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

Jacqueline J O N van den Bosch,1,2 Vincenzo Pennisi,1 Kaweh Mansouri,3,4 Robert N Weinreb,5 Hagen Thieme,1 Michael B Hoffmann,1,6 Lars Choritz1

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 ∆ IOP increase (mean±SEM) was 59.1±9.6 mm Hg (p<0.001) from baseline. It was 42.2±5.8 mm Hg (p<0.0001) for eyelid squeezing, 3.8±0.6 mm Hg (n=9, p<0.01) for eyelid closure and 11.6±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.4,5

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.1 In addition, it is not possible to measure IOP conventionally with closed eyes, and eyelid movements are also likely to affect the readout.6 Hence, conventional methods 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
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 al15 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-Noary 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, keratocones, 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.

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<table>
<thead>
<tr>
<th>Table 1 Patient characteristics</th>
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<td>Characteristic</td>
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<td>Gender</td>
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<tr>
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<td>PSD (dB)</td>
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<td>CCT (µm)</td>
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<td>Glaucoma surgery†</td>
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<td></td>
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<td>Glaucoma medications‡</td>
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Normal distributed continuous 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 IO 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).
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 eyelids 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 not to 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.

### 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±SD) was 59.1±9.6 mm Hg (p<0.001, corrected as well as uncorrected). For eyelid squeezing, average peak Δ IOP was 42.2±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±0.6 mm Hg (p<0.001 and p<0.001 Bonferroni-Holm corrected), followed by the previously reported decrease in IOP. For instructed blinking, average peak Δ IOP (mean±SD) was 11.6±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., 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).
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. 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 ‘forced’ eyelid closure, while the sustained decrease in IOP below baseline occurs on subsequent relaxation of the eyelid muscles (see also van den Bosch et al15). 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 al21 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).6,15 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.5,12 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.

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 JIONvdB 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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Competing interests JIONvdB has been funded via Implantada as a beneficiary of the EGRET plus international training programme; KM and RW are consultants of Implantada.

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


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Supplementary table 1: Biometrical data

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<td>1</td>
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<tr>
<td>2</td>
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<td>11</td>
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Axis length and anterior chamber depth expressed in millimetres in individual patients.
**Supplementary table 2:** individual prostaglandin analogue usage

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<th>Patient</th>
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<td>5</td>
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<td>8</td>
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<td>9</td>
<td>latanoprost</td>
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</tr>
<tr>
<td>11</td>
<td>timolol/latanoprost</td>
<td>3.7</td>
</tr>
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</table>

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.