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INVITED COMMENTARY

Quantitative Pupillometry: Not a Clear Predictor of Delayed Cerebral Ischemia After Subarachnoid Hemorrhage

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Pupil assessment is a fundamental tenet of the neurological examination. Historically, pupil abnormalities including asymmetry in size or reactivity, or the absence of reactivity, were one of the more objective physiologic indicators of neurologic disruption [1]. However, like many observed phenomena, accurate identification of nuanced pupillary abnormalities requires highly trained assessors, which can limit the reliability of the measurement [2, 3] and its full potential as a noninvasive longitudinal biomarker.

More recently, with the advent and increasing adoption of quantitative devices that measure and record pupil characteristics [4], the field has an opportunity to both better understand the range of abnormalities that occur in healthy and unhealthy populations and leverage the device to track changes in individuals over time.

In the study by Bogossian and colleagues [5], the authors investigated whether and to what extent poor pupil reactivity, defined as a Neurologic Pupil index (NPi) score of less than 3, predicted delayed cerebral ischemia (DCI) in patients with subarachnoid hemorrhage (SAH). The NPi is a composite metric ranging from 0 to 5 based on pupil characteristics that include resting and constricted pupil size, percent change, constriction velocity, dilation velocity, and latency. The manufacturer suggests that values less than 3 are abnormal. A prior single center study of 56 patients showed there was a significant association between decreasing NPi and the occurrence of DCI [6]. However, the study by Bogossian et al. [5] did not find that an abnormal NPi less than 3 was predictive of DCI.

There may be several reasons for the lack of association. The study by Bogossian et al. [5] treated NPi as a dichotomous rather than a continuous variable, which may have more clinical use but may not capture a more nuanced association. Moreover, the frequency with which pupil observations were taken (every 8 h) may not have been sufficient to capture pupil abnormalities that occur close in time to DCI.

Finally, although the authors hypothesized that the pupillary light reflex could be affected by ischemic injury due to DCI after SAH, the mechanism by which the hypothesized decreased reactivity is unclear. DCI is a phenotypic phenomenon that is presumed to be attributable to vascular dysfunction, inflammation, and spreading depolarization [7]. Whether patients who experience DCI experience these contributing factors in similar proportions or in similar locations is poorly understood. Presumably, neuronal dysfunction resulting in pupillary light reflex abnormalities would most likely occur either along the pathway of the pupillary light reflex as it traverses the midbrain or along the sympathetic and parasympathetic pathways that extend from the frontal lobes down to the cervical and thoracic spine that modulate pupil size and reactivity. The varied ways in which DCI manifests, including decreased arousal or worsening motor function, suggests that the pathophysiologic processes resulting in DCI are heterogenous and likely occur in a variety of locations, only some of which may involve pupillary pathways. Unlike hypoxic ischemic injury after cardiac arrest, in which reversible or irreversible injury to the brainstem more regularly occurs and in which poor

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NPi has been shown to be a marker of outcome [8], it is not clear to what extent DCI after SAH regularly disrupts pathways responsible for pupil reactivity, which the authors acknowledge in their discussion.

The authors are to be commended for the strengths of this study, which include its multicenter nature, the standard definition of DCI, and the relatively large sample size for this disease condition. It is worth noting that the authors observed that overall NPi was lower in patients with higher grade SAH compared with those with lower grade SAH. Pupil reactivity is more commonly incorporated into risk profiling in other conditions, including trauma and cardiac arrest, and the authors' suggestion that it could be helpful in stratifying SAH is worth pursuing.

More study is needed to understand how clinicians can leverage quantitative pupillary data over time to better monitor and treat patients. Although Bogossian and colleagues [5] concluded that abnormal NPi collected every 8 h did not predict DCI, further investigation of frequent, longitudinal pupil observations and their relation to neurologic decline in various conditions is warranted to optimally leverage this noninvasive, safe, and physiologic biomarker.

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