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Effect of eyelid muscle action and rubbing on telemetrically obtained intraocular pressure in patients with glaucoma with an IOP sensor implant

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ABSTRACT

Background Patients with glaucoma on topical glaucoma medication are often affected by dry eye symptoms and thus likely to rub or squeeze their eyelids. Here, we telemetrically measure peak intraocular pressure (IOP) during eyelid manoeuvres and eyelid rubbing.

Methods Eleven patients with primary open-angle glaucoma (POAG) previously implanted with a telemetric IOP sensor (Eyemate-IO) were instructed to look straight ahead for 1 min as a baseline measurement. Next, 6 repeats of blinking on instruction with 10 s intervals in between were performed. In addition, 5 repeats of eyelid closure (n=9), eyelid squeezing and eyelid rubbing (n=7) were performed with 15 s intervals in between. IOP was recorded via an external antenna placed around the study eye. Average peak IOP increases from baseline were analysed and tested against zero (no change) with one-sample t-tests.

Results For eyelid rubbing, the average peak Δ IOP increase (mean \pm SEM) was 59.1 \pm 9.6 mm Hg (p<0.001) from baseline. It was 42.2 \pm 5.8 mm Hg (p<0.0001) for eyelid squeezing, 3.8 \pm 0.6 mm Hg (n=9, p<0.01) for eyelid closure and 11.6 \pm 2.4 mm Hg (p<0.001) for voluntary blinking. No IOP change except for a short irregularity in the ocular pulse was observed during involuntary blinking.

Conclusion Eyelid manoeuvres in patients with POAG elicited brief increases in IOP that were particularly large with squeezing and rubbing. Further investigation of the potential implications for glaucoma progression is warranted.

INTRODUCTION

The only modifiable risk factor for the treatment of glaucoma is intraocular pressure (IOP).¹ The gold standard to measure IOP is by infrequent and brief measurements with Goldmann Applanation Tonometry (GAT).² However, GAT is prone to measurement errors,³ and therefore less than ideal to accurately study the physiological variations of IOP.⁴⁻⁶

The infrequent measurements are in particular inadequate to study short-term IOP variations on a time scale of less than a second, including the ocular pulse, blinking and eye movements.⁷ In addition, it is not possible to measure IOP conventionally with closed eyes, and eyelid movements are also likely to affect the readout.⁸ Hence, conventional methods

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Data on short-term intraocular pressure (IOP) fluctuations during eyelid manoeuvres in humans are very limited.

WHAT THIS STUDY ADDS

⇒ This is the first study to present continual IOP readings during eyelid manoeuvres in patients with glaucoma.
⇒ Eyelid squeezing and moderate eyelid rubbing temporarily increased IOP by over 40, voluntary blinks by 12, eyelid closure by 4 mm Hg.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ As eyelid blinking, squeezing and rubbing occur throughout the day, frequently in response to prolonged use of eye drops, the presence of short-term pressure fluctuations during these manoeuvres as observed in the present study may be relevant in diseases such as glaucoma.

are not suitable to study IOP variations due to blinking, eyelid closure, squeezing and rubbing.

Consequently, there is not much previous literature about short-term IOP fluctuations in humans or their relevance to glaucoma. The most detailed investigations of short-term IOP spikes have been performed in non-human primates using an implantable wireless telemetry system.⁹⁻¹² Eyelid blinks induced IOP spikes of several mm Hg in rhesus macaques. Turner *et al* also reported impressive IOP increases up to 310 mm Hg due to eye rubbing in these monkeys.¹² The same study group found that small transient IOP fluctuations even appear to exhibit a cyclic pattern over several weeks, which has been hypothesised to be induced by hormonal changes.¹³

Previous attempts to measure IOP during eyelid movements in humans include the work of Coleman and Trockel,⁶ who measured IOP manometrically in a cannulated eye just before enucleation surgery. They registered increases of about 6 mm Hg during instructed eyelid closure, and off-scale values during squeezing (exceeding 70 mm Hg). More recently, telemetric measurements with the help of a contact lens sensor (CLS) have shown distinct spikes in the readout during blinking, that

Table 1 Patient characteristics

Characteristic		Study eye (n=11)	Fellow eye (n=11)
Age (years)		72±5	
Gender	Male	6 (55)	
	Female	5 (45)	
Glaucoma stage*	Early	8 (73)	11 (100)
	Moderate	2 (18)	–
	Severe	1 (9)	–
Sensor in the right eye		8 (73)	3 (27)
BCVA (ETDRS letter score)		83 (79, 86)	82±4
MD (dB)		–3 (–6, –1)	–2±2
VFI (dB)		95 (90, 99)	97 (92, 99)
PSD (dB)		2.5 (1.5–6.5)	2.0 (1.7–3.9)
CCT (µm)		568±49	566±44
Glaucoma surgeries†	0	9 (82)	9 (82)
	1	1 (9)	2 (18)
	2	1 (9)	–
Glaucoma medications‡	0	4 (36)	3 (27)
	1	1 (9)	2 (18)
	2	3 (27)	3 (27)
	3	3 (27)	3 (27)

Normal distributed continuous data presented as mean±SD, non-normal distributed data presented as median (IQR) and counts presented as number (%).

*One female patient of 77 years was staged with severe glaucoma in the study eye (BCVA=58, MD=–21.46 and PSD=13.23 dB, left eye). Two patients were staged with moderate glaucoma in the study eye, one male of 78 years (BCVA=88, MD=–10.29, PSD=8.81, left eye) and one female of 76 years (BCVA=86, MD=–6.98, PSD=6.4, right eye). The other eight patients were staged with mild glaucoma in the study eye.

†One patient had previously undergone selective laser treatment in the study eye. Another patient had trabeculectomy and selective laser trabeculoplasty in the study eye. The filtering bleb in the latter patient was not functional (being flat and scarred), and pressure-lowering medication was necessary at the time.

‡Four patients did not use medication at the time of experiments. Lack of compliance was the main reason for not using antiglaucomatous medication in two patients. In two other patients, IOP stabilised within an acceptable range without medication after cataract surgery with implantation of the Eyemate IOP sensor. BCVA, best-corrected visual acuity (using ETDRS letters); CCT, central corneal thickness; MD, mean defect in visual field; PSD, visual field—pattern SD; VFI, visual field index (Humphrey Field Analyzer III).

may, however, not fully reflect IOP increases due to the working principle of the CLS.¹⁴

As short-term pressure fluctuations such as eyelid blinking and rubbing occur throughout the day, the presence of such high IOP amplitudes might be relevant in diseases such as glaucoma. In the current study, we investigated IOP fluctuations during eyelid blinking, careful eyelid closure, eyelid squeezing and eyelid rubbing using a novel telemetric implantable IOP sensor approved for use in humans (Eyemate-IO) in a group of patients with primary open-angle glaucoma (POAG).

METHODS

Methods parts *Telemetric IOP measurements*, *Participants*, *Procedures* and [table 1](#) are as per van den Bosch *et al*¹⁵ and repeated below for clarity.

Telemetric IOP measurements

The present study is a follow-up study to the ARGOS-02 study, which assessed the safety and performance of a novel, telemetric IOP sensor (Eyemate-IO, Implandata Ophthalmic Products, Hannover, Germany) that was implanted in the ciliary sulcus at

the time of cataract surgery in patients with POAG. The system has received CE certification. A detailed description of the study and validation of IOP readings are given elsewhere.¹⁶ In brief, the Eyemate-IO system comprises a pressure sensor and a hand-held reader device. In the present study, continuous communication between sensor and reader device was established by means of an external antenna attached to the reader and placed around the patient's sensor eye, not touching the eyelids. A figure of the antenna placement around the eye has been published by Al-Nowairy *et al*.¹⁷ In this configuration, data acquisition was possible for a maximum of 2 hours at a sampling rate of approximately 9 Hz.

The current study was conducted at the Department of Ophthalmology of Magdeburg University Hospitals.

Participants

Participants were a subset of the 22 patients with POAG originally implanted with the IOP sensor during the ARGOS-02 study at least 3 years ago, with relatively strict inclusion and exclusion criteria.¹⁶ Eleven patients were willing and able to take part in the present study.

Inclusion criteria

1. Mentally competent and willing to provide written informed consent.
2. Male or female aged 50–85 years.
3. Functional Eyemate-IO sensor.

Exclusion criteria

1. Non-functioning Eyemate-IO sensor.
2. Severe general diseases which make the participation in most of the examinations impossible in the investigator's opinion.
3. Ocular diseases, which preclude comparative conventional IOP measurements (eg, corneal ulcer, corneal scar, keratoconus, severe irregular astigmatism).
4. Paralysis of the outer ocular and eyelid muscles, which preclude the IOP measurements in different viewing conditions.

All 11 patients (aged 61–78 years; 5 female), who were diagnosed with POAG for up to 34 years, were eligible and thus included in the present study. The Eyemate-IO system was functional in all patients and calibrated to within 2 mm Hg of GAT measurements. Data on demographics and other patient details are given in [table 1](#). Individual biometrical data are provided in online supplemental table 1. There were no other eye diseases apart from POAG.

Procedures

All patients underwent a comprehensive ophthalmological exam prior to study procedures, including best-corrected visual acuity (BCVA) by ETDRS letter charts, visual fields (Humphrey Field Analyzer III), corneal pachymetry, slit-lamp biomicroscopy and funduscopy. Glaucoma was staged according to the Hodapp classification.²

Experimental procedure

Patients were seated in front of a tangent wall (Tangententafel nach Harms, Heuser Medizintechnik, Germany) with a fixation target at 1.29 m height, at a distance of 2.50 m, in a standard chin rest with a head strap and the centre of the wall (primary position) at eye height. One investigator instructed the patients to perform specific eyelid movements, while a second investigator video-recorded the experiment and reminded patients to maintain a stable head position throughout the experiment.

Table 2 Procedure of eyelid manoeuvres

Eyelid manoeuvre	Time		Repeats	Instruction
	Intervention	Baseline		
Instructed blinking	Punctual	10 s	6	Brief but without squeezing
Closure	10 s	15 s	5	Without force
Squeezing	5 s	15 s	5	Maximum force
Rubbing	3 s	15 s	5	Normal intensity and hand position

Overview of performed eyelid manoeuvres, the timing of the experimental procedures, number of repeats and the instruction given to the patients.

The present study started with an initial baseline recording in primary position lasting 1 min, during which patients' involuntary blinks were recorded. Next, patients were instructed to perform and repeat eyelid movements as indicated in table 2 and elaborated below.

To mark the start of each experiment, patients started with a brief eyelid squeeze. Between each repeat, patients returned their gaze to the primary position as a baseline measurement for 10 or 15 s depending on the eyelid manoeuvre. For *instructed blinking*, patients maintained in primary position with a baseline measurement of 10 s between each blink. Patients were instructed to blink shortly but without force for a total of 6 times. The other eyelid manoeuvres were repeated 5 times. For *eyelid closure*, patients closed their eyes carefully on instruction and kept them closed (10 s), with a baseline period in between each eyelid closure (15 s). For *eyelid squeezing*, patients squeezed the eyelids with maximum force (5 s) with a baseline period in between each eyelid squeeze (15 s). Patients were coached to squeeze their eyelids as much as possible during each manoeuvre of 5 s. For *eyelid rubbing*, patients rubbed the eyelid of the sensor eye (3 s) with a baseline period in between each eyelid rub (15 s). Patients were instructed to place their hand in such a way as they would normally do and to rub with normal intensity. In practice, rubbing had to be performed with caution in some cases in order to not displace the antenna around the eyelid. During the baseline period of eyelid rubbing, patients rested their elbow on a table and/or cushion if needed, and placed their hand several cm away from the eyelid.

Missing and excluded measurements

Two patients (patient numbers 4 and 10) did not perform eyelid closure. Patient 9 had missing measurements during peak IOP for eyelid squeezing and rubbing. Four patients did not do eyelid rubbing (1, 4, 7 and 10), and in 2 patients (2 and 9) missing measurements occurred during peak IOP, potentially due to exceeding the measurement range of the sensor (absolute recordable pressure range 800–1150 hPa, corresponding to approximately 120 mm Hg at normal atmospheric pressure).

Data analysis and statistics

For each eyelid manoeuvre, peak Δ IOP was calculated by subtracting the mean IOP during the preceding baseline period from the maximum IOP value during the eyelid manoeuvre. The eyelid manoeuvres were repeated 5 to 6 times to minimise the effect of artefacts such as irregular breathing and small body movements. The average peak Δ IOP was used for statistical analysis. Data were assessed for normality. One-sample t-tests of the Δ -values compared with a test value zero were performed and a Bonferroni-Holm correction for multiple testing was

applied.¹⁸ The statistical analysis was performed using JupyterLab (V.3.0.11).

RESULTS

Data on patient characteristics are shown in table 1. In total, 11 patients took part, of which, however, only 9 performed the manoeuvre of eyelid closure and 7 of eyelid rubbing. Example IOP recordings in one test subject are shown in figure 1. Calculations on group data are depicted in figure 2.

For eyelid rubbing, average peak Δ IOP (ie, peak increase over baseline) (mean \pm SD) was 59.1 \pm 9.6 mm Hg ($p<0.001$, corrected as well as uncorrected). For eyelid squeezing, average peak Δ IOP was 42.2 \pm 5.8 mm Hg ($p<0.0001$ and $p<0.001$ Bonferroni-Holm corrected). For eyelid closure, average initial peak Δ IOP was 3.8 \pm 0.6 mm Hg ($p<0.001$ and $p<0.01$ Bonferroni-Holm corrected), followed by the previously reported decrease in IOP. For instructed blinking, average peak Δ IOP (mean \pm SD) was 11.6 \pm 2.4 mm Hg ($p<0.001$, corrected as well as uncorrected). No IOP change was visually observed for involuntary blinking except for irregularities in the ocular pulse, and therefore left out of the quantitative analysis.

DISCUSSION

Summary

This is the first study that provides continual IOP readings during eyelid manoeuvres in patients with glaucoma. Both eyelid squeezing and moderate eyelid rubbing elicited IOP increases that exceeded 40 mm Hg above baseline. While voluntary blinks elicited brief increases of 12 mm Hg, we observed peaks of only 4 mm Hg during the act of eyelid closure, which was then followed by a decrease in IOP compared with baseline.

Addition to previous investigations

Rubbing

Our results show temporary IOP elevations during eyelid rubbing of approximately 60 mm Hg over baseline. While these values are not as high as those previously reported by Turner *et al*,¹² who measured IOP increases of up to 310 mm Hg in rhesus macaques, our data confirm that eyelid rubbing leads to substantial IOP increases, that may potentially be detrimental, especially in patients with glaucoma. Notably, in monkeys the rubbing action was elicited with an ophthalmic ointment sufficient to blur vision. The highest IOPs were observed when the back of the hand or wrist was used. We did not use ophthalmic ointments and for safety reasons deliberately instructed patients with glaucoma to rub cautiously and to avoid values that would exceed normal situations. Thus, lower values are to be expected in the present study. Also, the placement of the antenna did not allow patients to use a large area of the backhand or wrist. In addition, as at least two patients had missing measurements during the expected IOP peaks, we assume that the highest IOP values were not captured in those patients due to the limitations in the measurement range of the sensor. These data may be relevant to glaucoma treatment as it is possible that the burning sensation reported by many patients with glaucoma on instillation of topical glaucoma medications may cause them to rub their eyes more vigorously than in the present study.

Squeezing

Similar to eyelid rubbing, many patients with glaucoma react to eye drops by briefly squeezing their eyelids shut. In our experiments, we saw an average increase of IOP by 42 mm Hg over baseline during eyelid squeezing, which is similar in range to

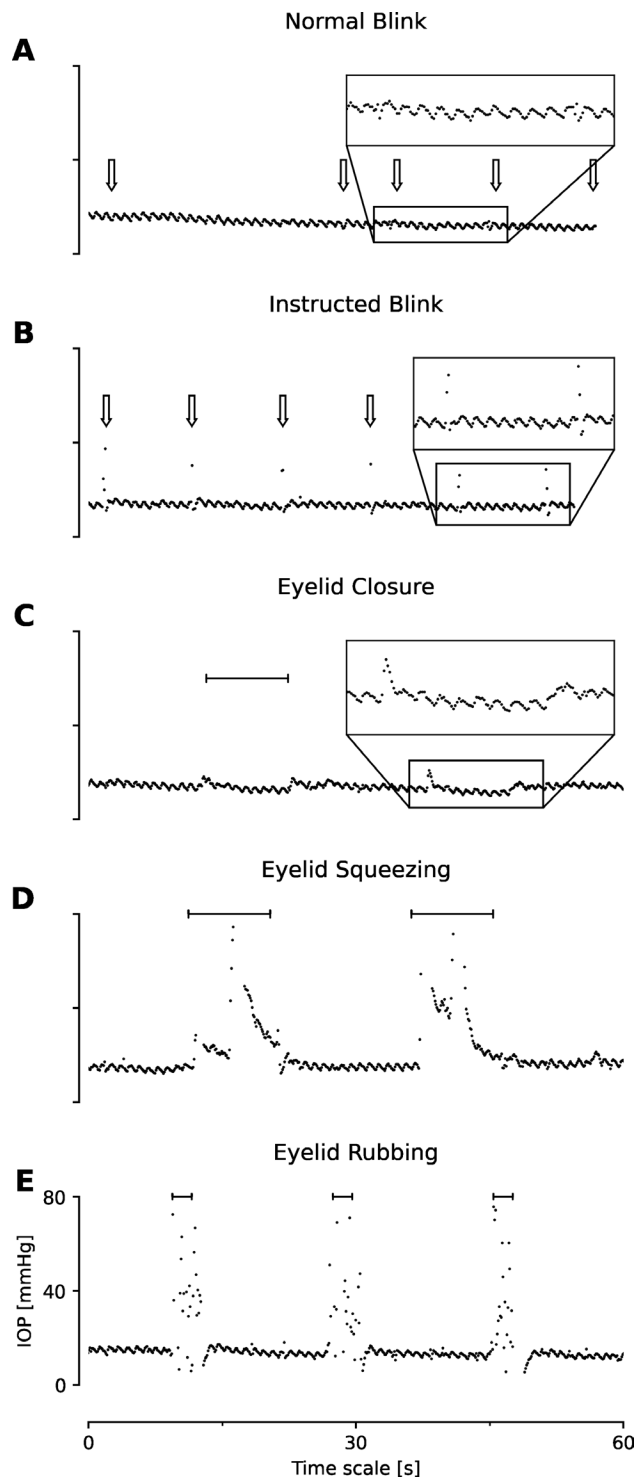


Figure 1 Example intraocular pressure (IOP) timeseries during all eyelid manoeuvres. Timeseries of IOP recordings for one representative test patient (number 5) for the performed eyelid manoeuvres. Panel (A) depicts an IOP recording while the patient looks straight ahead for 1 min without further instruction. Arrows depict the blinks recorded on video. No IOP changes apart from irregularities in the ocular pulse were observed on visual inspection. This is clearer in the extra panel in the upper right with an enlarged selected IOP trace of 15 s that covers two involuntary blinks. The ocular pulse is interrupted slightly before the registered blinks in this example, possibly due to a slight difference in time synchronisation, but no clear IOP drops or peaks can be identified. Panel (B) depicts IOP changes on 6 times of blinking on instruction (every 10 s). Arrows depict the moments of a blink registered during each instruction except for the last two arrows. Instead, an enlarged 15 s IOP trace in the extra panel is shown, covering the last two voluntary blinks. Panel (C) depicts IOP changes on two of a total of five repeats of eyelid closure. The bar depicts the period during which the eyelids were closed the first time (10 s). The second repeat of eyelid closure is not indicated with a bar. Instead, the extra panel with the enlarged 15 s IOP trace covers the IOP changes occurring during the second eyelid closure. A peak on closing the eyes can be observed followed by a gradual drop in IOP. Panel (D) depicts IOP changes on two of a total of five repeats of eyelid squeezing. Bars depict the period during which the eyelids were squeezed (5 s). Panel (E) depicts IOP changes on three of a total of five repeats of eyelid rubbing. Bars depict the period during which eyelid rubbing was performed (3 s).

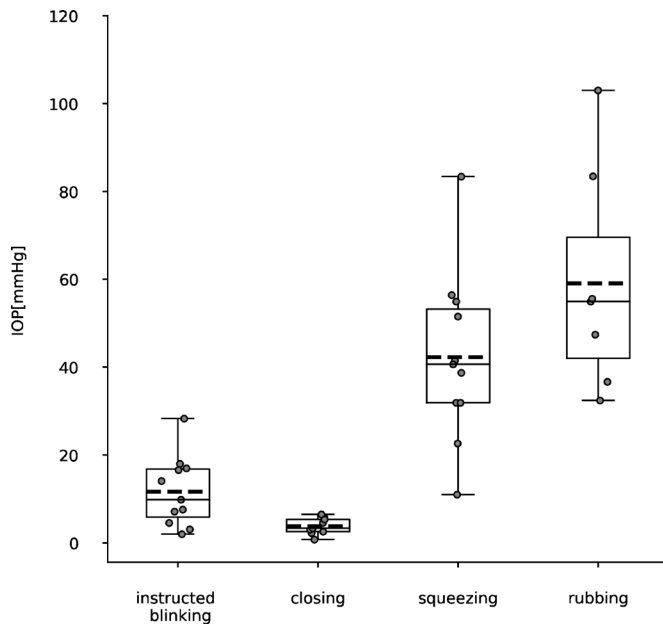


Figure 2 Average peak intraocular pressure (IOP) for the tested eyelid manoeuvres. Eyelid manoeuvres are depicted on the x-axis, IOP values (mm Hg) on the y-axis. Box plots indicate the median (line) and the mean (interrupted line) of the average Δ -peak IOP values over test participants (instructed eyelid blinking: n=11, eyelid closure: n=9, eyelid squeezing: n=11, eyelid rubbing: n=7), lower and upper quartile values (box) and data range (whiskers). Individual data points are also indicated in the figure (grey dots). Peak IOP values were compared with a preceding 5 s baseline period. Although generally higher IOP values were observed throughout the time course in all conditions, IOP tended to drop during eyelid closure directly after the initial IOP peak related to the act of closing the eyelids (see figure 1), which entered the analysis of the present figure. All conditions were significantly different from a baseline of zero (eyelid closure: $p < 0.01$, all other conditions: $p < 0.001$, Bonferroni-Holm corrected, see 'Results' section).

IOP values reported by Miller *et al.* Using a scleral contact lens/balloon combination, they indirectly estimated an average IOP increase of 54 mm Hg in 10 healthy volunteers.¹⁹ Coleman and Trockel⁶ reported increases of 90 mm Hg during eyelid squeezing in a single young patient during intracameral measurements prior to enucleation of the eye. While they took great care to avoid measurement artefacts due to movement of the cannula probing the eye, the difference in method as well as the nature of the eye disease and the youth of the patient may account for the larger IOP difference in their experiment.

Eyelid closure

Coleman and Trockel⁶ reported increases around 6 mm Hg during eyelid closure. We have observed before, however, that careful eyelid closure initially increases IOP on shutting the eyes, followed by a more prolonged IOP decrease, which can occur after a few seconds.¹⁵ We believe that the initial peak in IOP is due to the deliberate and thus potentially slightly 'forceful' eyelid closure, while the sustained decrease in IOP below baseline occurs on subsequent relaxation of the eyelid muscles (see also van den Bosch *et al.*¹⁵). The difference in IOP readings during deliberate and involuntary blinking seems to support this notion, as we only see IOP increases during the former, but not the latter. We further suspect that the sustained decrease in IOP on eyelid is due to a relief in pressure on top of the eye globe

caused by the retracted position of the upper eyelid during open eyes. This remains speculative, however, until more detailed MRI-based anatomical studies can be performed that estimate volume, pressure and rigidity of the eyelids in different positions and include volume and turgor of the orbital tissues as well as changes in the position of the eye globe during eyelid movements. In our study presented here, we instructed patients to carefully close their eyes and keep them closed without force to most closely mimic closed eyes during sleep and distinguish eyelid closure from squeezing.

Eyelid blinking

Although we could sometimes observe an interruption in the ocular pulse pattern within the IOP trace during the video recorded involuntary blinks, we did not find statistically significant or biologically meaningful IOP differences during involuntary blinks. This is in contrast to Gisler *et al.*,¹⁴ who observed distinct readout spikes during involuntary blinks and even used these to determine the circadian blink rate in over 200 patients. Their contact lens sensor, however, is placed on the cornea and may therefore be prone to mechanical deformation directly by eyelid movement and thus potentially cause an increased readout value without corresponding increase in IOP.^{14 20}

Conversely, the relatively low sampling rate of 9.2 Hz of the intraocular sensor in our study cannot fully capture IOP fluctuations on a millisecond scale. The sensor also does not measure fully continuously, but rather integrates the pressure signal for only 20 ms every 100 ms, thus potentially missing a substantial part of any pressure fluctuations on very short time scales. Thus, we were likely limited in involuntary blink detection by the relatively low temporal resolution of the measuring device. This notion is supported by the results of Turner *et al.*, who found IOP spikes due to blinking of 2–11 mm Hg in three rhesus macaques.¹⁰ Their measurement device works at a sampling rate of 500 Hz and therefore is far more likely to capture even extremely brief eyelid motions and blinks. Similarly, Miller,¹⁹ who used an analogue setup for truly continuous measurements, found average peak IOPs of 7 mm Hg for light-stimulated blinks and 11 mm Hg for touch-stimulated and sound-stimulated blinks. Flower *et al.*¹¹ reported about 5 mm Hg increase in a single rhesus macaque case study. Lastly, another possibility why the present study did not register IOP spikes during involuntary blinks may be due to viscoelastic damping of the IOP transient by the implant coating.

Deliberate voluntary blinking in contrast did induce IOP increases in the present study at values (12 mm Hg) comparable to the case studies by Coleman and Trockel (5–10 mm Hg) and by Miller (13 mm Hg).^{6 19} The voluntary blinks in the present study might have been performed with slightly more force than in Coleman and Trockel to explain our slightly higher observed IOP increases.

Implications

In the present study, we observed brief, but substantial increases during eyelid squeezing and rubbing. It is currently unknown, however, whether these IOP changes are clinically relevant. Eyelid rubbing-induced glaucoma has been suggested before.^{21 22} Also, one study observed that a group of healthy participants who performed eyelid squeezing had lower IOP shortly after the manoeuvre compared with a group of normotensive volunteers with a positive glaucoma family history. The difference was even greater compared with a group of ocular hypertensives, and a group of patients with glaucoma, respectively.²³ Transient IOP

fluctuations have only been correlated with visual field progression of glaucoma using the Triggerfish contact lens sensor. As it is assumed that the transient volume changes measured by the contact lens sensor are related to IOP, De Moraes *et al* was able to model the effect of specific components of transient IOP fluctuations on visual field progression in patients with POAG. Interestingly, the more prominent fluctuation peaks while patients were awake, were associated with faster visual field progression in patients with POAG.²⁴ Hence, it might be of importance to advise patients with glaucoma to avoid eyelid squeezing and rubbing. In addition, patients with glaucoma with itchy eyes (ie, allergies, dry eyes) might have a greater risk to progress. Of note, 52.6% of 20 506 patients with glaucoma in Germany suffered from dry eyes, most likely from the chronic use of topical glaucoma medication.²⁵ Both a greater number of glaucoma medications and longer duration of glaucoma disease increased the reported prevalence of dry eyes in the glaucoma group. In addition, significantly more local symptoms (mainly foreign body sensation and red eyes) were reported in patients with glaucoma with dry eyes compared with patients with glaucoma without dry eyes (11–12 times more frequent). We infer that patients with glaucoma with dry eyes might squeeze or rub more often, consequently causing more frequent IOP increases.

Limitations

A major limitation to our study is due to the low number of participants with the telemetric IOP sensor Eyemate-IO, the small but heterogeneous patient group on various different treatment regimens. Future studies should include other, larger patient groups and ideally healthy volunteers.

Furthermore, the applied force of eyelid manoeuvres remains problematic to standardise. An MRI study that investigates the amount of tissue mass and the shape of the eyeball during the manoeuvres may provide more insight in how the applied eyelid force relates to mechanical stress and IOP variations.

Of note, as almost half of our patient group used prostaglandin analogues on a daily basis, some may suffer from prostaglandin-associated periorbitopathy (PAP), a condition that includes sulcus deepening, eyelid tightening and periorbital fat loss.^{26–28} Individual prostaglandin analogue usage is provided in online supplemental table 2. PAP appears to be a common finding in patients with glaucoma.²⁸ The associated tight eyelids may elevate IOP, as one study suggested that a ‘tight eyelid syndrome’ may lead to high IOP and progressive visual field loss despite maximal treatment.²⁹ Unfortunately, we did not assess PAP in the present study, nor the possible effects of PAP on IOP in a systematic fashion, as there is currently no generally accepted method of quantifying the condition. Retrospectively, two of the patients on prostaglandin analogues showed clear sulcus deepening (patients 1 and 8). Patient 1 showed very moderate IOP increases during the eyelid experiments, but showed greater IOP excursions during gaze experiments in a previous study.¹⁵ Patient 8 showed high peak IOP values during the present experiments. More research is needed to elucidate the effect of PAP on IOP.

In addition, it is possible that mechanical aspects and position of the Eyemate in the eye may have affected the IOP measurements during eyelid manoeuvres as presented. While no dislocation or malpositioning of the sensor was noted during the study, eyelid squeezing and rubbing could have briefly altered the position of the Eyemate with possible additional mechanical effect on the anterior chamber angle and the trabecular meshwork. More studies are needed to elucidate whether and how the implant could affect aqueous outflow during eyelid manoeuvres.

In conclusion, while both eyelid rubbing and squeezing elicited IOP increases above 40 mm Hg, voluntary blinking elicited increases of 12 mm Hg and eyelid closure a brief increase by 4 mm Hg, followed by a sustained decrease. More research is needed to study whether the IOP increases during squeezing and rubbing are contributing to glaucomatous damage.

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Contributors LC and JJONvdB accept full responsibility for the work, the conduct of the study, have access to the data and controlled the decision to publish. Please see Declarations in the manuscript for more details on author’s contributions.

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Patient consent for publication Not applicable.

Ethics approval This study was approved by Ethics Committee of the Otto von Guericke University at the Medical Faculty and at the University Clinic Magdeburg (reference number: 209/17). The study protocol adhered to the tenets of Declaration of Helsinki. Patients provided written informed consent after a detailed explanation of the study prior to participation.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. Within the limits of privacy issues of clinical data, the data of the present study will be made available on reasonable request.

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REFERENCES

- Heijl A, Leske MC, Bengtsson B, *et al*. Reduction of intraocular pressure and glaucoma progression: results from the early manifest glaucoma trial. *Arch Ophthalmol* 2002;120:1268–79.
- European Glaucoma Society. *Terminology and guidelines for glaucoma*. 4th edn, 2014. http://www.eugs.org/eng/EGS_guidelines4.asp
- Whitacre MM, Stein R. Sources of error with use of Goldmann-type tonometers. *Surv Ophthalmol* 1993;38:1–30.
- Blumenthal M, Blumenthal R, Peritz E, *et al*. Seasonal variation in intraocular pressure. *Am J Ophthalmol* 1970;69:608–10.
- Liu JHK, Zhang X, Kripke DF, *et al*. Twenty-four-hour intraocular pressure pattern associated with early glaucomatous changes. *Invest Ophthalmol Vis Sci* 2003;44:1586–90.
- Coleman DJ, Trockel S. Direct-recorded intraocular pressure variations in a human subject. *Arch Ophthalmol* 1969;82:637–40.
- Johnstone M, Martin E, Jamil A. Pulsatile flow into the aqueous veins: manifestations in normal and glaucomatous eyes. *Exp Eye Res* 2011;92:318–27.
- Jamal KN, Gürses-Ozden R, Liebmann JM, *et al*. Attempted eyelid closure affects intraocular pressure measurement in open-angle glaucoma patients. *Am J Ophthalmol* 2002;134:186–9.
- Downs JC. IOP telemetry in the nonhuman primate. *Exp Eye Res* 2015;141:91–8.

- 10 Turner DC, Edmiston AM, Zohner YE, *et al.* Transient intraocular pressure fluctuations: source, magnitude, frequency, and associated mechanical energy. *Invest Ophthalmol Vis Sci* 2019;60:2572–82.
- 11 Flower RW, Maumenee AE, Michelson EA. Long-Term continuous monitoring of intraocular pressure in conscious primates. *Ophthalmic Res* 1982;14:98–106.
- 12 Turner DC, Girkin CA, Downs JC. The magnitude of intraocular pressure elevation associated with eye rubbing. *Ophthalmology* 2019;126:171–2.
- 13 Jasien JV, Turner DC, Girkin CA, *et al.* Cyclic pattern of intraocular pressure (IOP) and transient IOP fluctuations in nonhuman primates measured with continuous wireless telemetry. *Curr Eye Res* 2019;44:1244–52.
- 14 Gislser C, Ridi A, Hennebert J, *et al.* Automated detection and quantification of circadian eye blinks using a contact lens sensor. *Transl Vis Sci Technol* 2015;4:4.
- 15 van den Bosch JJON, Pennisi V, Invernizzi A, *et al.* Implanted microsensor continuous IOP telemetry suggests gaze and eyelid closure effects on IOP-A preliminary study. *Invest Ophthalmol Vis Sci* 2021;62:8.
- 16 Choritz L, Mansouri K, van den Bosch J, *et al.* Telemetric measurement of intraocular pressure via an implantable pressure Sensor-12-Month results from the ARGOS-02 trial. *Am J Ophthalmol* 2020;209:187–96.
- 17 Al-Nosairy KO, van den Bosch JJ, Pennisi V. Interaction of intraocular pressure and ganglion cell function in open angle glaucoma. *Br J Ophthalmol* 2020:1–8.
- 18 Holm S. A simple sequentially Rejective multiple test procedure. *Scandinavian J Stats* 1979;6:65–70.
- 19 Miller D. Pressure of the lid on the eye. *Arch Ophthalmol* 1967;78:328–30.
- 20 Mansouri K, Shaarawy T. Continuous intraocular pressure monitoring with a wireless ocular telemetry sensor: initial clinical experience in patients with open angle glaucoma. *Br J Ophthalmol* 2011;95:627–9.
- 21 Osuagwu UL, Alanazi SA. Eye rubbing-induced changes in intraocular pressure and corneal thickness measured at five locations, in subjects with ocular allergy. *Int J Ophthalmol* 2015;8:81–8.
- 22 Pecora L, Sibony P, Fourman S. Eye-rubbing optic neuropathy. *Am J Ophthalmol* 2002;134:460–2.
- 23 Green K, Luxenberg MN. Consequences of eyelid squeezing on intraocular pressure. *Am J Ophthalmol* 1979;88:1072–7.
- 24 De Moraes CG, Mansouri K, Liebmann JM, *et al.* Association between 24-hour intraocular pressure monitored with contact lens sensor and visual field progression in older adults with glaucoma. *JAMA Ophthalmol* 2018;136:779–85.
- 25 Erb C, Gast U, Schremmer D. German register for glaucoma patients with dry eye. I. Basic outcome with respect to dry eye. *Graefes Arch Clin Exp Ophthalmol* 2008;246:1593–601.
- 26 Shah M, Lee G, Lefebvre DR, *et al.* A cross-sectional survey of the association between bilateral topical prostaglandin analogue use and ocular adnexal features. *PLoS One* 2013;8:e61638.
- 27 Procianny F, P L Lang M, J L Bocaccio F. Lower eyelid horizontal tightening in prostaglandin associated Periorbitopathy. *Ophthalmic Plast Reconstr Surg* 2021;37:S76–9.
- 28 Kucukcilioğlu M, Bayer A, Uysal Y, *et al.* Prostaglandin associated periorbitopathy in patients using bimatoprost, latanoprost and travoprost. *Clin Exp Ophthalmol* 2014;42:126–31.
- 29 Lee GA, Ritch R, Liang SY-W, *et al.* Tight orbit syndrome: a previously unrecognized cause of open-angle glaucoma. *Acta Ophthalmol* 2010;88:120–4.

Supplementary table 1: Biometrical data

Patient	Axis length (mm)	Anterior chamber depth (mm)
1	22.79	2.60
2	23.52	3.51
3	22.28	3.53
4	24.00	2.50
5	23.00	2.70
6	23.70	2.80
7	27.65	3.05
8	24.00	3.00
9	23.00	3.52
10	23.99	3.22
11	23.00	3.00

Axis length and anterior chamber depth expressed in millimetres in individual patients.

Supplementary table 2: individual prostaglandin analogue usage

Patient	Generic Name	Duration (Years)
1	timolol/travoprost	4.0
5	timolol/travoprost	4.3
8	bimatoprost	3.8
9	latanoprost	2.3
11	timolol/latanoprost	3.7

Minimum duration in years and specific generic name of PG analogues used by each participant taking prostaglandine analogues. We could acquire information on prostaglandine use up to 4.3 years before the start of the present follow-up study.