Automated Applanation Tonometry

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Purpose of the Study

The purpose of this study is to develop new methods of measuring eye pressure that are more objective, reproducible, and portable. In this study, we will be comparing the eye pressure measurements using 2 investigational methods to GAT and pneuumotonometer.

Background & Significance

Goldmann Applanation Tonometry (GAT) is considered the clinical gold standard for eye pressure measurements and yet it is known to be a subjective measurement with limited repeatability and limited portability. It requires the subjective alignment of applanation mires, which can introduce systematic bias into the measurement depending on the user. For example, studies have reported a higher frequency of even numbered GAT IOP measurements compared to odd numbers, which corresponds to the even numbered tick marks on the GAT dial. Additionally, a number of studies have demonstrated that the intra-observer and inter-observer coefficients of repeatability for GAT is as high as 4.3 and 5.7 mmHg respectively. Furthermore, standard GAT requires large, expensive equipment and can only be performed in the upright position. Taken together, there is a need to make GAT more objective with improved repeatability as well as a need to develop more portable applanation based methods for use in both the upright and supine positions.

The measurement of intraocular pressure (IOP) is an integral part of the standard eye exam and elevated IOP is the greatest risk factor for the development of glaucoma, the most common cause of irreversible blindness. IOP remains the only modifiable risk factor in the management of glaucoma. While the measurement of IOP, called tonometry, is frequently represented as a single number, IOP is very dynamic with pulsations due to the cardiac cycle, squint, blink, and saccadic eye movement. During the systolic phase, the ocular blood volume increases to create the IOP peak while during the diastolic phase, the IOP trough occurs. The difference between the systolic and diastolic IOP is called the ocular pulse amplitude (OPA).

Clinicians have long been aware of these ocular pulsations; Schiøtz tonometers, first introduced in 1905, were observed to pulsate during tonometry measurements. The current clinical gold standard for measuring IOP is Goldman Applanation Tonometry (GAT), where under the Imbert-Fick principle, the IOP is derived by dividing the force used to applanate (flatten) the eye by the area of the resulting flattened surface. During GAT, the applanation force is adjusted until a specific applanation area (viewed as semi-circular mires) is achieved and pulsations are commonly observed. In fact, the presence of these pulsations can make it difficult to properly align the applanating mires and the traditional textbook teaching is to measure the IOP as the midpoint of the observed pulsating mires. However, these pulsations can be as high as 7.2 mmHg in some individuals, which can significantly confound IOP measurements. In eyes with large OPA, measurement of IOP using tonometers that only assess instantaneous IOP, such as the ocular response analyzer, demonstrated high IOP measurement variability. This variability is clinically relevant as precise IOP measurements are crucial in the management of glaucoma.

The Ocular Hypertension Treatment Study demonstrated that every 1 mmHg higher baseline IOP was associated with a 10% increase in risk of developing glaucoma. The Early Manifest Glaucoma Trial showed a 10% decrease in risk of progression with 1 mmHg IOP reduction. Clinical decisions are often made based on differences of 2-3 mmHg. Fundamentally, the historical method of using a single, snapshot IOP to represent such a dynamic element, results in greater variability than desired and ignores much of the physiology of IOP and its effect on the eye.

In spite of our limited understanding of OPA in healthy and diseased states and disease progression, there is evidence that alterations in ocular blood flow and vascular regulation are associated with many pathological conditions of the eye. Some studies have observed reduced OPA in eyes with glaucoma compared to controls or reduced OPA in eyes with normal tension glaucoma compared to controls. Other studies report that reduced OPA is associated with worse glaucoma severity and a higher risk for glaucoma progression. In contrast, a very recent secondary analysis of the United Kingdom Glaucoma Treatment Study examined the role of OPA, diurnal IOP fluctuations and longitudinal (between clinic visit variation) and found that only elevated OPA was associated with faster glaucoma progression. Beyond glaucoma, the OPA may be an important variable in other ocular diseases. Patients with biopsy-proven giant cell arteritis demonstrated reduced OPA and OPA measurements have been incorporated in an algorithm developed to predict the probability of biopsy- positive giant cell arteritis. The OPA may also be relevant to retina pathology with reduced OPA observed in eyes with exudative age-related macular degeneration compared to non-exudative eyes and also reduced in eyes with diabetic macular edema. While there are many preliminary studies that suggest the importance of OPA in the health of the eye, further study and has been hampered by the lack of devices to measure OPA.

Design & Procedures

This is a prospective study. Patients presenting for their scheduled eye appointments will be recruited by verbal communication. Following informed consent, intraocular pressure (IOP) measurements may be made by the following 3 upright methods

1) Standard Goldmann Applanation Tonometry (GAT): this is the standard method for IOP measurement in clinical practice. The eye is given topical fluorescein/anesthetic, the GAT prism contacts the eye while the observer looks through the slit lamp machine ocular using blue light illumination to visual the applanation mires. The GAT dial is adjusted until mire alignment is achieved and the IOP measurement is read off the GAT dial.

2) Fixed force GAT: From the patient perspective, this method will feel identical to the standard GAT. The eye is given topical fluorescein/anesthetic. The GAT dial is set at 1.8 or 2.0, a C-MOS camera is connected to one of the oculars of the slit lamp machine and under blue light illumination, the GAT prism contacts the eye while the CMOS camera makes a video of the mire appearance through the ocular. The diameters of the recorded mire images are measured and

the IOP is calculated based on the mire diameter. A similar method using an iPod touch camera has been previously published by this PI (1).

3) Upright applanating prototype: With this prototype, an applanating prism (custom manufactured with medical grade acrylic in an ISO-13485 certified facility) is attached to a fixed-force spring that creates a force equivalent to 1.8 or 2.0 on the GAT dial. Blue LED lights on the prototype are used to create the blue illumination similar to the blue light used in clinical practice on the slit lamp or Perkins tonometer. A C-MOS camera is aligned with the GAT prism to image the applanation mires. The eye is given topical fluorescein/anesthetic. Like fixed-force GAT, the GAT prism contacts the eye while the CMOS camera makes a video of the mire appearance. The diameters of the recorded mire images are measured and the IOP is calculated based on the mire diameter.

4) Pneumatonometer: The pneumatonometer is the only device currently available in the United States with the ability to measure ocular pulse amplitude (OPA)
The order of the above 3 measurements will be randomized.

If not already documented within the patient's medical records, a measurement of their corneal thickness using a pachymeter will be performed.

The subject's blood pressure and heart rate may also be measured using a portable blood pressure cuff.

No additional follow ups will be scheduled. Review of medical records may be conducted to ascertain baseline demographics, ocular conditions, prior ocular surgeries, medications, systemic health conditions, eye examination findings, biometry if available, imaging and visual field testing if available to characterize disease severity if present. This information would be stored in PACE or deidentified and exported for analysis and would be available for 6 years or until completion of the study.

Optimization pilot study on human eyes.
Prior to the repeatability and reproducibility study, we will conduct a pilot study with the goal of ensuring proper and expected functioning of both the hardware and software components of both devices on living eyes. We will enroll 10 subjects (20 eyes) presenting for routine eye care and OPA will be measured using both devices. These recordings and the algorithm analysis of these recordings will be inspected on a frame-by-frame basis to ensure accurate segmentation. Manual labeling and segmentation of these videos will be performed and compared to the algorithm segmentation. The parameters of the algorithm will then be adjusted to refine performance as needed.

Repeatability and Reproducibility Study.
At the Duke Eye Center, patients presenting for routine eye care in the glaucoma or comprehensive clinics will be recruited. Enrolled subjects will be seated upright and will have topical fluorescein anesthetic applied to each eye. A baseline GAT IOP measurement will be

obtained. For the GAT attachment measurement, the subject's chin will be positioned within the slit-lamp in the routine manner for GAT with the GAT dial set to 2.5 g. A 5 to 10 second measurement recording (duration may be less pending data from Aim 1) will be made to encompass at least 5 cardiac cycles. For the handheld tonometer, patients will be upright and the handheld tonometer tip will contact the eye for a similar duration as the GAT attachment. The previously developed algorithm will be used to determine the IOP and OPA measurements for each prototype device. For pneumatonometry, the subject will be upright and the tonometer probe used to contact the anesthetized eye to measure the IOP and OPA. Measurements will be performed by 2 operators and each operator will perform 3 OPA measurements using each device on each eye. There will be at least 30 seconds separating each measurement and a 2-minute pause between measurements taken by different tonometers or operators. The order of the measurements will be randomized by device and operator. If not previously documented, a pachymetry measurement will be performed to assess central corneal thickness. The subject's blood pressure and heart rate will also be measured. Coefficients of repeatability will be calculated and reproducibility between operators and agreement between devices will be assessed using Bland-Altman analysis.33 Interoperator and intraoperator variability will also be evaluated using intraclass correlation coefficients. Associations between OPA and IOP, central corneal thickness and systemic blood pressure will be assessed using linear regression. At total of 60 subjects (120 eyes) will be included in this study, with at least 30 eyes with IOP > 21 mmHg. Many prior studies have shown that higher OPA correlates with higher IOP, so it is important to include hypertensive eyes to assess device performance at higher IOP measurements.

Selection of Subjects

Inclusion:
Presenting for a routine eye exam
≥ 18 years of age
Able and willing to give consent

Exclusion:
History of corneal scarring
Active infection of the eye
Ocular surface trauma or infection

Subject Recruitment and Compensation

Subject recruitment will be done at the Duke University Eye Center clinics and satellites. The study will also utilize D.E.D.U.C.E (Duke Enterprise Data Unified Content Explorer) an on-line research tool providing Duke investigators with access to clinical information collected as a by-product of patient care. The study will apply for a waiver of consent to identify potential subjects for the study. The PI or a provider known to the patient will introduce potential eligible

subjects to the study during their visit to the eye clinics, and if they are determined eligible a delegated key personnel will obtain consent from the subject. In addition, once the subject has the consent signed we will request access to their medical records through a medical records release form to obtain the participant's general medical history, previous use of systemic medications, previous use of ophthalmological medications, previous ocular examinations, previous ocular procedures, and results of other medical tests.

Participants will be given a daily parking pass at the Eye Center Parking Garage for participation in this study.

Total additional time to the clinic visit (including time for consent) is estimated to be 30 minutes (10 minutes for consent, 20 minutes for study procedures).

Consent Process

Complete the consent section in the iRIS Submission Form.

Subject's Capacity to Give Legally Effective Consent

Subjects who do not have the capacity to give consent will be excluded.

Risk/Benefit Assessment

Risks from participating in the study are very low. The primary risks for all participants are some discomforts, which are similar to those encountered in any complete eye examination. In routine clinical practice, the IOP is commonly measured a number of times by technicians, trainees and attending physicians with reapplication of the fluorescein/anesthetic drops as needed. There is the theoretical risk of corneal abrasion or infection anytime an IOP measurement is performed but this is very rare. The IOP measurements made using the experimental methods/devices are very similar to existing devices used commonly in clinical practice (e.g. standard GAT, Perkins tonometer, Schiøtz tonometer). There is the potential risk of loss of confidentiality. Every effort will be made to keep the information confidential; however, this cannot be guaranteed. Subjects may take a break at any time during the study or stop their participation in this study at any time.

In addition to the risks and discomforts listed here, there may be other risks that are currently not known. Subjects will be informed if any other potential risk becomes known through the duration of the study. Also, the risks and discomforts may occur more often or be more severe than have been seen before and written in this form.

Benefits

Subjects are unlikely to benefit directly through their participation in this study. However knowledge generated from this study may improve future methods for measuring IOP and may contribute to developing a novel method for measuring the ocular pulse amplitude.

Data Management, Analysis and Statistical Considerations

For external collaborators/personnel who are NOT ENGAGED in the research but are handling de-identified or a limited data set of Duke data, include their name, role and a description of the data.

All video recordings will be stored on a Duke server (Duke Box). Videos will not contain any identifiable features. Videos will be broken down into their individual frames and the mire diameters contained within the frames will be delineated and measured using a previously developed algorithm (1). The mire diameters are converted to an IOP measurement using the Imbert-Fick principle (relating pressure to applanating force and applanating area). For each video, the median IOP measurement will be taken as representative for that measurement and will be compared to standard GAT using a Bland-Altman.

Within a video, when IOP values regularly oscillate between 2 measurements at a frequency corresponding to the heart rate, this is suggestive of the ocular pulse that reflects the IOP at the diastolic and systolic blood pressures. The differences between the upper and lower IOPs will be taken and averaged to estimate the ocular pulse amplitude (OPA). These OPA values will be compared among study subjects with different diagnoses (glaucoma versus non-glaucoma) to assess for differences using Student t tests. An alpha level will be generally set at 0.05, unless there is a need to correct for multiple comparison testing which will then be performed by procedures such as false discovery rate.

Data & Safety Monitoring

In accordance with federal regulations the PI will monitor for, review, and promptly report to the IRB, appropriate institutional officials, and the appropriate regulatory agency head all unanticipated problems involving risks to subjects or others that occur in the course of a subject's participation in a research study (45 CFR 46.103(b)(5)(i) and 21 CFR 56.108(b)(1)), and all reportable adverse events (AEs) will be submitted per the DUHS IRB policies.