RESEARCH

Short and mid-term changes in CORVIS ST parameters in successful, adult orthokeratology patients

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ABSTRACT

Clinical relevance: The analysis of the changes in various biomechanical and tomographic characteristics of the cornea associated with orthokeratology may allow to identify potential mid- and long-term structural alterations, resulting in a better understanding of the governing mechanisms of this procedure and in its optimization.

Background: The study aimed at describing short and mid-term changes in CORVIS ST® parameters and indices in orthokeratology (ortho-k), and their diurnal variations.

Methods: A prospective observational study was designed in which several CORVIS ST® parameters of 75 new adult participants successfully fitted with overnight ortho-k Seefree® (Conóptica - Hecht Contactlinsen) contact lenses were explored. Measurements were conducted in baseline (BL) conditions and in the morning and evening at the one night (1NM / 1NT), one week (1WM / 1WT) and 3 months (3MM / 3MT) follow-up visits.

Results: Statistically significant differences were found in DARatio_2mm, IntRad, ARTh, CBI and TBI following overnight ortho-k, when compared with BL values, with most values reaching stability at 1WM or reverting to BL values at 3MM. The ARTh and CBI parameters showed some of the most significant temporal variations (both $p<0.001$), probably reflecting the encountered differences in central corneal thickness between BL and 1WM ($p=0.010$) and between BL and 3MM ($p=0.016$). In general, corneal rigidity was higher in the morning at all follow-up visits, and decreased during the day. No statistically significant changes in adjusted intraocular pressure values were found.

Conclusion: Ortho-k in adults may be considered a safe procedure in terms of short and mid-term changes in CORVIS ST® parameters. The observed alterations in most of the parameters provided by the Corvis ST® probably responded to the well-described changes in corneal pachymetry and tomography, rather than to actual alterations in corneal rigidity.

KEY WORDS: Contact lens; Corneal biomechanics; Corneal pachymetry; Corneal topography; Orthokeratology

INTRODUCTION

Orthokeratology (ortho-k) provides a transient refractive error correction by reshaping the cornea with specially designed rigid corneal contact lenses worn overnight.[1] As a reversible clinical procedure, it relies on the viscoelastic properties of the corneal tissue (especially corneal epithelium), although with the current available technology, the actual interaction between corneal biomechanics and corneal reshaping remains elusive.[2]

Previous research employing the Ocular Response Analyzer® system (ORA: Reichert Ophthalmic Instruments, Depew, NY) has explored parameters such as corneal hysteresis (CH) and corneal resistance factor (CRF) in small samples of ortho-k patients.[3-5] Chen and co-workers did not find any significant change in CH following one night of ortho-k lens wear, but decreased values of CRF were observed with increasing duration of lens wear.[3] Mao and co-workers noted a reduction in the values of CH and CRF after one week of overnight ortho-k, which the authors attributed to the initial corneal deformation, and a return to baseline values and biomechanical stability at the 3-month follow-up visit.[4] A similar trend was observed by Yen and co-workers, with a statistically significant reduction in CH and CRF values up to 30 days following ortho-k treatment, although these authors did not interrupt lens wear to determine whether these parameters reverted to baseline values.[5] Several limitations of the ORA have been described, amongst others the lack of a direct relationship between CH and modulus of elasticity, advising caution when interpreting the results of this instrument.[6]

A new device, the Corvis ST® (*Corneal Visualization Scheimpflug Technology,* Oculus, Wetzlar, Germany), combining air tonometry and Scheimpflug image analysis, has recently become available to explore corneal biomechanical properties. This instrument has been used extensively in refractive surgery, to explore both patient suitability and post-operative corneal biomechanics,[7,8] and for the early detection of keratoconus.[9-12] In addition to biomechanical parameters and indices, the Corvis ST® also provides other parameters, such as intraocular pressure (IOP) and central corneal thickness (CCT). Hon and Lamb reported good repeatability of CCT measurements with this device, as well as good intersession reproducibility for some of the provided biomechanical parameters.[13]

The aim of the present research was to evaluate the possible changes in CORVIS ST® parameters and indices at various times following a successful ortho-k contact lens fit. For this purpose, a large sample of new adult successful ortho-k lens wearers was recruited, and Corvis ST® parameters were explored in baseline (BL) conditions, and following one night (1N), one week (1W) and three months (3M) of ortho-k treatment. In addition, in all follow-up visits participants were explored twice, in the morning upon lens removal and in the evening, eight hours later, to determine changes in the various parameters and indices as the cornea progressively recovers from the deformation created during overnight lens wear. As some of these parameters were developed for the early detection of corneal ectasia, the ultimate purpose of this study was to explore whether ortho-k may lead to changes that practitioners could falsely associate with pathology and, if so, to advise them to interpret their results within the framework of the actual ortho-k procedure.

METHODS

Study sample

A prospective observational study was designed. Participants were recruited from those attending to the University Clinic of the School of Optics and Optometry of Terrassa between February 2019 and April 2020 to follow an ortho-k treatment. All participants were 18 years old or older, had myopia between -0.50 D and -5.00 D, corneal and refractive astigmatism of -1.25 D or less and best corrected monocular visual acuity of 0.10 logMAR or better in both eyes. Only participants with no previous ortho-k treatments were included in the study. Wearers of soft and rigid corneal lenses were instructed to refrain from wearing them during at least one week and one month, respectively, prior to baseline measurements and the start of the ortho-k treatment. Participants with ocular or systemic conditions incompatible with contact lens wear in general or ortho-k in particular were excluded from the study, as were those using drugs known to influence tear film integrity. Participants with a history of ocular complications related or unrelated to contact lens wear, ocular or refractive surgery, unstable corrected refractive error, irregular corneal topography or strabismus were also excluded. Participants had to be available for all follow-up visits (mornings and evenings) and be able to sleep seven or eight hours each night to ensure an adequate ortho-k effect.[3,14,15]

All participants provided written informed consent after the study procedures were explained to them. The study followed the tenets of the Declaration of Helsinki and received the approval of the Ethics Review Board of the Fundació Assistencial Mútua de Terrassa.

Procedure

All participants were given a complete ophthalmic exam to determine their suitability for ortho-k and for inclusion in the present study. Corneal topography with the Easygraph® (Oculus, Wetzlar, Germany) was conducted for all suitable candidates to calculate the parameters of the Seefree® double inverse geometry contact lenses, according to the recommendations of the manufacturer (Conóptica – Hecht Contactlinsen). This contact lens is a four-curve design consisting of an spherical back optical zone of radius 6.30 mm, calculated according to the refraction to be treated and considering a +0.75 D Jessen factor, which was the same for all participants, irrespective of their age; a first reverse curve of 0.70 mm in width (radii from 6.00 to 9.50 mm, adjusted to obtain an apical clearance of 10 µm); a second aspheric reverse curve (radii from 6.50 to 10.00 mm, adjusted for peripheral alignment) of width determined by the overall diameter of the lens, which was calculated by subtracting 1 mm from the value of the horizontal corneal diameter; a fourth and final curve, or edge lift, of radii ranging from 10.50 to 13.50 mm and width of 0.50 mm (for overall lens diameters ≤ 10.50 mm) or 0.60 mm (for overall lens diameters > 10.50 mm). If necessary, subsequent parameter adjustments were implemented to arrive at a satisfactory fit, as evidenced by fluorescein patterns, anterior corneal topography, lens movement, centration and area of treatment. All participants received free of charge solutions for the duration of the study (3 months), consisting of Cleadew GP® (Ophtecs - Japan), which is a povidone iodine-based disinfecting solution[16] and HyLub®, (Conóptica – Barcelona), which is a non-preserved tear substitute used for lens insertion. These solutions were selected according to the recommendations of the manufacturer of the ortho-k contact lenses.

Corneal evaluation with the Corvis ST® system (software version v1.6r2031) was conducted prior the start of the ortho-k treatment (BL), and at the 1N, 1W and 3M visits. Each follow-up visit consisted of a morning (1NM, 1WM, 3MM) and an evening series of measurements (1NT, 1WT, 3MT). All morning measurements were conducted one hour after lens removal, which was consistent for each patient, and all evening measurements took place approximately eight hours later. Three consecutive measurements were performed, with an interval of 5 minutes between them, as recommended by previous researchers.[17,18] The average of these measurements was used for statistical analysis.

The Corvis ST® explores corneal response to deformation over an area of 8.5 mm through the combination of air tonometry and Scheimpflug image analysis with a blue LED at 470 nm. The technical characteristics of this device have been described in the literature.[19] This instrument offers multiple parameters and indices, of which, in accordance with previous research,[20,21] those included in the Vinciguerra report (DARatio, IntRad, ARTh, SP-A1, CBI and TBI), and those related to CCT and to intraocular pressure (bIOP and IOPnct) were explored.

Briefly, DARatio_2mm (deformation amplitude ratio at 2 mm) is the deformation at the corneal apex divided by the average of the deformation 2 mm on both sides of the apex;

IntRad (Integrated Radius) is the area under the inverse concave radius as a function of time; ARTh (Ambrósio's Relational Thickness Horizontal) is the division between corneal thickness at the thinnest point along the horizontal meridian and the Pachymetric Progression Index[9]; SP-A1 (Stiffness Parameter at A1) is the resultant pressure at the corneal surface (adjusted pressure minus bIOP), divided by deflection amplitude at the first applanation occurrence (A1)[10]; CBI (Corvis Biomechanical Index) is a combined index used to screen for keratoconus (range of values between 0 and 1 in increasing probability of keratoconus); TBI (Tomographic Biomechanical Index) is also a combined index including corneal Scheimpflug tomography data and biomechanics for the detection of keratoconus (range of values and interpretation similar to CBI).[11] Finally, bIOP and IOPnct refer to biomechanically corrected and non-corrected IOP values, respectively. Given the known diurnal variation in IOP,[22] morning or evening measurements were used to assess changes at 1N, 1W and 3M according to the moment (morning or evening) at which BL measurements were obtained.

Data analysis

The IBM Statistical Package for the Social Sciences (SPSS) Statistics v.26 (IBM Corp. NY, US) was used for statistical analysis. Only data from right eyes was used for the analysis. The Kolmogorov-Smirnov test was employed to examine the normality of the data, revealing the presence of several data collections non-normally distributed. Accordingly, results were summarized either as mean ± standard deviation (SD) and 95% confidence intervals, or as median and interquartile range (IQR). The repeated measures ANOVA (analysis of variance) or Friedman (for non-parametric analysis) tests were used to analyse the differences between the visits (BL, 1NM, 1WM, 3MM) and, if statistical significance was found, pairwise comparisons were conducted with the post-hoc test of Bonferroni or Dunn Bonferroni (for non-parametric analysis). Finally, the Student's t-test for matched pairs or the Wilcoxon tests were employed to analyse the differences between morning and evening visits within the same day at 1N, 1W and 3M, that is, 1NT-1NM, 1WT-1WM and 3MT-3MM, respectively. Associations between variables were explored with the Pearson or Spearman coefficients of correlation. A p-value of 0.05 or less was considered to denote statistical significance.

The estimation of the required sample size was based on previous research on corneal topography changes related to ortho-k, as the analysis of the Corvis ST® parameters is relatively new and data normality is scarce. Considering an α-error of 0.05, a β-error of 0.20 and a patient drop-out rate of 20%, an initial sample size of 72 participants was required to detect 0.10 mm changes in corneal curvature (given a SD of ±0.27 mm).

RESULTS

Sample demographics

The study included 75 participants (51 females) with ages ranging from 18 to 62 years. Of these, 6 participants left the study before reaching the 1-month visit and an additional 20 before the 3-months final visit. Main reasons for ortho-k discontinuation were poor or fluctuating vision and halos in mesopic conditions (6 participants), decentred treatment zones (3 participants), unreasonable visual expectations (3 participants), and wearing discomfort (2 participants). The other 12 participants either reported logistic difficulties using their contact lenses each night (2 participants) or could not attend the last follow-up visit due to restrictions imposed by the COVID-19 lockdown of March 2020 (10 participants). Thus, the final sample consisted of 49 participants (33 females), with ages ranging from 18 to 52 years (median 30 years) and BL refraction in spherical equivalent of -3.01 ± 1.39 D (range from -0.63 D to -5.00 D) and refractive cylinder of -0.57 ± 0.32 D (range from 0.00 D to -1.25 D).

Temporal evolution of the Corvis ST® parameters and indices

Table 1 presents a summary of the Corvis ST® parameters and indices under study at BL, 1NM, 1NT, 1WM, 1WT, 3MM and 3MT. For comparison purposes, an analysis of the relative pairwise differences at BL, 1NM, 1WM and 3MM was performed for each parameter not related to intraocular pressure (**Table 2**). Overall, statistically significant differences were found in all parameters with the exception of SP-A1. The Bonferroni or Dunn-Bonferroni tests revealed pairwise differences at several moments in time. When compared with BL values, the majority of parameters presented statistically significant differences at 1WM and 3MM, with changes being less significant when comparing BL and 1NM and, in particular, 1WM and 3MM, thus denoting that alterations were more profound at one week of lens wear and reached a relative stability thereafter. **Figure 1** and **Figure 2** display temporal variation of the parameters ARTh and CBI, respectively. Statistically significant differences in CCT were only found between BL and 1WM (p=0.010) and between BL and 3MM (p=0.016). No statistically significant correlations were found between the attempted myopia correction (refractive error in spherical equivalent at 1N, 1W and 3M compared with BL values) and changes in any of the CORVIS ST® parameters (all p>0.05). In addition, no statistically significant differences were found in any of the BL parameters between the successful ortho-k fittings and participants who abandoned ortho-k before the 3M follow-up visit (all p>0.05).

Table 2 also presents the relative pairwise differences of the Corvis ST® intraocular pressure parameters under study at BL, 1N, 1W and 3M. Whereas bIOP remained stable, statistically significant differences were found in IOPnct between BL and 3M (p=0.029).

An analysis of the correlation of age with the changes associated to different biomechanical parameters evaluated after orthokeratology was investigated. Only very weak, although statistically significant correlations, were found for the relationships of age with: change bIOP 1N-BL (r=0.161, p=0.049), IntRad 1NM-BL (r=-0.297, p<0.001), ARTh 1NM-BL (r=0.198, p=0.015), SP-A1 1NM-BL (r=0.178, p=0.030), CBI 1NM-BL (r=-0.163, p=0.047), TBI 1NM-BL (r=-0.175, p=0.033), and ARTh 1NT-1NM (r=-0.246, p=0.003). Therefore, the impact of age in those changes observed in the biomechanical parameters evaluated seems limited.

Finally, **Table 3** presents the differences between morning and evening measurements for each of the follow-up visits (intraocular pressure parameters were excluded from this comparison given the diurnal variations noted above). With the exception of CBI and TBI, all parameters and indices showed statistically significant differences between morning and evening measurements at all follow-up visits. Whereas increased values for DARatio, IntRad and ARTh were obtained in the evening, SP-A1 and CCT values were found to decrease when compared with morning values, and these differences were evidenced at each of the follow-up visits.

DISCUSSION

The present research explored changes in Corvis ST® parameters and indices in a large sample of participants up to three months after the start of the ortho-k treatment, also investigating diurnal variations in some of these parameters. A relatively small number of publications have examined these Corvis ST® parameters (**Table 4**). Except for the CBI index, the present BL values are similar to those previously reported in a sample of normal patients,[11] in candidates for refractive surgery,[23] and in patients prior to cataract intervention (**Table 4**).[24]

The Corvis ST® provides multiple parameters and indices to describe corneal biomechanics, relative corneal thickness and other corneal characteristics. Lower values of DARatio_2mm reflect an increase in corneal rigidity, that is, smaller differences between the amplitude of the deformation at the apex and at 2 mm from the apex. A statistically significant reduction in this parameter (-0.09 ± 0.22; p=0.007) was found after the first night of ortho-k, with values returning to BL levels at the 3MM follow-up visit. A similar interpretation is given to IntRad, in which lower values denote a gain in rigidity, albeit these parameters are not interchangeable. In fact, a statistically significant increase in this parameter was found at 1WM, when compared with 1NM (median of 0.22 mm^2; range from 0.01 to 0.44 mm^2; p=0.018), with an overall increase of 6.8% over BL values at 3MM (p<0.001). Although changes in SP-A1 are also associated with changes in rigidity, no statistically significant differences were found in this parameter. It may be assumed that SP-A1 informs of a different aspect of corneal biomechanics.

The ARTh parameter was originally developed for the early detection of keratoconus and may not be considered a biomechanical parameter.[9] Keratoconic corneas present an anomalous thickness progression from the centre to the periphery, not dissimilar to that of ortho-k for myopia, which displays a central area of thinning and a ring of peripheral thickening over a treatment area of approximately 6 mm.[25,26] Therefore, given that ARTh explores a corneal area of 8.5 mm in diameter, a reduction of this parameter with ortho-k may be expected. Indeed, a 14.1% reduction in ARTh was observed after the first night of ortho-k (p<0.001), and a further reduction was found at the 1WM follow-up visit (p<0.001), without any additional changes at the 3MM visit.

Both the CBI and TBI are combined indices also used for the detection of keratoconus and interpretation of their values in terms of corneal biomechanics may not be immediate. For instance, the CBI includes the ARTh and the DARatio_2mm, amongst other parameters and constants, with lower values of ARTh leading to an increase in CBI. Accordingly, when compared with BL values, the most significant increase in CBI was found at 1NM (0.082 ± 0.138; p=0.029) and at 1WM (0.093 ± 0.128; p<0.001), without further statistically significant changes at 3MM. Similarly, as the TBI is based on corneal tomography and other parameters, the encountered variations with ortho-k may be expected, as this procedure has a major effect on anterior corneal surface radii.

The different behavior of DARatio_2mm and SP-A1 at the 3M follow-up visit, as compared with ARTh and CBI, may reflect that these last two parameters are more influenced by corneal thickness distribution than by actual corneal rigidity. Therefore, and in view of the documented reversion of the corneal thickness profile after the discontinuation of overnight ortho-k,[27] it may be assumed that the values of ARTh and CBI (and probably of TBI) would also eventually revert to BL values if ortho-k was discontinued. Previous research using the ORA described a reversion of CH and CRF values to those measured in BL conditions, even in patients still using their ortho-k lenses.[10] Further clinical studies are needed to explore long-term changes in the various Corvis ST® parameters, and their progression after ortho-k has been discontinued. It may be interesting to highlight that, as no statistically significant BL differences were found between the successful ortho-k fittings and participants who abandoned the study, it may be assumed that BL parameters are not good predictors of ortho-k success, that is, ortho-k treatment involves a certain degree of unpredictability, which practitioners should convey to their patients before the start of the treatment.

As far as we know, no previous research has explored the Corvis ST® parameters and indices in ortho-k patients. However, other studies in patients submitted to refractive surgery and cross-linking procedures may assist in the contextualization of the present results. Indeed, refractive surgery studies documented an increase in DARatio_2mm and IntRad and a reduction in ARTh and SP-A1, in accordance with a reduction in corneal rigidity. Changes in these parameters were influenced by the type of intervention, ablation depth, and other factors, and were observed even following cataract surgery.[23,24,28,29] As expected, the opposite trend was found in patients following cross-linking procedures to increase corneal rigidity in keratoconus.[30,31] It is relevant to mention that some of these authors recommended caution when interpreting

CBI values in corneas submitted to cataract intervention, as the encountered abnormal values in these patients did not necessarily reflect an increased risk of keratoconus.[24]

Both DARatio_2mm and IntRad were found to increase in the evening, in all follow-up visits, that is, there was a diurnal reduction in corneal rigidity. Values of ARTh also increased during the day, denoting a recovery of the corneal thickness profile. Diurnal changes in the Corvis ST® parameters and indices in ortho-k require careful consideration as many of these parameters may be influenced by confounding variables, namely by the physiological diurnal variations of both corneal thickness and intraocular pressure. Thus, whereas Shen and co-workers did not report diurnal variations of the CRF and CH parameters provided by the ORA,[32] other researchers noted that the Corvis ST® parameters may be influenced by IOP and, in a lesser extent, by corneal thickness.[33,34] In the present study, corneal thickness was found to decrease from morning to evening measurements at all follow-up visits, in agreement with published research by Read and Collins, reporting an average diurnal reduction in CCT of 3.46%.[35] In addition, the alteration of the curvature induced by ortho-k could potentially affect the detection (curve fitting) of the corneal boundaries and lead to changes in the Corvis ST measurement. Regarding curvature, other authors have also noted that central and peripheral corneal stress responses changed with increased corneal curvature, although these authors investigated corneal reshaping in ortho-k with the finite element method and did not consider the contribution of the tear film.[36]

Regarding the intraocular pressure parameters under study, no statistically significant changes were found in bIOP, which is adjusted for corneal rigidity and pachymetry. This finding is consistent with the review of Liu and Xie on the safety of ortho-k[37] and with the research of Yin and co-workers on a sample of 69 young patients with different degrees of myopia.[38] When considering the non-adjusted IOPnct, a small change of -0.5± 1.2 mm Hg (p=0.029) was found between BL values and the follow-up visit at 3M, as documented in published literature.[39,40] A small albeit statistically significant diurnal reduction in both bIOP and IOPnct was found at all follow-up visits, in agreement with the known physiological variation in IOP throughout the day.[41] In summary, ortho-k was not found to lead to clinically significant alterations in IOP values, although it is recommended to assess IOP with adjusted parameters considering corneal pachymetry and biomechanical properties.

The present findings need to be viewed within the context of the actual modifications created by ortho-k on corneal structures. In effect, as far as it is known, the ortho-k procedure is associated with central epithelial thinning and mid-peripheral stromal thickening.[42,43]. The CORVIS ST®, however, provides measurements of the whole cornea, without layer by layer differentiation. The characterization of the biomechanical properties of the corneal epithelium is critical to better understand the mechanisms governing ortho-k and to predict the success of this procedure, albeit current in vivo research remains inconclusive. For instance, Ziaei and co-workers used the CORVIS ST® to explore the biomechanical properties of corneas with keratoconus, before and after epithelial debridement, documenting a significant role of this layer in corneal biomechanics, in contrast with previous ex vivo research describing a lesser contribution of the corneal epithelium.[44,45] Other authors, comparing corneal cellular structures examined by in vivo corneal confocal microscopy with CORVIS ST® parameters in normal and keratoconic corneas, found a significant correlation between biomechanical deformation parameters and endothelial cell properties, but no correlation with basal epithelial cell density.[46]

One critical point of the present study was the clinical significance of all changes that were found to be statistically significant. In summary, the parameters or indices that showed statistically significant changes at 3 months of treatment compared to BL conditions were: IntRad (mean increase of 0.57±0.81 mm^{-1}, a variation of 6.8% with respect to BL conditions), which may be compared to previous research reporting an increase of 23% after photorefractive keratectomy (PRK) and of 32% following femtosecond-guided laser in situ keratomileusis (FS-LASIK);[23] ARTh (mean decrease of -145.26 µm [-178.84/-83.09], a variation of 27% with respect to BL conditions), compared with a previously observed significant reduction of 62% after PRK and of 58% after FS-LASIK;[23] CBI (mean increase of 0.210±0.197), as compared to a mean increase after LASIK of 0.445±0.316;[28] and TBI (mean increase of 0.122±0.207). The increase in IntRad, CBI and TBI as well as the decrease in ARTh would theoretically indicate an alteration of the mechanical properties of the cornea, but to a much lesser degree than that reported after some refractive surgery techniques.[23,28,29] Given that these refractive surgery techniques are considered safe, the percentages of change observed after ortho-k in the explored CORVIS parameters and indices may not be of clinical concern.

It must be noted that the present findings refer to a very specific type of contact lens, characterized by several parameters which may differ from other ortho-k lens designs. Indeed, some authors have suggested that four-zone lens designs could lead to larger treatment areas than those obtained with five-zone designs,[47] an effect which may benefit adult patients with stable myopic refractive error. However, it must be assumed that all lens designs base their ortho-k effect on comparable changes in corneal parameters to those described in this study. Therefore, albeit caution may be advised when extrapolating these results to other designs, these findings may be considered fairly independent of the type of contact lens under study. Similarly, although ortho-k is used primarily for the management of myopia in children, the final sample of participants included only adults (age range from 18 to 52 years). Previous research has noted that that older patients display a reduced or delayed response to ortho-k in the short term,[48] although the present findings only evidenced very weak correlations between age and some of the parameters under study. Further research is needed to explore the response to ortho-k of younger participants, including children aiming at myopia control. Unfortunately, as a consequence of the COVID lockdown, a patient drop-out of 32% was slightly superior to the initial estimation of 20% considered for sample size analysis, thus increasing the probability of Type II error. Furthermore, the restrictive Bonferroni correction required to avoid Type I error may have also resulted in an underestimation of some statistically significant differences.

CONCLUSION

In conclusion, the present research employing an instrument combining non-contact tonometry and Scheimpflug image analysis revealed that changes in corneal parameters and indices are probably more related to the alterations in corneal pachymetry associated with overnight ortho-k than to actual changes in corneal rigidity. Indeed, given that some of the indices provided by Corvis ST® were originally developed as a warning sign of early corneal ectasia, practitioners should be advised that, should they encounter changes following ortho-k, these should be interpreted within the framework of the normal corneal thickness and tomography modifications created by this procedure.These findings, obtained in a sample of adult, successful ortho-k patients, added to the lack of clinically significant changes in the adjusted IOP measurements, give support to the short and mid-term safety of ortho-k.

REFERENCES

1.- Mountford J, Ruston D, Dave T. Orthokeratology: principles and practice. Edinburgh: Butterworth-Heinemann; 2004.

2.- Vincent SJ, Cho P, Chan KY, et al. CLEAR – Orthokeratology. *Cont Lens Anterior Eye* 2021;44:240-269.

3.- Chen D, Lam AKC, Cho P. A pilot study on the corneal biomechanical changes in short-term orthokeratology. *Ophthalmic Physiol Opt* 2009;29:464-471.

4.- Mao XJ, Huang CC, Chen L, et al. [A study on the effect of the corneal biomechanical properties undergoing overnight orthokeratology]. *Zhonghua Yan Ke Za Zhi* 2010;46:209-213.

5.- Yeh TN, Green HM, Zhou Y, et al. Short-term effects of overnight orthokeratology on corneal epithelial permeability and biomechanical properties. *Invest Ophthalmol Vis Sci* 2013;54:3902-3911.

6.- Piñero DP, Alcón N. Corneal biomechanics: a review. *Clin Exp Optom* 2015;98:107-116.

7.- Fernández J, Rodríguez-Vallejo M, Martínez J, et al. Corneal biomechanics after laser refractive surgery: Unmasking differences between techniques. *J Cataract Refract Surg* 2018;44: 390–398.

8.- Guo H, Hosseini-Moghaddam SM, Hodge W. Corneal biomechanical properties after SMILE versus FLEX, LASIK, LASEK, or PRK: a systematic review and meta-analysis. *BMC Ophthalmol* 2019;19:167.

9.- Vinciguerra R, Ambrósio R, Elshekh A, et al. Detection of keratoconus with a new biomechanical index. *J Refract Surg* 2016;32:803-810.

10.- Roberts CJ, Mahmoud AM, Bons JP, et al. Introduction of two novel stiffness parameters and interpretation of air puff-induced biomechanical deformation parameters with a dynamic Scheimpflug analyzer. *J Refract Surg* 2017;33:266–273.

11.- Ambrósio RJr, Lopes BT, Faria-Correia F, et al. Integration of Scheimpflug-based corneal tomography and biomechanical assessments for enhancing ectasia detection. *J Refract Surg* 2017;33: 434–443.

12.- Flockerzi E, Häfner L, Xanthopoulou K, et al. Reliability analysis of successive Corneal Visualization Scheimpflug Technology measurements in different keratoconus stages. *Acta Ophthalmol* 2022;100:e83-e90.

13.- Hon Y, Lam AK. Corneal deformation measurement using Scheimpflug noncontact tonometry. *Optom Vis Sci* 2013;90:e1-e8.

14.- Swarbrick H, Wong G, O'Leary D. Corneal response to orthokeratology. *Optom Vis Sci* 1998;75:791-799.

15.- Haque S, Fonn D, Simpson T, et al. Corneal and epithelial thickness changes after 4 weeks of overnight corneal refractive therapy lens wear, measured with optical coherence tomography. *Eye Contact Lens* 2004;30:189-193.

16.- Cheung SW, Boost MV, Cho P. Effect of povidone iodine contact lens disinfecting solution on orthokeratology lens and lens case contamination and organisms in the microbiome of the conjunctiva. *Cont Lens Anterior Eye* 2021;44:101412

17.- Ali NQ, Patel DV, McGhee CN. Biomechanical responses of healthy and keratoconic corneas measured using a noncontact Scheimpflug-based tonometer. *Invest Ophthalmol Vis Sci* 2014;55:3651–3659.

18.- Wang W, He M, He H, et al. Corneal biomechanical metrics of healthy Chinese adults using Corvis ST®. *Cont Lens Anterior Eye* 2017;40:97–103.

19.- Lanza M, Iaccarino S, Bifani M. In vivo human corneal deformation analysis with a Scheimpflug camera, a critical review. *J Biophotonics* 2016;9:464–477.

20.- Luz A, Faria-Correia F, Salomão MQ, et al. Corneal biomechanics: Where are we? *J Curr Ophthalmol* 2016;28:97–98.

21.- Esporcatte LPG, Salomão MQ, Lopes BT, et al. Biomechanical diagnostics of the cornea. *Eye Vis (Lond)* 2020;7:9.

22.- David R, Zangwill L, Briscoe D, et al. Diurnal intraocular pressure variations: an analysis of 690 diurnal curves. *Br J Ophthalmol* 1992;76:280-283.

23.- Lee H, Roberts CJ, Kim TI, et al. Changes in biomechanically corrected intraocular pressure and dynamic corneal response parameters before and after transepithelial photorefractive keratectomy and femtosecond laser-assisted laser in situ keratomileusis. *J Cataract Refract Surg* 2017;43:1495–1503.

24.- Hirasawa K, Nakakura S, Nakao Y, et al. Changes in corneal biomechanics and intraocular pressure following cataract surgery. *Am J Ophthalmol* 2018;195:26–35.

25.- Coon LJ. Orthokeratology. Part II: evaluating the Tabb method. *J Am Optom Assoc* 1984;55:409-418.

26.- Swarbrick H, Wong G, O'Leary D. Corneal response to orthokeratology. *Optom Vis Sci* 1998;75:791-799.

27.- Haque S, Fonn D, Simpson T, et al. Corneal and epithelial thickness changes after 4 weeks of overnight corneal refractive therapy lens wear, measured with optical coherence tomography. *Eye Contact Lens* 2004;30:189-193.

28.- Abd El-Fattah EA, El Dorghamy AA, Ghoneim AM, et al. Comparison of corneal biomechanical changes after LASIK and F-SMILE with CorVis ST. *Eur J Ophthalmol* 2021;31:1762-1770.

29.- Liu M, Shi W, Liu X, et al. Postoperative corneal biomechanics and influencing factors during femtosecond-assisted laser in situ keratomileusis (FS-LASIK) and laser-assisted subepithelial keratomileusis (LASEK) for high myopia. *Lasers Med Sci* 2021;36:1709-1717.

30.- Jabbarvand M, Moravvej Z, Shahraki K, et al. Corneal biomechanical outcome of collagen cross-linking in keratoconic patients evaluated by Corvis ST. *Eur J Ophthalmol* 2021;31:1577-1583.

31.- Sedaghat MR, Momeni-Moghaddam H, Ambrósio RJr, et al. Long-term Evaluation of corneal biomechanical properties after corneal cross-linking for keratoconus: A 4-year longitudinal study. *J Refract Surg* 2018;34:849-856.

32.- Shen M, Wang J, Qu J, et al. Diurnal variation of ocular hysteresis, corneal thickness, and intraocular pressure. *Optom Vis Sci* 2008;85:1185–1192.

33.- Valbon BF, Ambrósio RJr, Fontes BM, et al. Ocular biomechanical metrics by Corvis ST® in healthy Brazilian patients. *J Refract Surg* 2014;30:468–473.

34.- Clement CI, Parker DG, Goldberg I. Intra-Ocular pressure measurement in a patient with a thin, thick or abnormal cornea. *Open Ophthalmol J* 2016;10:35–43.

35.- Read SA, Collins MJ. Diurnal variation of corneal shape and thickness. *Optom Vis Sci* 2009;86:170-180.

36.- Wu J, Fang W, Xu H, et al. The biomechanical response of the cornea in orthokeratology. *Front Bioeng Biotechnol* 2021;9:743745.

37.- Liu YM, Xie P. The safety of orthokeratology – A systematic review. *Eye Contact Lens* 2016;42:35-42.

38.- Yin Y, Zhao Y, Fu Y, et al. Clinical results of orthokeratology therapy in adolescents with low to moderate myopia. *Zhong Nan Da Xue Xue Bao Yi Xue Ban* 2020;45:966-972.

39.- Chang CJ, Yang HH, Chang CA, et al. The influence of orthokeratology on intraocular pressure measurements. *Semin Ophthalmol* 2013;28:210–215.

40.- Ishida Y, Yanai R, Sagara T, et al. Decrease in intraocular pressure following orthokeratology measured with a noncontact tonometer. *Jpn J Ophthalmol* 2011;55:190–195.

41.- Wilensky JT. Diurnal variations in intraocular pressure. *Trans Am Ophthalmol Soc* 1991;89: 757–790.

42.- Mohidin N, Mat Yacob A, Norazman FN. Corneal thickness and morphology after orthokeratology of six-month lens wear among young Malay adults. *Med J Malaysia* 2020;75:538-542.

43.- Kim WK, Kim BJ, Ryu IH, Kim JK, Kim SW. Corneal epithelial and stromal thickness changes in myopic orthokeratology and their relationship with refractive change. *PLoS One* 2018;13:e0203652.

44.- Ziaei M, Gokul A, Vellara H, Lu LM, Patel DV, McGhee CNJ. Measurement of in vivo biomechanical changes attributable to epithelial removal in keratoconus using a noncontact tonometer. *Cornea* 2020;39:946-951.

45.- Meek KM, Knupp C. Corneal structure and transparency. *Prog Retin Eye Res* 2015;49:1-16.

46.- Alvani A, Hashemi H, Pakravan M, Mahbod M, Amanzadeh K, Seyedian MA, et al. Dynamic corneal biomechanics in different cell layers: in keratoconus and normal eyes. *Ophthalmic Physiol Opt* 2021;41:414-423.

47.- Marcotte-Collard R, Simard P, Michaud L. Analysis of two orthokeratology lens designs and comparison of their optical effects on the cornea. *Eye Contact Lens* 2018;44:322–329.

48.- Jayakumar J, Swarbrick HA. The effect of age on short-term orthokeratology. *Optom Vis Sci* 2005;82:505–511.

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FIGURE LEGENDS

Figure 1. Temporal progression of the ARTh parameter (mm^{-1}) measured at baseline (BL) and follow-up visits at one night morning (1NM) and evening (1NT), one week morning (1WM) and evening (1WT), and three months morning (3MM) and evening (3MT).

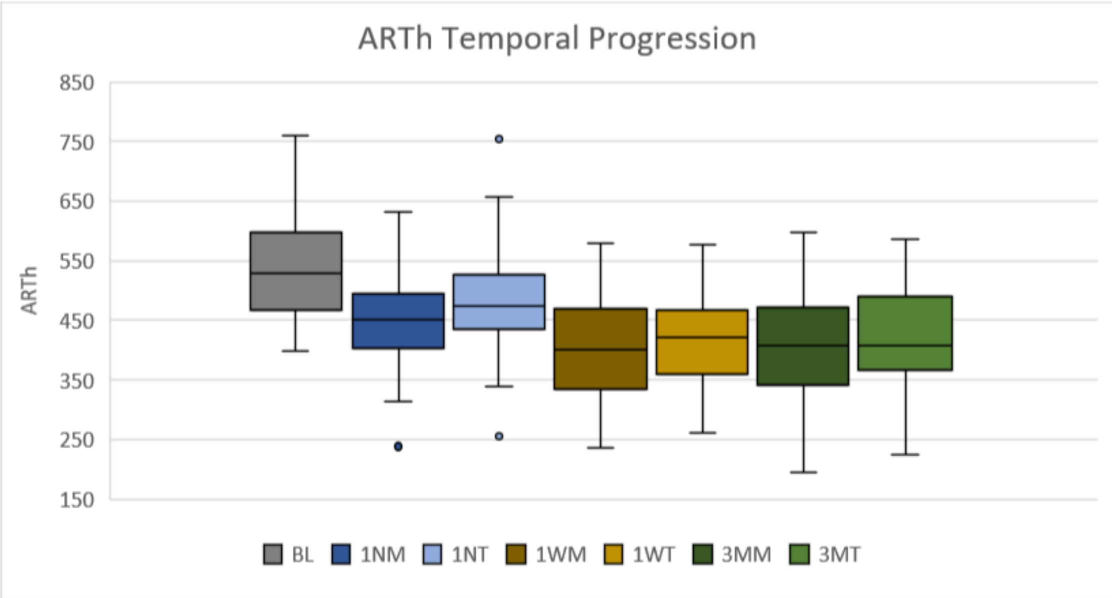

Figure 2. Temporal progression of the CBI parameter measured at baseline (BL) and follow-up visits at one night morning (1NM) and evening (1NT), one week morning (1WM) and evening (1WT), and three months morning (3MM) and evening (3MT).

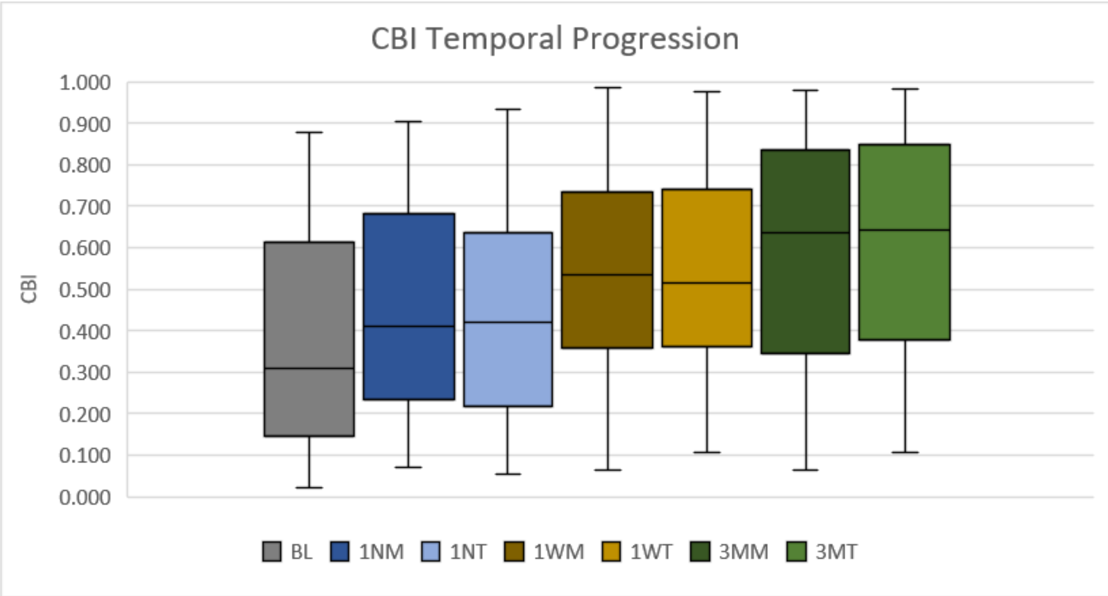

Table 1. Corvis ST® parameters and indices measured at baseline (BL) and follow-up visits at one night morning (1NM) and evening (1NT), one week morning (1WM) and evening (1WT), and three months morning (3MM) and evening (3MT). Results are shown either as mean ± SD (and 95% confidence intervals) or median (interquartile range).

	BL	**1NM**	**1NT**	**1WM**	**1WT**	**3MM**	**3MT**
DARatio	4.57±0.48 (3.63; 5.51)	4.48±0.42 (3.66; 5.30)	4.62±0.42 (3.80; 5.44)	4.49±0.43 (3.65; 5.33)	4.59±0.43 (3.75; 5.43)	4.64±0.45 (3.76; 5.52)	4.79±0.50 (3.81; 5.77)
IntRad (mm^{-1})	8.40±1.04 (6.36; 10.44)	8.45±0.96 (6.57; 10.33)	8.65±0.87 (6.94; 10.36)	8.62±0.93 (6.80; 10.44)	8.84±0.91 (7.06; 10.62)	8.98±0.99 (7.04; 10.92)	9.25±1.01 (7.27; 11.23)
ARTh (µm)	538.72±90.14 (362.05; 715.39)	450.23±70.39 (312.27; 588.19)	478.22±79.11 (323.16; 633.28)	400.71±85.29 (233.54; 567.88)	414.41±79.94 (257.73; 571.09)	397.61±98.07 (205.39; 589.83)	414.05±93.83 (230.14; 597.96)
SP-A1 (mm Hg/mm)	101.98±15.46 (71.68; 132.28)	107.52±17.29 (73.63; 141.41)	101.02±16.23 (69.21; 132.83)	105.90±17.57 (71.46; 140.34)	101.50±15.32 (71.47; 131.53)	105.43±15.81 (74.44; 136.42)	100.08±16.46 (67.82; 132.34)
CBI	0.311 (0.146/0.613)	0.411 (0.232/0.681)	0.420 (0.217/0.635)	0.542 (0.357/0.722)	0.516 (0.361/0.741)	0.578 (0.344/0.836)	0.603 (0.378/0.847)
TBI	0.053 (0.014/0.276)	0.116 (0.017/0.305)	0.061 (0.016/0.251)	0.283 (0.112/0.415)	0.253 (0.062/0.400)	0.284 (0.076/0.396)	0.142 (0.033/0.438)
CCT (µm)	550.4±33.4 (484.9; 615.9)	558.3±33.7 (492.2; 624.3)	549.3±31.9 (486.8; 611.8)	542.1±34.6 (474.3; 609.9)	542.7±32.6 (478.8; 606.6)	542.6±38.10 (467.9; 617.3)	536.3±37.2 (463.4; 609.2)
IOPnct (mm Hg)	14.9±2.0 (11.0; 18.8)	15.1±2.3 (10.6; 19.6)	14.4±1.9 (10.7; 18.1)	15.0±2.2 (10.7; 19.3)	14.4±1.8 (10.9; 17.9)	14.7±1.8 (11.2; 18.2)	14.1±2.2 (9.8; 18.4)
bIOP (mm Hg)	14.7±1.8 (11.2; 18.2)	14.8±2.1 (10.7; 18.9)	14.3±1.8 (10.8; 17.8)	14.9±1.9 (11.2; 18.6)	14.4±1.6 (11.3; 17.5)	15.0±1.7 (11.7; 18.3)	14.2±2.1 (10.1; 18.3)

Table 2. Differences in Corvis ST® parameters and indices measured at baseline (BL) and follow-up visits at one night morning (1NM), one week morning (1WM) and three months morning (3MM). For intraocular pressure, morning or evening measurements were used at one night (1N), one week (1W) and three months (3M) according to the moment (morning or evening) at which BL measurements were obtained. Results are shown either as mean ± SD (and 95% confidence intervals) or median (interquartile range). The results of the ANOVA or Friedman group analysis for each parameter (significance, p) are show, as well as the results of the corresponding Bonferroni or Dunn-Bonferroni pair-wise analysis.

	p	**1NM-BL**	**1WM-BL**	**3MM-BL**	**1WM-1NM**	**3MM-1NM**	**3MM-1WM**
DARatio	<0.001	-0.09±0.22 (-0.52; 0.34) p=0.007	-0.08±0.19 (-0.45; 0.29) p=0.003	-0.04±0.31 (-0.65; 0.57) p=1.000	0.01±0.16 (-0.30; 0.32) p=1.000	0.09±0.27 (-0.44; 0.62) p=0.029	0.09±0.23 (-0.36; 0.54) p=0.012
IntRad (mm^{-1})	<0.001	0.01 (-0.36/0.35) p=1.000	0.20 (-0.13/0.53) p=0.154	0.57 (-0.07/1.11) p<0.001	0.22 (0.01/0.44) p=0.018	0.31 (0.03/0.89) p<0.001	0.16 (-0.03/0.63) p=0.331
ARTh (µm)	<0.001	-75.91±63.37 (-200.12; 48.30) p<0.001	-139.21±85.65 (-307.08; 28.66) p<0.001	-145.26±90.08 (-321.82; 31.20) p<0.001	-50.94±60.99 (-170.48; 68.60) p<0.001	-58.03±69.45 (-194.15; 78.09) p<0.001	-5.15±52.16 (-107.38; 97.08) p=1.000
SP-A1 (mm Hg/mm)	0.129	2.49±9.42 (-15.97; 20.95)	4.29±9.15 (-13.64; 22.22)	3.01±9.28 (-15.18; 21.20)	1.35±8.28 (-14.88; 17.58)	1.20±9.20 (-16.83; 19.23)	-0.11±10.23 (-20.16; 19.94)
CCT (µm)	<0.001	-2.3±13.3 (-28.4; 23.8) p=1.000	-7.0±14.3 (-35.0; 21.0) p=0.010	-5.3±17.0 (-38.6; 28.0) p=0.016	-4.3±13.0 (-29.8; 21.2) p=0.053	-4.3±14.8 (-33.3; 24.7) p=0.331	2.1±11.9 (-21.2; 25.4) p=1.000
CBI	<0.001	0.082±0.138 (-0.188; 0.352) p=0.029	0.174±0.143 (-0.106; 0.454) p<0.001	0.210±0.197 (-0.176; 0.596) p<0.001	0.093±0.128 (-0.158; 0.344) p<0.001	0.093±0.162 (-0.225; 0.411) p<0.001	0.031±0.139 (-0.241; 0.303) p=1.000
TBI	<0.001	0.001±0.193 (-0.377; 0.379) p=0.708	0.151±0.216 (-0.272; 0.574) p=0.002	0.122±0.207 (-0.284; 0.528) p<0.001	0.052±0.229 (-0.397; 0.501) p=0.255	0.082±0.212 (-0.334; 0.498) p=0.060	0.001±0.184 (-0.360; 0.362) p=1.000

	p	**1N-BL**	**1W-BL**	**3M-BL**	**1W-1N**	**3M-1N**	**3M-1W**
IOPnct (mm Hg)	0.032	-0.3±1.3 (-2.8; 2.2) p=1.000	-0.3±1.4 (-3.0; 2.4) p=0.303	-0.5±1.2 (-2.9; 1.9) p=0.029	-0.1±1.3 (-2.6; 2.4) p=1.000	-0.3±1.2 (-2.7; 2.1) p=0.823	-0.1±1.5 (-3.0; 2.8) p=1.000
bIOP (mm Hg)	0.153	-0.2±1.2 (-2.6; 2.2)	-0.1 ±1.3 (-2.6; 2.4)	-0.4±1.2 (-2.8; 2.0)	0.00±1.2 (-2.4; 2.4)	-0.1±1.1 (-2.3; 2.1)	-0.2±1.4 (-2.9; 2.5)

Table 3. Differences between morning and evening in Corvis ST® parameters measured at the follow-up visits at one night (1N), one week (1W) and three months (3M). Results are shown either as mean ± SD (and 95% confidence intervals) or median (interquartile range). The results of the Student t-test or the Wilcoxon test pair-wise analysis for each parameter (significance, p) are shown.

	1NT-1NM	**1WT-1WM**	**3MT-3MM**
DARatio	0.14±0.21 (-0.27; 0.55) p<0.001	0.11±0.17 (-0.22; 0.44) p<0.001	0.14±0.22 (-0.29; 0.57) p<0.001
IntRad (mm^{-1})	0.24±0.44 (-0.62; 1.10) p<0.001	0.22±0.44 (-0.64; 1.08) p<0.001	0.26±0.37 (-0.47; 0.99) p<0.001
ARTh (µm)	19.35 ±41.01 (-61.03; 99.73) p<0.001	15.09±29.52 (-42.77; 72.95) p<0.001	16.44±26.53 (-35.56; 68.44) p<0.001
SP-A1 (mm Hg/mm)	-3.27±9.97 (-22.81; 16.27) p=0.006	-4.32±7.65 (-19.31; 10.67) p<0.001	-5.34±7.34 (-19.73; 9.05) p<0.001
CCT (µm)	-3.8 (-8.1/0.5) p<0.001	-5.0 (-9.3/-0.6) p<0.001	-6.3 (-12.5/-0.3) p<0.001
CBI	-0.001 (-0.054/0.046) p=0.742	0.008 (-0.043/0.060) p=0.457	0.021 (-0.029/0.058) p=0.067
TBI	0.010 (-0.108/0.018) p=0.002	-0.003 (-0.069/0.028) p=0.262	-0.014 (-0.059/0.026) p=0.274

Table 4. Comparison of baseline CORVIS ST® parameters obtained in the present study with those reported in the literature.

	Ambrósio et al (2017) [11]	**Lee et al** (2017) [21]	**Hirasawa et al** (2018) [22]	**Present study**
DARatio_2mm	4.30 ± 0.50	4.27 ± 0.35	4.42 ± 0.33	4.57 ± 0.48
IntRad (mm^{-1})	-	8.20 ± 0.90	8.52 ± 0.86	8.40 ± 1.04
ARTh (µm)	-	459 ± 101	552.5 ± 160.0	538.72 ± 90.14
SP-A1 (mm Hg/mm)	106.30 ± 17.65	94.7 ± 17.0	98.4 ± 22.5	101.98 ± 15.46
CBI	0.06 ± 0.14	-	0.15 ± 0.29	0.311 (0.146/0.613)
TBI	0.07 ± 0.10	-	-	0.053 (0.014/0.276)