Quantitative pupillometry: normative data in healthy pediatric volunteers

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Objective. The authors describe the prospective use of a new hand-held point-and-shoot pupillometer (NeurOptics) to assess pupil function quantitatively.

Methods. Repetitive measurements were made in 90 pediatric participants ranging in age from 1 to 18 years, providing a total of 100 measurements under ambient light conditions. The participants consisted of 45 patients without known intracranial or ophthalmological pathological conditions as well as 45 volunteers in the outpatient setting. Quantitative pupil measurements were reliably replicated in the study participants. The mean resting pupil aperture was 4.11 mm and the minimal diameter after stimulation was 2.65 mm, resulting in a 36% change in pupil size. The mean constriction velocity was 2.34 mm/second, with a mean dilation velocity of 2.2 mm/second.

Conclusion. Pupil symmetry was impressive in the entire cohort.

Key Words • light stimulation • pupil response • pupillometry • resting pupil diameter • pediatric neurosurgery

Pupillometry has been widely used in the evaluation of numerous pathological conditions. The association of pupillometry findings and clinical outcome in patients with Alzheimer disease, depression, multiple sclerosis, and systematic connective-tissue diseases has been well established.11 Moreover, the association of the pupil reaction and the autonomic nervous system has been meticulously explored in healthy and pathological conditions.2,13,14 Sizes, speed of reactivity, and abnormalities in pupil shape have been studied for almost 100 years. Describing the term “pupil correctopia,” Wilson15 published one of the pioneering studies in the field. Years later, Fisher6 focused on intracranial catastrophes associated with what he described as oval or football-shaped pupils. Marshall, et al.,12 described changes in pupil shape in association with very low ICP measurements. It is likely that changes in other pupil functions may also be observed in patients with an ICP lower than 20 mm Hg, particularly with lesions adjacent to the brainstem. Taylor, et al.,13 proposed that measurements of pupil sphincter function reveal subtle changes associated with rising ICP. Unfortunately, the application of pupillometry has been limited by the unavailability of both a uniform standard for pupil assessment and an instrument allowing reliable acquisition of quantitative measurements. This lack has undoubtedly restricted our capabilities to assess accurately and to make quantitative use of one of the most vital components of the neurological examination, namely, the light reflex. Previous research has focused on descriptive reports of the dramatic and late changes in pupil responsiveness, as well as their relationship to clinical outcome.1–5,7,9,10

Recently, the release of a revolutionary pupillometer and the publication of a well-designed clinical study in which was examined the role of quantitative pupillometry in patients with acute head injuries gave us the stimulus to use this noninvasive method in the pediatric population. To establish normal ranges and consequently to define abnormal values, we performed a prospective clinical study, obtaining multiple quantitative pupil measurements in healthy volunteers. In this paper, we present these measurements, thereby establishing a normal databank in the pediatric population.

Clinical Material and Methods

The pupillometer (Fig. 1) is a stand-alone hand-held battery-operated instrument (NeurOptics, Inc., Irvine, CA). The system comes with a charger and a thermal printer, which can be activated using wireless infrared technology.

Abbreviations used in this paper: CNS = central nervous system; ICP = intracranial pressure; LCD = liquid crystal display.
The pupillometer is a sophisticated computer with a color LCD screen, a self-contained digital camera, and an integral illumination source. The device illuminates the eye of a patient with a set of infrared light rays at 850 nm, a level beyond the normal response of the human eye. Images are acquired with the digital camera, which uses an infrared-sensitive sensor array. The device analyzes 124 images in each measurement sequence and provides detailed information regarding a number of pupil functions within 3 to 4 seconds.

The stem contains a menu-driven graphic user interface consisting of a color LCD screen for readout and a keypad for input. These features allow the user to enter specific information about the patient manually (such as the patient’s identification number). A 4.2-V rechargeable battery is the power source.

The instrument is designed to produce minimal risk to both user and patient. The only designated mechanical contact point with the patient is the headrest, a disposable, protective attachment. All levels of radiation fall below threshold values recommended by the International Commission on Non-Ionizing Radiation Protection. The worst-case scenario limits the infrared exposure to a factor of 30 below the maximal permissible exposure, with visible radiation kept well below the safety limit.

The data typically displayed by the device are illustrated in Fig. 2. The device has the capacity to store more than 150 consecutive measurements. The data are sent directly to a printer through an infrared port for ease of charting. Information can also be transmitted through an infrared port to a multiparameter monitor for automatic medical record updates or downloaded to a computer via a universal serial bus port. Each time the device is used, a patient’s identification number, the eye being examined (right or left), and the ICP are recorded. The data are time labeled, documenting compliance with the medical protocol. Such electronic documentation is designed to eliminate the types of errors that can complicate manual data entry.

During a 6-month period, a quantitative pupillometer was used to study 45 healthy pediatric volunteers and 45 patients with no evidence of neurological or ophthalmological deficits under ambient light conditions. The participants were divided into four age groups: Group 1, 0 to 2 years of age (17 participants); Group 2, 2.01 to 6 years of age (28 participants); Group 3, 6.01 to 12 years of age (30 participants); and Group 4, 12.01 to 18 years (15 participants). These studies were necessitated by the influence that light, a number of genetic factors, and various classes of drugs can have on the resting size and reactivity of pupils. Furthermore, the speed of constriction, here referred to as the constriction velocity, depends on the resting diameter of the pupil; that is, the larger the initial pupil size, the higher the rate of constriction. There is also a constant, direct correlation between initial pupil diameter and the corresponding poststimulus aperture. Thus, we also determined the relationship between the initial diameter and the poststimulus pupil size in the previously described light conditions.

Forty-five pediatric patients undergoing nonintracranial surgical or endoscopic procedures and 45 healthy volunteers who had no history of intracranial or ophthalmological disease were studied to provide a databank of normative data. In addition, in the latter series of participants, the capability of the device to measure the size of the pupil was compared with estimations of pupil size made by the principal investigator and a nurse, as well as with another nurse’s measurement obtained using a ruler.
Results

All quantitative pupillometry measurements could be replicated repeatedly under the same ambient light conditions in healthy pediatric volunteers and in patients in the inpatient setting. In our study population, the mean maximal resting aperture was 4.11 mm and the mean minimal diameter after stimulation was 2.65 mm. The mean constriction velocity in healthy volunteers was 2.34 mm/second, and the mean dilation velocity was 2.2 mm/second. The mean percentage of reduction in pupil size after stimulation was 36%, with three individuals having readings less than 20%. Figures 3 through 6 summarize these findings by age group.

The latency period ranged between 130 and 520 msec and seemed more strongly correlated with age than other variables. The device was much more accurate than the nurse’s estimate of pupil size. In patients in whom the mean pupil size was larger than 4 mm, the pupillometer and the ruler were significantly more accurate than the investigators’ judgments.

Pupil asymmetry measuring less than 0.5 mm is difficult to detect with the naked eye. In the present study, an asymmetry of up to 0.5 mm was frequently observed in healthy volunteers and patients without head injury, indicating that asymmetry less than 0.5 mm is within the normal range.

Discussion

Our study represents, to the best of our knowledge, the first detailed application of quantitative pupillometry to a
cohort of pediatric volunteers under ambient light conditions.

Quantitative pupillometry can produce reliable, reproducible pupil measurements that are clearly superior to those obtained at the patient's bedside by a nurse or physician. Although these data are preliminary, a number of observations in our participants are evidence based. First, the light conditions in the hospital and other patient-care environments, including physician offices, fall within ranges that permit accurate pupil measurements. Second, all quantitative studies were reliably reproducible within study participants without technical challenges or clinical complications.

The databank of normal values obtained herein indicates that parameters routinely used in patient assessment at the bedside can be assessed quantitatively and are potentially useful in assessing ICP. The clinical observation of briskly reactive, sluggish, or nonreactive pupils is likely to be a combination of several physiological factors, including latency, constriction, and dilation velocities. The difference in mean constriction velocity and all other parameters in the previously defined age groups are consistent with the proposition of time-dependent CNS myelination. It has been postulated that 95% of the CNS becomes myelinated from the core out between birth and 2 years of age, with the remaining 5% occurring in stages between 3 to 6, 7 to 12, and 13 to 18 years of age.11

In clinical practice pupils have been considered to be symmetrical when the interpupil size difference exceeds 1 mm. This gauge clearly reflects the inability of the unaided human eye to quantify asymmetry of less than 0.5 mm. In the present series, a difference in pupil size of more than 0.5 mm was rarely appreciated, either at rest or after stim-
ulation. This finding shows that with the aid of quantitative pupillometry, the diameter at which pupil asymmetry indicates the possibility of an intracranial pathological entity or brainstem compression can be reduced to 0.5 mm. The device has been used in 90 children, both in the outpatient and inpatient setting. In the outpatient environment, a skilled pediatric nurse was able to obtain repetitive measurements in 45 children ranging in age from 5 to 13 years. In the inpatient environment, the case of use was similar to that with outpatients, because of a special forehead attachment.

The observations reported here in both healthy pediatric volunteers as well as in patients suffering from neurological or ophthalmological problems are based primarily on traditional parameters that have been used in outpatient and hospital settings (that is, the size of the pupil and the speed at which it reacts). Quantitative pupillometry is clearly capable of providing much more detailed information than the conventional characteristics currently used in physical examinations. It has also proved capable of measuring subtle changes in the shape of the pupil not detectable by the unaided human eye. Such variables may be extremely important in providing more sensitive information than the results reported here. Just as in measurements of traditional vital signs such as blood pressure and heart rate—in which wide variations fall within a normal range—it is likely that relative rather than absolute changes in patients’ pupil function may be more important in detecting early changes in ICP. A databank of normative measurements may be much more useful in reliably predicting changes in brain volume that precede or are concurrent with changes in ICP.

The uniform symmetry of pupil responses for the analyzed variables, as demonstrated in 100 observations in healthy pediatric volunteers to date, further substantiates our proposal that subtle differences in pupil size and reactivity measured using the NeurOptics pupillometer may be more sensitive in detecting potentially dangerous changes in ICP prior to their progression to irreversible pathological entities.

The high incidence of death associated with pupil changes, using traditional methods of assessment, suggests that early detection of subtle increases in ICP may correlate with improved clinical outcomes.

**Conclusions**

Quantitative pupillometry is a reliable and safe method of pupil assessment and of signaling associated ICP changes and seems to provide detailed and accurate information on physiological pupil responsiveness. Our findings appear to be consistent with the stages of CNS myelination. As speculated, pupil velocities of dilation, constriction, and percentage of diameter change peak in the group of participants 2.01 to 6 years of age, after myelination of more than 95% of brain is complete. Further studies focused on assessing the correlation between elevated ICP and respective pupil response parameter changes in pediatric patients with invasive ICP monitors in place are in progress. Furthermore, the ICP values at which pupil function is altered, and the significance of midline shifts as detected on computerized tomography scans and magnetic resonance images of the brain should be evaluated for completeness and reliability. The effects on pupil function of a variety of medications such as opioid agents, as well as anemic states, should also be addressed for the sake of completeness.

**Acknowledgment**

We thank Robert L. Farrall, M.B.A., for his contributions to the statistical analysis of our data.

**Disclaimer**

None of the authors has received any compensation from the company cited in this manuscript.

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Manuscript received March 21, 2005. Accepted in final form September 6, 2005. This study was supported by the Alpha Omega Medical Honor Society.

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