Overview of Spreading Depolarization Monitoring

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Basic science

Clinical Translation
1. Basic science of how spreading depolarizations mediate infarct development

2. How to monitor spreading depolarizations in patients

3. Clinical importance of spreading depolarization monitoring
SPREADING DEPRESSION OF ACTIVITY IN THE
CEREBRAL CORTEX*

ARISTIDES A. P. LEÃO
Department of Physiology, Harvard Medical School,
Boston, Massachusetts

(Received for publication August 14, 1944)
Spreading depolarizations are near-complete collapse of electrochemical membrane gradient

from Ghadiri et al., Cephalalgia 32(2):116-24, 2012
**Spreading depolarizations** = class of pathologic waves characterized by sustained depolarization of neurons/astrocytes that propagate through gray matter at 2-8 mm/min

**Spreading depression** = loss of synaptic cortical activity as a consequence of spreading depolarization
Spreading depression vs. depolarization

Spreading depression vs. depolarization

Spreading Depolarization
A self-propagating wave of abruptly developing, near-complete breakdown of transmembrane ion gradients in neurons and astrocytes *en masse* that spreads through contiguous cerebral gray matter at a typical velocity of 2–5 mm/min (range: 1–9 mm/min) and is locally sustained for at least 15 s. Depolarization can be recorded as a negative shift of the extracellular direct-current potential (frequency range <0.05 Hz).

Spreading Depression
A wave of depression in spontaneous activity of the electrocorticogram (>0.5 Hz) that propagates through contiguous cerebral gray matter at a typical velocity of 2–5 mm/min. *Spreading depression is a consequence of spreading depolarization.*

Spreading depolarization can occur without spreading depression (tissue with no spontaneous activity), but spreading depression is always caused by spreading depolarization.

Dreier et al., *JCBFM*, 2016 Jun 17 (in press)
Hartings et al., *JCBFM*, 2016 June 21 (in press)
Spreading depolarization: a required mechanism of acute cortical lesions

Global ischemia

Subarachnoid hemorrhage

Mild ischemia
(endothelin)

EAAT inhibition

Focal ischemia

Traumatic brain injury
Continuum of spreading depolarizations

Describes the wide spectrum of depolarization characteristics that can be observed depending on local tissue conditions. These characteristics include varying durations and metabolic responses.
Persistent depolarization establishes characteristics of ischemic core (ion pump failure, membrane failure)

Persistent depolarization induces cytotoxic edema / diffusion restriction

Murphy et al., J. Neurosci. 28(7):1756-72, 2008
Persistent depolarization induces cytotoxic edema / diffusion restriction
Persistent depolarization is reversible if blood flow is restored

Hinzman JM and Hartings JA, unpublished
Severe ischemia + persistent depolarization = infarction

Three requirements for infarction:
- ischemia
- depolarization
- persistence of both (time)
Ischemic core

- Ischemic core
  - Persistent depolarization (anoxic or asphyxial depolarization)

Delayed lesion growth

- Delayed lesion growth
  - Persistent depolarization

Spreading depolarizations decrease cerebral blood flow


SD induces spreading ischemia
Triggers of secondary spreading depolarizations

Susceptible to increase in demand

Susceptible to decrease in supply

Energy supply-demand mismatch in penumbra

Summary

- Ischemia, depolarization, and time are required for infarction
- Ischemia can be triggered by:
  - vascular insult (initial depolarization), or
  - depolarization wave itself (delayed growth)
- Secondary lesion growth (hrs to days) mediated by recurrent ‘spontaneous’ depolarization waves
  - triggered by supply-demand mismatches in penumbra
  - cause expansion of terminally depolarized core

Key Interpretations

- Spreading depolarizations are causal, requisite factor in lesion development
- Occurrence of depolarizations indicates
  - critical metabolic instability, and
  - ongoing lesion growth
Clinical Translation
measuring spreading depolarizations in the clinic

Stroke 33: 2738-43, 2002

Expedited Publication

Spreading and Synchronous Depressions of Cortical Activity in Acutely Injured Human Brain

Anthony J. Strong, DM; Martin Fabricius, DMSc; Martyn G. Boutelle, PhD; Stuart J. Hibbins, MSc; Sarah E. Hopwood, PhD; Robina Jones, MRCS; Mark C. Parkin, BSc; Martin Lauritzen, DMSc

1. Placing electrode strips and recording set-up
2. Display and interpretation of data
3. Practical value of monitoring
Electrocorticography in acute brain injury
Electrode strip placement

Ideal placement
• Targets penumbra
• Lies along single gyrus

Poor placement
• Remote from injury
• Crosses major sulcus

Key tips
• Exit through burr hole
• Tunnel sufficiently
• Coil and anchor exteriorized lead
In the intensive care unit

1. Place ground electrode on shoulder or scalp; reference (subdermal platinum needle) at mastoid or frontal apex

2. Connect electrode strip to cable

3. Plug electrodes into amplifier and begin monitoring
Electrocorticography in patients

1. Negative direct current shift identifies depolarization
2. Depolarization causes depression of high frequency activity

Electrocorticography in patients

1. Compressed time scale (≥ 30 min / page)
2. DC or near-DC amplifier to record slow changes
3. Large amplitude signals
... vs. EEG

100 µV

1 sec
Brain activity contains a mixture of frequencies

![Diagram showing various frequency components: DC, AC f₁, AC f₂, AC f₃, AC f₄.](image)
Electrocorticography in patients

https://www.charite-academy.de/spreading-depolarization-and-spreading-ischemia/
Electrocorticography: bedside display
LabChart (ADInstruments) Review
> 800 neurosurgical patients monitored in 12 centres (Europe and USA)

**Incidence of spreading depolarization findings:**

- Traumatic brain injury: 50-60%
- Intracerebral hematomas: 50-60%
- Aneurysmal subarachnoid hemorrhage: 75-80%
- Malignant ischemic stroke: 90-100%
### Spreading depolarizations in TBI

**Table 3: Outcome prediction (multivariate ordinal regression analysis)**

<table>
<thead>
<tr>
<th>Common odds ratio (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prognostic score</td>
<td>1.76 (1.26–2.46)</td>
</tr>
<tr>
<td>Depolarisation</td>
<td>1.0</td>
</tr>
<tr>
<td>None</td>
<td>1.0</td>
</tr>
<tr>
<td>CSD</td>
<td>1.56 (0.72–3.37)</td>
</tr>
<tr>
<td>ISD</td>
<td>7.58 (2.64–21.8)</td>
</tr>
</tbody>
</table>

CSD=cortical spreading depression. ISD=isolectric spreading depolarisation.

- **n = 138 surgical TBI**

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Hartings et al., *Brain* 134: 1529-40, 2011
Spreading depolarizations in aneurysmal SAH

- 86% PPV and 100% NPV for DCI

Dreier et al., *Brain* 129: 3224-37, 2006
Dreier et al., *Brain* 135: 259-75, 2012
Spreading depolarizations induce hypoxia-ischemia

Dreier et al., *Brain* 132: 1866-81, 2009
Bosche et al., *Ann Neurol* 67: 607-17, 2010
### Depolarizations occur independent of other secondary insults

<table>
<thead>
<tr>
<th></th>
<th>Number of SDs (patients)</th>
<th>Normal range</th>
<th>Abnormal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure</td>
<td>1,657 (54)</td>
<td>1,602 (97%) (&gt; 70 mm Hg)</td>
<td>55 (3%) (&lt; 70 mm Hg)</td>
</tr>
<tr>
<td>Intracranial pressure</td>
<td>1,226 (48)</td>
<td>1,196 (98%) (&lt; 20 mm Hg)</td>
<td>30 (2%) (&gt; 20 mm Hg)</td>
</tr>
<tr>
<td>Brain tissue oxygenation</td>
<td>510 (19)</td>
<td>393 (77%) (&gt; 20 mm Hg)</td>
<td>117 (23%) (&lt; 20 mm Hg)</td>
</tr>
<tr>
<td>Cerebral blood flow</td>
<td>234 (14)</td>
<td>165 (71%) (&gt;18 ml/100g/min)</td>
<td>69 (29%) (&lt;18 ml/100g/min)</td>
</tr>
</tbody>
</table>

See also Hartings et al., J Neurotrauma 26:1857-66, 2009
Depolarizations occur independent of other secondary insults


- GCS = 13
- ICP = 13
- CPP = 69
- Temp = 37.7
Remote detection of relative ischemia by ECoG/SD monitoring

Adapted from:
Dreier et al., *JCBFM*, 2016 Jun 17 (in press)
Why monitor spreading depolarizations in patients?

- Direct measure of neuronal health and function
- Clinical indicator of ongoing lesion growth
- Clinical indicator of critical metabolic instability
- Propagating nature of depolarizations allows remote detection
- Independent of other prognostic factors and monitoring variables
- Etiologic basis for clinical deterioration or lack of recovery
- Provide indication for continued critical care and intensified therapy
- Heterogeneous mechanism as a basis for personalized therapy
- Mechanistic targeting for neuroprotection
Hartings et al., The continuum of spreading depolarizations in acute cortical lesion development: examining Leão’s legacy. JCBFM 37(5):1571-94, 2017

Dreier et al., Recording, analysis, and interpretation of spreading depolarizations in neurointensive care: review and recommendations of the COSBID research group. JCBFM 37(5):1595-1625, 2017
iCSD2019 will be held July 1-3 in Yokohama, Japan

The Co-Operative Studies on Brain Injury Depolarizations is an international research consortium focused on the role of spreading depolarizations in acute neurologic injury.
COSBID documentary
History and Perspectives on Spreading Depolarization Monitoring in the Clinic

Moberg YouTube channel:
www.youtube.com/watch?v=JbhTbtxWaSo
braintsunamis.org