The association between ocular surface measurements with visual field reliability indices and gaze tracking results in preperimetric glaucoma

Takahiro Arai, Hiroshi Murata, Masato Matsuura, Tomohiko Usui, Ryo Asaoka

ABSTRACT
Background/aims To investigate the relationship between gaze tracking (GT) results and ocular surface condition in glaucoma.
Method The Humphrey 24–2 visual field (VF) was measured in 34 eyes of 30 patients with open-angle glaucoma without VF damage. Tear break-up time, Schirmer’s test, tear meniscus volume (TMV) and presence of superficial punctate keratopathy (SPK) were also measured in order to describe the condition of the ocular surface. Various GT parameters were calculated: the average frequency of eye movements per stimulus between 1° and 2° (move1-2), the average frequency of eye movements per stimulus between 3° and 5° (move3-5), the average frequency of eye movements per stimulus more than 6° (move6+), the average tracking failure frequency per stimulus (TFF) and the average blinking frequency. The relationship between GT parameters, reliability indices and ocular surface measurements was investigated using linear mixed modelling.
Results SPK was positively associated with high rates of move6+ (coefficient=0.052 for SPK+, p=0.023). High TMV was significantly related to TFF (coefficient=0.37, p=0.023). Fixation losses, false-positives and false-negatives were not significantly associated with any GT parameters or ocular surface measurements.
Conclusion SPK is associated with increased frequency of eye movements (move3-5 and move6+). In addition, large TMV is associated with increased rate of TFF. Careful attention should be paid when interpreting GT parameters in patients with SPK or a large TMV.

INTRODUCTION
Reliable visual field (VF) results are imperative for the accurate diagnosis of glaucoma and early detection of disease progression. Fixation losses (FLs), false-positives (FPs) and false-negatives (FNs) are measures of reliability implemented in the Humphrey Field Analyzer (HFA, Carl Zeiss Meditec, Dublin, California, USA). FLs are recorded when the patient perceives a stimulus that is presented in the physiologically blind spot. FPs were traditionally measured using catch trials, and a FP would be recorded when the patient reported seeing a stimulus when one was not presented; however, in the Swedish Interactive Threshold Algorithms (SITA), FPs are measured through the use of ‘listening windows’. These windows are intervals between stimulus presentations when no patient response is anticipated. FNs are recorded when the patient fails to respond to a more intense stimulus than one previously perceived at the same location. All three VF reliability indices are important clinical markers. Elevated FLs can mask early scotoma, increased FP errors indicate ‘trigger-happy’ patients, while a high FN rate may suggest patient inattention or fatigue during the VF examination. Previous studies have reported the usefulness of these indices; however, their limitations have also been reported in more recent studies. For instance, FLs can be increased by mislocalisation of the blind spot, and fixation instability can be experienced even in well-trained examinees. Furthermore, a high FN rate is significantly associated with the amount of field loss, rather than threshold reproducibility, and therefore this index is no longer used in the HFA.

We have investigated the usefulness of gaze tracking (GT) in assessing the reproducibility and overestimation/underestimation of the VF. GT is a record of eye movement monitored throughout the VF measurement. Currently, the GT results are represented as a printed line diagram at the bottom of the VF printout and can only be subjectively evaluated by clinicians. In our prior studies, GT results were evaluated objectively and quantitatively. However, GT uses a record of infrared video recording of the fixation stimulus (corneal reflex), and hence it may be largely influenced by the scattering of light associated with the condition of the corneal surface, such as superficial punctate keratopathy (SPK) and an abnormal tear film state. Indeed, examples of poor GT due to dry eye have been reported; however, no study has quantitatively analysed the relationship between GT and dry eye. Thus, the purpose of the current study is to investigate the relationship between GT results and ocular surface condition in patients with glaucoma. The purpose of the current study was to investigate the effect of dry eye to GT parameters in glaucomatous eyes and not in normative subjects. However, as GT parameters are significantly related to VF deterioration, only glaucomatous eyes — with no measurable VF damage — were analysed in the current study. We recently reported that, even if a VF criterion for VF damage is not satisfied, VFs of glaucomatous eyes are different from those from normal eyes. Thus, only ‘preperimetric’ glaucomatous VFs were included in the current study to mitigate the effects of obvious VF deterioration.
Figure 1  Illustrated gaze tracking record. An upward bar in the chart indicates fixation disparity and the length of the bar represents the magnitude of disparity. A short downward bar represents tracking failure, while a long downward bar indicates eyelid closure. Gaze tracking parameters were calculated as follows: average TFF per stimulus, the average frequency of eye movement per stimulus between 1° and 2° (denoted by move$_{1-2}$), 3° and 5° (denoted by move$_{3-5}$) and more than 6° (denoted by move$_{>6}$). BF, blinking frequency; TFF, tracking failure frequency.

METHODS
The study was approved by the Research Ethics Committee of the Graduate School of Medicine and Faculty of Medicine at The University of Tokyo. Written consent was given by patients for their information to be stored in the hospital database and used for research. This study was performed according to the tenets of the Declaration of Helsinki.

Subjects
Thirty-four eyes of 30 patients with open-angle glaucoma (16 male and 14 female) were prospectively included in the study. All patients visiting the glaucoma clinic at The University of Tokyo Hospital during the period of February 2016–July 2016 who fulfilled the following criteria were included in the current study: (1) glaucomatous changes in the optic nerve head with or without a retinal nerve fibre layer defect as confirmed by a glaucoma specialist (HM or RA); (2) glaucoma was the only disease causing VF damage; (3) patients were followed for at least 6 months at The University of Tokyo Hospital; and (4) no glaucomatous VF defect, which was defined as a cluster of three or more points in the pattern deviation plot within a single hemifield (superior or inferior) with p values <5%, one of which must have a p value <1%, and/or Glaucoma Hemifield Test results outside normal limits and/or abnormal pattern SD with p <5%.14 All VFs were measured using the HFA (24–2, SITA standard program), and those with FL >50%, FP >50% or FN >50% were excluded following our previous report.7 9

GT measurements
The GT system monitors patients' gaze position at each stimulus presentation. As detailed elsewhere and summarised in figure 1, fixation disparity is represented by an upward bar with the length of the bar showing the magnitude of disparity. A short downward bar represents tracking failure, and a long downward bar indicates eyelid closure. Following our previous reports,7 9 GT data were exported as JPEG images from the Beeline (Tokyo, Japan) data filing system. The following GT parameters were calculated: average tracking failure frequency per stimulus (TFF), average blinking frequency (BF), the average frequency of eye movement per stimulus between 1° and 2° (denoted by move$_{1-2}$), 3° and 5° (denoted by move$_{3-5}$) and more than 6° (denoted by move$_{>6}$). Total magnitude of eye movement was calculated as the movement degree × the average frequency of eye movement (denoted by total move).

Ocular surface condition measurements
Prior to VF measurements, SPK was assessed by fluorescein staining.15 The area of SPK was estimated in four gradations: 0 (no SPK), 1 (less than one-third of cornea), 2 (between one-third and two-thirds of cornea) and 3 (larger than two-thirds of cornea). The density of SPK was graded as 0 (no SPK was present), 1 (SPK was sparse), 2 (moderately dense) and 3 (SPK was high and the lesions overlapped). As the current study included only mild dry eye cases (only one eye had an area score larger than 2 and only three eyes had density scores larger than 2), SPK was defined in a binary fashion: SPK− (SPK area and density scores were 0) or SPK+ (SPK area or density score was >0). Then, tear break-up time (TBUT) was measured three times and the average value was calculated. Alcon Schirmer Standard Tear Test Strips (Fort Worth, Texas, USA) were used to assess anaesthetised tear secretion. In addition to these measurements, after the VF test, tear meniscus volume (TMV) was measured using anterior segment optical coherence tomography (SS-1000; Tomey, Tokyo, Japan), following our previous reports.16–18 Details of the TMV measurement are described elsewhere.16–18 In short, the TMV value was calculated automatically with the integrated tear meniscus area values of the consecutive central 11 images, where the TM area value was defined as an inferior triangular TM area formed by the corneal anterior boundary, the anterior boundary of the lower eyelid and the anterior borderline of the TM.

Statistical analysis
The relationships between GT measurements, FLs FP$s and FNs and ocular surface measurements were first analysed using the Wilcoxon test for comparing numeric values between two groups and also Spearman test for analysing the relationship between two numerical values. Linear mixed modelling, whereby eyes were nested in each patient, was also applied. Standard linear regression analysis makes the assumption that all observations

Table 1  Subject demographics

<table>
<thead>
<tr>
<th>Variables</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean±SD (range)</td>
<td>62.8±12.4 (31–82)</td>
</tr>
<tr>
<td>Gender (male:female)</td>
<td>16:14</td>
</tr>
<tr>
<td>Eye (right:left)</td>
<td>25:9</td>
</tr>
<tr>
<td>MD (dB), mean±SD (range)</td>
<td>−0.5±1.5 (--4.6 to 3.9)</td>
</tr>
<tr>
<td>FL (%), mean±SD (range)</td>
<td>6.5±7.7 (0.0–28.6)</td>
</tr>
<tr>
<td>FP (%), mean±SD (range)</td>
<td>2.1±2.8 (0.0–12.0)</td>
</tr>
<tr>
<td>FN (%), mean±SD (range)</td>
<td>0.2±0.7 (0.0–3.0)</td>
</tr>
<tr>
<td>move$_{1-2}$ (per stimulus), mean±SD (range)</td>
<td>0.70±0.14 (0.15–0.92)</td>
</tr>
<tr>
<td>move$_{3-5}$ (per stimulus), mean±SD (range)</td>
<td>0.12±0.14 (0.0044–0.66)</td>
</tr>
<tr>
<td>move$_{&gt;6}$ (per stimulus), mean±SD (range)</td>
<td>0.02±0.03 (0.0–0.11)</td>
</tr>
<tr>
<td>TFF (per stimulus), mean±SD (range)</td>
<td>0.02±0.03 (0.0–0.15)</td>
</tr>
<tr>
<td>BF (per stimulus), mean±SD (range)</td>
<td>0.03±0.10 (0.0–0.59)</td>
</tr>
</tbody>
</table>

BF, average blinking frequency; FL, fixation loss; FN, false-negative; FP, false-positive; MD, mean deviation; move$_{1-2}$, average frequency of eye movement per stimulus between 1° and 2°; move$_{3-5}$, average frequency of eye movement per stimulus between 3° and 5°; move$_{>6}$, average frequency of eye movement per stimulus more than 6°; TFF, average tracking failure frequency per stimulus.

are independent of each other; however, in the current study, both eyes are nested within patients. Ignoring this grouping of the measurements will result in the underestimation of SEs of regression coefficients, but the linear mixed model adjusts for the hierarchical structure of the data, modelling in a way in which measurements are grouped within subjects.

All analyses were performed using the statistical programming language R V.3.1.3 (The Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Table 1 summarises the study patients’ characteristics. Twenty-four eyes in 21 patients had SPK and 10 eyes in 10 patients did not have SPK. Figure 2 shows the histograms of TBUT, Schirmer’s test result and TMV. Thirty-one eyes in 28 patients had a TBUT shorter than 10 s, and 17 eyes in 14 patients had a Schirmer’s test result shorter than 5 mm.

TBUT was not significantly different between SPK− and SPK+ groups (p=0.94, Wilcoxon-Mann-Whitney test). Similarly, Schirmer’s test result and TMV were not significantly different between SPK− and SPK+ groups (p=0.79 and 0.72, respectively, Wilcoxon-Mann-Whitney test). TBUT was significantly related to Schirmer’s test result (coefficient=0.30, p=0.041, Spearman test) but not TMV (p=0.91, Spearman test). TMV and Schirmer’s test result were not significantly associated (p=0.91, Spearman test). As shown in table 2, similar results were obtained with the linear mixed model; TBUT was not significantly different between SPK− and SPK+ groups (p=0.85, linear mixed model). Similarly, Schirmer’s test result and TMV were not significantly different between SPK− and

Table 2 Comparison of TBUT, Schirmer’s test result and TMV in eyes with and without SPK

<table>
<thead>
<tr>
<th></th>
<th>SPK+ (n=21)</th>
<th>SPK− (n=10)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBUT (s), mean±SD (range)</td>
<td>6.6±2.2 (3.0–11.0)</td>
<td>6.8±3.6 (3.0–13.7)</td>
<td>0.85</td>
</tr>
<tr>
<td>Schirmer’s test result (mm), mean±SD (range)</td>
<td>5.3±3.4 (1–16)</td>
<td>5.6±4.7 (1–16)</td>
<td>0.82</td>
</tr>
<tr>
<td>TMV (mm³), mean±SD (range)</td>
<td>0.034±0.067 (0.0016–0.32)</td>
<td>0.016±0.0092 (0.0016–0.029)</td>
<td>0.41</td>
</tr>
</tbody>
</table>

SPK, superficial punctate keratopathy; TBUT, tear break-up time; TMV, tear meniscus volume.
Relationship between age, gender, TBUT, Schirmer’s test result, TMV and SPK, and various gaze tracking parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Move 1-2</th>
<th>Move 3-5</th>
<th>Move ≥6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender (male)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TBUT (s)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schirmer’s test result (cm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TMV (mm^3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence of SPK</td>
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</table>

- BF: none of the predictors were significantly associated.
- Move 1-2: none of the predictors were significantly associated.
- Move 3-5: only SPK (coefficient=0.12 for SPK+, p=0.0025) was significantly associated.
- Move ≥6: only SPK (coefficient=0.052 for SPK+, p=0.023) was significantly associated.
- Total move: only SPK (coefficient=0.46 for SPK+, p=0.023) was significantly associated.
- TFF: only TMV (coefficient=0.37, p=0.023) was significantly associated.
- BF: none of the predictors were significantly associated.

Table 5 shows the relationship between the outcome variables of FLs, FPs, FNs and the predictor variables of age, gender, TBUT, Schirmer’s test result, TMV and SPK. None of the predictors were significantly related to any of the outcomes. Figure 3 illustrates the GT records of four sample cases.

**DISCUSSION**

In the current study, TBUT, Schirmer’s test result, TMV and SPK were measured in patients with glaucoma, but without glaucomatous VF defects. A number of GT summary parameters were calculated and their relationships with these ocular surface condition measurements were investigated. As a result, it was suggested that SPK is positively associated with move 3-5, and move ≥6. Further, a high TMV was significantly related to TFF. None of the ‘standard’ reliability indices (FLs, FPs and FNs) were related to any of the GT parameters or ocular surface condition measurements.

In glaucoma, ocular surface disease is frequently observed because patients are usually treated with a variety of ocular hypotensive drugs, often in combination. Furthermore, the prevalence of both glaucoma and dry eye increases with increasing age. Many eye-drops that are used to treat glaucoma contain preservatives that can cause ocular surface disease, such as SPK.

VF measurements may exacerbate patients with dry eye, because they are required to fixate on a bright target for a considerably long duration. Previous reports have suggested that the prevalence of ocular surface disease is considerably higher in patients with glaucoma compared with the general population, and as many as half of patients with glaucoma have ocular surface disease symptoms or signs related to dry eye.^{19} In the current study, only 29.4% (10 eyes) had SPK symptoms; only one eye had an SPK area score of 3, and only three eyes had an SPK density score of 2 or 3. This may be because only glaucomatous eyes without glaucomatous VF defects were included in the current study, and extensive intraocular pressure reduction treatments (such as combination therapy) are rarely prescribed in these eyes. In addition, functioning bleb due to trabeculectomy intensifies ocular surface disease,^{20} but it is rarely performed in eyes without VF defects (no one in the current study had undergone a functioning bleb).

SPK+ groups (p=0.82 and p=0.41, respectively, linear mixed model). TBUT was significantly related to Schirmer’s test result (coefficient=0.30, p=0.011, respectively, linear mixed model) but not TMV (p=0.72, linear mixed model). TMV and Schirmer’s test result were not significantly associated (p=0.44, linear mixed model).
this procedure). Despite the relatively low prevalence of SPK in the studied population, there were obvious symptoms of dry eye, as suggested by a high prevalence of a short TBUT (31 eyes) and a short Schirmer’s test result (17 eyes).

A previous study suggested that patients with dry eye exhibit atypical VF defects, such as a defect that does not respect the horizontal meridian and/or has a rather central location in any quadrant; this is probably because these patients tend to avoid blinking during the tests. Indeed, the use of artificial tears before VF testing improved VF results in patients with glaucoma and dry eye. In the current study, the presence of SPK was significantly associated with increased rates of move 3–5 and move 3–5, suggesting poor fixation in patients with dry eye during VF measurements. However, scattered reflex light can be induced by the presence of SPK on the cornea. As a result, increased rates of move 3–5 and move 3–5 could actually be an artefact of the scattered corneal reflex. However, move 3–5 and TFF were not increased with SPK, which suggests our finding is unlikely to be purely due to the scattered corneal reflex.

BF was not associated with TBUT, Schirmer’s test result, TMV or SPK. Van Went et al investigated the corneal sensitivity in patients with glaucoma or ocular hypertension, and reported that intraocular pressure-lowering medications, including benzalkonium chloride, were associated with decreased corneal sensitivity. Furthermore, corneal sensitivity decreases with increasing age. This may explain why increased BF was not correlated with ocular surface condition. In addition, Wang et al investigated the occurrence of blinking during VF measurements, using a video eye-tracker system, and suggested that, for suprathreshold stimuli, blinks often occurred after the presentation, although there was no relationship to presentation time for subthreshold presentations. The HFA GT measurement is recorded at the time of the target presentation, and this may be another reason why BF was not associated with TBUT, Schirmer’s test result, TMV or SPK.

There is no well-defined reference range for TMV; however, in normal subjects it has been reported as 0.1327±0.051 mm³ which is much larger than observed in the current study, where TMV averaged 0.034 and 0.016 mm³ in the SPK+ and SPK− groups, respectively, and only one eye had a TMV larger than 0.1327 mm³. This difference may be due to the large difference in ages studied because it has been reported TMV decreases with increasing age; the average age in the prior study was 36.5±6.8 years, while the average age in the current study was 62.8±12.4 years. Furthermore, TMV was measured after VF testing, which may have reduced TMV due to decreased blinking. However, in the current study, high TMV was associated with increased rates of TFF. This implies the GT record is less reliable in eyes with high TMV. We have recently reported that a high TFF rate is associated with poor VF test–retest reproducibility. High TMV is also observed in patients with other ocular disorders. Ohtomo et al compared TMV before and after dacryocystorhinostomy and showed that TMV is decreased after the procedure. The obstruction of the lacrimal drainage system is frequently seen in elderly patients and careful consideration is recommended when interpreting VFs in patients with high TMV or a high TFF.

The age range of patients in the current study was wide (31–82 years old); however, age was not related to any of the classic reliability indices (FLs, FPs and FNs) or GT parameters, and the same was also true of gender. However this does not deny a relationship between age and GT parameters, and a different outcome may be observed if a larger population is analysed. Nonetheless, it was suggested there is a significant relationship between dry eye and GT parameters in the current study.

In the current study, FLs, FPs and FNs were not related to ocular surface measurements. On the other hand, Yenice et al compared TMV with other ocular disorders. Ohtomo et al investigated the corneal sensitivity in patients with glaucoma or ocular hypertension, and reported that intraocular pressure-lowering medications, including benzalkonium chloride, were associated with decreased corneal sensitivity. Furthermore, corneal sensitivity decreases with increasing age.

**Figure 3** Four example GT records with high TFF, move 3–5 and move 3–5, rates. Top: A case with high TFF (short downward bars) and TMV: TFF, 0.15 per stimulus; TBUT, 7.0 s; Schirmer’s test, 4 mm; TMV, 0.32 mm³; SPK area, 0; SPK density, 0; FL, 7.1%; FP, 1.0%; FN, 0.0%. Second from top: A case with high TFF and TMV: TFF, 0.071 per stimulus; TBUT, 3.3 s; Schirmer’s test, 1 mm; TMV, 0.13 mm³; SPK area, 0; SPK density, 0; FL, 0%; FP, 0%; FN, 2%. Second from bottom: A case with high move 3–5 and move 3–5 (short and long upward bars) rates and SPK score: TBUT, 9.0 s; Schirmer’s test, 4 mm; TMV, 0.02 mm³; SPK area, 1; SPK density, 2; FL, 0%; FP, 5%; FN, 0%. Bottom: A case with high move 3–5 and move 3–5 rates and SPK score: TBUT, 3.0 s; Schirmer’s test, 5 mm; TMV, 0.03 mm³; SPK area, 1; SPK density, 3; FL, 0%; FP, 1%; FN, 0%. BF, average blinking frequency; FL, fixation loss; FN, false negative; FP, false positive; GT, gaze tracking; move 3–5, average frequency of eye movement per stimulus between 3° and 5°; move 3–5, average frequency of eye movement per stimulus more than 6°; SPK, superficial punctate keratopathy; TBUT, tear break-up time; TFF, average track rate; TMV, tear meniscus volume.

**Table 5** Relationship between age, gender, TBUT, Schirmer’s test result, TMV and SPK, and FL, FP and FN rates

<table>
<thead>
<tr>
<th>FL</th>
<th>FP</th>
<th>FN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td><strong>Coefficient</strong></td>
<td><strong>SE</strong></td>
</tr>
<tr>
<td>Gender (male)</td>
<td>0.0057</td>
<td>0.0013</td>
</tr>
<tr>
<td>TBF (s)</td>
<td>-0.0079</td>
<td>0.030</td>
</tr>
<tr>
<td>Schirmer’s test result</td>
<td>0.0023</td>
<td>0.0043</td>
</tr>
<tr>
<td>TMV (mm³)</td>
<td>-0.092</td>
<td>0.27</td>
</tr>
<tr>
<td>Presence of SPK</td>
<td>-0.011</td>
<td>0.033</td>
</tr>
</tbody>
</table>

FL, fixation loss; FN, false-negative; FP, false-positive; SPK, superficial punctate keratopathy; TBUT, tear break-up time; TMV, tear meniscus volume.
reported that the use of artificial tears improved these indices in patients with glaucoma and dry eye. These somewhat contradictory results could be ascribed to differences in the enrolled patients. In our study, the presence of dry eye was not required. As a result, very few patients suffered from severe dry eye, as suggested by the mild SPK scores. Thus, a different outcome may have been observed if the current investigation had been carried out in patients with severe dry eye. It should also be noted that the number of studied eyes was based on a sample size calculation to analyse the relationship between dry eye status and GT parameters, using linear mixed modelling. The comparison between SPK+ and SPK− groups, carried out as a subanalysis, may require a different sample size; hence the results of the comparison between these two groups could be different with a different sample size.

In conclusion, the presence of SPK is associated with increased rates of move<sub>1</sub>, and move<sub>4</sub>. In addition, high TMV is associated with an increased rate of TFF. Careful consideration is needed when assessing GT results in patients with these characteristics.

**Contributors**  
Conception or design of the work: RA, HM, TU. Acquisition, analysis or interpretation of data: RA, HM, TU, TA, MM. Drafting the work or revising: RA, HM, TU, TA, MM. Final approval of the version published: RA, HM, TU, TA, MM.

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**Competing interests**  
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**Patient consent**  
Obtained.

**Ethics approval**  
Ethics Board of Tokyo University.

**Provenance and peer review**  
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