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Not a simple plumbing problem: Updating our understanding of delayed cerebral ischemia in aneurysmal subarachnoid hemorrhage

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Aneurysmal subarachnoid hemorrhage (SAH) accounts for one in twenty strokes, yet claims one quarter of all life years lost due to stroke. General improvements in critical care over the past several decades have increased survival, yet mortality remains high. Many who initially survive subsequently die or suffer permanent neurological disability due to poorly understood secondary processes, collectively referred to as *delayed cerebral ischemia* (DCI).

The twelve articles in this issue of the *Journal of Clinical Neurophysiology* describe our emerging understanding of the mechanisms underlying DCI, how they relate to signals that can be monitored clinically, and the clinical implications of these relationships. These articles cover a wide range of important issues in three areas: pathophysiology of DCI, continuous EEG monitoring for detection of ischemia, and promising new methods for early detection of DCI.

Historically, DCI has been viewed as a simple ‘plumbing’ problem, caused simply by spasm of large cerebral arteries. The first group of articles in this issue detail revisions to this classical view of DCI. The first article (Foreman, 2016) reviews the new picture in which DCI occurs via a complex interplay between several concurrent processes including early small distal artery vasospasm with microthrombosis, disruption of neurovascular coupling, mismatch of metabolic supply and demand, inflammation, and cortical spreading depolarizations (SD). The second article (Maciel and Gilmore, 2016) reviews the literature on seizures and related epileptiform EEG abnormalities that occur in SAH, their impact on patient outcomes, and their possible relationship to cortical SD and to DCI. The authors suggest a practical approach to EEG monitoring and anticonvulsant therapy. The third article (Chung et al, 2016) describes findings from animal models of cortical SD. SD have recently been established as a key mechanism and promising target for intervention in SAH, and also in a wide range of acute brain injuries including trauma and stroke. The authors describe how SD cause secondary damage in injured brain by increasing metabolic demand, decreasing blood supply, predisposing to seizures, and possibly by worsening brain edema.

The second series of articles examines the growing role of continuous EEG monitoring (cEEG) in SAH for early detection of DCI. The first contribution (van Putten and Hofmeijer, 2016) explains how the differential sensitivity of various neuronal processes to energy restriction explains the effects of ischemia on scalp EEG signals, and how monitoring for ischemia-related EEG changes can be used in clinical applications ranging from carotid surgery, acute ischemic stroke, and prognostication after cardiac arrest. These authors also describe how EEG can be summarized into useful quantitative indices (quantitative EEG, qEEG), critical for dealing with the large volumes of data that accrue and require interpretation in near real-time in clinical applications. The article that follows (Gaspard 2016) examines the evidence to date supporting the use of cEEG and qEEG specifically in the setting of SAH for early detection of DCI. The conclusion is that although not perfect and requiring further study and improvement, they appear to perform reasonably well and to allow detection of DCI prior to other available methods. The third article (Muniz et al., 2016) summarizes one group's experience with implementing a protocol for cEEG in clinical practice. The authors provide advice on a variety of practical issues, including timing and duration of monitoring; ways to avoid skin lesions from prolonged use of scalp electrodes; and methods for interpreting and reporting clinical cEEG findings. To some extent, the work described in the preceding articles all depends on visual interpretation of cEEG data by experts. Interpretation by experts can be operator dependent and subject to intermittent availability. To overcome these issues, the fourth article (Wickering et al, 2016) examines whether 'classical' methods can be automated. The authors conclude that more work remains before EEG-based monitoring of DCI can be fully automated. The preceding work on cEEG monitoring also presupposes that DCI can be diagnosed reliably, but in practice diagnosis can be challenging. DCI diagnosis requires recognition of new deficits and infarctions which can be challenging in critically ill patients with depressed levels of consciousness, in addition to exclusion of other factors that may lead to the same new deficits as DCI, including rebleeding, complications of procedures, increases in intracranial pressure, and metabolic derangements. Therefore the final paper in this group (Zafar et al, 2016) examines the problem of inter-rater reliability of DCI diagnoses. The authors find that good diagnostic agreement is achievable, but caution that future studies should employ strict case definitions, careful adjudication of cases with subtle findings, and high quality imaging (MRI rather than CT) to discriminate edema from infarction in order to ensure rigorous diagnostic validity of DCI diagnoses.

Papers in the final group cover methods that have shown value but are not yet commonly used for early detection of DCI. The first (Roh, Morris, Claassen, 2016) explores the status of intracranial multimodality monitoring for detecting impending DCI, including the use of sensors for intracranial pressure, cerebral perfusion and autoregulation, cerebral oxygenation, electrocorticography (ECoG), and cerebral metabolites. These authors argue that it is only by becoming better at integrating these data that we can hope to deliver optimal care tailored to individuals. The second article (Drenckhahn et al, 2016) provides new data regarding the safety of ECoG in SAH patients. These authors compare rates of complications in a group of 30 prospectively enrolled SAH patients who received ECoG monitoring to 30 matched controls without invasive monitoring. They found no evidence that ECoG neuromonitoring caused brain tissue damage or increased the rate of infections,

and found no significant difference in final functional outcome scores. This reassuring safety data should open the way for other neuro-ICUs to institute clinical ECoG monitoring. The third article (Bouzat et al, 2016) reviews the utility of trans-cranial Doppler ultrasonography, cerebral near-infrared spectroscopy (NIRS) and CT perfusion brain imaging to detect cerebral vasospasm and DCI. They advocate that non-invasive methods of bedside monitoring (EEG, NIRS, TCD, and clinical examination) provide complementary information and should be integrated in a multimodality algorithm to optimize DCI detection. The final article (Schmidt, 2016) examines the potential role of monitoring heart rate variability (HRV) to predict DCI. This work capitalizes on the role of systemic inflammation in SAH and its effect on autonomic control of heart rate. The author gives evidence that changes in HRV leading up to DCI may have a relatively specific signature, distinguishable from confounding effects of medications and diurnal HRV variations.

We hope by presenting current knowledge on DCI to the international community of clinical neurophysiologists that we can shorten the time for translation of new knowledge may ultimately improve outcomes patients with SAH. We must move beyond current ICU practices of monitoring solely with serial neurologic exams and transcranial ultrasound. Maximizing the potential benefits of existing interventions and developing new more better treatments will require wider adoption of methods such as continuous scalp EEG monitoring and invasive multimodal neurophysiologic monitoring, to monitor the full spectrum of relevant physiology. New monitoring methods will also contribute to progress, including near infrared spectroscopy and heart rate variability trend monitoring. It is time to move beyond the oversimplified view of DCI as resulting solely from spasm of large cerebral arteries.