Title: Corneal Biomechanics and Biomechanically-corrected Intraocular Pressure Measurements of Primary Open Angle Glaucoma and Ocular Hypertension.

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ABSTRACT

Purpose: To compare the biomechanically-corrected IOP estimate (bIOP) provided by the Corvis with Goldmann Applanation Tonometry(GAT-IOP) in patients with high and normal tension primary open angle glaucoma (POAG; HTG and NTG), ocular hypertension (OHT) and normal controls. Further, we aimed to assess and compare corneal biomechanics parameters (DCRs) in the POAG, OHT and control groups, and evaluate the correlation between global visual field parameters (MD and PSD) and corneal biomechanics in the POAG group.

Design: Prospective, single centre, clinical trial

Participants: One hundred and fifty-six eyes of 156 patients were included, namely 74 POAG patients (41 HTG and 33 NTG), 45 OHT cases and 37 controls.

Methods: Central corneal thickness (CCT), GAT-IOP and bIOP were measured in all participants, GAT-IOP was also adjusted for CCT (GATAdj). Corneal biomechanics with DCRs provided by Corvis ST, MD and PSD were recorded by 24-2 full-threshold Humphrey visual field.

Main Outcome Measures: Values of bIOP, GAT-IOP, GATAdj-IOP, CCT, DCRs, MD and PSD.

Results: There was a significant difference between GAT-IOP, GATAdj and bIOP in high and normal tension POAG, OHT and controls. In all groups, bIOP was significantly lower than GAT and GATAdj ($p< 0.01$). Biomechanical analysis, which took age, sex CCT, IOP and treatment into account, showed that NTG patients had significantly softer corneas compared to controls, OHT and HTG. This was demonstrated by significantly lower values of Stiffness Parameter A1 and Highest concavity (both $p< 0.05$) and significantly higher values of Inverse Concave Radius (both $p< 0.05$). When considering the correlation between global visual field parameters (MD, PSD) POAG patients with softer corneas were significantly more likely to show visual field defects compared to those with normal

biomechanics. This was demonstrated by significant correlation($p<0.05$) between MD and PSD and many DCRs.

Conclusions: Our study suggests that corneal biomechanics might be a significant confounding factor for the measurement of IOP that should be considered in clinical decision making. The abnormality of corneal biomechanics in POAG (HTG and NTG) and the significant correlation with visual field parameters might suggest abnormal corneal biomechanics as a new risk factor for the development or progression of POAG.

INTRODUCTION

Glaucoma, a major cause of irreversible blindness,[1] is a disease characterised by progressive optic neuropathy and visual field loss with or without raised intraocular pressure (IOP). Normal tension glaucoma (NTG) is a form of primary open angle glaucoma (POAG), in which IOP remains within normal levels (≤21 mmHg); while high-tension POAG (HTG) is associated with elevated IOP (>21 mmHg). The role of IOP in the pathogenesis of NTG is controversial and other factors have been hypothesized to have a role in glaucoma neuropathy in NTG such as vascular dysregulation, hypotension, and lamina cribrosa abnormalities.[2] Biomechanical properties of the optic nerve head and peripapillary scleral connective tissue have been postulated to determine how these structures respond to IOP, which may account for why some patients are susceptible to glaucomatous damage even under normal levels of IOP.[3] Nevertheless, since the cornea and sclera are continuous collagenous sheaths, made up of similar extracellular matrix constituents, the biomechanical properties of the cornea may be related to those of the lamina cribrosa (LC), which determine the response of the optic nerve head (ONH) to IOP and the amount of axonal nerve damage.[4, 5] Assessment of corneal biomechanics may therefore offer an indirect measurement of the LC elasticity, and hence an indication of susceptibility to glaucomatous damage. This link has been confirmed in certain forms of glaucoma (NTG) which showed that a low corneal hysteresis (CH) measured by the Ocular Response Analyzer (ORA, Reichert Ophthalmic Instruments, NY, USA) was associated with progressive visual field loss.[4, 6]

Ocular hypertension (OHT), on the other hand, describes elevated IOP in the absence of glaucomatous optic nerve damage or visual field loss. It affects 3-5% of the UK population over the age of 40 and represents a major risk factor for the development of POAG (NICE CKS 2016).

There is overwhelming evidence from several prospective randomised multi-centre studies that the reduction of IOP is neuro-protective, in the sense that it delays or even prevents the structural and functional damage of optic nerve axons in different forms of glaucoma including NTG.[7-9] For this reason, the accurate measurement of IOP is an essential component of glaucoma management including case definition and in planning treatment. However, the accuracy of IOP measurement is influenced by the biomechanical properties of the cornea, of which the most important are corneal thickness and material stiffness.[10] The challenge to produce IOP measurements with reduced biomechanics effect has been addressed by the non-contact tonometer CorVis ST (Oculus, Wetzlar, Germany) in the form of biomechanically-corrected IOP (bIOP). The bIOP algorithm is based on a finite element model (FEM) which can compensate for CCT, age and biomechanics[11] and was recently validated by ex-vivo validation experiments (data in-press).

The aim of this study was to compare the bIOP estimates with Goldmann Applanation Tonometry IOP (GAT-IOP) in patients with primary open angle glaucoma (HTG and NTG), ocular hypertension (OHT) and in healthy controls. Further, we aimed to assess and compare corneal biomechanics parameters, provided by the CorVis ST, in the POAG, OHT and control groups, and evaluate the correlation between visual field parameters and corneal biomechanics in the POAG group.

MATERIALS AND METHODS

Population

Patients diagnosed using the criteria described below with primary open angle glaucoma (POAG: HTG and NTG), ocular hypertension (OHT) and healthy subjects were recruited over a period of eight months in St Paul's Unit, Royal Liverpool University Hospital, UK. The

study data was acquired under ethical approval for service development audit purposes. All patients provided informed consent for using their anonymised data in the study prior to the study commencement.

Inclusion Criteria

- HTG: open angle gonioscopy, progressive visual field defects confirmed by at least two successive visual field tests and/or ONH cupping and an untreated GAT-IOP greater than 21 mmHg.
- NTG: open angle gonioscopy, progressive visual field defects confirmed by at least two successive visual field tests and/or ONH cupping and an untreated GAT-IOP less than or equal to 21 mmHg.
- OHT: open angle gonioscopy, no progressive visual field defects in at least two successive visual field tests and/or ONH cupping and an untreated GAT-IOP greater than 21 mmHg.
- Healthy controls: the participants were recruited in the cataract clinic, the inclusion criteria were an untreated GAT-IOP lower than 21 mmHg, healthy discs and no previous ocular pathologies.

The definition of glaucomatous visual field defect was defined by two glaucoma hemifield tests graded “outside normal limits” and a cluster of three contiguous points at the 5% level on the pattern deviation plot, using the threshold test strategy with the 24-2 test pattern of the Zeiss-Humphrey field analyzer.[12]

Exclusion Criteria

Exclusion criteria included refractive errors that could falsely influence applanation tonometry or optical coherence tomography (OCT) assessment of retinal nerve fiber layer (hypermetropia or myopia >5 diopters [D], and/or astigmatism >3 D), best-corrected visual

acuity <20/40, ocular conditions that could mimic glaucomatous visual field loss particularly congenital or acquired optic nerve diseases, or systemic conditions that could affect ocular blood flow – particularly diabetes mellitus and cerebrovascular diseases. Exclusion criteria also included previous ocular or intraocular surgery (such as cataract surgery, trabeculectomy, deep sclerectomy and laser refractive procedures – LASIK and PRK); previous ocular trauma or corneal scarring.

Ophthalmological examination

All participants underwent initial uncorrected and corrected Snellen visual acuity, slit-lamp anterior segment examination, fundus examination using slit-lamp biomicroscopy, assessment of optic disc including vertical cup-disc ratio and gonioscopy. Patients in the OHT and POAG groups also underwent automated perimetry using Humphrey Field Analyzer II (Carl Zeiss Meditec, Jena, Germany), with a full threshold 24-2 SITA-standard program for visual field testing. Global visual field parameters including mean deviation (MD) and pattern standard deviation (PSD) were recorded.

IOP (a mean of 3 measurements) and CCT measurements (a mean of 5 measurements) were recorded using Goldmann applanation tonometry (GAT-IOP ,Haag-Streit, Switzerland) and ultrasound pachymetry (DGH 55B Pachmate 2), respectively, as well as corneal biomechanics and IOP measurement using the Corvis ST. GAT-IOP was adjusted for pachymetry (GATAdj) using the manufacturer's correction algorithm provided with the Pachmate 2, which is based on a reference corneal thickness of 545 μm from the work of Kohlhaas et al.[13] All measurements were taken between 09:00 and 17:30 and recorded. Risk factors for glaucoma were also recorded for each patient.

Corvis Measurements

All measurements with the Corvis ST were captured by automatic release upon alignment with the corneal apex and by the same experienced researchers (S.F, R.V, N.V.). Only examinations with a quality score of 'OK' were included in the analysis. Factors that influenced the quality of measurements included alignment, model deviation (e.g. unreliable edge detection), image obscured by lids or eyelashes, lost images (e.g. if patient blinks) and deviation of the air pressure pulse from the reference air pulse.

Dynamic Corneal Response Parameters

The Corvis ST provides a set of Dynamic Corneal Response parameters (DCRs) based on monitoring of the dynamic corneal response to air pressure (summarized in Table 1). [14, 15] All these parameters were previously described.[16, 17] The Corvis software also included two novel stiffness parameters; SP-A1 (recorded at point of first applanation) and SP-HC (recorded at highest concavity), both defined as the resultant pressure divided by corresponding displacement.[18] Analysis in the current study concentrated on the Inverse Concave Radius, SP-A1, SP-HC and Deformation Amplitude Ratio as they were shown in earlier studies to be well correlated with corneal biomechanics and relatively independent of IOP.[17, 18]

bIOP

Together with DCRs, Corvis ST offers standard IOP and pachymetry measurements, and a novel, validated biomechanically-corrected IOP estimate (bIOP).[19] bIOP was developed using numerical, finite element simulations of the Corvis ST procedure applied on human eye models with different topographies, thickness profiles, material properties and IOP values, and was shown to be significantly less affected by corneal parameters.[20-22] Recently, the bIOP correction has been successful in providing close estimates of true IOP in ex-vivo

tests conducted on human donor eye globes, and in reducing association with the cornea's thickness (data in press in Experimental Eye Research).

Statistical analysis

Only one eye per patient was randomly selected and included in the analysis to avoid the bias of the relationship between bilateral eyes that could influence the analysis result.

All study data was recorded in a spreadsheet and all statistical analyses were performed using the SPSS software (Version 24, IBM corporation, US). Descriptive statistics were calculated for the dynamic corneal response parameters, as well as GAT-IOP, GATAdj and bIOP. Additionally, descriptive analysis was done to evaluate differences in patient characteristics for the three patient groups and normal controls. Differences between the groups (OHT, POAG, NTG and normal) were evaluated with analysis of variance (ANOVA) and Bonferroni post-hoc test or Logistic regression when appropriate. Additionally, comparison among the 4 groups was also performed by analysis of covariance (ANCOVA) after adjustments were made for the differences in the patients' age, CCT and bIOP. Furthermore, to correct these findings with the type of treatment, a General Linear Model (GLM) was used with age and sex as fixed factors and type of treatment and diagnosis as covariates. The association between the dynamic corneal response parameters and visual field indexes such as mean deviation (MD) and pattern standard deviation (PSD) was expressed with Spearman correlation coefficient. A p-value <0.05 was considered statistically significant.

RESULTS

One hundred and fifty-six eyes of 156 patients were included in the study: 74 POAG (41 HTG and 33 NTG), 45 OHT and 37 healthy controls. Patient demographics and intraocular

pressures are summarised in Table 2. The mean central corneal thickness (CCT) in NTG was significantly lower than in normal (p< 0.001) and OHT (p= 0.004) groups, but similar to HTG (p= 1.0).

Table 3 shows the number and percentage of patients under each type of topical glaucoma medications. There was no significant difference between the groups (OHT, NTG and HTG) in terms of medication for prostaglandin analogues (p=0.260) and alpha agonists (p=0.837), similarly carbonic anhydrase inhibitors (p=0.053), and beta blockers (p=0.058) did not reach statistical significance but the p-values were close to 0.05.

Intraocular Pressure

Comparative analysis showed a significant difference between the values of GAT-IOP, GATAdj and bIOP among the groups and within the groups (p< 0.001, Figure 1).

WITHIN THE GROUPS

The main result of this analysis was the significant difference between the values of GAT-IOP, GATAdj and bIOP in all groups (p< 0.001). In controls and OHT, the mean values of GAT-IOP were significantly higher than GATAdj and bIOP, equally GATAdj was significantly higher than bIOP (all p values < 0.01). In contrast, GATAdj was significantly higher than GAT-IOP in HTG, NTG and POAG groups, and GAT-IOP was significantly higher than bIOP (all p values < 0.01).

The mean values with standard deviations of the different intraocular pressure measurements in all the groups are summarized in Table 2 and Figure 1.

BETWEEN THE GROUPS

GAT IOP between the groups

The Bonferroni postHoc tests showed that mean GAT-IOP in OHT group was significantly higher than in all other groups (p< 0.001). Similarly, HTG POAG patients showed higher values of GAT-IOP compared to NTG (p= 0.003) and lower than OHT (p< 0.001) but very

similar to normal (p = 1.00). The values of GAT-IOP of OHT were on average 5.6 mmHg higher than controls.

GATAdj IOP between the groups

The comparative analysis of GATAdj showed that the mean values of OHT and HTG were significantly higher compared to controls (p< 0.001 and p= 0.009, respectively, Table 2).

bIOP between the groups

The results for bIOP displayed a non-significant difference between the values in POAG (HTG and NTG) and control groups but a significant difference with OHT. The mean difference between OHT and normal was 3.6 mmHg (p< 0.001).

Corneal Biomechanics

The analysis of the Corvis Dynamic Corneal Response parameters (DCRs) showed a significant difference between the groups in all evaluated parameters (p< 0.001), Table 4. The main result of this sub- analysis is the evidence that NTG patients show significantly softer corneas compared to controls, OHT and HTG patients. This was demonstrated by significantly lower values of Stiffness Parameter A1 (p<0.001 for ANCOVA and p=0.002 for GLM) and HC (p<0.001 for ANCOVA and p=0.022 GLM) and significant higher values of Inverse Concave Radius (p<0.001 for ANCOVA and p=0.014 GLM) and Deformation Amplitude Ratio (p<0.001 for ANCOVA and p=0.714 GLM), Figures 4 and 5. The comparative analysis was confirmed by the ANCOVA when taking age, CCT and IOP deviations into account and by the general linear model (except for Deformation amplitude ratio) when taking into account age, sex and medication.

Visual Field and Corneal Biomechanics

A subgroup of POAG (HTG and NTG) and OHT patients who had a visual field test at the same day of Corvis examination were analysed. Visual Field indices of these patients are

summarized in Table 5. The comparative analysis between the OHT, NTG and HTG groups showed significant differences in mean deviation (MD $p<0.001$) and pattern standard deviation (PSD $p<0.001$). As expected, all parameters showed a significantly worse visual field in POAG (HTG and NTG) compared to the OHT group.

The correlation analysis of corneal biomechanics and MD showed a significant negative correlation with Deformation Amplitude Ratio (cc= -0.261 p=0.018), Inverse Concave Radius (cc= -0.242, p=0.028) and a significant positive correlation with SP-A1 (cc= 0.279, p=0.011) and SP-HC (cc= 0.240, p=0.030). Similarly, the correlation analysis of corneal biomechanics and PSD showed a significant positive correlation with Deformation Amplitude Ratio (cc= 0.299, p=0.006), Inverse Concave Radius (cc= 0.305, p=0.005) and a significant negative correlation with SP-A1 (cc= -0.346, p=0.001) and SP-HC (cc= -0.329, p=0.003). The main result of this sub-analysis is the evidence that POAG patients with softer corneas are significantly more likely to show visual field defects than those with normal biomechanics.

DISCUSSION

Glaucoma is a complex disease and difficult to manage in some cases since other factors than IOP play an essential role, like vascular factors and impaired autoregulation.[23] Progression of a glaucomatous visual field defect or a poorly controlled IOP are two of the the main clinical findings that can lead to a change in medical therapy or surgical intervention. The present gold standard for IOP measurement is the Goldmann applanation tonometry. However, the accuracy of the Goldmann method of IOP measurement is influenced by corneal stiffness which varies with thickness and the cornea's material behaviour.[24] Previous studies showed that IOP measurements by GAT, are affected by a margin that varied between 0.7 and 7.1 mmHg per each 100 micron change in CCT.[25-27]

The significance of this error margin should be evaluated critically given that the progression risk in patients with diagnosed glaucoma is reported to be increased between 10-12% for each 1 mmHg increase in IOP[28], and hence the consequence of this error could produce significant numbers of false-positives and false-negatives in glaucoma risk-profiling.

The effect of corneal material properties, and in particular the mechanical stiffness or resistance to deformation, on GAT-IOP is also expected to be considerable.[10, 29] While many studies have concentrated on GAT when assessing the effect of CCT on IOP measurements, due to its prominence in ophthalmology healthcare, the effect on other tonometers, contact and non-contact, has also been covered although to a much lesser extent.[17, 26, 30, 31]

This study aimed to evaluate and compare the biomechanically-corrected bIOP algorithm with the Goldmann Applanation Tonometry IOP(GAT) in patients with primary open angle glaucoma (POAG: NTG and HTG), ocular hypertension (OHT) and controls. Subsequently, as secondary and tertiary endpoints, we aimed to assess and compare corneal biomechanics in the described groups and if those biomechanical factors were correlated with the visual field defect.

Intraocular pressure results

The comparative analysis showed a significant difference between the values of GAT-IOP, GATAdj and bIOP in POAG (HTG and NTG), OHT and controls. In all the groups, bIOP was significantly lower than GAT and GATAdj. Additionally, the mean value of bIOP, GAT and GATAdj in patients with OHT were significantly higher compared to normal and POAG (NTG and HTG). However, when comparing them with controls, mean GAT-IOP of OHT (22.1 ± 4.8) were on average 5.64 mmHg higher while bIOP of OHT (17.0 ± 4.1) were 3.56 mmHg higher.

This difference might be due to intrinsically lower values of bIOP compared to GAT-IOP or to one of the three confounding factors that bIOP takes into account, namely CCT, age and corneal biomechanics. From a previous study, the mean bIOP value in the normal population was shown to be 15.0 ± 2.2 mmHg[17] which was comparable to the mean GAT-IOP value published[32] (15.5 ± 2.2 mmHg).

For this reason, the difference between the bIOP values of OHT has to be due to one of the three factors that this algorithm compensates, namely age or corneal biomechanics since CCT was not significantly different between controls and OHT.

This result suggests that with the use of bIOP, OHT patients (who are patients that, even with high IOP did not yet progress to glaucoma) present an IOP that is within normal limits (<21 mmHg) whereas with GAT the IOP is higher than the normal range.

Given that our comparative analysis of corneal biomechanics showed significant difference in corneal biomechanics between the groups and also age was different, biomechanics and age were proved to be a significant confounding factor for IOP measurement, confirming previous studies.[10]

A particularly relevant numerical model confirms our findings which showed that differences in corneal biomechanics across individuals may have greater impact on IOP measurement errors than corneal thickness or curvature.[10]

The difference between the IOP values across the groups could also be explained by the higher accuracy and repeatability of Corvis ST IOP measurements found by previous studies[33] compared with Goldmann tonometry and ultrasound pachymetry, which could be down to a measurement triggered by a standardised air-puff compared to the variability of angles and contact locations on the cornea associated with a handheld or slit lamp pachymeter.[34]

The results of this sub-analysis suggest that IOP measurement may be over- or underestimated when not corrected for biomechanics, age and CCT. bIOP may be a better

indicator of ‘true IOP’ and able to more accurately differentiate between OHT patients at a higher risk of progression to glaucoma. This might be a clinical significant finding which will require further investigation. As a matter of fact, the better differentiation of OHT from POAG represents a major challenge in glaucoma diagnosis and population-based screening programmes. A better estimate of IOP could help to separate OHT patients at high risk of progression to Glaucoma with those that are only over-estimated by standard tonometers improving diagnosis and reducing public health costs. However, it must be noted that all previous clinical trials were done with GAT, so further studies are needed to evaluate if bIOP would be able to provide a better way to define OHT.

Corneal biomechanics

The main result of this sub-analysis is the evidence that NTG patients showed significantly softer corneas (more deformed by the air puff) compared to controls, OHT and HTG. This was demonstrated by significantly lower values of Stiffness Parameter A1 and HC and significant higher values of Inverse Concave Radius. The comparative analysis was also confirmed even when taking age, sex, corneal thickness, IOP and medications into account. A softer cornea, in general, would be more deformed by the air puff, which will be identified by the Corvis with a higher Inverse Radius of concavity and Deformation amplitude ratio. Similarly, it will show lower values of the stiffness parameters (SP-A1 and SP-HC) which are two parameters correlated with overall stiffness.[18]

The analysis of covariance (ANCOVA) and General Linear Model, implemented in the current study, was essential to confirm the significant biomechanical difference between NTG and controls to exclude confounding factors such as IOP, CCT, age, sex and topical medications such as prostaglandins and carbonic anhydrase inhibitors.

Based on the evidence that NTGs have corneas that are more deformed by the air puff (so presumed softer) the evaluation of corneal biomechanics might help in the management of glaucomatous patients. The rationale is that the softer the cornea and, subsequently the LC, the higher would be the deformation of the latter for the same load (IOP). Indeed, it has been reported significant correlation between laminar compliance and corneal hysteresis in glaucoma.[35] This has also been shown in an animal study which demonstrated that in experimental early glaucoma in monkeys the LC was showing higher posterior deformation compared to controls.[36] On the other side, it has also been showed that glaucoma is associated with a stiffer scleral ring.[37]

Correlation between visual field defect and corneal biomechanics

The main finding of this sub-analysis is the evidence that corneas that are more deformed by the air puff are significantly more likely to show visual field defects than those with normal biomechanics. This was demonstrated by significant correlation between MD and PSD and many Dynamic Corneal Response Parameters. Few reports have already suggested that the progression of glaucoma is related to the magnitude of CCT itself[38, 39], while other studies have revealed that some corneal biomechanical parameters measured either with the Corvis ST[40] or with the Ocular Response Analyzer are more closely related to the progression of glaucoma.[35]

A previous report used the Corvis ST to assess the progression of POAG patients was also in agreement with our findings. The authors created a mathematical model aimed to include the relationships between ocular/systemic parameters (age, mean GAT, standard deviation of GAT, CCT, axial length, and the total deviation of the first visual field), the Corvis Dynamic Corneal Response Parameters and the progression rate of the VF.[40] Their conclusions were that Corvis ST measurements are useful when assessing VF progression in glaucoma patients. More in details, the patients at higher risk of progression were those with low

applanation 1 and applanation 2 time, with wider applanation area and higher deformation amplitude. It must be noted that the cited study did not evaluate the new DCRs provided in the latest software of the Corvis, which are less influenced by IOP, and so the results might be influenced by this last confounding factor.

In conclusions, corneal biomechanics confirmed to be a significant confounding factor for the measurement of IOP that should be considered before making clinical decisions. The abnormality of corneal biomechanics in NTG compared to controls, HTG and POAG, together with the significant correlation with visual field defects may suggest a new risk factor for the development and progression of glaucoma.

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