Developmental Changes of Normal Pupil Size and Reactivity in Children

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ABSTRACT

Purpose: The goal of this study was to establish normative values for measurements of quantitative pupillometry in children.

Methods: Quantitative pupillometry measurements were obtained from children between 1 and 18 years of age being seen for either a well child check or other outpatient appointment.

Results: Maximum and minimum pupil size increased slightly with age; however, the correlation was weak ($r = 0.29$ and 0.19, respectively). Similarly weak correlations with age also were observed for maximum constriction velocity ($r = -0.29$) and dilation velocity ($r = 0.27$). Maximum (5.56 vs 4.97 mm) and minimum (3.74 vs 3.40 mm) pupil sizes were significantly larger in whites than in African Americans.

Conclusions: Pupil size and reactivity show little correlation with age and are therefore suitable for further exploration in using pupillometry as a biomarker across the pediatric age range. Differences in race should be taken into consideration when pupillometry is used in mixed populations.

pupillary dilatation reflex (in response to a standardized noxious stimulus). The clinical application of pupillometry has been shown to be a more sensitive marker of pain and analgesic drug response in children and adults when compared to traditional hemodynamic markers. Proof of concept work using pupillometry as a functional pharmacodynamic biomarker to quantitate pain intensity has also been performed in children. Further development of pupillometry as a biomarker of pain and analgesic response requires more detailed generation of normative data in children to evaluate the impact of development on pupil size and reactivity.

Several prior studies have evaluated normal pupil size and reactivity in children in a variety of ways. When compared, these studies had varying sample sizes and dissimilar methods (including different pupillometers), and dynamic measures of pupil response (eg, constriction velocity in response to a light stimulus) were omitted. The purpose of this study was to further characterize normal pupil size and reactivity, assess the feasibility of using pupillometers in children as young as 12 months of age, and determine differences in age, sex, and race.

**PATIENTS AND METHODS**

This was an institutional review board approved, multicenter study of healthy male and female children between the ages of 1 and 18 years using convenience sampling. Participants were recruited during well child checks or other outpatient clinic appointments. Normative values were also obtained preoperatively from otherwise healthy patients with pectus excavatum undergoing corrective surgery. Participants were excluded if they had any major chronic illness that might affect pupil size, were currently in pain, were taking any medication known to affect pupil size (eg, opioids or stimulants), or were unwilling or unable to participate. Parents or guardians completed a self-report questionnaire to ascertain the participant’s age, race, ethnicity, current state of pain (based on a scale from 1 to 10), and current medications.

Pupil size and reactivity were obtained using either a NeurOptics PLR-100 or PLR-200 pupillometer (NeurOptics, Irvine, CA). Pupil measurements were based on the average of one to three readings. If no valid readings were obtained after three tries, no additional readings were attempted. Initially, a rubber cup on the pupillometer is placed around the child’s eye to block out peripheral light. Once the pupil is detected, the pupillometer determines the resting (maximum) pupil diameter (mm), flashes a brief standardized light stimulus, and then determines the resulting average and maximum pupil constriction velocity (mm/s), minimum pupil diameter (mm), time to minimum diameter (s), constriction amplitude (resting minus minimum diameter), and dilation velocity (mm/s) (Figure 1). The validity of each reading is displayed in the output and determined by the software integrated within the device. This procedure is brief, non-invasive, and has no associated risk.

Maximum and minimum pupil sizes are presented as means with standard deviation grouped as yearly age groups. Independent t tests were used when comparing pupil parameters between sex and race. Pearson correlation tests were performed to assess the relationship between age and pupillometry parameters.

**RESULTS**

A total of 272 participants were approached for study participation. Of these, 7 participants were ineligible due to taking a medication known to
affect pupil size and reactivity, whereas 7 reported pain scores greater than 1 (based on a scale of 1 to 10). Fifty-seven participants were excluded due to invalid readings as determined by the software. Readings deemed invalid by the software tended to occur more frequently in children younger than 5 years. Data from 201 participants (52% male) were analyzed, with the exception of pupil dilation data, which was incomplete for 31 participants (usable n = 170). The self-identified race distribution of the enrolled sample was 64% white, 24% African American, and 12% other. Of the total population, 16% self-identified as Hispanic.

Average maximum and minimum pupil sizes by age are displayed in Table 1. Overall, both maximum and minimum pupil size increased slightly with age (Figure 2). Although this finding was found to be statistically significant, the correlation between age and maximum/minimum pupil size was weak \( (r = 0.29, P < .05, \text{ and } r = 0.19, P < .05, \text{ respectively}) \). These increases in maximum and minimum pupil size correlated well with previously established normative values\(^{17}\) for size of the eye over time as determined by axial length \( (r = 0.79 \text{ for maximum; } r = 0.86 \text{ for minimum}) \). Weak correlations with age were also observed for maximum constriction velocity \( (r = -0.29, P < .05) \) and dilation velocity \( (r = 0.27, P < .05) \) (Figure 3). These changes in maximum constriction and dilation velocities correlated fairly well \( (r = 0.66 \text{ for maximum constriction velocity; } r = 0.59 \text{ for dilation velocity}) \) with previously established normative values for eye size.\(^{17}\) Average constriction velocity showed no correlation with age \( (r = 0.01, P > .05) \).

No differences were observed between males and females for any of the pupil parameters. Mean maxi-

### Table 1

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>No. of Participants</th>
<th>Maximum Pupil Size (mm [SD])</th>
<th>Minimum Pupil Size (mm [SD])</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–2</td>
<td>8</td>
<td>4.82 (1.13)</td>
<td>3.44 (0.71)</td>
</tr>
<tr>
<td>2–3</td>
<td>7</td>
<td>4.64 (0.84)</td>
<td>3.10 (0.64)</td>
</tr>
<tr>
<td>3–4</td>
<td>6</td>
<td>5.02 (0.83)</td>
<td>3.28 (0.73)</td>
</tr>
<tr>
<td>4–5</td>
<td>13</td>
<td>5.27 (0.60)</td>
<td>3.50 (1.09)</td>
</tr>
<tr>
<td>5–6</td>
<td>16</td>
<td>4.90 (0.60)</td>
<td>3.34 (0.53)</td>
</tr>
<tr>
<td>6–7</td>
<td>14</td>
<td>5.11 (0.73)</td>
<td>3.52 (0.61)</td>
</tr>
<tr>
<td>7–8</td>
<td>11</td>
<td>5.31 (0.87)</td>
<td>3.73 (0.65)</td>
</tr>
<tr>
<td>8–9</td>
<td>8</td>
<td>4.99 (1.02)</td>
<td>3.42 (0.66)</td>
</tr>
<tr>
<td>9–10</td>
<td>14</td>
<td>5.48 (1.17)</td>
<td>3.79 (0.82)</td>
</tr>
<tr>
<td>10–11</td>
<td>18</td>
<td>5.56 (0.44)</td>
<td>3.79 (0.44)</td>
</tr>
<tr>
<td>11–12</td>
<td>13</td>
<td>5.95 (0.79)</td>
<td>3.81 (0.56)</td>
</tr>
<tr>
<td>12–13</td>
<td>20</td>
<td>5.36 (0.83)</td>
<td>3.63 (0.48)</td>
</tr>
<tr>
<td>13–14</td>
<td>11</td>
<td>5.82 (0.77)</td>
<td>3.93 (0.51)</td>
</tr>
<tr>
<td>14–15</td>
<td>12</td>
<td>5.38 (0.92)</td>
<td>3.64 (0.62)</td>
</tr>
<tr>
<td>15–16</td>
<td>12</td>
<td>5.74 (0.64)</td>
<td>3.70 (0.43)</td>
</tr>
<tr>
<td>16–17</td>
<td>10</td>
<td>6.01 (1.12)</td>
<td>3.92 (0.66)</td>
</tr>
<tr>
<td>17–18</td>
<td>8</td>
<td>5.10 (1.45)</td>
<td>3.42 (0.64)</td>
</tr>
<tr>
<td>Total/average</td>
<td>201</td>
<td>5.36 (0.90)</td>
<td>3.62 (0.65)</td>
</tr>
</tbody>
</table>

SD = standard deviation

![Figure 2. Scatter plot of maximum and minimum pupil sizes.](image)

![Figure 3. Scatter plot of maximum constriction velocity and dilation velocity.](image)
mum pupil size was significantly larger in whites than in African Americans (5.56 vs 4.97 mm) (P < .05), as was minimum pupil size (3.74 vs 3.40 mm) (P < .05). Additionally, the mean maximum constriction velocity for white participants (-4.92 mm/s) was significantly faster compared to African-American participants (-4.42 mm/s) (P < .05).

**DISCUSSION**

Advances in the technology of pupillometers have led to an increased use of pupillometry as an assessment tool in several areas. However, it is difficult to fully understand results without adequate characterization of normal pupil size and reactivity values. Establishing normative values in pediatrics is imperative to accurately assist in the interpretation of pediatric studies that employ pupillometry as a tool. This study is the first to provide quantitative data of pupil size and reactivity under ambient light conditions across a representative sample of healthy children of all ages. These results add to the existing body of literature on normal ranges of pupil size and reactivity throughout child development. Both maximum and minimum pupil sizes were shown to increase slightly until approximately 11 years of age and subsequently plateau, similar to previously described changes in eye size throughout childhood. Similarly, dilation velocity showed a slight increase over the pediatric age range, whereas maximum constriction velocity decreased. These changes correlated fairly well with changes in eye size throughout childhood; however, they may also be affected by developmental changes of the pupillary light reflex. It also is important to note that no differences between males and females were found in pupil parameters; however, significant differences were found in three parameters (maximum and minimum pupil size and maximum constriction velocity) when comparing white and African-American children.

Although approximate values for age ranges can be estimated from the data, we found a considerable amount of inter-individual variability for maximum and minimum pupil sizes (Figure 2). As a result, it may be likely that the most relevant information is gained by examining changes in an individual’s own dynamic values (ie, constriction/dilation velocity and percent constriction) or change in pupil size from their baseline values. Furthermore, this study shows that pupil readings are feasible in children as young as 12 months of age, although, as previously stated, valid measurements were more difficult to obtain for children younger than 5 years. To increase the likelihood of obtaining a reading from a child younger than 5 years, parents assisted in helping to steady the child’s head long enough to obtain a reading. Although an advantage of the pupillometer is its ease of use, patient–operator interaction and operator proficiency is still required when obtaining readings. The development of a pupillometer requiring less active participation for obtaining readings in younger children (eg, obtaining readings from a distance or software that integrates motion better) may be useful.

This study adds important information to the existing knowledge related to normal pupil size and reactivity in healthy children. Due to methodological differences, previous studies in this area have produced varying results. Machlachlan and Howland used a large sample size of participants 1 to 19 years of age to quantify typical pupil parameters; however, their results are limited to only resting pupil diameter and interpupillary distance under low light conditions. Similarly, Kohnen et al. reported only mean pupil size values under scotopic conditions in children between 0 and 15 years of age; of note, these researchers similarly found an increase in pupil size until approximately 11 years of age. Taylor et al. reported size and reactivity data in healthy volunteers between 1 and 87 years of age but collapsed data across the entire age range. Finally, Boev et al. reported normative quantitative pupillometry data in 90 children 1 to 8 years of age. Results from the Boev et al. study contrasted with our findings in that mean values for maximum and minimum pupil size from our study were larger overall.

The study was limited by the exclusion of children younger than 1 year. Given that a significant amount of neurodevelopment occurs prior to 1 year of age, it is possible that pupil size and/or reactivity may appreciably change throughout this timeframe. Future studies to assess quantitative pupillometry in children younger than 1 year will likely require technological advancements in the way these readings are obtained. Although unlikely, it is also possible that pathology affecting the eye may have influenced pupil metrics because an ophthalmologist did not rule out eye pathology.

Pupil size and reactivity as quantified by pupillometry appear to be relatively independent of ontogeny in children older than 1 year, and therefore
are suitable for further exploration in using pupil-lometry as a biomarker across the pediatric age range. Due to the absence of significant changes with age, extrapolation of adult pupil-lometry data to the pediatric population may be reasonable. Additionally, future studies using pupil-lometry in mixed racial populations must take into account that differences may exist. These data provide an important baseline and are critical considerations for interpretation of future pediatric studies using pupil-lometry as a pharmacodynamic biomarker.

REFERENCES