The usefulness of CorvisST Tonometry and the Ocular Response Analyzer to assess the progression of glaucoma

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Corneal Visualization Scheimpflug Technology (CST) and Ocular Response Analyzer (ORA) measurements were carried out in 105 eyes of 69 patients with primary open-angle glaucoma. All patients had axial length (AL), central corneal thickness (CCT), intraocular pressure (IOP) with Goldmann applanation tonometry (GAT) and eight visual fields (VF)s with the Humphrey Field Analyzer. VF progression was summarized using a time trend analysis of mean total deviation (mTD) and the association between mTD progression rate and a number of ocular parameters (including CST and ORA measurements) was assessed using mixed linear regression analysis. The optimal model of VF progression selected based on the corrected Akaike Information Criteria (AICc) included ORA’s corneal hysteresis (CH) parameter as well as a number of CST measurements: mTD progression rate = 1.2 – 0.070 * mean GAT + 0.090 * CH – 1.5 * highest concavity deformation amplitude with CST + 9.4 * A1 deformation amplitude with CST – 0.05 * A2 length with CST (AICc = 125.8). Eyes with corneas that experience deep indentation at the maximum deformation, shallow indentation at the first applanation and wide indentation at the second applanation in the CST measurement are more likely to experience faster rates of VF progression.

Glaucoma is the second leading cause of blindness worldwide, affecting approximately 60 million peoples1. The disease causes irreversible visual field (VF) damage so it is very important to predict its progression and make appropriate interventions as soon as possible. The principal target of glaucoma treatments is to reduce and control intraocular pressure (IOP), which has been shown to reduce VF progression by numerous clinical trials and research studies2–10. Tonometry measurements of IOP can be greatly influenced by structural properties of the eye; in particular, IOP measured with Goldmann applanation tonometry (GAT) has been shown to be affected by central corneal thickness (CCT)11–23. Thus, CCT should be considered when interpreting GAT-measured IOP and making clinical decisions. Furthermore, studies have suggested that CCT is associated with the progression of glaucoma4,24. Other biomechanical properties of the cornea have also been shown to affect the progression of glaucoma. In particular, corneal hysteresis (CH) and corneal resistance factor (CRF), measured with the Ocular Response Analyzer (ORA, Reichert Ophthalmic Instruments, Depew, NY, USA), have been reported to impinge on progression25,26.

The Corneal Visualization Scheimpflug Technology instrument (Corvis ST tonometry: CST; Oculus, Wetzlar, Germany) is a new device, integrated with an ultra-high-speed Scheimpflug camera, to quantitatively measure biomechanical properties of the cornea during the application of a rapid air-puff27. As a result, very detailed corneal movement during the air puff application can be observed, such as velocity of corneal deformation at the first and second applanations and the maximum depth of corneal deformation (Fig. 1). Although CST and ORA both measure the biomechanical properties of the cornea, their mechanisms are completely different, and the relationship between CST-measured corneal parameters and the progression of glaucomatous VF damage...
has not been reported in detail. Jung et al. have reported the relationship between maximum depth of corneal deformation against peripapillary atrophy area and the disc tilt ratio in patients with glaucoma, however more detailed investigation has not been reported, such as the relationship between visual field progression rate and various (twelve) CST parameters, including maximum depth of corneal deformation.

Therefore, the purpose of the current study is to investigate the effect of ORA- and CST-measured parameters on the progression of glaucomatous VF damage in patients with primary open angle glaucoma (POAG).

**Method**

The study was approved by Research Ethics Committee of the Graduated School of Medicine and Faculty of Medicine at The University of Tokyo. Written informed 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.

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**Figure 1. Corneal movement during the CST measurement.** In the CST tonometry measurement, a rapid air puff is applied to cornea and cornea moves inward whereas ORA measures air jet pressure at the events of first and second applanations. The figures show the corneal shape in each phase: (A) prior to air puff applanation, (B) first applanation, (C) highest concavity, (D) second applanation, and (E) posterior to air puff applanation. CST: Corvis ST tonometry, ORA: Ocular Response Analyzer.
Subjects. One hundred and five eyes of 69 POAG patients (36 males and 33 females) were included in this study. POAG was defined as (1) presence of typical glaucomatous changes in the optic nerve head such as a rim notch with a rim width <0.1 disc diameters or a vertical cup-to-disc ratio of >0.7 and/or a retinal nerve fiber layer defect with its edge at the optic nerve head margin greater than a major retinal vessel, diverging in an arcuate or wedge shape; and (2) gonioscopically wide open angles of grade 3 or 4 based on the Shaffer classification. All patients had at least 9 VFs measured with the Humphrey Field Analyzer II (HFA, Carl Zeiss Meditec Inc., Dublin, CA, USA), with the SITA standard 24-2 or 30-2 program. Reliable VFs were defined as Fixation loss (FL) rate <20% and False positive (FP) rate <15% following the criteria used in the HFA software; false negative (FN) was not used as an exclusion criterion. Reliable VFs were identified and eyes with at least eight reliable VFs were investigated, excluding the first VF measurement. We chose a minimum of eight VFs because it has recently been reported that this number is needed to precisely analyze VF progression29–33. Eyes that experienced any surgical procedure, including trabeculectomy and cataract surgery, during or prior to this VF series period were excluded. Inclusion criteria were no abnormal eye-related findings except for OAG on biomicroscopy, gonioscopy and funduscopy. Eyes with a history of other ocular disease, such as age-related macular degeneration were also excluded. Eyes with significant cataract which affects VF were carefully excluded. Only subjects aged ≥20 years old were included and eyes with IOP > 25 mmHg or contact lens wearers were excluded. If both eyes satisfied the inclusion criteria, then both were included in the study. Axial length (AL) and CCT were also measured in all patients using the IOL Master, ver. 5.02 (Carl Zeiss Meditec Inc., Dublin, CA, USA) and CST, respectively. CST was performed after the final (8th) VF measurement.

ORA measurements. ORA records two applanation pressure measurements, prior to and following indentation by a rapid jet of air. Due to its viscoelastic property, the cornea resists the air puff, resulting in delays in the inward and outward applanation events, which causes a measureable difference in air puff values. This difference is called CH, while CRF represents the resistance of cornea34.

Both ORA and CST were carried out three times (on the same day) prior to the GAT-IOP measurement and within 180 days from the eight VF measurement. The average value of the three measurements was used in the analyses. The order of ORA and CST measurements was decided randomly. All data were of sufficient quality, as guaranteed by analyzing only eyes with a quality index >7.5.

Corvis ST tonometer measurements. The principles of CST are described in detail elsewhere27. In short, the instrument’s camera records a sequence of images that capture corneal deformation following a rapid air puff. The device is capable of capturing 4,330 images per second that are analyzed to quantify CCT, deformation amplitude, applanation length and corneal velocity. Each measurement is further distinguished as follows: ‘A1’/’A2 time’ is the length of time from the initiation of the air puff to the first (cornea moves inwards) or second applanation (cornea moves outwards); ‘A1/2 length’ is the length of the flattened cornea at the first or second applanation; ‘A1/2 velocity’ is the velocity of the movement of cornea during the first or second applanation; ‘A1/2 deformation amplitude’ is the movement of the corneal apex of the flattened cornea at the first or second applanation; ‘peak distance’ is the distance between the two surrounding peaks of the cornea at the highest concavity; ‘highest concavity deformation amplitude’ is the magnitude of movement of the corneal apex from before deformation to its highest concavity; ‘highest concavity time’ is the length of the time taken to reach highest concavity from pre-deformation of the cornea; ‘radius’ is the central curvature radius at the point of highest concavity.

CST (software version; 1.2r1092) was performed three separate times, on the same day, with at least a one minute interval between each repeat measurement of ORA and CST. Averages of CST parameters were calculated for the three repeated tests. All CST measurements were considered reliable according to the “OK” quality index displayed on the device monitor.

Other measurements. The mean and standard deviation (SD) of all GAT-IOP measurements during the follow up period were calculated.

VF data. The mean total deviation (mTD) of the 52 test points used in the 24-2 HFA VF test pattern was calculated, for both of 24-2 and 30-2 HFA VFs. The progression rate of mTD was calculated using the eight VFs collected from each eye, similarly to the MD trend analysis employed in the HFA.

Statistical analysis. The relationship between ORA (CH and CRF), CST parameters (A 1/2 time, A 1/2 length, A 1/2 velocity, A 1/2 deformation amplitude, highest deformation amplitude, highest concavity time, peak distance, and radius) and other ocular/systemic parameters (age, mean GAT, SD of GAT, CCT, AL, and mTD in the initial VF) against mTD progression rate was investigated using a linear mixed model with patient as a random effect (because one or two eyes of a patient were included). The optimal linear mixed model (model\textsubscript{full}) to describe mTD progression rate using ocular/systemic parameters was selected according to the second order bias corrected Akaike Information Criterion (AIC\textsubscript{c}) index. Two further models were selected adding only ORA parameters and also both ORA and CST parameters (model\textsubscript{ORA} and model\textsubscript{ORA,CST}, respectively). The AIC\textsubscript{c} is the corrected form of the common statistical measure of AIC. AIC\textsubscript{c} gives an accurate estimation even when the sample size is small35. In a multivariate regression model, degrees of freedom decreases as the number of variables increases, hence it is recommended to use model selection methods to improve the model fit by removing redundant variables36,37. Any magnitude of reduction in AIC\textsubscript{c} suggests an improvement of the model, and the probability that one particular model is the model that minimizes ‘information loss’ can be calculated; when there are \( n \) candidate models and the AIC\textsubscript{c} values of those models are AIC\textsubscript{c1}, AIC\textsubscript{c2}, AIC\textsubscript{c3}, ..., AIC\textsubscript{cn}. If AIC\textsubscript{cmin} is the minimum of these values then exp((AIC\textsubscript{cmin} - AIC\textsubscript{i})/2) describes the relative probability that the ith model minimizes the information loss (i.e. is the ‘optimal model’)38. Relative probabilities were calculated among all candidate models.
All statistical analyses were performed using the statistical programming language ‘R’ (R version 3.2.3; The foundation for Statistical Computing, Vienna, Austria).

**Results**

Characteristics of the study subjects are summarized in Table 1. The mean ± standard deviation (SD) [range] age was 63.2 ± 9.7 [43 to 85], 36 patients were male and 33 patients were female. Eight VFs were measured over an average period of 2412.2 ± 868.9 [630 to 6881] days. GAT was conducted 29.0 ± 7.1 [18 to 69] times during the follow up period (between the initial VF and the eighth VF). Mean GAT-IOP was 13.5 ± 2.2 [8.9 to 20.2] mmHg with an SD value of 1.5 ± 0.47 [0.79 to 3.6].

Summary statistics of CST and ORA measurements are shown in Table 2. The modelled relationships between mTD progression rate and mean GAT, SD of GAT, ORA parameters and CST parameters are shown in Table 3. A significant relationship was observed for age and CH (p = 0.032 and 0.049, respectively, linear mixed model).

As a result of model (parameter) selection, the optimum equation for model basic was: mTD progression rate = 0.32 (intercept) − 0.0094 * age (AICc = 132.3); thus all other variables (mean GAT, SD of GAT, CCT, AL and mTD in the initial VF) were not deemed to improve the model. The equation for model ORA was: mTD progression rate = −0.35 − 0.0083 * age + 0.065 * CH (AICc = 131.4). The equation for model ORA_CST was: mTD progression rate = 1.2−0.070 * mean GAT + 0.090 * CH + −1.5 * highest deformation amplitude + 9.4 * A1 deformation amplitude − 0.05 * A2 length (AICc = 125.8). The probability that model ORA minimizes information loss compared to model basic was 36.2%. The probability that model ORA_CST minimizes information loss compared to model ORA and model basic was 93.9% and 96.1%, respectively.

**Discussion**

In the current study CST and ORA measurements were carried out in 105 eyes of 69 patients with POAG. In models describing the progression rate of mTD, the inclusion of CH and CST parameters resulted in the most favorable model. This model included mean GAT-IOP (higher IOP leads to faster progression) and CH (lower CH indicates faster progression) agreeing with previous studies, as well as highest concavity deformation amplitude (the higher the amplitude, the faster progression), A1 deformation amplitude (lower amplitude suggests faster progression), A2 length (larger length leads to faster progression).

Interestingly, model basic did not include mean GAT-IOP, despite its undoubtedly influence on VF progression. However, this does not deny the importance of IOP control in the management of glaucoma. The current study analyzed clinical data from a real world setting where IOP reduction interventions would be
calculated as the area surrounded by the loading and unloading curves, which is thought to reflect less compression and the magnitude of the energy absorption can be calculated as the area surrounded by the loading and unloading curves. Baseline VF damage may or may not be related to faster VF progression. In particular, baseline CH and highest deformation amplitude are related to faster progression of glaucoma. Surprisingly, age was not included in model ORA_CST, however, this parameter is related to age. In particular, highest deformation amplitude increases as age increases. Thus, the current results may suggest that the acceleration of age on VF progression may actually be driven by a change in CH and/or highest deformation amplitude. This is clinically very important because an eye with a low CH and a large highest deformation amplitude has a greater risk of progression at any age.

CCT has also been reported to be associated with the progression of glaucoma, however, CCT was not selected in any of our models in the current study. Recent studies have reported that CH is a stronger risk factor for the progression of glaucoma than CCT. Baseline VF damage may or may not be related to faster VF progression; however, in the current study, mTD in the initial VF was not included in any of the optimal models.

Interestingly, the AICc of model ORA_CST was significantly smaller than the AICc of model ORA, suggesting that eyes with corneas experiencing a deeper indentation following the CST air-puff are likely to progress at a faster rate. The hysteresis of a viscoelastic material is defined as the amount of energy absorption during the ‘loading/unloading’ stress/stRAIN cycle and the magnitude of the energy absorption can be calculated as the area surrounded by the loading and unloading curves, which is thought to reflect less compliance of the lamina cribrosa and thus provide further information about glaucoma risk. A deeper highest deformation amplitude indicates the change of shape of the loading/unloading curves. Its effect on the progression of glaucoma has not been examined in detail so a further study should be carried out to shed light on this finding. Further, a wide planed area at the second applanation (A2 length) may be related to a deeper indentation at the maximum deformation. Smaller movements of the corneal apex at the first applanation were related to faster progression in the current study. A smaller movement of the corneal apex at the first applanation may be related to faster progression in the current study. A smaller movement of the corneal apex at the first applanation may be related to faster progression in the current study.

Table 3. The relationship between CST/ORA parameters and various ocular parameters, and visual field progression rate. Bold characters represent $p < 0.05$. CST: Corvis ST tonometry, ORA: ocular response analyzer.

| Parameter                      | Coefficient | Standard error | p value | AICc |
|--------------------------------|-------------|----------------|---------|------|
| age (years old)                | 0.0094      | 0.0043         | 0.032   | 132.3|
| mean GAT (mmHg)                | -0.017      | 0.019          | 0.38    | 136.2|
| SD of GAT (mmHg)               | -0.076      | 0.092          | 0.41    | 136.3|
| CCT (mm)                       | 0.00070     | 0.00120        | 0.52    | 136.5|
| axial length (mm)              | 0.019       | 0.026          | 0.47    | 136.5|
| mTD in the initial VF          | 0.0057      | 0.0057         | 0.40    | 136.2|
| A1 time (ms)                   | 0.21        | 0.15           | 0.16    | 134.9|
| A1 length (mm)                 | -0.20       | 0.60           | 0.74    | 136.9|
| A1 velocity (m/s)              | -2.7        | 3.1            | 0.37    | 136.3|
| A1 deformation amplitude (mm)  | 6.7         | 5.2            | 0.20    | 135.1|
| A2 time (ms)                   | -0.026      | 0.094          | 0.78    | 136.9|
| A2 length (mm)                 | -0.18       | 0.19           | 0.33    | 136.1|
| A2 velocity (m/s)              | 0.72        | 0.55           | 0.20    | 135.1|
| A2 deformation amplitude (mm)  | -0.11       | 0.60           | 0.86    | 136.9|
| highest deformation amplitude (mm) | -0.59     | 0.39           | 0.13    | 134.7|
| highest concavity time (ms)    | 0.0019      | 0.075          | 0.98    | 137.0|
| Peak distance (mm)             | -0.053      | 0.051          | 0.30    | 135.4|
| Radius (mm)                    | 0.072       | 0.050          | 0.15    | 134.8|
| CH (mmHg)                      | 0.076       | 0.038          | 0.049   | 132.8|
| CRF (mmHg)                     | 0.045       | 0.030          | 0.14    | 134.6|
CST parameters in long-term follow-up, it should be investigated in a future study. Also, it is the mTD (or mean deviation) slope trend analysis most frequently used at the clinical settings, and hence we used this method to evaluate VF progression. However it is also true mTD slope analysis may miss focal progression. There is no gold standard method to evaluate the focal progression, but it may be the best way to divide VF into small clusters and evaluate the influence of CST parameters in each sector, which should be carried out in a following study. Also, it would be needed to further confirm the current result using an independent population.

In conclusion, it is advantageous to carry out CST tonometry in addition to ORA when assessing the progression of glaucomatous VF change. Careful glaucoma management is required in eyes with any of the following characteristics: a low CH, a large highest concavity deformation amplitude, a large A2 length, or, a small A1 deviation) slope trend analysis most frequently used at the clinical settings, and hence we used this method to evaluate VF progression. However it is also true mTD slope analysis may miss focal progression. There is no gold standard method to evaluate the focal progression, but it may be the best way to divide VF into small clusters and evaluate the influence of CST parameters in each sector, which should be carried out in a following study. Also, it would be needed to further confirm the current result using an independent population.

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Acknowledgements
This work was partially supported by Japan Science and Technology Agency (JST) - CREST and Grant 26462679 from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

Author Contributions
M.M. and K.H. prepared the material. M.M. and R.A. wrote the main manuscript text prepared figures. M.M., K.H., H.M., S.M., Y.K., and R.A. reviewed the manuscript.

Additional Information
Competing financial interests: The authors declare no competing financial interests.

How to cite this article: Matsuura, M. et al. The usefulness of CorvisST Tonometry and the Ocular Response Analyzer to assess the progression of glaucoma. Sci. Rep. 7, 40798; doi: 10.1038/srep40798 (2017).

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