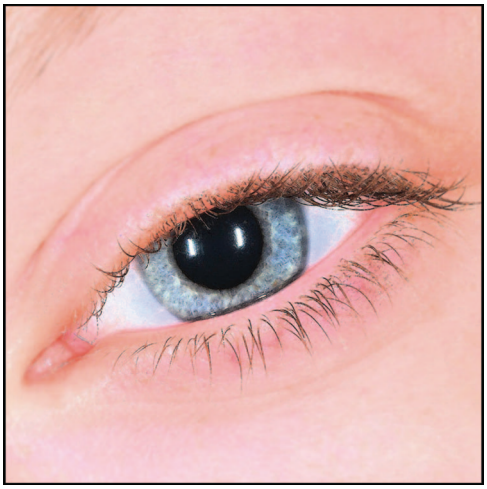
Pupillometry to Guide Postoperative Analgesia

POSTOPERATIVE pain, by its very nature, is unpleasant for patients and can prolong their recovery. Although it provokes a variety of autonomic responses that are likely to be harmful, pain by definition is subjective. In conscious subjects, pain is thus best evaluated simply by asking. And of course this is the routine clinical approach in which visual analog or verbal response scores are used to guide therapy. However, Aissou *et al.* make the valid point that many patients in the immediate postoperative period have difficulty evaluating and/or communicating pain intensity.[1]

Infants, the demented, nonverbal patients, and those with delirium cannot accurately convey pain intensity. Patients who are obtunded from residual effects of anesthetics may also be unable to distinguish pain from other sensations, or to express the amount of pain they experience. In addition, some patients will relate pain scores that are inconsistent with their behavior, as mentioned by Aissou *et al.*

Adverse effects of untreated acute postoperative pain include limited mobility, impaired ventilation, and increased stress hormones. Untreated perioperative pain may lead to a greater risk for chronic postsurgical pain.[2,3] Conversely, overtreatment of drug-seeking or especially expressive patients promotes respiratory toxicity and aggravates opioid-induced side effects such as nausea and vomiting, ileus, sedation, and hyperalgesia.[4,5] An objective measure of perioperative pain that is independent of patient consciousness and communication would thus help guide postoperative opioid administration.

Aissou *et al.* evaluated a simple and well-known bedside test: pupillary dilation in response to a standardized noxious stimulus (PDR).[6] Although their proposed use is to guide opioid administration in patients who cannot accurately convey their need, these investigators compared verbal response pain scores with the PDR in conscious and communicative patients. They found a direct relationship between the magnitude of the PDR brought about by a controlled amount of pressure on the surgical wound and the patient's requirements for morphine in the postanesthesia care unit. Magnitude of the PDR was also directly related to the patient's own verbal assessment of their pain.



"The [pupillary dilation response] can … be used as a measure of pain, but only in controlled situations when confounding factors are well controlled."

These are important findings, and readers who are interested in this technique might find reviews of the subject useful.[7] The PDR has been studied extensively since it was described more than 300 yr ago by Philippe de La Hire.[8] The imminent 19th century physiologist Moritz Schiff (1823–1896) thought the PDR was an accurate measure of pain and promoted the reflex as an "anesthesiometer."[9] His work on the pupil and nociception are a logical starting point for those interested in this fascinating subject. There is copious literature on the PDR, and several contemporary investigators have studied the PDR as a measure of nociception and analgesia.[10–14] There are several overriding themes.

First, the PDR is not specific for pain. Rather it is an alerting response that can be elicited by any stimulus that is strong enough to increase the level of arousal. The PDR can thus be used as a measure of pain, but only in controlled situations when confounding factors are well controlled. Only under these circumstances is the PDR magnitude closely related to noxious stimulus intensity and reliably demonstrates dose-dependent depression by opioids and nitrous oxide.[12,14]

Second, it would be a mistake to conclude that "pain dilates the pupil and opioids ablate pain, and thus decrease pupillary dilation." Anyone who makes acute pain rounds will observe patients with constricted pupils consequent to opioid administration who nonetheless have severe pain. And as Aissou *et al.* have shown, patients with severe pain in the postanesthesia care unit had constricted pupils just like other patients. It was thus not their pupil size that differed; instead, it was their pupillary response to an evoked stimulus,

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wound pressure, which confirmed the need for additional morphine.

Third, although pupillary response is brisker and more robust than either hemodynamic or electroencephalograhic responses to painful stimuli,[15] dilation nevertheless is too sluggish to be quantified without an infrared pupillometer.[6,16] For example, Aissou *et al.* found that the average pupillary dilation was less than 1 mm over a 10-s time period, which is far too small to be observed by the unaided eye.

Fourth, the PDR is a supraspinal parasympathetic reflex during general anesthesia. Nerve blocks prevent transmission of noxious stimuli to the brain. But the dilation reflex to perceived noxious stimulation remains intact in the presence of general anesthesia, and coadministration of sympatholytic drugs. Blocking the preganglionic sympathetic fibers during thoracic epidural does not block the PDR.[17] Consequently, pupillary dilation in response to noxious stimulation can be used to determine the dermatomal extent of epidural anesthesia, even during general anesthesia, and with block of the upper thoracic dermatomes.[18] An unexplored use of PDR is to test for the efficacy of extremity blocks during general anesthesia. In unanesthetized subjects, PDR is primarily a sympathetic reflex, so interventions that interfere with sympathetic reflexes might conceivably block PDR and leave sensory pain mediated fibers intact.

And finally, there are important species differences in the pharmacological and physiologic properties of the PDR. It is thus best to rely on human studies when extrapolating to clinical situations. In cats, for example, the PDR has a strong humoral component that is not observed in humans, and the pharmacological properties of the reflex differ substantially.[6,19,20] Furthermore, the strong suppressant effect of opioids on the PDR that is observed in humans has not been observed in any experimental animal.[13]

The PDR has substantial potential value to the extent that can be used as a measure of analgesia, especially in uncommunicative patients. Certainly, pupillary dilation as a measure of analgesia has distinct advantages over other autonomic responses to pain, such as blood pressure and heart rate, neither of which is sensitive or specific.[21] Special brain imaging techniques and cerebral evoked potentials might be used in certain situations to measure pain, but they are impractical at the bedside.[22,23]

Clinicians need to consider, though, that pupil size and the pupillary response to pain are influenced by various factors besides pain. For example, ambient light falling on the unmeasured pupil reduces dilation of the measured pupil in response to painful stimuli. Similarly, miosis that accompanies accommodation can result if patients focus on near objects. There are also various rare syndromes that impair pupillary responses to noxious stimulation, including Adie's pupil, senile miosis, Horner's syndrome, and tonic pupils.[24] An intraocular lens can alter the dynamic characteristics of pupillary reflexes. Dopamine 2 receptor antagonists such as metoclopramide can depress the PDR,[25] and the effects of residual neostigmine on the PDR remains to be evaluated. Fortunately, most of these problems are rare or can be minimized by good technique.

More seriously, Aissou *et al.* only evaluated alert and cooperative patients. Measuring PDR in the nonverbal subjects may prove more difficult. For example, obtunded patients tend to blink and squint, and are unlikely to remain still when pain is elicited by wound pressure. It remains to be confirmed that their technique can be extended to the very population that would benefit most: those who cannot themselves evaluate or communicate pain intensity. Validating the proposed method in its designated target population is thus an obvious next step. That said, the method Aissou *et al.* propose is novel and has substantial potential for improving our ability to titrate our analgesic agents in the perioperative period.

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References

1. Aissou M, Snauwaert A, Dupuis C, Atchabahlan A, Aubrun F, Beaussier M: Objective assessment of the immediate postoperative analgesia using pupillary reflex measurement: A prospective and observational study. Anesthesiology 2012; 116: 1006–12
2. Kehlet H, Wilmore DW: Multimodal strategies to improve surgical outcome. Am J Surg 2002; 183:630–41
3. Nicholson G, Hall GM: Effects of anaesthesia on the inflammatory response to injury. Curr Opin Anaesthesiol 2011; 24:370–4
4. Angst MS, Clark JD: Opioid-induced hyperalgesia: A qualitative systematic review. Anesthesiology 2006; 104:570–87
5. Kehlet H, Rung GW, Callesen T: Postoperative opioid analgesia: Time for a reconsideration? J Clin Anesth 1996; 8:441–5
6. Yang LL, Niemann CU, Larson MD: Mechanism of pupillary reflex dilation in awake volunteers and in organ donors. Anesthesiology 2003; 99:1281–6
7. Loewenfeld IE: The pupil: Anatomy, physiology and clinical applications. Detroit: Wayne State University Press; 1993
8. de La Hire P: Explication de quelques faits d'optique, de la maniere dont se fait la vision. Mem Acad Roy Soc 1709: 119–32
9. Schiff M, Foa P: La pupille condideree comme esthesiometre. Paris: J. B. Bailliere and Fils; 1883, reprint 1974
10. Höfle M, Kenntner-Mabiala R, Pauli P, Alpers GW: You can see pain in the eye: Pupillometry as an index of pain intensity under different luminance conditions. Int J Psychophysiol 2008; 70:171–5
11. Ellermeier W, Westphal W: Gender differences in pain ratings and pupil reactions to painful pressure stimuli. Pain 1995; 61:435–9
12. Oka S, Chapman CR, Kim B, Nakajima I, Shimizu O, Oi Y: Pupil dilation response to noxious stimulation: Effect of varying nitrous oxide concentration. Clin Neurophysiol 2007; 118:2016–24
13. Larson MD, Kurz A, Sessler DI, Dechert M, Bjorksten AR, Tayefeh F: Alfentanil blocks reflex pupillary dilation in response to noxious stimulation but does not diminish the light reflex. Anesthesiology 1997; 87:849–55
14. Barvais L, Engelman E, Eba JM, Coussaert E, Cantraine F, Kenny

GN: Effect site concentrations of remifentanil and pupil response to noxious stimulation. Br J Anaesth 2003; 91:347–52

15. Leslie K, Sessler DI, Smith WD, Larson MD, Ozaki M, Blanchard D, Crankshaw DP: Prediction of movement during propofol/nitrous oxide anesthesia. Performance of concentration, electroencephalographic, pupillary, and hemodynamic indicators. ANESTHESIOLOGY 1996; 84:52–63
16. Larson MD, Berry PD, May J, Bjorksten A, Sessler DI: Latency of pupillary reflex dilation during general anesthesia. J Appl Physiol 2004; 97:725–30
17. Larson MD, Tayefeh F, Sessler DI, Daniel M, Noorani M: Sympathetic nervous system does not mediate reflex pupillary dilation during desflurane anesthesia. ANESTHESIOLOGY 1996; 85:748–54
18. Larson MD, Sessler DI, Ozaki M, McGuire J, Schroeder M: Pupillary assessment of sensory block level during combined epidural/general anesthesia. ANESTHESIOLOGY 1993; 79:42–8
19. Larson MD, Talke PO: Effect of dexmedetomidine, an alpha2-adrenoceptor agonist, on human pupillary reflexes during general anaesthesia. Br J Clin Pharmacol 2001; 51:27–33
20. Loewenfeld IE: Mechanism of relex dilation of the pupil: Historical review and experimental analysis. Doc Opthalmol 1958; 12:184–448
21. Larson MD, Sessler DI, Washington DE, Merrifield BR, Hynson JA, McGuire J: Pupillary response to noxious stimulation during isoflurane and propofol anesthesia. Anesth Analg 1993; 76:1072–8
22. Brown JE, Chatterjee N, Younger J, Mackey S: Towards a physiology-based measure of pain: Patterns of human brain activity distinguish painful from non-painful thermal stimulation. PLoS One 2011; 6:e24124
23. Chapman CR: Evoked potentials as correlates of pain and pain relief in man. Agents Actions Suppl 1986; 19:51–73
24. Thompson HS, Newsome DA, Loewenfeld IE: The fixed dilated pupil. Sudden iridoplegia or mydriatic drops? A simple diagnostic test. Arch Ophthalmol 1971; 86:21–7
25. Larson MD: The effect of antiemetics on pupillary reflex dilation during epidural/general anesthesia. Anesth Analg 2003; 97:1652–6