SCIENTIFIC REPORT

Subretinal membranes are associated with abnormal degrees of pupil “evasion”: an index of clinical macular dysfunction

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Aim: To assess whether macular dysfunction caused by unilateral subretinal neovascular membranes (SRNs) is associated with pupil “evasion” (that is, increased initial rate of re-dilation following a brief light stimulus).

Methods: Comparative observational series. 20 eyes of 10 participants, all with unilateral SRNs and healthy fellow eyes. Dynamic infrared pupillography at seven stimulus intensities (duration 1100 ms, intensities over 2 log unit range). Pupil evasion ratio (PEVR; defined as the ratio of light response amplitude to amount of recovery at the mid-time point of re-dilation expressed as a percentage) was calculated for each stimulus intensity (mean of five recordings).

Results: Inter-eye PEVR is significantly reduced in eyes with SRN (that is, greater pupil evasion in SRN eyes: range $p = 0.002$ to $p = 0.05$ (paired t test)) and is most apparent at higher stimulus intensities.

Conclusions: PEVR is a novel parameter that is analogous to the pupil escape ratio, but measured following a short rather than a sustained light stimulus. PEVR is significantly altered by macular disease. Clinically PEVR may be used to detect occult unilateral or asymmetric maculopathy in situations such as ocular media opacities like cataract, when pupil reactions are unaffected or augmented, while other tests of retinal function are diminished. PEVR represents altered neuronal firing in cones and macular ganglion cells.

A brief light stimulus produces an initial transient or “phasic” pupillary constriction.^{1,2} An uninterrupted prolonged light stimulus produces a sustained pupillary constriction, followed sometimes as quickly as after a few milliseconds by slow dilation called escape.^{1,2} Escape is amplified with central field loss.³ The present study describes a novel form of pupil escape (pupil “evasion”) which for the first time is elicited and measured using a very short stimulus. Evasion was determined in patients with unilateral subretinal neovascular membranes (SRNs) allowing assessment of both retinal ganglion cell and grading of visual potential.^{3–5} This may be clinically useful as pupil escape correlates with the relative afferent pupillary defect (RAPD) and, unlike comparative investigations of retinal and optic nerve function, is undiminished or even augmented by media opacities, including common conditions such as cataract that restrict visualisation of the fundus.^{5,6}

MATERIALS AND METHODS

Inclusion and exclusion criteria

Ten consecutive patients with unilateral SRNs and no other ocular pathology in either eye were recruited. There were seven women and three men aged 39–82 (mean 73). Ethics

committee approval was obtained (St Mary’s NHS Trust). An information sheet was provided and informed consent obtained (Declaration of Helsinki). Patients with diabetes mellitus or medication affecting autonomic function were excluded.

Digital recordings of fundus fluorescein angiography (FFA) of suspected subretinal membranes were screened with diagnoses confirmed by clinicians with special retinal expertise at the Western Eye Hospital in London.⁷ Unilateral SRNs were unusual as most were attributable to age related maculopathy (ARM). Participants underwent a battery of psychophysical and clinical tests including logMAR acuity, colour discrimination (Ishihara pseudo-isochromatic plates), perimetry (Humphrey 24-2 and 120-2 full threshold test or Goldmann), pupil reactions and swinging flashlight tests, and dilated funduscopy. Efferent lesions were excluded by clinical signs of autonomic dysfunction using pupillometric measurements of size, and reactivity in dark and light. Patients abstained from caffeine, stimulants, chocolates, and undue physical exercise for 24 hours before the recordings were made, 2 days to 2 weeks after initial tests. Following 20 minutes of dark adaptation the eye was stimulated and the pupil recorded with a modified binocular P_Scan 100 infrared pupillometer (Circuit Solve, Cambridge, UK) previously described in the literature (spatial resolution >0.01 mm, temporal resolution 20 ms).⁸

Following an audible cue, the tested eye was stimulated in non-Maxwellian view using a cathode ray tube display (Iiyama, Japan, Vision Master 506, Model MS103DT). The light stimulus was a square achromatic patch (22×14 degrees). The untested eye was occluded with a covering patch.

An adapting stimulus was presented before each series of stimuli, as first pupil response to light series can poorly represent subsequent reflex behaviour. Seven stimuli in ascending intensity were employed (range $2 \log \text{cd m}^{-2}$), duration 1100 ms each, each presented five times and repeated with the fellow eye. Presentation of stimuli in ascending order of intensity reduces the effect of light adaptation (International Society for Clinical Electrophysiology of Vision).⁹ Time interval between identical stimuli was >10 seconds. The time taken to record all 70 reflex responses in both eyes was approximately 30 minutes.

Recording began 500 ms before stimulus onset and continued for 10 seconds afterwards. Pupil diameter had usually recovered fully to baseline before presentation of a subsequent stimulus; when full recovery did not occur within the 10 seconds a regression function was used to extrapolate

Abbreviations: ARM, age related maculopathy; FFA, fundus fluorescein angiography; MDA, mid-dilation amplitude; PEVR, pupil evasion ratio; PDT, photodynamic therapy; RA, reflex amplitude; RAPD, relative afferent pupillary defect; SRNs, subretinal neovascular membranes

Figure 1 Pupil diameter versus time. (Top) 1100 ms stimulus presented at 500 ms. After reflex latency the pupil constricts, peak constriction amplitude (reflex amplitude, RA) reached at 1400 ms (black arrow). The pupil then dilates (max 3400 ms, indicated by vertical green line), with no further dilation for at least 10 seconds from stimulus onset (not shown). Time interval, t , from time of RA (maximum constriction) to onset of maximal dilation is shown by the horizontal green arrow; half time, $t_{1/2}$, is shown by the blue arrow, and corresponds to the mid-dilation amplitude (MDA). $PEVR = RA / MDA \times 100$. Bottom left, normal pupillogram of participant 4 (stimulus 14 cd m^{-2}). Bottom right, pupillogram from fellow eye of participant 4, but with SRN, same stimulus intensity. PEVR (derived using RAs) correctly identified greater evasion in the pupillogram, bottom right, with the subretinal membrane, despite gross observation suggesting that evasion might be greater in the pupillogram at bottom left. This is because the higher RA in the normal eye, bottom left, in participant 4 at this stimulus intensity creates the false visual impression of evasion, while mathematical calculation of PEVR using the above formula correctly identified the eye at bottom right as the one with the subretinal membrane.

the initial resting diameter. In a few cases the reflex response was superimposed on a shifting baseline and time to full recovery could not be computed—such traces were excluded from the subsequent averaging. Excessive eye movement (erratic fixation >1 degree) was rare but the involved pupillograms were excluded. Digital data filtering removed blink artefact and improved signal to noise ratio. A mean pupillogram (average of five recordings) for each of the seven stimulus intensities was computed for each eye of each participant.

Pupil waveform parameters were measured with P_Scan software using cross hairs, and/or transfer as text (.txt) files to Microsoft Excel. Reflex amplitude (RA, mm) and mid-dilation amplitude (MDA, mm) were calculated from each mean pupillogram of each stimulus intensity (fig 1(top)). A novel index was derived which we term the pupil evasion ratio (PEVR), defined as: $PEVR = (RA/MDA) \times 100$. Multiplication by a factor of 100 is in common with previous electrodiagnostic indices facilitating a readily understandable percentage index.¹⁰

RESULTS

The relation to the RAPD is described (table 1).

Mid-dilation amplitude (MDA) was linearly correlated with the amplitude of the reflex response (RA). Larger reflex amplitudes produced by higher intensity stimuli were associated with greater MDA measurements (fig 2, top). This co-variation masks any independent effect of macular disease on pupil evasion and so MDA estimates were normalised with respect to reflex amplitude by calculating

the pupil evasion ratio. Figure 2 (second plot from top) shows how this estimate is independent of reflex amplitude and better serves as an index of pupil evasion (analogous to escape), with low values for PEVR indicating greater evasion. Figure 2 (lower two plots) indicates how PEVR estimates varied considerably between individuals for the same stimulus intensity (range $<10\%$ to $>1000\%$).

PEVR was consistently smaller in the eyes with SRNs compared with the healthy fellow eyes (fig 3). Figure 3 (top) (participant 2) represents a large subfoveal predominantly classic SRN, $3000 \mu\text{m}$ in diameter, treated with three courses of PDT. At all stimulus intensities except $0.6 \text{ log cd m}^{-2}$ the PEVR is grossly reduced in the diseased eye (paired t test significant (mean difference in PEVR between SRN and control eye = 1954.0% ; $p = 0.002$)) showing macular disease is associated with significantly greater pupil evasion. In most participants the difference in PEVR was not as significant: a more typical example is illustrated in figure 3 (middle plot) (participant 6) with a large untreated subfoveal age related disciform scar $1500 \mu\text{m}$ across. Inter-eye PEVR difference was smaller (range 5–30%) but significant (mean difference = 12.9% , $p = 0.005$ (paired t test)). The least convincing case is nevertheless the participant in whom PEVR was first detected (fig 3, bottom). This participant (4) has a small ($<500 \mu\text{m}$) untreated subfoveal SRN of presumed inflammatory origin. PEVR estimates were distinctly smaller in the diseased eye at four out of the seven stimulus intensities (mean difference in PEVR = 25% ; $p = 0.05$ (paired t test), or $p = 0.04$ (paired t test) excluding the lowest intensity stimulus).

Table 1 Clinical features of the 10 participants with unilateral subfoveal subretinal membranes^{7 11}

Participant	Aetiology	RAPD	Age	Sex
1	Infective. Presumed ocular histoplasmosis. Untreated	No RAPD	39	M
2	ARM with predominantly classic SRN. Treated by three courses of PDT	In diseased eye	53	F
3	ARM with occult membrane. Untreated	In diseased eye	53	F
4	Inflammatory. Suspected punctate inner choroidopathy complicated by SRN formation several years previously. Untreated	No RAPD	55	F
5	ARM. Classic membrane treated by three courses of PDT	In diseased eye	60	F
6	ARM. Occult membrane. Untreated	In diseased eye	68	M
7	ARM. Disciform scar. Untreated	In diseased eye	69	F
8	ARM. Classic membrane treated by one course of PDT	In diseased eye	71	M
9	ARM. Disciform scar. Untreated	In diseased eye	77	F
10	Infective. Presumed ocular histoplasmosis	No RAPD	82	F

ARM, age related maculopathy; PDT, photodynamic therapy; RAPD, relative afferent pupillary defect.

Difference in PEVR between diseased and healthy eyes is slightly more apparent at higher stimulus intensities (fig 2, lower two plots). Greatest inter-eye PEVR differences were generally observed at higher stimulus intensities.

Compared to fellow control eyes, statistically significant reduction in PEVR (greater pupil evasion) was found in all diseased eyes, including participant 4 with a tiny SRN (fig 3).

There was no apparent association between reduction in PEVR and SRN aetiology. There is a possible association with

extreme sizes of SRN. SRNs on FFA ranged from 3000 μm to <500 μm in diameter, and the largest and smallest were associated respectively with the largest and least statistically significant difference in PEVR between fellow eyes, including at all stimulus intensities ($p < 0.002$ and 0.05 , respectively, mean difference in inter-eye PEVR 1954.0% and 25.0%,

Figure 2 (Top) MDA versus constriction amplitude (RA) in a patient, (second from top) PEVR (%) versus RA (same patient); (second from bottom) mean difference in inter-eye PEVR versus stimulus intensity (mean 10 patients), magnified at the bottom. Error bars signify 95% confidence intervals (mean $\pm$ 2 SD).

Figure 3 PEVR versus light intensity. (Top) Participant 2 with a large age related subfoveal SRN previously treated with PDT. (Middle) Participant 6 with a large but untreated age related subfoveal SRN. (Bottom) Participant 4 with a small <500 μm subfoveal SRN of presumed inflammatory origin, with fundus photograph and FFA showing very small SRN.

respectively). This suggests an association between PEVR and visual field may be likely, but χ^2 analysis of all 10 subjects showed no significant overall association between size of SRN and reduction in PEVR ($p > 0.1$). There was no association between the degree of loss of visual acuity (counting fingers or worse in all diseased eyes) and extent of PEVR reduction, presumably as all SRNs involved the fovea. Sex, age, and treatment status had no association with reduction in PEVR in this study.

DISCUSSION

Pupil escape arises because of both retinal and central adaptation processes, and probably includes photopigment bleaching, disappearance of the phasic component and diminution of the tonic component to the "ON" signal in the afferent limb of the reflex, and resetting of the gain in the reflex loop at the level of the midbrain.^{1,2} Patients with lesions of the anterior visual pathways show exaggerated pupil escape.²

Measurement of pupil escape in relation to the peak of the sustained contraction is ineffective in detecting pupil escape.¹² A shortened time period between stimulus onset to when pupil area was greater than 63% of baseline in 13 out of 16 eyes with optic neuritis has been taken to indicate greater pupil escape, perhaps with central field loss, though confounding may have occurred.¹³ When pupil escape is expressed as a ratio incorporating the amplitude of the preceding phasic contraction, the resultant pupil escape ratio can be used to indicate greater pupillary escape.²

When mid-dilation amplitude is expressed as a function of peak phasic constriction with a short duration stimulus, the ratio, called PEVR, is reduced in eyes with SRNs, denoting greater pupil evasion. Concerns about PEVR are that (i) it shows wide variability between eyes (inter-test variability) and fluctuation (intra-test variability), (ii) overlap of PEVR between normal and abnormal eyes; (iii) wide confidence intervals that diminish its differentiating value (fig 2). However, these problems are overcome by the strategy of inter-eye comparison of PEVR between diseased and healthy eyes, where PEVR is greater in normal eyes (less evasion): statistically significant in all participants at all light intensities. This is because inter-eye comparison takes into account the similar autonomic arousal and degree of background sympathetic tone in the iris muscles of both eyes.¹⁴

PEVR correlates with and is more sensitive than the RAPD—for example, only 70% of patients, all with detectable differences in PEVR, had clinically detectable RAPDs (table 1). PEVR aids diagnosis in cases where the RAPD is equivocal (fig 1, bottom).¹¹

Inter-eye PEVR and PER incorporate maximum phasic constriction (reflex constriction). In the 1960s the pupil was modelled using both a rate sensitive process filtering temporal information (transient phasic constriction) and a proportional process dependent on steady state processes (sustained constriction), which is neurally correlated with ganglion cell firing.^{15,16} PEVR algebraically incorporates phasic constriction (representing the sum neuronal firing from both sustained and phasic ON ganglion cells) compared with the subsequent loss of firing from sustained ON ganglion cells only (MDA), making inter-eye PEVR a powerful tool in selected cases. Functionally the PEVR may also represent the activity of the cone rich macula, which partly drives sustained pupillary constriction—this is physiologically plausible as cones are biological sensors of high intensity light and augment pupillary constriction.

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