WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.074
Volume 7, Issue 13, 308-326. Review Article ISSN 2277– 7105

CORNEAL HYSTERESIS: LOOKING BEYOND GLAUCOMA: A SYSTEMATIC REVIEW

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Article Received on
05 May 2018,

Revised on 25 May 2018,
Accepted on 15 June 2018

DOI: 10.20959/wjpr201813-12748

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ABSTRACT

Corneal Hysteresis is emerging as an important tool in management of many ocular conditions like corneal ectasia, refractive surgery screening but the data available till now is lacking to provide a conclusive guideline regarding the normative database. This review suggests that corneal hysteresis can be utilized as a marker of many ocular pathologies and its diagnostic and prognostic capacity needs to be explored further. The application of corneal hysteresis in glaucoma is just the tip of iceberg of its clinical utilities. The most significant application of corneal hysteresis in recent years is in the field of refractive surgery and corneal ectasia. In the latest software version of Ocular Response Analyzer (ORA) multiple specific parameters for keratoconus have been included – The keratoconus match probability (KMP) index - (KMP-KC normal, suspect, mild, moderate and severe) and keratoconus match index. The recent literatures have proven its efficacy in management of not only glaucoma but other pathologies also, but the normative values and dedicated markers are needed to be invented for different clinical conditions.

INTRODUCTION

Corneal hysteresis represents the biomechanical property of cornea or its ability to resist against the external force and depends on relative balance of its different constituents. The device most commonly used for its measurement is Ocular Response Analyzer(ORA).

The concept of corneal resistance factor and corneal hysteresis has been used widely and accepted in glaucoma management but the recent understanding in the patho-physiology of

different corneal pathologies, a new spectrum of its utility has opened up. Corneal ectasias, their treatment in form of contact lenses, collagen cross linking or surgery, corneal dystrophies, refractive surgeries and their different modifications; they all have their implications on the corneal biomechanics or corneal hysteresis.

To conduct a systematic review to understand how corneal hysteresis changes in various ocular pathologies and to understand its utility in management of conditions other than glaucoma. Evidence review – A database search was done for literature available on corneal hysteresis in last 10 years, till early months of 2018.

Articles available on Pubmed, Cochrane library, Wiley online library and other sources were considered in this review. Findings – The corneal hysteresis value changes with age, sex, gender, race and other systemic and ocular diseases. The value of corneal hysteresis reported is lesser in myopia than in emmetropia and hypermetropia but the direct relationship between the amount of myopic changes and decrease in value of corneal hysteresis has not been proven yet.

So, it is important to know how the corneal hysteresis changes in various ocular pathologies, according to literature available to us. The structure and properties of cornea depends upon physical and biochemical nature of the constituents present and their amounts relatively. The tissue mechanical properties depend on how the cells, fibers, and ground substance are organized into a structure.[1] Corneal hysteresis (CH) represents the biomechanics or dynamic properties of cornea. 'Hysteresis' in Greek language means 'lagging behind', i.e. when we apply a force to a structure how much it resists while getting deformed and reformed. CH is reflection of ability of cornea to absorb and dissipate energy during a two directional applanation process (where energy is lost as heat during the rapid loading/unloading of the cornea).[2] Human cornea has got viscoelastic property due to two major constituents of its stroma – collagen and ground substance.

Collagen fibers are responsible mainly for the strength and elasticity i.e. the ability to come back to original shape after removing external force, whereas the ground substance, composed of proteoglycans (PGs) and glycosaminoglycans (GAGs), offers viscosity i.e. the ability to maintain the deformed shape.[3] Thus any change in collagen component changes corneal resistance factor (CRF) and change in ground substance affects CH.

The elastic property of a substance is defined by Young's module i.e. the ratio of the stress (load per unit area) and the strain (deformation/displacement per unit length). Materials show viscous behavior when the deformation velocity is more rapid than the rate of relaxation.

Any ocular pathology or surgery which affects cornea has an impact on its biomechanics or the CH. A study which was based on ex vivo experiments to know the stress-strain-time corneal properties have shown that cornea has non-linear mechanical properties over an extended range.[4] Corneal hysteresis is measured clinically with Ocular Response Analyzer (ORA)(Reichert Inc., Depew, New York)(Figure 1 ORA). ORA has been used widely and it measures the response of cornea to air puff to deflect the cornea. An infrared beam tracker tracks the changes in the shape in response to the puff of air applanation.

Two measurements P1 and P2 are taken within 20milliseconds during the both outward and inward deviation of cornea in response to air pressure and the resultant infrared waveform is analyzed. The difference (P1-P2) of these two measurements and average ((P1+P2)/2) are recorded as Goldman-correlated IOP (IOPg) and CH, respectively (Fig 2 waveform). In addition, ORA also providesCRF and corneal-compensated IOP (IOPcc).CRF denotes the overall corneal resistance and is correlated significantly with IOP and central corneal thickness by Goldmann applanation tonometer (GAT).

It is derived by formula (P1 – kP2), in which k is a constant. This constant, k, was developed by empirical evaluation of relationship between P2,P1 and CCT, such that the k value is associated more strongly with CCT than CH.[5] IOPcc is an IOP measurement which doesnot depend on corneal properties such as thickness or elasticity.

Shah et al in their study comprising 207 normal individualusing ORA has reported the value of mean hysteresis as 10.7 +/- 2.0 (SD) mm Hg.[6] The Corvis ST, produced by Oculus (Wetzlar, Germany), was developed also for assessment of biomechanical properties of the eye. It utilizes a jet of air tonometer to record pressure and a Scheimpflug camera of high speed to monitor movement of cornea simultaneously.

It can recode various parameters; but, there is limited data available and the device has not been approved yet by Food and Drug Administration(FDA) for measurement of biomechanical properties.[2]

Variables affecting CH - Age - Structural changes in cornea with increasing age cause an increase in diameter of collagen fiber due to increase in number of molecules of collagen and intermolecular space expansion. These changes ultimately affect the corneal biomechanics.[7] Although there are studies showing not a significant difference in ORA measurements with ageing,[8] contradictory results also been published.

Sharifipour et al[9] did a study to know the variations related to age in biomechanical properties of cornea by ORA and have reported higher values of CH and CRF in younger age and this is negatively correlated with age i.e. decrease in CH and CRF occurs with increasing age. They postulated that low CH accompanied by low CCT is attributed to collagen weakness like keratoconus, while low CH with high CCT is more likely due to hydration changes. The declining rate of CH over time is estimated in range of 0.24 to 0.7 mmHg/decade in normal eyes.[10] Based on these contradictory reports, it's not easy to come to a definite conclusion at present and it needs a detailed evaluation in a defined population considering other compounding factors like ethnicity of study population,[8,11] various other disorders which can affect the corneal biomechanics.

Gender – Hormones have a significant role in corneal biomechanics. Estrogen reduces stiffness on the cornea by increasing release of prostaglandins and thereafter activating collagenases, and by acting as a breaker of chain. Progesterone also inhibits production of prostaglandin which leads to decreased production of collagenases.[12] The net balance of female hormones exercise influence on corneal biomechanical properties and CH value changes during menstrual period[13] and pregnancy.[14] Various studies do report conflicting reports on association between gender and corneal hysteresis.

Allam et al[15] based on their finding of 350 normal eye, male and female in equal number have reported higher value of CH in female gender (10.41 ± 1.65 mm Hg) than male(9.69 ± 2.05 mm Hg) while Strobbe et al[16] comparing the CH of 168 male and 232 female have reported CH higher in male gender.

Diabetes mellitus - The corneal changes occurring with diabetes mellitus, known as diabetic keratopathy, can present in the form of diminished corneal sensation, epitheliopathies, markedly thickening of basement membrane of corneal epithelium.

Glucose acts as collagen cross-linking agent with the aid of advanced glycosylation end products. Advanced Glycation products accumulate in collagen proteins resulting in the formation of covalent cross-linking bonds formation and may lead to increase in corneal thickeness and biomechanical changes. The CCT is reported to be more in diabetes patients[17] especially in those having diabetes for last 10years.[18] Hager et al[19] reported a higher value of CH in diabetes patients after correcting for IOP, age and CCT whereas lower value of CH is also reported in diabetics by Sahin et al.[20]

CH and Glaucoma

One of the basic limitations of GAT is its basic corneal consideration as an infinitely thin sphere. In GAT the finite thickness, rigidity of cornea and asphericity is intended to correct by assumption of constant corneal thickness and that the surface tension which draws the applanation instrument towards the cornea compensates for corneal rigidity factor. But these assumptions do not hold true in practical.

GAT overestimates IOP in corneas having higher CCT, CRF and CH as it needs more force in order to applanate these corneas and opposite holds true for thinner corneas. ORA provides IOPCC which is not affected by CH and CCT and is more reliable indicator of IOP in these situations.

CH and different kinds of glaucoma – Relationship between CH and various types of glaucoma have been studied widely.

The basis of these surveys was considering CH as the marker of overall globe biomechanics and as a marker for susceptibility of optic nerve to glaucomatous damage. Role of CH has been evaluated in various kinds of glaucoma – primary open angle[21] andclosed angle glaucoma,[22] congenital glaucoma,[23] normotensive glaucoma,[24] and pseudoexfoliation glaucoma.[25] All these studies report decreased level of CH in eyes affected with glaucoma.

CH and refractive error – Controversies exist between association of refractive error and CH. The corneal biomechanical properties change with increase in axial length of eye.[26] Longer eyes have flat cornea and thinner corneas.[27] Eyes with higher axial length and myopia reports to have lower value of CH by most the studies published so far.[28,31] Fontes et al studying the association of refractive error and biomechanical properties of cornea reported no association in between CH and spherical equivalent of refractive error but the mean

spherical equivalent refractive error in their study was only -1.16+/-3.48D.[32] But none of the studies so far have reported increased CH in myopic eyes.

Whether the corneal biomechanical changes are a part of overall change in biomechanics of eye or is a separate entity, is yet to be decided as this could explain the higher growth of axial length of these myopic eyes. On other end hyperopes have been found to have higher value of CH.[9]

CH and keratoconus – Evaluation of corneal biomechanical properties for early detection of keratoconus.

It has got a wide spread use in screening of kerato- refractive surgery patients. The overall value of CR and CH has been analyzed in patients of keratoconus suspects and keratoconus. In comparison to normal eye, they have been found to have lower value of CR and CH but they alone are not sufficient to diagnose keratoconus suspect.[33] In the recent software version of ORA, 6 specific parameters for keratoconus have been included –keratoconus match probability (KMP) index - (KMP-KC normal, suspect, mild, moderate and severe) and The keratoconus match index (KMI-KC score).

KMI is the result of a neural network calculation of 7 waveform scores and it represents the similarity between waveform of examined eye and the same average waveform scores of the suspected keratoconus eyes in the machine's database. The keratoconus match probabilities indices aims to quantify the possibility that whether certain eye is normal, suspect or keratoconic by comparing the given waveform with population data reference. The keratoconus is classified into mild, moderate and severe categories.

KMI classified the parameters measured into 5 model stages which are incorporated in the ORA database –
Normal: KMI from 0.761 to 1.642,
Keratoconus suspect: KMI from 0.352 to 0.757,
Mild keratoconus: KMI from -0.08 to 0.313,
Moderate keratoconus: KMI from -0.345 to -0.091, and
Severe keratoconus: KMI from -1.003 to -0.359.34

Studies are going on for assessing the reliability of these specific indices in staging of keratoconus & monitoring its progression.

To explore the diagnostic potency of these indices Labiris et al[35] used them along with indices of Pentacam topography and found that KMI presented predictive accuracy of 97.7%, with sensitivity 91.18% and specificity 94.34%. On the other hand, KMP in their study was found to have limited clinical significance in differentiating Keratoconus from normal corneas.

Pniakowska et al[34] in their study to detect keratoconus based on the corneal biomechanical property in refractive procedure candidates, divided these patients in 3 groups on the basis of predefined KMI range i.e. Group 1 (0.352 to 0.757), Group 2 (0.08 to 0.313) and Group 0 - control group (0.761 to 1.642). Waveform score (WS) higher than 3.50 was utilized in this survey to consider the measurements to be reliable.

In both study groups, IOP, CH and CRF were found to be decreased when compared to their respective control ($P < 0.0001$). Their study concluded that, CRF and CH together with IOP and WS, consist a clinically significant adjunct in order to diagnose subclinical keratoconus in patients who have been referred for keratorefractive surgery on basis of KMI staging.

CH and pellucid marginal degeneration (PMD)– Use of these indices in diagnosing corneal ectasias has been also studied in PMD. Labiris et al[36] studied the diagnostic capability of KMI and KMP in 40 PMD cases comparing them with the control group of 40 normal eyes. They reported KMI as a promising index for PMD diagnosis but KMP had limited value in diagnosis as it identified a significant number of topographically defined PMD eyes as normal. Sedaghat M R[37] studied the CRF and CH value in 102 cases of PMD, 202 cases of keratoconus and compared them with 208 normal control eyes.

The CRF and CH were lower in the PMD patients than in the normal group but it was close to the keratoconus group. In spite of having lower value for CH, the sensitivity and specificity of ORA biomechanical parameters (CH, CRF) were not very strongly indicative for diagnosis and clinical application in cases of PMD. This limitation could be because of different location of cornea (inferior) getting affected in PMD, whereas we measure CH in central location.

CH and collagen crosslinking (CXL) – CXL works by changing the overall corneal biomechanical properties. It forms bond covalently between the collagen fibers to make the cornea stiff and halts the ectasia progression.

The studies based on change in corneal biomechanics parameters after crosslinking have shown variable results so far. Vinciqueraet al[38] reported significantly increase in CRF and CH after CXL intra and postoperatively at follow-up after one month. Postoperatively, at 6 and 12 months, CRF and CH were not different significantly from pre-procedure level.

Study published by Sedaghat M[39], on 56 eyes of 51 patients of keratoconus, have reported no change significantly in CRF or CH as measured by biomechanical waveform analysis after 6 months of crosslinking. Another study based on patients of both post refractive surgery ectasia and keratoconus and compared custom ORA variables set that characterize the temporal, signal intensity of applanation, and pressure of the corneal deformation response as produced by the ORA.

A subset of these variables was more specific and sensitive than CRF and CH for differentiating eyes with keratoconus from normal eyes. This study also reported changes in new custom ORA variables after CXL procedure that is in consistence with an increase in resistance of bending 3 months after CXL in post-refractive ectatic corneas but not keratoconus.[40] Looking at these customized variables, it clearly shows us the need of better applicability of ORA and development of certain new variables derived for a particular disorder.

CH and Contact lens wear – Soft contact lenses usually give rise to corneal edema in stromal layer which do increase spacing between individual collagen fibrils and thus affecting the biomechanical properties and CCT. Corneal thickness stabilizes in 74% of patients after first week of contact lens wear and in 26% of patients the second week of wear.[41] A study published by Lu et al, comprising 20 patients, to determine whether CH was associated with CCT increase induced by wearing of soft contact lenses during eye closing found that CH did not have an association with corneal edema induced by soft contact lens wear.

The patching duration was 3hrs and the measurements were taken till 100 minutes after removing contact lens.[42] But how the CH is affected by difference in wearing schedule, lens material and dioptric power of lens is still not very clear. The study by Radaie -MoghdamS et al had a longer follow up period of 3 months for 66 eyes wearing soft toric contact lenses.

They have reported change in CH value significantly between week 1 and month 1 but not beyond that.[43] Another study published on the orthokeratology effect has reported slower

correction of refractive error in higher CH value corneas after 3 hours of OK lens wear. CRF was found to decrease with increased duration of lens wear.[44]

CH and refractive surgery – The latest development in the field of keratorefractive surgery has dramatically increased the need to study corneal biomechanics in details.
The different effects of various lasers, the flap and the flapless refractive procedures; they all have their own impact on corneal biomechanics. During photorefractive keratectomy (PRK), laser in situ keratomileusis (LASIK), phototherapeutic keratectomy and other ablation procedures, circumferential severing of anterior corneal lamellae occurs immediately in the zone of ablation.

The resultant alteration in cornea structurally has been found to decrease the resistance to the stromal swelling pressure peripheral to the ablation zone, shifts tension to the intact lamellae which is deep to the interrupted lamellae, and generates centripetal forces that do favor central corneal flattening and a farsightedness shift. Because intraocular pressure (IOP) also do manifests as a force acting against the posterior corneal surface, deeper zone ablations which are concentrated in the cornea's thinnest regions may lead to offsetting corneal steepening effects.

These unintentional biomechanically mediated effects can be an important source of variability in surgery outcomes and in some cases may contribute to refractive instabilty, ectasia, and loss of visual acuity.[45] Significant difference in CH has been reported in LASIK patient in comparison to normal subjects.[46] Medeiroset al[45] attempted to compare the corneal biomechanics and ablation profile of myopic and hypermetropic lasik and measured the CRF and CH of 13 myopic eyes and 11 hypermetropic eyes. hey concluded that with similar attempted ablation volumes and flap thickness , myopic photoablation procedures were associated with greater decrease in CRF and CH than hypermetropic procedures. The results indicated that preoperative corneal biomechanical property, volume of ablation, and its spatial distribution are important factors that affect resistance of cornea and property of viscous dissipation differently.

In a recent article by Al- Nashar and Awad[47] the CRF and CH were compared in patients undergoing SMILE surgery and PRK. CRF and CH decreased from pre-operative value in both the groups but the difference was insignificant in these biomechanical variables in between the groups. But PRK is reported to cause lesser decrease in CH ad CRF than LASIK,

making PRK a less invasive surgical approach from biomechanical viewpoint than LASIK.[48] Most of these changes are reported to occur in early after surgery.[49] Table 1 - Summary of literature published on CH.

CH and the role it play in other corneal pathologies and interventions – Any corneal disorder affecting arrangement of its constituents like various dystrophies (example Fuch's endothelial dystrophy[50]) and degenerations will have an effect on CH. Similarly, any corneal surgeries like implantation of intrastromal rings and segments, various keratoplasties; will have an impact on corneal biomechanics.

By measuring these parameters probably we can find out a way to know and modify prognosis of these disorders.

		Concise review of literature on Corneal Hysteresis
Factor -		
Age		**Study group Result**
Sharifipour et al[9]	N-302	Decrease in CH with age
Shimmyo et al[8]	Eyes-840	CH is not correlated significantly with age
Celebi et al[51]	N-2039	CH decreased 0.011 mmHg per year with increasing age
		CH is not correlated significantly with age
Race		
Morel et al[11]	59 African -30 N + 29 POAG	CH-N Africans < N caucasians p< 0.001
	55 Caucasian - 25 N + 30 POAG	CH-POAG Africans < POAG caucasians p0.033
Shimmyo et al[8]	Eyes-840	CH - Blacks < Asians < Hispanics < Caucasians
Gender		
Allam et al[15]	175 Men, 175 Women	CH higher in women
Strobbe et al[16]	168 Men, 232 Women	CH higher in men
Arfaj et al[52]	133 Men, 88 Women	CH higher in women
Diabetes		
Hager et al[19]	385 N eyes, 99 DM eyes	CH higher in diabetics
Sahin et al[20]	120 N eyes, 81 DM eyes	CH lower in diabetics
Kotecha et al[53]	121 N eyes, 61 DM eyes	No significant difference in CH
Glaucoma		
Sullivan et al[21]	71 N, 58 OH, 70 GS, and 99 POAG	Lower CH in POAG than N, OH, GS
Narayanaswamy[22]	131 PACG, 162 POAG, and 150 N	Significantly lower CH in PACG than N
Kirwan et al[23]	Eyes-81 N, 11-congenital glaucoma	Lower CH in congenital glaucoma than N
Kaushik et al[24]	71 N, 101 GS, 38 OH, 59 PACD, 36 POAG, and 18 NTG	Lower CH in POAG and NTG than N
Beyazyildiz[25]	46 EXG, 66 POAG, 50 N	Lower CH in EXG than POAG and N.
Refractive error		
Altan et al[26]	Eyes-83 AL>26mm, 82 AL<26mm	Lower CH in eyes AL >26mm
Song et al[28]	1233 children with mean age 14.7yr	Lower CH in eyes with higher axial length
Shen et al[29]	45 with SE>-9D, 90 with SE between 0 to -3D	CH lower in high myopes

Qiu et al[31]	Eyes-135 with SE between −1 to −13.25D	Lower CH with increasing myopia
Fontes et al[32]	Eyes-260 with mean SE -1.16+/-3.48D	CH is not affected by SE refraction.
Sharifipour et al[9]	42 M, 45 H, 215 E	CH higher in H
Keratoconus		
Saad et al[33]	N-252, K-172, KS-80	CH and CRF can not be used alone for KS identification.
Labiris et al[35]	N-109, K-114	KMI - reliable index in K diagnosis/staging
Pniakowska et al[34]	N-80, KS-45, Mild K-52	CH and CRF together with WS and IOPg useful for detecting subclinical K
Shimmyo et al[54]	Eyes-N-202, K-76, Prelasik-98, Postlasik -98	CH and CRF significantly reduced in K and after lasik.
Pellucid Marginal Degeneration		
Labiris et al[36]	Eyes-N-40, PMD-40	KMI promising index for diagnosing PMD
Sedaghat et al[37]	Eyes-N-208, K-106, PMD-102	CH and CRF were lower in K and PMD than N
Collagen cross linking		
Vinciquera et al[38]	Eyes- K-24	significantly increase in CH and CRF after CXL at 1month
		but not at 6 month and 1yr
Sedaghat et al[39]	Eyes-K-56	No significant change in CH and CRF after CXL at 6month.
Rehman et al[55]	Eyes-K-29	Increased CH with ART at 1 and 6moth but not with ORA
Hallahan et al[40]	Eyes - K- 24	No significant change in CH and CRF after CXL at 3month.
		Need to develop customized variables.
Contact Lens		
Lu et al[42]	Eyes - 20	CH not associated with corneal swelling induced by soft CL wear.
Moghdam S et al[43]	Eyes - 66	CH and CRF decreased significantly 1 month after fitting toric soft CL
Chen t al[44]	20 M CRF decreases with increasing duration of ortho-K lens wear	
Refractive surgery		
Mendoza et al[46]	N-66, Lasik - 48	CH decreases significantly after Lasik surgery
Medeiros et al[45]	M-13, H-11	Lasik for myopia cause greater decrease in CRF and CH than hyperopia
Al- Nashar[47]	Eyes - PRK-28, SMILE-28	No differences in CH and CRF between SMILE and PRK.

kamiya et al[48]	Eyes - PRK-27, Lasik-31	Decrease in CH and CRF was significantly larger after Lasik than after PRK
CH- corneal hysteresis, N- Normal, POAG- Primary open angle glaucoma, DM- Diabetes mellitus, OH- Ocular hypertension, GS- Glaucoma suspect		
PACG- Primary angle closure glaucoma, PACD- Primaryangle closure disease, NTG – Normotensive glaucoma, EXG-Exfoliateve glaucoma, AL-Axial length		
SE- Spherical equivalent, M – Myopia, H- Hypermetropia, E- Emmetropia		
K-Keratoconus, KS- Keratoconus suspect, CRF – Corneal resistance factor, KMI – Keratoconus match index, WS- waveform score, IOPg - Goldman-correlated IOP		
LASIK- laser-assisted in situ keratomileusis, PMD- Pellucid marginal degeneration, CXL- Collagen cross linking, ART- applanation resonance tonometer		
ORA- Ocular response analyzer, CL- Contact lens, PRK – Photorefractive Keratectomy, SMILE-small incision lenticule extraction		

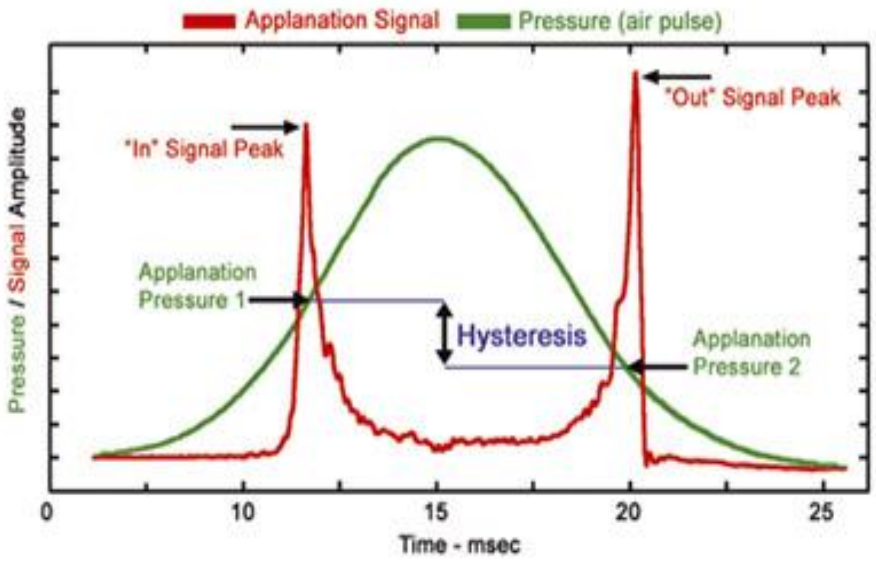

Fig.:- 1.

CONCLUSION

Biomechanics of cornea is an entity of great clinical and research value which hasn't been completely understood and explored. This explains the contradictory results published so far in literature.

Probably we are oversimplifying the parameters related to it and dedicated parameters should be developed for different clinical situations as has been done in cases of keratoconus. Applying clinically knowledge of CH in glaucoma is merely the tip of iceberg of its clinical utility. We should look beyond this to understand its full implications and to make more of its clinical importance.

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