Comparison of Pupil Perimetry and Visual Perimetry in Normal Eyes: Decibel Sensitivity and Variability

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PURPOSE. To compare the sensitivity and variability of pupil perimetry with visual perimetry at the same retinal locations in normal subjects.

METHODS. Pupil perimetry was performed on the right and left eyes of 10 normal subjects using a computerized infrared pupillometer equipped to present perimetric light stimuli and record pupil light reflexes. Eleven locations were tested at different intensities along the horizontal meridian of each eye, and the decibel sensitivity of the pupil light reflex was compared with the visual threshold at the same location.

RESULTS. The shape and height of the hill of vision (retinal sensitivity) was very similar between the right and left eyes of each individual using either pupil perimetry ($R^2 = 0.69$) or standard threshold perimetry ($R^2 = 0.62$) but was less similar between subjects. Comparisons between pupil and visual sensitivity revealed a lack of correlation at the same retinal location in normal eyes ($R^2 = 0.19$).

CONCLUSIONS. The high intereye correlation for either pupil or visual sensitivity may provide an important tool for detecting focal or asymmetric visual field damage. Although the basic shape of the sensitivity profile of pupil and visual responses was similar under the conditions of testing, the two did not correlate well within each eye among the normal subjects. This highlights that similarities do exist in the sensitivity profile of the two pathways, but they do not seem to vary in the same proportion between normal individuals. (Invest Ophthalmol Vis Sci. 2001;42:957–965)

Although standard visual field perimetry has become the accepted clinical tool for evaluating the effect of disease on visual field threshold, inherent limitations exist in the method. These include subjectivity of the patient’s response, learning effect, inability of some patients to maintain central fixation during the thresholding task, and higher variability of the threshold determination in more peripheral locations and in damaged locations of the visual field. In an effort to circumvent these limitations and to supplement the presently available perimetric information, we have developed a method of “pupil perimetry.” Other investigators have also reported the use of the pupil light reflex to obtain visual field information.

In pupil perimetry, an objective neuronal reflex, the pupil light reflex, is quantified using a computerized infrared pupillometer coupled to an automated perimeter. In visual field locations with reduced sensitivity, the pupil contracts less to a standard light stimulus, whereas locations with normal sensitivity elicit a larger pupil contraction in comparison. This method of perimetry has the advantage of being objective, requires little patient effort and attention, and may reflect damage at an earlier stage of disease. In addition, it can also be used to evaluate and quantify perimetric sensitivity at both threshold and suprathreshold levels of light stimuli by taking advantage of the graded pupil response to increasing intensities of light stimuli. This last advantage may be important in understanding how eye disease affects the visual system over a range of light intensities and not just at threshold levels of perception, where almost all current testing is assessed. Preliminary results in our laboratory have indicated that optic nerve damage may cause greater deficits in pupillary response to brighter light stimuli than dimmer light stimuli.

The purpose of this investigation is to derive the pupil sensitivity in units of decibel sensitivity at locations along the horizontal meridian of the visual field in normal subjects and to compare these values with the visual threshold (also in units of decibel sensitivity) obtained at the same locations. This strategy allows a direct comparison between the pupil and visual sensitivity profiles of the hill of vision. In addition, we also wanted to determine how the pupil and visual sensitivity profiles vary between the right and left eyes of the same subject and between normal individuals. This information is important to understand what may constitute an abnormal pupil sensitivity profile in patients with focal or asymmetric damage to the visual pathway.

METHODS

The study was conducted according to the tenets of the Declaration of Helsinki. Ten normal volunteers, three men and seven women, who were between 28 and 44 years of age (mean, 36 years) were included for this study and examined in our clinic. Normal subjects tested by pupil perimetry were not receiving any medications known to influence the pupil light reflex. All the normal subjects had visual acuity of at least 20/20 in each eye, normal stereo vision, normal slit-lamp and fundus examination, and normal Humphrey 24-2 SITA standard perimetry satisfying normal machine criteria for reliability.

Pupillometer

A new computerized binocular infrared video pupillometer (Tom Cornsweet, Visual Pathways, Inc., Prescott, AZ) was used to record pupil responses over a range of stimulus light intensities (Fig. 1). The infrared pupillometer consisted of a monochrome VGA monitor with viewing optics used to present light stimuli to the subject, two identical systems for pupil tracking, one for each eye, and two CCD cameras for recording the pupil response of each eye simultaneously. Stimuli were generated on the monochrome VGA monitor located inside the machine. There was a converging lens system with polarizing filters between each eye and the internal VGA monitor, so that the left eye sees only the left side of the monitor and the right eye only the...
right side. The internal monitor can be driven in the Z-axis with a stepper motor toward or away from the patient to change its optical distance from the eyes over a range of about ±7.00 diopters of refractive error, so that the plane of the stimulus is at optical infinity for the patient. The infrared pupillometer portion of the instrument used the bright pupil images in conjunction with two Philips CCD video cameras (type VC6250ST) to record pupil responses 60 times/sec with a m-resolution of pupil diameter from an infrared video image of the pupil. The video output of each camera was processed in a circuit board that measured the horizontal diameter of the pupil every 1/60th of a second.

**Perimetric Stimulus**

A mesopic background of 3.15 apostilbs was used for this study. Previous studies in our laboratory have shown that a higher mesopic background of 31.5 apostilbs (like that used in standard Humphrey perimetry) causes the pupil to become too small in some individuals, limiting its response range of movement. We stimulated at a centrally located fixation point and 10 other locations that were located 5° above the horizontal meridian and separated by 6° (see inset in Fig. 3B). Unlike standard threshold perimetry, which uses a test target size of 0.4° in diameter (Goldmann target III), a larger 4° target was used in this pupil perimeter study. We have recently found that stimuli of smaller size (e.g., 1.7° or Goldmann size V) sometimes fail to elicit a large enough pupil response (e.g., >0.3 mm of contraction) in the nasal visual field in normal subjects. Therefore, the larger 4° stimulus was used to ensure that we could obtain adequate pupillary responses over the range of stimulus intensities used in this study. Stimulus duration was kept at 0.2 seconds (similar to standard threshold perimetry), and a stimulus interval of 2.5 seconds was used. The units of stimulus intensities were calculated as equivalent to the units used in Humphrey automated perimeters so that the visual sensitivity results from patients tested on the perimeter could be compared directly. Because the Humphrey perimeter uses a neutral density filter wheel interposed in the light path to attenuate the light stimulus, a higher value of decibel attenuation is equivalent to a dimmer light. The following stimulus light intensities were used (given in units of decibels of attenuation above background; e.g., 0 dB attenuation = 10,000 apostilbs or 5183 cd/m² above background): 37 dB (0.64 cd/m²), 30 dB (3.18 cd/m²), 25 dB (10.07 cd/m²), 21 dB (25.28 cd/m²), 17 dB (63.51 cd/m²), and 13 dB (159.53 cd/m²). Subjects were asked to fixate on a crosshatched fixation target in the eye being tested (2° in diameter) during the test. A background adaptation of 30 seconds was given before the test. We stimulated perimetric locations in the nasal and temporal fields alternately for one eye at a time. Testing time for 11 locations at six different intensities was 2.42 minutes. Subjects were tested by this strategy with three repetitions for each eye, and the right eye was tested first. We averaged the three repetitions of pupil response for the analysis of this study.

**Analysis of Pupil Responses**

Details of the method that we are currently using to analyze pupil responses have been published elsewhere. We developed an automated software program that analyzes all pupil movements to obtain the contraction amplitude, maximum velocity, maximum acceleration, and latency time of each pupil light reflex (Fig. 2). On the basis of quantitative studies of the dynamics of random pupil movements that occur without a light stimulus, we also established a software routine to help differentiate a small pupil response that was likely due to a light stimulus from a small random movement that was noise. From previous analyses of pupil movements in response to small, focal light stimuli, we found that when the start of a pupil contraction (time at which the maximum acceleration occurred) fell within a finite time window (200–450 ms after the onset of a 0.2-second duration stimulus) the contraction was a candidate for a true pupil light reflex. In addition, if either the maximum contraction velocity or maximum acceleration exceeded 0.1 mm/sec or 0.1 mm/sec², the pupil contraction was considered a pupil light reflex. If the pupil movement that occurred during the specified time window did not equal or exceed the dynamic constraints imposed, then the pupil response was considered a ‘no response’ with a contraction amplitude of zero. Using this method in conjunction with the Naka-Rushton curve-fitting technique, described below, resulted in the pupil response approaching zero at intensities well below absolute threshold.
The pupil threshold was determined from “stimulus–response curves” characterizing the pupil contraction amplitude (average of right and left pupil contraction for each stimulus) over a 24-decibel range of stimulus intensities (Fig. 3). A sigmoid curve was fit to the data using a Naka-Rushton equation fit that solves for three parameters ($R_{\text{max}}$, $n$, and log$k$), which define the shape of the function. $^{25–27}$The iterative curve fit that maximizes the correlation coefficient, $R^2$, was performed in Microsoft Excel (Microsoft Corp., Redmond, WA) using the Solver function. The Naka-Rushton equation was as follows:

$$y = \frac{R_{\text{max}} \times 10^{nx}}{10^{nx} + 10^{\log k}}$$

where

- $y$ = millimeters of pupil contraction,
- $x$ = stimulus intensity in log units attenuation of light,
- $R_{\text{max}}$ = maximum pupil contraction (this parameter is solved for by the equation),
- $n$ = slope of function (this parameter is solved for by the equation), and
- $\log k$ = intensity at which $\frac{1}{2} R_{\text{max}}$ is reached (parameter solved by equation).

Using the curve fit for each location, the decibel sensitivity was calculated for arbitrarily defined response criteria levels of 0.1, 0.3, 0.5, and 0.7 mm of contraction of the pupil. For example, at a criterion level of 0.7 mm, the decibel attenuation ($x$-axis on graph in Fig. 3) was calculated that would give a 0.7-mm pupil contraction based on the curve fit. This in effect, represented the decibel sensitivity of the pupil light reflex needed to elicit a criterion response of 0.7 mm. Decibel sensitivities calculated for lower criterion levels such as 0.1 mm were closer to visual threshold sensitivity. This strategy was used to provide a method by which the pupil response would be expressed in units of decibel sensitivity so that it could be compared with similar units of visual threshold sensitivity at the same location. Visual threshold was determined at the same perimetric locations with standard sized stimuli (0.4° diameter, Goldmann size III) using a Humphrey automated perimeter (24-2 program, SITA test strategy, 31.5 apostilb background). In two subjects, a customized Humphrey perimeter was used to determine visual threshold using a 4° diameter stimulus on a 3.15 apostilb background, similar to that used for pupil perimetry.

**RESULTS**

The stimulus–response curves were fit for each location tested by pupil perimetry and showed an excellent fit to the Naka-Rushton equation (Fig. 3). In the one example shown, 17 stimulus intensities were used to verify that the Naka-Rushton curve fit did reflect the true shape of the stimulus–response function for the pupil light reflex (Fig. 3A). In general, more peripheral locations that were less sensitive resulted in a shift of the stimulus–response function to the right (Fig. 3B). The mean value of the correlation coefficient, $R^2$, which is a measure of the goodness of fit was $0.94 \pm 0.05$ (11 perimetric locations × 2 eyes × 10 subjects = 220 curve fits). The profile of decibel sensitivity along the horizontal meridian is shown for the right and left eye of each of the 10 normal subjects in Figure 4. In this figure it is apparent that the sensitivity peaks at the foveal location and decreases toward the periphery. The shape of the profile varied among the 10 subjects, particularly in terms of the foveal peak. However, the shape of the profile was quite similar between the right and left eyes of the same subject. This was also true for the profile plots of visual threshold for the same subjects (Fig. 5). A small decrease in sensitivity at the peripapillary area (15° temporally and 3° superiorly) was observed with visual threshold (0.4° diameter stimulus, 31.5 apostilb background) but not with pupil threshold (4° diameter stimulus, 3.15 apostilb background).

Comparisons between the right and left eyes for visual threshold and pupil sensitivity are shown in the scatter plots in Figure 6. The effect of different criterion levels (0.1, 0.3, 0.5, 0.7 mm contraction) on the right and left eye comparisons for pupil sensitivity is also shown. It was apparent that the inter-eye correlations were much higher when criterion levels > 0.1 mm were used. When higher criterion levels were used, the correlation coefficient ($r^2$) was similar for pupil sensitivity and visual threshold ($r^2 \sim 0.6$). With higher criterion levels, the decibel pupil sensitivity also decreased, because a brighter light (less attenuated) was needed to produce a greater level of pupil contraction. This caused a greater difference in absolute threshold between the pupil and visual sensitivity at the higher criterion levels of pupil contraction. This was seen as an increase in separation between the visual threshold data points (open triangles) and the pupil threshold data points (closed circles) in the scatter plots in Figure 6.

The effect of criterion level on the shape of the horizontal profile of pupil sensitivity is shown in Figure 7, which repre-
sents the average threshold for all 10 subjects. For higher criterion levels, the profile is shifted downward, and the foveal sensitivity peak became flatter and less conspicuous. It can also be noticed that the SD between subjects at each location was much higher using the lower criterion levels. A similar plot of visual threshold across the horizontal meridian is shown in Figure 8 for the same subjects using either the standard stimulus size (0.4° diameter on a 31.5 apostilb background) or the same conditions as pupil perimetry (4° diameter spot size on a 3.15 apostilb background). The profile shape for visual threshold was very similar to that shown for pupil sensitivity when standard clinical testing conditions were used, but the profile shape flattened considerably at the foveal location and differed from the pupil sensitivity profile when a lower mesopic background and larger stimulus was used, like that used for pupil perimetry. The SD among the right eyes of the 10 subjects was much less for visual threshold than for pupil perimetry (2 SDs ~3 decibels for visual threshold versus 6 decibels for pupil perimetry).

Comparisons between the visual sensitivity (standard clinical testing conditions) and pupil sensitivities at the same locations for all normal subjects showed very little correlation, regardless of the criterion level used for pupil threshold (Table 1), even though the overall profile shape was similar.

**DISCUSSION**

In this study, we were able to define the stimulus–response function of the pupil light reflex at each perimetric location to derive the threshold sensitivity at different response criteria of pupil contraction. This approach enabled us to quantify the
Figure 4. These graphs depict the "hill" of pupil threshold sensitivity across the horizontal meridian in 10 normal subjects (each subject is a different graph). Solid line: left eye pupil sensitivity profiles; broken line: right eye pupil sensitivity profiles; x-axis (+ degrees, temporal field; − degrees, nasal field): horizontal location in degrees; y-axis: the decibel sensitivity for a criterion level of 0.5-mm contraction for all subjects; a higher decibel (dB) sensitivity on the y-axis represents a more sensitive location. Note the variability in shape of the island among the 10 subjects (particularly in the height of the foveal peak), but the similarity in shape of the island between the two eyes of each subject. Pupil testing was performed with stimulus size of 4° in diameter and background = 3.1 apostilbs.
Figure 5. These graphs of visual threshold are for the same normal subjects in the same order shown in the graphs of pupil threshold in Figure 4. Note that the shape of the hill of vision for visual threshold is more similar between the 10 subjects compared with their pupil threshold. As with pupil threshold, there is a high correlation between the sensitivity profiles between the right and left eyes. Visual threshold was determined under standard clinical testing conditions (0.4° stimulus size, background = 31.5 apostilbs).
pupil light reflex sensitivity of the retina in decibel units, the same measurement unit used in clinical practice to quantify visual sensitivity. Expressing the pupil light reflex sensitivity in decibel units has the advantage of allowing a direct comparison with visual sensitivity and its variability in normal and diseased states. Although the variability in pupil sensitivity between individuals was greater than for visual sensitivity, the two methods revealed almost the same high correlation between the right and left eyes when comparing matching locations. As will be discussed later, this result may provide a powerful means for detecting focal damage, when it is asymmetric between the two eyes, either by visual or pupil perimetry. To our knowledge, this intereye analysis strategy has not been previously reported, and it may be a useful means of assessing the sensitivity and specificity of pupil and visual perimetry in different forms of unilateral or asymmetric optic neuropathy, compared with normal subjects.

Compared with visual perimetry, pupil perimetry has the added appeal of being an objective reflex, allowing the results to be scrutinized without having to rely on a patient’s judgment, which can sometimes be unreliable. The objectivity of pupil perimetry may provide a means of validating the results of visual perimetry in cases where the results are questionable. In addition, central fixation during pupil perimetry appeared to be less of a problem during the test because the patient is not required to make judgments (and hence, they do not have a tendency to look toward peripheral stimuli). In patients with large central scotomas, the fixation target size can be easily increased or the other eye can be used for fixation with our binocular instrument. Eye position monitoring during the test is also possible with the current instrument and will be used in the future to determine actual stimulus location on the retina.

**FIGURE 6.** Correlation between right and left eyes for pupil sensitivity at different criterion levels of pupil contraction (0.1, A; 0.3, B; 0.5, C, and 0.7-mm, D). Visual threshold in each graph for the 10 normal subjects. Each symbol represents the threshold for the same location in the right and left eye for the same subject. The linear correlation ($r^2$ value) between pupil threshold of the right and left eyes at the same perimetric locations was much higher when criterion levels $>$0.1-mm pupil contraction were used. Also, with higher criterion levels there was a greater difference in threshold level between the pupil and visual sensitivity (e.g., more separation between solid dots and open triangles in D).

**FIGURE 7.** Average profile of pupil threshold ± two SDs (between subject variability) across the horizontal meridian for the right eyes of 10 normal subjects. The tested locations, in degrees from the fovea (+ degrees, temporal field; − degrees, nasal field), are shown along the x-axis. Each line profile represents the pupil threshold based on increasing criteria (0.1, 0.3, 0.5, and 0.7 mm of pupil contraction). At higher criterion levels, it takes a brighter light (decibel sensitivity is a lower number) to reach that criterion response, shifting the profile downward. The shape of the profile remains similar except for the foveal peak, which becomes more blunted at higher criterion levels. The SD between subjects at each location was much higher using the lower criterion levels but appears to remain constant across the different locations.
during the test, should a small shift in fixation occur during the stimulus presentation.

In this study, we chose arbitrary criterion levels of pupil contraction to calculate decibel sensitivity based on intensity-response functions. The pupil light reflex is a graded response that increases in proportion to stimulus light intensity. Characterization of how pupil contraction increases with increasing light intensity may be an indirect measure of how neuronal firing rates change with increasing stimulus light intensity. In this sense, pupil contraction amplitude may serve as an objective indicator of the behavior of retinal neurons to incremental changes in light intensity over a 2 to 3 log unit range. The quantification of pupil sensitivity at increasing criterion levels of pupil contraction provides a means to study the decibel sensitivity near threshold levels (lower criterion levels) and at increasing suprathreshold levels (higher criterion levels). This method will enable us to determine whether the effect of disease on retinal sensitivity is more pronounced at higher stimulus levels (low versus high neuronal firing rates) in patients with different causes of damage (i.e., compression, ischemia, inflammation). Preliminary results from our laboratory in patients with unilateral optic neuropathy have shown that the damage, as revealed by the difference in pupil response amplitude between the two eyes, is intensity dependent.

Calculation of the pupil decibel sensitivity using lower criterion levels brought the pupil threshold nearer to the range of values for visual threshold. The actual decibel value of pupil sensitivity depends not only on the criterion level chosen, but also on the properties of the light stimulus such as size, background, and stimulus duration. In fact, the steepness of the pupil sensitivity profile from the fovea to the periphery may vary depending on the size of stimulus used. Smaller sized stimuli have been shown to cause a steeper fall off of sensitivity away from the fovea, whereas larger sized stimuli cause a more flattened sensitivity profile. This implies that spatial summation properties of the pupil light reflex may be a major determinant in the sensitivity profile across the retina. We used a larger sized target for pupil perimetry (4° in diameter) than for standard visual perimetry (0.4° in diameter) to flatten the pupil sensitivity profile so it would coincide more to the profile of visual perimetry. The larger-sized stimuli were also used to produce a robust pupil contraction, even in the peripheral locations of the 27° radius field at stimulus intensities within the range where scatter of light is negligible. The background level of adaptation may also influence the profile shape of pupil sensitivity and the mechanical range of pupil size over which the pupil moves. We chose a lower mesopic background for pupil perimetry compared with visual perimetry (3.1 versus 31.5 apostilbs) to allow the baseline pupil size to stay in a more advantageous size range that is not as susceptible to mechanical constraints. Therefore, although the stimulus conditions were different between visual and pupil perimetry, it accomplished the objective of producing flattened sensitivity profiles outside of the fovea that were comparable between visual and pupil perimetry.

Other factors besides retinal sensitivity may affect pupil sensitivity. These include supranuclear levels of inhibition or excitement (wakefulness), the innervational status of the pupil sphincter, and iris mechanics (e.g., pupil size and “stiffness” of iris tissue). These other factors influence the overall “gain” of the pupil light reflex but would not necessarily affect one perimetric location differently than a neighboring one. These factors may help explain the difference in the overall upward or downward shift in the pupil sensitivity profile across the 30° radius field observed among normal individuals and may be responsible for a greater SD in sensitivity between different subjects compared with visual sensitivity. However, any differences in the shape of the pupil sensitivity profile across the field that seemed to vary from one individual to another would have to be explained more by interindividual variations in the density and distribution of retinal neurons that provide input into the pupil light reflex. This variation in shape of the sensitivity profile does not seem to be random, because there were remarkable similarities in the shape of the profile between the right and left eyes of the same individual. From this we conclude that retinal factors may provide a major influence on the shape of the pupil sensitivity profile across the field. These retinal factors, such as ganglion cell distribution and number, seem to be more similar between the two eyes of the same subject than between the two eyes of different subjects. The topographical similarities of pupil sensitivity between the right and left eyes of the same normal subject might be exploited in the application of pupil perimetry (and visual sensitivity) to clinical problems to detect dissimilarities as an early sign of retinal or optic nerve disease.

It was also interesting that at lower criterion levels of pupil response there was lower correlation of decibel sensitivity between the same retinal location of the right and left eye than at higher criterion levels (Fig. 6). Lower criterion levels also resulted in a higher interindividual variability in pupil decibel sensitivity (Fig. 7). This implies that lower levels of neuronal

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<th>Pupil Threshold</th>
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firing, which are represented by lower criterion levels, are associated with higher variability of retinal sensitivity. This is reflected by the flatter, nonlinear shape of the stimulus–response function at lower stimulus intensities; at the lower intensity end of the stimulus–response function, larger changes in sensitivity are associated with only small changes in pupil contraction (Fig. 3). Therefore, small changes in pupil contractions at the lower, flat end of the response function are associated with relatively large sensitivity changes compared with the steeper, more linear portion of the curve. The relationship between neuronal firing rate and variability or retinal sensitivity could have important implications in understanding what testing conditions are best suited for detecting worsening or improvement in retinal sensitivity over time in patients with disease. For example, under standard visual field testing, retinal sensitivity is measured at threshold (low neuronal firing rates), and this is known to be associated with very high subject variability over time once damage has occurred. Pupil perimetry will lend itself to studying the effect of disease on retinal sensitivity and its variability at different neuronal firing levels, which are represented by different criterion levels, and hence different levels of light stimulation.

Comparison of visual and pupil sensitivity in the same decibel units revealed that these two measures of retinal sensitivity are not highly correlated across the horizontal retina in normal subjects. Differences between the visual and pupil sensitivity profiles in the same eye have been reported previously. The extent of this dissimilarity is influenced to a large extent by the state of adaptation, stimulus size, and stimulus duration. Differences in the ganglion cell type, number, and receptive field properties between the visual and pupillary systems help to explain why the retinal sensitivity measured by either the visual or pupillary system may not correlate. The differences between the ganglion cell type and organization in the visual and pupillary systems may provide a basis for why diseases of the retina and optic nerve may produce specific patterns of damage in the two systems. From this standpoint, it will be of interest to compare the perimetric visual and pupil sensitivity in normal and damaged eyes. A differential effect of disease on the pupil and visual system in an eye may be of clinical importance because it may help to reveal the etiology of damage, it may provide earlier detection of damage, and it may yield a better assessment for the effectiveness of treatment. It is hoped that future studies in our laboratory will clarify these issues.

References