**Development and Validation of a new Intraocular Pressure Estimate for Patients with Soft Corneas**

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**Running head:** bIOPs, a new validated IOP estimate for patients with soft corneas.

**ABSTRACT**

**Purpose:** To introduce and clinically validate in patients with keratoconus a new method for estimating intraocular pressure (IOP) in patients with soft corneas with the aim of significantly reducing dependence on corneal biomechanics.

**Setting:** Vincieye Clinic in Milan, Italy, and Rio de Janeiro Corneal Tomography and Biomechanics Study Group – Rio de Janeiro, Brazil.

**Design**: Multicenter Retrospective case series.

**Method:** 722 eyes of 722 participants, enrolled in two hospitals situated in 2 different countries. Numerical analysis based on the finite element method was conducted to simulate the effect of tonometric air pressure of the CorVis ST (Oculus, Wetzlar, Germany) on eye globes with wide variations in thickness, geometry and tissue. The numerical predictions of ocular behavior with a simplifying assumption of homogenous material properties were used to develop a new algorithm to produce biomechanically-corrected predictions of IOP for patients with soft corneas (bIOPs). Predictions of bIOPs were assessed in the keratoconic clinical datasets (as these patients are on average softer) and compared with the previously developed bIOP algorithm predictions obtained for the normal, healthy eyes.

**Results:** The main outcome of the study was the absence of a significant difference (p> 0.05) in the values of IOP between healthy and kc patients, using the bIOP and bIOPs algorithms, while there was a significant difference with uncorrected CorVis-ST IOP (p< 0.001) for both. Further, bIOPs predictions were significantly less affected by both corneal thickness and age than CorVis IOP.

**Conclusions:** bIOPs is proposed as an algorithm for more reliable estimation of intraocular pressure in patients with soft corneas and is validated in the present study in those with keratoconus.

**Introduction**

The measurement of intraocular pressure (IOP) is an essential part of eye examination and is mandatory for the screening and treatment of pathologies such as glaucoma and ocular hypertension. The Goldmann applanation tonometer (GAT) is the most common method for measuring IOP by applying a force to the cornea, and relating the resulting deformation to the internal pressure. When GAT was introduced in 1957, it was assumed to comply with the Imbert-Fick law, which considers interaction of a flat object with a perfectly dry, flexible, elastic and infinitely thin, spherical surface.1 As the cornea does not comply with these conditions, its thickness and tissue biomechanics (which affect the overall stiffness) are expected to affect GAT-IOP measurements as demonstrated in several studies2, 3. It is important to define overall stiffness which is formed by geometrical stiffness and material stiffness. Geometrical stiffness is controlled mainly by corneal thickness and curvature while material stiffness describes the actual properties of the tissue/material. The IOP of patients with soft corneas (with lower overall stiffness, either caused by lower geometrical or material stiffness) will be ununderestimated by GAT-IOP, whereas stiffer corneas tend to have overestimated values.2 Furthermore, GAT readings are affected by hydration and curvature, and fail to account for the variations in corneal biomechanical properties.4 One subset of patients with softer corneas that represent a challenge for IOP measurement are those with keratoconus (kc). As a matter of fact, kc patients have thinner, steeper and more compliant corneas (lower material and geometrical stiffness), do not comply with most of the assumptions of GAT and therefore an accurate IOP measurement is known to be a challenge.5, 6 There are several studies in the literature that attempted to find the best instrument to estimate IOP in kc patients6-9, many of which suggested the use of either the Ocular Response Analyzer (ORA-Reichert Ophthalmic Instruments, Depew, NY, USA) with its IOPcc or the Dynamic Contour Tonometer (DCT-Pascal, Swiss Microtechnology AG, Port, Switzerland).5-9

The CorVis ST (Oculus, Wetzlar, Germany) is a relatively new non-contact tonometer that monitors corneal deformation using an ultra-high speed Scheimpflug camera. It was shown to be able to detect significant differences between healthy and keratoconic patients in terms of dynamic corneal response parameters (DCRs including, most notably the stiffness parameter, SP, and the Deflection Amplitude, DA)10. CorVis ST was also able to detect kc with high sensitivity and specificity using a new combined biomechanical index (CBI), which was developed using statistical analysis to use the DCRs to distinguish between the more compliant kc corneas and the stiffer healthy corneas11. Together with the DCRs, Corvis ST offers a novel and validated, biomechanically-corrected IOP (bIOP) estimate for eyes with normal topography.12, 13 The bIOP was created using numerical finite element modelling of the CorVis ST air puff and its induced deformation on human eyes with representative material properties, topographies and IOP values.14-18 The bIOP estimates for healthy eyes proved to be significantly less affected by corneal parameters than uncorrected CorVis IOP.12

The aim of this paper is to extend this work and introduce an IOP algorithm that is newly developed specifically for patients with soft corneas (bIOPs). To validate the algorithm, we decided to test it in a population that is known to have both thinner and softer corneas: keratoconus. The study compares the IOP estimates obtained for patients with normal and keratoconic corneas using the bIOP and bIOPs algorithms, respectively, followed by their correlation with corneal thickness and age19 (as markers for tissue stiffness) in two large clinical datasets from two different continents.

**MATERIALS AND METHODS**

*bIOPs ALGORITHM DEVELOPMENT*

The bIOPs algorithm was developed via numerical simulation by the Biomechanical Engineering Group at the University of Liverpool, following the same procedure as the bIOP for normal eyes 11, 12. Briefly, the CorVis ST air puff effect was simulated on numerical models of whole eye globes, in which true IOP was varied between 10 and 35 mmHg. The 3D anterior and posterior topographies of the keratoconic eyes included in the clinical validation part of this study were analyzed, and 5 topography and thickness profiles, including one with no distortion, one with the most severe distortion, and 3 intermediate profiles, were considered in the 3D numerical models, Figure 1.

The 3D numerical models were analyzed using the finite element solver Abaqus (Release 6.14-2, Dassault Systemes, Rhode Island, US). The models included 65712 six-noded C3D6H continuum elements including 3750 elements in the cornea and 61962 elements in the sclera, Figure 2. Additionally, the models included 30981 fluid elements covering the internal space of the eye globe, representing the effects of IOP and enabling consideration of the interaction between the cornea and sclera on one hand, and the aqueous and vitreous on the other. The fluid elements were assumed to have incompressible behavior and a density of 1000 kg/m3.

The models were supported to prevent axial rigid-body motion at the equator and lateral motion at the corneal apex and posterior pole. Third-order, hyperelastic Ogden models were used to represent the ocular tissue’s mechanical behavior and its variation with age within the 30-90 year range19. Scleral age-related variation in stiffness and the stiffness gradual reduction from the limbus towards the optic nerve were incorporated in the models20.

Analysis started with determining the stress-free form of each model (model form under zero IOP) following an iterative process that ensured that the mean difference between the coordinates of the stress-free model after deformation under IOP and those of the initial idealized model were below 1 micron21. The models in their stress-free forms were then subjected to the true IOP in each case, followed by a simulation of the air puff effect of the CorVis ST, and the resulting deformation parameters were exported. A database of the input parameters (true IOP, topography profile, thickness profile, material behavior) and output parameters (applanation pressures and cornea’s dynamic response parameters, DCRs) was assembled and analyzed to produce estimates of true IOP or biomechanically-corrected IOP in the form:

$bIOP\_{kc}=f (TP, CCT, AP1,SP, CVS-IOP)$ (Eq. 1)

Where TP is a parameter with a value between 1 and 5 depicting the degree of match between the horizontal cross-section recorded by the CorVis ST and the 5 topography profiles identified from analysis of topography maps of soft corneas (keratoconus in this case), CCT is the central corneal thickness (microns), AP1 is the first applanation pressure (mmHg), SP is the stiffness parameter at the highest-concavity radius of curvature (mmHg/mm), and CVS-IOP is the IOP measurement by CorVis-ST (mmHg). AP1 and SP were selected from the several available DCRs for their relatively strong correlation with IOP11 and material behavior22, respectively.

*CLINICAL VALIDATION*

Seven hundred and twenty-two patients were included in this multicenter retrospective study. The patients were enrolled in two hospitals situated in 2 different countries to include variability from more than one continent. Dataset 1 included 315 subjects (164 healthy and 151 keratoconic) from the Vincieye Clinic in Milan, Italy, while Dataset 2 originated from the Rio de Janeiro Corneal Tomography and Biomechanics Study Group – Rio de Janeiro, Brazil, with a total of 407 participants (205 healthy and 202 keratoconic).

Institutional review board (IRB) ruled that approval was not obligatory for this record review study. However, the ethical standards set in the 1964 Declaration of Helsinki, and revised in 2000, were observed. All patients provided informed consent before using their data in the study. All patients had a complete ophthalmic examination, including the CorVis ST and Pentacam (Oculus Optikgeräte GmbH; Wetzlar, Germany) exams.

The inclusion criterion for the keratoconic groups was bilateral keratoconus without any former ocular surgeries, such as collagen cross linking or intracorneal rings. For healthy subjects, the inclusion criteria were a Belin/Ambrósio Enhanced Ectasia total deviation index (BAD-D) of less than 1.6 standard deviations (SD) from normative values in both eyes23, no previous ocular surgery or disease, myopia less than 10D and no concurrent or previous glaucoma or hypotonic therapies. Moreover, to confirm the diagnosis, all exams of each clinic were blindly re-evaluated by a corneal expert at the other clinic.

Only CorVis ST exams with good quality scores (QS) that enabled calculation of all DCRs were included in the analysis. All measurements with the CorVis ST were acquired by the same experienced technicians, and an additional manual, frame-by-frame evaluation of the exams, made by an independent masked examiner, was implemented to ensure quality of acquisitions. Also, anterior and posterior topography maps were acquired using a Pentacam (Oculus, Optikgeräte GmbH; Wetzlar, Germany) and analyzed to determine the topography and thickness profiles of keratoconic eyes, which were then considered in the numerical parametric study.

Only one eye per patient was randomly included in the analysis to avoid the possible effect of the relationship between bilateral eyes on the analysis results.

Further evaluation of bIOPs was carried out by considering its effectiveness in keratoconic eyes with different disease stages. For this purpose, the kc datasets were divided into three groups each; Mild, Moderate and Advanced, based on the Topographic Keratoconus Classification (TKC) provided by the Pentacam.24 According to this classification, mild keratoconus was defined with TKC classification of: “Abnormal”, “Possible”, “-“ and “1”, Moderate keratoconus included TKC grade “1-2”, “2” and “2-3”, and advanced keratoconus included TKC grade “3”, “3-PMD”, “3-4” and “4”.

*STATISTICAL ANALYSIS*

The statistical analysis was done using IBM SPSS Statistics 24. Before starting the analysis, the data were divided into two groups (Dataset 1-Milan and Dataset 2-Rio) and each group further divided into two sub-groups of eyes with normal corneas and soft corneas (Keratoconus in this study). Since the data were not expected to be normally distributed, and normal and soft groups were completely independent of each other, nonparametric Mann-Whitney U test and Kruskall-Wallis test were performed to compare the differences between various groups in CCT, age, CorVis IOP and biomechanically-corrected IOP (bIOP for normal and bIOPs for soft corneas). Levene’s test was also used to assess the differences in variance in patients with soft corneas with the three IOP estimates (bIOP, bIOPs and CorVis IOP).

**Results**

*ANALYSIS OF DATASET 1 (MILAN)*

In Dataset 1, the mean age of participants with normal corneas was 35±13 years (range 14-73), which was similar to the mean age of patients with keratoconic corneas, 33±12 (14-73) years (p= 0.507). In contrast, CCT was considerably higher, as expected, in normal eyes, 543±32 (458-635) µm, than in soft eyes, 482±45 (239-595) µm (p< 0.001). For both groups, the mean bIOP was almost the same; bIOP=14.7±1.6 (10.6-20.4) mmHg for normal eyes and bIOPs=14.6±1.2 (10.9-18.1) mmHg for keratoconic eyes (p= 0.121), while CorVis IOP was lower in keratoconus [13.1±2.2 (5.0-19.5) mmHg] than in normal cases [15.1±1.6 (11.0-23.0) mmHg] (p< 0.001), Figure 3. There were also significant differences between bIOP and CorVis IOP obtained for patients keratoconus (p< 0.001), but not for participants with normal corneas (p= 0.103), Figure 3. Furthermore, there was a significant difference between variances of bIOPs compared to CorVis IOP in kc patients (p< 0.001, Levene’s test).

*ANALYSIS OF DATASET 2 (RIO)*

Similar to Dataset 1, the participants with normal and keratoconic corneas in Dataset 2 had similar age ranges; [40±13 (18-72)] years and [39±13 (18-72)] years, respectively (p= 0.228), but different CCT ranges [540±33 (454-629)] µm and [491±41 (381-586)] µm (p< 0.001). Similar IOP results were obtained with the mean bIOP being similar between normal eyes [bIOP=14.4±2.2 (9.9-24.3)] mmHg and keratoconic eyes [bIOPs=14.4±1.1 (11.5-17.2)] mmHg (p= 0.319), while CorVis IOP in soft eyes, [12.6±2.5 (4.5-20.0)] mmHg, was significantly lower than in normal eyes [14.8±2.6 (9.0-29.0)] mmHg (p< 0.001). The bIOPs values were also significantly different from CorVis IOP in keratoconic eyes (p< 0.001, Figure 3), while there were no significant differences between bIOP and CorVis IOP in normal eyes (p= 0.091). Analogous to the results of Dataset 1, the comparative analysis of the variances of patients with keratoconus showed significantly different variances of bIOPs compared to CorVis IOP (p< 0.001, Levene’s test).

*CORRELATION OF IOPs ESTIMATES WITH AGE AND CORNEAL THICKNESS*

The degree of dependency of bIOPs and CorVis IOP on CCT and age in patients with keratoconus of both datasets is assessed in Figure 4. The results show large reductions in IOP dependency on CCT from 1.7 mmHg/100 µm (with CorVis IOP) to -0.8 mmHg/100 µm (with bIOPs) in Dataset 1, and from 2.7 mmHg/100 µm (with CorVis IOP) to -0.3 mmHg/100 µm (with bIOPs) in Dataset 2. On the other hand, the dependency of IOP on age, which was small with CorVis IOP, experienced only small reductions with bIOPs – it changed from 0.12 mmHg/decade (with CorVis IOP) to 0.10 mmHg/decade (with bIOPs) in Dataset 1, and from 0.17 mmHg/decade (with CorVis IOP) to 0.02 mmHg/decade (with bIOPs) in Dataset 2.

*COMPARISON OF bIOP and bIOPs IN KERATOCONIC PATIENTS*

Although bIOP and bIOPs were developed for the two distinctive populations of patients with normal and keratoconic corneas, respectively, an assessment is presented here of the relative effectiveness of the two algorithms in the latter group. This assessment is conducted while decomposing the kc datasets into sub-groups according to the TKC classification. As shown in Figure 5, the group in Dataset 1 was decomposed into 30 mild, 50 moderate and 29 advanced cases, while in Dataset 2, the subgroups included 20 mild, 51 moderate and 19 advanced cases.

Analysis of Dataset 1 shows no significant difference between bIOP and bIOPs in cases with mild (p= 0.168, Levene’s test), moderate (p= 0.649) and advanced cases (p= 0.329). The results also show significantly smaller standard deviations of bIOPs compared to bIOP in patients with mild and moderate keratoconus (p< 0.001 for mild, p= 0.035 for moderate) but not in advanced patients (p= 0.067), Table 1.

Dataset 2 shows slightly different results with the mean values of bIOP being significantly lower than bIOPs in mild (p< 0.001) and moderate keratoconus (p= 0.008), but not in advanced cases (p= 0.155). There were also significantly smaller standard deviations of bIOPs compared to bIOP in all stages of keratoconus (p< 0.001 for mild and moderate and p= 0.035 for advanced cases).

**DISCUSSION**

The reliable measurement of IOP in patients with soft corneas including those with keratoconus (kc), has always been a challenge.6 Being thinner, steeper, softer and less regular than healthy tissue, soft corneas usually suffer from systematic underestimations of IOP,8 which can cause problems when using eye-drops (such as steroids) or undergoing procedures that can induce a rise in IOP – making it difficult to evaluate whether a borderline IOP measurement represents a clear abnormality.

The challenge in accurately measuring IOP stems from the way in which tonometry techniques work, where the cornea’s resistance to deformation, under an external mechanical effect, is correlated to IOP. This common methodology, means that the natural variations in corneal stiffness, caused by several factors such as changes in thickness, curvature or tissue biomechanical properties, affect the accuracy of IOP measurements. This problem becomes particularly serious in keratoconus, where the cornea experiences significant reductions in thickness and tissue stiffness in addition to notable changes in geometry. This study is an attempt to separate the effects of corneal mechanical stiffness from those of IOP in the IOP measurement process, and hence provide more representative IOP values compared with CorVis IOP. The method used relied on numerical simulation of the CorVis ST procedure in eye models with wide variations in true IOP, anterior surface profile, CCT, thickness profile and material properties. The method, which was similar to that reported earlier for normal, healthy eyes,12, 25 led to the development of an algorithm providing estimates of biomechanically-corrected IOP values for soft eyes including those with Keratoconus (bIOPs). The algorithm considers, and attempts to minimise, the effects of material properties and cornea geometry on IOP estimation, and therefore includes within its parameters the Stiffness Parameter, SP, the central corneal thickness, CCT and a shape factor, TP.

Validation of the bIOPs algorithm involved applying it to ocular populations with thin and soft corneas (keratoconus in this study) and comparing the results to those of bIOP for healthy populations recruited in the same clinical centres. While the CorVis IOP measurements in normal and keratoconus eyes were significantly different – being lower in keratoconus eyes, as expected – the bIOPs and bIOP for patients with keratoconus and normal corneas participants were similar. Based on the hypothesis that patients with keratoconus should have the same “true” IOP as for normal patients with a similar composition, this result suggests that bIOPs is able to correct for the confounding biomechanical factors that make IOP measurements in keratoconus unreliable. Further evidence is in the reduced dependency of bIOPs estimates on two major stiffness parameters; corneal thickness and age, similar to what has been found in the results of the bIOP algorithm when applied to eyes with healthy tomography 11, 12. However the use of bIOPs should not be limited to patients with keratoconus but it could also be applied to patients with normal but thin corneas, particularly if they are undergoing refractive surgery.

The question of whether keratoconus eyes have intrinsically lower IOP could be partly addressed by considering the prevalence of glaucoma in kc patients. While the incidence of kc is higher in younger populations, glaucoma is more frequent in older patients26. In earlier studies, kc was found to be more clearly associated with normal tension glaucoma27, which is also more frequent in younger patients including those without kc.28 However, the studies that used methods to compensate for confounding factors for IOP measurements have found that the IOP in kc patients were in normal range values29, as was assumed in this study.

Another important point is the evidence that corneal epithelium, which is known to be softer compared to stroma30, is irregular in kc corneas compared to controls because it follows corneal curvature gradient31 – thinning over the apex and thickening around the cone32. However, previous studies have compared advanced kc to normal controls and the minimum epithelial thickness was around 12μm lower and the maximum thickness was around 25μm higher than normal.33 This can be compared to the difference in stromal thickness between kc and normal, which was 50μm lower at the thinnest point and 30μm lower at the thickest point in the kc group.34 Hence, compared to the stromal changes, the epithelial remodeling would have a negligible effect on the corneal overall stiffness difference between healthy and keratoconic eyes.

The inclusion of two large datasets from two different continents was necessary to assess the reliability of the bIOPs algorithm in populations with different ethnic backgrounds. It is the first time, to the authors’ knowledge, that an IOP estimate for soft eyes is tested in a keratoconus population and is able to show the same mean values and standard deviations as for normal eyes in such a large dataset. Previous studies illustrated the variable performance of different tonometers with disagreement still persisting on which tonometer provides the most reliable measurement of IOP in kc. Earlier reports noted the relatively low reliability of the Goldmann and Tonopen tonometers 6, 9, 35 and the ability of both the ORA and the DCT to provide more reliable estimates of IOP.6-9, 36-38 A particularly relevant study has been done by Mollan, Wolffsohn 39 where authors showed that DCT was not significantly affected by CCT. Ozbek et al. used the DCT to measure IOP and observed no statistically significant difference between the normal (16.1±2.9 mmHg) and keratoconic groups (15.7±3.1 mmHg, p= 0.21). On the other hand, the difference in GAT measurements was significant between normal (14.3±4.1 mmHg) and keratoconic eyes (13.0±3.9 mmHg; p= 0.004).35

Another important finding of the study was provided by the analysis of the variances in kc severity. The differences in bIOPs between sub-groups with mild, moderate and advanced kc were limited to 0.2mmHg in Milan Dataset (2) and 0.5 mmHg in Rio Dataset (1) and were not significant, and in all sub-groups, bIOPs provided a smaller spread compared to CorVis IOP (Figure 4). While this finding is of significant importance when evaluating the IOP in patients with keratoconus, where measurements are known to vary much between devices 6, note should be made of the differences in the number of kc patients included in each sub-group, which may have affected the statistical analysis of IOP results. A similar finding was reported in an earlier study, which demonstrated no significant differences in the DCT and IOPcc measurements among patients with different Amsler-Krumeich kc classifications, but in that study the mean IOP values were still different compared to healthy subjects.6

Finally, a comparative analysis of bIOP and bIOPs in patients with keratoconic corneas showed the absence of significant differences in means between bIOP and bIOPs estimations, a finding that was repeated in patient sub-groups with mild, moderate and advanced kc. However, bIOPs values had significantly smaller standard deviations compared to bIOP in most sub-groups (Figure 5). These results indicate that while bIOP could potentially be used to estimate IOP in soft and kc patients, the results may not be as reliable as the bIOPs. The results are also assuring that in suspicious keratoconus cases, the selection of which bIOP algorithm to use is not critical. However, it must be noted that if bIOPs is implemented in clinical practice, the instrument would need to select which formula to use, and a possible solution could be based on the CBI, which has been shown to be highly sensitive and specific to diagnose kc.40 In the few, very mild and borderline cases, since the material properties of these corneas as measured using deformation along the horizontal meridian would not be significantly different from the healthy controls, both bIOP and bIOPs equations would produce similar results.

A limitation of this study was the absence of comparison with GAT, DCT and IOPcc. Moreover, the authors had to assume that the mean “true” intraocular pressure of patients with soft corneas should be the same as normal ones. As a matter of fact, there is no current strong evidence that true IOP should be different in soft eyes. Furthermore, given the recent evidence of the reliability of bIOP on healthy ex-vivo eyes with manometric measurements we believe that is an acceptable assumption.13 Another significant limitation was assuming the cornea to have uniform material behavior across its surface, and therefore not considering the focal softening that could exist, to different extents, within the keratoconus cone area. This assumption was necessary as the challenge set for this study was producing more accurate estimations of IOP based on the cornea’s initial form and deformation profile as could be observed along the horizontal center line monitored by the CorVis ST. While more representative modelling of the KC cone would require additional topographic data that can only be obtained with a videokeratographer and avoid the use of only CCT, it would additionally make the optimization problem addressed in this study significantly more challenging to solve as the number of parameters involved would considerably increase.

An interesting future application of bIOPs would be to evaluate it in progressive keratoconus cases, where two points could be assessed: whether bIOPs is still accurate and if in progressive kc the bIOPs is increased (which is a currently debated topic).

In conclusion, based on our findings, we propose bIOPs as a new algorithm for a more accurate estimate of intraocular pressure in patients with soft corneas including those with keratoconus. The routine use in clinical practice of this algorithm may help consider the well-known systematic errors that affect other tonometers, including Goldmann, caused by the particular irregularities in material properties, anterior topography and thickness profile of thin corneas and those with Keratoconus patients.

**WHAT WAS KNOWN:**

* Changes in overall stiffness can take place in eyes with thin corneas and those with keratoconus, resulting in incorrect IOP estimates.
* Previous IOP estimates were not proven to be able to provide accurate measurements in patients with soft and/or keratoconic corneas.

**WHAT THIS PAPER ADDS:**

* The bIOPs algorithm proved to be able to compensate for variations in geometry and biomechanics of eyes with keratoconic corneas.
* Application on clinical data showed no significant differences in mean values when compared to healthy

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Figure 1 Five anterior topography profiles (TP 1 to 5) based on analysis of topography maps of thin and KC corneas and adopted in numerical models

Figure 2 Overview of a typical numerical model of an eye in different stages of behavior. Figure shows stresses in model (a) under no load, (b) under IOP, and (c) under both IOP and external CorVis ST air pressure.

Figure 3 CorVis IOP, bIOP and bIOPs values obtained for patients with normal and soft corneas in both Datasets 1 and 2. Results illustrate the stability in predicting IOP values using the bIOP and bIOPs algorithms for normal and soft eyes, respectively, compared to the large differences in CorVis IOP. Both bIOP and bIOPs further exhibit lower standard deviation values compared to CorVis IOP. \*\* indicates significant differences in means (p<0.05).

Figure 4 Analysis of the degree of dependency of both bIOPs and CorVis IOP on CCT and age in the Milan dataset (a,b) and Rio dataset (c,d)

Figure 5 Means and standard deviations of bIOP and bIOPs in the patients with mild, moderate and advanced keratoconus included in both datasets