Raw and Quantitative EEG for Identification of Ischemia

Susan T. Herman, MD
Assistant Professor of Neurology
Beth Israel Deaconess Medical Center
Harvard Medical School
Boston, MA
Disclosures

- None relevant to this presentation
- Scientific Advisory Board
  - Eisai Inc.
  - Biotie, Inc.
- Research
  - UCB Pharma
  - Acorda Therapeutics
  - Epilepsy Therapy Development Project
  - Sage Pharmaceuticals
  - NeuroPace, Inc.
  - Pfizer
Detection of Ischemia

- During and after vascular neurosurgical or interventional neuroradiology procedures
- After subarachnoid hemorrhage
- In patients with hemodynamic lesions and borderline flow
- In other patients at risk for in-hospital acute ischemia

Cerebral Ischemia

- EEG changes occur within 5 minutes of acute ischemia
  - Superior to current imaging techniques
  - Reversible stage

<table>
<thead>
<tr>
<th>ml/100g/min</th>
<th>EEG change</th>
<th>Reversibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>35-70</td>
<td>Normal</td>
<td>No injury</td>
</tr>
<tr>
<td>25-35</td>
<td>Loss of beta</td>
<td>Reversible</td>
</tr>
<tr>
<td>18-25</td>
<td>Theta slowing</td>
<td>Reversible</td>
</tr>
<tr>
<td>12-18</td>
<td>Delta slowing</td>
<td>Reversible</td>
</tr>
<tr>
<td>&lt; 8-10</td>
<td>Suppression</td>
<td>Irreversible</td>
</tr>
</tbody>
</table>

EEG and Cerebral Ischemia

- Intraoperative monitoring during carotid artery occlusion
  - EEG can detect important changes in CBF
- Hemispheric EEG slowing
  - Correlates with moderate to severe reductions in CBF on stable Xenon CT
- Mean dominant EEG frequency
  - 6.5 Hz correlated with CBF 33 to 39 ml/100 g/min
  - 7.8 Hz correlated with CBF 47 ml/100 g/min

Vespa et al., EEG Clin Neurophys 1997;103:607-615
Carotid Endarterectomy: Baseline
Carotid Endarterectomy: Intra-op
Carotid Endarterectomy: Post-CEA
Carotid Endarterectomy: Trends
Carotid Endarterectomy: Alpha-Delta
Beta Asymmetry

FFT Spectrogram 01, Left Hemisphere, 12 - 32 Hz

FFT Spectrogram 01, Right Hemisphere, 12 - 32 Hz

Artifact Reduction ON
Beta Asymmetry
Carotid Endarterectomy: Ischemia
Carotid Endarterectomy, Ischemia
Delayed Cerebral Ischemia (DCI)

- New focal or global neurological deficit and/or new infarction after SAH (exclude rebleeding / hydrocephalus)
- Days 3 – 14 after SAH
- Major cause of cerebral ischemia and morbidity
- Occurs in 19-46% of patients
  - Infarct in ~ 60%
  - Subclinical in 25%, associated with poor outcome
- Risk factors
  - Poor Hunt-Hess grade
  - Large amounts of cisternal blood

Subarachnoid Hemorrhage

- Pathophysiology
  - Vasospasm of large vessels
  - Microembolism
  - Vasospasm of peripheral arteries and arterioles (as opposed to proximal large vessels)
  - Cortical spreading ischemia

- DCI is treatable if diagnosed during reversible phase
  - Hypertension
  - Volume expansion
  - Intraarterial nicardipine, papaverine
  - Angioplasty

- Long window for intervention (2-6 hours)

Connolly ES et al. Stroke 2012;43:1711-1737
Monitoring for Vasospasm

- Clinical examination
  - Patient often sedated, uncooperative
- Daily Transcranial Dopplers (TCDs)
  - “Snapshot” in time
  - Only monitors for vasospasm, not other causes of ischemia
  - Mediocre sensitivity and specificity
- Conventional angiography
  - Performed if above suggestive of ischemia
  - Invasive
- Brain imaging (CT, CTA, and MRI)
  - Performed if above suggestive of ischemia

Diringer MN et al. Neurocrit Care 2011;15:211-240
Labar: EEG Monitoring in SAH

- 21 patients with aneurysmal SAH
- 2 channel EEG (Cz-T3, Cz-T4)
- Automatic artifact detection methods (excess of the dynamic range of amplifiers, zero-derivative signals, and excessive 60 Hz interference)
- Compressed spectral analysis (1-30 Hz)
- Trend analysis
  - Sum of the power (total power), 1-30 Hz
  - Centroid of the frequency, 1-30 Hz
  - Power 7.5-15 Hz / power 1-7 Hz ('alpha ratio')
  - Power 1-3.5 Hz / power 1-30 Hz ('percent delta')

Labar DR et al., Electroencephalogr Clin Neurophysiol 1991;78:325-332
### Labar: EEG Monitoring in SAH

<table>
<thead>
<tr>
<th>EEG Finding</th>
<th>EEG Parameter</th>
<th>Focal CT lesions (N)</th>
<th>All ischemic events (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in power</td>
<td>Trend analysis</td>
<td>100% (5)</td>
<td>91% (11)</td>
</tr>
<tr>
<td></td>
<td>Compressed spectral array</td>
<td>33% (6)</td>
<td>44% (18)</td>
</tr>
<tr>
<td>Change in frequency</td>
<td>Centroid</td>
<td>60% (5)</td>
<td>55% (11)</td>
</tr>
<tr>
<td></td>
<td>Relative alpha</td>
<td>60% (5)</td>
<td>64% (11)</td>
</tr>
<tr>
<td></td>
<td>Percent delta</td>
<td>80% (5)</td>
<td>45% (11)</td>
</tr>
<tr>
<td></td>
<td>Compressed spectral array</td>
<td>17% (6)</td>
<td>39% (18)</td>
</tr>
</tbody>
</table>

Labar DR et al., Electroencephalogr Clin Neurophysiol 1991;78:325-332
Vespa: EEG Monitoring in SAH

- 32 patients with aneurysmal SAH
- Reduction in variability of theta-alpha content (6-14Hz)
  - Ratio of power in 6-14Hz band relative to power in 1-20Hz band
- Sensitivity 100%
- Specificity 50% (increased ICP, recurrent hemorrhage, hydrocephalus, embolic stroke during angio)
- Preceded clinical onset of vasospasm and elevated TCD velocities in 70%
  - Mean 2.9 days

Vespa et al., EEG Clin Neurophys 1997;103:607-615
Alpha Variability

0 – 0.5 µV/Hz
Bilateral frontal ischemia - decrease in alpha variability

Clinical deterioration - sedation / intubation

Disconnected 2 hrs for angiogram: Improvement in alpha variability after angio
Claassen: EEG Monitoring in SAH

- 34 of 78 consecutive Hunt-Hess grade 4 or 5 SAH patients
- Continuous EEG post-op day 2 to post-SAH day 14
- 20 artifact-free, 1 min EEG-clips after alerting stimulus
  - 10 clips on monitoring day 1 (baseline)
  - 10 clips on days 4-6 (follow-up)
  - In DCI patients, follow-up clips after the onset of deterioration and before infarction

Claassen J et al., Clin Neurophysiol 2004;115:2699-2710
Nine of 34 patients (26%) developed DCI

Alpha/delta ratio (alpha power/delta power; ADR) demonstrated the strongest association with DCI
- Median decrease of ADR in DCI was 24%
- Median increase of 3% without DCI (p<0.0001)

Clinically useful cut-offs
- 6 consecutive recordings with >10% decrease in ADR from baseline (sensitivity 100%, specificity 76%)
- Any single measurement with a >50% decrease (sensitivity 89%, specificity 84%)

Claassen J et al., Clin Neurophysiol 2004;115:2699-2710
SAH: Alpha-Delta Ratio

F3-C3
F4-C4
C3-T3
C4-T4
P3-O1
P4-O2
Left
Right

12:30 13:30 14:30
Comprehensive Panel
Alpha-Delta Ratio

Time (2 min. running ave.), FFT PowerRatio, 8-13/1-4 Hz, Left Hemisphere and FFT PowerRatio, 8-13/1-4 Hz, Right Hemisphere, 0 - 1

Time (2 min. running ave.), FFT PowerRatio, 8-13/1-4 Hz, Left Anterior and FFT PowerRatio, 8-13/1-4 Hz, Right Anterior, 0 - 1

Time (2 min. running ave.), FFT PowerRatio, 8-13/1-4 Hz, Left Posterior and FFT PowerRatio, 8-13/1-4 Hz, Right Posterior, 0 - 1

Asymmetry, Relative Spectrogram, Asym Hemi, 1 - 18 Hz

Asymmetry, Absolute Index (EASI), 1 - 18 Hz, Asym Hemi, -50 - 50 %, Asymmetry, Relative Index (REASI)01, 1 - 18 Hz, Asym Hemi, -50 - 50 %
Case 1

- 56 year old man with SAH
  - Hunt-Hess grade 3
  - Fisher grade 3
  - GCS 10
- Angiography revealed a 7 mm left AComm aneurysm
- Aneurysm was clipped uneventfully
Alpha-Delta: 8 hours
Raw EEG: 30 minutes
Raw EEG: 6 hours
Alpha Variability: 8 hours
Alpha-Delta: 16 hours
Alpha Variability: 16 hours
Raw EEG: 12 hours
Case 2

- 62-year-old woman with SAH
  - Hunt-Hess grade 2
  - Fisher grade 3
  - GCS 14

- Angiography revealed a 8 mm right internal carotid supraclinoid aneurysm and a 4 mm left anterior communicating artery/anterior cerebral artery junction aneurysm

- Both aneurysms were clipped uneventfully
Alpha-Delta: 8 hours
Alpha-Delta: 8 hours
Alpha Delta: 8 hours, day 4
QEEG: Intracortical EEG

- Improved signal: noise and reduced artifact
- 5 patients with poor grade SAH (Hunt-Hess grade 4 or 5)
- 8 contact depth electrode (2.2 mm spacing)
- QEEG: average over 4-6 hrs baseline vs. prior to angio
  - Alpha/delta ratio (ADR, 8–13 Hz/1–4 Hz)
  - Mean amplitude
  - Suppression percent (percent below 5 uV)
  - Total power (TP, 0–23 Hz)
  - Superior to alpha-delta ratio of scalp EEG

Stuart RM et al. Neurocrit Care 2010;13:355-358
QEEG: Intracortical EEG

- 3/5 SAH patients had vasospasm on follow-up angiography
- Mean ICE ADRs prior to angiography
  - Decreased by 42% for those with vasospasm
  - Decreased by 17% for those without vasospasm
  - Dropped by at least 25% for >4 h in all patients with vasospasm 1–3 days before angiographic confirmation of vasospasm
- No false negatives
- Surface EEG was limited by significant artifact and poor signal quality, despite application of automated artifact rejection

Stuart RM et al. Neurocrit Care 2010;13:355-358
Systematic Review

- 8 publications included from 760 citations
  - All single-center case series, half retrospective
  - All affected by high risk of bias related to patient selection
  - 50% high risk of bias for EEG methodology

Systematic Review

- Reference standard: CT, DSA, and TCD (120 to 140 cm/min) in most but not all studies
  - 4 studies: DCI based on clinical diagnosis, presence of radiological vasospasm or increased TCD flow velocities was supportive but not mandatory

- Conclusion
  - CEEG monitoring after SAH may predict clinically symptomatic episodes of DCI many hours in advance
  - Unknown if more aggressive treatment alters outcome

QEEG for DCI: Confounders

- Sedation and other medications
- Increased intracranial pressure
- Reduced global cerebral perfusion pressure
- Metabolic changes
- Hydrocephalus
- Rebleeding
- Focal edema
- Artifacts
- Large variety of DCI definitions
  - New definition: infarct and functional outcome
**Summary: CEEG after SAH**

- EEG and QEEG trends on cEEG (performed on days 2–10) correlate with delayed cerebral ischemia
- QEEG trends designed to detect increased slow and loss of fast frequencies
- May detect ischemia prior to neurological exam and other diagnostic tests
- Sensitivity up to 90%
- Specificity 75%
- Optimal duration not defined
- Most studies examined poor grade patients
- No interventional trials using EEG as detection method

Ischemic Stroke

- 91 patients with acute ischemic stroke
  - 33 (36%) initially had normal CT scans
    - 16 (48%) showed lateralized EEG abnormalities
    - All 16 showed cortical infarctions on follow-up CT scans corresponding to the EEG findings
  - 58 cortical infarctions
    - Lateralized EEG abnormalities
      - 80% of MCA
      - 86% of watershed

- 12 lacunar infarctions with negative initial CT scans had normal acute EEGs

Macdonell RA et al., Arch Neurol 1988;45:520-524
Prediction of Malignant Course

- RAWOD
  - Regional Attenuation WithOut Delta
  - Patients with large acute ischemic stroke
  - Less likely to benefit from thrombolysis
  - Likely to develop cerebral edema

RAWOD: QEEG
Prediction of Malignant Course

- 25 patients with large (>50%) middle cerebral artery (MCA) infarction
  - 12 malignant, 13 benign course
- EEG within 24 hours, visual analysis
- Predictors
  - Benign course: absence of delta activity, presence of theta and fast beta frequencies
  - Malignant course: diffuse slowing (< 8 Hz), slow delta activity (< 1 Hz), loss of fast beta in the ischemic hemisphere

Asymmetry Indices

- Brain Symmetry Index (BSI)
  - Single numerical value: sums absolute values of the differences at each homologous electrode pair for all frequencies
    - 0: perfect symmetry
    - 1: maximal asymmetry
  - Correlates with clinical stroke scales
  - Has been used to follow effect of tPA
BSI for Carotid Endarterectomy

BSI and NIH Stroke Scale

Ischemic Stroke: Confounders

- Spontaneous or provoked state changes
- Variations in physiological parameters (BP, ICP, cerebral perfusion pressure)
- Sedative medications
- Artifacts (EMG, electrode)
Ischemic Stroke: Caveats

- Differential diagnosis of lateralized slowing / loss fast
  - Focal postictal states
  - Hemiplegic migraine
- Cortical infarctions < 3 cm may not show EEG changes
- Lacunar infarcts often show normal EEG
- Medial lesions may produce bilateral rather than focal EEG changes
- Almost no data on continuous EEG monitoring to detect worsening ischemia in real time
Conclusions

- EEG is a useful monitoring tool for cerebral ischemia
  - Large vessel territorial ischemia
  - Good sensitivity, moderate specificity
- Retrospective studies have demonstrated helpful QEEG methods in CEA, SAH
  - Limited by
    - Lack of specificity (hydrocephalus, sedatives, etc)
    - Artifacts
- No prospective real-time analysis
- Need prospective randomized blinded trials