DISCLOSURES

- I receive research support as PI of R01NS102574-01A1
- I receive research support from Bard Medical, Inc. for the INTREPID Study (NCT02996266)
- I serve as editor-in-chief for Seminars in Neurology
Case

A 56-year-old woman suffered a cardiac arrest

Initial rhythm VF, then PEA

Estimated “code time” 40 minutes

Underwent therapeutic hypothermia (32-34°C) for 24 hours

Day 7 (off all sedation): comatose, no eye opening; intact pupillary, corneal and OCRs, but extensor posturing.
Case

- Frequent myoclonic jerking: face, trunk and limbs
- EEG at 48 hours: burst suppression
- Later EEGs: generalized slowing, occasional triphasic waves
- Day 13: still comatose, extensor posturing
- What will her outcome be?
IMPORTANT THINGS OFTEN COME IN TWELVES!!!

THE NUMBER OF YEARS I'VE ENJOYED
SINCE YOU GAVE ME BACK MY LIFE.

Amazing, how time flies! My gratitude to you always grows, and appreciation of your skill in determining treatments.

Happy, Happy Thanksgiving to you and yours!

Love always,
Problems that have plagued the field

- Most studies have inherent biases
- Aside from TTM, there have been limited advances in neuroprotection
- Even with TTM, many questions remain
- Advances can be made in every phase of the disease
What can we use to predict neurological outcome?

* Clinical examination
* Electrophysiology
* Biomarkers
* Neuroimaging
BIASES: Cardiac Arrest Outcome Studies

- Meds, NCSE, temperature and metabolic disturbances influence the exam – but are often not accounted for.
- Clinical exam tells little beyond the brainstem.
- **Technique** is almost never described.
- **Hypothermia** may not be accounted for.
- Every study is biased by early withdrawal of life-sustaining therapy (**WLST**).
How does hypothermia influence prognostication?

- Delayed recovery is more common
- Neurons may be dysfunctional but not dead
- Medication effects are prolonged
- Electrophysiology and neuroimaging may show delayed or attenuated changes
Prognosis in Nontraumatic Coma

Figure 3. Estimating prognosis in posttraumatic coma. All patients meeting criteria for admission to ICU.
What’s the matter with the Levy data?

- Old – study performed in the mid 1970s
- Limited data collected
- Self-fulfilling prophecy bias
- What was “coma”???
it gave outcomes from coma in a small number of patients and only on a 1-month basis. We have now extended the analysis to 500 patients in coma from nontraumatic causes and lengthened the follow-up to 1 year.

**Methods**

Coma was defined as sleeplike unresponsiveness without evidence of awareness of the self or environment, a state from which patients could not be aroused. The operational criteria were that such patients failed to open their eyes either spontaneously or in response to noise; they expressed no comprehensible words; and they neither obeyed commands nor moved their extremities appropriately to localize or resist painful stimuli.

**PATIENT POPULATION**

The study was conducted on 500 patients with medical coma admitted between September 1973 and June 1977 to the New York Hospital-Cornell Medical Center, the Royal Victoria Infirmary (Newcastle-upon-Tyne), and (beginning January 1976) the San Francisco General Hospital. All patients over 12 years
| 14 | Coma (12)  | 25 | 67 | 8 | 0 | 0 | 0 |
| 14 | Vegetative (36) | ... | 64 | 33 | 0 | 0 | 3 |
| 14 | Conscious (101) | ... | ... | 28 | 19 | 53 |

* Coma means eyes do not open or open only in response to pain, motor response of withdrawal or poorer, and verbal response no better than incoherent sounds. Vegetative means eyes open in response to noise or spontaneously, otherwise, like coma. Conscious means localizing motor responses, obeying commands, or production of comprehensible words, regardless of eye opening. Numbers in parentheses are numbers of patients.

First week, and less than one quarter (121) the first month (Figure 1). During the first month, 306 (61%) died without ever awakening from coma, 62 (12%) never improved beyond the vegetative state, 60 (12%) recovered state persisted for 1 week or more, however, the likelihood of achieving a moderate disability or good recovery within the year declined to only 7%. Early recovery of consciousness significantly increased the chances of sub-
Figure 2. Estimating prognosis in post-traumatic coma. All patients aged under 30 years. (Reprinted from Ropper AH, Samuels MA. Neurology. New York: McGraw-Hill, 1988, with permission.)
How does the AHA define coma (for consideration of therapeutic hypothermia)?

“Lack of meaningful response to verbal commands.”

Practice Parameter: Prediction of outcome in comatose survivors after cardiopulmonary resuscitation (an evidence-based review)

Report of the Quality Standards Subcommittee of the American Academy of Neurology

E.F.M. Wijdicks, MD; A. Hijdra, MD; G.B. Young, MD; C.L. Bassetti, MD; and S. Wiebe, MD

AAN Guidelines: Clinical Exam

“The prognosis is invariably poor in comatose patients with absent pupillary or corneal reflexes, or absent or extensor motor responses 3 days after cardiac arrest (recommendation level A).”
Importance of technique
Do other brainstem signs matter?
ELECTROPHYSIOLOGY

- SSEP
- EEG
- Other EP’s?
Primary somatosensory cortex

High cervical spinal cord

Stimulator

Electrode

10 msec

N20

N13

N9/10

Median nerve

Brachial plexus

Electrophysiology - Evoked Potentials

- Thalamo-cortical (N20) responses most important
- Very helpful if patient paralyzed or sedated
- May be inaccurate with focal structural lesions or hypothermia
- Misleading if performed too early...
Improvement in SSEP within first 24 hours in a single patient studied serially post-cardiac arrest

Evoked Potentials

* Useful for prediction of **poor** outcome
* PROPAC Study: 407 patients, 32 Dutch ICUs:
  * 45% with bilateral absent N20s on SSEP, all had poor outcome (FPR 0-3%)

* Self-fulfilling prophesy bias?
  * **23%** had withdrawal of care at 24 hours
  * **28%** at 48 hours

Guidelines: SSEPs

AAN: “The assessment of poor prognosis can be guided by the bilateral absence of cortical SSEPs (N20 response) within 1 to 3 days (recommendation level B).”

ESICM: Bilaterally absent SSEP after 24 hours without TH, after 72 hours with TH
How does hypothermia influence prognostication?

- Hypothermia decreases conduction velocities by 2 m/s for every 1°C decrease in body temperature.

- 2 separate reports of TH-treated patients with bilaterally absent N20 responses 3 days after cardiac arrest regained consciousness and cognitive function.

SSEP – new data

* Meta-analysis of 35 studies, 2133 patients
* 594 with absent N20s, 14 had good functional outcomes
* Rate of WLST for patients with absent SSEPs could be estimated in 14/35 studies.
* **FPR for absent N20s, adjusted for WLST rate of 80%, is 7.7%**

Evoked Potentials: take home lessons

- SSEPs may help predict poor outcome in comatose cardiac arrest patients
- Least susceptible to medication/metabolic effects
- Timing is crucial - wait at least 48 hours post-arrest or post-complete rewarming if TH/TTM
- False positives can occur in setting of TH
- Newer data suggests amplitude of present responses may also be helpful

Electrophysiology - EEG

- There is a natural evolution of EEG changes during recovery following cardiac arrest
  - Initial intermittent cortical activity -> delta -> theta -> alpha rhythms
- Effect of hypothermia on EEG: decreased voltage (likely to decreased metabolism, medication effects)
3 hrs

7 hrs

17 hrs

33 hrs
myoclonic status epilepticus = poor outcome, right?

- 50 comatose cardiac arrest survivors with seizures or myoclonus
  - Only 1 patient with survived to 6 months.
- 11 comatose cardiac arrest survivors with MSE, all with burst suppression EEG’s
  - no survivors
- 107 comatose cardiac arrest survivors
  - 40 in myoclonic status - all died

Krumholz et al. Neurology 1988
Young et al. Neurology 1990
Beware the self-fulfilling prophesy!

- 1995: myoclonic status following cardiac arrest; respiratory support withdrawn on day 4 → she survived and regained normal cognitive function.

- 1998: 3 patients with myoclonic status following cardiac arrest, all had good recoveries

Arnoldus et al. *Ann Neurol* 1995

Morris et al. *J Neurol Neurosurg Psych* 1998
AAN Guidelines: MSE

“Patients with myoclonic status epilepticus* within the first day after a primary circulatory arrest have a poor prognosis (recommendation level B).”

• How is this defined?
• Is an EEG required?
Patients with myoclonic status epilepticus* within the first day after a primary circulatory arrest have a poor prognosis (recommendation level B).

*Defined as “spontaneous, repetitive, unrelenting, generalized multifocal myoclonus involving the face, limbs and axial musculature”

No EEG required!
So, why do patients with MSE do poorly?
Clinically Distinct Electroencephalographic Phenotypes of Early Myoclonus after Cardiac Arrest

Jonathan Elmer, MD, MS,1,2 Jon C. Rittenberger, MD, MS,1 John Faro,3
Bradley J. Molyneaux, MD, PhD,2,4 Alexandra Popescu, MD,4
Clifton W. Callaway, MD, PhD,1 and Maria Baldwin, MD,5
for the Pittsburgh Post-Cardiac Arrest Service

Two patterns:

1. Suppression-burst with high amplitude polyspikes in lockstep with myoclonic jerks
2. Continuous background with narrow vertex spike-wave discharges in lockstep with myoclonic jerks

Pattern 1 poorly amenable to treatment with conventional AEDs

Ann Neurol 2016;80:175-184
Can patients in *status epilepticus* after cardiac arrest have a good outcome?

- 6 TH-treated patients with post-CA SE survived to better than vegetative state (3 MSE, 3 NCSE)
  - 1 returned to baseline
  - 3 with moderate impairment

- All had preserved brainstem reflexes, intact cortical SSEP responses, and *reactive EEG backgrounds*

Identical Bursts

Courtesy of Larry Hirsch MD
AAN Guidelines: EEG

AAN: “Burst suppression or generalized epileptiform discharges on EEG predicted poor outcomes but with insufficient prognostic accuracy (recommendation level C).”

ESICM: Poor outcome very likely with unreactive burst-suppression or status epilepticus on EEG
Neuroprognostication: EEG (initial 72h post-CA)

- Absent reactivity
- Burst suppression/discontinuous
- Voltage attenuation

Helpful in predicting poor outcome, but susceptible to effect of drugs, temperature, seizures.

Recording evolves over time: trend is invaluable!
EEG: take home lessons

- EEG helpful in the evaluation of comatose cardiac arrest patients
- If you see seizures, treat them!
- MSE may not portend a poor outcome
- Reactivity may be a key to outcome
- Newer EEG signs may correlate with poor outcome: identical bursts
NSE – dimeric enzyme, catalyzes an enzymatic reaction in the glycolytic pathway. Also found in RBCs and platelets, neuroendocrine tumors, pancreatic CA.
BIOMARKERS

* 407 cardiac arrest patients studied with NSE and S-100 at 24, 48 and 72 hours

* 138 patients (60%) with NSE >33 mcg/L at any time had a poor outcome (95% CI of FPR 0-3%)

* S-100 had unacceptably high false positive rates.

Guidelines: Biomarkers

AAN: “Serum NSE levels >33 ug/L at days 1 to 3 post-CPR accurately predict poor outcome (recommendation level B).”

ESICM: Poor outcome very likely with “high NSE levels”
NSE – larger studies

- 1053 post-arrest patients, all treated with TH to 33 degrees for 24 hours
- NSE > 90 ug/L predicted poor outcome with PPV 99%, FPR 0.5%, sensitivity 48%
- All with CPC 1-2 despite NSE >90 had confounders.
- NSE <17 ug/L excluded CPC 4-5 with NPV 92%; those who died did so for non-neuro causes

Streitberger et al. *Crit Care Med* 2017;45:1145-51
BIOMARKERS – but wait . . .

- Reports of patients regaining consciousness despite NSE > 200 mcg/L
- BIASES: WLST, lack of blinding
- Other biomarkers: CK-BB, strong ion gap, lactate, high mobility group box 1, mRNAs, malondialdehyde, MMPs (7,8,9), procalcitonin, neurofilament, copeptin
- What makes an optimal biomarker?
- Perhaps serum trend is more important than absolute value...
New biomarkers: Tau

- From the TTM study, 689 patients with serum tau at 24, 48 and 72 hours
- Increased tau associated with poor outcome, regardless of temperature
- Tau had a FPR of 2% (95% CI 1-4%) with 66% sensitivity.
- AUC for Tau 0.91, vs. 0.86 for NSE
- Caveat: testing, WLST bias

Biomarkers: take home lessons

- Biomarkers are questionably useful in the prediction of poor outcome
- Sensitivity is relatively weak
- Multiple reports of false positives, especially in the setting of TH
- Laboratory delays and variation can be significant
- CSF results may be more sensitive and specific
- Newer biomarkers (Tau) are showing great promise
NEUROIMAGING
Benefits of Neuroimaging post-CA

* Gives insight into both injury and recovery
* Timing is important
* Technique important
Predicting Clinical Outcome in Comatose Cardiac Arrest Patients Using Early Noncontrast Computed Tomography

Ona Wu, PhD; Leonardo M. Batista, MD, DDS; Fabricio O. Lima, MD; Mark G. Vangel, PhD; Karen L. Furie, MD, MPH; David M. Greer, MD, MA

Background and Purpose—Early assessment of the likelihood of neurological recovery in comatose cardiac arrest survivors remains challenging. We hypothesize that quantitative noncontrast computed tomography (NCCT) combined with neurological assessments, are predictive of outcome.

Methods—We analyzed data sets acquired from comatose cardiac arrest patients who underwent CT within 72 hours of arrest. Images were semiautomatically segmented into anatomic regions. Median Hounsfield units (HU) were measured regionally and in the whole brain (WB). Outcome was based on the 6-month modified Rankin Scale (mRS) score. Logistic regression was used to combine Glasgow Coma Scale (GCS) score measured on Day 3 post arrest (GCS_Day3) with imaging to predict poor outcome (mRS>4).

Results—WB HU (P=0.02) and the ratio of HU in the putamen to the posterior limb of the internal capsule (PLIC) (P=0.004) from 175 datasets from 151 patients were univariate predictors of poor outcome. Thirty-three patients underwent hypothermia treatment. Multivariate analysis showed that combining median HU in the putamen (P=0.0006) and PLIC (P=0.007) was predictive of poor outcome. Combining WB HU and GCS_Day3 resulted in 72% [61% to 80%] sensitivity and 100% [73% to 100%] specificity for predicting poor outcome in 86 patients with measurable GCS_Day3. This was an improvement over prognostic performance based on GCS_Day3<=8 (98% sensitive but 71% specific).

Discussion—Combining density changes on CT with GCS_Day3 may be useful for predicting poor outcome in comatose cardiac arrest patients who are neither rapidly improving nor deteriorating. Improved prognostication with CT compared with neurological assessments can be achieved in patients treated with hypothermia. (Stroke. 2011;42:985-992.)
CT data

- 200 comatose cardiac arrest patients
- 151 underwent CT within 72 hours of arrest
  - (175 datasets, some had multiple CTs)
- Variables evaluated:
  - Hounsfield units globally
  - Hounsfield units in specific regions
  - Correlation with 6 month outcome
    - (good outcome = mRS ≤4)
  - Compared with GCS score for prediction
CT data

- Median whole brain HU’s significantly correlated with poor 6 month outcome (p=0.001)
- Multivariate analysis: mean HU in putamen (p=0.006) and PLIC (p=0.008) were predictive of poor outcome
- Combining mean whole brain HU and GCS on day 3 resulted in 72% [62-81%] sensitivity and 100% [73-100%] specificity for predicting poor outcome
<table>
<thead>
<tr>
<th>Parameter</th>
<th>All Studies 14/102 or 13.7%</th>
<th>Excluding Hypothermia 6/73 or 8.2%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity</td>
<td>Specificity</td>
</tr>
<tr>
<td>GCS_Day3\leq 8</td>
<td>98 [91–100]</td>
<td>71 [42–90]</td>
</tr>
<tr>
<td>PLR absent</td>
<td>24 [16–34]</td>
<td>100 [73–100]</td>
</tr>
<tr>
<td>M\leq 2</td>
<td>82 [72–89]</td>
<td>79 [49–94]</td>
</tr>
<tr>
<td>WB</td>
<td>1 [0–7]</td>
<td>100 [73–100]</td>
</tr>
<tr>
<td>Putamen+PLIC</td>
<td>23 [15–33]</td>
<td>100 [73–100]</td>
</tr>
<tr>
<td>WB+GCS_Day3</td>
<td>72 [61–80]</td>
<td>100 [73–100]</td>
</tr>
<tr>
<td>WB+M\leq 2</td>
<td>44 [34–55]</td>
<td>100 [73–100]</td>
</tr>
<tr>
<td>Putamen+PLIC+M2</td>
<td>42 [32–53]</td>
<td>100 [73–100]</td>
</tr>
<tr>
<td>Putamen+PLIC+AAN</td>
<td>45 [35–66]</td>
<td>100 [73–100]</td>
</tr>
<tr>
<td>Putamen/PLIC+GCS_Day3</td>
<td>10 [5–19]</td>
<td>100 [73–100]</td>
</tr>
<tr>
<td>Putamen/PLIC+AAN</td>
<td>2 [0–9]</td>
<td>100 [73–100]</td>
</tr>
<tr>
<td>GCS_Day3+Regions</td>
<td>91 [82–96]</td>
<td>100 [73–100]</td>
</tr>
</tbody>
</table>

*The number of data sets from patients with good outcome (mRS\leq 4) and total data sets are provided in parenthesis as well as percentage.*
Neuroimaging - MRI
Timing of Imaging?

Comatose Patients with Cardiac Arrest: Predicting Clinical Outcome with Diffusion-weighted MR Imaging

Chung Wu, PhD
A. Gregory Sorensen, MD
Thomas Penner, PhD
Aneesh B. Singhal, MD
Karen L. Furie, MD
David M. Greer, MD

Purpose: To examine whether the severity and spatial distribution of reductions in apparent diffusion coefficient (ADC) are associated with clinical outcomes in patients who become comatose after cardiac arrest.

Materials and Methods: This was an institutional review board–approved, HIPAA-compliant retrospective study of 80 comatose patients with cardiac arrest who underwent diffusion-weighted magnetic resonance imaging. The need to obtain informed consent was waived except when follow-up phone calls were required; in those cases, informed consent was obtained from the families. Mean patient age was 57 years ± 16 (standard deviation); 31 (39%) patients were women. ADC maps were semiautomatically segmented into the following regions: subcortical white matter; cerebellum; insula; frontal, occipital, parietal, and temporal lobes; caudate nucleus; putamen; and thalamus. Median ADCs were measured in these regions and in the whole brain and were compared (with a two-tailed Wilcoxon test) as a function of clinical outcome. Outcome was defined by both early eye opening in the first week after arrest (either spontaneously or in response to external stimuli) and 6-month modified Rankin scale score.

Results: Whole-brain median ADC was a significant predictor of poor outcome as measured by no eye opening (specificity, 100% [95% confidence interval {CI}: 86%, 100%]; sensitivity, 30% [95% CI: 18%, 45%]) or 6-month modified Rankin scale score greater than 3 (specificity, 100% [95% CI: 73%, 100%]; sensitivity, 41% [95% CI: 29%, 54%]). Patients with poor outcomes having significantly lower ADCs for both outcome measures ($P \leq .001$). Differences in ADC between patients with good and those with poor outcomes varied according to brain region, involving predominantly the occipital and parietal lobes and the putamen, and were dependent on the timing of imaging.

Conclusion: Spatial and temporal differences in ADCs may provide insight into mechanisms of hypoxic-ischemic brain injury and, hence, recovery.

1 From the Athinoula A. Martinos Center for Biomedical Imaging, Department of Radiology, Massachusetts General Hospital, 149 13th St, CNY 2301, Charlestown, MA 02129 (C.W., A.G.S., T.P.); and Department of Neurology, Massachusetts General Hospital, Boston, Mass. (A.B.S., D.G., D.M.G.)
MRI for Cardiac Arrest

- 200 comatose cardiac arrest patients
- 80 underwent MRI within 3 weeks of arrest
  - 10 patients underwent more than one MRI
- Variables evaluated:
  - ADC depression globally
  - ADC depression in specific regions
- Outcome measures
  - Modified Rankin Scale Score
## Results:
**mRS≤3 (N=16) vs mRS>3 (N=74)**

<table>
<thead>
<tr>
<th>Region</th>
<th>P-value</th>
<th>Threshold (10^{-6} mm²/s)</th>
<th>Sensitivity (%) [95% CI]</th>
<th>Specificity (%) [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole Brain</td>
<td>0.0006</td>
<td>731.5</td>
<td>39 [28-51]</td>
<td>100 [76-100]</td>
</tr>
<tr>
<td>White Matter</td>
<td>0.002</td>
<td>698</td>
<td>39 [28-51]</td>
<td>100 [76-100]</td>
</tr>
<tr>
<td>Caudate</td>
<td>0.02</td>
<td>700</td>
<td>30 [20-42]</td>
<td>100 [76-100]</td>
</tr>
<tr>
<td>Putamen</td>
<td>0.0006</td>
<td>690</td>
<td>49 [37-60]</td>
<td>100 [76-100]</td>
</tr>
<tr>
<td>Thalamus</td>
<td>0.06</td>
<td>670</td>
<td>23 [14-34]</td>
<td>100 [76-100]</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>0.004</td>
<td>720.5</td>
<td>36 [26-49]</td>
<td>100 [76-100]</td>
</tr>
<tr>
<td>Frontal lobe</td>
<td>0.001</td>
<td>730</td>
<td>31 [21-43]</td>
<td>100 [76-100]</td>
</tr>
<tr>
<td>Insula</td>
<td>0.002</td>
<td>760</td>
<td>30 [20-42]</td>
<td>100 [76-100]</td>
</tr>
<tr>
<td>Occipital Lobe</td>
<td>&lt;0.0001</td>
<td>725</td>
<td>45 [33-57]</td>
<td>100 [76-100]</td>
</tr>
<tr>
<td>Parietal Lobe</td>
<td>0.0008</td>
<td>690</td>
<td>39 [28-51]</td>
<td>100 [76-100]</td>
</tr>
<tr>
<td>Temporal Lobe</td>
<td>0.004</td>
<td>755</td>
<td>27 [18-39]</td>
<td>100 [76-100]</td>
</tr>
</tbody>
</table>

ADC values in all regions except the thalamus were significantly lower in patients with poor outcome (mRS>3).
Results: mRS vs whole brain ADC

Whole brain ADC < 665x10^{-6} mm^2/s have poor outcomes regardless of time-to-MRI

No Eye Opening: Specificity=100% [88-100]; Sensitivity=27% [17-41]

6 month mRS=6: Specificity=100% [80-100]; Sensitivity=21% [13-33]
There is a temporal evolution to the changes seen radiographically in different brain regions

This had been previously only suggested by imaging different patients at different time points (not serially within the same patients)
Day 0 – minimal changes

Day 1-5 – cortical and marked basal ganglia

Day 6-12 – white matter

Day >12 – minimal changes on DWI (mostly T2 shine through)
Hippocampal Magnetic Resonance Imaging Abnormalities in Cardiac Arrest are Associated with Poor Outcome

David M. Greer, MD, MA, FCCM, FAHA,*† Patricia D. Scripko, MD, MA,† Ona Wu, PhD‡
Brian L. Edlow, MD,† James Bartscher, MD,§ Jonathan R. Sims, MD,†
Erica E. C. Camargo, MD, PhD,† Aneesh B. Singhal, MD,†
and Karen L. Furie, MD, MPH†

Background: The role of neuroimaging in assessing prognosis in comatose cardiac survivors appears promising, but little is known regarding the import of particular spatial patterns. We report a specific spatial imaging abnormality on magnetic resonance imaging (MRI) that portends a poor prognosis: bilateral hippocampal hyperintensities on diffusion-weighted imaging (DWI) and fluid-attenuated inversion recovery (FLAIR) sequences. Methods: Eighty sequential comatose cardiac arrest patients underwent MRI scans. Qualitative and quantitative regional analyses were performed. Patients were categorized as HIPPO+ (n = 18) or HIPPO− (n = 62) based on whether they had bilateral hippocampal hyperintensities. Poor outcome was defined by a modified Rankin Scale (mRS) score ≥4 at 6 months. Results: Patients with bilateral hippocampal abnormalities had a higher frequency of poor outcome (P = .032). HIPPO+ patients suffered more severe cerebral injury, with lower whole brain apparent diffusion coefficient values (P = .043) and a greater number of affected regions on DWI (P = .001) and FLAIR (P = .001) than HIPPO− patients. The hippocampal approach was 100% specific for a poor prognosis; only 1 patient survived and remained in a vegetative state. Conclusions: Bilateral hippocampal hyperintensities on MRI may be a specific imaging finding that is indicative of poor prognosis in patients who suffer global hypoxic–ischemic injury. More research on the prognostic significance of this and similar neuroimaging patterns is indicated. Key Words: Cardiac arrest—coma—magnetic resonance imaging—prognosis.

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“Bright Hippocampus Sign”

Greet DM et al. *J Stroke Cerebrovasc Dis* 2012
## “Bright Hippo Sign”

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive Predictive Value</th>
<th>Negative Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hippocampus</td>
<td>27%</td>
<td>100%</td>
<td>100%</td>
<td>23%</td>
</tr>
<tr>
<td>GCS</td>
<td>94%</td>
<td>57%</td>
<td>91%</td>
<td>80%</td>
</tr>
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</table>

### Table:

<table>
<thead>
<tr>
<th></th>
<th>Hippo +</th>
<th>Hippo -</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of other brain regions affected</td>
<td>9 [7-10]</td>
<td>5 [1-9]</td>
<td>0.001</td>
</tr>
<tr>
<td>Whole brain ADC</td>
<td>731.1 (668.4-781.9)</td>
<td>789.4 (723.6-841)</td>
<td>0.043</td>
</tr>
<tr>
<td>Poor Outcome</td>
<td>100%</td>
<td>77%</td>
<td>0.032</td>
</tr>
</tbody>
</table>

Greet DM et al. *J Stroke Cerebrovasc Dis* 2012
DTI in HIE

A. Good Outcome

B. Bad Outcome

Review article

Quality of evidence in studies evaluating neuroimaging for neurologic prognostication in adult patients resuscitated from cardiac arrest

David K. Hahn, Romergryko G. Geocadin, David M. Greer

Aim: Neuroimaging has been proposed as a predictor of neurologic outcome in comatose survivors of cardiac arrest. We reviewed the quality and level of evidence of the current neuroimaging literature for predicting neurologic outcome in cardiac arrest patients treated with or without therapeutic hypothermia (TH).

Data Sources: Medline, EMBASE, and Cochrane Databases were searched using the terms “cardiac arrest,” “cardiopulmonary resuscitation,” “brain hypoxia,” “brain anoxia,” “brain hypoxia-ischaemia,” “neuroimaging,” and “prognosis.” Eligible studies were reviewed and classified by level of evidence and methodological quality as defined by the International Liaison Committee on Resuscitation (ILCOR).

Results: 928 studies were identified, 84 of which met inclusion criteria: 74 were supportive of neuroimaging to predict outcome, eight unsupportive, and two equivocal. Several studies investigated more than one imaging modality: 27 investigated computed tomography (CT), 46 magnetic resonance imaging (MRI), and 18 alternate imaging modalities, including positron emission tomography and single photon emission computed tomography. No randomized controlled trials were identified. Seven cohort and case control studies were identified, only one of which was graded “good” quality, two were “fair” and four were “poor.”

Conclusion: Neuroimaging is an evolving modality as a prognostic parameter in cardiac arrest survivors. However, the quality of the available literature is not robust, highlighting the need for higher quality studies before neuroimaging can be supported as a standard tool for prognostication in the patient population.
Guidelines: Neuroimaging

AAN: “There are inadequate data to support or refute whether neuroimaging is indicative of poor outcome (recommendation level U).”

ESICM: Poor outcome very likely with “diffuse anoxic injury on brain CT/MRI”
Clinical examination for prognostication in comatose cardiac arrest patients

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Modernizing Levy

- Prospective observational study at MGH 2000-07
- 500 patients with non-traumatic coma
  - 200 with cardiac arrest
- Clinical exam on days 0, 1, 3, 7
- Modified Rankin at 3 and 6 months
  - Also using eye opening and GCS change as outcomes
- Additional clinical variables
  - Temperature, ICP, CPP, infection, nutrition, transfusion
  - Co-morbid illnesses
  - Therapies - hypothermia, ventriculostomy, etc.
- Neuroimaging - CT, MR, MR spectroscopy
- EEG, SSEP, biomarkers
"Good" outcome = mRS 3 or better

Day 0 cardiac arrest patients at baseline

- **Pupillary reflex**
  - Absent: Good 15% (17) Bad 85% (99)
  - Present: Good 4% (3) Bad 96% (96)

- **Corneal reflex**
  - Absent: Good 20% (11) Bad 80% (44)
  - Present: Good 16% (6) Bad 90% (55)

- **Spontaneous eye open**
  - Absent: Good 22% (7) Bad 78% (25)
  - Present: Good 15% (7) Bad 85% (4)

- **Motor response**
  - Absent: Good 15% (7) Bad 85% (4)
  - Present: Good 9% (4) Bad 91% (49)

Day 1

- **OVR**
  - Absent: Good 20% (11) Bad 80% (44)
  - Present: Good 3% (2) Bad 97% (75)

- **Verbal response**
  - Absent: Good 100% (1) Bad 0% (0)
  - Present: Good 17% (15) Bad 83% (71)

- **Spontaneous eye opening**
  - Absent: Good 100% (1) Bad 0% (0)
  - Present: Good 18% (9) Bad 82% (6)

Day 3

- **OVR**
  - Absent: Good 27% (19) Bad 73% (32)
  - Present: Good 86% (6) Bad 14% (1)

- **Verbal response**
  - Absent: Good 3% (1) Bad 97% (32)
  - Present: Good 20% (13) Bad 80% (51)

- **Pupillary reflex**
  - Absent: Good 7% (1) Bad 93% (13)
  - Present: Good 0% (0) Bad 100% (9)

Day 7

- **OVR**
  - Absent: Good 75% (9) Bad 25% (3)
  - Present: Good 23% (11) Bad 77% (36)

- **Verbal response**
  - Absent: Good 0% (0) Bad 100% (10)
  - Present: Good 17% (1) Bad 83% (5)

- **Spont eye opening**
  - Absent: Good 0% (0) Bad 100% (10)
  - Present: Good 32% (10) Bad 68% (21)

Greer et al. *Resuscitation* 2013
Take Home Messages

- Pupils and corneals – still reliable
- Motor response extensor or none – 8.1% still made good recovery
- Myoclonic status – multiple with good recovery
- Study also biased by observational nature, self-fulfilling prophecy
AAN guidelines

Cardiac arrest

Days 1-2

CT
Status Myoclonus

Days 3-5

EEG - NSE
SSEP

Exclude confounders, particularly residual sedation

Unconscious patient, M=1-2 at ≥ 72h after ROSC

One or both of the following:
- No pupillary and corneal reflexes
- Bilaterally absent N20 SSEP wave (at ≥24h after ROSC in patients not treated with targeted temperature)

YES

 Poor outcome very likely (FPR <5%, narrow 95% CIs)

NO

Wait at least 24h

Two or more of the following:
- Status myoclonus ≤ 48h after ROSC
- High NSE levels
- Unreactive burst-suppression or status epilepticus on EEG
- Diffuse anoxic injury on brain CT/MRI

YES

Poor outcome very likely

NO

Indeterminate outcome
Observe and re-evaluate

Use multimodal prognostication whenever possible

Magnetic Resonance Imaging (MRI)
Part 8: Post–Cardiac Arrest Care
2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care

Clifton W. Callaway, Chair; Michael W. Donnino; Ericka L. Fink; Romergrko G. Geocadin; Eyal Golan; Karl B. Kern; Marion Leary; William J. Meurer; Mary Ann Peberdy; Trevonne M. Thompson; Janice L. Zimmerman
AHA Guidelines 2015

- Wait 72 hours after return to normothermia
- **Exam**: PLR still valuable. Corneals and motor no longer.
- **MSE** within 72-120 hours helpful in combination with other tests
- **EEG**: use reactivity, intractable SE, persistent B-S pattern
- **EP**: 24-72 hours post-rewarming
- **Imaging**: marked reduction of GWR w/in 2 hours; extensive restriction of diffusion on MRI 2-6 days post arrest
- **Biomarkers**: NSE and S-100B should not be used alone. Consider “high levels” to support poor prognosis.
Back to our lady …

How long do we wait?
Are we “pulling the plug” too early?

- Albaeni et al, 2014:
  - 189 patients, 63% had WLST <72 hours post-arrest (median time 2 days).
  - Only 19% had advance directives
Delayed awakening (>48h) is frequent

- 29% of patients - median 93h (IQR 70- 117) from discontinuation of sedation
- 10% of late awakeners had no pupillary reflex and no motor response 48h after sedation was completely discontinued

Risk factors for delayed awakening

- >59 years, post-resuscitation shock, renal insufficiency at admission, shock liver, post-anoxic status epilepticus
Hypoxic-Ischemic Brain Injury – Numbers

Impact of WLST-N

* WLST-N < 72h occurred in 1/3 of subjects who died in the hospital in a large OHCA trial

* Adjusted analysis predicted that those subjects would have 26% survival and 16% favorable survival if no WLST-N (mRS<4 – conscious, walking without assistance!)

Can’t we study this better?

- Standard evaluations and testing at standard time points
- More advanced imaging and electrophysiology techniques
- Allow patients to live for longer
Potential Translational Opportunities

- **Inhaled nitric oxide (iNO)** – to aid with reperfusion (no reflow phenomenon) by acting at the endothelial level; measure downstream mitochondrial effect

- **Glibenclamide** – to aid with reperfusion by inhibiting Sur1, perhaps in conjunction with hypothermia; may decrease apoptosis

- Both still at animal study phase
Hypoxic-Ischemic Brain Injury – What’s next?

Post-cardiac arrest care

- **TTH48** -- completed
  - 24 vs 48h – less myocardial injury in 48h group, but more coagulopathy and no change in outcomes

- **TELSTAR** trial
  - EEG status epilepticus
  - VPA, PHT, LEV, MDZ, propofol and thiopental

- **COMACARE** – pCO2, pO2 and MAP goals
  - interim results

- **Cooling on demand**
  - Who benefits from ↓T, duration, rate of rewarming
Hypoxic-Ischemic Brain Injury – What’s next?

Post-cardiac arrest care

- **HYPERION trial**
  - 32.5 – 33.5°C vs 36.5 – 37.5°C in nonshockable rhythm

- **VIGAB-STAT**
  - GABA-T inhibition as add on tx of post-anoxic status epilepticus

- **TAME trial**
  - PaCO$_2$ 35–45 mmHg vs PaCO$_2$ 50–55 mmHg
33 °C vs 37 °C

All nonperfusing rhythms, except for unwitnessed asystole

Cardiac and non cardiac etiology

500 of 1900 enrolled thus far (anticipate completion mid-2020)

35 sites active, 25 planned to start

US and Europe
Hypoxic-Ischemic Brain Injury – What’s next?

Prognostication

* **HOPE**
  * active education of families and staff regarding flaws in the literature and the potential effect of WLST
  * another trial (same name) exploring neuroprognostication in ECMO-CPR patients

* Several studies targeting novel biomarkers.
MOCA Study

Multimodal network connectivity architecture of the brain and its role in the recovery of consciousness in comatose cardiac arrest patients

Serial advanced EEG and MRI techniques to evaluate changes of injury and recovery.

OOH CA only

Must be comatose 24 hours post-arrest or post-rewarming if TTM

Must be able to undergo MRI
Hypoxic-Ischemic Brain Injury – What’s next?

*SPARE* - cooperative study with Brazil: Self-fulfilling Prophecy in cardiac ARrest (SPARE)

**Neurological Function**

- Good outcome
- Poor outcome

Post-arrest time points and neurological assessments (a-g):

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<tr>
<td>a</td>
<td>serum biomarkers</td>
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<td>b</td>
<td>continuous EEG</td>
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<td>window for MRI</td>
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<td>d</td>
<td>SSEP</td>
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<td>e</td>
<td>daily neurologic exam</td>
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<td>CPC-Ex1, CPC, mRS, MoCA</td>
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<td>CPC-Ex2, CPC, mRS or BTACT, MoCA</td>
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Combined Approach
PRACTICAL ADVICE

- Clinical exam: pupils and corneals 72 hours post-arrest/rewarming
- EEG: daily, continuous if possible. Treat seizures, check reactivity
- SSEP: 48 hours post-arrest/rewarming
- NSE: trend over 3-5 days
- CT: admission (r/o bleed), day 2-3 for prognosis
- MRI: day 3-5 post-arrest/rewarming (if CTunhelpful)
CONCLUSIONS

- Neuroprognostication is a moving target
- All studies to date have had significant biases
- Any and all tests should be viewed within the clinical context
- Hypothermia impacts neuroprognostication
- When in doubt, give more time!