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Corneal Viscoelastic Properties Related to Glaucoma

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1. Introduction

Although elevated IOP is clearly the most frequent causative risk factor for glaucomatous optic nerve atrophy, it is not the only factor, and attempts to define glaucoma on the basis of ocular tension are no longer recommended. Considering IOP as a risk factor in the appearance of the glaucomatous lesions at the level of the optic nerve, it's important to establish the mechanisms which may enhance or reduce this risk. These complex processes refer to the way in which the IOP is transmitted from the ocular structures to the optic nerve head. (Downs et al., 2005)

For a better understanding of our work, some physical parameters must be defined and known. We found them used in materials physics: stress, stretch, strain, deformability, elastic and viscous materials, etc. A short special subchapter is dedicated to these mechanical characteristics.

The Reichert device named Ocular Response Analyzer (O.R.A.) is a special device used to measure intra ocular pressure correlated with the viscoelastic properties of the cornea - named IOPcc. In order to monitor the influence of IOPcc on the optic nerve we also made measurements on the Retinal Nerve Fiber Layers (RNFL). For that purpose, we used a Zeiss device named Stratus OCT on the Optical Coherence Tomography.

Using clinically measured values with Ocular Response Analyzer for IOPcc and the computed value which describes the performance, the efficiency (%) of eliminating the overpressure /for cycle of loading - named by us the specific damping capacity (φ) - we made a graphical representation of these two parameters, to grade the particular effort of the ocular structure and implicitly of the retinal nervous fibers layer of the studied patient. We named this graphic the Effort Staging System (ESS) (Demea et al., 2008) and we use it to classify glaucoma risk for our patients. In order to make our work easier we developed a computerized application which practically takes the data measured by us and calculates the specific damping capacity, so the patient is automatically introduced in the ESS scale. Consequently we obtain the class of the glaucoma risk, damage effort of RNFL, where that patient is situated.

The application has a user-friendly interface and helps the ophthalmologists in the clinical diagnosis.

2. Physical definitions – The dynamic of the expansion effort of the ocular structures

For a better understanding of the viscoelastic properties of the cornea we considered important to mention some elements from the material physics that help to characterize the properties of the ocular structures from the mechanical point of view.

2.1 Materials resistance to deformation

The Materials resistance to deformation is studied in accordance with two parameters: stress (σ) and strain (ξ).

The stress (σ) is defined as a measure of internal forces that arise in a body being deformed as a result of external forces and the stress intensity is given by the force which operates on the surface unity $dF/dS = dP$.

The strain can be characterized by more parameters. Thus, the stretch (dS) represents the expansion difference the material can reach, after the stress was applied. If the stretch ratio dS/S increases, the surface becomes elastic and can be deformed. If dS/S decreases, the surface becomes rigid and its deformability decreases as well.

At the same time, we can talk about the deformation effort dP/dS which can increase either due to the stress growth (dP), or due to the surface rigidity (dS decreases).

2.2 The viscoelasticity of the soft tissues

From the perspective of the stress factor, if we take into account the time factor (t) and its application frequency (f), the materials have an elastic or viscose behavior.

In the case of an elastic behavior the deformation is independent of the stress factors “ t ” and “ f ”. For example, an elastic arch submitted to the compression is deformed in a linear way, according to the applied force size, and this deformation doesn’t depend on the application time or on the behavior. The releasing of the tension takes place linearly as well, while the stress intensity decreases. Elastic materials strain instantaneously when stretched, and just as quickly return to their original state once the stress is removed.

In the case of a viscose behavior, the strain depends on the application time and/or on the application frequency. In this way, the applied stress resistance is mainly dynamically dependent on the force application speed, high speed means great resistance. Viscous materials resist shear flow and strain linearly with time when a stress is applied.

Viscoelasticity is the materials’ property to exhibit both viscous and elastic characteristics when undergoing deformation. Cornea and all the soft tissues are viscoelastic and their response to the stress is a combination between an instantaneous response (elastic) and a response dependent on time (viscous – reaction time latency). Viscous-elastic materials have elements of both of these properties and exhibit time dependent strain (Jonas & Budde, 2000).

3. Ocular Response Analyzer (ORA) and the calculation of specific damping capacity

From the actual instruments for intraocular pressure measurement we chose the non-contact tonometer called Ocular Response Analyzer (Figure 1). This device determines 2 types of parameters:

- the ones related to the “stress” generated by the increase of the intraocular pressure named: IOP cc - intraocular pressure corrected and IOPg - intraocular pressure according to Goldman norms.
- the ones related to the “material behavior”, such as cornea, submitted to this stress, named: CH - Corneal Hysteresis and CRF - Corneal Resistance Factor

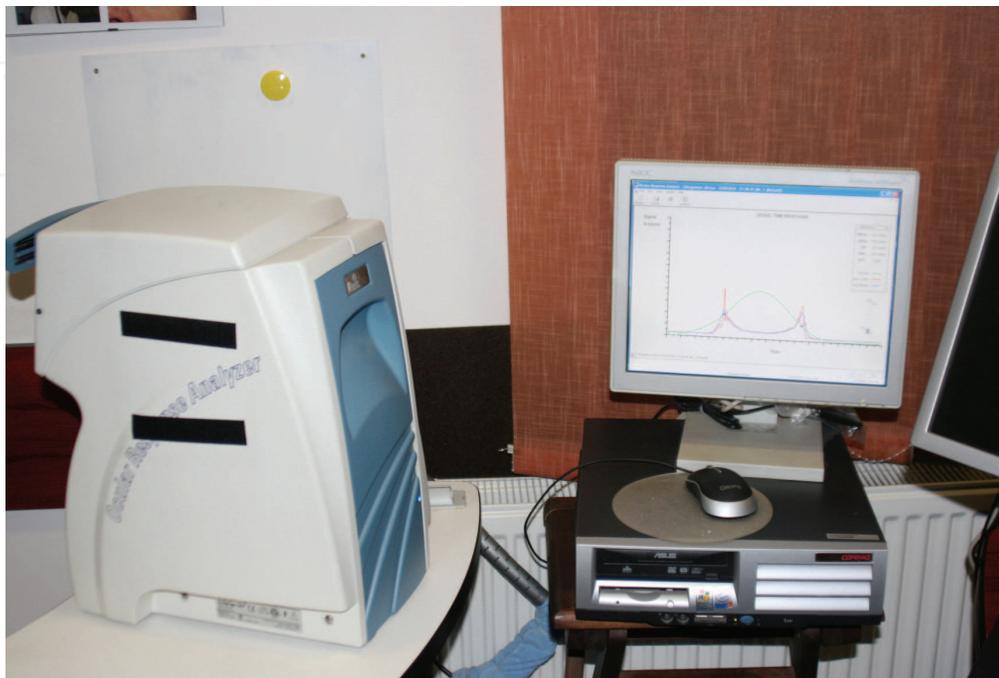


Fig. 1. Ocular Response Analyzer

The producer of ORA specified that:

1. IOPg- is the real IOP measured by the instrument, dependent on the cornea biomechanics.
2. IOPcc - this is the intraocular pressure measurement that is less affected by corneal properties than other methods of tonometry, such as Goldman. The instrument automatic adjusts the IOPg to IOPcc. The recommendation of Reichert Company is for use in clinical evaluation of intraocular pressure the value of IOPcc instead of IOPg.
3. CH - is the pressure lost during an upload cycle. This parameter is a measure of corneal tissue properties, a result of viscous damping in the corneal tissue.

The normal values for IOPcc and CH are shown in Table 1, as in (Allingham & al., 2005; Kevin & al., 2004; Luce & Taylor, 2006).

IOPcc (mmHg)	Normal		< 20
	Pathologic	Suspect	20 - 30
		Sure	> 30
CH (mmHg)	Normal		> 10
	Pathologic	Suspect	8 - 10
		Sure	< 8

Table 1. Normal values for IOPcc and CH

For example, the situation in which IOPcc < 20 mmHg and CH > 10 mmHg is a normal one, where cornea and the other ocular structures have functional reserves, which are able to absorb the loaded IOP and to reduce the tensional stress impact on the posterior pole (optic nerve). The situations where IOPcc reaches at values > 20 mmHg and CH ≤ 10 mmHg represent the “balance break point”, that is, the moment where cornea loses the compensation capacity of the tensions and the “loaded stress” is transmitted to the ocular posterior pole.

To detect this situation of balance break point, we calculate the efficiency of eliminating the overpressure / cycle of loading and we named this: Damping capacity (φ). The damping capacity can specifically be calculated as the ratio between the lost energy and the stocked energy during a loading cycle.

$$\varphi = \frac{CH}{2IOPg} \quad (1)$$

Normal values for specific damping capacity (φ) are over 30 %.

O.R.A. may offer deductive, indirect data on the ocular structures strain (σ) characteristics. Thus, for instance, a low specific damping capacity (φ) is characteristic for the “rigid” viscoelastic systems, and this situation frequently occurs in glaucoma because of the non-enzymatic glycation of the glucose with the collagen fibers, which leads to sclera stiffness.

4. Cornea – The specific damping capacity in glaucoma etiopathogeny

It has been long suspected that corneal biomechanical properties influence the results and outcomes of various ocular measurements and procedures, and may hold clues to diagnosing and managing ocular diseases. Human corneal tissue is a complex viscoelastic structure (Ethier et al., 2004). Almost all known glaucoma evaluating systems consider an elastic ocular model, where IOP measured at the anterior eye segment is totally transmitted to the posterior eye pole. We consider the viscous-elastic ocular model (Sigal et al., 2004), where only a part of this IOP is considered to be transmitted toward posterior pole, because of the specific damping capacity or partial absorption of the pressure in the ocular walls and other ocular structures. A high damping capacity (more viscoelastic ocular structures) reduces the risk of the glaucoma, by decreasing the transmitted pressure toward optic nerve in the posterior pole. In reverse order, a reduced damping capacity (a more rigid eye, for example - an aged person) increases the risk of the optic nerve damage even at the medium IOP.

We studied the correlation between the most important factors in diagnosis and evaluating a glaucoma suspect patient: IOPcc - as a loading factor (stress) and CH - as unloading factor (protective). We noticed that it is most important to appreciate the efficiency of pressure elimination depending on each cycle of charging, reason for which we calculated the specific damping capacity (φ).

5. Evaluation method of the pressure risk in glaucoma

In order to quantify the mechanical risk of lesion in glaucoma we emphasized (Demea et al., 2008) the need to determine two important parameters from a pathophysiological point of view: the IOPcc - Compensated Intraocular Pressure and the CH - Corneal Hysteresis. We used O.R.A to measure these values, the most important factors in diagnosing and

evaluating a patient suspected of glaucoma. The optical coherence tomography was also used to measure retinal nerve fiber layers around the head of the optic nerve. The risk of lesion for the retinal nerve fibers – implicitly the risk of glaucoma – is determined in any unbalance of these two factors.

Because the pressure loading (IOPcc) and unloading (CH) of the ocular system is fluctuant, we defined the efficiency [%] of eliminating the overpressure/cycle of loading as being the specific damping capacity (ϕ). This parameter is defined as the energy loss per cycle (D) divided by the stored peak energy (U), which, for a spring mass system, is the energy stored in the spring at maximum deflection (Stone, 2007). The energy loss per cycle is in our case a hysteretic damping factor (D) introduced and defined by the O.R.A. engineers as CH (Figure 2). In the same O.R.A. system, the peak energy stored (U) is $2 \times \text{IOPg}$. The specific damping capacity is then $\phi = D/U$

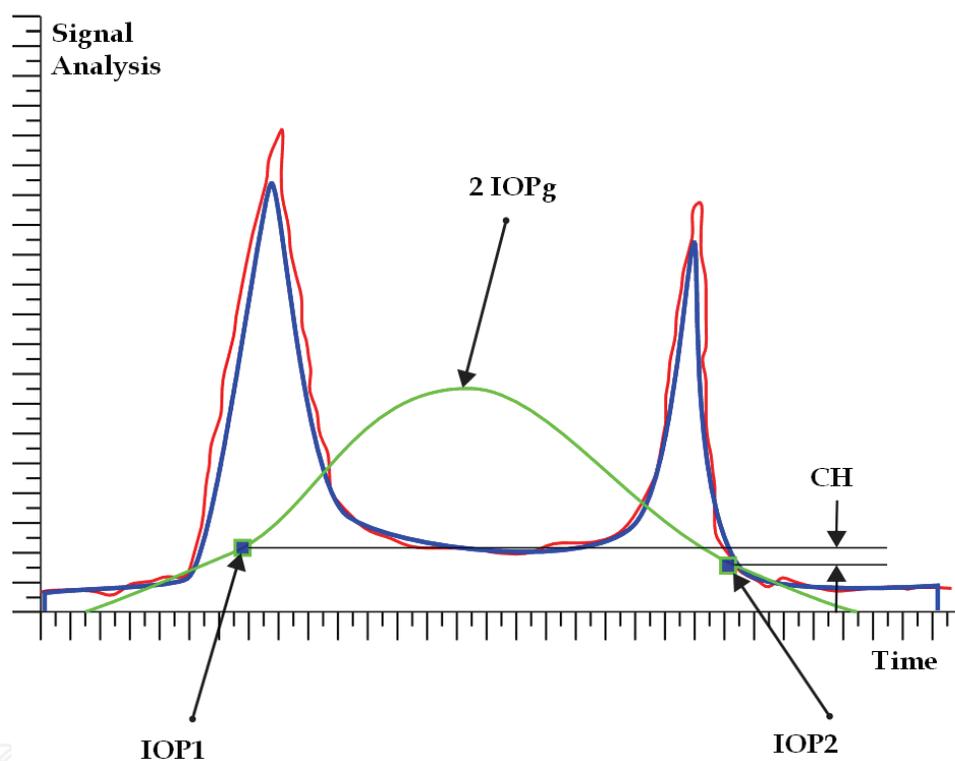


Fig. 2. Ocular Response Analyzer (O.R.A.) system signal response (CH – Corneal Hysteresis, $\text{CH} = \text{IOP1} - \text{IOP2}$, IOP1 and IOP2 are two determinations of intraocular pressure at two different moments of time : at the cornea inflection and at the corneal deflection, $2 \times \text{IOPg}$ – is the peak of loading process delivered by O.R.A. , which is calculated at the double of IOPg)

A common basis for measuring damping involves energy loss and the determination of the energy lost per cycle. The normal and pathologic values for the specific damping capacity (ϕ) are specified in Table 2.

The condition of pressure protection and so the lack of risk of glaucoma is fulfilled when at any high value of the intraocular pressure (IOPcc) the system responds by a corresponding elimination of the overpressure (CH) and the efficiency of elimination (ϕ) is at least 30 %. The CH measurement is an indication of viscous damping in the cornea, or in other words, it represents the ability of the tissue to absorb and dissipate energy.

Specific damping capacity	Clinical Evaluation
> 30 %	Normal
18 - 30 %	Suspect
< 18 %	Pathologic

Table 2. Specific damping capacity- values and clinical categories

Damping is the conversion of mechanical energy of a structure into thermal energy. Damping is most beneficial when used to reduce the amplitude of dynamic instabilities, or the resonance in a structure.

A viscous-elastic material is characterized by possessing both viscous and elastic behavior. A purely elastic material is one in which all the energy stored in the sample during loading is returned when the load is removed.

A complete opposite of an elastic material is a purely viscous material, which does not return any of the energy stored during loading. All the energy is lost as “pure damping”, once the load is removed.

We call viscous-elastic material, and the eye is one of them, anything that does not fall into one of the above extreme classifications. Some of energy stored in a viscous-elastic system is recovered upon removal of the load, and the remainder is dissipated in the form of heat.

Structural engineering analysis tools have been used to improve the understanding of the biomechanical behavior of the cornea. These data were used to facilitate the construction of accurate finite-elements models, being adapted to study the response of the cornea to tonometry procedures used to measure the intra-ocular pressure as in (Kevin et al., 2004).

Normal and pathological values for corneal hysteresis (CH) are given in Table 1, and are calculated using formula (1). We used values that are considered statistically normal for CH and IOPcc in previous studies (Luce & Taylor, 2006).

6. The Effort Staging System (ESS)

Using clinically measured values with O.R.A. for IOPcc and the computed value for the specific damping capacity (φ), we made a graphical representation to grade the particular effort of the ocular structure and implicitly of the layer of nervous fibers (RNFL) in the studied patient (Figure 3). We named this graphic the Effort Staging System (ESS) and we use it to categorize glaucoma risk in our patients.

The ESS is the improved alternative of a previous study (Demea et al., 2008) and brings an original correlation between φ and IOPcc, resulted from Reichert Ocular Response Analyzer measurements.

We define stress as a physical factor (pressure in our case) which functions upon the studied material (the eye structures in our case. Mechanical stress is directly proportional to the IOPcc, and is inversely proportional to Specific Damping Capacity (φ).

6.1 ESS clinical approach

Using normal and pathological values indicated in (Kothecha et al., 2006), for the specific damping capacity (φ) and IOPcc we made a graphical representation to grade the particular effort of the ocular structures and implicitly of the layer of RNFL in the studied patient

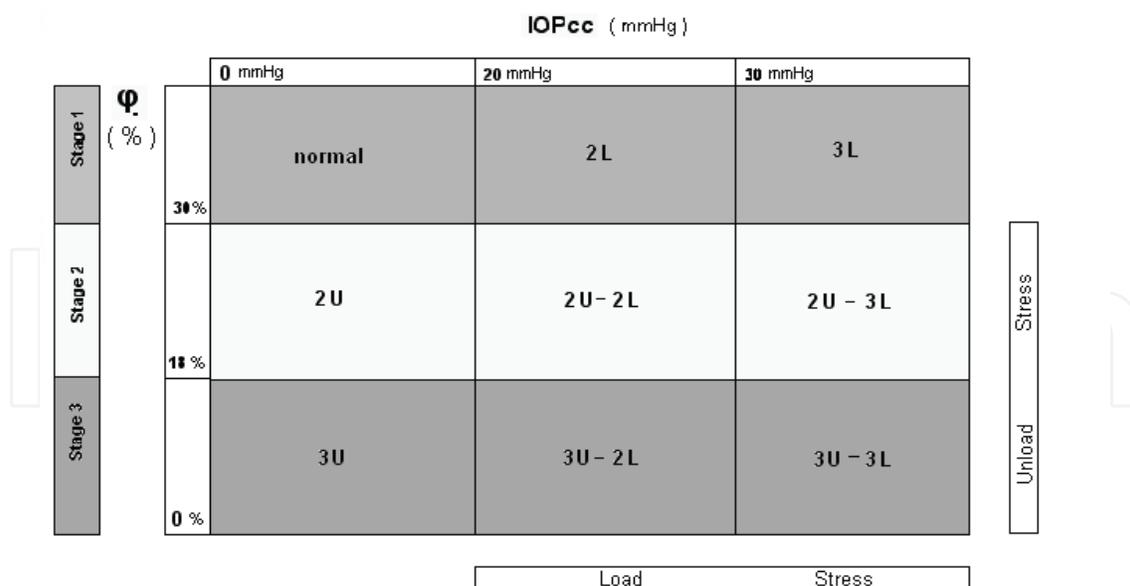


Fig. 3. The Effort Staging System (ESS) (L - Load Stress, U - Unload Stress, IOPcc-Compensated IOP, ϕ - specific damping capacity)

(Allingham et al., 2005; Brusini & Filacorda, 2006) as in Figure 3. We named this graphic the Effort Staging System (ESS) and it may be used in the automated calculation of the eliminating ocular pressure efficiency. We defined three types of stress (Table 3) and named them: L - Load stress (when IOPcc is high); U - Unload stress (when CH is low) and M - mixed stress (with IOPcc high and CH low). The defined types of the stress offer information about the pathophysiological mechanisms in glaucomatous nervous damage (Burgoyne et al. 2005): high intraocular pressure or low resistance in the optic nerve head.

Type of stress		IOPcc	CH	ϕ
Load stress	L	High	Normal	Normal or Low
Unload stress	U	Normal	Low	Low
Mixed stress	U-L	High	Low	Low

Table 3. Type of stress correlated with IOPcc and ϕ

The effect of this mechanical stress upon the eye walls may be better understood if we introduce another physical parameter: the strain. During testing of a material sample, there is relationship between stress, derived from measuring the load applied on the sample, and strain, derived from measuring the deformation of the sample, i.e. elongation, compression, or distortion (McCrum et al., 2003; Mayers & Chawla, 1999; Roylance, 2001). In our case the material sample is the eye, IOPcc is the mechanical stress and the specific damping capacity ϕ is the equivalent of the strain.

To better understand the connection between IOPcc and damping capacity, the principle is this: "even if the structure is subjected to a high-loaded stress, measured by IOPcc, it will last as long as it has good damping capacity, over 30%, and will not appear optic nerve damage. Corneal effort is defined by the stress and the strain, under different IOPcc.

We consider, clinically important, the following three different stages of ESS for the risk of lesion of Retinal Nerve Fiber Layer (RNFL) in glaucoma:

Stage 1: Normal – the system has an adequate efficiency, $\varphi > 30\%$ in pressure elimination. CH is high enough to efficiently compensate any increase of IOPcc, both in medium (2L) and high quotas. There can be three alternatives: normal, 2L and 3L. For normal- both parameters CH and IOPcc are in normal quotas; for 2L- the system has normal efficiency but increased pressure demands (IOPcc increases at medium quotas) and for 3L- the system has normal efficiency and much increased pressure demands (IOPcc increases at high quotas)

Stage 2: Borderline – The system has a medium efficiency, φ is between 18 - 29% and the patient must be surveyed, different alternatives of pressure effort being possible: 2U – stress of unloading of medium severity (determined by the medium decrease of CH); 2U-2L – mixed stress of medium severity (determined by the medium increase of IOPcc and medium decrease of CH) and 2U – 3L – mixed stress of medium severity.

Stage 3: Pathological – the efficiency of the system is decreased, $\varphi < 18\%$, due to the decreased capacity of damping, the system can not efficiently compensate the increases in pressure efforts not even in normal charging quotas. There can also be three alternatives: 3U–stress of unloading of high severity (determined by the great decrease of CH); 3U-2L – mixed stress of high severity (determined by the great decrease of CH and medium increase of IOPcc); 3U-3L– mixed stress of high severity with high pressure charges (determined by the great decrease of CH and great increase of IOPcc).

6.2 Effort Staging System computerized analysis application

To facilitate our work we developed a computerized application which automatically takes our measured data, calculates the specific damping capacity, and introduces it in the ESS scale. Therefore, we obtain the class of the glaucoma risk (damage effort of Retinal Nerve Fiber Layer) where the patient is situated. The application based on the Effort Staging System provides a better view of the clinical diagnosis and offers the physician a user-friendly interface for the patients' management and investigation, and also for the results' displaying and printing.

The application was implemented by using Visual Studio IDE (Integrated Development Environment) and a QT cross-platform application framework for developing the C++ code and the graphical user interface (GUI). The reasons for choosing these technologies are: C++ native implementation, which takes the best - when it comes to performance - from the available computing power and minimizes dependencies on other runtime application or components; QT technology, which provides a cross-platform powerful framework that gives access to multiple operating systems as target for future development. The application has some important features that make it an easier and quick way to diagnose. This way, there is the possibility to import and analyze CSV O.R.A. files and the patients' lists in order to be displayed.

An important feature of QT in development of this application is its international support, which means that the application can be translated in other languages, when required. Consequently, in the code, each displayed text was wrapped with the QT translation directives. For drawing the main ESS diagnose diagram, QT technologies are used in order to create scenes with graphic objects. In this way, a dynamical scene is obtained, which is easy to be modified and adapted to the other requirements. All the scene components are present as objects derived from CGraphicsObject with scale support according to the user's needs or to the custom printing mode. This approach allows the user to change the ESS values in the diagram without being necessary to step in the drawing code.

The application has a familiar native interface which is easier to be used by the operator (familiar controls, menus and user interface aspect). The application main window (Figure 4) is divided in four areas with different specific functions: toolbar, patients' lists, filter areas and results area. The patients' lists are displayed in two different ways: the principal tree list (above) which appears all the time and the list (below) which appears only when the user activates the filters. The tree list displays hierarchically all the available patients, with the possibility to expand this list for both right and left eyes. The files that contain the eyes information can be expanded as well, in order to have access to the patient measurement data.

The filters area is situated above the EES diagram and it contains two fields: patient condition and age intervals. The patient conditions can be selected by checking the "suspect" or/and "normal" and the age interval can be selected by using the available combined box-type control. In this way, under the main patients' list, the final list will include all the filtered patients that match the selected criteria. By clicking a certain result in this list, the name of the corresponding patient and his ESS diagram will be displayed:

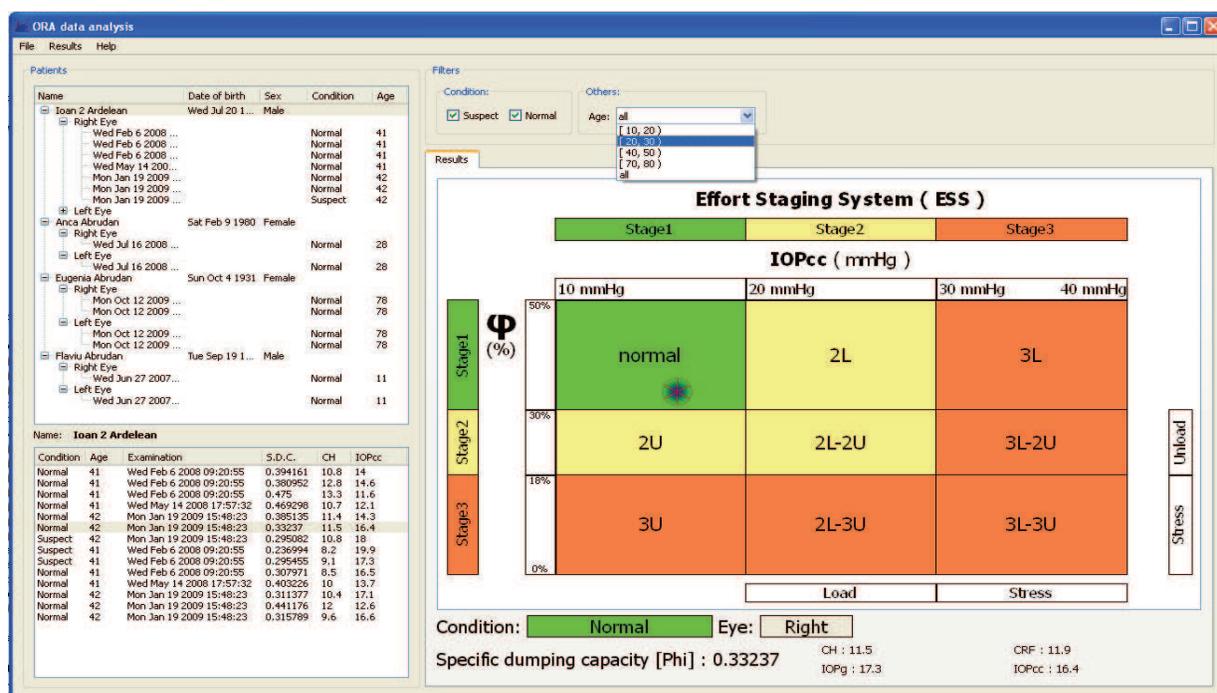


Fig. 4. The ESS application main window

The result area is represented mainly by the diagnose diagram (ESS) but it also contains the significant outcome values. For highlighting the risk region where the patient is situated, the application uses a cursor and pulsing animation. The diagram content changes dynamically and all the elements are recalculated, thus the user is the one who controls the displaying mode. The results and the patient's file can be previewed before printing and then they can be sent (including the ESS diagram) to a printer. The results can also be exported in a PDF file format.

The application's design is opened and improvements and changes can be made in the future. The filter zone is dynamically populated only with values found in the patients list. The supported file has a comma separated value format (CSV) as it is exported by the Ocular Response Analyzer application.

7. Clinical experimental

Once the ESS system was established as a quantifier of the pressure efficiency of the eye, we worked at the clinical validation of the method. Some experimental preliminary results are available (from Table 4 to Table 11) in a group of 150 eyes of the tested patients.

Our study sought to show the importance of protective factors to dissipate pressure. Therefore, efficiency calculation is very important to eliminate the pressure loaded at each loading cycle. We mention that in this clinical trial we studied the value of φ as a screening test in the cases in which we knew from preliminary studies that either they are healthy (with no lesions RNFLavg) or they have glaucoma (with damage to the RNFLavg).

All other pathological situations of optic nerve damage were excluded. The statistics presented here are focused on the relationships (Person index), clinical investigation and screening (sensitivity, specificity, PPV, NPV, PLR) analyses.

7.1 Preliminary results

To test out the glaucomatous damage in a person with certain IOPcc and φ , we focused on structural eye parameters like average Retinal Nerve Fiber Layers (RNFLavg) measured with Optical Coherence Tomography (OCT) (Figure 5).



Fig. 5. Zeiss Status OCT

In order to validate the study we calculated a series of statistic parameters regarding the correlation between IOPcc and φ and avgRNFL values. So the positive values of avgRNFL represent the real positive values, and the negative values of avgRNFL represent the real negative values in this study. In defining the parameters we used the following abbreviations: RP = the number of the real positive cases; RN = the number of the real negative cases, FN = the number of the false negative cases; FP = the number of the false positive cases. The

sensitivity and specificity reflect the performance level of a test (in this case IOPcc and φ). The *sensitivity* of a test measures the degree to which a correct positive case is identified as being positive. On the other hand, the *specificity* represents the degree to which a correct negative case is identified as being negative. The ideal values of these parameters are of 100% or 1. The two parameters are calculated according to the relations (2) and (3).

$$\text{Sensitivity} = \frac{RP}{RN + FN} \quad (2)$$

$$\text{Specificity} = \frac{RN}{RN + FN} \quad (3)$$

The positive predictive value (PPV) represents the proportion of the correct cases identified as being positive from the total number of cases identified as being positive. In other words, PPV reflects the probability of a patient, diagnosed with a disease, to suffer of the respective disease. The negative predictive value (NPV) represents the proportion of the correct cases identified as being negative from the total number of cases identified as being negative. The two parameters are calculated according to the relations (4) and (5).

$$\text{PPV} = \frac{RP}{RP + FP} \quad (4)$$

$$\text{NPV} = \frac{RN}{RN + FN} \quad (5)$$

The Prequential Likelihood Ratio represents the probability of a positive test to indicate the presence of the disease. This is calculated according to the relation (6):

$$\text{PLR} = \frac{\text{sensitivity}}{1 - \text{specificity}} \quad (6)$$

The activity of medical research was structured as follows:

- a. Initially the lot of 150 eyes was divided in normal and pathologic (Table 5) taking as indicator the average thickness of RNFL. As mentioned before, in these two groups we knew from previous studies, which are the healthy eyes (with RNFLavg normal) and which are the eyes with glaucoma (with damage of the RNFLavg). Using the criterion RNFLavg one case has been declared normal, without lesions, if RNFLavg thickness is higher than 94 μm , and pathologic if RNFLavg thickness is lower than 94 μm . The group of 150 eyes was divided in 69 % normal eyes and 31% pathologic eyes with RNFLavg in lesion quotas.

Eye analyzed (150 eyes)		RNFLavg	Glaucoma classification
Number	%		
103	69%	> 94 μm	Normal
47	31%	< 94 μm	Pathologic

Table 4. Classification of the eyes depending of RNFLavg

- b. The group of 150 normal and pathologic eyes was also divided from the pressure stress point of view. According to the criterion IOPcc (Table 5) a case is declared normal (without risk of load pressure effort) if IOPcc is lower than 20 mmHg and pathologic (with risk) if IOPcc is higher than 20 mmHg. The studied group had a percentage distribution of 73 % eyes with IOPcc in normal quotas and 37 % eyes with IOPcc in pathologic quotas.

IOPcc (mmHg)	Normal		< 20 mmHg	109	73%
	Pathologic	Suspect	20 - 30 mmHg	32	21%
		Sure	> 30 mmHg	9	6%

Table 5. Classification of the eyes depending of IOPcc

According to the φ (Table 6) criterion, a case is declared normal (without risk of RNFL effort) if φ is higher than 30 % and pathological (with risk) if φ is lower than 30 %. The studied group had a percentage distribution of 75 % cases with φ normal and 25 % cases with pathologic φ .

φ (%)	Normal		> 30 %	112	75%
	Pathologic	Suspect	18 - 30 %	17	11%
		Sure	< 18 %	21	14%

Table 6. Classification of the eyes depending of φ

- c. The next step was to study the predictive value of φ and IOPcc in assessing the risk of illness (quantified with the change of RNFLavg) through the correlation parameters: PPV, NPV, and PLR (Table 7).

Statistical index	test	value
PPV	φ	0.82
	IOPcc	0.79
NPV	φ	0.92
	IOPcc	0.91
PLR	φ	0.92
	IOPcc	0.91

Table 7. Positive Predictive Value (PPV), Negative Predictive Value (NPV), Positive Likelihood Ratio (PLR)

Collected data were analyzed and we observed that all these indicators are statistically significant, with strong correlations for tests φ and IOPcc: PPV being ≤ 0.8 , NPV and PLR > 0.9 .

- d. The sensitivity and specificity odds of φ and IOPcc were also assessed; the results of the tests applied to the lot of 150 eyes are presented in detail in Table 8.

Statistical index	test	value
Sensitivity	φ	0.78
	IOPcc	0.74
Specificity	φ	0.94
	IOPcc	0.93

Table 8. Sensitivity and specificity odds

It can be noticed that the sensitivity (positive in disease) of the two tests is > 0.7 and the specificity ("negative in disease") is also very good, being > 0.9 .

- e. The capacity of correlation between the two performed tests (φ and IOPcc) and the value RNFL avg. (as indicator of disease) with Pearson correlation index (r) (Table 9) has also been determined.

Statistical index	test	value
Pearson index (r)	φ	0.56
	IOPcc	- 0.45

Table 9. Pearson correlation index (r)

The values in Table 9 show a reasonable negative correlation of -0.45 between RNFLavg and IOPcc, meaning that higher IOPcc is associated to lower RNFLavg. There is also a reasonable positive correlation of 0.56 between RNFLavg and φ , meaning that a lower φ is associated to lower RNFLavg.

The calculation of this indicator: the specific damping capacity is important for a more realistic estimate of the risk-loaded. For example, there have been situations in which patients with pathologic IOPcc > 30 mmHg but with normal $\varphi > 30\%$ do not have any RNFLavg lesion, and situations where IOPcc is normal < 20 mmHg but with pathologic $\varphi < 18\%$ which have low RNFLavg.

- f. In the final stage of our study the ESS computerized analysis application was used and a quick quantification of the studied eyes was obtained (Table 10).

ESS stage I	normal type: 100 eyes (66.67 %)
	2L type: 11 eyes (7.33 %)
	3L type: 1 eye (0.66 %)
ESS stage II	2U type: 8 eyes (5.33 %)
	2U-2L type: 6 eyes (4 %)
	2U-3L type: 3 eyes (2 %)
ESS stage III	3U type: 1 eye (0.66 %)
	3U-2L type: 15 eyes (10 %)
	3U-3L type: 5 eyes (3.33%)

Table 10. The ESS computerized analysis results

7.2 Discussions

This study is the first clinical investigation that calls into question the system's efficiency to eliminate ocular pressure. The purpose of calculating the yield is a better estimate of the risk-loaded to prevent glaucomatous damage.

The statistic analysis on the presented lot showed a good correlation between specific damping capacity (ϕ) and the occurrence of lesions in the layer of retinal nervous fibers (indicator: RNFLavg). Considering the elements above, it is possible to make a complex clinical evaluation of the patients. After they were measured with the Reichert Ocular Response Analyzer, we found IOPcc and calculated specific damping capacity (ϕ). Introducing these data in the mentioned graphic, we established a certain stage and type of the stress for their eyes. We verified other clinical, structural or functional parameters to appreciate the presence or absence of glaucoma.

We propose ESS computerized analysis to be used in clinical daily practice to appreciate the ϕ as a very good indicator of the RNFL effort for an eye in a glaucoma suspect patient. There are many parameters to look for, when we try to distinguish between a normal and a glaucomatous patient. The variability between individuals and within an individual over a lifetime makes it difficult to appreciate the situation of a patient at one moment. The biomechanical properties of the eye structures are very important in assessing a glaucoma suspect, and there are many studies focused on these properties (Burgoyne et al., 2005). Measurements of the corneal biomechanical properties with the Ocular Response Analyzer give us an additional parameter for a better assessment of the glaucoma risk in a patient with a high IOP.

By now, nearly everyone recognizes that the current gold standard for measuring IOP, the Goldmann tonometer, has considerable flaws. The measured IOP is affected by corneal properties including rigidity, thickness, structure, hydration curvature and perhaps other factors not yet identified. The Ocular Response Analyzer is capable to provide pressure measurements that are less affected by corneal properties and give us additional information. O.R.A. is more accurate, faster and easier to use in clinical practice. The parameters determined by this device: IOPcc, CH, CRF, IOPg and the proposed specific damping capacity (ϕ) allow us a better appreciation of the risk-loaded. The main disadvantage of this device is the high price compared to applanation tonometer, and not his lack of reliability.

Taking into account the above-mentioned aspects, we make a step forward to introduce these data into our daily medical practice.

Recent studies (Sigal et al., 2005) show that IOP induces a certain amount of stress and strain on the optic nerve head and leads to apoptosis of the ganglion cells; this process depends on biomechanical properties of sclera and lamina cribrosa. Our stress grading system takes these findings into consideration and tries to contribute to a better assessment of the patient's glaucoma risk.

ESS computerized system represents an original contribution, complementary in glaucoma diagnosis; compared to previously reported methods, this grading ocular stress resulted from IOPcc and specific damping capacity values.

8. Conclusions

Our clinical algorithm for a glaucoma suspect patient includes the next steps:

1. The gathering of personal and clinical data

2. The IOP measurement with ORA
3. The automatic data acquisition in the proposed application
4. The classification of patients according to the ESS system (risk group / stage)
5. The decision regarding further surveillance / investigation / treatment

Further studies on corneal biomechanics and its clinical importance are indicated. We actually consider three research directions:

- a. Validation of the method in a statistically representative number of patients. After O.R.A. measurements, patients are categorized using ESS grading system: normal, borderline and pathological indices. Each of them will follow a standardized protocol of investigation: optic nerve head photography, visual field and OCT - retinal nerve fiber layers, optic nerve head scan; this structural and functional analysis will show or not glaucomatous typical damages. The results and their statistical analyses will be in further papers.
- b. Other factors responsible for a reduced damping capacity will be in study (Oncel et al., 2009). Besides referring to the increase/decrease of the rigidity in the ocular structures, which modify CH and φ , there are other specific illnesses responsible for this, as: keratoconus, endothelial corneal dystrophy Fuchs (Spoerl et al., 2005). Therefore, reduced CH or φ may be considered structural normal variation or possible signs of corneal pathology and other investigations are useful to be considered, such as: Specular Endothelial Corneal Microscopy (SEM), corneal topography or pachimetry, Zernike analysis.

Generally, increases of the corneal thickness will determine the increase of the damping capacity (CH), but this study does not take into consideration the establishment of correlations between φ and the amount of corneal thickness (CCT).

- c. ESS system offers a dynamic model for treatment efficiency follow-up, because both IOPcc and φ are important to be normalized, to reach at a minimum stage in ESS. For example, patients with low φ : 18- 30 % , IOPcc over 20-25 mmHg, ESS stage over 2 have a greater risk for glaucomatous damages. On the other hand, patients with the same IOPcc, but greater φ over 30 % , ESS stage 1, have no risk for glaucomatous damage. The last described situation is necessary to be considered for an appropriate anti-glaucomatous treatment.

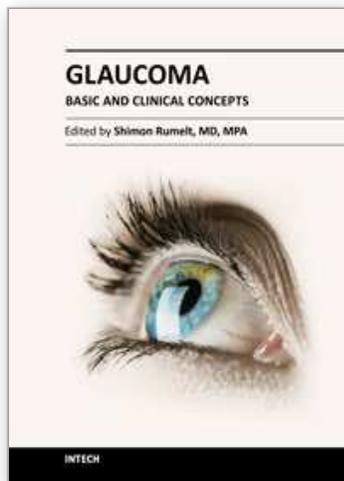
The proposed ESS computerized analysis method enhances the possibility to categorize automatically the examined patients as normal, borderline, or a pathologic. The two studied parameters: IOPcc and specific damping capacity φ are useful in daily clinical practice and reliable indicators of this disease.

Using the Effort Staging System (ESS) we have an objective and quantifiable instrument to categorize our patients' glaucoma suspects. We have the possibility to have an objective assessment of stress related to their eyes; for example - a high IOPcc associated with a high specific damping capacity is not as stressful for the eye as a medium IOP associated with a low specific damping capacity. The defined type of stress offers valuable information about the pathophysiological mechanisms in glaucomatous nervous damage (Kothecha et al., 2006)

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This book addresses the basic and clinical science of glaucomas, a group of diseases that affect the optic nerve and visual fields and is usually accompanied by increased intraocular pressure. The book incorporates the latest development as well as future perspectives in glaucoma, since it has expedited publication. It is aimed for specialists in glaucoma, researchers, general ophthalmologists and trainees to increase knowledge and encourage further progress in understanding and managing these complicated diseases.

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