Portable Pupillography of the Swinging Flashlight Test to Detect Afferent Pupillary Defects

Nicholas J. Volpe, MD,[1,2,3] Elizabeth S. Plotkin, MD,[1] Maureen G. Maguire, PhD,[1] Ravi Hariprasad, BS,[1] Steven L. Galetta, MD[1,2]

Objective: To investigate the ability of a portable, personal computer-driven, pupillometer to record the pupillary response curve during the swinging flashlight test. Also, to determine whether these response curves can be used to identify and quantify relative asymmetry in the pupillary light reflex between eyes in healthy volunteers with simulated afferent pupil defects (APDs) and patients with optic neuropathies.

Design: Comparative, observational case series and instrument validation.

Participants: Healthy volunteers with no known ocular disease and patients (n = 20) with various optic neuropathies noted to have relative APDs on examination.

Methods: Pupillary response curves of the right eye were recorded with a portable, electronic, infrared pupillometer from healthy volunteers (with and without simulated APDs) and patients with APDs while the light stimulus alternated between eyes, simulating the swinging flashlight test. Simulated APDs in healthy volunteers were created with increasingly dense neutral density filters in front of the left eye.

Main Outcome Measures: Differences in constriction amplitude, latency, and constriction velocity of the pupillary response with right eye stimulation versus left eye stimulation in both groups of subjects.

Results: A significant correlation between neutral density filter strength and intereye differences was seen for all measurement parameters in volunteers with simulated APDs. Depending on the measurement parameter and stimulus intensity, simulated APDs of 0.6 log units or more could be distinguished from normal responses. Clinically graded true APDs had intereye differences similar to simulated APDs of the same density. Those with real and simulated APDs of 0.9 log units or more could be distinguished from healthy volunteers with 80% sensitivity and 92% specificity. Responses from those with real and simulated small APDs of 0.3 to 0.6 log units could not be distinguished reliably.

Conclusions: Portable, personal-computer driven, electronic, infrared pupillography can record the swinging flashlight test accurately and identify large afferent pupillary defects. An affordable, portable, reliable device for identifying relative APDs would be useful in the identification and follow-up of patients with neurogenic vision loss. *Ophthalmology 2000;107:1913–1922 © 2000 by the American Academy of Ophthalmology.*

A relative afferent pupillary defect (APD), established by the swinging or alternating flashlight test, is an important clinical sign that, when abnormal, is one of the best ways to localize vision loss to the pregeniculate afferent visual pathways (retina, optic nerve, chiasm, and optic tract). Since its original description by Levitan,[1] the alternating light test has been studied extensively, both clinically[2–11] and with pupillography.[12–16] The pupillary reaction during the swinging flashlight test consists of an initial contraction followed by redilation followed by contraction when the other eye is illuminated. In the setting of a relative APD, differences in the amount and duration of contraction as the light is "swung" from side to side are the clinical observations that are considered.

Various techniques have been described to quantify or measure APDs. These include the use of neutral density filters,[10] crosspolarized filters,[17] and subjective grading based on the amount of initial contraction and subsequent redilation of each pupil as the light is swung.[2] Although these techniques have been shown to be effective and accurate, a number of factors influence the validity, variability, and reliability of such measurements. These techniques, although objective in their quantification, are unfortunately

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[1] Department of Ophthalmology, the Scheie Eye Institute, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania.

[2] Department Neurology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania.

[3] Department of Neurosensory Sciences, Albert Einstein Medical Center, Philadelphia, Pennsylvania.

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Correspondence to Nicholas J. Volpe, MD, Scheie Eye Institute, 51 North 39th Street, Philadelphia, PA 19104; E-mail: nickvolp@mail.med.upenn.edu.

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subjective in their endpoint. Human factors, including examiner bias, light position variability, and endpoint determination, can all influence the identification and appropriate quantification of APDs. Other factors, unique to any given individual, include dark irides, anisocoria or small pupils,[18] and efferent defects, all of which can make it much more difficult to detect small amounts of asymmetry in pupillary reactions. Kawasaki et al[13] noted the variability of pupillomotor output that any two consecutive pupillary reactions to the same light stimulus may produce and emphasized that this variability may lead an examiner to an incorrect conclusion.

Formal pupillography has led to a more detailed understanding and more careful quantification of the alternating light test for APDs. Lowenstein[19] and Lowenstein and Loewenfeld[20] introduced modern pupillography and described abnormalities of the recorded response in patients with optic nerve disorders. Thompson et al[12] used pupillography to confirm the advantage of swinging a light and looking for pupillary escape compared with simply holding the light in front of each eye and looking for redilation. Fison et al[14] created APDs using neutral density filters (1–4 log units) in healthy volunteers and were able to use pupillography (swinging light) to record statistically significant trends in the reduced amount of pupillary constriction as the filter density over one eye increased. They also used pupillography to quantify APDs in patients with optic nerve disease by eliminating differences in constriction amplitudes of the pupillary responses between the eyes using neutral density filters. Cox[16] described the pupillography of an APD in one patient and concluded that the most sensitive indicator of a relative APD is an initial pupillary constriction in the suspected eye that is smaller with direct than consensual stimulation. Cox[15] subsequently reported on pupillographic characteristics of simulated APDs and once again found that identifying constriction amplitudes that were greater with consensual responses than direct responses was the best method for APD detection. Cox did not attempt to define an absolute cutoff for the presence of an APD and did not report on how sensitive or specific his testing parameters were for distinguishing healthy individuals from those with simulated APDs of varying density. Cox[15] pointed out that the pupillographic study of APDs by Sugasawa et al[21], which demonstrated differences in constriction velocity and latency that varied linearly with the density of APDs, was less applicable because of the difficulty seeing these variables clinically without a pupillometer. Finally, Kawasaki et al[13] used pupillography with computer image analysis to study the variability of APDs. They found that with only a few stimulus pairs, their 95% confidence interval on the depth of the APD was more than 0.5 log units in healthy persons with simulated APDs. They needed to analyze 200 stimulus pairs to obtain the 95% confidence interval on the depth of the APD to 0.1 log unit. The pupillometers used in each of the experiments described above were infrared video pupillometers.

Pupillography has provided valuable information about and insight into the clinical swinging flashlight test. However, because of a lack of availability, technical limitations, and lack of portability and affordability, pupillography is not routinely performed during ophthalmic or neuro-ophthalmic examinations, nor is it available for screening patients for neurogenic vision loss. If capable of efficiently recording, detecting, and quantifying relative afferent pupillary defects, a portable pupillometer could be used to screen patients with vision loss. Also, such a device would provide ophthalmologists with a readily available and objective means of documenting and potentially quantifying the "swinging flashlight test" and the course of optic neuropathies.

Patients and Methods

Study Design

Thirteen healthy volunteers and 20 patients with clinically quantified APDs underwent pupillography with a portable electronic pupillometer. Pupillary response curves were recorded from the healthy volunteers with relative APDs simulated by placing neutral density filters in front of the left eye to dim the light. Filters of increasing density (0.3 log unit increments from 0.3–1.8) were used to create increasingly dense APDs in the healthy volunteers. Simulated APD patients were compared with patients with true APDs. Verbal informed consent was obtained from each person after the nature of the recording was explained. The study was reviewed and approved by the University of Pennsylvania's Institutional Review Board.

Patient Selection

The healthy volunteers were aged 20 to 45 years and had no known eye disease, normal vision and no anisocoria, and no APD on clinical examination. Patients with APDs represent a nonconsecutive series of patients with APDs on examination who underwent pupillography.

Clinical Grading of Afferent Pupillary Defects

Patients in the APD group all had APDs on clinical examination. In each patient, the density of the APD was graded by one of us (NJV) using neutral density filters as described by Thompson et al.[10] To perform this technique, increasingly dense photographic neutral density filters (0.3 log unit increments) were placed in front of the good eye until the amplitude of constriction appeared equal and pupillary early release or escape was abolished. Each of these clinical pupillary examinations was accomplished with only a "few swings" of the light to avoid dark adaptation of the normal eye resulting from reduced illumination secondary to the filter.

Pupillometer

Pupil responses to alternating light stimuli were measured with the Pupilscan II Type 9 Optical Unit (Fairville Medical Optics, Larkins Green, England; Fig 1). The unit weighs 550 grams and can either run completely self-contained or interface with operating software running from a personal computer. The optical unit is controlled by a circuit board that generates a real-time pupillary image that is displayed on a 256 × 256 pixel array. One eyepiece (adjustable interpupillary distance) has two pairs of infrared-emitting diodes of an 880-nm wavelength (automated intensity adjustment for pupillary pigmentation and ambient light). These diodes illuminate the pupil and project the image onto an electronic image sensor. Pupillary diameter is measured every 0.05 seconds.

Figure 1. Pupilscan pupillometer during testing. The instrument is lightweight and approximately the size of a flashlight. A real-time pupillary image is seen during testing on the liquid crystal diode (LCD) display as well as on the computer screen. The patient maintains distance fixation in a dimly lit room through the hole in one of the eyepieces (left eye in this photograph). The instrument simply can be flipped to record from the other eye if desired.

The stimulus light source is a pair of high-intensity green diodes of a 565-nm peak wavelength. These stimulating diodes are located in both eyepieces. The green diodes are mounted at an angle of 22°, and their centerlines converge at a point 2.5 cm from the plane in which they are mounted. This convergence is at the pupillary plane. Their overlapping projections flood the eye with light at the focal distance of the instrument corresponding to the pupillary plane. Recordings were made at two different stimulus intensities; the brighter was 23 milliwatts/cm^2 and the dimmer was 2 milliwatts/cm^2. The brighter stimulus intensity produced a pupillary response that was similar to the response produced by a hand-held light source during clinical examination. Only the brighter stimulus was used to test the patients with true APDs. Stimulus cycles were set for alternating eye stimulation of 200 milliseconds in duration every 1.2 seconds. This cycle time was used to keep the dark interval at 1 second, as suggested by Kawasaki et al.[13] During ophthalmologic examination and clinical grading of APDs, similar rapid light alteration was used with a short stimulus duration and dark interval.

Recording the Swinging Flashlight Test

Each healthy volunteer or patient was placed in a dimly lit examination room for approximately 3 to 5 minutes to dark adapt. The participant was then asked not to blink and to maintain distance fixation on a dimly lit fixation light through the open hole of the pupillometer that was placed each time in front of the right eye. The instrument can be rotated 180° to make recordings of the left eye pupillary diameter as well (Fig 1). The curves produced in this experiment represent right pupillary diameter versus time as the stimulus alternates from one eye to the other. If excessive blinking occurred during the test, it was repeated after a 1-minute pause. For simulated afferent pupillary defects, photographic neutral density filters that fit within the left eyepiece were used to dim the light. Recordings were made for simulated APDs increasing in increments by 0.3 log units from 0.3 to 1.8 log units (except for 1.5 log units). A 1- or 2-minute pause (in the dimly lit room) was taken between each successive recording. Approximately 90% of the curves could be obtained with a single stimulus run of 10 seconds without blink artifact.

Pupillary Response Curves

Raw data (pixels of diameter of the right pupil versus time) were then exported to and analyzed by a computer algorithm. Simultaneous curves representing the diameter versus time and its slope (constriction velocity) were plotted (Fig 2). For each response, the latency (time from light stimulation to initial contraction), constriction amplitude (difference between maximum and minimum diameter), and constriction velocity (rate of change of the diameter) were tabulated (Fig 2). Calculations were carried through using the pixel value because it is directly related to millimeters of pupillary diameter (19 pixels = 1 mm). For the six curves (0 filter, 0.3, 0.6, 0.9, 1.2, and 1.8 log unit filter) on each volunteer with a simulated APD (Fig 3) or the single response curves in patients with true APDs differences in the three measurement parameters were calculated to compare the results when the right pupil was stimulated versus when the left pupil was stimulated. The average value of each measurement parameter for the four right stimulations was compared with the average value of the four left stimulations.

Data Analysis

Data were analyzed using SAS statistical software (SAS Institute, Cary, North Carolina). The intereye responses of volunteers with no filter (without simulated APDs) were tested for a systematic change from a mean of zero by using a paired *t* test. Mean intereye differences among the various filter strengths used in testing volunteers compared with the mean intereye difference with no filter in place were evaluated also with a paired *t* test. Spearman's ρ was used as the correlation coefficient for assessing the association between intereye differences and filter strength in volunteers. Comparisons of intereye differences between those with simulated APDs and those with true APDs were made using independent *t* tests. Assessment of the mean intereye difference among volunteers with no filter and the two groups with APDs (simulated and true) categorized by the degree of APD were made using a one-way analysis of variance and Tukey's test for multiple comparisons. The best parameter for distinguishing volunteers from patients with APDs of 0.9 log units or more was identified through logistic regression, and the value of the parameter that maximized the sum of sensitivity and specificity was used to categorize patients.

Results

Clinical Recordings and Contraction Anisocoria

Pupillary response curves were easily generated in all volunteers and patients. No one found the test uncomfortable and every participant was able to complete the test. For patients with true APDs, a single recording with a short dark adaptation time took 2 or 3 minutes. Blink artifacts occasionally necessitated repeating the test. If only a single blink was present and pupil diameter went to zero, the pixel diameter was changed manually in the spreadsheet program so as to keep the curve smooth and avoid artifactiously high values for constriction amplitude and velocity.

The neutral density filters we used in this experiment prevented us from recording the pupil with the filter in front of it. Therefore, we introduced contraction anisocoria (direct pupillary response is larger than the consensual response).[13,15,22–25] This phenomenon, although usually underappreciated in clinical examinations and studies, is apparent in most pupillographic studies of APDs.[13,15] For constriction velocity and constriction amplitude, we did demonstrate asymmetry between direct and consensual responses (Figs

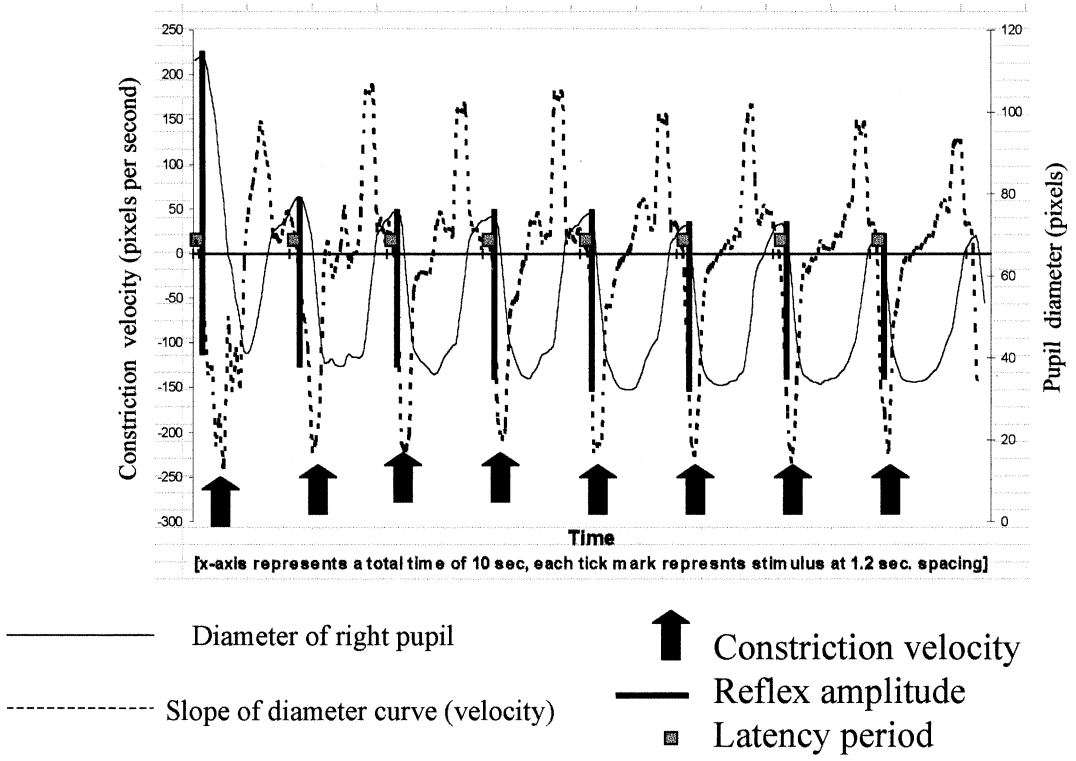

Figure 2. Measurement parameters characterizing a typical pupillary response curve. Values for pixels (diameter) of the right pupil at any given time are recorded as the light alternatively flashes from right eye to left eye (direct and consensual stimulation of the right eye). Diameter values are loaded into a spread sheet program that plots the curve against time along with a secondary curve of its slope (velocity). Latency is the time between stimulation and the first constriction. The constriction amplitude is the difference between the maximum and minimum diameters for each response. The constriction velocity is the maximum negative value for velocity.

4 and 5; "0 filter"). The difference illustrated was of the appropriate "sign" (consensual response less than direct) but was statistically significant only for the dimmer stimulus and the measurement parameter of constriction amplitude ($P < 0.01$). Furthermore, the statistically significant defects we demonstrated with the simulated APDs were always based on comparison with the unfiltered responses. Therefore, the contraction anisocoria was factored out because it was present in both recordings.

Simulated Afferent Pupillary Defects

Figures 4, 5, and 6 summarize our results for the three measurement parameters for our volunteers with simulated APDs. For constriction amplitude (Fig 4), a strong linear relationship between APD density and intereye differences was demonstrated for both the brighter ($r = 0.70$) and dimmer ($r = 0.78$) stimulus. Standard errors for the mean intereye difference in constriction amplitude for all filter densities in both stimulus groups was less than 2 pixels. For the dimmer stimulus, *P* values for the mean difference from the normal mean ranged from nonsignificant for the 0.3-log unit filter to 0.009 for the 0.6-log unit filter to 0.0001 for the 1.8-log unit filter. For the brighter stimulus, the mean difference was not significant for the 0.3-log unit filter, 0.08 for the 0.6-log unit filter, and less than 0.001 for all of the denser filters. The results for constriction velocity were very similar (Fig 5). Statistically significant differences from the unfiltered volunteers occurred with the 0.9-log unit filter at both stimulus intensities ($P < 0.05$). There was once again a strong correlation between the intereye differences and the strength of the filter for both the brighter ($r = 0.73$) and dimmer ($r = 0.73$) stimulus. The standard error range for each filter strength ranged from 4 to 10 pixels. The results for latency measurement were not quite as strong as for the two other measurements. The correlation coefficients were 0.66 for the brighter and 0.60 for the dimmer stimulus. Statistically significant differences from volunteers did not occur until 0.6-log unit APDs were simulated with the dimmer stimulus and not until 0.9-log unit defects were simulated using the brighter stimulus.

Patients with True Afferent Pupillary Defects versus Volunteers with Simulated Afferent Pupillary Defects

We compared the results for each measurement parameter in patients with true APDs with those of volunteers with simulated APDs to see if simulated APDs of varying densities were equal pupillographically to clinically graded APDs in patients with optic neuropathies. First, with the brighter stimulus there was once again a statistically significant correlation between intereye differences and the grade of the APD in patients with true APDs for all three measurement parameters. The correlation was best for constriction velocity (correlation coefficients = 0.66). Second, when we compared the magnitude of intereye differences of our volunteers with simulated APDs with those with the same grade of true APD with the brighter stimulus, we found only small, statistically insignificant mean differences in any of the measurement parameters. Figure 7 illustrates such a comparison with simulated and true APDs of 1.8 and 0.3 log units. The curves show large intereye differences in constriction velocity whether it is a true or simulated

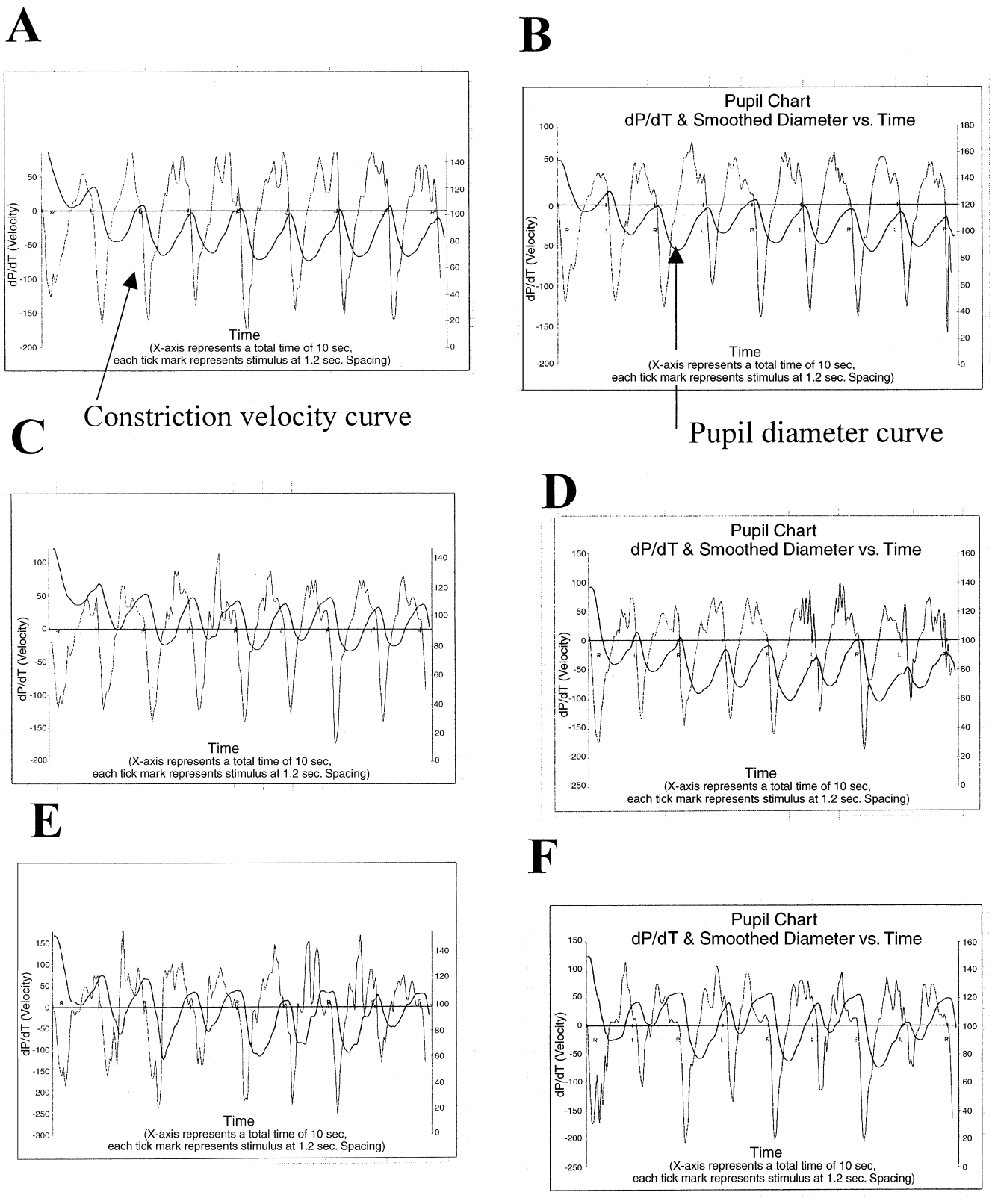

Figure 3. Data series for one volunteer with a simulated APD using a neutral density filter of the left eye. Recordings are of the right eye, and the right eye is the first to be stimulated in each set. "A" is the normal response without any filter, "B" uses a 0.3-log unit filter in the left eye, "C" uses a 0.6-log unit filter in the left eye, "D" uses a 0.9-log unit filter in the left eye, "E" uses a 1.2-log unit filter in the left eye, and "F" uses a 1.8-log unit filter in the left eye. A diameter and velocity curve are seen for each filter density. Increasing intereye differences for each stimulus pair in the diameter and velocity curves (right eye versus left eye stimulation of the right eye) are seen.

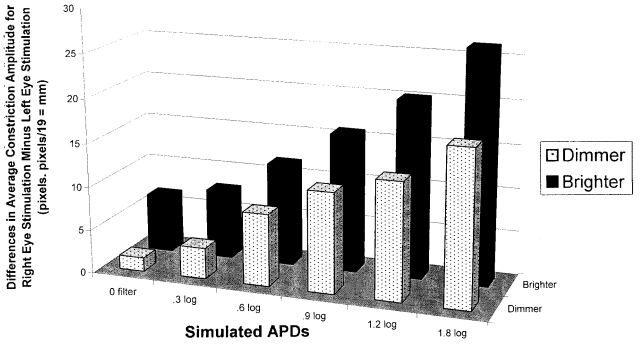

Figure 4. Constriction amplitude difference for simulated afferent pupillary defects. Each diameter difference value represents the average of four right-eye stimulations minus the four left-eye stimulation values in 10 participants. Results for both the dim and bright lights are seen. In both cases, a highly statistically significant correlation between filter density and difference between right and left eye is seen. The difference seen in healthy volunteers without filters likely represents contraction anisocoria (see text).

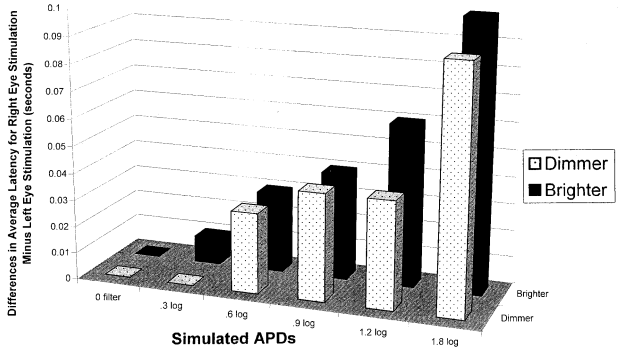

Figure 6. Latency differences for simulated afferent pupillary defects. Each latency difference value represents the average of four right-eye stimulations minus the four left-eye stimulation values in 10 participants. Results for both the dim and bright lights are seen. In both cases, a statistically significant correlation between filter density and difference between right and left eyes is seen at the 0.6-log unit filter and more (not for 0.3-log unit filter).

1.8-log unit APD (Fig 7A, C). The differences are much smaller in the simulated and true APDs of only 0.3 log units (Fig 7B, D). Figure 7C, D is of the same patient and demonstrates the partial recovery of the pupillary response in the right eye in a patient with optic neuritis (spontaneous recovery after 3 weeks).

Patients with True Afferent Pupillary Defects versus Healthy Volunteers

Our ultimate goal was to see if this pupillometer and testing setup could predictably distinguish healthy volunteers from those with true APDs. Therefore, we compared the three pupil parameters (brighter stimulus) among patients with true APDs of 0.9 log units or more, patients with true APDs of 0.3 to 0.6 log units, and healthy volunteers tested with no filter. We detected statistically significant differences (Tukey's test for multiple comparisons) for intereye differences in all three measurement parameters between volunteers and those with true and simulated APDs of 0.9 log units or more. As well, the intereye differences of these denser APDs were statistically significantly different from patients with APDs of 0.3 and 0.6 log units. Using the constriction velocity parameter, we calculated an 80% sensitivity and 92% specificity for distinguishing volunteers from those with simulated and true APDs of 0.9 log units or more. However, because of significant overlap between the groups, we were unable to demonstrate a statistically significant difference between the group of volunteers and the group of patients with true APDs of 0.3 log units, 0.6 log units, or both (Fig 8). Our calculated sensitivity and specificity for distinguishing volunteers from those with true APDs of any density using constriction velocity was 69% and 84%, respectively.

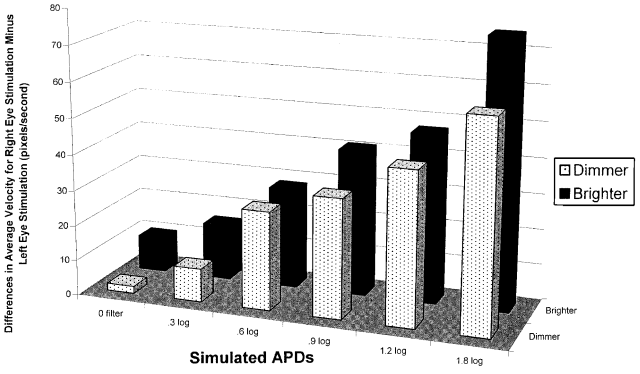

Figure 5. Constriction velocity differences for simulated afferent pupillary defects. Each velocity difference value represents the average of four right-eye stimulations minus the four left-eye stimulation values in 10 participants. Results for both the dim and bright lights are seen. In both cases, a highly statistically significant correlation between filter density and the difference between right and left eye is seen.

Stimulus Intensity

Overall, except for some minor differences (brighter stimulus showed best correlation between intereye differences and APD density with constriction velocity and dimmer stimulus with constriction amplitude), both stimulus intensities yielded similar results in our volunteers with simulated APDs.

Discussion

Pupillography has been used to characterize further the features of the swinging flashlight test, but it has not become a tool that is used in ophthalmic practice to identify or observe patients with neurogenic vision loss. This is true even though the pupillary examination is a critical part of the eye examination that can be used to identify patients with more serious causes of vision loss. The limitations of pupillography largely have been its expense, technical demands, lack of portability, and lack of familiarity to most ophthalmologists and neuro-ophthalmologists. There are, however, other examples in ophthalmology where technological advances such as automated perimeters have had significant impact on clinical practice and are now part of routine patient care. With this pupillometer, infrared electronic image sensors replace the video units that create the pupillary image that are in most other pupillometers.

In these experiments with a relatively inexpensive, portable pupillometer, we were able to record and quantify the swinging flashlight test. We demonstrated increasing intereye differences in latency, constriction amplitude, and constriction velocity of the pupillary response as simulated

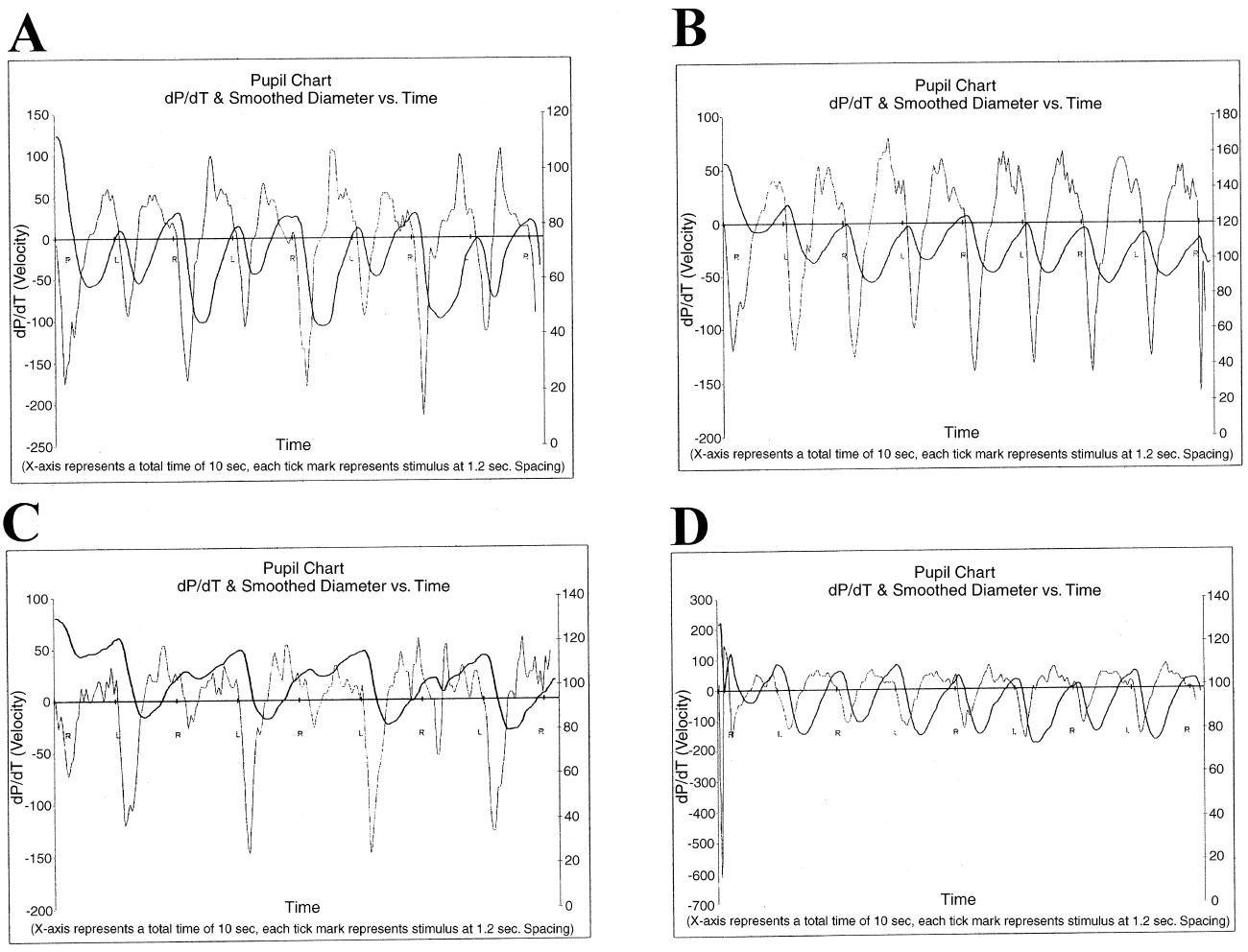

Figure 7. Pupillary response curves of simulated and real afferent pupillary defects (APDs). **A,** pupillary response curve of a healthy volunteer with a 1.8-log unit filter in front of the left eye. Each left eye stimulation results in a smaller constriction amplitude and velocity compared with the preceding right stimulus. **B,** pupillary response curves of a healthy volunteer with a 0.3-log unit filter in front of the left eye. Differences between left eye and right eyes are less apparent but present. **C,** patient with optic neuritis in the right eye and a clinically graded 1.8-log unit true APD. The magnitude of intereye differences in constriction amplitude and velocity are similar to those of the simulated 1.8-log unit APD (**A**). **D,** the same patient as in (**C**) but 3 weeks later with symptomatic recovery. Clinical examination at the time found an APD of 0.3 log units in the right eye. Pupillary responses with right and left eye stimulation are similar, but subtle differences in amplitude and velocity persist. The magnitude of intereye differences is similar to those for the simulated 0.3-log unit APD in the left eye seen in (**B**).

APDs created with neutral density filters increased. Each recording takes only 10 seconds and is easily obtained. In our patients with optic neuropathies and clinically apparent APDs, we were able to detect similar intereye differences in the measurement parameters compared with the intereye differences in healthy volunteers with simulated APDs of similar density. As a group, patients with APDs of more than 0.9 log units were statistically different from volunteers in all three measurements parameters. We were unable to identify a variable that could be used to establish reliably a value that would distinguish volunteers without APDs from patients with APDs. We found that our volunteers with simulated APDs were similar to patients with APDs resulting from optic neuropathies. The magnitude of intereye differences with different levels of APDs for each parameter was the same regardless of whether it was a simulated APD or a true APD.

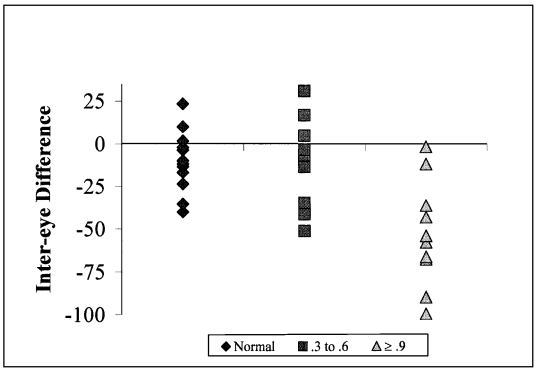

Figure 8. Scatter diagram showing the values for intereye differences in constriction velocity in healthy volunteers, patients with 0.3- to 0.6-log unit true APDs, and patients with 0.9-log unit and more true APDs. Overlap among the three groups (particularly between the volunteers and the low-grade APDs) makes absolute distinction of the two groups difficult and limits sensitivity and specificity.

In volunteers with simulated APDs, we found a strong and statistically significant correlation between the intereye differences and the filter density for all three measurement parameters (constriction amplitude, constriction velocity, and latency). The correlation was strongest for constriction amplitude and constriction velocity. Latency was less strongly correlated (although still statistically significant) with filter density. Sugasawa et al[21] found latency and constriction velocity to be the most highly correlated to filter density. Cox[15] chose not to evaluate constriction velocities because this parameter is not easily observed during clinical examination without a pupillometer. Cox[15] found that the amplitude of the initial constriction was the best indicator of an afferent pupil defect and suggested it be used as the comparison value clinically. In his patients with 0.6-log unit APDs, contraction amplitudes differed from healthy persons by approximately 0.5 mm of contraction, which is a relatively small intereye difference to count on observing during clinical testing without a pupillometer. Because our goal was not to refine the clinical swinging flashlight test further but to explore the suitability of portable pupillography to be part of routine examination, we chose to look at all three values in hope of increasing the instrument's sensitivity and specificity. We chose not to look at the loss of the initial pupillary constriction ("pupillary escape") or minimum pupil diameter because these parameters have already been shown to be insensitive for detecting APDs.[15] In our participants with true and simulated APDs, constriction amplitude and constriction velocity were equally effective in identifying those with APDs.

The variability of the swinging flashlight test is often underappreciated clinically and underemphasized when the test is being taught. The detailed experiment of Kawasaki et al[13] sheds light on the variability that is present in the pupillary light reflex, a biologic fact that ultimately may limit the ability of pupillography to identify or exclude absolutely APDs in a short (few seconds) test. In their experiment, they recorded pupillary responses from 10 healthy persons with simulated APDs. Similar to our experiment, they compared constriction amplitudes of paired responses and varied the stimulus intensity and duration. They recommend a shorter dark interval for testing (swing quickly to the other eye) and found short and long duration light stimuli to provide equally reproducible APD measurements. Their results showed significant variability, and in their experiment, approximately 200 stimulus pairs with recording durations of 4 to 10 minutes were required to attain a 95% confidence interval of $\pm$ 0.1-log unit APD. With only a few stimulus pairs, their 95% confidence intervals increased to $\pm$ 0.5 log units. These conditions, although demonstrating the superiority of pupillography over the clinical swinging flashlight test, could never be used clinically because we do not have the ability to summate mentally in our minds more than a few cycles. They then went on to show that many patients without symptoms, known disease, or visual field defects could have up to a 0.3-log unit APD and that this difference should not be considered clinically significant.[26]

Similarly in our experiment, a single recording (four stimulus pairs, $<$10-second test) can reliably distinguish normal from highly abnormal pupils (0.9 log units). For patients with clinically graded true APDs of 0.9 log units or more, our sensitivity and specificity for distinguishing these patients from our volunteers (using constriction velocity) was 80% and 92%, respectively. However, patients with true APDs of 0.3 to 0.6 log units could not be distinguished reliably from patients without APDs. Given this "variability" identified with pupillography by Kawasaki's experiments and clinically when the swinging flashlight test ends up as "possible APD" or "questionable subtle APD" when deficits are in the 0.3- to 0.6-log unit range, it is not surprising that we could not distinguish low-grade APDs from normal pupillary responses. Also, the presence of low-grade APDs in volunteers[26] may have limited our ability to attain higher sensitivity and specificity for distinction between volunteers and patients that included those low-density APDs. Because we were able to obtain a high correlation between intereye differences and filter density, it seems that this pupillometer is able to accurately record the 10-second swinging flashlight test. Because of biologic variability, we may ultimately be limited in our ability to analyze these curves and identify patients with low-grade APDs.

Our results may have been limited also by bias introduced by contraction anisocoria (direct response better than consensual response). The experiment design favored detection of differences based on contraction anisocoria because the filters were placed on the consensually stimulating eye. Because we compared simulated APDs with the "0" filter results of volunteers, the contraction anisocoria should be present in both responses and therefore would not affect the difference between the two responses. However, contraction anisocoria likely did affect our comparisons of volunteers with simulated APDs with patients with true APDs. Because all recordings were made from the right eye and there was a nearly equal mixture of right- and left-eye APDs in our patients with true APDs (nine in the right eye and 11 in the left eye) and all the simulated APDs in volunteers were in the left eye, we may have overestimated our APDs in the left eyes of patients with true APDs and underestimated them in right eyes of patients with true APDs because the contraction anisocoria favored a lesser response when the left eye was stimulated (consensual stimulation of the recorded right eye). Despite this, we were able to show no significant differences between our clinically graded APDs in patients with true APDs compared with our volunteers with simulated APDs.

Our experiment may have been affected also by retinal dark adaptation in the volunteers with simulated APDs. The neutral density filter in front of the left eye (because of retinal dark adaptation) leads to a larger preconstriction diameter and resulting constriction amplitude for the right eye stimulation and in a smaller preconstriction diameter and constriction amplitude for the left eye stimulation. Cox[15] and Sun et al[27] also found that as filter density increased, the nonfiltered eye had increased response, whereas the filtered eye had a diminished response. Lastly, with 13 volunteers and 20 patients with true APDs, our statistical power to detect some differences was limited.

Clinically, there is controversy concerning the optimal

intensity of light used during the swinging flashlight test. In our volunteers with simulated APDs, we found that constriction amplitude and constriction velocity were each strongly correlated with filter density for both stimulus intensities. All of our volunteers were fairly young with large, briskly reactive pupils, and perhaps our dimmer stimulus was already suprathreshold. In other circumstances, such as with patients with optic neuropathies or patients with smaller or less reactive pupils, different stimulus intensities may reveal different results.

Further modifications of this pupillometer may include simultaneous recording of both pupils, with average diameter used for each stimulus comparison.[13] This would correct for the effect of contraction anisocoria and hopefully improve on the instrument's sensitivity and specificity for distinguishing healthy volunteers from patients with true APDs. Ultimately, the level assigned to an APD at the clinical examination may prove to be less accurate or exact then pupillography. Therefore, conclusions on the ability of a pupillometer to distinguish healthy volunteers from patients with true APDs may be dependent on a different definition of a patient with a true APD, that is, an APD on examination would be only one of several criteria used to identify patients with neurogenic vision loss.

Portable pupillography is able to record the swinging flashlight test. Practically, however, various biologic variables may ultimately limit the true threshold of this clinical test (whether performed with a hand-held flashlight or pupillometer) to identify accurately and predictably all patients with subtle unilateral neurogenic vision loss. However, portable electronic pupillography does demonstrate significant intereye differences in patients with denser APDs and easily provides a record of the swinging flashlight test.

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