Spreading Depolarizations: What are they and why do they matter for my patient?

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Disclosures

• No commercial or financial conflicts of interest.

• Deidentified clinical data are shown under IRB protocol 10-01760 for quality improvement and teaching purposes.
Objectives

1) Compare and contrast spreading depolarization with synaptic signaling and seizure activity.

2) Recognize spreading depolarization as a feature of traumatic brain injury and a contributor to delayed lesion expansion.

3) Identify opportunities to detect and target spreading depolarizations to improve clinical practice.
Compare and contrast spreading depolarization with synaptic signaling and seizure activity.
Physiologic signaling

4 mM K^+

10-100 µs

10-100 m/s

[ATP]
Seizure

8 mM K^+

1-2 min

[ATP]
Spreading depolarization

12 mM K⁺
Presynaptic nerve terminals

Ischemia
Trauma
Coordinated depolarization

K$^+$

Glu

K$^+$

Glu

K$^+$

Glu

2-6 mm/min

30-300 s

[ATP]
Consequences of SD: Ion flux

Outward currents

Inward currents

Time

SD

30% net cation influx

Electric field gradient

~10 s
Consequences of SD

Depression of cortical activity


Recognize spreading depolarization as a feature of traumatic brain injury and a contributor to delayed lesion expansion.
SD triggered mechanically

Chick retina

Yu et al 2009 PNAS
SD in metabolically heterogeneous tissue

Swine cortex

Strong AJ et al, Brain 130(4);2007:995-1008.
SD occurs in TBI

SD associated with stepwise progression of injury

+ 8 hours
**Participants (n=103)**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>44 (30 to 60, 18 to 79)</th>
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</thead>
<tbody>
<tr>
<td>Glasgow coma scale motor score*</td>
<td></td>
</tr>
<tr>
<td>No response</td>
<td>24 (23%)</td>
</tr>
<tr>
<td>Extension</td>
<td>4 (4%)</td>
</tr>
<tr>
<td>Flexion</td>
<td>5 (5%)</td>
</tr>
<tr>
<td>Withdraws</td>
<td>18 (17%)</td>
</tr>
<tr>
<td>Localises</td>
<td>30 (29%)</td>
</tr>
<tr>
<td>Obey</td>
<td>22 (21%)</td>
</tr>
</tbody>
</table>

**Pupils***

| Both reacting | 66 (64%) |
| One reacting | 16 (15%) |
| Neither reacting | 21 (20%) |

**Marshall CT category***

| Diffuse injury (2) | 3 (3%) |
| Swelling (3) | 4 (4%) |
| Shift (4) | 3 (3%) |
| Evacuated mass lesion (5) | 63 (62%) |
| Non-evacuated mass lesion (6) | 29 (28%) |

**Traumatic subarachnoid haemorrhage**

| 83 (81%) |

**Hypotension***

| 15 (15%) |

**Hypoxia***

| 19 (18%) |

| Prognostic score | 0.1 (0.5 to 1.2, -2.0 to 3.1) |

Data are n (%) or median (IQR, range). *16 (1.9%) of the 824 covariate values were missing and were replaced by imputation, comprising four values for Glasgow coma scale motor score, one for pupillary reactivity, six for hypotension, four for hypoxia, and one for Marshall CT category.

**Table 2: Covariates for outcome prediction**

**Common odds ratio (95% CI) p**

| Prognostic score | 1.76 (1.26 to 2.46) | 0.0009 |
| Depolarisation |
| None | 1.0 |
| CSD | 1.56 (0.72 to 3.37) | 0.26 |
| ISD | 7.58 (2.64 to 21.8) | 0.0002 |

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

**Table 3: Outcome prediction (multivariate ordinal regression analysis)**
Identify opportunities to detect and target spreading depolarizations to improve clinical practice.
Recording and monitoring SD in standard clinical practice

Ch1

Ch3

Ch4

700 µV

1 hour
Hypotension, hypoxia, and fever trigger SD

Hartings et al J Neurotrauma 2009

Sukhotinsky et al JCBFM 30(6);2010:1168-1177
Cerebral perfusion pressure modulates SD
Ketamine inhibits SD

Hartings et al JNS 2018
Ketamine inhibits SD

Hartings et al. JNS 2018
Ketamine inhibits SD

Hertle et al. Brain 2012
Next steps:
Testable hypotheses from preclinical data

• Hypoxia and alkalosis should increase incidence of SD.

• Hyperosmolar therapies should decrease incidence of SD.
Is systemic alkalosis a risk factor for SD?

Unpublished data
Can hyperosmolar therapy prevent SD?
Summary and Conclusions

SD is a profound, prolonged depolarization which propagates through grey matter via feed-forward release of excitatory neurotransmitters and potassium.

SD is a feature of traumatic brain injury, and contributes to secondary injury in the days following initial insult.

SD incidence and characteristics are affected by physiologic parameters within our control in the ICU environment. More research is needed to determine best practices.
For more information

• COSBID.org
• braintsunamis.com

• britta.lindquist@ucsf.edu
Next steps:
Noninvasive detection and real-time SD alarms

• SDII substudy within TRACK-TBI.
  • Scalp EEG vs subdural ECoG recordings.

• Real-time bedside alarm and risk-stratification of SD
  • Moberg module in beta testing.
Spreading depolarization is carried by:

A. Glia
B. Neurons
C. Blood vessels
D. Potassium
E. Glutamate
F. Gap junctions
G. NMDA receptors
H. Calcium
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• If possible, SD should be suppressed in brain injury patients
  A. Yes
  B. No
  C. Show me outcome data
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  A. Yes
  B. No
  C. Show me outcome data
• Sick injured brain is prone to SD. The proximate trigger for any given SD might be:
  A. Hypotension
  B. Fever
  C. Touching the patient
  D. Elevated ICP
  E. Vasospasm
  F. Seizure activity
  G. Hyponatremia/electrolyte disturbance
  H. Hyper/hypoventilation
  I. Hypoxemia
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• If I have an acute brain injury, give me:
  A. Intracranial monitoring and goal-directed therapy
  B. Hypertension, hypervolemia, hemodilution
  C. Anticonvulsants
  D. Pressors
  E. Ketamine
  F. Hypernatremia
  G. Targeted temperature management
If I have an acute brain injury, give me:

A. Intracranial ECoG monitoring and goal-directed therapy
B. Hypertension, hypervolemia, hemodilution
C. Anticonvulsants
D. * Pressors – targeting CPP > ??
E. * Ketamine – targeting malignant patterns (iSD, clusters) in real time
F. Hypernatremia
G. Targeted temperature management -- euthermia
• If I have an acute brain injury, give me:
  A. Intracranial monitoring and goal-directed therapy
  B. CPP (until it hurts)
  C. Real time SD alarms and responsive ketamine bolus