

Raw data from Ocular Response Analyzer applied for differentiation of normal and glaucoma patients

AGNIESZKA JÓŻWIK^{1*}, MAGDALENA ASEJCZYK-WIDLICKA¹, AGNIESZKA BOSZCZYK¹, HENRYK KASPRZAK¹, PATRYCJA KRZYŻANOWSKA-BERKOWSKA²

¹Department of Optics and Photonics, Wrocław University of Science and Technology, Wybrzeże Wyspiańskiego 27, 50-370 Wrocław, Poland

²Department of Ophthalmology, Wrocław Medical University, Wybrzeże Ludwika Pasteura 1, 50-367 Wrocław, Poland

*Corresponding author: agnieszka.jozwik@pwr.edu.pl

Purpose: Presented study describes new parameters calculated from the Ocular Response Analyzer (ORA) raw data. Such an approach can increase the applicability of the ORA in ophthalmic diagnosis. Among many proposed and examined by us parameters from raw data of the air pressure and applanation curves, only a few were chosen and then applied for characterizing a selected group of patients. *Methods:* The study included healthy subjects in a control group and patients divided into 2 groups: suspect and glaucoma. A series of four ORA measurements were taken from each subject. The raw ORA data were numerically analyzed and new parameters were calculated from the ORA curves for each measurement. Comparative analysis was carried out for the newly proposed parameters (and original parameters from the ORA device). *Results:* This interesting finding is that the new parameters showed a statistically significant ability to distinguish the glaucoma suspect group from healthy and glaucomatous patients. Moreover comparable or higher repeatability than for IOPg and CH was obtained. *Conclusion:* Raw data from the ORA enables definition and numerical analysis of new parameters, characterizing every measurement, which can be successfully used for describing an individual eye and differentiating between some specific groups of patients.

Keywords: glaucoma, intraocular pressure, Ocular Response Analyzer, raw data, tonometry.

1. Introduction

The value of intraocular pressure (IOP) is a crucial and clinical parameter for the screening, diagnosis and management of glaucoma. Despite many different methods and devices of IOP measurements, the problem of the reliable measurement of IOP is still open and challenging.

Different results obtained for the same eye may depend on quasi-periodical variations of IOP with blood pulsation [1], as well as on other variations of the biomechanical properties of the anterior eye. Measurements of IOP dynamics taken by the Pascal dynamic contour tonometer (DCT) or the SmartLens dynamic observing tonometer demonstrate IOP pulsations with amplitude in the range of 2–6 mmHg [2, 3]. Apart from these dynamical changes, there are some static parameters such as corneal geometry (thickness and curvature) or the individual elastic features of the anterior eye segment that have an influence on the measured value of IOP. The necessary corrections of the obtained IOP results, due to these parameters, should be considered. However, this is not very often taken into account. Goldman tonometry gives the value of IOP without considering corneal thickness. Researchers have shown that central corneal thickness (CCT) affects the pressure value of IOP [4–6]. Higher values of IOP are observed for higher values of the central corneal thickness. In turn, thinner corneas result in lower IOP readings [4, 5]. Correction of corneal thickness during the measurement of IOP is used in commercially available tonometers. Other corneal properties, such as radius of curvature or elastic moduli, could have a more significant influence on the correctness of this measurement [7, 8]. Viscoelastic properties of the cornea and the anterior eye, and also its behaviour during measurement, are important and investigated problems. High complexity and dynamical variability of the eye structures and their biomechanical properties make the exact measurement of temporary IOP value difficult.

New generation of tonometers, such as Ocular Response Analyzer (ORA, Reichert Technologies, Depew, NY) and Corneal Visualization Scheimpflug Technology (Corvis ST, Oculus, Wetzlar, Germany) start to evaluate some biomechanical properties of the anterior eye and their correlations with eye pathologies. The ORA is a noninvasive air-puff tonometer that measures the biomechanical response of the eye to the impulse of air [9] and some biomechanical properties of the cornea [10]. The device registers values of the air pressure outgoing from the air jet, and the light intensity, reflected from the corneal apex during corneal deformations. These two parameters are presented in form of two curves given by the device. The second, applanation curve should have two local maxima, representing temporal positions of both corneal applanations, where the intensity of light reflected from the corneal apex is the highest. However, in some cases, the applanation curve shows fast local variations. Therefore, ORA's software smooth this curve to better visualize temporal positions of both applanation times t_{1a} and t_{2a} . Air pressures corresponding to both applanations (inward and outward) are called P_1 and P_2 (see Fig. 1).

Next, software of the device analyzes the interactions between these two curves and estimates IOP as well as other parameters describing the anterior eye properties. Apart from the results related to IOP, such as Goldmann-correlated intraocular pressure (IOPg) and corneal-compensated intraocular pressure (IOPcc), the ORA generates two values related to corneal biomechanics: corneal hysteresis (CH) and corneal resistance factor (CRF). Calculation of pressure IOPcc is based on the mutual relationship between the first and the second applanations with appropriate constants and is not di-

rectly related to the thickness of the cornea [9]. CH and CRF can demonstrate specific properties of the anterior segment in case of keratoconus or glaucoma [11–13]. It has been shown that IOP_g and IOP_{cc} are higher in the case of glaucoma when CH and CRF are lower [14, 15]. Earlier research showed that CH and CRF do not change during the daily cycle. However, intraocular pressure changes throughout the day and is higher in the nocturnal period in comparison to the diurnal one [16]. ORA gives 37 additional parameters that mainly describe the applanation curve, allowing a more detailed analysis of the corneal deformation process. They are not commonly used in ophthalmic practise, but could be more useful in the detection of corneal changes in specific corneal conditions [17–19]. Some authors have implemented new additional parameters to characterize the properties of the cornea [11, 17, 20]. Variability of ORA measurements is associated, to a lesser degree, with the quality of waveform scans [21]. The quality of each measurement is described by a waveform score parameter, ranging between 0 and 10.

ORA device provides access to raw data of both air pressure and applanation curves allowing application of different numerical procedures in order to define new parameters characterizing the anterior eye. Single measurement on the patient eye gives the already mentioned four basic ORA parameters. However, different measurements on the same eye give less or more different results. The averaged values obtained from these few measurements can be used as characteristic value of obtained parameters. However, as it was shown in the paper [22] there exists some individual dependency between P_1 , P_2 pressures and some other raw parameters from different measurements, characteristic for the patient. So, such approach needs a few measurements on a single patient eye to define new characteristic parameters. These parameters, characterizing different measurements (multimeasurements parameters) for the same patient eye, can be also used for differentiations of the eye properties [22]. Despite the differences in the form of these two curves given by the ORA for individual measurements on the same eye, there still exist some characteristic dependences and correlations between selected parameters for the individual eye.

The aim of this study was to propose the new approach for the analysis of ORA raw data and to ascertain how the parameters measured by the Ocular Response Analyzer and those calculated from the raw data can be best utilised to improve the diagnosis of glaucoma and early detection of glaucoma suspects.

2. Materials and methods

The prospective study included 338 participants. Only one eye of the patient was measured. Control group included 43 healthy volunteers without any eye disease. Patients were divided into two groups: 107 patients were classified as glaucoma group and 86 subjects as glaucoma suspect group. Patients from the glaucoma suspect group were diagnosed with glaucomatous optic disc appearance after clinical assessment. Patients with normal visual field, open angle and intraocular pressure below or equal 21 mmHg,

but with neuretinal rim narrowing with concentric enlargement, concentric enlargement, localized notch or both, were qualified for this group. Glaucoma group included patients with the primary open angle glaucoma and with the primary angle closure glaucoma. Diagnosis of them was based on glaucomatous changes in the optic nerve head with associated visual field defects. The criteria for exclusion from the study were: any systemic disease, intraocular surgery less than twelve months before the study start date, refractive surgery, conjunctival or intraocular inflammation, corneal abnormalities such as edema or scars, and contact lens wear. In the glaucoma group, patients were taking beta-blocker drops (27%), prostaglandins (36%), carbonic anhydrase inhibitor eye drops (28%) and alpha agonists (9%). Twenty-eight percent of patients in the suspect group were taking medications. Patients were taking beta-blocker drops (12%), prostaglandins (7%), carbonic anhydrase inhibitor eye drops (8%) and alpha agonists (1%).

All patients were recruited from the Glaucoma Clinic at the Department of Ophthalmology of the Wrocław Medical University and were informed about the process of measurement, to which they voluntarily agreed. The study had the approval of a local ethical committee (Ethics Committee of the Wrocław Medical University agreement, KB 503/2011), and the informed consent, according to the tenets of the Declaration of Helsinki, was obtained from each participant before examination.

Each measurement by the Ocular Response Analyzer gives a total of 800 measured points describing air pressure and applanation curves (each 400 data points). The analysis was carried out on results taken from the raw data, exported directly from the device. Both curves were processed using numerical procedures (Matlab, Math Works, Inc., Natick, MA, USA, version 2011a). First, the Gaussian filter (size of window 17 data points) was applied for smoothing both curves. As in our previous work, measurements below 2 in the waveform score quality parameter were rejected from further processing due to their noise [22]. Four consecutive measurements with the waveform score greater than 2 were analyzed.

The raw data and smoothed curves are presented in Fig. 1. Times of the first t_{1a} and the second t_{2a} applanations, the time of the maximum air pressure curve t_m and the corresponding applanation pressures P_1 and P_2 , as well as the maximal air pressure MP were numerically calculated. Additionally, value P_a was calculated as the arithmetic average of P_1 and P_2 .

During the extended numerical analysis of the point positions characterizing both curves and their mutual dependencies, some new parameters were defined (HM, P_1/CCT , P_a/CCT , P_a/smm , dm , $b_{1.45}$). The parameter smm was already described previously [22],

$$smm = \frac{t_m}{\sqrt{dm_1 dm_2}} - 1 \quad (1)$$

where t_m – the time of appearance of maximal air pressure curve, dm_1 – the time between the first applanation and the maximal air pressure curve, and dm_2 – the time between the

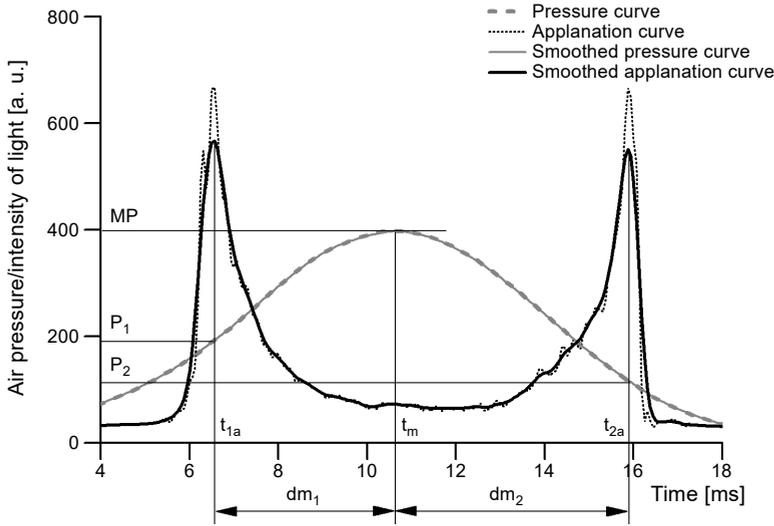


Fig. 1. Data obtained from the Ocular Response Analyzer – raw and smoothed data.

maximal air pressure curve and the second applanation (Fig. 1). Parameter dm specifies the time between two applanations ($dm_1 + dm_2$). The constant reference value smm_r was calculated as the arithmetic mean of the smm parameter for all the measurements and the value of $smm_r = 1.45$ was accepted for further analysis. As it was shown in [22] the parameter smm for each patient is strongly correlated with applanation pressures P_1 , P_2 and their average value P_a . Results with a higher correlation were observed and recorded for the dependence between $P_a^{-1/smm}$ and smm . Pearson correlation coefficients are included in the range 0.995 to 0.999 (mean value 0.997, median 0.999) for all patients.

For each patient, the multimeasurement parameter $b_{1.45}$ was based on four measurements and calculated from the following equation:

$$b_{1.45} = A P_a^{-1/smm_r} + B \quad (2)$$

where A and B represent the coefficients of the linear regression of the dependence between $P_a^{-1/smm}$ and smm parameters.

Additionally, two parameters: P_a/smm and HM (hysteresis modified) are proposed, where HM is described by the following equation:

$$HM = \frac{MP - P_2}{MP - P_1} \quad (3)$$

where the parameter MP is the maximal value of the air pressure curve. CH takes into account the difference between pressures P_1 and P_2 (Fig. 1), while neglecting the max-

imal value of the air pressure MP. However, it can occur that the values P_1 , P_2 and CH are respectively the same for the two measurements with the pressure curves having different values of MP. The HM parameter gives different values in both cases. The central corneal thickness CCT was then measured using ultrasonographic pachymetry.

Repeatability and reproducibility of the considered parameters for four measurements on each patient were evaluated by the intraclass correlation coefficient (ICC) and the coefficient of variation (CV). ICCs above 0.75 are usually considered to indicate good repeatability. The statistical analysis of the results for normal, suspect and glaucoma groups was applied. The Shapiro–Wilk test was used to define the distribution of results. Normality was rejected in the majority of cases ($p < 0.05$). Multicomparison for independent groups has been performed using the Kruskal–Wallis test for IOPg, IOPcc, CH, CRF, CCT (Statistica, ver. 14, StatSoft, Inc., USA). To test the new parameters between each pair of groups, the Mann–Whitney test for two independent groups was used. Statistical significance was taken as $p < 0.05$.

3. Results

The main group demographics together with the group number of subjects, mean age, CCT, IOPg, IOPcc, CH, CRF are shown in Table 1. Statistically significant differences (Kruskal–Wallis test, multicomparison for independent groups, $p < 0.05$) between the median age, IOPg, CH and CRF for all considered groups were obtained.

Proposed new parameters: HM, P_a /smm, dm, as well as the values of intraocular pressure IOPg and corneal hysteresis CH were included for analysis. Table 2 shows

T a b l e 1. Number of subjects, mean (\pm SD) and range of age, CCT, IOPg, IOPcc, CH and CRF and the result of the Kruskal p -value (ANOVA) statistical difference for each parameter between the groups for the three considered groups. Statistically significant results ($p < 0.05$) are shown in the bold font.

	Normal	Suspect	Glaucoma	p -value
Number (M/F)	43 (13/30)	86 (25/62)	209 (58/151)	–
Age [years]	73 \pm 11 (38–95)	54 \pm 17 (20–84)	64 \pm 12 (18–82)	<0.001
CCT [μ m]	560 \pm 50 (447–725)	560 \pm 34 (450–665)	552 \pm 38 (424–648)	>0.050
IOPg [mmHg]	15.8 \pm 3.4 (9.7–23.7)	18.2 \pm 5.5 (8.3–45.0)	16.5 \pm 4.5 (8.0–41.4)	0.007
IOPcc [mmHg]	16.5 \pm 3.3 (10.3–23.9)	17.6 \pm 5.3 (10.1–46.8)	16.9 \pm 5.0 (6.8–41.3)	>0.050
CH [mmHg]	10.2 \pm 1.4 (7.1–13.4)	11.1 \pm 1.7 (5.45–14.2)	10.3 \pm 1.9 (4.2–16.7)	<0.001
CRF [mmHg]	10.3 \pm 1.6 (7.7–14.9)	11.8 \pm 2.0 (7.0–15.7)	10.6 \pm 1.7 (5.3–15.8)	<0.001

T a b l e 2. The intraclass correlation coefficients (ICC) and coefficients of variation (CV) [%] calculated for 5 parameters and also their quotients by corneal central thickness (CCT).

	IOPg	$\frac{\text{IOPg}}{\text{CCT}}$	CH	$\frac{\text{CH}}{\text{CCT}}$	HM	$\frac{\text{HM}}{\text{CCT}}$	$\frac{P_a}{\text{smm}}$	$\frac{P_a}{\text{smm} \cdot \text{CCT}}$	dm	$\frac{\text{dm}}{\text{CCT}}$
ICC	0.91	0.92	0.69	0.69	0.57	0.88	0.83	0.99	0.86	0.96
CV	28	29	17	16	4	9	3	10	6	11

the variability of the above 5 parameters and their quotients by corneal central thickness for all patients.

IOPg is characterized by greater repeatability (ICC = 0.91) than CH (ICC = 0.69). It also has a wider distribution of results in comparison to CH. Both parameters, when divided by corneal thickness, show very similar values to ICC and CV.

The analysis of $P_a/(s\text{mm}\cdot\text{CCT})$ shows that this parameter differentiates patients better than IOPg or CH, and its variation CV is smaller (10%) than variations of intraocular pressure IOPg (28%) and CH (17%). Similar high values of ICC and low CV are obtained for the parameter dm/CCT . As was expected, the parameter HM is strongly correlated with CH ($r = 0.91, p < 0.05$). HM represents similar biomechanical characteristics as CH. However, if corneal thickness is taken into account (HM/CCT), it has higher repeatability than CH and CH/CCT.

For further analysis, every parameter measured four times for one patient was averaged. Most of the analyzed parameters, including the intraocular pressure IOPg and the corneal hysteresis CH, differentiate normal–suspect and suspect–glaucoma groups, without registering any differences between the normal and glaucoma groups. This is most likely due to the pharmacological treatment applied for glaucoma patients. Moreover, the parameters P_1/CCT and P_a/CCT were also considered in the analysis due to a very high ICC being obtained for both parameters (0.93 for P_1/CCT and P_a/CCT). The results for four exemplary parameters are presented as box plots (Fig. 2).

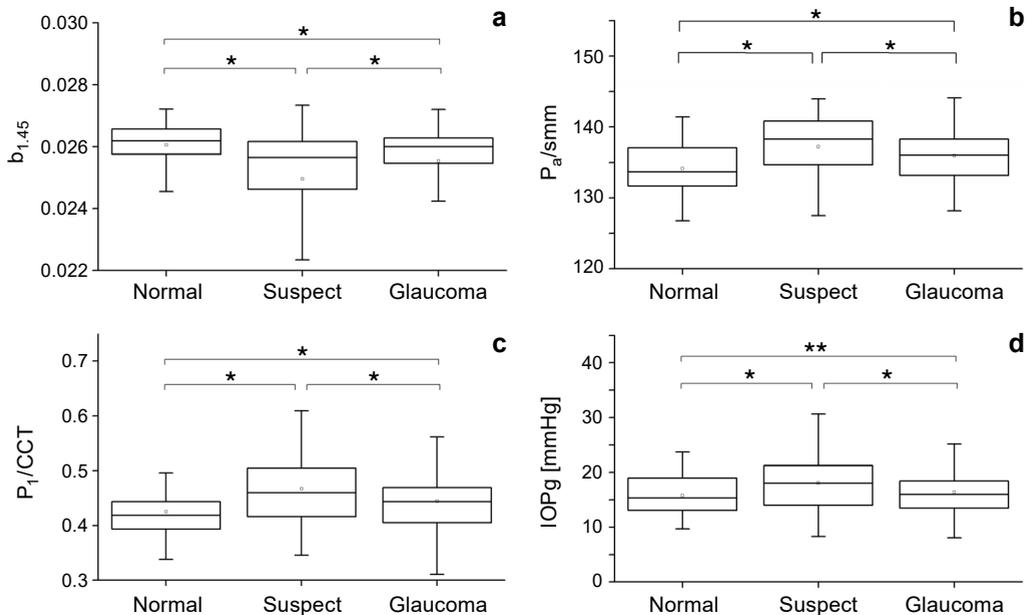


Fig. 2. Box plots of four parameters $b_{1,45}$ (a), P_a/smm (b), P_1/CCT (c), and intraocular pressure IOPg (d) for patients divided into three groups. Stars represent the interpretation of p -values: one star (★) means a statistical significant difference and two stars (★★) – no difference between the two compared groups.

T a b l e 3. Mean values \pm SD for IOPg, CH and the new parameters calculated from raw data.

	Normal	Suspect	Glaucoma
P_a /smm	134.1 \pm 3.4	137.2 \pm 4.5	135.3 \pm 3.5
$b_{1.45}$	-0.0261 \pm 0.0007	-0.0250 \pm 0.0024	-0.0256 \pm 0.0019
P_a /CCT	0.36 \pm 0.05	0.39 \pm 0.08	0.37 \pm 0.06
P_1 /CCT	0.43 \pm 0.05	0.44 \pm 0.06	0.47 \pm 0.07
HM	1.31 \pm 0.04	1.33 \pm 0.05	1.31 \pm 0.06

T a b l e 4. The results of the Mann–Whitney test (p -values) comparison of medians between two groups for the output parameters of the ORA (IOPg, CH, CRF) and those calculated from the raw ORA data (HM, P_1 /CCT, P_a /CCT, P_a /smm, dm, $b_{1.45}$). Statistically significant results ($p < 0.05$) are shown in bold font.

	Normal vs. glaucoma	Normal vs. suspect	Suspect vs. glaucoma
IOPg	0.580	0.010	0.004
CH	0.960	0.003	<0.001
CRF	0.952	<0.001	<0.001
P_a /smm	0.002	<0.001	0.002
$b_{1.45}$	0.010	<0.001	0.002
P_a /CCT	0.060	0.003	0.030
P_1 /CCT	0.020	<0.001	0.007
HM	0.750	0.005	0.004

The mean values and standard deviations for the parameters calculated from ORA raw data are shown in Table 3.

The results of comparing two independent samples using the Mann–Whitney test for the proposed parameters (HM, P_1 /CCT, P_a /CCT, P_a /smm, dm, $b_{1.45}$) and the original parameters from the ORA device (IOPg, CH, CRF) are shown in Table 4.

For IOPg, CH and CRF significant differences ($p < 0.05$) were found between three pairs of considered groups. Significant differences were found between suspect and normal, suspect and glaucoma groups. Higher discrimination between the groups was achieved with P_a /smm, $b_{1.45}$ and P_1 /CCT where significant differences were recorded for three considered groups. No significant differences were found between the normal and glaucoma group for IOPg, CH, CRF, P_a /CCT and HM.

Next, the Pearson correlation coefficient r between the proposed parameters HM, P_1 /CCT, P_a /CCT, P_a /smm, dm, $b_{1.45}$ and IOPg and CH was assessed. Parameters P_a /CCT ($r = 0.91$, $p < 0.05$) and P_1 /CCT ($r = 0.90$, $p < 0.05$) are strongly correlated with the intraocular pressure IOPg. The interesting results were obtained for the parameters P_a /smm and $b_{1.45}$, because they do not show such strong linear relationships with IOPg. They are less related to the intraocular pressure, so they could represent some other eye properties, indirectly related to IOPg. The Pearson correlation coefficient between P_a /smm and IOPg is $r = 0.69$ ($p < 0.05$), and between $b_{1.45}$ and IOPg it is $r = 0.75$

($p < 0.05$). Analysis showed that the parameters (P_1/CCT , P_a/CCT , P_a/smm , dm , $b_{1.45}$) are not correlated with CH ($p > 0.05$).

4. Discussion

Some ocular diseases have a mechanical etiology and these include some types of glaucoma, keratoconus and Fuchs corneal dystrophy. The explanation of causes of those pathologies requires the knowledge of mechanical properties of eye tissues. This knowledge include both the physiological phenomenon taking place within the eyeball and the effects of the diagnostic actions, one of which is the procedure of the intraocular pressure measurement.

The Ocular Response Analyzer is a commercially available clinical instrument that has been proposed to characterize corneal biomechanical responses using the noncontact tonometry process. The CH is considered an indicator of corneal viscosity and CRF is considered an indicator of the overall resistance of the cornea (corneal rigidity). Recently, 37 parameters were derived from the ORA software allowing a detailed analysis of the corneal deformation signal. Several research studies have investigated the clinical relevance of some of these parameters and reported they could be more useful in diagnosis in some kind of the corneal ectasia and prognosis after refractive surgery treatments [11, 18, 19, 23, 24].

Additionally, the device provides an access to raw data of both air pressure and applanation curves allowing application of different smoothing procedures to the raw data during numerical processing in order to evaluate air pressure and applanation curves in healthy eyes, glaucoma suspects and glaucoma [25]. Based on this analysis, we have proposed new parameters (HM, P_1/smm , P_a/smm , dm , $b_{1.45}$) that describe the interrelations between the two curves. The importance of these new parameters can be verified by numerical analysis of their repeatability in different measurements carried out on one eye. Our examinations showed that even though some of these parameters vary for different measurements, they are characterized by a specific type of variability for an individual eye. The obtained results show that some of the parameters indicate a very high repeatability for four measurements on one eye, with the ICC coefficient higher than 0.95 and CV of about 10%. Such ICC values are significantly higher and the values of CV are lower than those given by typical parameters from the ORA such as IOPg and CH.

Finally, this work sought to determine whether differences in unique Ocular Response Analyzer parameters (CH and CRF) as well as new parameters calculated from raw ORA data (HM, P_1/smm , P_a/smm , $b_{1.45}$) exist in glaucomatous eyes and in glaucoma suspect eyes independently from IOP value.

Since the introduction of ORA in clinical practice and glaucoma diagnostics, many research studies have been conducted looking for associations between both CH and CRF and different parameters like CCT considered as a risk factor for glaucoma, IOP,

glaucomatous changes in the optic disc or glaucomatous visual field defects [13, 14, 26–28]. AOKI *et al.* [29] reported a significant correlation between the parameters of the corneal deformation signal (ORA software) and glaucomatous visual field progression. However, according to our knowledge none of those studies propose new parameters for supporting the early glaucoma detection.

Statistical comparative analysis shows that the parameters proposed in this study better differentiate three considered groups (normal, glaucoma suspects and glaucoma group) in comparison to the values of IOPg and CH. The statistically significant importance of CH and CRF parameters in glaucoma diagnostics were reported in [30, 31]. A number of reports have suggested with evidence that CH is lower in glaucomatous eyes compared with normal eyes and eyes with ocular hyper tension [9, 14, 15, 31, 32]. It is known that CH is influenced by IOP value which means the differentiation between healthy subjects and glaucoma patients could be unclear if patients take medication to regulate IOP level. In this study glaucoma patients were taking medication, therefore the results may be less agreeable to some reported in literature [14, 30, 31]. However, SUN *et al.* [33] reported that even after pharmacologic reduction of IOP, CH was lower in glaucomatous eye than normal eyes. CRF parameter is more correlated with corneal ectasia and corneal structure degeneration connected with long term use of eye drops or systemic medication [6]. However, most papers presented the comparison of ORA parameters between healthy and glaucomatous eyes; little work has been conducted on glaucoma suspects.

The glaucoma suspects are difficult to diagnose as results are based on intraocular pressure values measured by tonometry. The unique output parameters of ORA and those proposed in this study (calculated from raw data) could make the diagnosis of glaucoma suspects easier and clearer. The results in Table 4 show significant differences for HM, P_1/smm , P_a/smm , $b_{1,45}$ parameters, the suspect group is statistically distinguishable ($p < 0.05$) from healthy eyes as well as from glaucomatous eyes.

The findings of this study indicate that the analysis of ORA parameters could be utilized in early glaucoma diagnostics and that the parameters calculated from raw ORA data seem to be promising as being more sensitive than others to detect glaucoma. It is worth emphasizing that repeatability of proposed parameters could be even higher (ICC for P_a/smm is 0.83 and for dm is 0.86) than repeatability of the original ORA parameters (ICC for CH is 0.69) (see Table 2).

The proposed HM parameter describes corneal viscoelasticity and is highly correlated with the CH, however it takes into account the value of the maximal air pressure MP during measurement. While CH is calculated from P_1 and P_2 : air pressures corresponding with two applanation states of the cornea. HM parameter does not differentiate normal and glaucoma groups, similarly as CH. However, repeatability of HM increases for the ratio of HM and CCT and then is higher than repeatability of CH. It would be interesting to examine and compare the repeatability of HM parameter with CH and their quotients with the corneal thickness on groups of patients with different eye pathologies. Probably this type of parameters carried information about the structure and material parameters of eye tissues that could be used in ophthalmology.

The relationship between ocular biomechanics and glaucoma is still unknown, but it offers a great potential for further investigations, the results of which may have a substantial impact on future glaucoma diagnosis and treatment.

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