Cortical Spreading Depression and Ischemia in Neurocritical Patients

Néstor Wainsztein, MD[a], Federico Rodríguez Lucci, MD[a,b,*]

KEYWORDS

• Spreading depolarization • Spreading depression • Delayed cerebral ischemia
• Cortical spreading depression • Cerebral blood flow • Subarachnoid hemorrhage
• Stroke • Spreading ischemia

KEY POINTS

- Spreading depolarization and spreading depression can be induced by hypoxic conditions in individuals with aneurysmal subarachnoid hemorrhage shortly after aneurysm rupture, delayed ischemia after subarachnoid hemorrhage, malignant stroke, intracranial hemorrhage, or traumatic brain injury. It has also been implicated in migraine aura.
- Cortical spreading depression is hypothesized to alter blood-brain barrier permeability by matrix metalloproteinase (MMP) activation and upregulation.
- The term spreading depression should be used only to describe the depression of spontaneous activity induced by spreading depolarization.
- The differentiation between spreading depolarizations with and without spreading depression could have diagnostic and prognostic significance.
- Spreading depolarizations exacerbate neuronal injury through prolonged ionic balance breakdown and spreading depolarization-related hypoperfusion (spreading ischemia).

Spreading depolarizations (SDs) are defined as waves of abrupt, near-complete breakdown of neuronal transmembrane ion gradients. They constitute a major pathophysiologic disruption of viable cerebral gray matter and are a crucial mechanism of secondary brain injury.[1] SDs are increasingly recorded during multimodal neuromonitoring in neurocritical care as markers of metabolic failure and excitotoxic injury. On the other hand, cortical spreading depression (CSD) is characterized by depression

Disclosure Statement: The authors have nothing to disclose.

[a] Department of Internal Medicine, Neurocritical Care Unit, Institute of Neurological Research, FLENI, Montañeses 2325, Buenos Aires, Argentina; [b] Stroke Unit, Comprehensive Stroke Center, Institute of Neurological Research, FLENI, Montañeses 2325, Buenos Aires, Argentina
* Corresponding author. Department of Internal Medicine, Neurocritical Care Unit, Institute of Neurological Research, FLENI, Montañeses 2325, Buenos Aires, Argentina.
E-mail address: frodriguezlucci@fleni.org.ar

Neurol Clin 35 (2017) 655–664
http://dx.doi.org/10.1016/j.ncl.2017.06.004 **neurologic.theclinics.com**

of evoked and spontaneous electroencephalography activity spreading at a rate of 2 to 5 mm across the cortical surface.[2]

Focal ischemia causes SD within minutes. Further SDs arise for hours to days due to energy supply-demand mismatch in viable tissue. SDs will exacerbate neuronal injury through prolonged breakdown of ionic balance and SD-related hypoperfusion (spreading ischemia).[1] Local duration of the depolarization indicates local tissue energy status and risk of injury. Therefore, SDs, spreading depression, and spreading ischemia are terms with different diagnostic and prognostic significance.[3]

In hypoxic, ischemic, glycopenic brain tissue, CSD will usually occur spontaneously, and recovery is slow.[4] The SD of neurons and glia is preceded by propagating field oscillations covering distances of up to 1 mm.[5] These oscillations indicate a brief state of hyperexcitability, which may relate to the observation of seizures and CSD in the same patients with acutely injured brain cortex.[6] The oscillations are followed by complete loss of neuronal activity, which can last for minutes, before complete recovery occurs. Biochemical and morphologic alterations manifested as neuronal cytotoxic edema is uniformly present. At the same time, the local tissue potential becomes negative with amplitudes of 15 to 30 mV.[7] This negative potential shift may be explained by sustained complete depolarization that is restricted to specific cell domains because there is an initial explosive opening of conductance along most of the pyramidal neuron followed by a wave-like centripetal closure toward the apical dendrites.[8] Local increases in tissue resistivity may contribute as well. Thus, neurons are likely to be responsible for the current signals initiating CSD, and for those involved with its propagation and termination.[9]

The electroencephalogram depression coincides with and is caused by a dramatic failure of brain ion homeostasis and efflux of excitatory amino acids from nerve cells. During CSD, extracellular potassium (K+) increases, whereas calcium (Ca2+) decreases, Cl decreases, and sodium (Na+) decreases.[10]

During the depolarization wave there is a massive release of amino acids, including glutamate and aspartate, and voltammetric recordings have shown that the massive neurotransmitter release follows the onset of depolarization.[10] The mechanism of initiation of CSD is uncertain, but slightly elevated levels of K+ and of neurotransmitters are sufficient to trigger the spread of CSD.[9] Furthermore, depolarization of neurons as a consequence of synaptic transmission is expected to remove the voltage-sensitive magnesium (Mg2+) block of the N-methyl-D aspartate (NMDA) receptor, and can sensitize this receptor to small increases in interstitial glutamate.[9,10] Interaction of glutamate with the NMDA receptor triggers K+ and glutamate release, as well as further neuronal depolarization that will propagate to neighboring regions and start the process all over again.[10] Clusters of depolarizations occur often at precise intervals ranging between 25 and 45 minutes.[10]

Astroglial cells protect against CSD initiation because of their high capacity for K+ buffering and glutamate uptake. Gamma aminobutyric acid (GABA) is released in high concentrations during SD.[11] Repetition of CSD waves in normal tissue results in a recoverable dysfunction of electrogenesis, but neuronal dysfunction may become complete and permanent in tissue deprived of glial function.[11]

A physiologic role of SD is unlikely and, therefore, these SDs should always be considered pathologic. The noxious conditions that provoke cortical depolarization are:

- Mechanical damage
- Vigorous electrical stimulation
- Hypo-osmolality