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Assessment of the Reliability of Standard Automated Perimetry in Regions of Glaucomatous Damage

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Purpose: Visual field testing uses high-contrast stimuli in areas of severe visual field loss. However, retinal ganglion cells saturate with high-contrast stimuli, suggesting that the probability of detecting perimetric stimuli may not increase indefinitely as contrast increases. Driven by this concept, this study examines the lower limit of perimetric sensitivity for reliable testing by standard automated perimetry.

Design: Evaluation of a diagnostic test.

Participants: A total of 34 participants with moderate to severe glaucoma; mean deviation at their last clinic visit averaged −10.90 dB (range, −20.94 to −3.38 dB). A total of 75 of the 136 locations tested had a perimetric sensitivity of ≤19 dB.

Methods: Frequency-of-seeing curves were constructed at 4 nonadjacent visual field locations by the Method of Constant Stimuli (MOCS), using 35 stimulus presentations at each of 7 contrasts. Locations were chosen a priori and included at least 2 with glaucomatous damage but a sensitivity of ≥6 dB. Cumulative Gaussian curves were fit to the data, first assuming a 5% false-negative rate and subsequently allowing the asymptotic maximum response probability to be a free parameter.

Main Outcome Measures: The strength of the relation (R^2) between perimetric sensitivity (mean of last 2 clinic visits) and MOCS sensitivity (from the experiment) for all locations with perimetric sensitivity within ±4 dB of each selected value, at 0.5 dB intervals.

Results: Bins centered at sensitivities ≥19 dB always had $R^2 > 0.1$. All bins centered at sensitivities ≤15 dB had $R^2 < 0.1$, an indication that sensitivities are unreliable. No consistent conclusions could be drawn between 15 and 19 dB. At 57 of the 81 locations with perimetric sensitivity <19 dB, including 49 of the 63 locations ≤15 dB, the fitted asymptotic maximum response probability was <80%, consistent with the hypothesis of response saturation. At 29 of these locations the asymptotic maximum was <50%, and so contrast sensitivity (50% response rate) is undefined.

Conclusions: Clinical visual field testing may be unreliable when visual field locations have sensitivity below approximately 15 to 19 dB because of a reduction in the asymptotic maximum response probability. Researchers and clinicians may have difficulty detecting worsening sensitivity in these visual field locations, and this difficulty may occur commonly in patients with glaucoma with moderate to severe glaucomatous visual field loss. *Ophthalmology 2014;121:1359-1369 © 2014 by the American Academy of Ophthalmology.*

Automated white-on-white perimetry remains the clinical standard for objective assessment of function in glaucoma. However, the test−retest variability is considerable and worsens with greater damage.[1−12] This necessitates repeated visual field testing when establishing a diagnosis of glaucoma or ascertaining disease progression.[13−17] For example, variability in patients with ocular hypertension required 3 confirmatory visual fields to reliably detect progression.[18] Studies of patients with glaucoma or ocular hypertension suggest that approximately 6 visual fields may be required to assess the rate of visual field progression.[14] Overall, the variability of visual field sensitivity, especially in patients with glaucoma, may delay detection and treatment of progressive glaucomatous visual field loss.

Static perimetry uses a contrast stimulus that, when presented, causes an increase in the firing rate of functioning retinal ganglion cells (RGCs). Ganglion cell axons transmit these action potentials to the visual cortex via the lateral geniculate nucleus. As stimulus contrast is increased, RGCs increase their firing rate, eventually reaching the point at which the observer detects and responds to the stimulus.[19] The generation of action potentials is probabilistic in that their exact timing cannot be predicted, and it is common to report the mean number of spikes within a set time period across repeated stimulus presentations. Because of this and other factors, in eyes free of disease, the probability of responding to a stimulus increases gradually from 0% for stimuli several decibels higher than threshold (lower contrast) to 100% for stimuli several decibels lower than threshold (higher contrast). The psychometric function, describing the probability that the observer will respond to a stimulus of a given contrast, is known in perimetry as the

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frequency-of-seeing (FOS) curve. In clinical perimetry, contrast sensitivity is defined as the reciprocal of the contrast that the subject will respond to on 50% of presentations. To maintain an acceptable test duration and avoid overly fatiguing the patient, this sensitivity is typically estimated on the basis of <10 presentations (usually substantially fewer) per location.[20]

Contrast sensitivities from automated perimetry are reported on a decibel scale. In standard static automated perimetry, a 10-dB increase corresponds to a log unit decrease in contrast, and 0 dB represents the instrument-dependent maximal contrast that can be presented by the perimeter. Therefore, with the commonly used Humphrey Field Analyzer (HFA; Carl Zeiss Meditec, Dublin, CA), a sensitivity of 0 dB indicates that the subject would respond to half of the stimuli presented at 317,000% contrast, whereas for an Octopus perimeter (Interzeag/Haag Streit, Koeniz, Switzerland), 0 dB corresponds to 135,000% contrast. Throughout this article, to avoid confusion, we use HFA decibel units, that is, 0 dB=317 000% contrast, such that the lower limit for the Octopus perimeter becomes 3.7 dB. We refer to these 0 dB values as the "technical" lower limit of the stimulus range of each perimeter.

However, the lower limit of the "reliable stimulus range," defined as the range over which reliable measures of sensitivity can be obtained by perimetry, may be higher than this.[21] At low sensitivities, the test–retest variability increases substantially.[1–3,5,7–12] When sensitivity has deteriorated to the point that it is reported as being 15 dB, the 95% confidence interval for the retest sensitivity at the same location covers more than half of the technical stimulus range of the perimeter.[7,22] This limits the utility of perimetry when sensitivity is low. This unreliability may not entirely be due to false-positives, false-negatives, or fixation losses. We refer to sensitivities as being "unreliable" when a change in reported sensitivity is not necessarily related to true change, and so the results are of limited clinical use. The reasons for the increase in variability are still unclear. Improved understanding of this sensitivity–variability relation should aid endeavors to reduce variability and may provide useful insights into some pathophysiologic aspects of glaucoma.

The responses of healthy RGCs saturate when high-contrast stimuli are presented.[23,24] Instead of the rate of generated action potentials increasing in proportion to contrast, it asymptotes to a maximum rate because of factors including the cell's refractory period. This response rate can be modeled according to a Michaelis–Menten function.[25–27] The implication is that when the firing rate approaches its asymptotic maximum because a high-contrast stimulus is being presented, increasing the contrast still further has little effect on the firing rate. If the RGC firing rate does not increase, the signal received by the visual cortex cannot increase, and so the subject's response probability should not increase. In the presence of such response saturation, any change in response probability as stimulus intensity increases is most likely due to response errors, eye movements, or light being scattered onto neighboring photoreceptors and RGC receptive fields, rather than being caused by a change in the responses of individual RGCs at the tested location. Some stimuli may be detected at contrasts considerably lower than the "true" threshold, whereas a proportion of considerably more intense stimuli will not be detected. This inherent physiologic unpredictability provides a feasible explanation for the flatter FOS curves and thus the higher variability that is observed when conducting static increment perimetry at locations with low sensitivity.[1,10]

The RGC saturation also implies that at locations with more severe damage, even if all remaining RGCs attain their asymptotic maximum firing rate, this reduced number of RGCs may not produce a sufficiently strong cortical signal to guarantee detection. The response probability could then remain <100%. At some of those locations, the asymptotic maximum response probability could be <50%, implying that even though some function remains at that location (because the response probability is above zero), the contrast sensitivity in its most common formulation is undefined. According to this hypothesis, once a visual field location has deteriorated to these levels, perimetric sensitivities would be inherently unreliable. The estimated sensitivity will be influenced by response errors, small eye movements, and light scatter but could contain little information concerning the true level of remaining function.

In this study, we measure FOS curves from patients with glaucoma in regions of the visual field with low sensitivity. Swanson et al[24] reported that in nonhuman primates, semi-saturation of RGCs (the point at which RGCs respond at half their asymptotic maximum firing rate) occurred at 24±2 dB. We therefore concentrate on locations with perimetric sensitivities that are below this level but are still nonzero (such that some function remains). We aim to determine the contrast beyond which perimetric sensitivities become unreliable, and so further changes in the reported sensitivity may not be related to true disease progression. This contrast can then be interpreted as the effective lower limit of the reliable stimulus range of static increment perimetry (although a reported sensitivity of <0 dB, indicating that the subject did not respond even to the highest available stimulus contrast, still could reliably indicate lack of measureable function). Our results will aid in the understanding of perimetric variability and inform researchers and clinicians about the ability to detect visual field progression at locations already substantially damaged by glaucoma.

Methods

We recruited subjects with moderate to severe primary open-angle glaucoma from a tertiary glaucoma clinic at Devers Eye Institute. Inclusion criteria were a diagnosis of primary open-angle glaucoma as determined by their clinician and at least 2 nonadjacent visual field locations with sensitivity from standard automated perimetry between 6 and 18 dB on both of their 2 most recent clinic visits (HFA, 24-2 test pattern, standard Swedish Interactive Threshold Algorithm [SITA]). Exclusion criteria were an inability to perform reliable visual field testing, best-corrected visual acuity <20/40 (because this could cause difficulties with maintaining fixation), cataract, media opacities likely to significantly increase light scatter, or other diagnoses or medications that may affect the visual field. All protocols were approved and monitored by the Legacy Health Institutional Review Board and adhered to the Health Insurance Portability and Accountability Act of 1996 and the tenets of the Declaration of Helsinki. All participants provided written informed consent once all of the risks and benefits of participation were explained to them.