Portable Infrared Pupillometry: A Review

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Portable infrared pupillometers provide an objective measure of pupil size and pupillary reflexes, which for most clinicians was previously only a visual impression. But despite the fact that pupillometry can uncover aspects of how the human pupil reacts to drugs and noxious stimulation, the use of pupillometry has not gained widespread use among anesthesiologists and critical care physicians. The present review is an introduction to the physiology of pupillary reflexes and the currently established clinical applications of infrared pupillometry, which will hopefully encourage physicians to use this diagnostic tool in their clinical practice. Portable infrared pupillometry was introduced in 1989. The technology involves flooding the eye with infrared light and then measuring the reflected image on an infrared sensor. Pupil size, along with variables of the pupillary light reflex and pupillary reflex dilation, is calculated by the instrument and displayed on a screen immediately after each time-stamped measurement. Use of these instruments has uncovered aspects of how the human pupil reacts to drugs and noxious stimulation. The primary clinical applications for portable pupillometry have been in the assessment of brainstem function. Portable pupillometry is useful in the management of pain because it allows for assessments of the effect of opioids and in the titration of combined regional–general anesthetics. (Anesth Analg 2015;120:1242–53)

In the 16th century, the French poet Guillaume de Sallustre Du Bartas (1544–1590) referred to the pupils as "those lovely lamps, the windows to the soul."[1] At that time it was a common perception that the brain expressed a vital energy outward through the pupil and made vision possible, a theory that had persisted since the time of the early Greek scholars, including Plato.[2] The thought that the pupils are lamps emitting energy has been replaced by modern optical theory, but the idea that they provide relevant information about pain, nociception, and cognition is a valid 20th-century discovery.

A simple retraction of the eyelid to observe the size and reactions of the pupil allows anesthesiologists to assess midbrain function, as both pupil diameter and pupil movements are regulated by nuclei in the midbrain. We do not usually take advantage of this opportunity because the eyelids are normally taped closed during general anesthesia, the pupillary reactions are difficult to quantify, and the reactions of the pupil are not fully understood and therefore cannot be interpreted. Consequently, this information is rarely retrieved.

Measurement of the pupil presents challenges. The pupillary reactions are too fast to be measured with a stopwatch. Examination of the pupil is further complicated by the fact that shining visible light in the pupil to visualize it not only alters the resting size of the pupil but also changes the sensitivity of the retina. As a consequence, precise methods to study the physiology and pharmacology of the pupil began to emerge only 50 years ago. Solid-state microchips sensitive to infrared light became available in the late 1970s and revolutionized the study of the pupil because they allowed continuous measurement of the pupil without altering pupil size and pupil movements at the same time. A light-emitting diode infrared light is directed toward the eye, and a sensor detects the reflected infrared light from the iris. The pupil is a blank circle in the center of the reflected image, and a computer readily calculates the area and the diameter of the pupil.[3,4] When this diameter is measured repeatedly (1 measurement every 30 milliseconds), it is possible to measure not only the average size of the pupil over several seconds (static measurement) but also the random fluctuations in pupil size (called hippus, or pupillary unrest), which are visible to the naked eye but impossible to quantitate without an instrument that measures the pupil objectively. Application of visible light or a noxious stimulus elicits the 2 pupillary reflexes: the pupillary light reflex (PLR) and pupillary reflex dilation (PRD). PLR is simply the change in pupil size that occurs after a light stimulus, and PRD is the change that occurs after an alerting stimulus. Variables of these 2 reflexes such as latency of onset, maximum amplitude of the reflex, duration of the reflex, and constriction and dilation velocities can be analyzed.

The goals of this review are to give clinicians an introduction to the anatomy and physiology of the pupil, summarize our clinical knowledge of the effects of anesthesia on pupil size and pupillary reflexes, and explain the clinical applications of portable infrared pupillometry that are relevant to anesthesiologists and intensivists. Since the introduction of portable infrared pupillometry in 1989,[a] numerous studies have extracted information out of the movements of the pupil that is relevant to our practice, resulting in clinical applications of pupillometry in neurosurgery,[5–8] psychology,[9] psychiatry,[10,11] emergency medicine,[12] cognitive science,[13] ophthalmology,[14,15] sleep medicine,[16,17] anesthesiology,[13,18–30] and pharmacology.[22,31]

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[a] Larson MD. Alteration of the human pupillary light reflex by general anesthesia. Anesthesiology Review 1989;16;25–29.

ANATOMY AND PHYSIOLOGY OF THE PUPIL

The pupil is controlled by the 2 divisions of the autonomic nervous system, and its reflexes are controlled by activation of 2 sets of antagonistic muscles embedded within the iris stroma (Fig. 1).[32]

The Radial Muscle

The sympathetically innervated radial muscle of the iris dilates the pupil by pulling outward on the pupillary margin. A cervical sympathectomy produces the pupillary constriction associated with Horner's syndrome, after the German ophthalmologist who described the clinical features in 1869.[33] The radial muscle is the weaker of the 2 muscles. Therefore, the diagnosis of unequal pupils (anisocoria) from a sympathetic deficit will be less obvious when ambient levels of light are high because the more powerful sphincter overcomes the radial pull of the normally innervated radial muscle.[34]

The sympathetic neuromuscular synapse in the iris is an α_1-adrenergic junction. It can be activated by α_1-adrenergic agonists administered topically, such as phenylephrine, norepinephrine, and ephedrine, and can be blocked by dapiprazole, an α_1-adrenergic antagonist.[35] In the day-to-day practice of anesthesia, circulating catecholamines do not reach plasma levels high enough to activate the radial muscle of the iris.[35] Much confusion has arisen concerning the action of circulating epinephrine on the pupil because the cat iris is highly sensitive to that hormone, whereas the primate iris fails to respond to injected epinephrine.[36] The lack of effect of the commonly used vasopressors, such as phenylephrine, epinephrine, and ephedrine, on the pupil can be readily observed by anyone with a device capable of measuring pupil size in anesthetized patients.

Pheochromocytomas can produce markedly exaggerated serum levels of epinephrine, norepinephrine, and dopamine.[37] These unusually high levels are adequate to produce pupillary dilation even after administrations of drugs such as opioids that activate the pupillary sphincter. Consequently, a dilated pupil during anesthesia that does not constrict to IV opioids should raise the suspicion of undiagnosed pheochromocytomas.[38,39] Patients having elective resections of pheochromocytomas also have high levels of catecholamines, but these patients take large doses of α_1-adrenergic blocking drugs, which prevents the pupillary dilation that would otherwise be apparent in the untreated patients.

The Sphincter Muscle

The tone of the sphincter that constricts the pupil is controlled by a group of parasympathetic neurons located within the cephalic portion of the oculomotor nucleus. These neurons are sometimes referred to as the pupilloconstrictor neurons or, by other authors, as the Edinger–Westphal (EW) neurons. The EW neurons receive excitatory input from the retina, increasing their firing rate in response to an increased intensity of ambient light. The light reflex pathway begins in the intrinsic melanopsin containing ganglion cells of the retina, traverses the optic nerve, and synapses in the pretectal area.[40]

Other significant factors that control the tone of the pupillary sphincter in the awake state are various centers within the brain that inhibit the EW nucleus (Fig. 2). The precise nature and location of these inhibitory sources are poorly understood and probably vary among species. EW cells are thought to be pacemaker cells with a rapid intrinsic firing rate. If synaptic input to the EW nucleus is interrupted by transections above and below the nucleus, then the pupil is

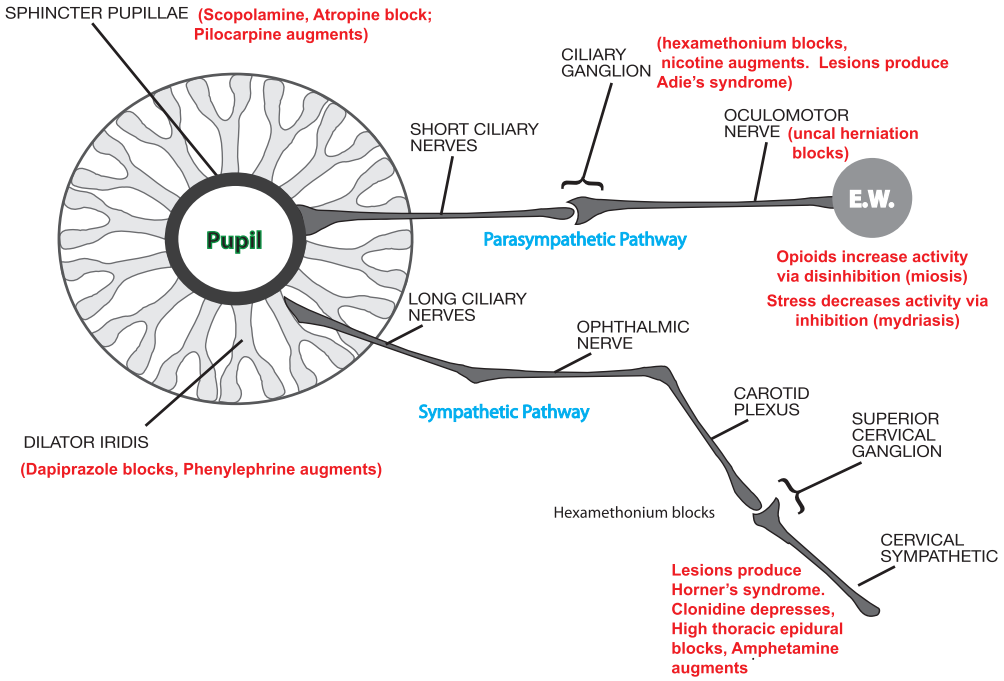

Figure 1. Anatomy and pharmacology of the pupil. Red script describes the effect of drugs on the pupil size and pupillary reflexes. Illustration was drawn by Mr. Michael Lee, who granted approval for its reproduction. EW = Edinger–Westphal.

tightly constricted and does not change in size when the animal is stimulated.[32,41,42] A similar clinical picture is observed in patients with pontine infarcts that interrupt both the sympathetic pathway and the inhibitory centers that depress the EW nucleus.[43] In the awake intact subject, these EW cells are inhibited by the arousal centers of the brainstem, keeping the pupil at midposition in most ambient lighting conditions.

Two cholinergic synapses are interposed between the EW nucleus and the pupillary sphincter. Within the ciliary ganglion is a typical nicotinic synapse that can be blocked by ganglionic blocking drugs such as hexamethonium. Neuromuscular blocking drugs in use today have negligible activity within the ciliary ganglion or at the neuromuscular junction of the sphincter muscle and consequently have no effect on pupillary size or reaction to light.[45]

The muscarinic synapse at the pupillary sphincter has its own unique manner of responding to cholinergic agonists and antagonists. Scopolamine is a strong antagonist in the iris, but a weak one at the sinoatrial node. Glycopyrolate is an effective antagonist at the sinoatrial node but has a weak effect on the iris.[46] Dilute topical solutions of pilocarpine (0.1%), an agonist at the sphincter muscle, will not overcome the antagonism of topical atropine or scopolamine but will readily constrict the pupil of the brain-dead subjects. Dilute pilocarpine has been used to analyze the etiology of a fixed and dilated pupil.[14,47]

USING THE PORTABLE INFRARED PUPILLOMETER

Measuring the Pupil Size Using Infrared Pupillometry

Determination of pupil size with infrared pupillometry can be performed with a rubber cup covering the measured eye and the operator's hand covering the nonmeasured eye (Fig. 3). A brief 2- to 3-second pause allows the pupil to dilate briefly at which time the measurement should be taken. Pupil size is the average diameter for the entire measurement time, which is typically 3 to 4 seconds. The full dark-adapted pupil size requires approximately 6 minutes of darkness, which is an impractical amount of time for clinical use. This described technique provides some control over the ambient light and prevents near-fixation, which would otherwise constrict the pupil. Without a standard technique of taking pupillary measurements, there can be no meaningful comparisons of pupil size in the same individual performed at different times. If measurements are taken with some attention to obliterating the ambient light, the remaining overriding factors that determine the size of the pupil in the hospital setting are the age of the patients[48] and the concomitant use of opioids. The resting size of the pupil decreases approximately 0.4 mm each decade of life after the age of 16 years.[32] Precise pharmacodynamic investigations of opioid effect using pupil size require strict control over ambient light, the age of the subjects, and the degree of dark adaptation.[23,49,50]

Although emotional factors and cognitive load can alter both the size of the pupil and the extent of the light reflex, the changes that are brought about by these mental states are small[9] compared with the effects of age and opioid therapy. Pupillary unrest in awake subjects is negligible when ambient light is excluded.[51,52] One portable infrared pupillometer is accurate to 0.05 mm,[53–55] and the interobserver agreement compares favorably with desktop infrared pupillometers.[56] Some instruments have been calibrated for interindividual differences in vertex distance, which can be of importance when repeated precise measures of pupil size are required. There are no pupillometers of any type that can measure the pupil through the closed eyelid.

Attempting to uncover relevant information from the pupillary reactions is not advisable unless the anesthesia provider reviews some of the rare pupillary syndromes that are described in the medical literature. Syndromes such as Adie pupil, Argyll Robertson pupil, Horner's syndrome, senile miosis, and tonic pupils are rare and can be readily detected with infrared pupillometry before any intervention. Topical drugs such as pilocarpine and atropine, iris–lens adhesions, and uveitis are other causes of altered pupil size and reactivity.

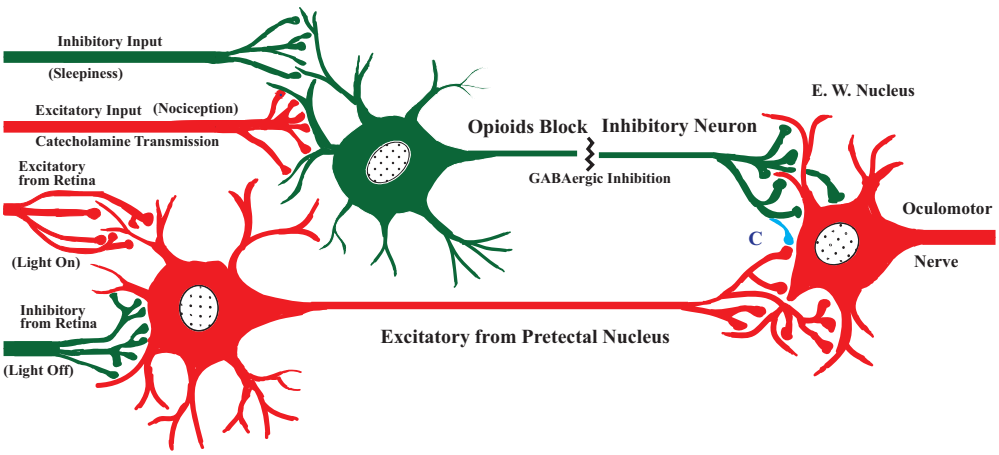

Figure 2. Simplified schematic illustrating the parasympathetic control of pupil size, pupillary light reflex, and pupillary reflex dilation from midbrain sites. Red denotes excitation and green inhibition. The Edinger–Westphal (EW) cells have intrinsic pacemaker activity in the absence of synaptic input. Inhibitory neurons are thought to depress the EW nucleus; pupillary dilation then results passively as the sphincter relaxes. These inhibitory neurons are activated by nociception and states of arousal, and their effect on the EW cells are blocked by opioids. The primary excitatory input (light) traverses the olivary pretectal nucleus. Presynapic inhibition of light input is shown at C. Modified from Larson with approval from the author.[44] Adaptations are themselves works protected by copyright. So in order to publish this adaptation, authorization must be obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

Figure 3. The Neuroptics portable infrared pupillometer in use. The screen has been modified for clarity. The author (MDL) has used portable infrared pupillometers for >20 years without complications resulting from their use. Consent for publication of this image was obtained from the subject.

Measuring the PLR

A transient flash of light will produce a decrease in pupil size. The reflex can be described by variables such as light reflex amplitude, latency of the light reflex, constriction velocity, and dilatation velocity. Because there is significant correlation among these measured variables,[57] the reflex amplitude is easy to measure and thus is the most commonly used variable to describe the light reflex. Examination of PLR is a mandatory portion of the physical examination. Preoperative evaluation of the light reflex with an infrared pupillometer is noninvasive, easily tolerated by patients, and takes only a few seconds. Presence of a normal light reflex confirms the integrity of the 2nd and 3rd cranial nerves and a functional uninterrupted neural pathway through the vital centers of the pretectum and upper midbrain.

Although the anatomical pathways from the retina to the pupillary sphincter have been well described, the neurotransmitters are unknown except those in the ciliary ganglion (nicotinic) and the pupillary sphincter (muscarinic). The synaptic currents in the brain at the pretectal nucleus and the EW nucleus appear to be rapidly acting ligand-gated channels, presumably glutamate excitatory synaptic junctions, because the latency and shape of PLR are essentially the same if the third nerve is directly stimulated compared with the reflex brought about by retinal stimulation with a light stimulus.[58]

The amplitude or magnitude of the contraction will depend on the intensity and duration of the stimulus. Constriction and redilation velocities are directly related to reflex amplitude except in cases of unusual pupillary syndromes.[57] Because different pupillometers have their own specifications, the pupillary response will differ depending on the instrument used to record the light reflex. This underscores the importance of serial measurements using the same instrument. Trends in pupil size, light reflex amplitude, and constriction velocity can provide more information than a single measurement if the same instrument is used for all measurements. Prior studies have revealed a direct relationship between the magnitude (amplitude) of the light reflex and the size of the pupil before the stimulus. If there is a question as to whether a drug or intervention has an effect on PLR, then this relationship between the light reflex amplitude and the pupil size must be considered.[59]

It is important to note that much of the research in pupillometry has been performed in animals in an effort to elucidate the mechanisms that drive the reflexes of the pupil. However, studies performed on animals cannot uniformly be applied to human clinical setting because of species differences, and 1 example is animal research on PLR. Most mammalians used in experimental models have light-sensitive contractile elements embedded within the iris musculature itself, so their pupils will react to light even when there is total loss of brainstem function. Primates require a functional pathway through the upper midbrain.[60]

Measuring PRD

An alerting stimulus in awake subjects dilates the pupil primarily by activating the sympathetic radial muscle. PRD is activated by diverse stimuli such as loud sounds or nociceptive stimuli. The subjects were extensively reviewed in 1958 in a classic work by Loewenfeld,[61] but our understanding of the neural pathways and transmitters involved in the human reflex is still not complete. In contrast to the light reflex, PRD is slow to develop and therefore difficult to appreciate by visual inspection. Accurate measurement of PRD depends on infrared pupillometry because shining visible light onto the iris to visualize the pupil will significantly depress the secondary amplified phase of PRD (Fig. 4).

Because a noxious stimulus of sufficient intensity will evoke PRD, the reflex can be used to detect potentially painful sensations in noncommunicating patients. The pupillary dilation and increase in the light reflex during painful stimuli have been used as objective measures of nociception in patients who are awake but unable to communicate pain levels with the commonly used visual

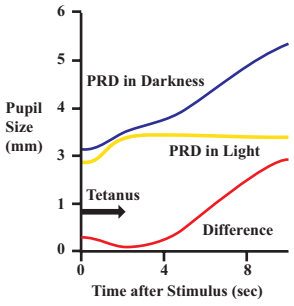

Figure 4. Effect of light on pupillary reflex dilation (PRD). Directing ambient light on to the eye will augment the early portion of the dilation reflex but markedly diminish the late portion of the reflex. Because of this effect of ambient light, it is advisable to observe the reflex in relative darkness. Appreciation of reflex dilation may be difficult without infrared pupillometry when a bright light is required to visualize the pupil. Adapted from Larson[44] with approval from author. Adaptations are themselves works protected by copyright. So in order to publish this adaptation, authorization must be obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

analog scales.[25] Painful labor contractions also dilate the pupil and increase the magnitude of PLR, and these measures can be used in noncommunicating patients to assess the degree of analgesia produced by epidural local anesthetics.[62] Because PRD is an evoked reflex, patients with steady unrelenting pain may commonly have small or midposition pupils,[63] but they will exhibit pupillary dilation when an abrupt painful stimulus is added.[25]

EFFECTS OF ANESTHESIA ON PUPILLARY MEASUREMENTS

Pupil Size in the Anesthetized Subjects

The observations of Guedel[64] and others 75 years ago led to the adoption of the classic Guedel signs of ether anesthesia. These signs included eyeball movements, respiratory patterns, and pupil size. Progressive dilation of the pupil indicated deepening levels of anesthesia and in conjunction with other signs was an indication to withdraw further administration of ether (Guedel). Anesthetics in use today, including desflurane, sevoflurane, propofol, isoflurane, halothane, and enflurane, do not produce significant dilation with deep levels of anesthesia.[65]

The sympathetic contribution to pupil size is absent during general anesthesia,[35,61] whereas sympathetic activity continues within other divisions of the sympathetic nervous system. The reason for this paradox is not fully understood. Sympathetic cardiovascular reflexes are completed within the lower brainstem,[66] whereas the sympathetic reflex that dilates the pupil traverses a pathway above the upper mesencephalon.[67] It appears that the unconscious state brought about by general anesthesia interrupts this supraspinal sympathetic pathway.[61] Consequently, if patients are anesthetized, it is not possible to detect the typical anisocoria of Horner's syndrome when the cervical sympathetic chain is damaged during surgery. Because of this block of sympathetic tone in the dilator muscle of the anesthetized subject and the lack of influence of circulating catecholamines on pupil size,[35] the pupillary size changes that are observed during anesthesia are the result of alterations in the tone of the pupillary sphincter, controlled by neuronal activity within the upper mesencephalon.

As one observes the pupil under anesthesia, it soon becomes apparent that the pupil does not behave in the same manner as it would in the awake state. During the awake state, as one enters a dark room, the pupil dilates because the retinal excitation of the EW nucleus decreases. In the anesthetized subjects, this dilation does not occur.[26,44] This paradox has received considerable attention over the past 300 years since Fontana[68] observed a similar phenomenon during natural sleep. As mentioned previously, the EW neurons are thought to be spontaneously active pacemaker cells.[41] In the awake state, the EW neurons are inhibited by impulses that arise from various centers within the midbrain including the reticular activating system and the posterior hypothalamus. During slow-wave sleep or during general anesthesia with propofol, barbiturates, or inhaled anesthetics, these centers are relatively quiescent, allowing the EW cells to fire at their rapid intrinsic firing rates. Loss of the light input during anesthesia thus fails to dilate the pupil because there is no background inhibition present to overcome the rapidly firing EW neurons.

With the induction of general anesthesia (IV or inhaled) and the loss of consciousness, the pupil decreases in size as the tonic inhibition of the EW nucleus decreases. Sympathetic tone of the dilator muscle is also lost, contributing to the anesthetic-induced miosis. After approximately 10 minutes, pupil size stabilizes close to 2 mm, but this "basal diameter" varies from 1 to 3 mm within subjects.[26,69,70] The skin incision and other nociceptive stimuli during surgery can reestablish inhibitory control over the EW nucleus, thus producing pupillary dilation that can be blocked by administration of opioids (Fig. 2).[44] Opening the peritoneum can produce a small dilation of the pupil away from the basal pupil diameter, an effect that is sometimes not antagonized by opioids. A similar effect can be observed during the initiation of cardiopulmonary bypass.[71] Because opioids are not effective in reducing the pupil size in these conditions, it seems likely that mobilization of some circulating factors brought about by the tissue destruction of surgery may produce a small dilation of the pupil. The pupil also dilates slightly after the onset of surgery in brain-dead subjects, and the effect is thought to be secondary to noncholinergic, nonsympathetic dilation.[67]

There is sometimes a gradual increase in the basal diameter of the pupil as the duration of anesthesia with volatile drugs increases, due possibly to an increase in inhibition of the EW nucleus, but the mechanism of this gradual dilation has not been studied.[72] Another reflex that can be rarely observed during general anesthesia is the trigeminus reflex, which consists of pupillary dilation after manually raising the upper eyelid.[32] One report has shown that there is a small (18%) dilation of the pupil away from the basal diameter during a continuous infusion of remifentanil.[19] Whether this is tolerance to the drug or a change in remifentanil concentration at the effect site is unknown.

It is worth mentioning that recent investigations have not confirmed the widely held clinical impression that mild hypoxia dilates the pupil and depresses the light reflex. Our studies could not detect any effect on either the light reflex or pupil size by brief periods of mild hypoxia brought about by breathing 10% oxygen.[b] Other investigators have demonstrated a mild depressant effect on the light reflex at high altitude.[73]

The PLR in Anesthetized Subjects

Because the light reflex involves at least 4 different synaptic events, it is not surprising that anesthetic drugs can alter the light reflex. However, the widely held opinion that the light reflex is severely depressed by commonly used drugs, given in therapeutic doses, has not held up under close scrutiny. Opioids, for example, do not alter light reflex amplitude or constriction velocity except for the expected changes that occur secondary to the change in pupil size.[74] Volatile anesthetics and propofol decrease the amplitude of the light reflex independently of any change in pupil size, but above-minimum alveolar concentration (MAC) anesthetic levels of these drugs are required to significantly alter the light reflex.[75] Ketamine and nitrous oxide decrease the reflex when added to an opioid/vapor-based anesthetic regimen.[26] Mild hypothermia has no effect on the light reflex,[76] but topical

[b] Daniel M, Bickler P, Larson MD. Hypoxia does not alter pupil diameter or the light reflex. Anesthesiology 1995;83:A320.

application of ice will produce a small decrease in light reflex amplitude.[77] Hyperthermia will dilate the pupil in the anesthetized subject, producing an increase in light reflex amplitude.[75] Doses of atropine of 1 mg do not depress the light reflex.[78,79] These effects of drugs and other interventions on the light reflex and pupil size become important when the clinician use pupillometry to assess midbrain function in patients with head injuries.[c] The pharmacological properties of PLR are also relevant because measurement of PLR has been used in the intensive care unit to evaluate the depth of sedation in paralyzed patients.[80]

The effect of other drugs on the light reflex has also been studied during general anesthesia when pupil size is stable. Using this technique, it has been shown that vecuronium, pancuronium, and rocuronium do not alter light reflex amplitude,[45] whereas dexmedetomidine slightly increases the amplitude of the reflex.[81]

PRD in Anesthetized Subjects

As previously discussed, the sympathetic pathway that activates the dilator muscle and produces PRD in awake subjects is blocked during general anesthesia. Nevertheless, PRD is a robust reflex during anesthesia. For >40 years, it has been known that anesthetics do not depress and typically enhance postsynaptic inhibition.[82] It should not be surprising therefore that PRD during anesthesia is generated through inhibition of the EW nucleus without a sympathetic contribution.[35] When the EW nucleus is inhibited, the pupil dilates passively as sphincter tone is lost.

A stimulus that will produce PRD during general anesthesia requires activation of nociceptors.[83] Stimulation of β-receptors by touch is unable to dilate the pupils of anesthetized humans, although electrical or mechanical stimulation of Aδ and C fibers produces a nearly 3-fold increase in pupil size (Fig. 5). The reflex can be elicited by a tetanic electric current of 120 mA delivered through surface electrocardiogram pads to the skin from dermatomes that are not blocked by prior local anesthetic injections.[84] These pads can be applied on any dermatome, but in unparalyzed patients, most locations will also activate muscular fibers located below the electrodes. The muscular contraction that occurs can be annoying to the surgeon, and possibly injure the patient. This difficulty can be circumvented by the use of muscle relaxants in doses sufficient to block all but one twitch resulting from the standard train-of-four stimuli. Alternatively, electrocardiogram pads can be placed on areas of the skin that do not have overly large muscle groups. PRD rapidly attenuates if stimuli are given in rapid succession,[85] but studies have shown that the response is stable if it is not repeated more frequently than once every 5 minutes.[86] One commercial portable infrared pupillometer that is able to deliver a tetanic stimulus during the pupillary measurement is available (IDMed, Marseilles, France: www.idmed.fr/).

PRD during anesthesia is slow to develop and is relatively prolonged compared with PLR. For example, the latency of PRD is approximately 800 milliseconds,[69] and its duration is up to several minutes after a brief tetanic stimulus (Fig. 5). In contrast, the light reflex latency is <300 milliseconds, and its duration is measured in seconds. Two studies have demonstrated that PRD is greater in magnitude at higher concentrations of volatile anesthetics compared with lower concentrations.[21,35] This suggests but does not prove that γ-aminobutyric acid type A (GABAa) chloride currents are involved in generating PRD. Volatile anesthetics have several effects on neurotransmission in the central nervous system, but it is generally agreed that these drugs enhance chloride currents generated at GABAa inhibitory synaptic junctions.[87,88] Contributing evidence to the theory that GABAa transmission is involved in generating PRD is that opioids depress PRD in a dose-related fashion.[45,74,89] Opioids interfere with GABAa transmission in the periaqueductal gray matter near the EW nucleus.[90]

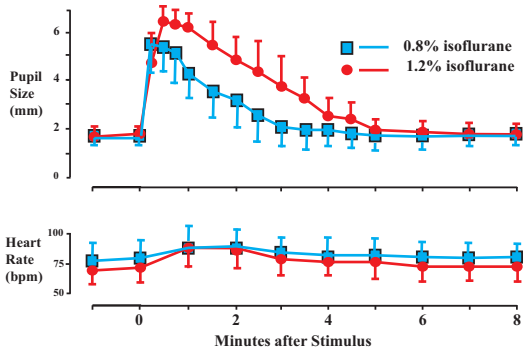

Figure 5. The complete pupillary reflex dilation lasts nearly 8 minutes after a 10-second tetanic stimulus. The higher concentration of isoflurane augmented the reflex in this study. The hemodynamic changes are small compared with the change in diameter of the pupil when measurements are made without prior administration of opioids. Error bars represent standard deviations. Adapted from Larson et al.[21] with approval from author. Adaptations are themselves works protected by copyright. So in order to publish this adaptation, authorization must be obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

There is evidence that pupillary dilation in response to nociceptor activation is associated with the release of catecholamines in the brainstem (Fig. 2).[67,81,91,92] For example, it has been demonstrated that dopamine-2 antagonists have a depressant effect on PRD.[92] Catecholamine nuclei influence endocrine functions by their connections to the paraventricular nucleus, the tuberoinfundibular area, and the hypothalamic–pituitary–adrenal axis.[93] However, there have been no studies that document the association of PRD during anesthesia with the release of stress hormones such as adrenocorticotropic hormone or cortisol. One study did reveal a weak association between pupillary dilation brought about by a rapid increase in desflurane concentration and serum epinephrine levels.[94]

APPLICATIONS OF PUPILLOMETRY IN ANESTHESIA AND INTENSIVE CARE MEDICINE

Monitoring Brainstem Function After Cardiac Arrest and Traumatic Brain Injury

Any assessment of brainstem function includes a measure of the presence or absence of PLR. Although perioperative insults to the brain are rare, when they do occur, a rapid

[c]Kardon R, Kirkpatrick, C, Swanson K, Denning G, Harland K, Full J. Pupillometry and the Neurological Pupil Index: Predicting Traumatic Brain Injury and Patient Outcome in the Emergency Department. Paper presented at: 30th Pupil Colloquium; September 8–12, 2013; Point Clear, AL.

assessment of midbrain function has prognostic value. Cardiac arrest, extreme hypotension or hypertension, air or fat embolus, stroke, or traumatic brain insults can all lead to questions as to whether brainstem function is absent, stable, improving, or deteriorating. Failure of an organism to provide an adequate supply of oxygen and glucose to the midbrain will result in loss of the light reflex and a gradual dilation of the pupil. Several previous studies have shown that the return of PLR is one of the most valuable prognostic tests for return of intact neurological function in patients who have survived cardiopulmonary resuscitation.[95–97] Often the PLRs during cardiopulmonary resuscitation are too small to be appreciated by simple visual inspection, but a recent study that used portable infrared pupillometry documented a light reflex in 83% of patients who were undergoing cardiopulmonary resuscitation (Fig. 6).[24]

The quality of PLR can provide information on brainstem integrity in paralyzed patients.[7,98] Other assessments of brainstem function such as calorics, doll's eyes, cough, swallowing, respiratory moments, and grimace rely on intact neuromuscular function. PLR is generated by smooth muscle and is unaffected by neuromuscular blocking drugs. Proper selection of sedative drugs that do not suppress the light reflex (*vide supra*) allows the intensivist to serially monitor brainstem function in the brain-injured patient.[5,53]

One supplier of infrared pupillometers, Neuroptics (Neuroptics Inc., Irvine, CA), has devised a quality measure of PLR termed the Neurological Pupillary index (NPi™), which is reportedly independent of the size of the pupil. The NPi is calculated using a proprietary algorithm based upon different pupillary measures including reflex amplitude, constriction velocity, redilation velocity, and latency.[7] It is stated that an NPi of zero indicates an absent light reflex; however, the absence of a PLR should be ascertained through strict validated criteria.[12]

Preliminary evidence indicates that the NPi is a valuable addition to monitoring the brainstem during pathologic states that increase intracranial pressure. Traumatic brain injuries lead to increases in intracranial pressure that in turn lead to compression of the midbrain and failure of the light reflex.[99] Intracranial pressure monitoring has been used to monitor the status of these patients but has not shown promise as a means to improve outcome.[100,101] Portable infrared pupillometry is another method of gauging the extent of the midbrain insult brought about by expanding intracranial mass lesions (Fig. 7).[7,8,55] Alterations of light reflex amplitude, constriction velocity, and NPi often precede increases in intracranial pressure and serve as a warning sign that adverse pathological processes might be evolving. Serial measurements with portable infrared pupillometers in the neurocritical care units are currently the most frequently used clinical application of these instruments.

Patients with new-onset coma are often administered naloxone, with the idea that a diagnosis of opioid toxicity can be rapidly ascertained if arousal occurs. In this circumstance, measurement of pupil size and light reactivity can provide useful and timely information. Totally absent light reflexes or asymmetry in the light reflexes with no pupillary dilation after naloxone suggests a structural lesion as a cause of coma.[43,102] If the pupil dilates and the patient does not awaken, there may be multiple drugs involved, and this would be suggested if the light reflex is present bilaterally but the reflex amplitude is abnormal.

Assessment of Nociception During General Anesthesia

The term nociception is often used to denote pain in the noncommunicating patients. Nociception is usually defined as the neural process of encoding noxious stimuli. PRD is one of the autonomic responses that result from encoding a noxious stimulus and can be measured using infrared pupillometry. There is evidence that nociception augments the stress response of surgery and that minimizing this stress response has beneficial effects on outcome.[103,104]

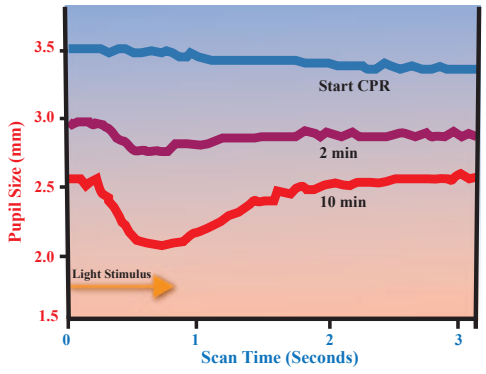

Figure 6. Measurement of the pupillary light reflex during cardiopulmonary resuscitation. Total loss of cardiac output with absent end-tidal CO_2 will produce total pupillary areflexia before the wide pupillary dilation that occurs when the arrest is more prolonged. In this case, cardiopulmonary resuscitation (CPR) was started within a few seconds and the reflex promptly returned to the normal range. Adapted from Behrends et al.[24] with approval from author. Adaptations are themselves works protected by copyright. So in order to publish this adaptation, authorization must be obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

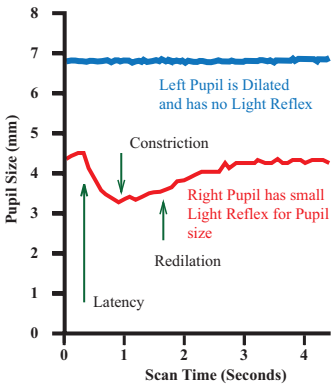

Figure 7. Pupillary light reflex (PLR) during uncal herniation from an expanding intracranial mass. The presence of a light reflex requires that the measurement exhibit a latency of constriction, an amplitude of constriction, and a redilation after the light is turned off. This patient had an intracranial mass lesion that resulted in compression of the oculomotor nerve on the left side and an absent light reflex on that side. The light reflex on the right side is present but reduced in amplitude. Adapted from Manley and Larson[5] with approval from author. Adaptations are themselves works protected by copyright. So in order to publish this adaptation, authorization must be obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

Other physiological responses such as heart rate variability,[105] skin conductance,[106] and the electroencephalogram[107,108] have been suggested as a means to detect nociception during anesthesia. PRD is different from these measures because it has a shorter latency[69,70] and does not depend on sympathetic nervous system activation to detect nociception. Accordingly, PRD is a more rapid response compared with the hemodynamic[70] and electroencephalogram measures,[28] and it is not blocked by β-adrenergic medications that are commonly used during anesthesia.[21]

A limitation of the use of PRD as a measure of nociception is its inhibition by high concentrations of opioids.[74] Opioids block the inhibitory influence on the EW nucleus that arise from activation of nociceptors, and when opioid levels are high they present no advantage over arterial blood pressure and heart rate as measures of nociception.[74] Furthermore, PRD as a measure of nociception can only be an intermittent measurement that requires access to the eyes during the surgical procedure.

The clinically established role of pupillometry as a tool to measure nociception is as a method to assess the quality and extent of a regional block before emergence from general anesthesia.[30,109] Regional anesthesia, either by neuraxial block or peripheral nerve block, is enjoying increasing popularity. Regional anesthetics provide pain relief into the postoperative period while avoiding the side effects of opioids. Regional anesthesia is frequently used in combination with general anesthesia, and if opioids have not or only sparingly been used, it becomes important to know the extent of the regional block before emergence. Waking a patient with an inadequate regional block will result in an unnecessary amount of pain in the postanesthesia care unit, whereas an extensive neuraxial block might result in unpleasant side effects such as dyspnea and upper extremity weakness.

This technique has recently been expanded to test for unblocked segments after peripheral nerve blocks in the anesthetized patients.[110] It has also been used in children in whom it is sometimes difficult to assess the extent of regional blockade even after emergence from general anesthesia (Fig. 8).[111] Instead of using stimulating electrodes, this study used skin incision to provide the nociceptive stimulus. Others have used PRD to predict the likelihood of an exaggerated autonomic response after endotracheal suctioning in tracheally intubated patients.[112]

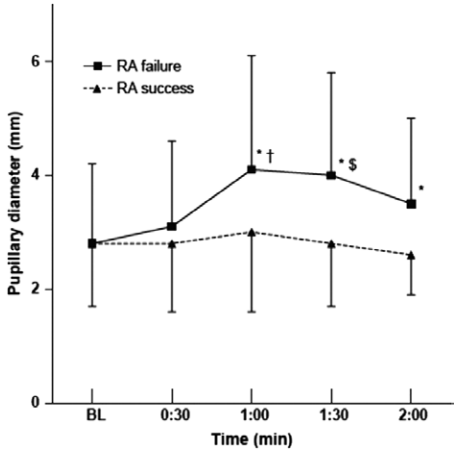

Figure 8. Pupil diameter in successful and in failed regional anesthetic blocks in children. General anesthesia was provided with sevoflurane and 50% nitrous oxide/oxygen. The skin incision provided the noxious stimulus. RA = regional anesthesia. Reproduced from Migeon et al.[111] where a more complete description of the methods can be found. Approved for republication by John Wiley and Sons, Inc.

Measurement of Opioid Effects

Opioids are often administered to anesthetized subjects without a precise end point, and patients can be adversely affected by their improper use. Opioid-induced hyperalgesia, protracted nausea, and vomiting in the postanesthesia care unit, and postoperative respiratory depression are a few examples of complications secondary to inappropriate use of opioids.[113,114]

Opioids are notorious for producing either exaggerated or attenuated responses in certain individuals. Much of this variability undoubtedly relates to differences in metabolism. For example, one study reported on opioid-induced respiratory depression after ingestion of small doses of codeine,[115] attributed to abnormally rapid (CYP2D6 enzyme) metabolism of the ingested drug into morphine. Several studies have documented the value of measuring pupil size as a pharmacodynamic measure of opioid effect in awake subjects.[23,50,116–120]

In the anesthetized patients, pupil size alone does not indicate opioid effect because general anesthesia in itself constricts the pupil. However, as already pointed out, opioids do depress PRD during general anesthesia in a dose-dependent fashion (Fig. 9).[74,89] PRD as elicited by standard ECG electrodes can

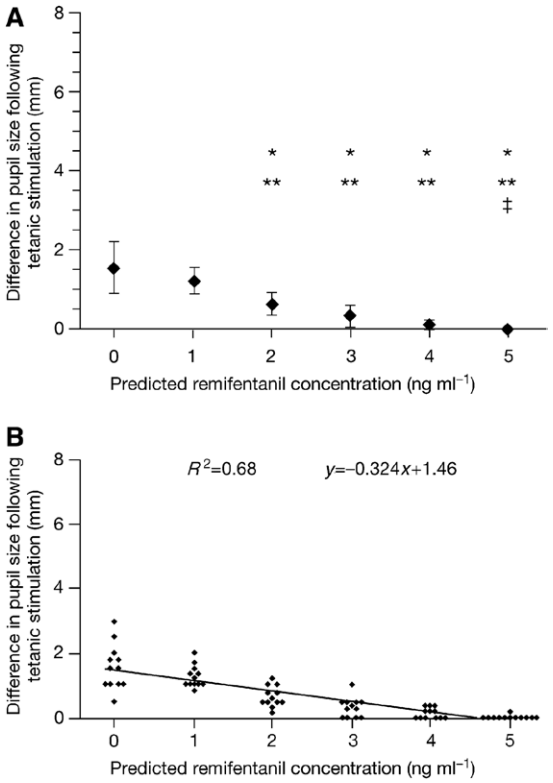

Figure 9. A and B, Pupillary reflex dilation after noxious stimulation during propofol anesthesia. The reflex is lost at remifentanil plasma concentrations of approximately 4 ng/mL. Reproduced from Barvais et al.[89] with permission.

offer insight with regard to the extent of opioid effect. Total ablation of PRD requires relatively large doses of opioid.[28,74,89] For example, 5 ng/mL of plasma remifentanil is required to block PRD in patients given propofol anesthesia.[89] This dose is reported to be 1.4 times (95% confidence interval, 1.25–1.6) the remifentanil concentration required to block hemodynamic responses to skin incision.[121] PRD can be detected during isoflurane anesthesia at alfentanil plasma concentrations of 100 ng/mL,[74] a blood level that is more than double the level that decreases MAC by 50% with this drug (mean = 28.8 ng/mL; 95% confidence interval, 0–71 ng/mL).[122] Consideration of PRD response, therefore, gives the clinician some measure of opioid effect during anesthesia and is a monitor that is not depressed by concomitant β-adrenergic blockade.[21] It is, however, important to recognize that dopamine-2 blocking drugs such as droperidol[92] or antipsychotic medications with D-2 antagonism can also block PRD.

CONCLUSIONS

In summary, study of the pupil in relation to anesthesiology is in its infancy because convenient and accurate instruments have only become available in the past 10 years. Today, the most common use of pupillometry for the anesthesiologists is in measuring the light reflex during and after insults to the brain and in defining the extent of regional sensory block in patients who are anesthetized. Pupillometry also has utility in measuring nociception, opioid therapy, and pain. Simply put, it is a technology that objectifies a measure that was previously only a clinical impression. To date, almost no attempt has been made to use the variables of pupillary unrest or the shape of PLR or PRD waveforms as diagnostic tools that might be of value to the anesthesiologist. These waveforms and the phenomenon of pupillary unrest have been described in normal subjects under controlled protocols,[123] but the alterations in the shape of these reflexes brought about by anesthetic drugs and disease have not been analyzed and might be useful topics for future research.

DISCLOSURES

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