INVITED EDITORIAL COMMENTARY

Pathophysiological Insights into Spreading Depolarization in Severe Traumatic Brain Injury

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Cortical spreading depolarization (SD) was first identified over 70 years ago by the Brazilian neurophysiologist Leão [1], and has emerged as a plausible mechanism to account for time-dependent expansion of cerebral dysfunction and injury [2]. SD is defined as a transient wave of cellular depolarization involving both neurons and astrocytes, which propagates within gray matter at a velocity of 1–9 mm/min³. It has been described in patients with ischemic stroke, aneurysmal subarachnoid hemorrhage (SAH), post-SAH delayed cerebral injury, intracerebral hemorrhage, and severe traumatic brain injury (TBI), and it is believed to play a role in the aura preceding migraine headaches [3]. SD has been successfully modeled in murine and large animal brain injury paradigms [4–6]. The depolarization of cell membranes is associated with cytotoxic edema, influx of Na⁺, Cl[−], and Ca²⁺ ions, efflux of K⁺ ions, and an extracellular accumulation of neurotransmitters. An ensuing loss of spontaneous electrical activity is defined as *spreading depression*. The duration of depolarization in individual cells may last from seconds to minutes and is influenced by the level of perfusion. In the absence of ischemia (e.g., in migraine), repolarization typically occurs without permanent injury to neurons, whereas with cerebral blood flow less than 10 ml/min/100 g, adenosine triphosphate (ATP) generation is insufficient to restore transmembrane electrochemical gradients and cells remain permanently depolarized and eventually die. Intermediate levels of perfusion usually result in delayed repolarization,

but recurrent waves of depolarization emanating from more ischemic regions overwhelm the cellular machinery required to restore transmembrane gradients and to defend against excitotoxic injury, leading to delayed cell death. A causal role for SDs in the expansion of infarction is supported by studies in which experimentally induced waves of SD produced larger infarctions [7, 8].

In this issue, Eriksen et al. studied patients with severe TBI to clarify relationships between SD, extra-axial hemorrhage (subdural and subarachnoid), parenchymal injury, and clinical outcome [9]. The authors studied 50 patients undergoing surgery for management of TBI who were in the Co-Operative Studies on Brain Injury Depolarization cohort. Each patient had a subdural electrode strip implanted and underwent electrocorticographic (ECoG) recording for a median of 79 h. Principal outcome was the dichotomized Glasgow Outcome Score Extended at 6 months. A novel feature of the study is the use of the Cavalieri stereology method to quantify the volume of the parenchymal lesion, subdural blood, and subarachnoid blood on head computed tomography (CT) scans obtained before surgery, after surgery, and after removal of the electrodes. Principal findings were that (1) the number of SDs was significantly associated with the volume of extra-axial (subdural plus subarachnoid) blood, but not with the initial parenchymal lesion volume; (2) temporal clusters of SDs predicted poor clinical outcome; (3) expansion of parenchymal lesion volume also predicted poor outcome; and (4) in a logistic regression model, SD clusters and parenchymal volume expansion were independently associated with unfavorable outcome.

This work has some methodological shortcomings, most notably the sparse description of the morphology and location of traumatic lesions identified on head CT and the lack of detail on the type and effectiveness on the surgeries and on the anatomical location of the ECoG

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This comment refers to the article available at <https://doi.org/10.1007/s12028-019-00692-w>.

recording strips. It would have been helpful, for instance, to create a topographical map of the SDs as they progress through cortical tissues, in particular to understand how the SDs relate spatially to extra-axial hematomas and intraparenchymal lesions. In addition, the presence and volume of intraventricular hemorrhage (IVH) are not reported, yet IVH is a well-known and significant predictor of outcome following severe TBI [10, 11]. The manual stereologic method described is of interest; however, such an approach is likely to be superseded by modern semi- or fully automated techniques [12]. Perhaps most importantly, the study does not resolve persisting uncertainty of where SDs lie in the causal chain of pathobiological events following brain injury.

Despite limitations, this report contains valuable pathophysiological insights. The association of SD frequency with extra-axial rather than parenchymal lesion volume is not immediately intuitive. Because SDs are thought to emanate from injured cells, one might have anticipated a direct correlation with the amount of damaged tissue. However, such a model fails to consider the important and complex effects of extravasated blood on the cerebral macro- and microvasculature. In a porcine model, injection of blood into the subdural space induced SDs and injury to a far greater extent than injections of a control fluid [6]. Such effects are potentially mediated by erythrocyte release of ATP, which binds purinergic receptor–pannexin hemichannel complexes known to play a role in SD [13], and oxidative stress arising from methemoglobin and ferryl hemoglobin formation and from the release of free iron and other non-heme-related factors such as thrombin. Hemorrhage-induced vasoconstriction may also compound the SD-associated brain injury. It has been shown that blood in the subarachnoid space induces early and delayed cerebral vasoconstriction via heme binding to nitric oxide, increased expression of endothelin, serotonin, and 20-hydroxyeicosatetraenoic acid, and by oxidation products of bilirubin [14]. Moreover, low cerebral blood flow and impaired pressure autoregulation in TBI may be exacerbated by further decreases in cerebral blood flow during SDs [15]. It is likely that SDs in TBI are characterized by ‘inverted neurovascular coupling’ analogous to that seen after experimental SAH where altered Ca^{2+} -activated K^+ channel function leads to a dysregulated hemodynamic response to neuronal activation [16]. Considered in the context of these other studies, the study of Eriksen et al., lends support to a model in which traumatic extra-axial hemorrhage, SDs, and macro- and microvascular dysregulation work in combination to aggravate the degree of underlying tissue injury.

As for the association between parenchymal lesion volume expansion (“blossoming”) and outcome, this is

a well known consequence of moderate and severe TBI, particularly among patients undergoing decompressive surgery [17, 18]. The relationship between temporal clusters of SDs and TBI outcome is also consistent with prior studies [19]. Taken together, these data indicate that SDs are a critical electrophysiologic signature of neurological deterioration and therefore a potential target for therapeutic (or preventive) intervention. Recent experimental and clinical investigations suggest a reduction in SDs during intravenous infusion of the N-Methyl-D-aspartic acid receptor antagonist ketamine [20–22], while the Gamma-Aminobutyric acid-A receptor agonist midazolam has been linked to a higher frequency of SDs [21]. Whether such findings could lead to improved clinical outcome for patients with severe TBI warrants evaluation in clinical trials.

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RDS and RCK conceived and wrote the paper together and equally contributed.

Source of support

RDS and RCK are supported by grants from the National Institutes of Health.

Conflicts of Interest

Authors report no conflicts of interest or disclosures in relation to the content of this manuscript.

Ethical Approval/Informed Consent

This article does not contain any studies with human participants or animals performed by any of the authors.

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Published online: 15 March 2019

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