Pupil Perimetry using M-Sequence Stimulation Technique

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PURPOSE. M-sequence stimulation technique allows mapping of the retinal function by multifocal electroretinographic (ERG) recordings. However, the information provided about visual field is limited to retinal function. Optic nerve diseases and diseases of the higher visual pathways usually show normal multifocal ERGs. Using pupillary responses instead of the electrical retinal responses might enhance the diagnostic possibilities of this system. The problems of local ERG recordings are very similar to those encountered in pupil perimetry: Local stimuli have to be dim to avoid or at least reduce stray-light responses. Dim stimuli, close to the absolute threshold, elicit only subtle pupillomotor responses. Therefore, techniques that are able to detect small focal responses are promising.

METHODS. Pupillography was done by means of an infrared video camera and real time image processing (50 Hz) using a custom-designed videoboard in a personal computer (486). Recording conditions: The stimulus was presented on a monitor (75 Hz) in 26 cm distance from the patient’s eyes. It contained 37 hexagons in a 25° visual field. Each element changed between black (1.6 cd/m²) and white (160 cd/m²) after a binary M-sequence independently from other elements. Four thousand ninety six different stimulus pictures of 120-msec duration were shown during a single pupillogram recording. Thirty-seven local pupillograms were calculated in a cross-correlation of stimulus sequence and the pupil diameter.

RESULTS. The pupillomotor fields in normals showed a shape and sensitivity distribution as known from conventional pupil perimetry techniques. Artificial paracentral scotomas (5°) created by masking different locations could be demonstrated convincingly. Even in patients with optic nerve lesions it was possible to demonstrate visual field defects.

CONCLUSIONS. Pupil perimetry using the M-sequence technique is a promising method of objective perimetry that may find its entrance into clinical application. (Invest Ophthalmol Vis Sci. 2000;41:1229–1238)

Visual field testing is an important method in ophthalmology and neurology, both for focal diagnosis and follow-up in diseases of the eyes and the visual pathways. However, perimetry remains a subjective technique even if performed by automated systems using sophisticated stimulus presentation and response evaluation algorithms. Objective perimetry is a strong demand, not only to disprove malingering but also to examine patients who have difficulty cooperating with conventional perimetry. Several attempts have been made using the pupil light reflex as response to a local perimetric stimulus.¹⁻¹⁸ None of those techniques has come into widespread use for different reasons.

Pupillomotor threshold using conventional perimetric stimuli is higher than visual threshold,¹⁹ and it varies considerably between individuals. Additionally, intrindividual variability exists. In most individuals stimulus intensity has to exceed the visual threshold considerably to provide a stable and repeatable pupillary response. On the other hand, brighter stimuli increase stray light and this limits the maximal level of stimulus brightness, because the local response is replaced by a stray-light response. In quite a few patients with visual field defects in conventional perimetry proven by objective morphologic findings, pupil perimetry fails to demonstrate a scotoma. If the stimulus is chosen too dim, it may remain below the pupillomotor threshold; if it is too bright, it will elicit a stray-light response. It is virtually impossible to find for each individual and each retinal location a stimulus that elicits a local response without an additional stray-light effect. Techniques that help to extract local responses from stray-light “noise” are therefore promising.

These problems encountered in pupil perimetry are similar to those met in focal electroretinography (ERG). Sutter and Tran have provided a new solution introducing M-sequence stimulation technique.²⁰,²¹ This visual evoked response imaging system (VERIS) has become a valuable tool in multifocal ERG recordings providing detailed functional topography in retinal disorders.²²⁻²⁴ It seemed to be logical to use the M-sequence system for pupillary evaluation as well. Instead of feeding an ERG curve to the system, pupil size in millimeters coded as a voltage (1 V = 1 mm) was used. The purpose of this article is to describe the
During a single recording 4906 different stimulus pictures were presented. Each stimulus picture was shown for the duration of nine monitor frames (120 msec). This does not mean that the complete stimulus was flickering with such a high frequency. Each single location of the stimulus changes considerably slower (i.e., each location remains unchanged for several frames). Our setup led to a total stimulation time of 8.19 minutes. This net time was divided into 40 segments. Between the segments the subjects were allowed to blink and move their eyes. If blinks and movements occurred during a segment, the data were discarded and the segment repeated. Before each segment the stimulus was presented for 960 msec without measuring the pupil diameter to allow the subject to find a stable fixation. The average time for the whole test was 30 minutes. Table 1 compares the setup parameters of ERG and pupil perimetry recording.

**Pupillography**

The pupil of the stimulated eye was recorded by means of an infrared-sensitive CCD-camera, while the contralateral eye was occluded. The video signal was processed by a custom-designed real-time frame-grabber board occupying the extension slot of a personal computer. The pupil was tracked horizontally with a frequency of 50 Hz. Pupil diameter was then converted into proportional voltage changes (0–10 V, 1 V for 1 mm). Instead of an ERG signal, this pupil diameter signal was transferred to a Macintosh Quadra 650 computer, harboring the VERIS software (provided by Erich Sutter, EDI, San Francisco, CA). It was stored as a digital signal each 6.67 msec.

**Signal Analysis**

The pupillary light response was analyzed for 37 stimulated areas with a fast M-transform algorithm, which generates the first order kernel, a linear approximation of the pupillary response. Amplitudes and peak times (i.e., time from stimulus onset to maximum constriction) were considered for evaluation. It has to be kept in mind that the latencies calculated by the VERIS software are not pupillographic latencies because the peak of the pupillary constriction is taken as the end point of the latency time, not the beginning of the constriction as usually occurs in pupillography. Therefore it is better to speak of peak time.

**Experiments**

Eleven healthy subjects (mean age: 36.8 ± 12.6 years) were examined by this method to test how the retinal pupillomotor sensitivity would be displayed by this method. They had given their informed consent and all experiments were done according to the Declaration of Helsinki.

**METHODS**

**Stimulation**

The stimulus is presented on a black and white monitor (75 Hz) at a 26 cm distance from the patient’s eye, and consists of 37 hexagonal elements within a 25° (radius, see Fig. 1). Each element changes its luminance between 1.6 cd/m² (black) and 160 cd/m² (white) after a binary M-sequence independently of other elements. In the center of the monitor a constant visible gray spot serves as a fixation target. The background of the stimulus-screen is otherwise black (1.6 cd/m²).

**Figure 1.** (A) Geometry of the test field with 37 stimulated areas. (B) Multifocal pupillogram recorded from the right eye of a normal volunteer. (C) For further analysis the responses were grouped either into 4 quadrants or into 5 concentric rings.

**Table 1.** Setup Parameters of ERG and Pupil Perimetry Recording

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<td>No. of time segments</td>
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FIGURE 2. Averaged pupillogram of the whole field. Temporal and spatial parameters of the pupillogram are similar to conventionally recorded pupillograms; however, the shape of the pupillogram is altered by averaging many pupillograms with small amplitudes and short peak times.

FIGURE 3. (A) When peripheral areas of the visual field are covered by black cardboard, the pupillary response is absent or reduced for this area. (B) The same is found when one hexagon remains black during recording.
Parts of the screen had been covered by black cardboard in one stimulation. In other subjects one element had been switched off (i.e., it remained black during the measurement). Altogether 6 patients who had given their informed consent were examined. They had been selected as representative of different types of visual field defects and according to their ability to perform the pupil perimetry. In 1 of them the record could not be completed because of blinks and unstable fixation, and in 2 of them (advanced glaucoma and advanced retinitis pigmentosa) the resulting pupillograms were extremely small, hardly distinguishable from noise. Three patients (optic neuritis, chiasmal lesion, and bilateral occipital lesion) are demonstrated here.

Conventional perimetry was performed using the Tuebingen Automated Perimeter (suprathreshold technique, 190 test locations in the 30° field = program 1). Stimulus size was 10°, duration 100 ms, luminance 1000 cd/m², and 10 cd/m² background. The shaded areas in Figures 5 through 7 give the areas in which the 1000 cd/m² stimulus was not seen.

RESULTS

The resulting 37 pupillographic traces are shown as a trace array, each response positioned at its approximate place of origin in the visual field. Amplitudes and latencies at the trough of the pupillographic trace were analyzed off-line.

Multifocal pupillograms could be extracted (Fig. 1B). The averaged pupillogram of the whole field showed an amplitude of approximately 1 mm (Fig. 2).
If part of the screen was covered by cardboard, the pupillographic response was absent or markedly reduced in this area. The same happened, if one hexagon remained black (Fig. 3).

It could be shown that the pupillographic response is highest in the center and lowest at the edge of the examined field. This difference was very pronounced. The upper temporal quadrant of the visual field is the most sensitive quadrant. The temporal half of the visual field is more sensitive than the nasal half. This is true for both eyes (Fig. 4).

In an optic neuritis patient with central scotoma the central pupil response was decreased and the peak time prolonged (Fig. 5). In a patient with temporal field loss the pupillary defect could also be shown (Fig. 6), but the method failed in a patient with occipital lobe lesion (Fig. 7).

**DISCUSSION**

The linear approximation of the multifocal ERG (first order kernel) provides a reliable functional topography of the lesion in diseases of the outer retina (i.e., Stargardt’s macular dystrophy and retinitis pigmentosa) but the amplitudes were found normal in patients with optic nerve or higher visual pathway diseases. Recently, Bearse and coworkers described a ganglion cell component extracted from the multifocal ERG. This component is too small to allow an objective perimetry in high resolution at the present state of development.

Visual evoked cortical potential (VECP) might be used for this purpose. However, the VECPs do not depend only on the position of the stimulus in the visual field but also on the spatial
relation between the cortical tissue in which the potentials are generated and the position of the recording electrodes on the scalp. Barrett et al. described the phenomenon of paradoxical lateralization of the VECP, that is, during hemifield stimulation potentials recorded over the ipsilateral occipital cortex were found to be larger than over the contralateral cortex as expected. With VECP recordings using the M-sequence stimulation technique cortical potentials evoked from different positions of the visual field were recorded simultaneously by Baseler and Sutter. But even in normal volunteers the recordings revealed a "Swiss cheese pattern" most probably due to cancellation of local responses generated in neighboring convolutions of the visual cortex. Kilstorner et al. obtained a good correspondence between Humphrey visual field and multifocal VECP using bipolar electrodes and evaluating upper and lower fields separately.

Pupillography as another objective method of visual testing deserves a closer look, and the first attempts have been made by Sutter himself. His results were promising, and therefore we decided to apply this method.

VERIS pupil perimetry proved to be possible. In normals, we obtained principally the same qualitative results as Kardon and Thompson with classic pupil perimetry using a Humphrey Field Analyzer equipped with pupillography. They found the highest response in the center of the visual field, markedly decreasing in the periphery, the same that we found using the M-sequence technique. This has also been visible on Sutter's first pupillographic fields. In former experiments using conventional pupil perimetry the upper temporal quadrant of the visual field showed the greatest, and the lower nasal quadrant the least, pupillomotor sensitivity. We found the same results concerning the most sensitive quadrant for both eyes.

When all focal pupillograms were averaged, the resultant summed pupillogram was very similar to a pupillogram elicited by a single light stimulus (Fig. 2). Amplitude and latency time were in the same range. However, an averaged
A pupillogram looks different than a single flash response: if many small pupillograms are superimposed, the latency time will be somewhat shorter, the peak time will remain approximately the same as in a single flash pupillogram, and the amplitude depends on the number and amplitude of the focal pupillograms. This explains why the summed pupillogram does not look exactly like a single flash response.

An experiment was done with one or more hexagons of the stimulus field covered to demonstrate that the technique is really able to provide local pupil responses. It has been possible to demonstrate that nonstimulated areas do not show a local pupil response.

There are important differences between electrophysiological recordings and pupillography. In ERG recordings sampling rates of more than 1000 Hz are possible, whereas in infrared videopupillography frame rates of 25 or 50 Hz (30 or 60 Hz, respectively) are used. Because the pupillary movements are comparatively slow and do not contain high frequency components, this sampling rate is appropriate for pupillography. On the other hand, even the stimulus modulation has to be slowed down. The pupil is much slower to follow light responses than the retina, because its flicker fusion frequency is as low as 3 Hz. Therefore, frequency of the local light flux change must meet the temporal bandwidth of the pupil (Table 1). This slows down the procedure, and the examination time would increase to several hours if we tried to reach the same quality as in ERG recordings. We managed to obtain reliable results with recording times around 8 minutes.

**Figure 6.** Patient with pituitary adenoma and temporal hemifield loss. The scotoma is shown as a gray shaded area. (A) Multifocal pupillograms: pupillary response is reduced in comparison to the nasal field. (B) The same can be demonstrated by averaged pupillograms from 4 quadrants as indicated in Figure 1C. The temporal quadrants that are usually more sensitive than the nasal show reduced sensitivity.
per eye. This recording was split into 40 segments, because artifacts such as blinks or fixation loss would deteriorate the results. Many segments had to be repeated, therefore the total examination time was approximately 30 minutes. Changes caused by fatigue may begin to interfere with the light responses.

Despite those problems it has been possible to apply the method in selected patients and to demonstrate their field defects. In two patients with a central scotoma caused by optic neuritis the foveal response was markedly reduced corresponding to the field defect. Why is it not missing completely as the ERG response in macular lesions? We have to keep in mind that conventional perimetric stimuli are much smaller than pupil perimetric stimuli. In our cases stimuli were used for conventional perimetry. Dense scotomas may contain small partially functional islands that may be stimulated by the large pupillomotor stimuli. We still do not know much about pupillomotor receptive fields and the contribution of different channels of the visual system to the pupillary light response.

The VERIS pupil perimetry still depends very much on the subject's cooperation, therefore it was not always possible to demonstrate field defects convincingly, mostly because of too much noise. Artifact management might be a solution, change of the stimulus field to a lower number of hexagons another. This leads of course to a reduction of the spatial resolution; however, this might not be a major problem. The purpose of pupil perimetry as a clinical application is not to replace conventional perimetry but simply to verify defects (e.g., in suspected malingering). Usually, it is not the question of small scotomas that could be feigned but large hemifield or quadrant

**Figure 7.** In a patient with so-called checkerboard visual field defect after bilateral occipital lobe infarction, it was not possible to demonstrate the field defect convincingly. However, the pupillary responses were relatively low in general. The visual field defect of the right eye is shown as a gray shaded area. (A) Multifocal pupillograms. (B) Averaged pupillograms in 4 quadrants.
defects or severe constriction. Under these circumstances a lower spatial resolution may be acceptable.

However, the recording of the patient with the occipital lobe lesion was technically good, but the defect did not show up convincingly, even the blind upper temporal quadrant showed the best response. One question still remains to be answered: Does VERIS pupil perimetry measure the very same visual function as conventional pupil perimetry? The pupil reacts not only to light but also to changing gratings and movement. In VERIS pupil perimetry light responses and responses to more complex stimuli may be combined. This might theoretically open new possibilities, because there are conditions where light responses and responses to complex stimuli are differently involved. The very central visual field has an especially high pupillomotor sensitivity, and defects in this area show clearly. Maybe the stimulation applied here is comparable to the checkerboard stimulation technique used by Slocer and van Norren who were able to measure visual acuity by means of pupillography. If the pupil response to M-sequence stimulation was purely a pattern response, it would not be very promising to try to find visual field defects. However, our experiments with artificial scotoma showed that the pupil response is absent in distinct areas if they are not stimulated. If we cannot detect scotomas in patients this cannot be explained by the inability of the VERIS system to extract local responses. Cooperation problems or a dissociation of the visual and the pupillomotor response may cause failure of the VERIS pupil perimetry. This has to be differentiated in further studies with simplified technique and shorter examination times.

Another question related to this problem is whether pupil perimetry really tests the complete visual pathways. It was previously thought that the pupillary light reflex depends completely on subcortical structures (i.e., will not be impaired in perimetry really tests the complete visual pathways. It was previously thought that the pupillary light reflex depends completely on subcortical structures (i.e., will not be impaired by conditions where light responses and responses to complex stimuli are differently involved. The very central visual field has an especially high pupillomotor sensitivity, and defects in this area show clearly. Maybe the stimulation applied here is comparable to the checkerboard stimulation technique used by Slocer and van Norren who were able to measure visual acuity by means of pupillography. If the pupil response to M-sequence stimulation was purely a pattern response, it would not be very promising to try to find visual field defects. However, our experiments with artificial scotoma showed that the pupil response is absent in distinct areas if they are not stimulated. If we cannot detect scotomas in patients this cannot be explained by the inability of the VERIS system to extract local responses. Cooperation problems or a dissociation of the visual and the pupillomotor response may cause failure of the VERIS pupil perimetry. This has to be differentiated in further studies with simplified technique and shorter examination times.

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Further technical improvements of pupillography will probably lead to a more widespread use of pupil perimetry. The VERIS pupil perimetry is a promising new method of objective perimetry that deserves further study.

Acknowledgment

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References


