Rapid, High-Accuracy Detection of Strabismus and Amblyopia Using the Pediatric Vision Scanner

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PURPOSE. The Pediatric Vision Scanner (PVS) detects strabismus by identifying ocular fixation in both eyes simultaneously. This study was undertaken to assess the ability of the PVS to identify patients with amblyopia or strabismus, particularly anisometropic amblyopia with no measurable strabismus.

METHODS. The PVS test, administered from 40 cm and requiring 2.5 seconds of attention, generated a binocularity score (BIN, 0%-100%). We tested 154 patients and 48 controls between the ages of 2 and 18 years. BIN scores of amblyopic children and controls were measured, and 21 children received sequential PVS measurements to detect any changes in BIN resulting from amblyopia treatment.

RESULTS. With the pass/refer threshold set at BIN 60%, sensitivity and specificity were 96% for the detection of amblyopia or strabismus. Assuming a 5% prevalence of amblyopia or strabismus, the inferred positive and negative predictive values of the PVS were 56% and 100%, respectively. Fixation accuracy was significantly reduced in amblyopic eyes. In anisometropic amblyopia patients treated successfully, the BIN improved to 100%.

CONCLUSIONS. The PVS identified children with amblyopia or strabismus with high sensitivity and specificity, while successful treatment restored normal BIN scores in amblyopic patients without strabismus. The results support the hypothesis that the PVS detects strabismus and amblyopia directly. Future strategies for screening by nonprofessionals may thus be based on diagnostic detection of amblyopia and strabismus rather than the estimation of risk factors, allowing for rapid, accurate identification of children with amblyopia early in life when it is most amenable to treatment.

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*Each of the following is a corresponding author: David G. Hunter, David G. Hunter et al.7–9 developed a device, the Pediatric Vision Scanner (PVS), that can identify even small angles of strabismus with high precision by detecting ocular alignment using binocular retinal birefringence scanning.6 It is a noninvasive test that requires little cooperation and no verbal response from the child and yields a binocularity score (BIN), indicating whether both eyes have simultaneously fixated on a target. In a previous study10 the device unexpectedly indicated low binocularity in three children with anisometropic amblyopia but no clinically detectable strabismus, consistent with the belief of some pediatric ophthalmologists that most patients with anisometropic amblyopia also have microstrabismus.11,12 We therefore decided to investigate whether the PVS could detect anisometric amblyopia as well as strabismus, a major advantage for detecting medical eye conditions in children. We also followed patients during treatment to determine whether their performance on the screening test would improve when vision was restored after treatment.

METHODS

Study Population

Subjects were consecutively recruited from the Department of Ophthalmology at Children’s Hospital Boston during their regular visit to the outpatient clinic from 2003 to 2007. All subjects were either referred to the pediatric ophthalmologist or had no referral but were siblings of children already being treated at the department for amblyopia, strabismus, or refractive errors. The study was approved by the appropriate institutional review board and written informed consent

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by the parents or guardian was a prerequisite for participation. The research adhered to the tenets of the Declaration of Helsinki.

The treating orthoptist and pediatric ophthalmologist performed a gold-standard examination, measuring best-corrected visual acuity (using the M&S Smart System electronic visual acuity chart; M&S Technologies, Chicago, IL) or LEA symbols (Good-Lite Co., Elgin, IL), stereopsis (using the Titmus Fly [4000 seconds] and Randot circles [discrete range of forced choice values from 400 to 20 seconds]; Stereo Optical, Inc., Chicago, IL), and ocular motility. The angle of strabismus, when present, was quantified using the prism-and-alternate-cover test. The pediatric ophthalmologist performed cycloplegic retinoscopy 20–30 minutes after administration of one drop of 1% cyclopentolate hydrochloride. Based on the gold standard examination, subjects were classified as either controls or patients. Children between 2 and 18 years old were eligible for inclusion.

Children with clinically obvious strabismus (≥15 PD) or ptosis were excluded since their conditions would be identifiable without special screening. In addition, our previous work9,10 had demonstrated that the PVS can detect large-angle strabismus with very high sensitivity and specificity, and the goal of this study was to evaluate performance in a population of patients most likely to have their conditions go undetected. Children were also excluded when they had a history of developmental delay, cognitive deficit, eye muscle surgery in the last 6 months, retinal disease, nystagmus, glaucoma, cataract (considered an developmental delay, cognitive deficit, eye muscle surgery in the last 6 months, retinal disease, nystagmus, glaucoma, cataract (considered an

**Sequential Measurements.** When possible, patients who had undergone treatment for amblyopia were rescanned during a follow-up visit. Amblyopia was treated according to the clinical practice of the treating pediatric ophthalmologist. Care was not standardized in any manner, but all treating clinicians in the department follow standard clinical care, treating with spectacle correction, occlusive eye patches, and/or atropine penalization.

**Diagnostic Classification.** The control group consisted of subjects with no strabismus, amblyopia, or anisometropia. Patients were categorized after enrollment based on visual acuity, refractive error, and binocular alignment. Visual acuity classification was based on the presence of amblyopia, defined for this study as an interocular visual acuity difference of at least two logMAR lines. Visual acuity in the amblyopic eye of better than 20/40 was categorized as “mild amblyopia”; visual acuity between 20/40 and 20/100 as “moderate amblyopia,” and visual acuity of 20/100 or worse was defined as “severe amblyopia.” Visual acuity in the nonamblyopic eye was 20/40 or better in all subjects, except in two patients with visual acuity of 20/125 in the amblyopic eye and 20/100 in the fellow eye (caused by high hypermetropia in one patient and high astigmatism in the other). Patients with strabismus were categorized as having “constant” strabismus in case of manifest ocular misalignment >0 prism diopter (PD) for near and/or at distance fixation or “intermittent” strabismus if ocular alignment could be controlled through either fusional mechanisms or a compensatory head position. Patients with refractive error were categorized as having “anisometropia (1.5 diopters [D]) or more difference in refractive error between the two eyes),” “hypermetropia (≥3.5 D),” “astigmatism (≥1.5 D),” or “anisostigmatism.” These patients did not have amblyopia; however, they were categorized separately from controls because young patients with refractive error might have an increased likelihood of developing amblyopia in the future. Patients with symmetric myopia of ≥4 D were not considered to be at risk for developing amblyopia, because myopic patients without anisometropia are able to obtain a focused image in both eyes at near and thus do not suffer the visual deprivation in one eye that can lead to amblyopia.

**Pediatric Vision Scanner: Bin, Fixation Accuracy, and Sensitivity to Defocus**

**Binocularity Score.** The full design, operation, software, and output of the Pediatric Vision Scanner (previously referred to as the ‘Pediatric Vision Screener’) have been reported elsewhere.7–9 Briefly, the PVS was designed to perform a retinal birefringence scan of both eyes simultaneously while a child fixated on a target consisting of a near-infrared blinking point source (presented at a distance of 40 cm) in combination with a synchronized beeping tone. This method, which we have described as retinal birefringence scanning, detects foveal fixation by identifying the unique polarization signature created by the birefringence of the nerve fibers emanating from the fovea. The device obtained a bilateral measurement in which either binocular or monocular fixation was identified. In cases where the child was unable or unwilling to fixate on the target, neither monocular nor binocular fixation was detected, and an “unable” measurement was obtained. The instrument obtained a series of five such binocular measurements in rapid sequence over a 2.5-second period to yield a binocularity score (BIN), which was calculated as [(number of bilateral readings / sum of unilateral and bilateral readings)] × 100%. At least three valid measurements (with either one or both eyes fixating) were required to calculate a binocularity score, so that the denominator for the BIN calculation ranged from 3 to 5. The BIN ranged from a maximum of 100% (binocular fixation during all valid measurements) to 0% (only unilateral fixation during all valid measurements).

For clinical testing, patients were scanned with the PVS before they underwent their eye examination. Children were seated unrestrained on a chair or a parent’s lap in a dimly lit room. An internal background measurement was first recorded by obtaining a scan from closed eyes, or from the parent’s forehead in cases where the child was unable to keep both eyes closed. Subjects were then encouraged to focus on the blinking target for approximately 3 seconds until the beeping tone ended. Testing was performed without any optical correction to reproduce the screening (prediagnosis) clinical scenario. The individuals performing the PVS test were not aware of the clinical diagnosis.

**Monocular Fixation Accuracy.** The accuracy of monocular fixation, or “fixation score,” was determined by asking subjects to fixate on the PVS target with one eye while the other eye was occluded with an eye patch. The fraction of measurements in which central fixation was detected was then recorded. The highest fixation possible score was 1.0, indicating central fixation; 0.0 indicated eccentric fixation during all measurements.

**Outcome Measures and Statistical Analysis**

The primary outcome measure was the degree of binocularity as measured with the PVS: BIN (0%–100%). The treating orthoptist and pediatric ophthalmologist performed the clinical examinations; the PVS measurements were carried out by an independent researcher. The examiners were masked to the BIN score at all times. Statistical analysis was carried out using commercially available software (SPSS 13.0, SPSS, Chicago, IL). The BIN for each of the category (Table 1) was calculated and described using descriptive statistics. The Kruskal-Wallis rank sum test, followed by the Mann-Whitney U test, was used to determine a difference in BIN between the children with amblyopia, strabismus, and refractive error and the control group. Significant P values were adjusted with the Bonferroni correction for multiple testing, such that P < 0.017 indicated statistical significance. Differences in BIN between the subgroups were also calculated using the Kruskal-Wallis rank sum test, followed by the Mann-Whitney U test and the Bonferroni correction, such that a P value of <0.007 was considered significant. The relationship between BIN, degree of anisometropia, and visual acuity in the amblyopic eye in children with anisometropia was assessed using Spearman’s correlation coefficient.

A Receiver Operating Characteristic (ROC) curve was generated to assess the screening performance of the PVS. The presence of amblyopia and/or strabismus on clinical evaluation was termed “disease” (groups no. 1–5; Table 1); compared to the subjects with refractive errors and the control group, termed “no disease” (groups no. 6–10; Table 1). These definitions emphasized the most clinically relevant task of investigating the ability of the PVS to detect any child with constant strabismus diagnosed by cover testing or with amblyopia of any etiol-
Refractive error

Controls

Mild

Strabismus

Anisometropia

Both

Hypermetropia

Moderate

Strabismus

Anisometropia

Both

Hypermetropia

Severe

Strabismus

Anisometropia

Both

Strabismus

Intermittent strabismus

Constant strabismus

Refractive error

Anisometropia

Hypermetropia

Anisostigmatism

Astigmatism

Controls

N

Mean BIN ± SD (range)

13% ± 25% (0–50)

11% ± 16% (0–36)

0%

100%

8% ± 13% (0–33)

29% ± 28% (0–75)

14% ± 22% (0–60)

0%

2% ± 5% (0–11)

0%

0%

21% ± 24% (0–80)

3% ± 6% (0–25)

90% ± 29% (0–100)

89% ± 13% (75–100)

67% ± 53% (20–100)

92% ± 11% (62–100)

* Amblyopia was categorized into mild (better than 20/40), moderate (20/40 to >20/100) and severe (20/100 or worse).

Mean age was 7.4 years, with 97 children aged 2–6, 69 aged 7–11, and 36 aged 12–18 years; 97 were boys and 105 were girls.

Study Outcome

BIN per Group. The relationship between BIN and visual acuity in the 48 control subjects is presented in Figure 1. The two-axis representation used in Figure 1 allows for a rapid visual estimation of the relationship and provides the data points used to generate box defining normal values. Figure 2 shows the relationship between BIN and visual acuity in the worse eye (logMAR) for children with mild, moderate, and severe amblyopia, demonstrating that most patients with amblyopia (of any cause) fell well below the normal range of BIN.

Figure 3 shows the same relationship for children with intermittent and constant strabismus, showing that just one patient with intermittent strabismus had a BIN within the normal range. Figure 4 shows the relationship for those patients with refractive error but no amblyopia, with just two patients falling below the normal range. Mean BIN for children with mild and moderate amblyopia was approximately equal (17% and 16%, respectively). Only one child with severe amblyopia was able to obtain a BIN >0%; mean BIN in this group was 1% (Fig. 2C).

BIN was lowest in the groups with amblyopia: 12% ± 23% and strabismus (8% ± 17%) (Table 1). Mean BIN was considerably higher in the groups with refractive error but no amblyopia (85% ± 27%) and in the control group: 92% ± 11% (95% CI, 67–100; see also boxes in Fig. 2). For 2- to 6-year-old children, the group most likely to have amblyopia or strabismus missed with standard screening protocols, mean BIN was 9% ± 18% in the group with amblyopia (N = 33); 8% ± 18% in the group with strabismus (N = 33); 88% ± 22% in the group with refractive error (N = 13); and 89% ± 13% (N = 26) in the control group.

There was a significant difference in BIN between the control group and the amblyopia and strabismus groups (both P < 0.001). To determine whether the PVS results were affected by anisometropia in the absence of vision loss, the control group was compared with the group with anisometropia and no amblyopia, and no significant difference was found (P = 0.171). BIN was negatively correlated with the visual acuity in the amblyopic eye (r = −0.66; P < 0.001) and degree of anisometropia (r = −0.56; P = 0.002). Visual acuity in the amblyopic eye was weakly correlated with the degree of anisometropia (r = 0.38; P = 0.49).

Monocular Fixation Accuracy. Fixation accuracy was tested in 46 children under monocular viewing conditions. The fixation score was highest in the control group (N = 17; 1.00 in each eye), lower in the group with refractive error but no amblyopia (N = 8; 0.73 in the nonpreferred eye and 0.91 in the preferred eye); even lower in the strabismus group (N = 14; 0.54 in the nonpreferred eye and 0.72 in the preferred eye); and lowest in the group with amblyopia (N = 17; 0.37 in the
nonpreferred eye and 0.78 in the preferred eye). The sound eye of amblyopic patients also had a lower fixation score than controls; \( P = 0.040 \).

**Anisometric Amblyopia.** Anisometropia was present in 34 children (17%); of these, 22 had amblyopia. Mean BIN and visual acuity in the nonpreferred eye were significantly lower, and degree of refractive difference significantly higher, in children with anisometric amblyopia, compared to the children with anisometropia but no amblyopia (Table 2).

Eight children with anisometric amblyopia received sequential measurements with the PVS during their treatment period (Table 5). BIN increased to 100% in the four children in whom visual acuity became equal through treatment; in these four children, stereopsis also improved slightly. In the four children with persistent amblyopia, BIN did not improve. Of the 13 children with strabismus and amblyopia whose visual

FIGURE 2. BIN and visual acuity in the amblyopic eye for children with (a) mild amblyopia (\( N = 13; \) median BIN 0% 25th and 75th percentile are 0% and 28%); (b) moderate amblyopia (\( N = 35; \) median BIN 0% 25th and 75th percentile are 0% and 29%); and (c) severe amblyopia (\( N = 16; \) median BIN 0% 25th and 75th percentile are both 0%). X, children with amblyopia caused by anisometropia (\( \geq 1.5 \) D); O, children with amblyopia caused by strabismus, both anisometropia and strabismus or hypermetropia (one case with mild amblyopia; BIN 100%). The boxes represent the 95% CI for the BIN score (67%–100%) and visual acuity in the eye (\(-0.05\)–0.30 logMAR) of the control group.

FIGURE 3. BIN and visual acuity in the worse eye for children with intermittent strabismus (\( N = 22; \) represented by \( \triangle \); median BIN 17% 25th and 75th percentile are 0% and 45%); and constant strabismus (\( N = 44; \) represented by +; median BIN 0% 25th and 75th percentile are both 0%). The boxes represent the 95% CI for the BIN score (67%–100%) and visual acuity in the eye (\(-0.05\)–0.30 logMAR) of the control group. One child with intermittent strabismus had BIN score of 80%; a six-year-old boy with visual acuity of 20/20 in both eyes but negative stereopsis in the office.

FIGURE 4. BIN and visual acuity for patients with refractive error but no amblyopia: anisometropia (\( N = 12; \) represented by \( \square \); median BIN 100% 25th and 75th percentile are both 100%); hypermetropia (\( N = 4; \) represented by O; median BIN 90% 25th and 75th percentile are 76% and 100%); anisoastigmatism (\( N = 1; \) represented by \( \triangle \)), and astigmatism (\( N = 7; \) represented by X; median BIN 80% 25th and 75th percentile are 48% and 100%). The boxes represent the 95% CI for the BIN score (67%–100%) and visual acuity in the eye (\(-0.05\)–0.30 logMAR) of the control group. Of the two individuals with low BIN scores, one ("X" at 20% BIN) was a 9-year-old boy with astigmatism (+1.5–2.25 × 121 right eye, +1.75–2.50 × 43 left eye), good stereopsis, and corrected visual acuity of 20/20 in each eye. The other ("\( \square \)" at 0% BIN) was a 7-year-old girl child with anisometropia (right eye + 5.75 sphere, left eye + 0.25 sphere) and visual acuity of 20/25 in the right eye and 20/20 in the left eye and good stereopsis.
acuity improved with treatment, 12 showed no improvement in BIN. One child with intermittent strabismus who had equal visual acuity and improved stereopsis (from no measurable stereopsis to 70°) with treatment showed an improvement in BIN to 67%.

Receiver Operating Characteristic (ROC). An ROC curve (Fig. 5) was generated to judge the performance of the PVS if used to test strictly for the presence of “disease.” The “disease” group (diagnosis of amblyopia and/or constant and intermittent strabismus; groups no. 1–5 in Table 1) contained 130 patients. There were 72 controls in the “no disease” group (diagnosis of amblyopia and/or constant and intermittent strabismus; groups no. 6–10). With a cutoff of 60% BIN, both the sensitivity and specificity of the PVS were determined to be 96%. When assuming that the prevalence of amblyopia or strabismus in the general population equals 5%, the Positive Predictive Value was 56% and the Negative Predictive Value was 100%.

**DISCUSSION**

This study demonstrated that the PVS was able to identify subnormal binocularity to detect strabismus and amblyopia with sensitivity and specificity not found using any other test. The PVS detected anisometropic amblyopia even in the absence of measurable strabismus, yet it did not refer anisometropic patients with normal corrected visual acuity. BIN improved to normal levels in anisometropic amblyopia patients who improved with treatment, whereas it did not improve in patients who were unresponsive to treatment. Considering these findings together, we believe that all children with anisometropic amblyopia have a microstrabismus or fixation instability that is too small to be measured by the clinical gold standard, the prism-and-cover test, and that is impossible to measure using photorefractive methods, but that is detected by the PVS. Since essentially all patients with amblyopia will have reduced fixation accuracy, this means that the PVS should identify all patients with amblyopia (of any cause) or strabismus. Patients with refractive error that is not sufficient to cause vision loss will not be referred until or unless the refractive error has caused amblyopia to develop. Such precise detection of amblyopia and strabismus in the primary care setting will allow for early, accurate referral of children most in need of treatment, reduction in the number of unnecessary referrals, and prevention of vision loss.

Previous authors have debated whether a microstrabismus that eludes clinical detection is present in children with anisometropic amblyopia. Our findings are in accordance with those of Helveston and von Noorden, who described 20 amblyopic patients with a suppression scotoma whose nondominant eye did not fixate centrally when the dominant eye was covered. This microstrabismus or fixation instability is also consistent with the fixation behavior observed by Johnson and by Siepmann et al. using scanning laser ophthalmoscopy in amblyopic eyes. The improvement in BIN scores observed in our patients suggests that fixation improves with successful amblyopia treatment.

Thus far, the PVS has been tested in the ophthalmology office setting only, and many children were enrolled after treatment for amblyopia had already been initiated. In future studies, the PVS should be tested by lay screeners in a pediatric office setting. The present study included a population that was enriched for disease; however, patients with obvious strabismus (likely to be detected by parents or primary care doctors) were excluded. The positive and negative predictive values were inferred from population prevalence to give more realistic values than would be obtained from the enriched population.

**TABLE 3.** Sequential PVS Measurements for 21 Amblyopic Children

<table>
<thead>
<tr>
<th>Cause of Amblyopia</th>
<th>Anisometropia</th>
<th>Persistent Amblyopia</th>
<th>Strabismus</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>BIN Improved &gt;60%</td>
<td>Amblyopia Resolved</td>
<td>Amblyopia Persistent</td>
<td>Strabismus</td>
<td>Total</td>
</tr>
<tr>
<td>Yes</td>
<td>4</td>
<td>0</td>
<td>1*</td>
<td>5</td>
</tr>
<tr>
<td>No</td>
<td>0</td>
<td>4</td>
<td>12</td>
<td>16</td>
</tr>
<tr>
<td>Total</td>
<td>4</td>
<td>4</td>
<td>13</td>
<td>21</td>
</tr>
</tbody>
</table>

BIN > 60% was chosen as the cutoff point for pass/refer. Strabismus surgery was not performed in any of these patients.

* Intermittent strabismus and equal visual acuity.

**FIGURE 5.** Receiver operating characteristic (ROC) curve. The maximum area under the curve (AUC) is 0.96. With a cutoff of 60% BIN, both the sensitivity and specificity of the PVS are 96%. Assuming that the prevalence of amblyopia or strabismus in the general population equals 5%, the positive predictive value is 56%, and the negative predictive value is 100%.
Most studies of vision screening protocols have evaluated patients for the presence of “risk factors” for amblyopia, setting arbitrary thresholds to identify children who may or may not have had hyperopic refractive error sufficient to induce amblyopia. Arnold\(^{16}\) estimated that only 13% of patients who have risk factors for amblyopia actually develop the condition, meaning that even a perfect photorefractive vision screener will refer seven children who do not have amblyopia or strabismus for every affected child. With the PVS it is possible to set diagnostic criteria, specifically to identify any patient who has been clinically diagnosed with either amblyopia or strabismus. Using this diagnostic performance standard, the PVS will be able to refer patients in need of treatment with accuracy far exceeding that of any known device. Future studies should eliminate “risk factor” criteria and instead judge test performance using diagnostic criteria, scoring the ability of a device or protocol to detect children with clinically diagnosed amblyopia or with poorly controlled strabismus requiring treatment.

The study design may have underestimated the true sensitivity and specificity of the PVS. Patients with intermittent strabismus were considered to be affected regardless of the degree of control (since this was not reliably documented at the time of the examination). Thus, patients with well-controlled intermittent strabismus and no amblyopia and who received a “pass” recommendation were, by study design, scored as “false negative” even though they did not require intervention. Using the disease detection approach, children with moderate amounts of hyperopia who have not developed strabismus, children with anisometropia who have not developed anisometropic amblyopia, and children with intermittent strabismus who have not lost binocular vision or developed strabismic amblyopia will not be referred unless or until they develop amblyopia. For this reason, the ideal application of PVS will be in the context of a program of annual screening during pediatric office visits to detect amblyopia while it is still amenable to treatment.

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