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SPREADING CORTICAL DEPOLARIZATION

Going with the Flow or Shockwave? How Systemic Circulation May Potentially be Affected by Anoxic Depolarization

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Brain tsunamis, or spreading depolarizations (SDs), are abrupt, massive, and self-propagating waves of depolarization in neurons and astrocytes that slowly travel across the brain's gray matter and often lead to the depression of cortical activity. This phenomenon, and the association of the nearly complete breakdown of transmembrane ionic gradient with regional blood flow, were first described in the 1940s by the Brazilian physiologist, Aristides Leão [1, 2]. It took 40 years for the recognition of the potential implications of brain tsunamis in acute brain disorders [3], but it was only in the early 2000s that traction emerged among the scientific community, when early electrocorticographic recordings demonstrated their surprisingly frequent occurrence in the acutely injured human brain [4]. Slow, steady scientific progress has been made since the recognition of the direct current (DC) shift—the characteristic electrophysiologic signature of SD—as a physiologic phenomenon and not as a mere artifact from experiments. We now know so much more about neurovascular coupling, uncoupling, SD triggers and their modulation by medications, a distinct susceptibility of various brain regions, the metabolic toll, propagation behavior, and the interplay of these factors with age, sex, and nuances across different species. Thus far, our understanding of the link between the systemic circulation and SDs has been rather simplistic: drops in cerebral perfusion pressure resulting in global and/or focal ischemia usually precede, and thus have been thought to be triggers for, brain tsunamis [5]. Although SDs and their effects on cerebral hemodynamics and metabolism have been extensively studied using multimodal experimental paradigms [6], Han et al. [7] take a closer look on blood pressure and heart rate *while* anoxic depolarizations were happening, hence unveiling for the first time a potential systemic shockwave effect from brain tsunamis.

The main hypothesis driving this study was that anoxic depolarizations—a subtype of transient SDs triggered by ischemia or anoxia [5], often in the setting of cardiac arrest—may have effects on the systemic circulation. Hence, the goal of this study was to analyze the peripheral downstream effects on blood pressure and heart rate from SDs in an established murine model of asphyxia-induced cardiac arrest. The investigators used well-accepted methods to study SD: two contiguous DC cortical electrodes to capture DC potential shift and electrocorticography in 14 animals (electrophysiologic monitoring only cohort) and laser speckle imaging and spatial frequency domain imaging via right parietal craniectomy in 10 animals (optical imaging plus electrophysiologic cohort). Optical imaging in the latter cohort also allowed for the concurrent characterization of cerebral blood flow, cerebral metabolic rate of oxygen consumption, and cerebral vascular resistance. Electrocorticography using alternating current electrodes was also employed in both cohorts, which allowed for the measurement of time to burst activity and burst suppression ratio. By virtue of using different DC cortical electrodes, the investigators were able to analyze delays on the detection of wave fronts between the electrodes, termed ΔSD1-2 period, which the authors interpreted as the period during which asynchronous SDs arose from different foci in the brain.

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The authors then took a deeper dive on what was going on in systemic and cerebral hemodynamics during the ΔSD1-2 period and their association to outcomes. Neurological function was assessed in the animals with an intact skull (electrophysiologic only cohort) by using two methods following resuscitation: the restoration of cerebral electrical activity (by using averaged burst suppression ratio and the time to first burst occurrence) assessed at 40–60 min, and functional outcomes at 24 h as graded by the Neurologic Deficit Scale (higher scores representing better neurologic status), a widely used functional outcome instrument in rodents.

The SDs, all persistent until the restoration of systemic circulation ensued in resuscitated animals, occurred between 1.7 and 3 min after the onset of asphyxia. The remarkably short time difference between SDs wave fronts at the DC electrodes yielded a calculated speed of wave propagation of 7–724 mm/s, far exceeding the traditionally reported few millimeters per minute [8] speed of propagation of SDs. The authors interpreted the short delay between SD onset times as reflecting independent SD foci, with separate wavefronts arriving at each electrode. The onset of systemic circulation collapse was reflected by the drop in diastolic and mean arterial pressures, which were steep, preceded the first detected SD, and sustained until 30 s after the second wave front. In contrast, the decreases in pulse and systolic blood pressures were steady but less steep across the same time frame, with no consistent pattern immediately before the first wave front, after the second wave front, or between the two wave fronts. Prior to the onset of SD, the heart rate changed in parallel with the peripheral blood pressure but then plateaued during the ΔSD1-2 period while the blood pressure continued to drop, with a statistically significant dissociation of the rate of changes between the two after the detection of the second wave front. This interesting finding could represent a transient uncoupling of heart rate and blood pressure during the asynchronous SD period. Optical imaging in the second cohort, performed through craniectomy, revealed that with the onset of SDs, cerebrovascular resistance increased through the duration of scattering changes associated with the depolarization. As anticipated, regional cerebral blood flow and cerebral metabolic rate of oxygen consumption declined consistently during SDs, returning to predepolarization baseline subsequently. As expected, a dramatic drop in their ratio during SD reflected a potential supply–demand mismatch, or a transient uncoupling between cerebral flow and metabolism. Animals with shorter latency between wave fronts and those experiencing faster decline in mean arterial and diastolic pressures with SD were noted to have better metrics representing the recovery of cerebral electrical activity (i.e., shorter time to burst and lower burst suppression ratio) and higher scores on the Neurologic Deficit Scale, indicative of better neurological outcomes.

In summary, the authors identified characteristic fluctuations in peripheral blood pressure and heart rate during the period of asynchronous SD. Animals that had a shorter latency between SD onsets (and thus shorter ΔSD1-2 periods) and the steepest development of systemic perfusion collapse, reflected by faster drops in mean arterial and diastolic pressures, achieved the best neurologic functional status following resuscitation. The authors are commended on the rigor of their work, making every effort to maximize the translational potential of the results with this experimental paradigm that required multimodal monitoring with high temporal resolution. Animals were randomly allocated to the different monitoring groups, and outcome assessors were blinded to details of experiment, including the physiologic variables being investigated. Allowing for washing out anesthetics before inducing asphyxia not only mimics better, real-life cardiac arrest setting but also mitigates confounding effect of this drug on the phenomenon being investigated; this is particularly important with isoflurane, which has been shown to affect SD thresholds [9]. Another strength of the methodology is the strict control of temperature and arterial partial pressure of carbon dioxide, which are other important physiological variables that have been shown to affect cerebrovascular flow, blood pH, and SD behavior. However, although these preliminary findings may represent a step forward in our understanding of the brain–heart axis, caution is warranted in the interpretation of these findings, which remain purely correlational in nature without corroborating mechanistic data. Moreover, Han et al. [7] interpreted the ΔSD period in the imaging group as the same as the ΔSD1-2 period in the electrophysiology-only group. However, this may not actually be true. An important distinction must be made between the variable reflecting the period between SD wavefronts, the ΔSD period, which may represent distinct elements between cohorts as a result of inherent characteristics of SD detection methods. The authors acknowledge important limitations of their work and lay out expected next steps for future research in this area. These include the optimization of the experimental paradigm by removing craniectomy as a confounding factor and allowing for the survival experiments and functional outcome assessments: the addition of DC electrodes in close proximity to the selected region of interest for optical imaging, which could have added real electrophysiologic time course to corroborate scattering information; monitoring different regions of the brain to detect regional discrepancies in the magnitude of findings, given the importance of laterality in autonomic

control (i.e., right sympathetic, left parasympathetic); and the need for factoring in sex and age as biological variables, which are both of particular importance, given their interaction with tissue susceptibility and regional hemodynamic effects related to SD.

Han et al. [7] argue for the need of detailed measurements to be able to identify a similar relationship of systemic perfusion to SD, citing the lack thereof as the underlying factor for a previous study having missed such a relationship despite the use of multimodal monitoring strategies [6]; however, could there be more than one variation in this interplay? The fact that, in this current study, rapid or synchronous onset of SDs and steeper collapse of systemic perfusion were associated with better neurological outcome may indicate that a quick but profound hit—a shockwave—is better tolerated than a prolonged but less drastic hit—a slow wave. However, let's not jump to conclusions just yet; these experiments were done with juvenile rats and may not represent the resilience of aged brains with less brisk brain connectivity for whom a shockwave may be much more impactful than a slower wave. Hence, many questions remain and a comparison of patterns between young and aged brains, and brains with global versus focal injury, could certainly be a worthy future endeavor.

In conclusion, this insightful study addresses an important knowledge gap pertaining to the complex interplay between brain and the cardiovascular axis, in which much is yet to be discovered. By employing a multimodal monitoring platform with high temporal resolution, it was possible to detect a correlation between the peripheral vascular tone and cerebrovascular resistance during SD—unveiling a potential mechanism of neurovascular decoupling. This experimental paradigm in preclinical studies will open the door for many potential breakthroughs in our understanding of the potential systemic ramifications of brain tsunamis, which were originally thought to be a local brain phenomenon not so long ago. Leonardo da Vinci's wisdom is quite fitting in this scenario: "A wave is never found alone, but is mingled with many other waves as there are uneven places in the object where the said wave is produced. At one and the same time, there will be moving over the greatest wave of a sea innumerable other waves proceeding in different directions" (Codex Atlanticus, circa 1500).

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