Reliability, normative data, and the effect of age-related macular disease on the Eger Macular Stressometer photostress recovery time

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Abstract

Purpose

To assess repeatability and reproducibility, to determine normative data, and to investigate the effect of age-related macular disease, compared with normals, on photostress recovery time (PSRT) measured using the Eger Macular Stressometer (EMS).

Method

The study population comprised of 49 healthy eyes of 49 participants. Four EMS measurements were taken in two sessions separated by one hour by two practitioners, with reversal of order in the second session. EMS readings were also taken from 17 age-related maculopthy (ARM), and 12 age-related macular degeneration (AMD), affected eyes.

Results

EMS readings are repeatable to within ± 7 seconds. There is a statistically significant difference between controls and ARM affected eyes ($t = 2.169$, $p = 0.045$), and AMD affected eyes ($t = 2.817$, $p = 0.016$). The EMS is highly specific, and demonstrates sensitivity of 29 % for ARM, and 50 % for AMD.

Conclusions

The EMS may be a useful screening test for ARM, however, direct illumination of the macular of greater intensity and longer duration may yield less variable results.

Keywords: photostress recovery time, Eger Macular Stressometer, glare recovery, age-related macular disease

Introduction

Exposure of the retina to an intense light source causes bleaching of photopigments and the subjective appearance of a scotomatous after image. Retinal sensitivity recovers upon resynthesis of the visual pigments in the retinal outer segments, which is dependent on the integrity of photoreceptors and retinal pigment epithelium (RPE) (Brindley, 1970). Photostress recovery time (PSRT) is not widely used as a clinical measure of retinal function, mainly due to the lack of standardization of techniques and variability of results (Collins and Brown, 1989).

Various techniques have been used to determine normal PSRTs and also to assess the effect of ocular disease. Macular inspection with a direct ophthalmoscope for 15 seconds yielded normal maximal PSRTs of 35 seconds for those up to the age of 50 years, and 70 seconds for those over 70 years. Anecdotal evidence suggested that glaucoma, age-related macular disease, diabetic retinopathy, and hypertensive retinopathy did not extend PSRT measured using this technique (Forsius et al., 1963). In a different study, macular inspection with a direct ophthalmoscope for 30 seconds produced normal PSRTs of 10 - 50 seconds, and it was concluded that a PSRT greater than 60 seconds should be considered pathologic. Additionally, PSRT was extended in macular edema and retinal detachment, although these observations were based on case studies (Chilaris, 1962). In a further study of 179 eyes, participants looked directly at a simple pen torch for ten seconds as it was held 2 - 3 cm from the eye. Normal PSRTs were 27 seconds up to the age of 60 years, and 30 seconds over the age of 60 years. In a group of 63 eyes affected by macular disease, the average PSRT was more than 2.5 minutes (Glaser et al., 1977). When PSRT was assessed using a xenon flash-tube and a Goldmann-Weekers adaptometer, contrast discrimination (not visual acuity) returned to normal in 30 - 70 seconds in normal eyes, and there was a significant difference in patients over the age of 40 years (Severin et al., 1967a). The same researchers also suggested that this test may be useful in distinguishing macular disease from optic nerve disease (Severin et al., 1967b). In an investigation into the recovery of contrast discrimination following exposure to a glare source, PSRT remained constant up to the age of 55 to 65 years [mean (± SD) 31.2 ± 23.7 seconds] and then became significantly prolonged (58.8 ± 43.1 seconds; t-test: t = 2.94, df

= 32, $p < 0.01$) when using a 500 W tungsten halogen bulb for 10 seconds.(Collins and Brown, 1989).

An investigation into the reliability of different PSRT assessment techniques involved comparing three different bleaching methods with the use of a single channel Maxwellian view optical system. This system produced a white, 6 log troland (log td), 16º diameter circular field, and viewing such a field for 30 seconds has been reported to bleach approximately 96% of cone photo pigment (Hollins and Alpern, 1973), and has been used in clinical research as a reference technique (Margrain and Thomson, 2002). The bleaching methods used were 1) shining an unfocussed pen torch from a distance of 3 cm for 10 seconds, 2) focusing the filament of a pen torch held 5 cm from the eye for 10 seconds in the plane of the pupil, 3) projecting the macula stop of a direct ophthalmoscope onto the macula for 30 seconds. The third method was shown to correlate best with the Maxwellian view optical system reference technique (Margrain and Thomson, 2002).

The Eger Macular Stressometer (EMS; Gulden Ophthalmics, PA, USA) was designed in an attempt to provide a standardized method of measuring PRST (Gulden Ophthalmics, 2001). This study complements an investigation that compared EMS PSRT recorded from patients with cataract, diabetic retinopathy, glaucoma, and age-related macular degeneration. Investigators concluded that there was no difference between these groups (Schmitt et al., 2003). The purpose of this study was to assess repeatability and reproducibility, to determine normative data, and to investigate the effect of age-related macular disease, compared with normals, on PSRT measured using the EMS.

The age-related macular disease affected eyes were classified according to the International Classification and Grading System for Age-related Maculopathy (ARM) and Age-related Macular Degeneration (AMD) (Bird et al., 1995). ARM refers to large soft drusen and pigmentary abnormalities of the retinal pigment epithelium (RPE) and the retina, and AMD refers to later stages of the disease such as geographic atrophy (GA), choroidal neovascularization, pigment

epithelium detachment and fibrous scaring of the macula (Bird et al., 1995). These terms will be used throughout the manuscript, and the term ‘age-related macular disease’ will be used to encompass ARM and AMD.

Method

Setting

A clinical practice setting at the Neurosciences Research Institute, Aston University, Birmingham, UK.

Subjects

Forty–nine normally sighted participants were recruited from staff, students and patients of the Division of Optometry and the Neurosciences Research Institute, Aston University, Birmingham, UK. This research adhered to the tenets of the Declaration of Helsinki. All participants gave informed consent to take part in the study, which was approved by the Institutional Human Ethics Committee. Participants varied in age from 18 to 76 years (mean ± SD, 44.6 ± 20.8 years). Review of the literature indicates that PSRT remains static up to the age of approximately 50 years, and then extends (Forsius et al., 1963; Collins, 1989; Hinrichs et al., 1992). Therefore, for analysis they were divided into two sub-groups; 28 participants aged < 50 years, from 19 to 46 (28.2 ± 8.8 years), and 21 participants aged ≥ 50 years, from 52 to 76 (67.0 ± 7.1 years). Chi-squared analysis for gender between these two groups yielded no significant association [χ^2 (1) = 2.59 P = 0.107].

Exclusion criteria were best corrected distance log MAR visual acuity (VA) of more than 0.1 log MAR (VA was measured under standard testing conditions using a log MAR chart, retro illuminated to a luminance of 130 cdm^{-2} (Bailey and Lovie-Kitchin, 1976). Each letter seen was scored as 0.02 log units, with guessing encouraged), retinal disease, abnormal Amsler grid test result; glaucoma, lenticular opacities greater than grade 1 on the Lens Opacities Classification System (LOCS) grading scale (Chylack et al., 1988), and prescribed medication associated with changes in retinal function. Fundus photographs were taken for all age-related macular disease

affected eyes, and all participants were patients of the Optometry clinic, Aston University, and had had an eye examination within the past year.

In order to assess the effect of age-related macular disease on PSRT measured with the EMS, readings were taken from 17 ARM affected eyes of 17 participants varying in age from 55 to 82 (69.4 ± 7.8 years), and 12 AMD affected eyes of 12 participants varying in age from 60 to 78 (71.0 ± 4.9 years). Log MAR VA for the ARM group ranged from - 0.10 to 0.20 (0.04 ± 0.09 log MAR), and for the AMD group ranged from 0.20 to 0.76 (0.50 ± 0.21 log MAR). The eyes included had non-exudative AMD, and did not have lenticular opacities greater than grade 1 on the LOCS grading scale (Chylack et al., 1988), or any other ocular condition.

Procedures

The EMS is a battery-operated, portable hand-held instrument (figure 1). Our clinical experience indicates that it allows assessment of PSRT for one eye within 3 - 4 minutes, including explanation of the procedure to the patient.

Insert figure 1 about here.

The instrument is switched on by firmly holding down the button on the left edge of the housing. A series of 8 figure eights appears on the window display at the top of the instrument. A second press of the button charges the flash and illuminates a red light emitting diode (LED). A faint whine is heard and a change in color of the LED to green indicates that the flash is charged. The patient wears their reading prescription (if required) and the eye not being tested is occluded. The instrument houses a 40.6 cm length of string, which, when extended, maintains a constant working distance while the subject determines the smallest letter size that can be read on the integrated VA chart. The test types range from Snellen equivalents of 6/6 to 6/30, with letter size decreasing from the top to the bottom of the chart. The working distance is then reduced to 15.2 cm (measured using a marker on the string) and the patient is directed to look at the centre of the flash tube, situated just above the test type. A third button press

simultaneously activates the flash and starts the timer. The device is then returned to 40.6 cm and the patient is asked to read the line of letters above the smallest line read before bleaching as soon as it becomes visible. A fourth button press stops the timer when the patient has recovered enough macular function to correctly identify three from the five letters on the designated line. A note of this PSRT is made and a fifth press of the button resets the instrument.

The same testing room was used for each test, and the integrated VA card on the instrument was illuminated by 900 lux, as suggested in the EMS User's Manual (Gulden Ophthalmics, 2001). When both eyes met inclusion criteria, the right eye was tested; when only one eye was suitable for inclusion, this eye was tested. Participants wore their own reading spectacle correction if necessary. Data were collected by two optometrists, HB and LD, in two sessions separated by one hour. A trial run was completed, followed by a 10 minute recovery period for each subject. The 10 minute recovery period has been used in other glare recovery investigations to allow retinal readaptation following bleaching (Collins, 1989). In session one, the first test was carried out (HB1) followed by a 10 minute recovery period. The second test was completed (LD1) followed by rest period of not less than one hour. In session two, the third test was carried out (LD2) followed by a 10 minute recovery period, after which the fourth test was completed (HB2). All between-test recovery periods were timed using a stopwatch and the EMS test procedure was carried out according to the manufacturer's operating procedure described in the EMS User's Manual (Gulden Ophthalmics, 2001).

Microsoft Excel for Microsoft Windows XP software was used for data analysis, employing the paired samples t-test for repeatability and reproducibility, and independent-samples t-test for normative data. The chi-squared test was used to compare proportion of males by group in analysis of the effect of age-related macular disease on PSRT. Linear regression analysis was carried out using SPSS software (version 11, SPSS Inc., Chicago, Illinois, US) for Microsoft Windows XP. Graphs were produced using SigmaPlot software (version 6, Systat Software UK Ltd, London, UK) for Microsoft Windows XP.

Results

Reliability

The study was designed to assess repeatability (HB1-HB2, LD1-LD2), and reproducibility (HB1-LD1, LD2-HB2). See figure 2 for a graphical example of the test-retest data.

Insert figure 2 about here.

Accurate analysis of test-retest data can be achieved using the coefficient of repeatability (Bland and Altman, 1986; Elliott and Sheridan, 1988). This gives the 95% confidence limits for the amount of difference between two sets of results. It is calculated as 1.96 multiplied by the standard deviation of the mean differences between the two sets of data. The coefficient of repeatability for all test-retest PSRT scores was between ± 4.98 seconds and ± 6.70 seconds (table 1).

Insert table 1 about here.

Normative data

Normal limits for EMS readings for each age-group were determined by calculating the 95% confidence limits (table 2). The EMS gives readings in whole seconds, and so the clinical upper confidence limit is given as a whole number.

Insert table 2 about here.

Review of the literature indicates that PSRT remains static up to the age of approximately 50 years, and then extends (Forsius et al., 1963; Collins, 1989; Hinrichs et al., 1992). In order to explore the relationship between age and EMS score, a linear regression analysis was carried out for each age group. There is a significant linear relationship between the two variables for the < 50 years group ($F = 6.757$, $p = 0.015$), but not for the ≥ 50 years group ($F = 0.290$, $p =$

0.597). For those aged under 50 years, 21.3 % of the variance in EMS score was explained by age, compared with only 1.5 % for those aged 50 years and over.

Insert figures 3 and 4 about here.

The clinical upper confidence interval for those aged under 50 years is 13 seconds (8.3 ± 2.3 seconds), and for those aged 50 years and over is 16 seconds (11.1 ± 2.7 seconds). This difference is statistically significant (t = 3.697; p = 0.001). Specificity analysis shows that the EMS correctly identifies 96 % of normals aged under 50 years, and 100 % of normals aged 50 years and over.

Effect of age-related macular disease

EMS readings from 17 ARM affected eyes were compared with the first reading taken by HB from 21 normal eyes. The age difference between the two groups is not statistically significant (t = 1.129; p = 0.266). Chi-squared analysis for gender between these two groups yielded no significant association [χ^2 (1) = 0.433 p = 0.795]. For the normal group, the clinical mean PSRT was 11 (11.1 ± 2.7 seconds) and for the ARM group, the clinical mean PSRT was 18 (17.9 ± 12.3 seconds). The difference between these groups is just statistically significant (t = 2.169; p = 0.045). The sensitivity of the EMS for ARM is 29 %.

EMS readings from the 12 AMD affected eyes were compared with first readings taken by HB from 21 normal eyes. The difference in age between these two groups is not statistically significant (t = 1.673; p = 0.104). Chi-squared analysis for gender revealed no significant association [χ^2 (1) = 0.535, p = 0.947]. For the AMD group, the clinical mean PSRT was 19 (19.2 ± 9.4 seconds), and for the normal group the clinical mean PSRT was 11 (11.1 ± 2.7 seconds). The difference between these two groups is significant (t = 2.817, p = 0.016). The sensitivity of the EMS for AMD is 50 %.

Insert table 3 about here.

Discussion

The repeatability data has been used to determine the increase in EMS reading that is needed to indicate a clinical change between patient visits. The EMS scores are shown to be repeatable to within ± 7 seconds, which means that significant change in EMS reading between visits is 14 seconds. So for example, a patient achieving an EMS PSRT of 12 seconds, could be suspected of having retinal pathology if the PSRT increased to at least 26 seconds at a follow-up visit. The standard deviations of these results indicate variability, which may be related to the nature of the test. It has been suggested that for clinical measurement of PSRT, a direct ophthalmoscope projected directly onto the macular for 30 seconds provides the most consistent results (Margrain and Thomson, 2002). This may be explained by the fact that in order to bleach a constant proportion of the photopigment, the duration of exposure and the retinal illuminance need to be well controlled. To reduce variability in the proportion of photopigment bleached, the subject should be exposed to retinal illumination in excess of 5.5 log td for at least 30 seconds (Margrain and Thomson, 2002). This may explain why the flash testing method employed by the EMS produces variable results. From our clinical experience, blinking and eccentric viewing appear to reduce PSRT, i.e if the participant is eccentrically viewing the flash, a shorter recovery time than expected may be recorded. Short recovery times thought to have been yielded for these reasons were included in the analysis as these artifacts may well occur in the clinical setting.

Normative data may be used to determine the upper limits of normal for age groups. Our data show that for patients aged less than 50 years, an EMS PSRT of more than 13 seconds may be indicative of retinal pathology. This critical value for patients aged 50 years and above is 16 seconds. Linear regression analysis was used to explore the relationship between age and EMS PSRT and found a significant increase in EMS reading with age for the under 50 years group, but no relationship between the two variables for those aged 50 years or over. It has been shown that visual function starts to decline at the age of 50 years (Elliott et al., 1989), and this may account for the increased variability of results from the older participants. The EMS is

highly specific, but correctly identified 50 % of AMD affected eyes, and 29 % of ARM affected eyes.

There was a significant difference between AMD affected eyes and age- and gender-matched controls. The comparison between ARM affected eyes and age- and gender-matched controls was just significant ($t = 2.169$, $p = 0.045$). It is worth noting that there were enough participants in each group to have 80 % chance of detecting a difference in means of 2.5 seconds at the 5 % level of significance using an unpaired t-test.

The results of a recent study investigating clinical use of the EMS (Schmitt et al., 2003) found no difference in EMS readings between AMD, cataract, diabetic retinopathy, and glaucoma affected eyes. In this study, one participant was graded with mild AMD, six with moderate AMD, 11 with severe AMD, and 12 with very severe AMD, according to the Age-Related Eye Disease Study (AREDS) system (The AREDS Research Group, 2001). It may be that a significant difference would have been found when analysis was performed on those with later stages of the condition alone. Our results appear to conflict with those of Schmitt et al, 2003, but cannot really be compared as our study did not include eyes affected by other ocular conditions.

In conclusion, the flash-test method employed by the EMS may be considered to be a useful screening tool for ARM, and for assessing the effect of an intervention on progression of age-related macular disease. However, direct illumination of the macular of greater intensity and longer duration may yield less variable results. We found that a change in EMS reading of more than 14 seconds between assessments is likely to indicate a significant clinical change.

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		HB1-LD1	LD2-HB2	HB1-HB2	LD1-LD2
Mean difference (MD)		-0.84	-0.63	0.93	0.95
Paired t-test		t=1.67; p>0.1	t=-1.67; p>0.1	t=2.38; p<0.05	t=1.96; p>0.05
Standard deviation (SD) of MD		3.26	3.42	2.54	3.16
SD of MD x 1.96		6.39	6.70	4.98	6.19
95% Confidence Limits	Upper	5.55	6.07	5.91	7.14
	Lower	-7.23	-7.33	-4.05	-5.24

Table 1: Results of paired-samples t-test analysis and 95% confidence limits for reproducibility and repeatability of the Eger Macular Stressometer (EMS).

Age-group (years)	n	Mean EMS reading (secs)	Standard deviation	Upper 95% CI	Clinical upper limit (secs)
15-24	10	7.8	2.1	11.9	12
25-34	10	8.8	1.8	12.4	12
35-44	5	9.9	2.0	13.9	14
45-54	6	9.8	1.3	12.4	12
55-64	4	13.4	2.1	17.6	18
65+	14	11.4	3.1	17.5	18

Table 2: Normal limits [(mean + (SDx1.96)] for Eger Macular Stressometer (EMS) reading by age-group.

	n	Age (mean ± SD years)	EMS reading (mean ± SD seconds)
Normal	21	67.0 ± 7.1	11.1 ± 2.7
ARM	17	69.4 ± 7.8	17.9 ± 12.3
AMD	12	71.0 ± 4.9	19.3 ± 9.4

Table 3: Mean ± SD EMS readings by group.

Abbreviated title: Clinical Evaluation of the EMS

Figure legends

Figure 1: The Eger Macular Stressometer (EMS)

Figure 2: Difference in Eger Macular Stressometer (EMS) reading between HB1 and HB2, compared with the mean (n = 49 eyes). The mean bias is represented by the solid line, and the 95% confidence limits are known by the dashed lines.

Figure 3: EMS readings plotted against age for participants aged < 50 years. The relationship between the two variables is significant ($F = 6.757$, $p = 0.015$), and $R^2 = 0.213$.

Figure 4: EMS reading plotted against age for participants aged ≥ 50 years. The relationship between the two variables is not significant ($F = 0.290$, $p = 0.597$).