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The prognostic potential of pupillometry in patients with acute brain injury

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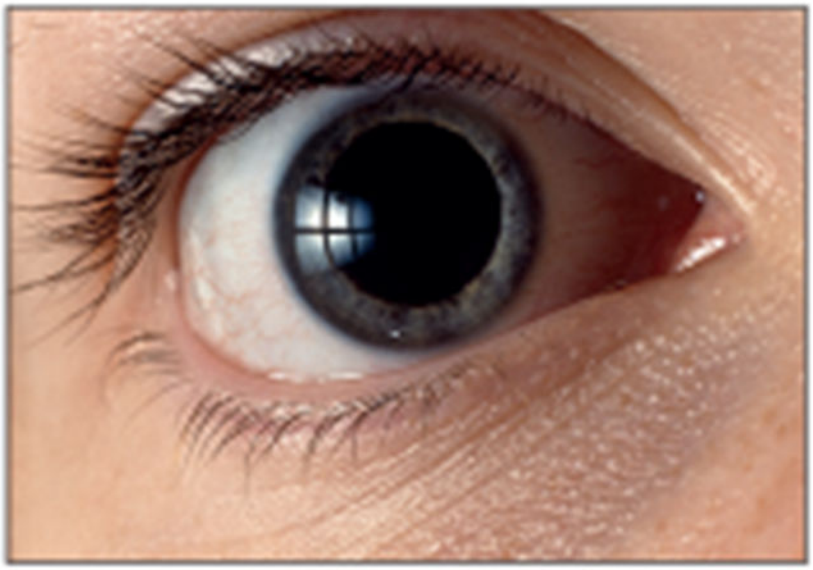
Graphical Abstract



Pupillary assessment is highly regarded by clinicians who are responsible for diagnosing neurological impairment. Abnormal or absent pupil reactivity can herald a neurological emergency due to either lifethreatening compression or intrinsic injury to pupillary pathways in the brainstem.[1] Conversely, normal pupil reactivity signifies brainstem integrity, which is an important marker of recovery. However, the diagnostic and prognostic potential of longitudinal pupillometry has been limited by the subjectivity and lack of reliability of pupil assessments.[2,3]

Quantitative pupillometry, in which an automated device records and stores information on pupil size, speed of constriction and dilation, and latency, has been used increasingly in intensive care units over the past decade. The technique is an improvement on previous manual assessment standards that often characterise pupils broadly as brisk, sluggish, and unreactive. Automated, quantitative pupillometry permits standardisation of the assessment of abnormalities and the tracking of subtle changes over time that could provide an early warning of catastrophic evolving injury—previously unfeasible without a quantitative

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tool. In a recent study, quantitative pupillometry was used in the assessment of patients with hypoxic-ischaemic brain injury after cardiac arrest.[4] The findings suggested that the Neurological Pupil index (NPi)—a proprietary composite measure of reactivity reported by the NeurOptics pupillometer (NeurOptics; Irvine, CA, USA), with scores ranging from 0 to 5 (values <3 are deemed abnormal)—might be sensitive and specific for identifying patients with poor recovery potential.

However, many questions remain regarding the clinical significance of quantitative pupillometry and the NPi. Is an abnormal NPi score also prognostic in patients with other acute brain injuries? Moreover, is it more clinically relevant to measure multiple pupil reactivity measurements than a single instance of abnormal or absent reactivity? Is an NPi of 3 the appropriate abnormal threshold for all critically ill patients? Finally, is abnormal pupil reactivity as important as absent reactivity?

In *The Lancet Neurology*, Mauro Oddo and colleagues aim to address some of these outstanding issues.[5] They report findings of the ORANGE study,[5] which was a prospective, multicentre study undertaken to elucidate the association of longitudinal pupil assessments within the first 7 days of hospital admission with poor neurological outcome at 6 months in patients with heterogeneous causes of acute brain injury. They assessed the association of poor neurological outcome (ie, a Glasgow Outcome Scale-Extended score ≥4) with the relative frequency of abnormal NPi (ie, scores <3) and NPi values equal to 0 (ie, absent reactivity) using multiple logistic regression models. They also investigated the association of pupil reactivity with mortality, using several time-dependent Cox proportional regression models. The handling of these exposures by Oddo and colleagues is complex, with consideration of at least two alternative NPi exposures in the logistic regression model and five in the extended Cox regression model. However, the methodological reporting is transparent and the study suggests which NPi features (NPi 0, <3, or purportedly normal values of 3–4) might have clinical relevance.

Oddo and colleagues recruited 514 patients with three types of acute brain injury: traumatic brain injury (n=224), aneurysmal subarachnoid haemorrhage (n=139), or intracerebral haemorrhage (n=151). Adjusting for confounders, a 10% increased frequency of abnormal NPi values (ie, <3) was associated with slightly increased odds of poor neurological outcome (odds ratio [OR] 1·42 [95% CI 1·27–1·64]) and a substantially increased risk of mortality (hazard ratio [HR] 5·58 [95% CI 3·92–7·95]). Every 10% increase in the frequency of an NPi value of 0 was also associated with increased odds of poor outcome (OR 1·70 [1·37–2·38]) and mortality (HR 12·05 [7·86–18·48]). The similar ORs probably reflect the fact that the finding of unreactive pupils often instigates either interventions to recover pupillary function or end-of-life discussions, making the overall frequency of an NPi of 0 relatively low per patient. Results remained significant in disease-specific subgroups and sensitivity analyses, suggesting generalisability across different disease states. Normally reactive pupils (ie, those with an NPi of 3–4) were also associated with increased mortality (hazard ratio 1·70 [1·13–2·56]), suggesting that low normal NPi values perhaps should be more closely scrutinised.

The prevalence of abnormal pupil reactivity in critically ill patients with neurological injuries is not well characterised, with previous estimates of 22–28%.[6–8] The ORANGE study begins to fill this gap. 59% of patients had poor neurological outcome, with abnormal NPi (<3) observed in 47% and NPi of 0 observed in 26%. NPi scores of 0 were seen in 39% of patients with poor neurological outcome and in 8% of patients with good neurological outcome, suggesting that absent pupil reactivity is frequently observed in patients with poor outcome, but is not a marker of unrecoverable disease in all patients.

The ORANGE study is limited by unmeasured confounders, including—but not restricted to—practice variation, ambient light, cognitive load, and medications.[9] Moreover, prognostic differences in pupillary dysfunction caused by intrinsic versus compressive mechanisms and unilateral versus diffuse injury processes might exist that were not studied. Finally, NPi is a proprietary algorithm; a better understanding of which pupil characteristics, including constriction velocity, dilation velocity, size, and latency, are most related to outcome would be an important ancillary pursuit.

Future priorities for the neurocritical field include the identification of indicators of a reversible injury, such as absolute NPi values or change in NPi scores over time based on disease or injury location, the addition of longitudinal pupillometry observations into existing risk models, and the investigation of whether NPi improvement is a marker of treatment efficacy.

Acknowledgments

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