

Intraocular Pressure and Corneal Biomechanical Changes after Water-Drinking Test in Glaucoma Patients

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Abstract

Purpose: To evaluate intraocular pressure (IOP) and corneal biomechanical changes after water-drinking test (WDT) in glaucomatous and normal eyes using Ocular Response Analyzer (ORA).

Methods: This prospective study included 30 medically controlled, 30 surgically treated glaucoma patients and 30 normal individuals. Baseline measurements included central corneal thickness (CCT), ORA-derived corneal hysteresis (CH), corneal resistance factor (CRF), corneal-compensated IOP (IOPcc), and Goldmann-correlated IOP (IOPg). Measurements were repeated 15, 30, and 60 min after drinking 1000 mL of water. Changes in ORA parameters were compared among the groups.

Results: All groups showed a significant increase in IOPg and IOPcc at all test points. Peak IOP occurred at 15 min and decreased gradually over time but did not reach the baseline values at 60 min. The surgery group had significantly lower baseline IOPg and IOPcc (10.7 ± 3.1 and 12.8 ± 3.7 mmHg, $P = 0.001$ and 0.01), lower peak IOPg and IOPcc (14.4 ± 4.6 and 16.2 ± 4.6 mmHg, $P = 0.003$ and 0.034), and lower percent IOPg and IOPcc fluctuations (13 ± 5.6 and 15 ± 5.9 , $P = 0.0001$ and 0.002), respectively, compared to the medical group. Baseline CH and its fluctuations were not significantly different among the groups. CH decreased to a trough corresponding to peak IOPcc. There was a significant negative correlation between IOPcc and CH ($r = -0.609$, $P < 0.001$). The medical group showed more CRF fluctuations compared to normal group ($P = 0.039$).

Conclusion: Surgically treated glaucomatous eyes show less IOP fluctuations and lower peak IOP after WDT compared to medically controlled and normal eyes.

Keywords: Glaucoma, Intraocular pressure, Ocular Response Analyzer, Water-drinking test

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INTRODUCTION

Elevated intraocular pressure (IOP) remains the major risk factor for glaucoma progression.¹ Glaucoma may progress in patients with apparently controlled IOPs due to large IOP fluctuations^{2,3} or IOP peaks outside office hours.⁴⁻⁶ Diurnal IOP measurement may not represent true IOP fluctuation,^{7,8} misses overnight IOP peaks, and is time-consuming.

Water-drinking test (WDT) is a provocative test indirectly evaluating the outflow system of the eye.⁹ IOP peaks detected during WDT could predict future progression of glaucoma¹⁰⁻¹² and correlate significantly with IOP peak on 24-h IOP measurements.¹³⁻¹⁵ This study aimed to evaluate IOP changes in glaucoma patients after WDT.

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METHODS

This prospective case–control study was performed at a tertiary eye center. The study protocol was approved by the local ethics committee (Ethics approval code: AJUMS.REC.1393.243) and adhered to the tenets of Declaration of Helsinki. Informed consent was obtained from all patients.

This study included 90 eyes (90 individuals) including 30 medically-controlled, 30 surgically treated glaucoma patients, and 30 normal individuals. Glaucoma patients aged 40–80 years with a diagnosis of primary open-angle glaucoma (POAG) were enrolled in this study. The patients had medically or surgically (trabeculectomy) controlled glaucoma with IOP between 5 and 20 mmHg. All patients in the medical group were receiving prostaglandin analog (PGA) latanoprost 0.005% (Latanoprost, Sina Darou, Tehran, Iran) every evening and timolol maleate 0.5%/dorzolamide 2% fixed combination (Zilomole, Sina Darou, Tehran, Iran) two times daily. The surgical group had functional blebs and controlled IOP without antiglaucoma medications. Normal subjects were recruited from spouses and friends of patients and had open angles, corrected vision of 20/25 or better, and normal eye examinations.

Exclusion criteria were uncontrolled IOP, previous ocular surgery other than trabeculectomy (e.g., shunt, cataract, LASIK), hyperopia (>+2 D) and myopia (<-4 D), only eye status, any current ocular infection or inflammation, corneal abnormality or opacity, pregnancy, diabetes, uncontrolled hypertension, and heart or renal failure.

The Ocular Response Analyzer (ORA) (Reichert Inc., Depew, New York) is an air puff tonometer that measures the corneal response to a steady air pulse. It makes two applanation measurements: a force-in applanation which has been attributed to the dampening effects of the cornea and a force-out applanation that occurs at a lower pressure than the initial values. The difference between the two pressures is corneal hysteresis (CH) and indicates viscous properties of the cornea, whereas corneal resistance factor (CRF) shows the elastic properties of the cornea. The instrument measures CH and CRF as the markers of corneal viscoelastic properties as well as corneal-compensated IOP (IOPcc), and Goldmann-correlated IOP (IOPg).¹⁶

Baseline measurements included central corneal thickness (CCT) with an ultrasound pachymeter (Tomey, Tomey Corp, Nagoya, Japan), and CH, CRF, IOPcc, and IOPg with the ORA. Then, the patients drank 1000 ml of water in 15 min, and the measurements were repeated 15, 30, and 60 min after water loading. Four ORA measurements were performed at each test time, and among the three closest readings, the one with the highest waveform score was used for analyses.

Statistical analysis

We used a comparison of two means formula to calculate the sample size with a two-sided test with a 1% level of significance

at a power of 90%, in agreement with the study performed by Danesh-Meyer *et al.*¹⁷ A sample size of 23 patients per group was obtained.

Statistical analysis was performed using SPSS software (version 13) (SPSS Inc. Chicago, IL, USA). To compare the baseline values, we used one-way analysis of variance (ANOVA). Data were presented as the mean \pm standard deviation. All analyses were adjusted for age and baseline IOP and number of medications. Repeated-measures ANOVA was used to compare fluctuations in the ORA parameters among the study groups. Fluctuations of IOPg, IOPcc, CH, and CRF were calculated by subtracting the baseline values from the peaks of these parameters during the test. To calculate percent IOP fluctuation, IOPg and IOPcc fluctuations were divided by baseline values multiplied by 100. Two-by-two comparisons were performed using Tukey's test. Correlations among ORA parameters and with CCT were also investigated using Pearson's correlation coefficient. $P < 0.05$ was considered statistically significant.

RESULTS

Overall, 90 individuals including 30 medically controlled glaucoma patients, 30 surgically treated glaucoma patients and 30 normal individuals were enrolled in this study. Table 1 shows demographic data and baseline characteristics in the study groups.

The medical group was older (59.4 ± 11.3 years) than the other groups ($P = 0.015$). The groups were not different in terms of gender and CCT. The surgery group had significantly lower baseline IOPg and IOPcc compared to the medical and control groups ($P = 0.001$ and 0.01 , respectively). All analyses were adjusted for age, baseline IOP, and number of medications.

Table 2 and Figures 1-4 show changes in the study parameters during the test. All groups showed a significant increase in IOPg and IOPcc at all time points. Peak IOP occurred 15 min after water loading and decreased gradually over time. However, it did not reach the baseline values after 60 min. After water loading, peaks of IOPg and IOPcc were significantly lower in the surgery group compared to the medical group [$P = 0.003$ and 0.034 , respectively, Figures 1 and 2]. IOPg and IOPcc fluctuations in the surgery group were lower than the medical group, although the difference did not reach the statistical significance level ($P = 0.253$ and 0.304 , respectively). However, percent IOPg and IOPcc fluctuations were significantly lower in the surgery group compared to the medical group (13 ± 5.6 and 15 ± 5.9 , $P = 0.0001$ and 0.002 , respectively, Table 2). IOPcc and IOPg were significantly correlated in all groups ($r = 0.877$, $P < 0.001$).

CH and CRF changed significantly after WDT. CH decreased to a trough as IOPcc and IOPg increased to the peak and then increased to a level less than baseline at 60 min [Figure 3]. CRF increased after water loading with a subsequent decrease to a level higher than baseline [Figure 4]. Peak CRF was significantly lower in the surgery group compared to the medical and control groups ($P < 0.001$ and

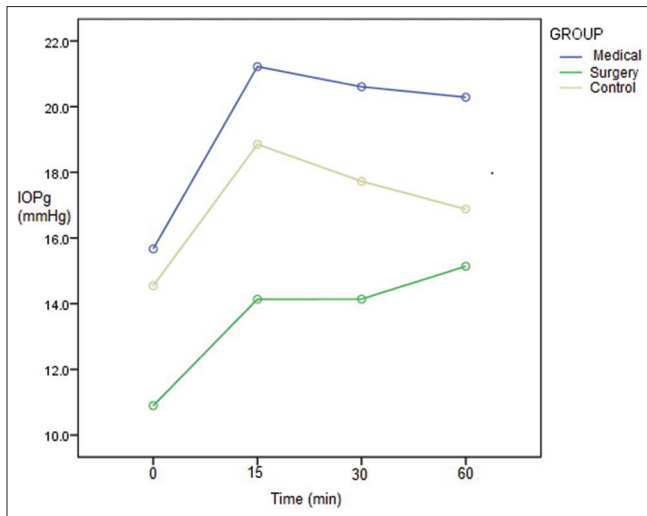


Figure 1: Changes in Goldmann-correlated intraocular pressure (IOPg) after water-drinking test in medically controlled and surgically treated glaucoma eyes and normal individuals. Peak IOPg occurred 15 min after water loading

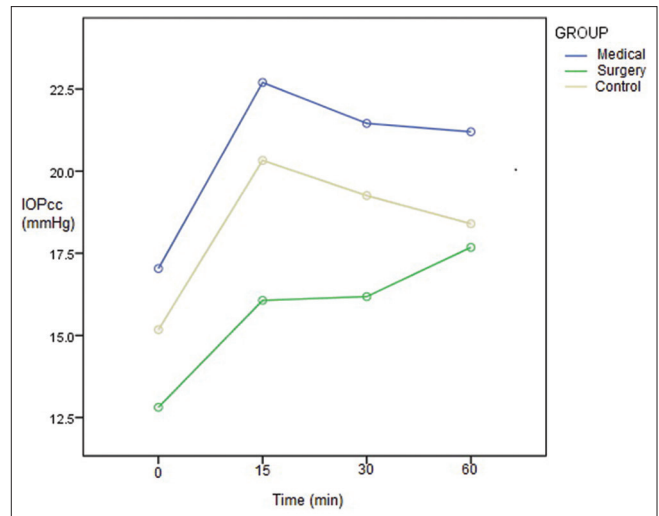


Figure 2: Changes in corneal-compensated intraocular pressure (IOPcc) after water-drinking test in medically controlled and surgically treated glaucoma eyes and normal individuals. Peak IOPcc occurred at 15 min

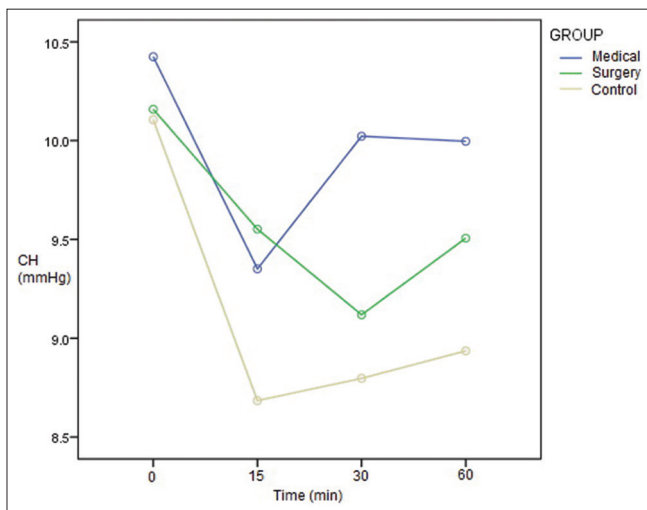


Figure 3: Changes in corneal hysteresis (CH) after water-drinking test in medically controlled and surgically treated glaucoma eyes and normal individuals. CH decreased to a trough at 15 min, corresponding to the Goldmann-correlated intraocular pressure and corneal-compensated intraocular pressure peaks

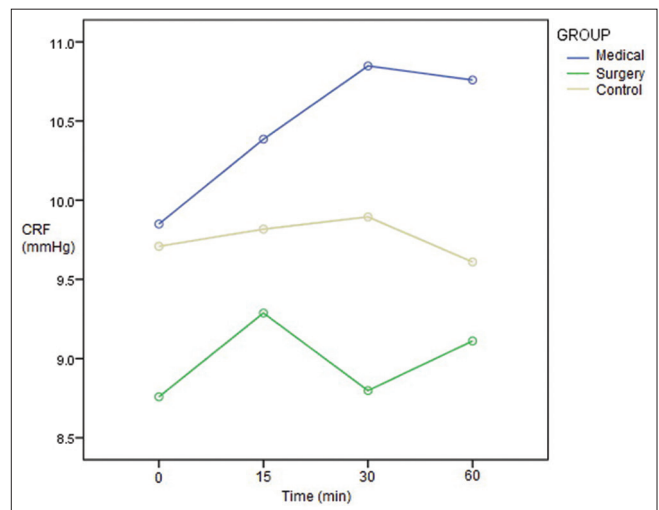


Figure 4: Changes in corneal resistance factor after water-drinking test

0.036, respectively). CRF fluctuation was significantly higher in the medical group compared to the normal group [$P = 0.039$, Table 2]. There was a significant correlation between IOPcc and CH ($r = -0.609$, $P < 0.001$), and IOPg and CRF ($r = 0.506$, $P < 0.001$). Correlations between IOPcc and CRF and between IOPg and CH were not significant. Neither IOPcc nor IOPg correlated with CCT. CH and CRF had significant weak correlation with CCT ($r = 0.288$, $P = 0.007$ and 0.229 , $P = 0.03$, respectively).

DISCUSSION

This study showed that the peaks of IOPg and IOPcc after WDT were significantly lower in surgically treated as compared to

medically treated glaucoma patients. In addition, IOP fluctuation in the surgical group was less than in the medical group.

Glaucoma progression may occur in patients with apparently controlled IOP. This has been attributed to IOP fluctuations outside office hours.⁴⁻⁶ In addition, studies have shown that peak IOP may be a better predictor than IOP fluctuation for glaucoma progression.¹⁰⁻¹² By 24-h IOP evaluation, Barkana *et al.* showed IOP peaks occurring in 62% of their patients outside office hours, which resulted in treatment change in 36% of the patients.⁴ While a 24-h diurnal tension curve (DTC) may be the best way to evaluate IOP profile, peak, and fluctuations, due to its limitations for both the patients and the physicians, it is not feasible in routine practice. An alternative method to assess 24-h IOP fluctuations is a special contact lens (Sensimed Triggerfish contact lens sensor (CLS) which provides data on

Table 1: Demographic data and ocular parameters before water-drinking test in glaucoma patients and normal individuals

	Medically controlled glaucoma (n=30) Group 1	Surgically treated glaucoma (n=30) Group 2	Control group (n=30) Group 3	P*	P† group 1 versus 2	P† group 1 versus 3	P† group 2 versus 3
Age (year) (range)	59.4±11.3 (48-80)	56.90±8.9 (42-74)	55.8±8.9 (42-62)	0.015*	0.047	0.010	0.288
Gender (male/female)	17/13	15/15	14/16	0.492*			
CCT (µm)	541±30	543±32	536±16	0.916*			
Baseline IOPg (range) (mmHg)	15.8±3.1 (9.3-19.3)	10.7±3.1 (5-17.5)	14.8±3.7 (7-20)	0.001*	<0.001	0.633	0.003
Baseline IOPcc (range) (mmHg)	17.1±3.1 (8.7-19.7)	12.8±3.7 (6.8-18.3)	15.2±3.8 (9.5-20)	0.01*	0.011	0.794	0.007
Baseline CH (mmHg)	10.4±1.5	10.2±2	10.1±1.3	0.647*			
Baseline CRF (mmHg)	9.8±1.6	8.8±1.9	9.7±1.5	0.088*			
number of glaucoma medications	3‡	0	0	<0.001*	<0.001	0.999	<0.001

*Based on ANOVA, †Based on Tukey’s HSD test, ‡All patients in medical group were receiving latanoprost 0.005% and Timolol maleate 0.5%/Dorzolamide 2% fixed combination. All analyses were adjusted for age and baseline IOP and number of glaucoma medications. IOP: Intraocular pressure, CCT: Central corneal thickness, IOPg: Goldmann-correlated IOP, IOPcc: Corneal-compensated IOP, CH: Corneal hysteresis, CRF: Corneal resistance factor, ANOVA: Analysis of variance, HSD: Honestly significant difference

Table 2: Ocular response analyzer parameters’ changes after water-drinking test in glaucoma patients and normal individuals

	Medically controlled group (n=30)	Surgically treated group (n=30)	Control group (n=30)	P*	P† group 1 versus 2	P† group 1 versus 3	P† group 2 versus 3
CCT changes (µm)	1.9±15	0.6±9	-2.2±15	0.527*			
Peak IOPg (mmHg)	21.7±4.3	14.4±4.6	19±4.6	0.003	0.001	0.276	0.015
IOPg fluctuation (mmHg)	5.9±4.2	5.2±3.4	5.2±3.1	0.253*			
IOPg fluctuation (%)	19.2±5.7	13±5.6	16.3±4.9	0.0001	0.001	0.174	0.347
Peak IOPcc (mmHg)	22.8±4.5	16.2±4.6	20.3±4.8	0.034	0.030	0.684	0.158
IOPcc fluctuation (mmHg)	5.8±4.4	3.5±4.3	5.1±4.2	0.304*			
IOPcc fluctuation (%)	21.3±6.1	15±5.9	18.3±5.4	0.002	0.015	0.294	0.154
CH trough (mmHg)	9.4±1.7	9.2±1.9	8.7±1.3	0.727*			
CH fluctuation (mmHg)	-1±1.6	-1±1.8	-1.2±1.2	0.552*			
Peak CRF (mmHg)	10.8±2	9.2±2	9.8±1.4	<0.001	0.010	0.070	0.036
CRF fluctuations (mmHg)	1.1±1.2	0.6±0.8	0.5±0.6	0.039	0.060	0.040	0.825

*Based on ANOVA, †Based on Tukey’s HSD test. All analyses were adjusted for age, baseline IOP, and glaucoma medications. Fluctuations of IOPg, IOPcc, CH, and CRF were calculated by subtracting the baseline values from the peaks of these parameters. To calculate percent IOP fluctuation, IOPg and IOPcc fluctuations were divided by baseline values multiplied by 100. ANOVA: Analysis of variance, CCT: Central corneal thickness, IOPg: Goldmann-correlated IOP, IOPcc: Corneal-compensated intraocular pressure, CH: Corneal hysteresis, CRF: Corneal resistance factor

relative changes in IOP rather than absolute IOP.¹⁸ In recent years, WDT has been proposed as a reasonable surrogate for 24-h DTC to measure IOP peak and fluctuation.¹³⁻¹⁵

Several studies have shown a significant correlation of IOP peaks detected during the WDT with 24-h DTC,¹³⁻¹⁵ as well as with the severity and progression of glaucoma.¹⁰⁻¹²

Most studies comparing IOP fluctuation in medically and surgically controlled glaucomatous eyes have revealed that surgery results in fewer IOP fluctuations and peaks.^{15,17,19-21} This might be beneficial to glaucoma patients, especially in advanced stages of the disease.

In a study by Danesh-Meyer *et al.*, IOP changes were evaluated after WDT in glaucoma patients using Goldmann applanation tonometry (GAT). They observed significantly lower peak IOP in the surgical group (11.7 ± 2.6 mmHg) compared to the medical group (17.3 ± 2.7 mmHg).¹⁷ We used ORA to

measure IOP and corneal biomechanical factors and observed lower IOPg and IOPcc in the surgical group [Table 2]. Corneal biomechanical factors have been investigated in glaucoma patients. Some studies have found lower CH in glaucoma patients and consider it a risk factor for glaucoma progression.²²⁻²⁵

Corneal biomechanics is affected by several factors including age, gender, IOP, CCT, antiglaucoma medications, especially PGA, corneal pathologies such as keratoconus and Fuchs endothelial dystrophy, type of glaucoma surgery, and diabetes.^{26,27} We excluded patients with corneal pathologies and diabetes. In our study, there was a statistically significant difference in terms of age, baseline IOP, and number of glaucoma medications among the study groups for which all analyses were adjusted. In addition, we compared both absolute and percent IOP changes among the groups. All patients in medically treated eyes were receiving PGA which

might affect corneal biomechanics. Surgically treated eyes had undergone the same type of surgery (trabeculectomy). However, baseline CH and CRF were not significantly different among the groups. Therefore, the net effects of confounding factors such as glaucoma medications on corneal biomechanics could be negligible.

CH and CRF changed significantly after WDT. While CH changes after WDT were not significantly different among the groups, CRF changes in the medical group were significantly higher than the control group ($P = 0.039$). We observed a significant negative correlation between IOPcc and CH. Since the only factor that changed over the 1-h study period was IOP, corneal biomechanical changes could be attributed mainly to IOP changes during WDT.

Ayala measured corneal biomechanical factors in glaucomatous eyes and healthy subjects using ORA. In their study, CH was significantly lower in pseudoexfoliative patients (8.0 ± 1.5 mmHg) compared to POAG patients (9.0 ± 1.9 mmHg) and normal individuals (9.8 ± 1.6 mmHg), but the difference between the POAG and the normal group was not significant.²²

Streho *et al.* evaluated corneal biomechanical factors in healthy subjects, POAG, and ocular hypertension patients using ORA. They showed that CH in glaucoma patients (9.8 mmHg) is less than healthy subjects (10.3 mmHg); however, after adjusting for age, there was no difference among the groups.²⁶ Ulaş *et al.* evaluated IOPcc and CH changes in young healthy subjects after WDT. IOPcc increased significantly 10 min after water loading ($P = 0.002$) and then decreased between 10 and 30 min ($P < 0.001$). There were no statistically significant changes in CH. In addition, there was a weak negative correlation between IOPcc and CH measurements. They concluded that IOP changes might alter corneal biomechanical properties.²⁸

In our study, baseline CH and its changes during WDT were not significantly different among the groups. However, peak CRF was significantly lower in surgical group compared to medical and normal groups. In addition, CRF fluctuation in medical group was significantly higher than normal individuals ($P = 0.039$). We found a significant correlation between IOPcc and CH ($r = -0.609$, $P < 0.001$), indicating that by increasing 1 mmHg of IOPcc, CH decreases by 0.609 mmHg, and thus, part of lower CH observed in glaucoma patients might be explained by higher IOP.

A major drawback to IOP measurement is that different devices are more or less affected by CCT and corneal biomechanical properties.

In a study by Furlanetto *et al.*, the correlation between CCT and IOP readings by GAT was investigated in glaucoma patients after WDT. No relevant correlation was detected between CCT and the IOP peak or fluctuation.²⁹ We observed no significant correlation between CCT and IOPg or IOPcc either.

Razeghinejad *et al.* studied the effect of shunt or trabeculectomy surgery on changes in IOP after WDT.³⁰ In the trabeculectomy group, the average IOP increased from 14.8 ± 2.9 to 18.8 ± 4.7 mmHg at 30 min but decreased at 60 min (18.0 ± 5.2 mmHg). In the tube group, IOP increased continuously until the last measurement (14.2 ± 3.9 , 18.8 ± 5.6 , and 19.7 ± 6.0 mmHg at baseline, 30, and 60 min, respectively), and IOP did not reach the baseline values at 60 min. In our study, peak IOP occurred 15 min after water loading and decreased afterwards but did not reach the baseline values at 60 min in none of the groups. CH showed a trough at 15 min, corresponding to peak IOP, indicating the negative correlation between IOPcc and CH.

In our study, eyes with prior trabeculectomy showed lower peak IOPs and IOP fluctuation after WDT as compared to medically controlled and normal eyes. Although this might be in part due to lower baseline IOPs in this group, percent IOP fluctuation was significantly lower in surgery group compared to the medical group indicating truly less IOP fluctuation in surgically treated eyes. Therefore, it may be logical to recommend surgery to patients with advanced glaucoma to lower IOP peak and fluctuation to prevent further disease progression.

The major shortcoming of our study was stopping measurements before baseline IOP was reached. The time interval to reach the baseline IOP might be different among the groups. Furthermore, the mean age was different between the groups although it was statistically addressed for analyses.

In summary, we observed that after WDT, surgically treated glaucoma eyes have a better IOP profile in terms of peak and absolute and percent IOP fluctuation compared to medically treated eyes.

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Conflicts of interest

There are no conflicts of interest.

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