Detecting IOP Fluctuations in Glaucoma Patients

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Abstract: Lowering intraocular pressure (IOP) remains the guiding principle of glaucoma management. Although IOP is the only treatable risk factor, its 24-hour behavior is poorly understood. Current glaucoma management usually relies on single IOP measurements during clinic hours, even though IOP is a dynamic parameter with rhythms dependent on individual patients. It has further been shown that most glaucoma patients have their highest IOP measurements outside clinic hours. The fact that these IOP peaks go largely undetected may explain why certain patients progress in their disease despite treatment. Nevertheless, single IOP measurements have determined all major clinical guidelines regarding glaucoma treatment. Other potentially informative parameters, such as fluctuations in IOP and peak IOP, have been neglected, and effects of IOP-lowering interventions on such measures are largely unknown. Continuous 24-hour IOP monitoring has been an interest for more than 50 years, but only recent technological advances have provided clinicians with a device for such an endeavor. This review discusses current uses and shortcomings of current measurement techniques, and provides an overview on current and future methods for 24-hour IOP assessment. It may be possible to incorporate continuous IOP monitoring into clinical practice, potentially to reduce glaucoma-related vision loss.

Keywords: 24-h IOP monitoring, fluctuations, intraocular pressure, glaucoma.

INTRODUCTION

Glaucoma is the most important cause of irreversible blindness worldwide [1]. Intraocular pressure (IOP) is not only one of the most significant risk factors in development of the disease, but also the only modifiable one. Accuracy of IOP measurement therefore is critical to predicting and monitoring the course of the disease.

IOP is the tension exerted by the aqueous humor as a result between its production and outflow from the globe. It is estimated as a transcorneal pressure gradient via indirect non-invasive tonometry, as there is at present time no safe and practical way to obtain the direct measurement. However, we will use the term “measurement” regarding IOP, as this has been used widely in the literature and in practice [2].

Many tonometry devices have been developed, each with applications in different clinical settings. Recent advances have aimed to address the biomechanical properties of the cornea, such as central corneal thickness (CCT) and corneal curvature, as they may confound accuracy. The most commonly used tonometers and their advantages and limitations are described here in detail. Goldmann applanation tonometry (GAT) currently is the gold standard, to which all other tonometers are compared. We also focus on new 24-hour IOP monitoring devices and methods, developed recently to record daily fluctuations especially during the nocturnal period.

APPLANATION TONOMETRY

Applanation tonometry is based on the Imbert-Fick law: [2] the force on the corneal outer surface reflects the
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The estimated IOP would approach the “true” IOP if the structural properties of the cornea were virtually insignificant and the applanated area were infinitely small relative to the corneal surface area. However, not only are these two assumptions untrue in reality, but also the cornea itself, with the corneal surface tear film, presents an opposing force on the applanator. Applanation tonometry is most precise at the average CCT of 525 μm, and more studies are currently underway to determine the particular influence of the other corneal structural properties.

**GOLDMANN APPLANATION TONOMETER**

Developed in the 1950s [3], GAT involves a slit-lamp mounted device with a prism on the tip of the tonometer. This tip is placed against the central cornea, which has been anesthetized and stained with topical fluorescein dye. The tonometer head is gently advanced to apply force to the cornea, until the inner edges of the two half-circle mires make contact as viewed with a cobalt blue filter through the slit-lamp [4].

Although GAT is the most widely used tonometer worldwide, it has its limitations. GAT IOP readings are influenced by corneal structural parameters, the most studied of which is CCT. Lower CCT (less than 525 μm) is associated with IOP underestimation, and higher CCT (greater than 525 μm) with IOP overestimation [5, 6]. Furthermore, some studies have found that corneal thinness could be an independent risk factor for the progression of disease [7].

Corneal irregularities also influence the accuracy of GAT measurements. With significant astigmatism (greater than 3 diopters), the area applanated is elliptical rather than circular. Diseases that affect the corneal shape and structure also interfere with GAT accuracy. The more conical corneal shape found in keratoconus, a disease of corneal degeneration, impedes the accuracy and precision of GAT IOP measurement [8, 9]. GAT tends to obtain much lower measurements at the conical apex, relative to the flatter and thicker regions of the cornea, and thus the overall GAT measurement in keratoconus tends to underestimate the IOP. Lastly, GAT IOP in eyes post corneal surgery is less accurate compared to non-surgerized eyes [10].

In summary, GAT is the most commonly used method of tonometry, but structural factors of the cornea limit its accuracy in practice. Formulas have been developed as an attempt to characterize and quantify these corneal properties, but no consensus exists regarding their use in the clinical setting [11]. Despite its limits, GAT remains the reference standard to which other, newer tonometers are compared.

**Perkins Handheld Tonometer**

The Perkins tonometer is a portable version of GAT, which does not require slit-lamp mounting. Therefore it is useful for patients unable to tolerate an upright slit-lamp examination, such as children, anesthesized or intubated patients, and patients who must be supine. Because the Perkins tonometer and GAT use the same principles of applanation tonometry, they share similar advantages and limitations. Their accuracy is similar, with a mean difference of 1.0 mmHg [12, 13]. The Perkins tonometer also offers reasonable reliability, as shown in a study comparing several tonometers to GAT [14]. Thus the Perkins tonometer is a good choice for portable tonometry, given its similarity to GAT in method and accuracy.

**Non-Contact Tonometer**

The non-contact tonometer (NCT), otherwise known as the pneumatic applanation tonometer (*not to be confused with the pneumatonometer*), is essentially a Goldmann tonometer that uses an air puff as the applanating force. A burst of pressurized air transiently applanates the cornea, while the surface reflects light from a laser beam. The amount of light reflected during the time of applanation is compared to the time during which the surface is applanated by the air, and the IOP measurement is determined electronically. Other measurements are obtained in this process, including the ocular pulse amplitude and several values that assess the efficiency of aqueous outflow through the trabecular meshwork [4].

The NCT offers notable advantages, such as increased level of automation and lack of direct contact (and thus no risk of infection transmission) [15 - 17]. Cook *et al.*, in a study comparing several tonometers, found that the NCT had the most precision in IOP measurement; more than 60% of its readings were within 2 mmHg of that obtained by GAT [14]. However other studies have found that the NCT systematically overestimates by 0.12-0.58 mmHg, compared to GAT [15, 16, 18]. In addition, CCT may influence the NCT to a greater extent than it does GAT [19]. Patients also may
squeeze their eyelids while awaiting the air puff, thereby interfering with accurate measurement using the NCT. Therefore, the NCT may be an easy-to-use IOP screening method, but measurements should be considered in light of the above limitations, especially corneal structural properties.

**OCULAR RESPONSE ANALYZER**

A modern version of non-contact tonometry is the ocular response analyzer (ORA). Its most noteworthy advantage is that it characterizes the biomechanical factors of the cornea that influence IOP measurement and can adjust readings in context of these properties. Using an air burst to applanate the cornea and an electro-optical system to measure readings, the ORA records two IOP values at the times the cornea is flattened: first, during inward applanation (as the cornea moves inward by the force of the air puff), and secondly, during outward applanation (as the cornea moves outward to return to its baseline). The cornea provides structural resistance during both processes, so the two IOP values are not the same. The difference between the values is corneal hysteresis (CH) \[20, 21\]. CH may offer glaucoma risk information \[4\], as increased corneal elasticity has been associated with progression of disease \[22, 23\].

The ORA obtains three other measurements, in addition to CH: the corneal-compensated IOP (IOP_{cc}), Goldmann-correlated IOP, and the corneal resistance factor (CRF) \[24\]. The IOP_{cc} is less influenced by corneal biomechanical properties (most notably CCT \[21\]), when compared to GAT IOP readings \[20, 25 - 28\]. Additionally, the ORA does not require direct contact and thus avoids need for anesthesia and for tip disinfection. When compared to other tonometers in the setting of glaucoma, keratoconus, and post corneal surgery, the ORA performs rather well. In eyes with glaucoma, Sullivan-Mee *et al.* determined the ORA had reasonable repeatability and reproducibility when compared to GAT and the DCT (discussed below). Another study found disagreement in the IOP readings from the different tonometers, and that the most consistent factors correlating with measurement dissimilarity were ORA-measured factors: CH and CRF \[29\]. Therefore in the setting of glaucoma, the ORA provides additional information to interpret accuracy in IOP measurement.

Even with improved accuracy and additionally clinically useful information, the ORA presents disadvantages as well. It lacks portability, as it requires mounting on a table, and requires frequent upkeep due to its complex electro-optical system \[4\]. But all in all, the ORA provides reliable and reproducible IOP measurements and clinically useful data, in various ophthalmologic settings \[30, 31\]. Future studies involving the instrument can aid in elucidating further the role of the corneal structural properties in IOP measurement.

**CORVIS ST**

Another relatively new variation of the NCT, the Corvis ST (CST) uses a high speed camera to record the dynamic deformation of the cornea \[32\]. This method also allows detailed investigation of how corneal biomechanical factors change with the deformation caused by applanation, including corneal velocity, corneal applanation length, and corneal deformation amplitude \[33\]. Good agreement has been found between GAT and CST measurements \[34\]. However, controversy still exists regarding the effect of CCT on CST compared to its effect on other tonometers.

**INDENTATION TONOMETRY**

With indentation tonometry, a force will indent into a soft object more so than into a hard object \[4\]. Thus with the eye, the higher the IOP, the more weight or force that is necessary to push against and indent the cornea.

**SCHIOTZ TONOMETER**

Developed in 1905, the Schiotz tonometer uses a weighted plunger: for every 0.5 mm that the plunger indents into the cornea, the needle shows an increase of 1 unit. This scale reading is then converted into IOP in mmHg. Its limitations include the requirement of the supine position for use, and a corneal abrasion theoretically is possible with the patient’s eye movement. Frequent or prolonged measurement also can induce aqueous humor leak from the eye, so that subsequent measurements may be falsely low. The Schiotz tonometer is also affected by scleral rigidity, elasticity, and other structural properties of the eye; for example, increased (versus decreased) elasticity overestimates (versus underestimates) IOP.

**MACKAY-MARG TONOMETER**

Using both indentation and applanation principles, the MacKay-Marg tonometer is generally regarded as the most accurate and precise tonometer, even when compared to GAT \[4\]. The MacKay-Marg tonometer correlates well with
other tonometers that use application [35].

*Versus* GAT, it may be less affected by corneal properties [36] and more accurate with scarred corneas [37]. The Tono-Pen uses the same principles, as a portable version of the MacKay-Marg tonometer.

**TONO-PEN XL**

The Tono-Pen XL is a direct successor to the MacKay-Marg tonometer and uses the same principles of indentation tonometry. It is portable, can be used in both supine and upright positions [38], and offers easy calibration and operation by using a digital readout. Besides basing the final IOP reading on a minimum of four measurements to increase precision, the Tono-Pen XL provides a value called the coefficient of variation: it must be less than 5% for the IOP measurement to be considered accurate. The instrument also uses disposable latex covers and thus does not require tip sterilization. The Tono-Pen XL can measure IOP through bandage contact lenses, which makes it useful in settings such as chemical burns and neurotrophic keratopathy [39, 40]. It is more accurate than GAT in measuring IOP of eyes with irregular corneas, as its tip has a smaller contact area (2.36 mm$^2$ for Tono-Pen XL *versus* 7.35 mm$^2$ for GAT) [40].

Although directly related to the MacKay-Marg tonometer, the Tono-Pen XL has not been determined to be as accurate or precise as its predecessor. Close correlation has been found with GAT [41 - 43], but other studies show that the measurements of the Tono-Pen XL are far too different to be considered appropriate for clinical use [44, 45]. In one study, the Tono-Pen XL correlated well with GAT for IOP less than 20 mmHg, but for readings greater than 20 mmHg, the Tono-Pen XL demonstrated significant underestimation [46]. Salvetat et al. found the opposite result: higher IOP readings (greater than 24 mmHg) correlated with overestimation [47]. The accuracy and precision of the Tono-Pen XL therefore needs further clarification and study. The device is useful as a portable instrument and in the setting of irregular corneas as it has a relatively small contact area, but its IOP readings should be interpreted within the context of other factors such as IOP range and corneal properties (for example, CCT).

**PNEUMATONOMETER**

The pneumatonometer (PT; *not to be confused with the pneumatic applanation tonometer*) similarly uses both indentation and applanation techniques [48]. The cornea is indented gently by a flat tip on a pneumatic sensor floating on a column of area, and IOP is measured when the pressure applied equals the pressure exerted by the anterior chamber. The reading is available on a digital readout or as a paper tracing to provide real-time data, over the course of five to ten seconds. No inherent force is transmitted to the eye, compared to other tonometry techniques.

Because actual corneal contact is negligible with the instrument, the PT can reliably measure IOP with abnormal corneas: in contact lens wearers [49], in patients with corneal scarring and edema, and in patients with negligibly visible corneas. Similarly, it can easily be used with neurotrophic corneas. In eyes post LASIK, the PT was found to be more accurate than GAT [50]. The PT does not require a specific probe orientation [38] or a slit-lamp mount [4].

Some studies, however, have determined that the PT underestimates IOP at lower ranges (less than 10 mmHg) and overestimates IOP at higher ranges (greater than 25 mmHg) [51]. The PT also has been found to have significant correlation with CCT [52, 53]. The PT also has practical limitations, namely cost; the probe tips, air canisters, and graph paper require frequent replacement. All in all, however, the PT offers a practical and relatively accurate screening method, especially in eyes with abnormal corneal structure and shape.

**OTHER TYPES OF TONOMETERS**

**Rebound Tonometer**

Described by Dekking and Coster in 1967 [54], the iCare rebound tonometer (RT) is a portable device that uses a magnetized probe to make gentle contact transiently with the cornea. Speed of probe deceleration is correlated directly with higher IOP. The main advantage of the RT is ease of use, given its portability, use of disposable tips, and lack of anesthesia requirement. To enhance accuracy, it requires six measurements and determines mean pressure and standard deviation, after disregarding the highest and lowest readings [55]. Also, RT readings at the corneal periphery correlate well with those done at the central cornea, so that probe orientation has relatively little bearing on measurement accuracy [56, 57]. Therefore the RT is notably useful for eyes with post-surgical or abnormally shaped corneas [58, 59].

However, controversy still exists regarding the accuracy of the device. It has been shown that the RT overestimates IOP when compared to GAT [60 - 62], with differences ranging from 0.6 mmHg [61] up to 7.7 mmHg in eyes with
higher IOP values [63]. Corneal properties, including CCT, CH, and CRF (but notably not corneal curvature) [56, 64], have been determined to affect RT IOP readings. A study did however determine that the intersession repeatability of the RT was similar to that of other tonometers, including the NCT and the Tono-Pen XL [65]. Other limitations of the RT include its inability of use in supine patients and its cost given the one-time use nature of the pins.

Overall, the RT is an easily used IOP screening device, which can be used among non-specialized personnel. It is mainly limited by its inability to account for corneal properties on IOP measurement [55].

**Dynamic Contour Tonometer**

The dynamic contour tonometer (DCT), i.e. the Pascal tonometer, was devised to be essentially free of corneal structural influence [66]. Instead of applanation or indentation, it operates via contour matching: the tip holds a cover shaped in the contour of the cornea, so that it avoids changing the shape of the cornea during the process. Theoretically the accuracy issues presented by corneal structural parameters are circumvented [67, 68]. The tip houses a pressure sensor that records IOP 100 times per second; from these readings, the device determines the mean IOP and the ocular pulse amplitude (OPA). The OPA is the difference between the average systolic and diastolic IOP, and thus a reflection of choroidal vessel filling. Therefore it can be used to represent ocular blood flow [55]. Low ORA has also been correlated with worsening glaucomatous progression [69].

Namely because of lessened influence of corneal biomechanical parameters, the DCT has been found to be more accurate compared to GAT [55]. Francis et al. determined that DCT readings are less influenced by CCT but still affected by the curvature of the cornea. However, the effect of this curvature on DCT still remained less than that of CCT on GAT [70]. With glaucomatous eyes, the DCT has improved repeatability and reproducibility compared to GAT and the ORA [71]. A study was done to compare GAT, the ORA, and the DCT on patients with primary open-angle glaucoma, ocular hypertension, normal-tension glaucoma, and glaucoma suspect [29]. There was a substantial dissimilarity in mean IOP measured by the three tonometers; the most consistent confounders of this discrepancy were determined by multi-regression analyses to be CH and CRF - values determined by the ORA. This is reasonable because the ORA records its measurements over more time and thus would be more influenced by corneal structure. Even though Milla et al. confirmed that corneal parameters had less impact on DCT readings, the group did determine that the DCT agreed well with GAT at CCT between 540 and 545 μm, but not at the extremes of corneal thickness [72].

The DCT has practical limitations as well. It lacks portability given it requires a slit-lamp mount, and it accrues cost associated with the disposable tips. It also requires prolonged tip contact, as well as specialized training for use. Despite limited evaluation thus far, the DCT promises to offer accurate and clinically useful evaluation of IOP measurement.

**Continuous IOP Monitoring**

The tonometers described above mainly measure IOP in single “snapshot” measurements, or over a span of at most several seconds. However it has been shown that IOP possesses a circadian rhythm with diurnal variation [73]. IOP can fluctuate as much as 4-5 mmHg in non-glaucomatous eyes, and even to a greater extent in eyes with glaucoma [74, 75]. As many as two-thirds of patients with glaucoma may have their highest IOP readings beyond regular clinic hours, especially during the night [76]. These large pressure shifts in fact play a role in dramatically worsening visual loss in patients with glaucoma [77, 78]. Therefore, continuous IOP monitoring would be a commendable goal especially to note IOP measurements at nighttime, when the highest IOP values occur [79].

Attempts to measure IOP frequently throughout the day have been made using two different strategies: (1) permanent and (2) temporary IOP monitoring. Several studies have offered promising results regarding permanent monitoring with non-human models, for example rabbit and non-human primate eyes [80, 81]. The major limitation of the methods using permanent IOP monitoring is the requirement for surgical implantation (in some cases, into bone) and the associated risks with such procedures. Surgical implantation may be circumvented with use of IOP sensors with intraocular lenses inserted during cataract extraction surgery. However, the use of these materials also has risks, including leakage of potentially toxic materials and need for regular invasive re-calibration. Also, only patients who participate in intraocular surgery could use such a method.

Temporary IOP monitoring may offer ways to avoid these risks and limitations of permanent monitoring. As early as the 1950s, researchers have been experimenting to find clinically useful, comfortable, and accurate portable ways to measure IOP continuously without permanent device implantation; these early models have ranged from metal indentating devices to magnetic pressure sensors to scleral buckle applanators [82, 83]. The ideal, clinically relevant 24-
hour IOP measuring device must easily implantable via a minimally invasive procedure, and must provide stable uninterrupted contact with the eye [84]. Chitnis et al. developed in 2011 an implantable transponder that measures the “true” IOP in the vitreous body via a hydraulic system [84]. More recently, the main method of temporary IOP monitoring has involved contact lens tonometry, which involves a soft contact lens that can determine small fluctuations in ocular circumference that parallel changes in IOP. In human enucleated eyes, Hjortdal et al. determined that a change in IOP of 1 mmHg was correlated with a change in corneal curvature of 3 μm, with a corneal radius of approximately 8 mm [85]. Another study corroborated the association between IOP and corneal curvature in vivo, by using positional change to induce change in IOP that corresponded well to change in ocular circumference measured at the limbus [86].

A gas-permeable, rigid contact lens was developed by Sanchez et al. in 2011 to measure IOP continuously for at least several hours [87]. Tested in enucleated porcine and in vivo human eyes, the contact lens is shaped similar to a doughnut, connecting to an on-person unit via sensor and recorder wires. IOP measurement correlated excellently with the lens sensor resistance response, even with blinking and eye movements. However, use of the device currently is restricted by poor transparency of the lens and limited tolerability by the patient.

Within the last several years, Leonardi et al. has tested a soft contact lens sensor (CLS) with embedded microfabricated strain gauges that measure changes in the dimensions of the globe, in response to changes in IOP [82]. This device was tested in enucleated porcine eyes, given that these eyes approached approximately the diameter of human eyes. The initial CLS used a wire connection between the contact lens and a recording instrument, and was able to approach rather well the “true” IOP (as measured by manometry inside the sample eyes) [88]. The wireless commercial device was subsequently developed by Sensimed and termed the Triggerfish CLS. The 14.1 mm diameter sensor on the lens measures changes in corneal curvature every five minutes for 30 seconds. The Triggerfish CLS possesses a microprocessor built to communicate with an external antenna, which is placed around the eye to transmit IOP measurement data to a recorder worn by the patient [83]. The recorder then transmits the data to a computer using Bluetooth technology. In a study of healthy volunteers over the course of several months, the Triggerfish CLS was found to measure IOP accurately and reproducibly, compared to the NCT and GAT [89]. It also confirms the presence of and aids to characterize the daily and nocturnal variations in IOP [90].

Prospective clinical investigations have studied the safety and side effect profile of the Triggerfish CLS in healthy and glaucomatous subjectspatients, with no significant safety issues found [91]. In a study of ten healthy students, De Smedt et al. determined that the Triggerfish CLS had high tolerability and scored well on comfort, despite transient effects such as mild corneal abrasions and decrease in visual acuity during/immediately after CLS wear in several subjects [92]. In a study of 15 glaucoma patients, Mansouri et al. similarly found good tolerability and safety, with complications typical of soft contact lens wear - here, one case of corneal erosion and several cases of dry eye syndrome and superficial punctate keratopathy [93]. The investigators also confirmed with the device that the peak IOP did in fact occur during the nocturnal period. In a follow up study, the group again found no significant adverse effects, only conjunctival hyperemia, which occurred in about half of the subjects [94].

In order to use the Triggerfish CLS, patients currently need a prescription and training by healthcare professionals for use. However in the future, patients ideally would be able to obtain and use a CLS device easily. Patients still would need to be educated about the safety of contact lens wear, and use may be limited in those with dry eye syndrome or other corneal pathologies.

Another recent CLS design, developed by Chen et al., lacks an embedded chip, instead using a capacitator and coil to sense corneal deformation [95]. Thus it is thinner than the Triggerfish CLS, which uses an embedded silicon chip. The thinner lens may potentially allow for improved contact with the corneal surface and more accurate measurements. Initial studies show promising linearity between IOP and sensing performance of the coil.

The CLS thus far proves to be a promising method for frequent, round-the-clock IOP measurements. Just as diabetic patients are encouraged to keep home logs to facilitate in-office evaluation and management, patients with glaucoma would greatly benefit from data available through 24-hour IOP monitoring.

**DISCUSSION**

Spanning from GAT to the newer methods, the various tonometry methods described above offer different advantages and limitations. Some tonometers demonstrate their ideal accuracy as in-office devices, to diagnose accurately and guide disease management, and others are best utilized as practical simple-to-use population screening
In the ophthalmology clinic setting, GAT remains the reference standard, even over fifty years after its development. GAT has benefited from decades of evaluation: it has determined our current definitions of “normal” and “goal” IOP in glaucoma management, and it has been the most widely used device to assess degree of IOP lowering by current glaucoma medications and procedures. However, other tonometers such as the DCT and ORA offer additional clinically useful data not provided by GAT, such as ocular pulse amplitude (former) and parameters describing corneal structure (latter). They also bypass certain limitations observed with GAT, including the unaccounted-for influence of corneal biomechanical properties and the structural irregularities of pathologic or post-surgical corneas.

On the other hand, ease of use is more critical in the screening setting. All featuring portability, the Perkins tonometer, Tono-Pen XL, PT, and RT are relatively simple to learn how to use, and are able to evaluate IOP sufficiently in non-ideal situations - for example, in the supine position or in eyes from which bandage contact lenses cannot be removed. Perhaps in the future these instruments may be used routinely in the home as well so that patients can learn to record their IOP measurements on a regular basis.

In-home IOP measurement is a goal that recently has become realistically attainable. In the last several years, 24-hour IOP monitoring devices have made substantial progress. Besides proving reasonable accuracy, comfort, and safety, they have also already contributed to understanding of IOP circadian variation, especially in the nocturnal phase. Development and evaluation of improved and commercially available continuous-wear devices are currently in the works. In the mean time, patients and their ophthalmologists have a variety of tonometry devices at their fingertips to aid in diagnosis and management of glaucoma.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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