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Design and Development of a Noninvasive Ocular Pressure Estimator

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Abstract:	Significance: A snapshot intraocular pressure (IOP) is ineffective in identifying the IOP peak and fluctuation, especially during sleep. Since IOP variability play a significant role in the progression of glaucoma, monitoring the IOP, especially during sleep is essential to capture the dynamic nature of IOP. Purpose: We aimed to design an ocular pressure estimator (OPE) that can reliably and accurately measure the IOP non-invasively over closed eyelid condition. Methods: OPE works on the principle that the external pressure applied by raising the intraocular pressure of the eyeball is transmitted through a compressible septum to the pressure sensor, thus recording the IOP. A fluid-filled pouch with a pressure sensor was placed over a rubber glove mimicking the eyelid (septum), covering the cornea of enucleated goat eyeballs. A pressure-controlled setup was connected to a goat cadaver eye which was validated by a rebound tonometer. Cannulation of eyeballs through the lower limbus had the least difference from the control setup values documented using rebound tonometer, compared to cannulation through the optic nerve. Intraocular pressures ranging from 3–30 mmHg were induced and the outputs recorded using OPE were amplified and recorded for 10 minutes (n=10 eyes). We stratified the randomization of the number of times and the induced pressures. Results: The measurements recorded were found to be linear when measured against an intraocular pressure range of 3–30 mmHg. The device has excellent reliability (Intraclass correlation coefficient 0.998). The repeatability coefficient and coefficient of variations were 4.24 (3.60–4.87) and 8.61% (7.33–9.90), respectively. The overall mean difference ±SD between induced IOP and the OPE was 0.22±3.50 (95% confidence interval: -0.35, 0.79) mmHg across all IOP ranges. Conclusion: OPE offers a promising approach for reliably and accurately measuring IOP and its

	fluctuation non-invasively under condition mimicking closed eye.

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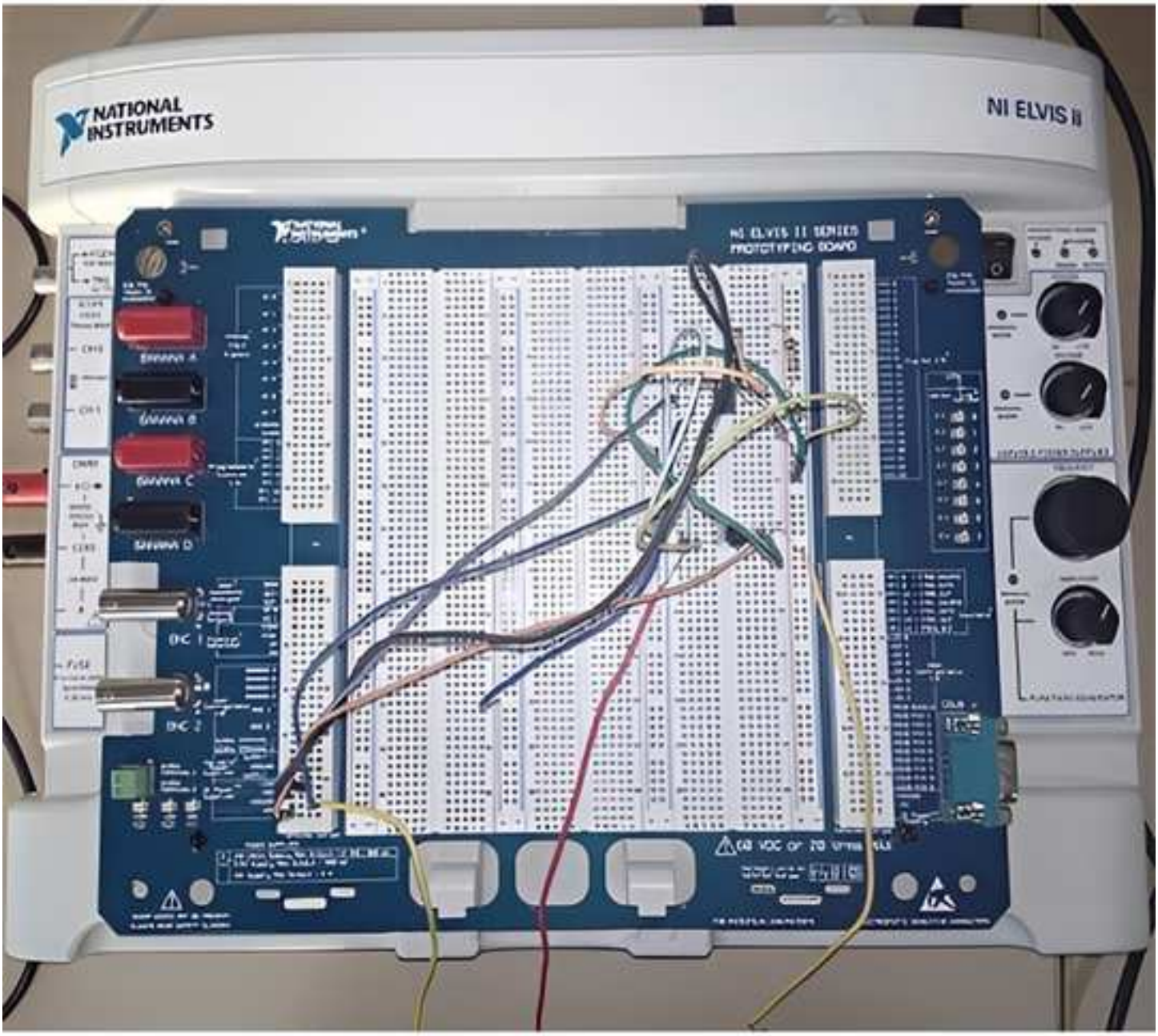

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Abstract

Significance:

A snapshot intraocular pressure (IOP) is ineffective in identifying the IOP peak and fluctuation, especially during sleep. Since IOP variability play a significant role in the progression of glaucoma, monitoring the IOP, especially during sleep is essential to capture the dynamic nature of IOP.

Purpose:

We aimed to design an ocular pressure estimator (OPE) that can reliably and accurately measure the IOP non-invasively over closed eyelid condition.

Methods:

OPE works on the principle that the external pressure applied by raising the intraocular pressure of the eyeball is transmitted through a compressible septum to the pressure sensor, thus recording the IOP. A fluid-filled pouch with a pressure sensor was placed over a rubber glove mimicking the eyelid (septum), covering the cornea of enucleated goat eyeballs. A pressure-controlled setup was connected to a goat cadaver eye which was validated by a rebound tonometer. Cannulation of eyeballs through the lower limbus had the least difference from the control setup values documented using rebound tonometer, compared to cannulation through the optic nerve. Intraocular pressures ranging from 3–30 mmHg was induced, and the outputs recorded using OPE were amplified and recorded for 10 minutes (n=10 eyes). We stratified the randomization of the number of times and the induced pressures.

Results:

The measurements recorded were found to be linear when measured against an intraocular pressure range of 3–30 mmHg. The device has excellent reliability (Intraclass correlation coefficient 0.998). The repeatability coefficient and coefficient of variations were 4.24 (3.60–4.87) and 8.61% (7.33–9.90), respectively. The overall mean difference ±SD between induced IOP and the OPE was 0.22 ± 3.50 (95% confidence interval: -0.35, 0.79) mmHg across all IOP ranges.

Conclusion:

OPE offers a promising approach for reliably and accurately measuring IOP and its fluctuation non-invasively under condition mimicking closed eye.

Introduction

Glaucoma is a progressive disease involving optic nerve head damage, retinal ganglion cell death, and corresponding visual field loss.[1] It is the second leading cause of blindness in the world, and intraocular pressure is the only modifiable risk factor.[1–6] However, intraocular pressure is a physiological parameter with cyclical diurnal variation and spontaneous changes throughout and across days.[7–9]

The current practice of measuring intraocular pressure using the Goldmann Applanation tonometry involves measuring a snapshot intraocular pressure, i.e., single visit office intraocular pressure which does not measure its peak or the fluctuation. Intraocular pressure is reported to be higher during the sleep period in both healthy and glaucoma eyes, especially in the supine position.[7,10–12] Moreover, Goldmann Applanation tonometry is performed in a sitting position, while circadian intraocular pressure measurement at night involves awakening and disrupting of the sleep cycle and circadian rhythm. Corneal biomechanical properties and operator bias also influence Goldmann Applanation tonometry. Even though the Perkins tonometer or TonoPen can be used in the supine position, it cannot be measured over closed eyelid condition during sleep, missing out on the crucial data of intraocular pressure during sleep.[5,13,14]

While the Sensimed triggerfish, a contact lens sensor based 24-hour intraocular pressure monitoring device is commercially available, it is limited by the lack of direct correlation between millivolt values and intraocular pressure in mmHg. Contact lens sensor can only describe the intraocular pressure rhythms, and do not quantify the absolute intraocular pressures.[5,15] Contact lens sensor is available only with three base curves, and the documented literature shows, a significant increase in corneal curvature irregularities, infection and corneal thickness with its

use.[5,16] Currently, contact lens sensor is the only device available for monitoring 24-hours intraocular pressure fluctuation.[5]

Post covid-19 pandemic, the regular glaucoma patient care practice has evolved from regular clinical visits for checking intraocular pressure and ocular examination every 3 to 6 months,[6] into a hybrid model of teleconsultation and traditional face to face encounters with patient.[17] This change might involve home-based monitoring of variability in intraocular pressure, to assist in better management of glaucoma. Thus, developing a simple cost-effective solution for accurate and repeatable home-based intraocular pressure measurement especially during sleep is vital.

Ocular pressure estimator was first designed to measure the intraocular pressure under condition mimicking closed eye, thus allowing its clinical application in measuring the intraocular pressure during sleep. Nevertheless, it is not commercially available and the custom design by Korenfeld et al,[18,19] is limited by the factors such as lack of repeatability testing and accuracy of the control setup.

This preliminary study in an ex vivo eye and eye lid model aim to design and develop an ocular pressure estimator that can repeatably and reliably estimate the intraocular pressure non-invasively over the eyelid.

Methodology:

The study was approved by the Institutional Animal Ethics Committee meeting, KMC Manipal, Manipal Academy of Higher Education (No. IAEC/KMC/20/2017). The ocular pressure estimator designed is a combination of a pressure transducer (sensor) connected to an amplifier and recorder. The hypothesis that underlies the mechanism of ocular pressure estimator is that the force of external compression will be conveyed to the transducer through a compressible septum.[18] This ocular pressure estimator was first validated using a calibrated control set up and

then the ocular pressure estimator recorded intraocular pressures against a range (3–30 mmHg) of induced intraocular pressures in freshly enucleated goat eyeballs.

Step 1: Ocular pressure estimator development phase:

First a fluid-filled pouch was constructed by heat-sealing two flexible but inelastic plastic sheets around a polyethylene tube, such that all heat-sealed junctions were watertight. The portion of the polyethylene tube that was fused with the plastic pouch was friction fit onto a pressure transducer (Honeywell, TBPDANS001PGUCV pressure sensor) that was pre-calibrated for a pressure range of 0 psi to 1 psi (51.71 mmHg). The transducer used in our model is stable with a lifespan of one million pressure cycle minutes with an accuracy of 0.25% full scale span at 25°C.[20] The pouch, which was directly connected to the transducer, allowed us to detect any changes in pressure inside the pouch accurately. The signal output produced by the pressure transducer was sent to a Data Acquisition System connected to a computer which was programmed using LabVIEW (LabVIEW 2017, National Instrumentation) to produce a linear amplification of the same. The LabVIEW records the intraocular pressure every second and displays the values with the graph after converting from millivolt in mmHg (described under the linearity of transducer below) using the slope-intercept formula (Figures. 1 and 2A).

Step 2: Control setup development and calibration phase:

The setup has 3 components: 1) a bottle of normal saline (Normal Saline, Infutec Healthcare Limited, India), 2) a calibrated tube beside the saline bottle with markings from 0 to 30 mmHg, and 3) a tube ending with a 23-gauge needle. All the three components were interconnected with the help of a three-way stopcock with high pressure hosing. The saline bottle and the calibrated tube formed a U-tube manometer and a tube with a needle was attached at the bottom of the U-tube; thus, the complete set-up looked like the alphabet “Y”. A continuous fluid column without

air bubbles was formed between the calibrated tube, the saline bottle, the stopcock, and the cannulated eye. Freshly enucleated Malabari goat eyes (experiments performed within 3 hours of enucleation) were obtained for experimentation. The needle was cannulated in the goat eye with a continuous fluid column emerging from the distal end. The intraocular pressure induced in the control set up was based on the principle that water pressure increases with an increase in column height. The pressure inside the eye can be varied by vertically moving the saline bottle up and down, and the corresponding pressure was read from the calibrated tube (Figure 2B). The eyeball was held in place by wet sponge (101 x 76 x 50 mm) inside a plastic mock orbit. The place of cannulation (limbus versus optic nerve) and the choice of eye (freshly enucleated versus preserved) was made based on the results of the first four (1–4) experiments with two eyes in each experiment that included 27 stratified random measurements per eye. Freshly enucleated eye, cannulated through the lower margin of limbus with needle in the anterior chamber (Experiment 3) had the lowest mean difference ± standard deviation (1.66 ± 1.95 mmHg) from the rebound tonometer value, over the other experiments on the choice of eye and cannulation (Details of experiment 1–4 in "Appendix.docx" file). Correspondingly, the test-retest variability was lowest for experiment 3 with the subject standard deviation: 1.82 (1.48, 2.17), repeatability coefficient: 5.05 (4.09, 6.01) and coefficient of variation: 11.10% (8.99, 13.21) compared to experiments 1, 2 and 4 (Appendix Table A1).

Calibration of the control set-up:

The needle (23-gauge) from the control setup cannulated the eye through the lower margin of the limbus, entering the anterior chamber and a continuous fluid column without air bubbles was formed between the control setup and the cannulated eye. The control setup was calibrated against a rebound tonometer (ICare Home). During the process of calibration, the freshly enucleated goat eyes were cannulated with the help of a needle at one end of the control set-up

through the lower margin of the limbus, entering the anterior chamber. The saline bottle was raised up and down to vary the pressure inside the eye from 3 to 30 mmHg and the pressure inside the goat eye was measured with the rebound tonometer and the iteration was done on the scale of the calibrated tube. A linear response was confirmed over the range of 3–30 mmHg.

Step 3: Linearity of the transducer output:

Next, the linearity of the output from the transducer was checked. Known air pressures (range 3–30 mmHg) were exerted into the transducer (3 sets of measurements, each set having 12 values selected randomly) with the help of a compressor connected with a manometer (PM-6205, HTC Instruments) and a regulator. The pressure from the compressor was controlled by the regulator connected to it. The output from the regulator (controlled air pressure) was measured with the help of the manometer connected in between the transducer and the regulator with the help of a "T-Connector". The corresponding signal output in the millivolt (unamplified) was taken with the help of (NI ELVIS 2 Series Prototyping board, Engineering Lab Workstation). Though the fluctuation was noted between the three sets of measurements while plotting them in the scatterplot, all three sets of measurements confirmed linearity in an increase in millivolt with an increase in air pressure (mm Hg) (Appendix Figure A2).

Step 4: Validation of ocular pressure estimator:

Ten enucleated goat eyes were used for the validation.[21] The fluid-filled pouch, the pressure transducer, and the cannulated eye, were all held at the same level (zero level). A freshly enucleated eye was placed within the mock orbit that consisted of a hydrated table sponge kept in a plastic container with holes carved out for the eye to avoid compressibility of the sponge over the eye, which was similar to the experiment set up described by Korenfeld et al.[18] The eye was then cannulated with the needle, thus forming a liquid continuum with aqueous. The cannulation

was performed while the fluid was running through it, therefore reducing the chance of tissue plugging the lumen and eliminating air bubbles in the line. The eye was positioned at the center of mock orbit in a way that the entire cornea is exposed above the surface of the hydrated sponge (Figure 2C).

The pouch (2 mm thick) was filled with distilled water without any air bubble. The pouch was placed over the cannulated eye in a way that the bottom surface facing the eye was in maximum contact with the cornea. Support for the pouch was given with the help of hanging height adjustable rooftop support attached to the mock orbit, which prevented the elevation of the pouch along with changes in corneal curvature, as the increase in pressure will increase the sagittal height of the cornea (Figure 3A). The support was in contact with the top surface of the pouch. The support also had a constant pressure over the pouch from the top and thereby assuring that the pouch did not move during the pressure change in the cannulated eye. The pressure being constant from one side (top surface) of the pouch, made it possible for measuring the variable pressure that was induced within the eye which got transmitted over to the pouch from the other side (bottom surface). A latex surgery glove of 1 mm thickness (Figure 3B) was placed in between the eye and the pouch to mimic the eyelid.[18]

To establish the baseline pouch pressure before starting the experiment, we positioned the pouch over the eye, covered with latex glove mimicking eyelid. While maintaining the induced intraocular pressure at 3 mmHg inside the eye, pressure was gradually increased using a height-adjustable rooftop support placed over the pouch. The support was height adjustable and allowed precise control over the pressure applied on the pouch. By gradually lowering the support using a screw mechanism, we aimed to reach a state of equilibrium between the pressure inside the eye and the pressure exerted by the rooftop support. Throughout this process, we closely monitored the output from the pressure transducer. The baseline pressure was determined when

the transducer consistently displayed a stable reading with minimal fluctuations. The baseline pressure was determined when the pressure on both sides of the pouch (intraocular pressure and the pressure exerted by the rooftop support) was equal and the transducer exhibited a consistent and stable reading with minimal fluctuations. Once the baseline pressure was established, we fixed the position of the rooftop support, ensuring a consistent zero-level reference point for the setup and the eye throughout the experiment.

The saline bottle in the control setup was raised above the zero levels at different heights. A linear response was confirmed with visual inspection over the range of 3–30 mmHg from the graph displayed on the computer. The corresponding output values were taken from the prototype. Following experiments 1–4 described above, the validation of ocular pressure estimator was carried out with two further experiments as mentioned below.

Experiment 5 (n=4): Considering that the output of the transducer is linear, a minimum pressure of 3 mmHg and a maximum pressure of 30 mmHg were induced in the first eye in this experiment, and corresponding output (in millivolt) was recorded. The induced versus resultant output slope was calculated using the slope-intercept formula in the LabVIEW. The resultant slope obtained for the first eye was used for the subsequent eyes before inducing the desired intraocular pressure for validation. During the validation process, pressure values were randomly generated between 3–30 mmHg and number of times induced were 3 (×2), 5 (×4), 7 (×8), 10 (×4), 12 (×6), 14 (×4), 15 (×4), 18 (×2), 19 (×2), 20 (×8), 24 (×4), 25 (×2), 29 (×2), 30 (×6). The corresponding measurements of pressure using the ocular pressure estimator were noted. As the constant pressure of the support over the pouch was not measurable, the next experiment 6 was performed.

Experiment 6 (n=6): The minimum and the maximum output were recorded in each cannulated eye in this experiment, and the resultant slope was obtained for each eye (instead of a common

slope from the first eye for all the following eyes in experiment 5) and entered in LabVIEW before inducing the desirable values of the intraocular pressure for validation. The pressure values were randomly generated between 3–30 mmHg and number of times induced were as follows: 5 (×4), 10 (×8), 12 (×8), 14 (×6), 15 (×8), 16 (×4), 17 (×4), 18 (×8), 20 (×6), 23 (×6), 24 (×6), 25 (×10), 30 (×8) with corresponding measurements recorded from the ocular pressure estimator .

To check for repeatability, the same set of measurements was repeated twice for experiments 5 and 6 (6 to 8 sets of measurements in each eye). The pressure values and the number of times each value induced, were decided with stratified randomization generated in Microsoft excel. In both experiments 5 and 6, the average of all the intraocular pressure measured by the ocular pressure estimator over 10 minutes were taken into consideration for analysis.

Statistical Analysis:

Statistical analysis was performed using Stata, version 14.0 (StataCorp). Agreement between the induced intraocular pressure and the measured intraocular pressure (by rebound tonometer and ocular pressure estimator) were evaluated using the exact method of two-sided tolerance factors by Carkeet,[22] which a modification of the plots originally described by Bland and Altman.[23] We used the instruction and spreadsheet provided by Carkeet.[24] Bland-Altman plots with the confidence limits provides a clear visual representation of the likely errors in the limits of agreement, especially when errors are large compared with the limits of agreement. Lin's Concordance Correlation Coefficient[25] was estimated between the induced intraocular pressure with the control set-up and the measured intraocular pressure (with rebound tonometer and ocular pressure estimator). Pearson's correlation coefficient was estimated between the pressure given to the transducer by the compressor (mmHg) and the output of the transducer (millivolt). Descriptive statistics were used to report the mean differences with standard deviation, between

the induced intraocular pressure and the measured intraocular pressure. Test-retest repeatability was computed with the within subject standard deviation, repeatability coefficient, and coefficient of variation.[26] The intraclass correlation coefficient was calculated and interpreted as follows: less than 0.75 represents poor to moderate reliability; 0.75 to 0.90 represents good reliability; greater than 0.90 represents excellent reliability. The confidence interval was set to 95% in all the analyses. A *P* value less than .05 was considered statistically significant.

Result

Linearity of the transducer:

Pearson's correlation coefficient between the induced and recorded intraocular pressures were 0.990, 0.983, and 0.942 for the first, second and third sets of measurements respectively, which were used to validate the ocular pressure estimator output (Appendix Figure A2).

Validation of ocular pressure estimator

The intraclass correlation coefficient of the device with experiment 5 (n=4 eyes), experiment 6 (n=6 eyes), and their combination were 0.998, 0.998, and 0.997, respectively (Table 1). Even though the mean differences between experiment 5 and 6 were comparable (-0.90 mmHg versus 0.97 mmHg), the standard deviation in experiment 5 was much higher compared to those in experiment 6 (4.79 mmHg versus 1.94 mmHg). The combined mean difference for experiments 5 and 6 was 0.22 ± 3.50 (95% confidence interval: -0.35, 0.79) mmHg (Tables 1 and 2).

Table 2 shows the mean differences between different ranges of induced intraocular pressure and the intraocular pressure measured from experiments 5, 6 and their combination. The mean difference for the entire range of intraocular pressure (3–30 mm Hg) was 0.22 mmHg (95% confidence interval: -0.35, 0.79). The mean differences were similar under low, normal, and high

intraocular pressure ranges (-1.07 to 1.65 mmHg), without any statistically significant difference between the groups. The test-retest variability was lower for experiment 6 with the within subject standard deviation, repeatability coefficient, and coefficient of variation of 1.53 (95% confidence interval: 1.30, 1.76), 4.24 (95% confidence interval: 3.60, 4.87) and 8.61% (95% confidence interval: 7.33, 9.90), respectively. However, experiment 5 and the combination had higher test-retest variability (Table 2).

Figure 4 shows the agreement between the induced and the measured intraocular pressure by ocular pressure estimator using Bland-Altman plot. The plots representing experiment 6 (Figure 4 C-D) shows lower variability compared to the others (Figures 4 A-D). The outer bands in the Bland-Altman plots represent a range or interval where we can be 97.5% confident that a minimum of 95% of the population is included. The inner bands indicate a range where there is a 2.5% confidence that a minimum of 95% of the population is included.[22,24] Lin's Concordance Correlation Coefficient was 0.863 and 0.847 for the first and the second set of measurements in experiment 5. Whereas in experiment 6, it is 0.946 and 0.943 with the first and the second set of measures, respectively and the overall Lin's Concordance Correlation Coefficient with the results of experiments 5 and 6 combined was 0.897 and 0.886 for the first and the second set of measurements respectively.

Discussion

The ocular pressure estimator described by us can be used to estimate intraocular pressure by measuring the external ocular compression from the eyeball into the pressure sensor transducer.[18,19] The intention of this study was to design and develop an ocular pressure estimator which can be potentially used to non-invasively measure the intraocular pressure and its fluctuation during sleep, over the eyelid without waking the patient up. Korenfeld et al.[18,19]

devised the ocular pressure estimator to primarily measure the intraocular pressure during procedures like digital ocular massage, using a fluid-filled pouch interposed between the mock eyelid and the finger. In our study, we adopted a similar principle of investigating intraocular pressure variations transferred to the pouch. However, our methodology differed as we apply minimal pressure (constant) to the pouch without any visible compression of the eye. This approach allows us to assess pressure dynamics within the eye under non-compressive conditions. It is worth noting that the pressure sensor used by Korenfeld et al.[18,19] had a wide-pressure range, with clinical testing showing a mean pressure of 104 ± 8 mmHg during digital ocular massage and no measurement of pressure below 15 mmHg. Normal intraocular pressure range among healthy individuals is 10–21 mm Hg, with a mean of 14.6 ± 3.1 mm Hg.[27] However, peak intraocular pressure can go much higher, around 30–35 mm Hg in case of high-tension glaucoma[28,29] and 25 mmHg during sleep.[7,8] Hence, we focused on measuring intraocular pressure within a pressure range, which was relatively lower, but more clinically relevant (3–30 mmHg). Additionally, the narrow sensitivity range (0 to 1 psi or approximately up to 51.71 mmHg) allows for greater sensitivity to variations in lower pressure levels. This might allow accurate exploration of this potential technique in capturing diurnal variations in intraocular pressure.

Validating ocular pressure estimator against the cannulated eye showed a good agreement in experiments 5 and 6, making the measurements by the ocular pressure estimator highly reliable in both the experiments ('excellent' intraclass correlation coefficient: 0.998; P<.001). Care was taken to ensure no leak in the pouch and at the place of cannulation on inducing the variable pressures ranging between 3 to 30 mmHg throughout the experiment. The reliability of the preparation was confirmed by checking the water level of the calibrated tube and the saline bottle, and also by checking the intraocular pressure pre- and post-experiment with the rebound

tonometer by placing the saline at 30 mmHg. The post-compression pressure measurement confirmed both the seal (no leak) and plugging of the lumen of the needle with the tissue.

Considering the lack of a tool to estimate the pressure given by the rooftop support on the fluid-filled pouch, which affected the intraocular pressure measured with the ocular pressure estimator, two experiments were conducted, one without taking the minimum and the maximum values (Experiment 5) and the second taking the maximum and the minimum values (Experiment 6).

To record the intraocular pressure fluctuation over time, we considered the average of all intraocular pressure values recorded for over 10 minutes. This approach allowed us to obtain a more correlated value with the least amount of time required. The correlation of the intraocular pressure was high after averaging the intraocular pressure over 10 minutes. Average time of 10 minutes was chosen considering multiple measurements to take and a delay in the time for experimenting enucleated eye ≤ 3 hours would render it unsuitable for the experiment due to the appearance of clouding and edematous changes in the cornea. Efforts were made to make sure that the pouch interposed in between had maximum contact with the eye and with the glove throughout the experiment, with the constant pressure given by the rooftop support.

The resultant intraocular pressure output slope obtained from the first eye was used to generalize the ocular response for the subsequent eyes. Probably, the variation in the results of experiment 5 was large because of the difference in the corneal physical and biomechanical properties in the following eyes, which influenced the measurement of intraocular pressure.[21] Subsequently, the intraocular pressure values derived through experiment 5 were less reliable with higher standard deviation and high test-retest variability (Tables 1-2, Figure 4 A-B). Whereas, in experiment 6, the correction slope was estimated for each eye individually by inducing the maximum, and minimum

value, so the results were more reliable with less variation (lower standard deviation and low test-retest variability, Figure 4 C-D, Table 2). Lower standard deviation and test-retest variability is indicative of better accuracy in IOP measurement. Clinically, the corneal biomechanical properties can be estimated using the instruments such as Corvis ST or Reichert 7CR ORA or Appl-OCE.[30–32] However, the correction factors derived for each eye require validation with the intraocular pressure.

The contact lens sensor showed high repeatability with a 95% confidence interval of ±0.2 mmHg in enucleated pig eyes.[21] In addition to the high expense and cost factor, the contact lens sensor has been reported to compress the eye, resulting in artificial elevation of the intraocular pressure, increase in corneal curvature irregularities, and infection.[5,16] Other limitation was base curve availability, which questions the good fit required for accurate working.[15] On inspecting the clinical accuracy of contact lens sensor in normal-tension glaucoma patients undergone selective laser trabeculoplasty, it was found to be have 4.6% variation from the Goldmann Applanation tonometry. The contact lens sensor curves had no significant change in the intraocular pressure for eyes under the Travoprost monotherapy (P=.27), even though the Goldmann Applanation tonometry showed a significant decrease P <.001).[33]

In an experimentally designed ocular pressure estimator, the error in pressure varied around 5% (based on graphical approximations) for a range of 15-100 mmHg.[18] Other limitations of the previous ocular pressure estimator are a lack of accuracy testing for the control set-up, non-evaluation of the repeatability of the measurements and the use of sensor with higher pressure range (implies reduced sensitivity to small changes) than the normal intraocular pressure. The test-retest variability of ocular pressure estimator measurements was low (repeatability coefficient and coefficient of variation of 4.24 and 8.61) with the overall mean difference between

the induced and the measured intraocular pressure of only 0.22 ± 3.50 (95% confidence interval: -0.35, 0.79) mmHg.

The ocular pressure estimator in this study could measure the intraocular pressure non-invasively over the gloves of thickness 1000 µm, which is similar to that of the average human eyelid 1127 ± 238 µm.[34] Since the disposable pouch from the device is solely placed over the eyelid, it is non-invasive, safe and will cause minimal discomfort to a patient during its use. Moreover, it will permit monitoring the intraocular pressure during sleep non-invasively over the eyelid without the need to exert any external pressure or open the eyelids, thus minimize disturbing the sleep cycle.

Covid-19 has significantly reduced regular clinic-based glaucoma care and replaced it with a mix of physical testing and teleconsultation.[17,35] The clinical development of an ocular pressure estimator device that can help in home-based intraocular pressure measurements is now warranted. The device shall have seamless connectivity to smartphone or internet of things platforms with value-added real-time intraocular pressure monitoring, cloud-based data sharing and tele-eye care modules to enhance home-based glaucoma care.

There are few limitations of the device. First of all, similar to most of instruments measuring intraocular pressure from the cornea, our ocular pressure estimator calibration depends on the corneal thickness and biomechanical properties of the cornea such as corneal stiffness.[21] We performed these experiments on goat eyes with an average corneal thickness of 616.9 ± 7.1 µm[36] which is relatively thicker than the average healthy human cornea with a range of 503–565 µm,[37] and those with glaucoma of 563 ± 29 µm.[38] The axial length (24.37 mm ± 1.16 mm), anterior chamber depth (3.28 mm ± 0.42 mm) and vitreous chamber (12.03 mm ± 0.83 mm) of the adult goat eye are similar to the human eye, the lens thickness (8.65 mm ± 0.61 mm) is nearly twice

that in humans.[39] Thus, ocular pressure estimator needs to be validated using clinical trials on human subjects. Utilizing a goat eye model in our current study, we primarily focused on establishing the feasibility of externally measuring the change in intraocular pressure over a mock eyelid. We developed this device with potential application in home monitoring/continuous measurement of IOP, so that we can observe the changes in IOP, while maintaining all physiological parameter constant across baseline and follow up. Nevertheless, we recognize the need for further exploration into the influence of the biomechanical properties and the anatomical variability of the physiological eyelid and cornea, for successful clinical application of the device. Secondly, some glaucomatous patients may exhibit significantly higher intraocular pressures beyond the range we investigated.[28,29] Considering this, we recognize the importance of exploring a wider measurement range in future studies, particularly to validate the applicability of our device for glaucoma models and scenarios involving higher intraocular pressures. Third, the instrument requires an additional set-up that provides a constant pressure over the pouch. This constant pressure might be difficult to achieve or might get affected with natural eye and head movements during sleep. Fourth, though we tried to mimic the eye lid with the latex gloves, it does not consider all the other layers of the eyelid which may vary in their compressibility.

In addition to physiological parameters, environmental factors can affect the repeatability of the ocular pressure estimator. Temperature plays a significant role, and the operational temperature range of our pressure transducer is -40° Celsius to 125° Celsius, with optimal accuracy between 0°Celsius and 85°Celsius. Maintaining a suitable temperature range is important for reliable measurements along with factors like humidity, vibration, and supply voltage to minimize interference and ensure accurate and repeatable measurements.[20]

Future directions

The objective of this study was to design an ocular pressure estimator and check its feasibility in measuring the fluctuation in intraocular pressure under conditions mimicking closed eye. Although the ocular pressure estimator designed in this study provided satisfactory level of agreement (high correlation coefficient and small mean difference) in IOP measurement variation over the scale of 3–30mmHg, the reproducibility was modest with a ±4 mm Hg range for any given IOP (Figure 4). Achieving a narrower range of IOP readings and enhancing the reproducibility of our measurements is important for its clinical use. Furthermore, the OPE can be adapted with wearable alternatives for prolonged use, such as an adjustable sleep mask-like setup worn over the OPE during sleep. This may help achieve equilibrium between the eye and the pouch by maintaining a constant pressure over the pouch, accommodating natural eye and head movements observed during sleep, further facilitating the natural measurement of IOP variation. This approach may ensure reliable and stable measurements during extended periods of sleep. Since, the study used latex glove as a substitute for eyelid, moving forward, testing the OPE through clinical trials exploring the influence of physiological parameters like the thickness and biomechanical properties of the cornea and eyelid (under closed and open conditions) are crucial.

Conclusion

While the design of the ocular pressure estimator described in this study provides reliable, repeatable, and moderately accurate IOP measurements under conditions mimicking close eye, it is vital to note that further exploration is necessary before any definitive conclusions can be made regarding its potential use in clinical settings. Despite the limitations of this study, OPE holds promise with the possibility to measure IOP during sleep.

Acknowledgement

Our heartfelt thanks to Mr Michael S Korenfeld, Department of Ophthalmology and Visual Sciences, Washington University for guiding us in designing the ocular pressure estimator ; Mr Rakesh Reddy S R, Mr Guru Charan M A, Mr Ratan Shenoy, students from the Department of Instrumentation and Control, Manipal Institute of Technology for their complete assistance in the prototype development and Mr Ramakrishnan who prepared pouches for the ocular pressure estimator and Manipal University Press for proofreading our manuscript for the English language.

Ethics approval: Animals used in this study were treated under the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research. The study was approved by the Institutional Animal Ethics Committee meeting, KMC Manipal, Manipal Academy of Higher Education (No. IAEC/KMC/20/2017).

Appendix

Appendix file: Appendix file provides information on the methods and results related to the choice of eye cannulation and calibration of the control set-up. Furthermore, the file includes the scatter plot graphs that confirm the linearity of the transducer. Together, these findings are significant as they validate the chosen cannulation method and demonstrate the accuracy and reliability of the control set-up and experimental procedures.

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Titles and legends to figures:

Figure 1 Block diagram of control setup and ocular pressure estimator.

Figure 2 Figure showing the (A) ocular pressure estimator, (B) control setup, (C) graphical representation of overall setup. Note: DAQ = Data Acquisition System, mV = millivolt

Figure 3 (A) Demonstration of the eye position and the support for the pouch placed over the cannulated eye in the mock orbit. (B) Latex gloves over the eye to mimic eyelid.

Figure 4 Bland-Altman with 95% confidence interval, (A) Induced intraocular pressure (IOP) and first set of measured IOP with ocular pressure estimator (OPE) – Results of experiment 5, (B) Induced IOP and second set of measured IOP with OPE – Results of experiment 5, (C) Induced IOP and first set of measured IOP with OPE – Results of experiment 6, (D) Induced IOP and second set of measured IOP with OPE – Results of experiment 6, (E) Induced IOP and first set of measured IOP with OPE – Results of experiments 5 & 6 together, (F) Induced IOP and second set of measured IOP with OPE – Results of experiments 5 & 6 together. Confidence intervals for limits of agreement calculated using the exact two-sided tolerance approach.[22,24]

Table

Table 1: Descriptive statistics of each eye used in the experiment 5 and 6 (Mean ±SD) with the intra-device difference for each eye and their reliability (intraclass correlation coefficient, ICC).

	Mean difference between IOP induced and first set of IOP measured with OPE mmHg: [1]	**Mean difference between IOP Induced and second set of IOP measured with OPE mmHg: [2]**	**Intra-device difference in mmHg: [1-2]**	**ICC**	
				95% confidence interval	***P* value**
	Experiment 5: -0.90 ±4.79 mmHg				
EYE 1	1.01 ±1.27	1.45 ±1.48	0.44 ±0.32	0.998 (0.996, 0.999)	<.001
EYE 2	3.83 ±1.63	4.22 ±1.82	0.40 ±1.35		
EYE 3	-7.01 ±2.14	-7.34 ±2.07	-0.32 ±0.47		
EYE 4	1.48 ±1.44	1.66 ±1.46	0.18 ±1.15		
	Experiment 6: 0.97 ±1.94 mmHg				
EYE 1	1.63 ±1.21	2.21 ±0.79	0.15 ±0.53	0.998 (0.996, 0.999)	<.001
EYE 2	-1.72 ± 1.91	-2.21 ±1.85	0.13 ± 2.49		
EYE 3	1.87 ±0.82	1.98 ±0.92	0.11 ±0.55		
EYE 4	1.87 ±0.82	1.98 ±0.92	0.11 ±0.55		
EYE 5	0.55 ±2.05	0.87 ±1.95	0.32 ±0.76		
EYE 6	1.01 ±1.27	1.45 ±1.48	0.44 ±0.32		
	Combining Experiments 5 and 6: 0.22 ±3.50 mmHg				
--	--	--	--	0.998 (0.997, 0.999)	<.001

ICC = Intraclass Correlation Coefficient, IOP = Intra Ocular Pressure, OPE = Ocular Pressure Estimator.

Table 2: Table showing the difference between the IOP induced by the control setup and the IOP measured by the OPE along with their repeatability indices from the results of the experiment 5, 6 and their combination for a different range of the IOP. The mean values are accompanied with their 95% confidence intervals

Mean difference and their 95% confidence intervals between IOP induced and the IOP measured for various ranges of IOP			
Range of IOP (mmHg)	**Mean difference between IOP induced and IOP measured by OPE in mmHg - in Experiment 5**	**Mean difference between IOP induced and IOP measured by OPE in mmHg - in Experiment 6**	**Mean difference between IOP induced and IOP measured by OPE in mmHg - in Experiments 5 & 6 combined**
3-12	-0.71 (-2.50, 1.09)	0.72 (0.05, 1.39)	0.01 (-1.32, 1.33)
13-21	-1.07 (-3.13, 0.99)	0.58 (-0.10, 1.27)	-0.03 (-1.26, 1.21)
22-30	-0.97 (-3.96, 2.03)	1.65 (0.95, 2.36)	0.78 (-2.01, 3.57)
Overall	-0.90 (-2.12, 0.33)	0.97 (0.56, 1.38)	0.22 (-0.35, 0.79)
Repeatability indices (Control setup versus OPE)			
	Sw	**RC**	**CVw (%)**
Experiment 5	3.42 (2.80, 4.04)	9.48 (7.75, 11.20)	20 (17.00, 24.57)
Experiment 6	1.53 (1.30, 1.76)	4.24 (3.60, 4.87)	8.61 (7.33, 9.90)
Experiment 5 & 6	2.47 (2.19, 2.76)	6.85 (6.06, 7.64)	14.35 (12.69, 16.00)

Sw = within subject standard deviation, RC = Repeatability Coefficient, CVw = Coefficient of Variation, IOP = Intra Ocular Pressure, OPE = Ocular Pressure Estimator.

Appendix Table A1: Table showing the repeatability indices with their 95% confidence intervals for experiments 1, 2, 3 and 4

	Sw	RC	CVw (%)
Control set-up versus rebound tonometer			
Experiment 1	10.39 (8.45, 12.34)	28.81 (23.42, 34.19)	41.93 (34.10, 49.77)
Experiment 2	12.80 (10.36,15.24)	35.48 (28.72, 42.23)	51.62 (41.80, 61.45)
Experiment 3	1.82 (1.48, 2.17)	5.05 (4.09, 6.01)	11.10 (8.99,13.21)
Experiment 4	6.17 (5.01, 7.32)	17.09 (13.90, 20.28)	45.79 (37.23, 54.35)

Sw = within subject standard deviation, RC = repeatability coefficient, CVw = coefficient of variation.

Figure 1

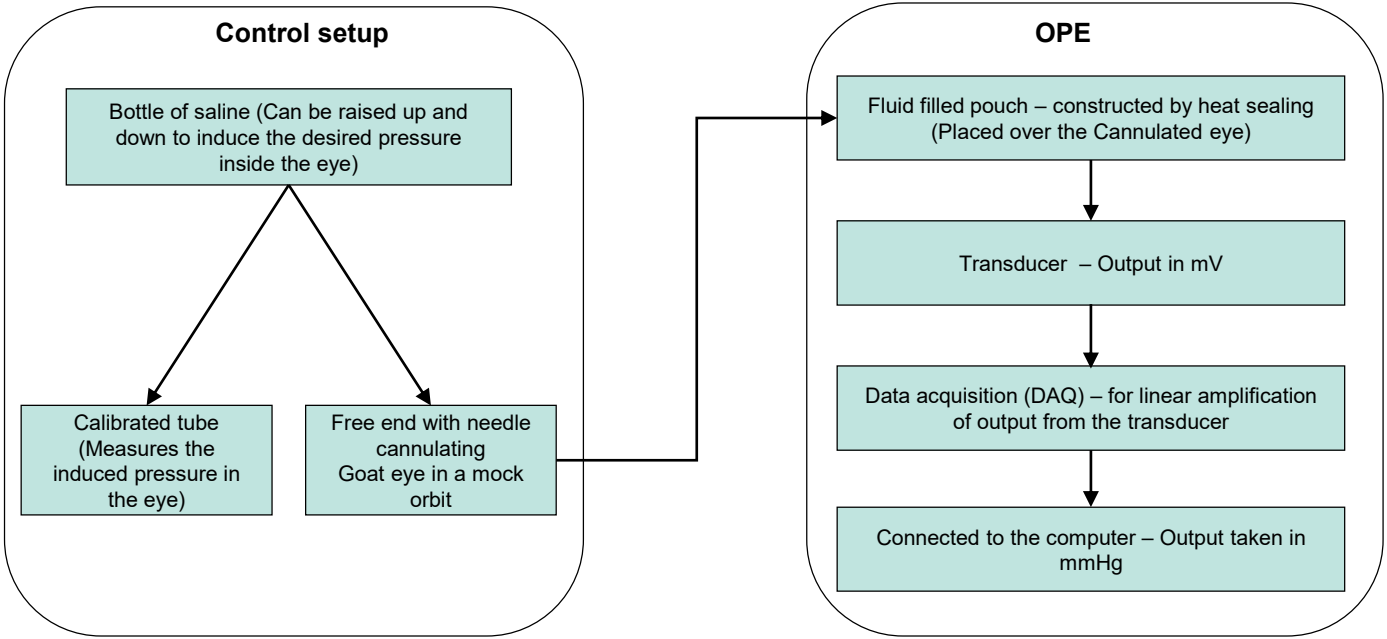
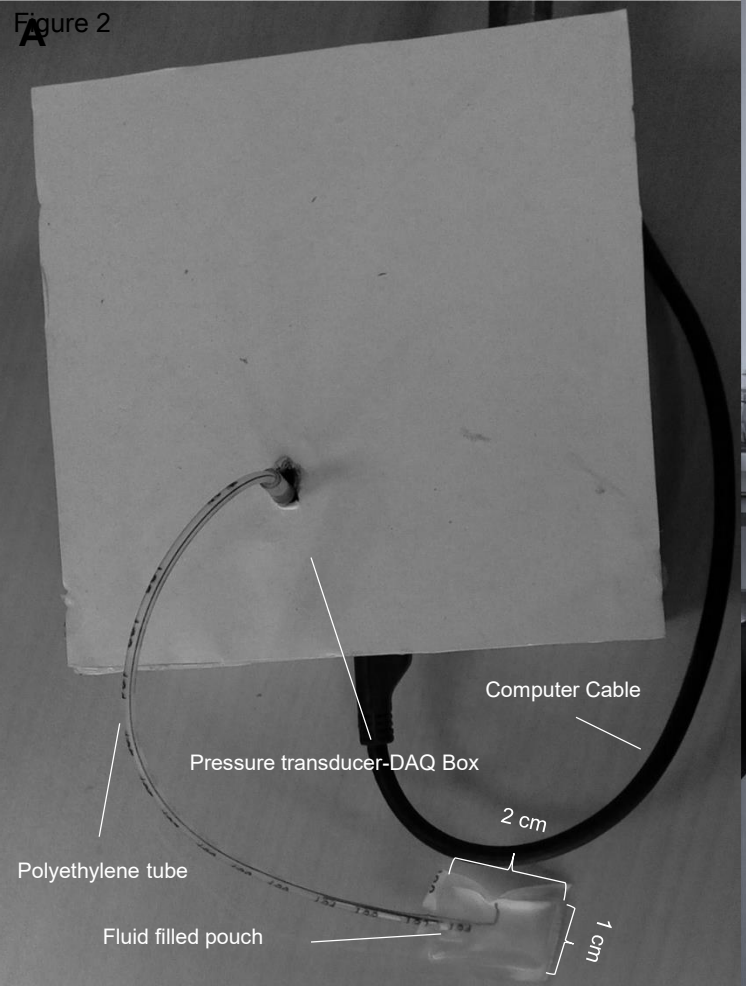
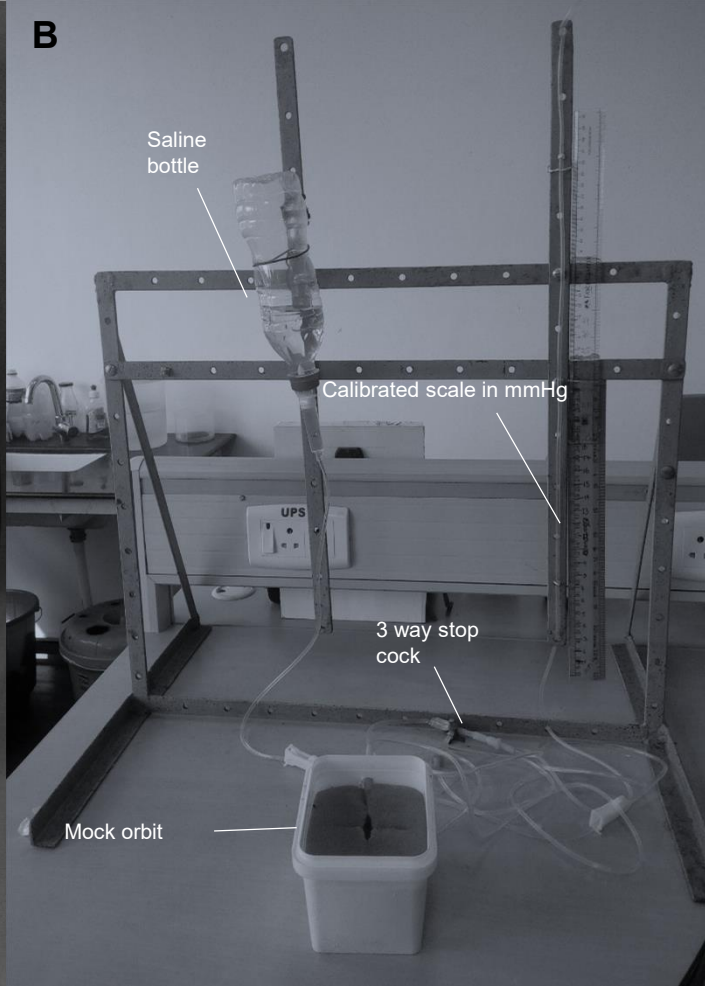

Control setup
Bottle of saline (Can be raised up and down to induce the desired pressure inside the eye)
Calibrated tube (Measures the induced pressure in the eye)
Free end with needle cannulating Goat eye in a mock orbit
OPE
Fluid filled pouch – constructed by heat sealing (Placed over the Cannulated eye)
Transducer – Output in mV
Data acquisition (DAQ) – for linear amplification of output from the transducer
Connected to the computer – Output taken in mmHg

Figure 2


A
Computer Cable
Pressure transducer-DAQ Box
2 cm
Polyethylene tube
Fluid filled pouch
1 cm


B
Saline bottle
Calibrated scale in mmHg
3 way stop cock
Mock orbit

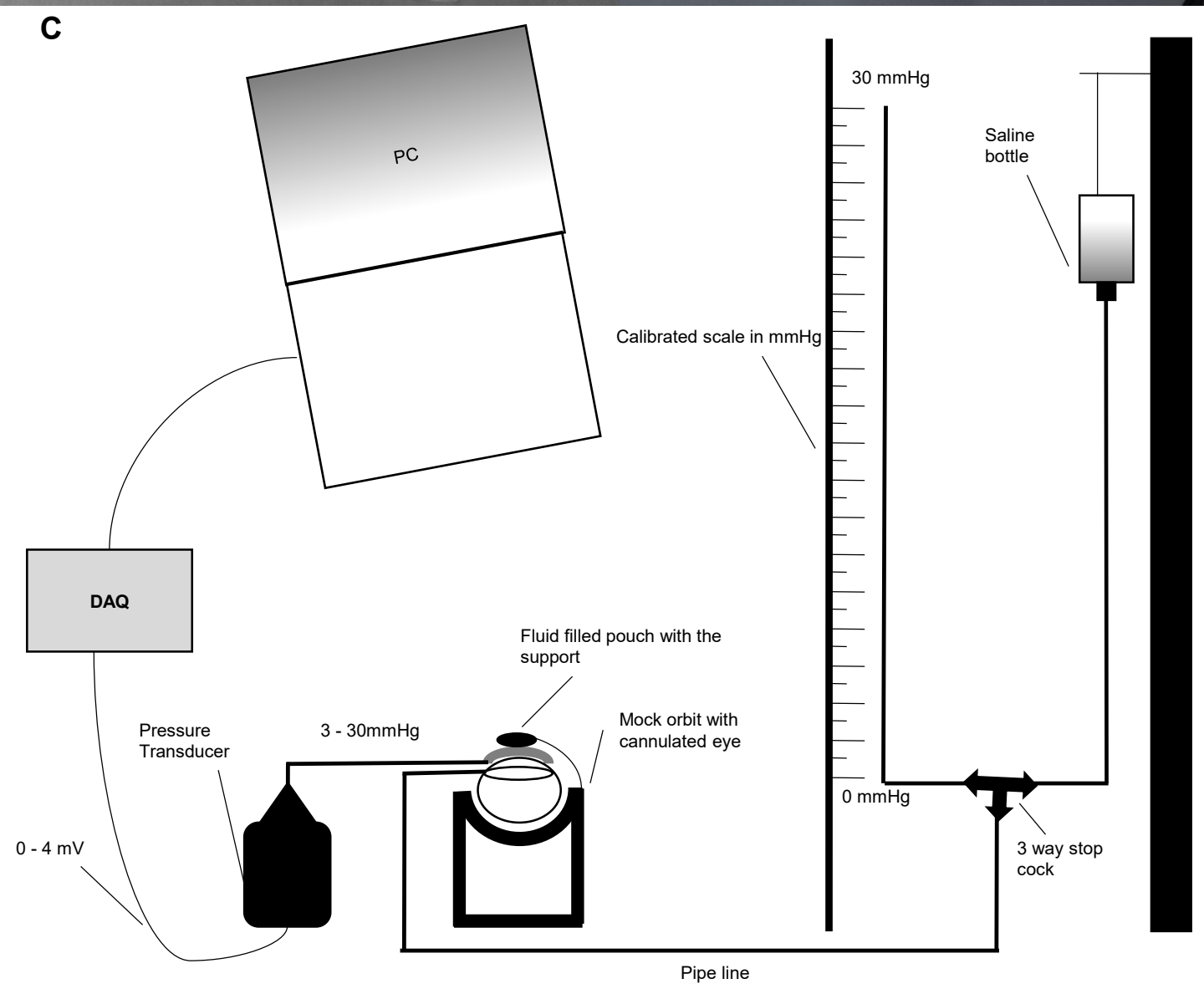

C
PC
DAQ
30 mmHg
Saline bottle
Calibrated scale in mmHg
Fluid filled pouch with the support
Mock orbit with cannulated eye
Pressure Transducer
3 - 30mmHg
0 - 4 mV
0 mmHg
3 way stop cock
Pipe line

Figure 3

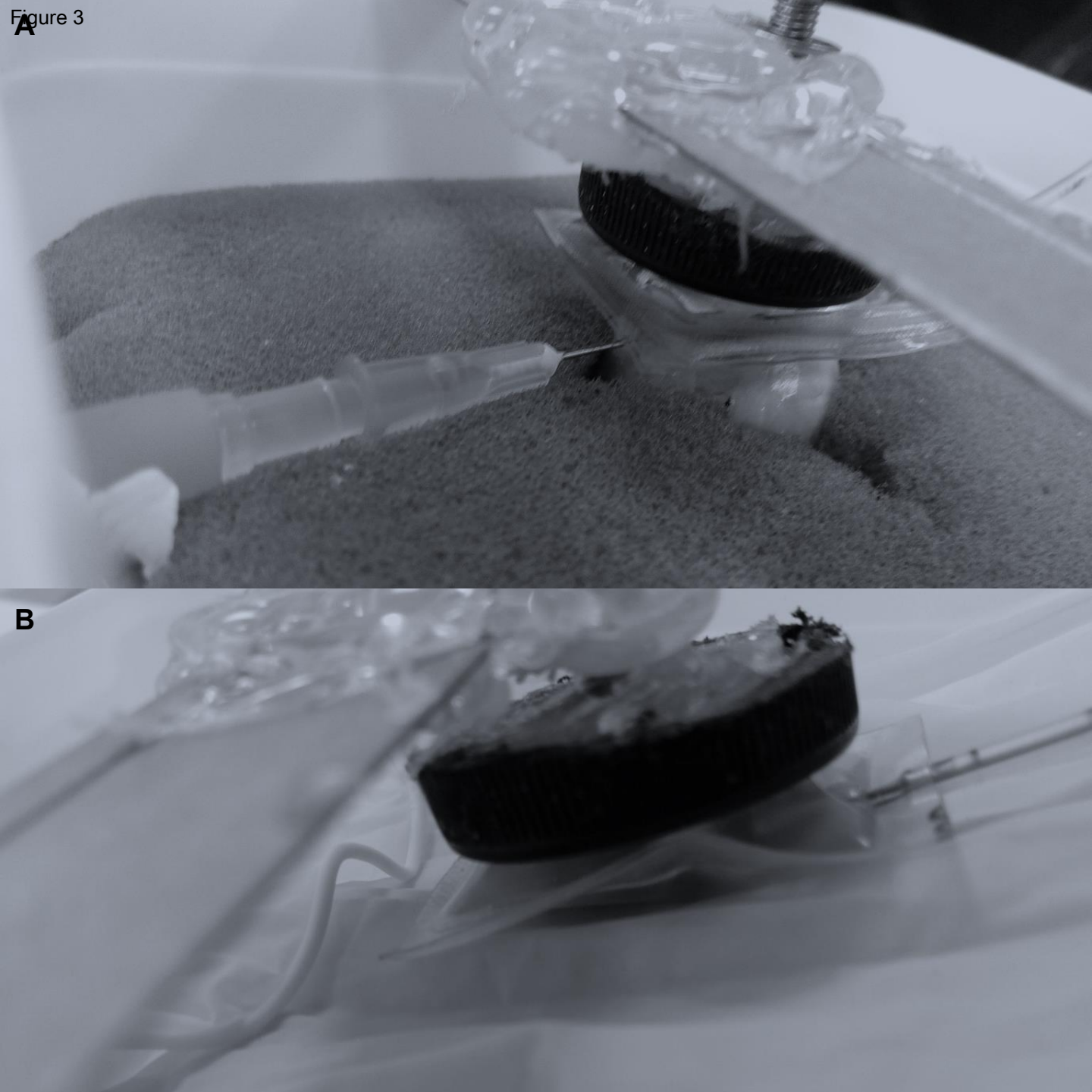
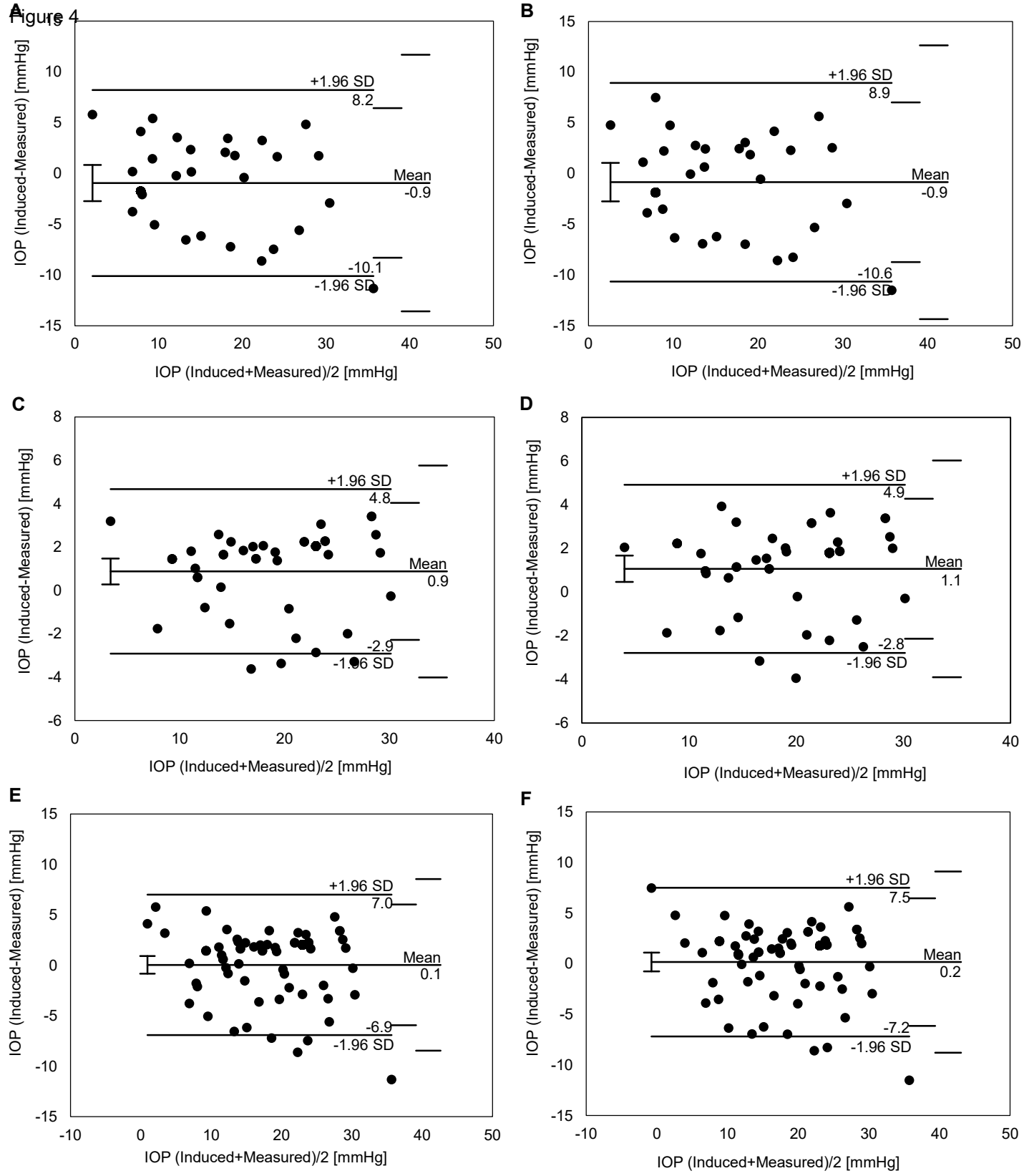
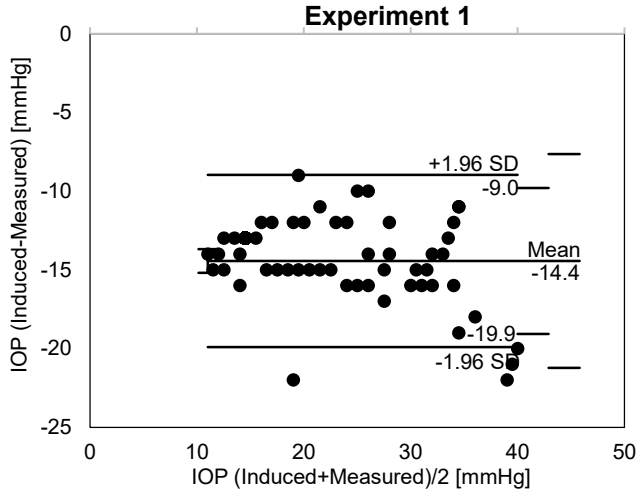
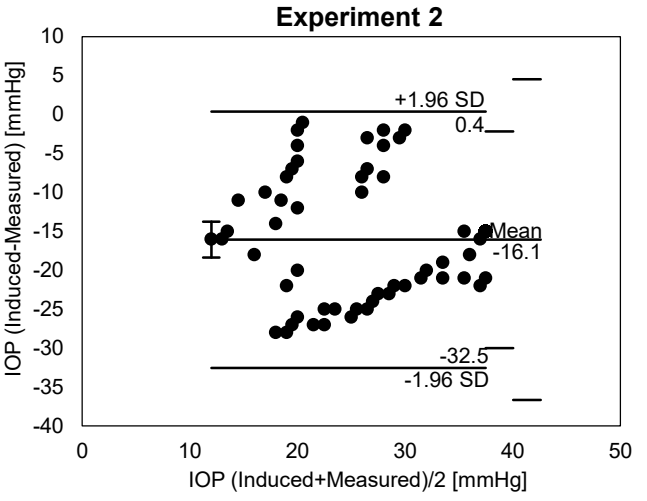


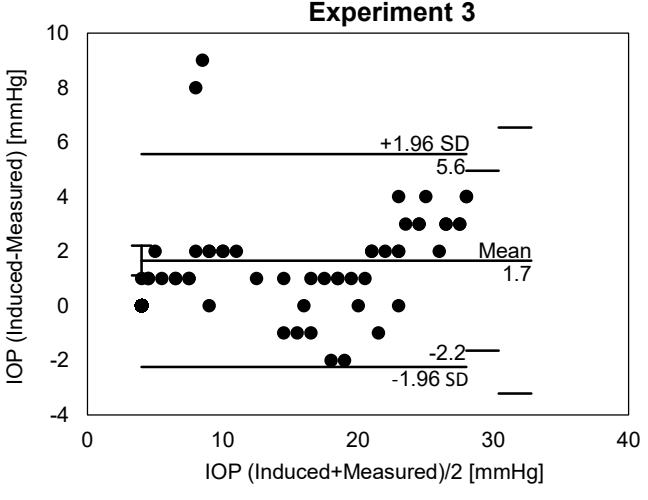
Figure 4

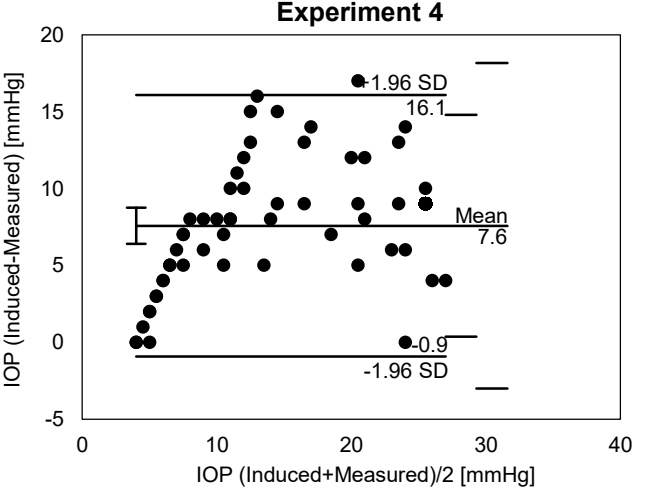

A
+1.96 SD
8.2
Mean
-0.9
-10.1
-1.96 SD
IOP (Induced-Measured) [mmHg]
IOP (Induced+Measured)/2 [mmHg]
B
+1.96 SD
8.9
Mean
-0.9
-10.6
-1.96 SD
IOP (Induced-Measured) [mmHg]
IOP (Induced+Measured)/2 [mmHg]
C
+1.96 SD
4.8
Mean
0.9
-2.9
-1.96 SD
IOP (Induced-Measured) [mmHg]
IOP (Induced+Measured)/2 [mmHg]
D
+1.96 SD
4.9
Mean
1.1
-2.8
-1.96 SD
IOP (Induced-Measured) [mmHg]
IOP (Induced+Measured)/2 [mmHg]
E
+1.96 SD
7.0
Mean
0.1
-6.9
-1.96 SD
IOP (Induced-Measured) [mmHg]
IOP (Induced+Measured)/2 [mmHg]
F
+1.96 SD
7.5
Mean
0.2
-7.2
-1.96 SD
IOP (Induced-Measured) [mmHg]
IOP (Induced+Measured)/2 [mmHg]

Appendix Figure A1

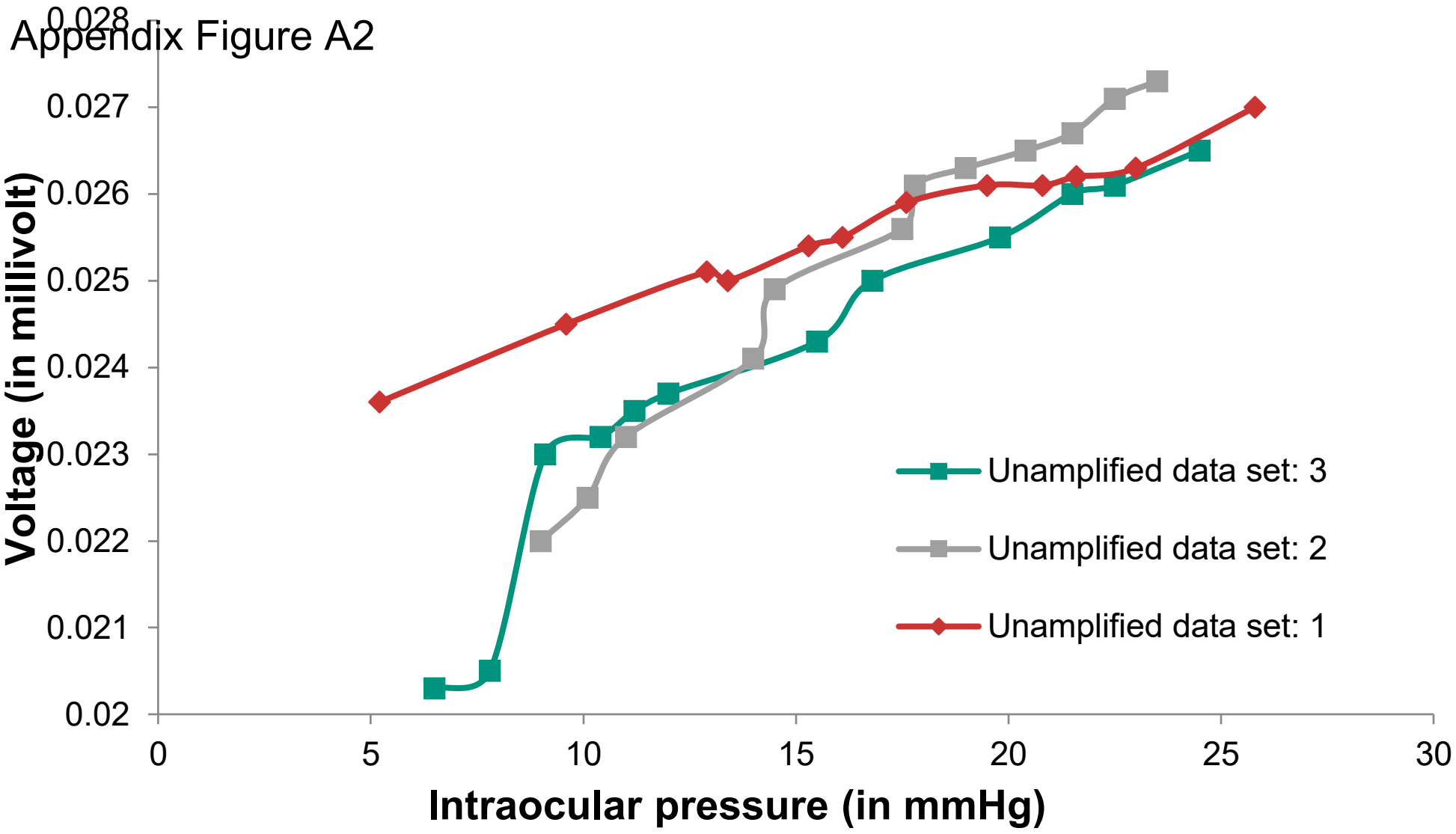








Appendix Figure A2



Appendix

Methods

Choice of eye and cannulation

In the calibration process, the decision to cannulate the fresh eye through the limbus was obtained from the results of the following experiments with two eyes in each experiment and 27 stratified random measurements in each eye.

Experiment 1: Enucleated goat eye was preserved in formalin for 8 hours and cannulated through the lower margin of the limbus into the anterior chamber with cannulating needle's bevel tip facing away from the lens. Adhesive was used to seal any leakage at the point of cannulation.

Experiment 2: Enucleated goat eye was preserved in formalin for 8 hours and cannulated through the optic nerve reaching the vitreous.

Experiment 3: Freshly enucleated goat eye was cannulated through the lower margin of the limbus, entering the anterior chamber with cannulating needle's bevel tip facing away from the lens. Adhesive was used to seal any leakage at the point of cannulation.

Experiment 4: Freshly enucleated goat eye was cannulated through the optic nerve reaching the vitreous.

In all four experiments, to the canulation procedure which was performed under microscope, the pressure was induced inside the cannulated eye with the control set-up and the pressure inside the eye was varied by raising the saline bottle up and down, to vary the pressure inside the eye from 3 to 30 mmHg. The change in pressure inside the cannulated eye was measured with the rebound tonometer to check which among the four experiments gave the best agreement with the rebound tonometer. The other possibility of cannulating the eye along the optic nerve and the needle entering the anterior chamber was also tried. However, in eyes where the anterior chamber is shallow, the needle punctured the cornea as the needle had to be inserted at the peripheral iris for stability, and to avoid the crystalline lens. Another possibility of cannulating the eye through the cornea was tried in which the aqueous humor was found to be leaking and we did not proceed further with that experimental set-up. As the results from experiment 3 demonstrated most reliable and repeatable results, we chose the same to validate ocular pressure estimator in further experiments.

Results

Choice of cannulation and calibration of control set-up:

Experiment 1 (n=2): The mean difference ± standard deviation (SD) between the intraocular pressure (IOP) by a control set-up and the rebound tonometer was 14.44 ± 2.76 mmHg.

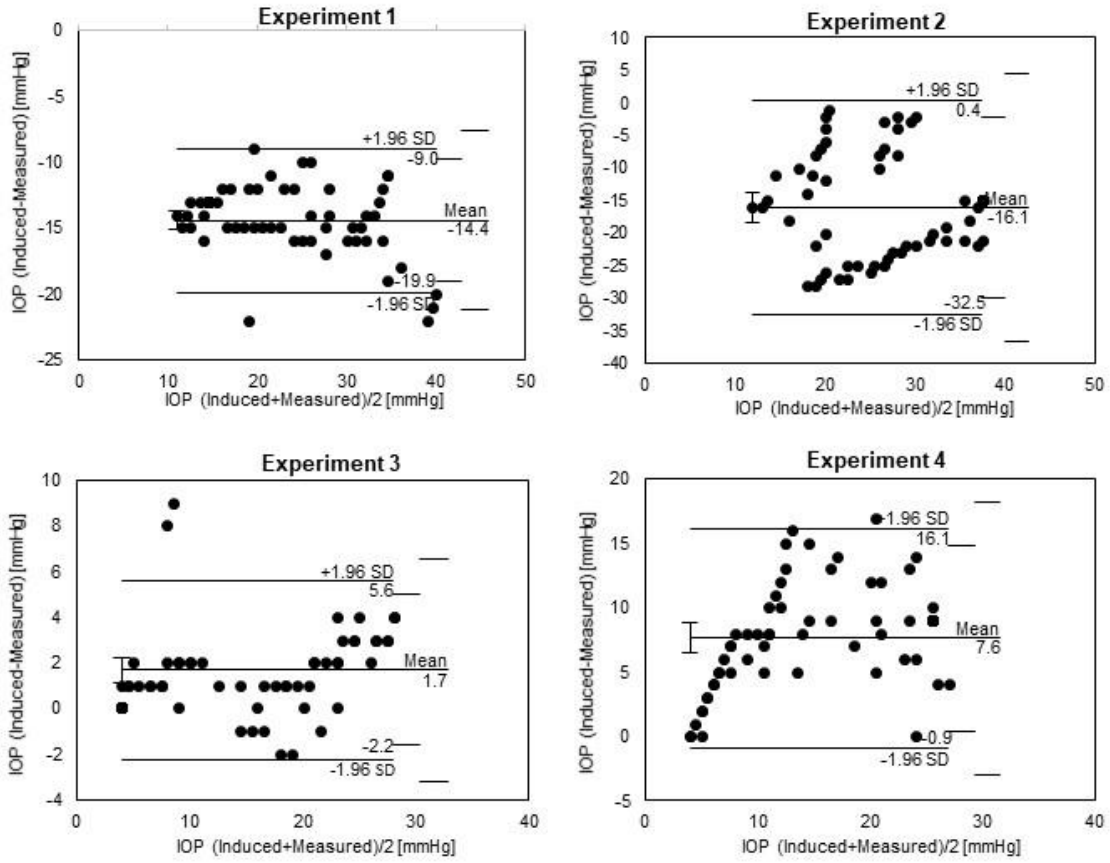
Experiment 2 (n=2): The mean difference ± SD between the IOP by control set-up and the rebound tonometer was 16.08 ± 8.32 mmHg.

Experiment 3 (n=2): The mean difference ± SD between the IOP by control set-up and the rebound tonometer was 1.66 ± 1.95 mmHg.

Experiment 4 (n=2): The mean difference ± SD between the IOP by control set-up and the rebound tonometer was 5.89 ± 4.63 mmHg.

Appendix Figure A1 shows the agreement between the induced IOP and the Measured IOP by rebound tonometer with Bland Altman. Lin's Concordance Correlation Coefficient was 0.374, 0.146, 0.943, and 0.524, respectively for the Experiments 1, 2, 3 and 4. Reliability indices also holds well with experiment 3 (Appendix Table A1).

Appendix Figure A1: Bland-Altman with 95% confidence interval for experiments 1, 2, 3 and 4 with their limits of agreement.



Appendix Table A1: Table showing the repeatability indices with their 95% confidence intervals for experiments 1, 2, 3 and 4

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Experiment 2	12.80 (10.36, 15.24)	35.48 (28.72, 42.23)	51.62 (41.80, 61.45)
Experiment 3	1.82 (1.48, 2.17)	5.05 (4.09, 6.01)	11.10 (8.99, 13.21)
Experiment 4	6.17 (5.01, 7.32)	17.09 (13.90, 20.28)	45.79 (37.23, 54.35)

Sw = within subject standard deviation, RC = repeatability coefficient, CVw = coefficient of variation.

The choice of cannulating the eye through the limbus was made from the results of experiments 1, 2, 3, and 4. In experiments 1 and 2, the cornea became oedematous post preservation which affected the measurements of the IOP, and that ended up with a poor agreement of measurements between the control set-up and the rebound tonometer. In experiment 3, the agreement between the IOP induced by the control set-up and the measured IOP by the rebound tonometer was better when compared with experiment 4. Because of this, the choice of cannulating through the limbus (Experiment 3) was preferred as there was good agreement between the calibrated control set-up and the rebound tonometer (Lin's Concordance Correlation Coefficient = 0.943) and high reliability indices (within subject standard deviation, repeatability coefficient and coefficient of variation) than the other techniques explained in experiment 1, 2 and 4, providing the validity of the control set-up (Appendix Table A1).