Corneal Hysteresis as a Marker for Patients with Secondary Glaucoma

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Research Article

Keywords: corneal hysteresis, ocular response analyzer, primary open-angle glaucoma, secondary glaucoma

Posted Date: September 23rd, 2022

DOI: https://doi.org/10.21203/rs.3.rs-2085188/v1

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Additional Declarations: No competing interests reported.
Abstract

Purpose

To investigate and compare the association of corneal hysteresis (CH) in patients with secondary glaucoma to those with primary open-angle glaucoma (POAG). Additionally, to determine the consistency of CH measurements in patients with secondary glaucoma.

Methods

A total of 84 patients (121 eyes) were prospectively included in this study. 23 patients (46 eyes) were healthy controls, 24 patients (40 eyes) were diagnosed with POAG, and 27 patients (35 eyes) were diagnosed with a form of secondary glaucoma. CH and intraocular pressure (IOP) were measured using the Ocular Response Analyzer. Three measurements per eye were performed and used for the analysis and to determine fluctuations in CH data. One-way ANOVA with post-hoc Bonferroni analysis and Chi-Squared testing was done to determine differences between groups.

Results

All patients were matched for age. Patients in both POAG and secondary glaucoma groups were matched for age and IOP. All groups had similar sex and racial compositions as well as similar proportions of diabetes, hypertension, and hyperlipidemia. CH was lower (p < 0.05) in patients with POAG (9.32 ± 1.64) and secondary glaucoma (7.89 ± 3.18) when compared to healthy controls (11.16 ± 1.60). Fluctuations in CH measurements were minimal in all groups. Further analysis of the secondary glaucoma group revealed no differences in CH between different types of secondary glaucoma (p > 0.05).

Conclusion

Patients with secondary glaucoma have lower CH when compared to POAG or control groups. The ORA exhibits precision of CH measurements for control, POAG, and secondary glaucoma groups.

Introduction

Corneal hysteresis (CH) is a biomechanical property of the cornea that represents the ability of corneal tissue to respond to the loading and unloading of a specific force, i.e. a bidirectional applanation stimulus. Early on its discovery, CH was mainly used by refractive surgeons in the study of keratoconus or in terms of influencing negative outcomes of refractive surgeries but has since been shown to influence the development and progression of glaucoma. A low CH value is associated with progressive optic nerve damage and has been proven as an independent risk factor for predicting the
development of glaucoma. As a result, CH has been promoted as being a tool for the screening, diagnosis, and prognosis of glaucoma.

Many of the studies that have investigated CH as a potential diagnostic or prognostic marker have focused on patients with primary open angle glaucoma (POAG) or patients after ocular surgeries. However, there has not been much investigation into the role of CH as a marker for secondary glaucoma, namely, neovascular, traumatic, uveitic glaucoma, or pigmentary glaucoma, among others. This is crucial given that forms of secondary glaucoma contribute to roughly 18% of the mean prevalence of POAG in the world, which constitutes more than 10 million individuals. Furthermore, secondary forms of glaucoma tend to have a more rapid onset and progression than POAG often leading to complications and potentially blindness if intervention isn’t initiated early enough. Therefore, the purpose of the current investigation is to study corneal hysteresis in patients with confirmed secondary glaucoma and compare it to an age-matched cohort of patients with POAG. Furthermore, the current analysis will evaluate CH in confirmed cases of secondary glaucoma to determine its efficacy as a potential marker for these conditions.

Materials & Methods

The study was approved by the Institutional Review Board of Rutgers New Jersey Medical School. Written informed consent was obtained by all participants. This study was performed in accordance with the tenets of the Declaration of Helsinki

Participants

The study population consisted of a total of 84 patients (121 eyes) and were all patients of the Department of Ophthalmology & Visual Science at Rutgers New Jersey Medical School that were prospectively and consecutively enrolled. Only patients with a confirmed clinical diagnosis based on biomicroscopic examination, structure and function testing were included. Patients with POAG or a form of secondary glaucoma were included in this study. A separate control group was also established. 23 patients (46 eyes) were healthy controls, 24 patients (40 eyes) were diagnosed with POAG, and 27 patients (35 eyes) were diagnosed with a form of secondary glaucoma. Secondary glaucoma diagnoses included neovascular glaucoma, traumatic glaucoma, uveitic glaucoma, and other forms of glaucoma which included both pigmentary glaucoma and childhood glaucoma.

Data Collection

Corneal hysteresis and Goldman-correlated intraocular pressure (IOP_g) and corneal-compensated intraocular pressure (IOP_cc) measurements were acquired using the Ocular Response Analyzer (ORA; Reichert Technologies, New York, USA). Three consecutive ORA measurements during the same visit were made on the eye that was affected. The average value of the three measurements was used for analysis. Fluctuations of corneal hysteresis measurements were determined by taking the standard deviation of the three consecutive measurements per patient. That standard deviation represents the fluctuations of
each CH measurement when compared to the average of the three measurements. The average of all standard deviations was taken for each group and plotted to represent the precision of CH measurements.

Statistical Analysis

All statistical analysis and graph creation was completed using GraphPad Prism software (Version 5.1). Differences in $IOP_{cc}$, $IOP_g$, CH, and fluctuations in CH measurements between control, POAG, and secondary glaucoma groups were analyzed using one-way ANOVA testing. Analysis of demographic variables (Table 1) was done using a Chi-square test. Differences between subgroups of secondary glaucoma were analyzed using one-way ANOVA testing.

Results

Patients were separated into control, POAG, and secondary glaucoma groups. Of the patients in the secondary glaucoma group, 7 (26%) had neovascular glaucoma, 4 (15%) had traumatic glaucoma, 10 (37%) had uveitic glaucoma, 3 (11%) had childhood glaucoma and 1 (3%) had pigmentary glaucoma. Patients in the control, POAG, and secondary glaucoma groups were matched for age (Table 1).

Demographic analysis of the three patient populations revealed a near-equal distribution of male and female patients and a high proportion of black and Hispanic patients when compared to white or Asian patients. No difference was observed in distribution of sex ($p = 0.83$), race ($p = 0.39$), or co-morbidities ($p = 0.67$) between the three populations. The majority of patients in the POAG and secondary glaucoma groups were on 2 or more glaucoma medications. However, nearly half of the patients in the secondary glaucoma underwent some form of surgery compared to only 28% of the POAG group.

The average of three ORA measurements was used to determine $IOP_g$, $IOP_{cc}$, and CH (Table 2). Patients in the control group did exhibit lower $IOP_g$ and $IOP_{cc}$ but only reached statistical significance when compared to the secondary glaucoma group. Patients in the secondary glaucoma group did exhibit higher mean $\pm$ SD $IOP_{cc}$ (25.8 $\pm$ 18.2 vs. 20.6 $\pm$ 8.4) and $IOP_g$ (22.1 $\pm$ 13.4 vs. 18.6 $\pm$ 7.9) when compared to the POAG group but did not reach statistical significance ($p = 0.11$; $p = 0.17$). Measurements of CH showed that that control group had a higher CH when compared to both POAG and secondary glaucoma groups ($p < 0.0001$). Furthermore, secondary glaucoma patients had a significantly lower CH when compared to POAG (7.89 $\pm$ 3.18 vs. 9.32 $\pm$ 1.64; $p = 0.02$).

Further analysis of CH measurements was done to determine the precision of CH as a marker for both POAG and secondary glaucoma. Standard deviation (SD) of the three measurements, a representation of fluctuation, was determined per patient and calculated for all groups (Table 2). Control, POAG, and secondary glaucoma groups exhibited low overall fluctuation and did not show any differences (0.38 $\pm$ 0.66 vs. 0.26 $\pm$ 0.34 vs. 0.33 $\pm$ 0.41; $p = 0.67$). The similarities in the fluctuations of CH measurements between the control, POAG, and secondary glaucoma groups is illustrated (Fig. 1). Subsequent analysis of the secondary glaucoma group was conducted to determine differences in various types of secondary
glaucoma (Table 3). No differences in IOP\textsubscript{cc} (p = 0.31), IOP\textsubscript{g} (p = 0.63), or CH (p = 0.35) were observed between any of the sub-groups of secondary glaucoma following one-way ANOVA testing.

**Discussion**

To our knowledge, this is the first study that investigates and compares corneal hysteresis in patients with secondary glaucoma to those patients with POAG. Overall, both POAG and secondary glaucoma groups had lower CH when compared to the control group. When matched for age and IOP, patients with secondary glaucoma exhibited lower CH when compared to POAG (p < 0.05). However, no differences in CH were observed between subgroups of secondary glaucoma. Furthermore, fluctuations in CH in the secondary glaucoma were similar to those observed in the control and POAG groups suggesting an equivalence in the precision of the CH measurements further supporting CH as a potential diagnostic and prognostic marker for patients with secondary forms of glaucoma.

There have been many studies that have investigated corneal hysteresis in the context of POAG showing a lower CH when compared to controls. CH was also shown to be independently correlated to glaucoma diagnosis, making it an excellent tool for diagnosis.\textsuperscript{10–12} More specifically, CH has been shown to be predictive of early changes in parts of the retina, i.e. thinning of peripapillary retinal nerve fiber layer and ganglion cell complex, both of which are first affected in glaucoma.\textsuperscript{13} Subsequent demographic analysis revealed that there are several demographic factors have also been shown to influence corneal hysteresis including the male sex, an increased age, and black ethnicity.\textsuperscript{14,15} Smoking, diabetes, and systemic lupus erythematosus have also been positively associated with CH.\textsuperscript{16} Other investigations into corneal hysteresis before and after glaucoma surgeries have also been conducted showing usefulness with certain surgeries, e.g. trabeculectomy\textsuperscript{3} and cataract surgery\textsuperscript{17}, but not others, e.g. trabecular microbypass stenting.\textsuperscript{18}

Unlike POAG, investigations studying corneal hysteresis in forms of secondary glaucoma have been scarce. Only two studies examined this, but only focused on congenital glaucoma showing lower CH in patients with congenital glaucoma when compared to controls.\textsuperscript{19,20} However, when comparing these two studies the measurements for CH for patients with congenital glaucoma were not consistent (6.3 ± 1.58 vs. 9.1 ± 1.6) suggesting the need for further investigation. Investigations into other forms of secondary glaucoma including neovascular, uveitic, and traumatic have yet to be studied. In the current study, neovascular, uveitic, traumatic, and other forms of secondary glaucoma are represented and analyzed (Table 3). No difference was observed between any of the subgroups of secondary glaucoma in terms of IOP\textsubscript{cc}, IOP\textsubscript{g}, and CH. However, further analysis of these groups is required given the trends in CH, most notably amongst patients with neovascular glaucoma.

The current study is not without limitations, most notably, the small sample size. While a small sample size is not ideal it was necessary to match patients in the POAG and secondary glaucoma groups, by both age and IOP, both of which are powerful confounding variables that undoubtedly affect a patient’s
glaucoma onset and development. Furthermore, the other two studies that have analyzed CH in patients with secondary glaucoma report similar total sample sizes of both 26 patients (40 eyes) and 42 patients (91 eyes), only 11 of which were confirmed with congenital glaucoma, suggesting the difficulty that comes with enrolling patients these patients into these types of studies.\textsuperscript{19, 20} Another limitation was the racial demographics of our patient population. For all study groups, the majority of patients were black or Hispanic with very few being white or Asian. This may potentially have effects on our CH data since black patients have been shown to have lower values of CH when compared to whites or Asians.\textsuperscript{16} Furthermore, it may be difficult to attribute these results to a population that consists more of a white or Asian population. However, the purpose of the current investigation was to determine CH in secondary glaucoma patients, compare it to control and POAG CH, as well as to test the efficacy of CH as a clinical tool in secondary glaucoma. Since there were near equal distributions of black and Hispanic patients in the control, POAG, and secondary glaucoma groups this concern was largely controlled for and therefore does not affect any comparisons made between groups. As a result, confident conclusions could still be drawn between differences in CH given the matching of these important demographic variables.

The purpose of the current investigation was to characterize and compare secondary glaucoma patients to POAG patients in terms of CH. Overall, our analysis showed a lower CH in patients with secondary glaucoma than in patients with POAG. This is the first time that CH was measured in patients with secondary glaucoma. Given the prevalence of secondary glaucoma and its relative severity, further investigation and study into diagnostic and prognostic tools, such as CH, is essential for improving patient management.

Declarations

\textbf{Funding:} No source of funding was used for this investigation.

\textbf{Competing Interests:} Disclosures for Albert S. Khouri: Grant support: Allergan, Optovue, NJ Health Foundation, Speaker Bureau: Aerie, Allergan, Bausch & Lomb. No conflicting relationship exists for the remaining authors. All other authors declare no conflict of interest exits.

\textbf{Author Contributions:} ASK was responsible for study conception and design. MO, AU, HS, & ZL were responsible for data collection. AU and MO were responsible for data analysis. MO was responsible for drafting the manuscript. All authors approved the final manuscript.

\textbf{Ethics Approval:} This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Institutional Review Board of the Rutgers New Jersey Medical School.

\textbf{Consent to participate:} Informed consent was obtained from all individual participants in the study.

\textbf{Consent to publish:} The authors affirm that human research participants provided informed consent for publication.
**Conflict of Interest:** Disclosures for Albert S. Khouri: Grant support: Allergan, Optovue, NJ Health Foundation, Speaker Bureau: Aerie, Allergan, Bausch & Lomb. No conflicting relationship exists for the remaining authors.

**References**


**Tables**

Tables 1 to 3 are available in the Supplementary Files section.

**Figures**
Figure 1

Fluctuations of CH measurements, represented as standard deviation (SD), between the control (●), POAG (○), and secondary glaucoma (◊) groups is shown. No statistical difference was observed amongst these groups.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1CH.docx
- Table2CH.docx
- Table3CH.docx