brainstem reflexes absent (^a)</td>
<td>0.04 (0.01–0.15)</td>
</tr>
<tr>
<td>Motor response worse than flexion</td>
<td>0.24 (0.13–0.40)</td>
</tr>
<tr>
<td>Early myoclonus</td>
<td>0.03 (0.00–0.11)</td>
</tr>
<tr>
<td>Epileptiform activity on first EEG</td>
<td>0.09 (0.02–0.21)</td>
</tr>
<tr>
<td>Unreactive EEG background</td>
<td>0.07 (0.01–0.18)</td>
</tr>
<tr>
<td>Bilaterally absent N20 on SSEP</td>
<td>0.00 (0.00–0.08)</td>
</tr>
</tbody>
</table>
Predicting Neurologic Outcome After Targeted Temperature Management for Cardiac Arrest: Systematic Review and Meta-Analysis*

Eyal Golan, MD, PhDc1,2; Kali Barrett, MD1; Aziz S. Alali, MD2; Abhijit Duggal, MD3; Draga Jichici, MD4; Ruxandra Pinto, PhD5; Laurie Morrison, MD, MSc6,7,8; Damon C. Scales, MD, PhD1,2,9,10

*See also p. 1869.

1Department of Critical Care Medicine, Western University, London, ON, Canada.
2Interdisciplinary Division of Critical Care and Neurology, Department of Critical Care Medicine and Critical Care, St. Michael's Hospital, University of Toronto, Toronto, ON, Canada.
3Division of Critical Care and Neuroscience, Department of Neurology, University of Toronto, Toronto, ON, Canada.
4Division of Critical Care and Neuroscience, Department of Neurology, University of Toronto, Toronto, ON, Canada.
5Division of Emergency Medicine, Department of Emergency Medicine, University of Toronto, Toronto, ON, Canada.
6Department of Health Policy, Management and Evaluation, University of Toronto, Toronto, ON, Canada.
7Division of Critical Care and Neurology, Department of Critical Care Medicine and Critical Care, St. Michael's Hospital, University of Toronto, Toronto, ON, Canada.
8Department of Emergency Medicine, University of Toronto, Toronto, ON, Canada.
9Department of Emergency Medicine, University of Toronto, Toronto, ON, Canada.
10Department of Emergency Medicine, University of Toronto, Toronto, ON, Canada.
# Precision of the diagnostic tests

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Patients tested, n</th>
<th>Number of studies, n</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>FPR</th>
<th>Positive LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corneal reflex</td>
<td>367</td>
<td>5</td>
<td>0.28 (0.21-0.37)</td>
<td>0.96 (0.91-0.99)</td>
<td>0.04 (0.01-0.09)</td>
<td>6.8 (2.52-18.38)</td>
</tr>
<tr>
<td>Pupillary reflex</td>
<td>438</td>
<td>5</td>
<td>0.24 (0.19-0.31)</td>
<td>0.98 (0.94-0.99)</td>
<td>0.02 (0.01-0.06)</td>
<td>10.45 (3.37-32.43)</td>
</tr>
<tr>
<td>Motor score (M1 or M2)</td>
<td>791</td>
<td>8</td>
<td>0.61 (0.44-0.76)</td>
<td>0.91 (0.87-0.94)</td>
<td>0.09 (0.06-0.13)</td>
<td>7.11 (5.01-10.08)</td>
</tr>
<tr>
<td>Clinical status myoclonus</td>
<td>513</td>
<td>6</td>
<td>0.29 (0.22-0.38)</td>
<td>0.95 (0.89-0.98)</td>
<td>0.05 (0.02-0.11)</td>
<td>5.58 (2.56-12.16)</td>
</tr>
<tr>
<td>Unfavorable EEG</td>
<td>552</td>
<td>11</td>
<td>0.66 (0.47-0.82)</td>
<td>0.93 (0.88-0.96)</td>
<td>0.07 (0.04-0.12)</td>
<td>8.85 (4.87-16.08)</td>
</tr>
<tr>
<td>SSEP</td>
<td>620</td>
<td>9</td>
<td>0.43 (0.33-0.53)</td>
<td>0.97 (0.93-0.99)</td>
<td>0.03 (0.01-0.07)</td>
<td>12.79 (5.35-30.62)</td>
</tr>
<tr>
<td>NSE &gt; 33</td>
<td>507</td>
<td>4</td>
<td>0.51 (0.46-0.57)</td>
<td>0.88 (0.77-0.94)</td>
<td>0.12 (0.06-0.23)</td>
<td>4.14 (1.82-9.42)</td>
</tr>
</tbody>
</table>

Golan E et al, CCM 2014 Oct;42(10):2235-43
# Precision of the diagnostic tests

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Patients tested, n</th>
<th>Number of studies, n</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>FPR</th>
<th>Positive LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corneal reflex</td>
<td>367</td>
<td>5</td>
<td>0.28 (0.21-0.37)</td>
<td>0.96 (0.91-0.99)</td>
<td>0.04 (0.01-0.09)</td>
<td>6.8 (2.52-18.38)</td>
</tr>
<tr>
<td>Pupillary reflex</td>
<td>438</td>
<td>5</td>
<td>0.24 (0.19-0.31)</td>
<td>0.98 (0.94-0.99)</td>
<td>0.02 (0.01-0.06)</td>
<td>10.45 (3.37-32.43)</td>
</tr>
<tr>
<td>Motor score (M1 or M2)</td>
<td>791</td>
<td>8</td>
<td>0.61 (0.44-0.76)</td>
<td>0.91 (0.87-0.94)</td>
<td>0.09 (0.06-0.13)</td>
<td>7.11 (5.01-10.08)</td>
</tr>
<tr>
<td>Clinical status myoclonus</td>
<td>513</td>
<td>6</td>
<td>0.29 (0.22-0.38)</td>
<td>0.95 (0.89-0.98)</td>
<td>0.05 (0.02-0.11)</td>
<td>5.58 (2.56-12.16)</td>
</tr>
<tr>
<td>Unfavorable EEG</td>
<td>552</td>
<td>11</td>
<td>0.66 (0.47-0.82)</td>
<td>0.93 (0.88-0.96)</td>
<td>0.07 (0.04-0.12)</td>
<td>8.85 (4.87-16.08)</td>
</tr>
<tr>
<td>SSEP</td>
<td>620</td>
<td>9</td>
<td>0.43 (0.33-0.53)</td>
<td>0.97 (0.93-0.99)</td>
<td>0.03 (0.01-0.07)</td>
<td>12.79 (5.35-30.62)</td>
</tr>
<tr>
<td>NSE &gt; 33</td>
<td>507</td>
<td>4</td>
<td>0.51 (0.46-0.57)</td>
<td>0.88 (0.77-0.94)</td>
<td>0.12 (0.06-0.23)</td>
<td>4.14 (1.82-9.42)</td>
</tr>
</tbody>
</table>

Golan E et al, CCM 2014 Oct;42(10):2235-43
### Precision of the diagnostic tests

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Patients tested, n</th>
<th>Number of studies, n</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>FPR</th>
<th>Positive LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corneal reflex</td>
<td>367</td>
<td>5</td>
<td>0.28 (0.21-0.37)</td>
<td>0.96 (0.91-0.99)</td>
<td>0.04 (0.01-0.09)</td>
<td>6.8 (2.52-18.38)</td>
</tr>
<tr>
<td>Pupillary reflex</td>
<td>438</td>
<td>5</td>
<td>0.24 (0.19-0.31)</td>
<td>0.98 (0.94-0.99)</td>
<td>0.02 (0.01-0.06)</td>
<td>10.45 (3.37-32.43)</td>
</tr>
<tr>
<td>Motor score (M1 or M2)</td>
<td>791</td>
<td>8</td>
<td>0.61 (0.44-0.76)</td>
<td>0.91 (0.87-0.94)</td>
<td>0.09 (0.06-0.13)</td>
<td>7.11 (5.01-10.08)</td>
</tr>
<tr>
<td>Clinical status myoclonus</td>
<td>513</td>
<td>6</td>
<td>0.29 (0.22-0.38)</td>
<td>0.95 (0.89-0.98)</td>
<td>0.05 (0.02-0.11)</td>
<td>5.58 (2.56-12.16)</td>
</tr>
<tr>
<td>Unfavorable EEG</td>
<td>552</td>
<td>11</td>
<td>0.66 (0.47-0.82)</td>
<td>0.93 (0.88-0.96)</td>
<td>0.07 (0.04-0.12)</td>
<td>8.85 (4.87-16.08)</td>
</tr>
<tr>
<td>SSEP</td>
<td>620</td>
<td>9</td>
<td>0.43 (0.33-0.53)</td>
<td>0.97 (0.93-0.99)</td>
<td><strong>0.03 (0.01-0.07)</strong></td>
<td><strong>12.79 (5.35-30.62)</strong></td>
</tr>
<tr>
<td>NSE &gt; 33</td>
<td>507</td>
<td>4</td>
<td>0.51 (0.46-0.57)</td>
<td>0.88 (0.77-0.94)</td>
<td>0.12 (0.06-0.23)</td>
<td>4.14 (1.82-9.42)</td>
</tr>
</tbody>
</table>

Golan E et al, CCM 2014 Oct;42(10):2235-43
### Precision of diagnostic tests by time performed

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Time post-ROSC, hours</th>
<th>Patients tested, n</th>
<th>Number of studies, n</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>FPR</th>
<th>Positive LR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Simple proportions</td>
<td>Continuity correction</td>
<td>Simple proportions</td>
</tr>
<tr>
<td>Corneal reflex</td>
<td>≤ 72</td>
<td>240</td>
<td>3</td>
<td>0.32 (0.22-0.44)</td>
<td>0.98 (0.92-1.00)</td>
<td>0.02 (0.00-0.08)</td>
<td>8.4 (2.7-26.5)</td>
</tr>
<tr>
<td></td>
<td>&gt; 72</td>
<td>127</td>
<td>2</td>
<td>0.20 (0.12-0.31)</td>
<td>1.00 (0.94-1.00)</td>
<td>0.00 (0.00-0.06)</td>
<td>4.3 (0.2-109.5)</td>
</tr>
<tr>
<td>Pupillary reflex</td>
<td>≤ 72</td>
<td>305</td>
<td>3</td>
<td>0.27 (0.19-0.36)</td>
<td>0.99 (0.96-1.00)</td>
<td>0.01 (0.00-0.04)</td>
<td>16.5 (4.1-66.8)</td>
</tr>
<tr>
<td></td>
<td>&gt; 72</td>
<td>133</td>
<td>2</td>
<td>0.18 (0.10-0.28)</td>
<td>1.00 (0.94-1.00)</td>
<td>0.00 (0.00-0.06)</td>
<td>4.7 (0.3-85.2)</td>
</tr>
<tr>
<td>Motor score (M1 or M2)</td>
<td>≤ 72</td>
<td>583</td>
<td>5</td>
<td>0.63 (0.43-0.80)</td>
<td>0.90 (0.86-0.93)</td>
<td>0.10 (0.07-0.14)</td>
<td>6.8 (4.7-9.9)</td>
</tr>
<tr>
<td></td>
<td>&gt; 72</td>
<td>208</td>
<td>3</td>
<td>0.59 (0.26-0.86)</td>
<td>0.96 (0.90-0.99)</td>
<td>0.04 (0.01-0.1)</td>
<td>9.5 (3.7-24.1)</td>
</tr>
<tr>
<td>Clinical status myoclonus</td>
<td>≤ 72</td>
<td>410</td>
<td>5</td>
<td>0.27 (0.19-0.38)</td>
<td>0.98 (0.93-1.00)</td>
<td>0.02 (0.01-0.07)</td>
<td>5.2 (2.0-13.4)</td>
</tr>
<tr>
<td>Unfavorable EEG</td>
<td>≤ 72</td>
<td>465</td>
<td>8</td>
<td>0.57 (0.32-0.79)</td>
<td>0.96 (0.92-0.99)</td>
<td>0.04 (0.01-0.08)</td>
<td>8.7 (3.8-19.7)</td>
</tr>
<tr>
<td></td>
<td>&gt; 72</td>
<td>87</td>
<td>3</td>
<td>0.80 (0.70-0.88)</td>
<td>1.00 (0.75-1.00)</td>
<td>0.00 (0.00-0.25)</td>
<td>7.3 (1.6-33.2)</td>
</tr>
<tr>
<td>SSEP</td>
<td>≤ 72</td>
<td>417</td>
<td>6</td>
<td>0.40 (0.25-0.57)</td>
<td>1.00 (0.97-1.00)</td>
<td>0.01 (0.00-0.03)</td>
<td>16.1 (5.6-46.2)</td>
</tr>
<tr>
<td></td>
<td>&gt; 72</td>
<td>157</td>
<td>2</td>
<td>0.44 (0.29-0.59)</td>
<td>1.00 (0.83-1.00)</td>
<td>0.00 (0.00-0.17)</td>
<td>7.5 (1.1-49.5)</td>
</tr>
<tr>
<td>NSE &gt; 33</td>
<td>≤ 72</td>
<td>507</td>
<td>4</td>
<td>0.51 (0.46-0.57)</td>
<td>0.89 (0.84-0.93)</td>
<td>0.11 (0.07-0.16)</td>
<td>4.1 (1.8-9.4)</td>
</tr>
</tbody>
</table>

Golan E et al, CCM 2014 Oct;42(10):2235-43
## Precision of diagnostic tests by time performed

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Time post-ROSC, hours</th>
<th>Patients tested, n</th>
<th>Number of studies, n</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>FPR</th>
<th>Positive LR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Simple proportions</td>
<td>Continuity correction</td>
<td>Simple proportions</td>
<td>Continuity correction</td>
</tr>
<tr>
<td>Corneal reflex</td>
<td>≤ 72</td>
<td>240</td>
<td>3</td>
<td>0.32 (0.22-0.44)</td>
<td>0.98 (0.92-1.00)</td>
<td>0.02 (0.00-0.08)</td>
<td>8.4 (2.7-26.5)</td>
</tr>
<tr>
<td></td>
<td>&gt; 72</td>
<td>127</td>
<td>2</td>
<td>0.20 (0.12-0.31)</td>
<td>1.00 (0.94-1.00)</td>
<td>0.00 (0.00-0.06)</td>
<td>4.3 (0.2-109.5)</td>
</tr>
<tr>
<td>Pupillary reflex</td>
<td>≤ 72</td>
<td>305</td>
<td>3</td>
<td>0.27 (0.19-0.36)</td>
<td>0.99 (0.96-1.00)</td>
<td>0.01 (0.00-0.04)</td>
<td>16.5 (4.1-66.8)</td>
</tr>
<tr>
<td></td>
<td>&gt; 72</td>
<td>133</td>
<td>2</td>
<td>0.18 (0.10-0.28)</td>
<td>1.00 (0.94-1.00)</td>
<td>0.00 (0.00-0.06)</td>
<td>4.7 (0.3-85.2)</td>
</tr>
<tr>
<td>Motor score (M1 or M2)</td>
<td>≤ 72</td>
<td>583</td>
<td>5</td>
<td>0.63 (0.43-0.80)</td>
<td>0.90 (0.86-0.93)</td>
<td>0.10 (0.07-0.14)</td>
<td>6.8 (4.7-9.9)</td>
</tr>
<tr>
<td></td>
<td>&gt; 72</td>
<td>208</td>
<td>3</td>
<td>0.59 (0.26-0.86)</td>
<td>0.96 (0.90-0.99)</td>
<td>0.04 (0.01-0.1)</td>
<td>9.5 (3.7-24.1)</td>
</tr>
<tr>
<td>Clinical status myoclonus</td>
<td>≤ 72</td>
<td>410</td>
<td>5</td>
<td>0.27 (0.19-0.38)</td>
<td>0.98 (0.93-1.00)</td>
<td>0.02 (0.01-0.07)</td>
<td>5.2 (2.0-13.4)</td>
</tr>
<tr>
<td>Unfavorable EEG</td>
<td>≤ 72</td>
<td>465</td>
<td>8</td>
<td>0.57 (0.32-0.79)</td>
<td>0.96 (0.92-0.99)</td>
<td>0.04 (0.01-0.08)</td>
<td>8.7 (3.8-19.7)</td>
</tr>
<tr>
<td></td>
<td>&gt; 72</td>
<td>87</td>
<td>3</td>
<td>0.80 (0.70-0.88)</td>
<td>1.00 (0.75-1.00)</td>
<td>0.00 (0.00-0.25)</td>
<td>7.3 (1.6-33.2)</td>
</tr>
<tr>
<td>SSEP</td>
<td>≤ 72</td>
<td>417</td>
<td>6</td>
<td>0.40 (0.25-0.57)</td>
<td>1.00 (0.97-1.00)</td>
<td>0.01 (0.00-0.03)</td>
<td>16.1 (5.6-46.2)</td>
</tr>
<tr>
<td></td>
<td>&gt; 72</td>
<td>157</td>
<td>2</td>
<td>0.44 (0.29-0.59)</td>
<td>1.00 (0.83-1.00)</td>
<td>0.00 (0.00-0.17)</td>
<td>7.5 (1.1-49.5)</td>
</tr>
<tr>
<td>NSE &gt; 33</td>
<td>≤ 72</td>
<td>507</td>
<td>4</td>
<td>0.51 (0.46-0.57)</td>
<td>0.89 (0.84-0.93)</td>
<td>0.11 (0.07-0.16)</td>
<td>4.1 (1.8-9.4)</td>
</tr>
</tbody>
</table>

Golan E et al, CCM 2014 Oct;42(10):2235-43
## Precision of diagnostic tests by time performed

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Time post-ROSC, hours</th>
<th>Patients tested, n</th>
<th>Number of studies, n</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>FPR</th>
<th>Positive LR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Simple proportions</td>
<td>Continuity correction</td>
<td>Simple proportions</td>
</tr>
<tr>
<td>Corneal reflex</td>
<td>≤ 72</td>
<td>240</td>
<td>3</td>
<td>0.32 (0.22-0.44)</td>
<td>0.98 (0.92-1.00)</td>
<td>0.02 (0.00-0.08)</td>
<td>0.03 (0.01-0.10)</td>
</tr>
<tr>
<td></td>
<td>&gt; 72</td>
<td>127</td>
<td>2</td>
<td>0.20 (0.12-0.31)</td>
<td>1.00 (0.94-1.00)</td>
<td>0.00 (0.00-0.06)</td>
<td>0.05 (0.00-0.64)</td>
</tr>
<tr>
<td>Pupillary reflex</td>
<td>≤ 72</td>
<td>305</td>
<td>3</td>
<td>0.27 (0.19-0.36)</td>
<td>0.99 (0.96-1.00)</td>
<td>0.01 (0.00-0.04)</td>
<td>0.02 (0.00-0.06)</td>
</tr>
<tr>
<td></td>
<td>&gt; 72</td>
<td>133</td>
<td>2</td>
<td>0.18 (0.10-0.28)</td>
<td>1.00 (0.94-1.00)</td>
<td>0.00 (0.00-0.06)</td>
<td>0.04 (0.00-0.46)</td>
</tr>
<tr>
<td>Motor score (M1 or M2)</td>
<td>≤ 72</td>
<td>583</td>
<td>5</td>
<td>0.63 (0.43-0.80)</td>
<td>0.90 (0.86-0.93)</td>
<td>0.10 (0.07-0.14)</td>
<td>0.10 (0.07-0.15)</td>
</tr>
<tr>
<td></td>
<td>&gt; 72</td>
<td>208</td>
<td>3</td>
<td>0.59 (0.26-0.86)</td>
<td>0.96 (0.90-0.99)</td>
<td>0.04 (0.01-0.1)</td>
<td>0.05 (0.02-0.11)</td>
</tr>
<tr>
<td>Clinical status myoclonus</td>
<td>≤ 72</td>
<td>410</td>
<td>5</td>
<td>0.27 (0.19-0.38)</td>
<td>0.98 (0.93-1.00)</td>
<td>0.02 (0.01-0.07)</td>
<td>0.05 (0.02-0.12)</td>
</tr>
<tr>
<td>Unfavorable EEG</td>
<td>≤ 72</td>
<td>465</td>
<td>8</td>
<td>0.57 (0.32-0.79)</td>
<td>0.96 (0.92-0.99)</td>
<td>0.04 (0.01-0.08)</td>
<td>0.06 (0.03-0.12)</td>
</tr>
<tr>
<td></td>
<td>&gt; 72</td>
<td>87</td>
<td>3</td>
<td>0.80 (0.70-0.88)</td>
<td>1.00 (0.75-1.00)</td>
<td>0.00 (0.00-0.25)</td>
<td>0.10 (0.02-0.39)</td>
</tr>
<tr>
<td>SSEP</td>
<td>≤ 72</td>
<td>417</td>
<td>6</td>
<td>0.40 (0.25-0.57)</td>
<td>1.00 (0.97-1.00)</td>
<td>0.01 (0.00-0.03)</td>
<td>0.02 (0.01-0.06)</td>
</tr>
<tr>
<td></td>
<td>&gt; 72</td>
<td>157</td>
<td>2</td>
<td>0.44 (0.29-0.59)</td>
<td>1.00 (0.83-1.00)</td>
<td>0.00 (0.00-0.17)</td>
<td>0.06 (0.01-0.32)</td>
</tr>
<tr>
<td>NSE &gt; 33</td>
<td>≤ 72</td>
<td>507</td>
<td>4</td>
<td>0.51 (0.46-0.57)</td>
<td>0.89 (0.84-0.93)</td>
<td>0.11 (0.07-0.16)</td>
<td>0.12 (0.06-0.23)</td>
</tr>
</tbody>
</table>

Source: Golan E et al, CCM 2014 Oct;42(10):2235-43
What about real life data?

- Consecutive OHCA patients that received TTM and survived to 72hrs post-arrest
- Multicentre (n=34 hospitals) in Southwestern Ontario from 2011-2014
- \( N=982 \)

Golan E et al, Data not yet published
## Results

### Neuroprognostic tests

<table>
<thead>
<tr>
<th>Neuroprognostic tests</th>
<th>Unadjusted OR (95%CI)</th>
<th>Unadjusted OR (95%CI)</th>
<th>Adjusted OR (95%CI)</th>
<th>Adjusted OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilaterally absent corneal reflex at 48 to 72 hours</td>
<td>28.33 (8.15-98.52)</td>
<td>&lt;0.001</td>
<td>7.34 (1.10-49.22)</td>
<td>0.040</td>
</tr>
<tr>
<td>Bilaterally absent pupillary reflex at 48 to 72 hours</td>
<td>23.79 (11.97-47.28)</td>
<td>&lt;0.001</td>
<td>7.71 (3.26-18.23)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bilateral Glasgow coma motor score of 1-2 at 48 to 72 hours</td>
<td>18.36 (12.90-26.12)</td>
<td>&lt;0.001</td>
<td>15.95 (9.58-26.56)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

### Clinical diagnostic test

<table>
<thead>
<tr>
<th>Clinical diagnostic test</th>
<th>False positive rate (percentage; 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilaterally absent corneal reflex at 48 to 72 hours</td>
<td>5.1 (1.4-12.8)</td>
</tr>
<tr>
<td>Bilaterally absent pupillary reflex at 48 to 72 hours</td>
<td>4.5 (2.2-8.1)</td>
</tr>
<tr>
<td>Bilateral Glasgow coma motor score of 1-2 at 48 to 72 hours</td>
<td>15.9 (12.8-19.5)</td>
</tr>
</tbody>
</table>

Golan E et al, Data not yet published
• Diagnostic tests beyond 72hr of arrest (72hr post-TTM intervention) yield FPR near 0% with narrow confidence intervals

  Golan E et al, Data not yet published

• TTM trial, neuroprognostication arm, expected to be published in Winter 2014 (diagnostic testing at 72hrs post-TTM intervention, 108hr post-arrest)

  Cronberg T et al, Data not yet published
Do we stop too early?

Feature Articles

Timing of neuroprognostication in postcardiac arrest therapeutic hypothermia*

Sarah M. Perman, MD, MS; James N. Kirkpatrick, MD; Angelique M. Reitsma, MD; David F. Gaieski, MD; Bonnie Lau, MD; Thomas M. Smith, RN; Marion Leary, RN; Barry D. Fuchs, MD; Joshua M. Levine, MD; Benjamin S. Abella, MD, MPhil; Lance B. Becker, MD; Raina M. Merchant, MD, MS

Objective: Early assessment of neurologic recovery is often challenging in survivors of cardiac arrest. Further, little is known about when to assess neurologic status in patients postcardiac arrest and the timing of therapeutic hypothermia. The authors in this study document the timing of neurologic recovery and neuroprognostication and the effect of therapeutic hypothermia on neurologic recovery. They also discuss the implications of these findings.

Methods: This study retrospectively reviewed patients who received therapeutic hypothermia after cardiac arrest. Neurologic status was assessed using the National Institutes of Health Stroke Scale (NIHSS) and the Glasgow Coma Scale (GCS). Neuroprognostication was performed using the Fisher scale and the Early Staging Score (ESS). The timing of neuroprognostication and the effect of therapeutic hypothermia on neurologic recovery were analyzed.

Results: In total, 200 patients were included in the study. The median age was 60 years, and 60% of patients were male. The overall survival rate was 67%. In patients who received therapeutic hypothermia, the median time to neuroprognostication was 15 hours. The Fisher scale was used for neuroprognostication in 70% of patients, and the ESS was used in 30% of patients.

Conclusion: The timing of neuroprognostication and the effect of therapeutic hypothermia on neurologic recovery were analyzed in this study. The results suggest that therapeutic hypothermia may improve neurologic recovery in survivors of cardiac arrest. Further research is needed to confirm these findings and to determine the optimal timing of neuroprognostication.
Timing of neuroprognostication in postcardiac arrest therapeutic hypothermia

Sarah M. Perman, MD, MS; James N. Kirkpatrick, MD; Angelique M. Reitsma, MD; David F. Gaieski, MD; Bonnie Lau, MD; Thomas M. Smith, RN; Marion Leary, RN; Barry D. Fuchs, MD; Joshua M. Levine, MD; Benjamin S. Abella, MD, MPhil; Lance B. Becker, MD; Raina M. Merchant, MD, MS
Timing of neuroprognostication in postcardiac arrest therapeutic hypothermia*

Sarah M. Perman, MD, MS; James N. Kirkpatrick, MD; Angelique M. Reitsma, MD; David F. Gaieski, MD; Bonnie Lau, MD; Thomas M. Smith, RN; Marion Leary, RN; Barry D. Fuchs, MD; Joshua M. Levine, MD; Benjamin S. Abella, MD, MPhil; Lance B. Becker, MD; Raina M. Merchant, MD, MS
Timing of neuroprognostication in postcardiac arrest therapeutic hypothermia

Sarah M. Perman, MD, MS; James N. Kirkpatrick, MD; Angelique M. Reitsma, MD; David F. Gaieski, MD; Bonnie Lau, MD; Thomas M. Smith, RN; Marion Leary, RN; Barry D. Fuchs, MD; Joshua M. Levine, MD; Benjamin S. Abella, MD, MPhil; Lance B. Becker, MD; Raina M. Merchant, MD, MS
Time to Death
-- All Sites --

72 hours

Episodes #

Time to Death (hr)

Cooled
Not Cooled

ROSIC for at least 20 minutes in ED and Died in ED or hospital
Episode from September 1, 2007 to August 10, 2009
Data as of August 10, 2009
The PremaTOR Study
(Preventing Premature Termination Of Resuscitation)
Aims:

1. To increase the use of evidence-based neurological prognostication for anoxic brain injury survivors in order to **prevent premature termination of life sustaining therapies**.

2. To understand reasons for very early termination of life sustaining therapy and barriers to using evidence-based neurological prognostication

PremaTOR Stepped-Wedge Design
## Results

**18 HOSPITALS**

**986 OHCA PATIENTS – SURVIVING TO ICU**

<table>
<thead>
<tr>
<th></th>
<th>PRE</th>
<th>POST</th>
<th>P-VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>WLST &lt; 72 HRS</td>
<td>92 (18%)</td>
<td>58 (12%)</td>
<td>P=0.02</td>
</tr>
<tr>
<td>WLST EVER</td>
<td>184 (36%)</td>
<td>135 (28%)</td>
<td>P=0.01</td>
</tr>
<tr>
<td>WLST &lt; 72 HRS OUT OF ALL WLST DEATHS</td>
<td>92 (50%)</td>
<td>58 (43%)</td>
<td>P=0.43</td>
</tr>
</tbody>
</table>

Data not yet published
Results

<table>
<thead>
<tr>
<th></th>
<th>PRE</th>
<th>POST</th>
<th>P-VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>SURVIVAL TO HOSPITAL DISCHARGE</td>
<td>156 (30%)</td>
<td>155 (33%)</td>
<td>P=0.3</td>
</tr>
<tr>
<td>SURVIVAL WITH GOOD OUTCOME</td>
<td>128 (25%)</td>
<td>133 (28%)</td>
<td>P=0.6</td>
</tr>
<tr>
<td>BRAIN DEATH</td>
<td>79 (15%)</td>
<td>97 (20%)</td>
<td>P=0.04</td>
</tr>
</tbody>
</table>

Data not yet published
# Results

<table>
<thead>
<tr>
<th></th>
<th>PRE</th>
<th>POST</th>
<th>P-VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SURVIVAL TO HOSPITAL DISCHARGE</strong></td>
<td>156 (30%)</td>
<td>155 (33%)</td>
<td>P=0.3</td>
</tr>
<tr>
<td><strong>SURVIVAL WITH GOOD OUTCOME</strong></td>
<td>128 (25%)</td>
<td>133 (28%)</td>
<td>P=0.6</td>
</tr>
<tr>
<td><strong>BRAIN DEATH</strong></td>
<td>79 (15%)</td>
<td>97 (20%)</td>
<td>P=0.04</td>
</tr>
</tbody>
</table>

86% patients that survive to hospital discharge will have a good neurological outcome (n=133)

Data not yet published
Prognostication is a hot topic... Guidelines currently being produced by multiple agencies
One man’s guide to prognostication in patients receiving TTM

A protocol-based strategy

- Do not attempt neuroprognostication until sedatives, paralytics have worn off, hypotension is treated
- Do not base decisions to stop life sustaining therapies on determinations of neurological prognosis within first 72 hours
- A delayed approach yields better results
  - (72hr post-arrest vs 72hr post-TTM intervention)
- Multiple prognostic tools (>2 tests)
One man’s guide to prognostication in patients receiving TTM

A protocol-based strategy

• Do not attempt neuroprognostication until sedatives, paralytics have worn off, hypotension is treated
• Do not base decisions to stop life sustaining therapies on determinations of neurological prognosis within first 72 hours
• A delayed approach yields better results
  (72hr post-arrest vs 72hr post-TTM intervention)
• Multiple prognostic tools (>2 tests)
One man’s guide to prognostication in patients receiving TTM

A protocol-based strategy

• Do not attempt neuroprognostication until sedatives, paralytics have worn off, hypotension is treated

• Do not base decisions to stop life sustaining therapies on determinations of neurological prognosis within first 72 hours

• A delayed approach yields better results (72hr post-arrest vs 72hr post-TTM intervention)

• Multiple prognostic tools (>2 tests)
A protocol-based strategy

• Do not attempt neuroprognostication until sedatives, paralytics have worn off, hypotension is treated
• Do not base decisions to stop life sustaining therapies on determinations of neurological prognosis within first 72 hours

• A delayed approach yields better results
  (72hr post-arrest vs 72hr post-TTM intervention)
• Multiple prognostic tools (>2 tests)
One man’s guide to prognostication in patients receiving TTM

A protocol-based strategy

• Do not attempt neuroprognostication until sedatives, paralytics have worn off, hypotension is treated
• Do not base decisions to stop life sustaining therapies on determinations of neurological prognosis within first 72 hours
• A delayed approach yields better results
  (72hr post-arrest vs 72hr post-TTM intervention)
• Multiple prognostic tools (>2 tests)
Thank you

- Damon Scales
- Laurie Morrison
- Jeff Singh
- Niall Ferguson
- Cliff Callaway