Introduction

The eye resembles a pressurized globe that is subject to expansile forces generated by the rhythmic filling of intraocular vessels during the cardiac cycle. The fluctuation in ocular blood volume leads to an oscillating variation in intraocular pressure (IOP) that is counterbalanced by the resistance to distention of the ocular outer shell [1]. These oscillations are represented by the ocular pulse amplitude (OPA) and are displayed in an ocular pulse wave that can be recorded via continuous measurement techniques, such as dynamic contour tonometry (DCT) [1, 2]. By recording the pulsatile component of the ocular blood flow over a period of time, the OPA may provide an indirect measurement of the uveal blood volume changes during the cardiac cycle, as the choroid represents most of the ocular blood volume and receives 80–90% of the local flow [3]. Accordingly, OPA has been proposed as an index of ocular hemodynamics [4, 5]. Furthermore, it has been suggested as a surrogate outcome for extraocular hemodynamics, the rationale being that anything that interferes with ocular perfusion will likely affect OPA measurements. This includes local factors as well as distant diseases like, for instance, carotid artery stenosis (CAS) [6]. Moreover, the OPA might also depend on ocular characteristics linked to compliance of the outer layers. For example, IOP measurement with a Goldmann applanation...
tonometer (GAT) is significantly influenced by the central corneal thickness (CCT), whereas when using a DCT – and thus avoiding applanation – the CCT would play a lesser role in IOP assessment [1, 7]. Other, non-CCT-related factors, such as the IOP level, scleral thickness, ocular elasticity, axial length (AL), and lens status, could influence OPA measurements [7–9]. As the characteristics and the pathophysiological variability of OPA remain partially unclear, several researchers are attempting to answer these open questions and find clinically useful applications. As expected, much of this research is being done in glaucoma patients, since both mechanical damage due to an elevated IOP and a higher susceptibility due to altered ocular hemodynamics are thought to contribute to disease progression [10, 11]. As changes in diagnosis and treatment strategies might depend on small differences in the measured IOP, it is of crucial importance to approximate the real IOP as closely as possible. Anterior chamber manometry is a very accurate but invasive method to determine IOP and hence is rarely used [12]. As the gold-standard GAT readings are significantly influenced by CCT (which can per se be an independent risk factor for disease progression), an increasing number of centers are using DCT to bypass that important limitation. While its use may have its caveats, such as interobserver reproducibility, it does provide intriguing additional information on ocular hemodynamics which may be of clinical relevance in glaucoma management [13].

The intent of this review is to present an overview of the current knowledge about using DCT and OPA, with emphasis on its application in glaucoma.

DCT versus GAT

DCT represents a relatively new technology for non-invasive IOP measurement that uses the principle of ‘contour matching’. Its function is described by the Pascal principle, referring to an equality of the pressures acting on the anterior corneal surface at the time of measurement:

\[ F_{\text{IOP}} + F_r + F_c + F_{\text{ap}} = 0, \]

where IOP is the actual aqueous pressure, \( r \) refers to ocular rigidity (OR), \( c \) to capillary attraction, and \( \text{ap} \) to a potential appositional element [1]. It uses a miniature piezo-resistive pressure sensor embedded within a tonometer tip which approximates the cornea’s shape when the pressures on both sides are equal (fig. 1). Therefore, this measurement is less dependent on the effect of inter- individual variation on corneal properties, in contrast to applanation tonometry [1, 7]. This is an important difference, since all forms of applanation tonometry use variable force-to-pressure translations, whereas the DCT always measures using a constant force. When, subsequently, the sensor is subjected to a change in pressure, the electrical resistance is altered and the computer of the DCT calculates a change in pressure in concordance with the change in resistance.

Another difference is that it measures IOP in a continuous way and provides a pressure curve that is synchronous with the cardiac cycle (fig. 2). These pulsatile variations in IOP are thought to be caused by the amount of blood that is pumped into the eye, mainly in the choriodcapiillary bed, during each systole [1]. The computer calculates the average IOP and gives the range of pulsation amplitude, together with a score for the quality of the measurement. Continuous measurement implies apposition of the measurement probe for an extended period (~8 s). Accordingly, some have reported that DCT measurements are significantly more time-consuming and more difficult to perform than GAT in routine practice, and that most eyes require repeated DCT measurements [14]. In contrast, the acoustic signal of the DCT that informs the examiner about the correct alignment and continuous measurement seems to encourage patients to remain still for the time needed.
GAT is an analogous technique where the clinician uses a force to flatten a circular surface (3.06 mm in diameter) of the central cornea and interprets the alignment of 2 hemicircles formed at the interface [15]. This measurement is thus dependent on corneal rigidity, since more force will be needed to flatten a thick cornea regardless of the actual IOP [16, 17]. Furthermore, it will only measure the IOP at a particular moment, not during a prolonged interval. This technique is time-efficient and less patient dependent than DCT [18]. Accordingly, GAT is currently considered the gold standard to measure and report IOP [19]. To reduce the error inherently linked to interindividual differences in CCT, researchers have proposed a correction of formulas [20]. These are not uniformly accepted or validated but do indicate the need for a more independent noninvasive method for IOP measurement.

Higher IOP values have been reported using DCT versus GAT, while others have found this to be true only in patients with low CCT values [21–25]. In fact, no statistically significant influence of anterior segment parameters on DCT-assessed IOP has been detected. Moreover, DCT measurements have shown a good concordance with anterior chamber manometry, in contrast to GAT-determined IOP values [1, 2, 8, 26]. Several studies have examined the differences between DCT and GAT according to corneal morphology [7, 22, 25]. An increased disparity in IOP readings between GAT and DCT has been reported in patients with high or very low CCT [25]. These findings are important, as the Ocular Hypertension Treatment Study (OHTS) showed CCT to be a significant risk factor for the development of glaucoma in patients with ocular hypertension. It showed that patients with a CCT below 555 μm had a 3 times greater risk of developing primary open-angle glaucoma (POAG) than patients with a CCT above 588 μm [28, 29]. There are several possible explanations for the association between CCT and glaucoma risk, and one of them is that a thinner cornea may be associated with a more flexible corneoscleral shell which could be more sensitive to IOP-induced stress. Iatrogenically changing CCT by either increasing it – by performing Descemet’s stripping endothelial keratoplasty – or decreasing it following a LASIK (laser-assisted in situ keratomileusis) procedure does influence IOP measurements [7, 30–33]. Following LASIK, the IOP decreased using GAT measurements but was unchanged when assessed with DCT [7, 33]. Furthermore, less intra- and interobserver variability was reported for DCT with respect to GAT, also demonstrating DCT measurements to be more repeatable and reproducible [27]. The better reproducibility of the DCT may result in more precise measurements for monitoring IOP changes over time.

**OPA and Glaucoma**

Glaucoma is thought to affect more than 80 million people worldwide [34]. It is a neurodegenerative disease that causes irreversible blindness and has a massive economic impact related to both treatment costs and the burden on care providers. The diagnosis is based on assessment of the visual field and imaging of the optic nerve head, with IOP being of paramount importance in disease management [35]. The mainstay of treatment remains lowering the IOP in order to prevent disease progression. Although very effective pharmaceuticals, laser treatments, and filtering surgery techniques have been described, a sig-
significant number of patients still show signs of disease progression despite excellent IOP control [36]. Some patients have proven to be more susceptible to the development of glaucomatous damage, even when the IOP falls within the normal range. This finding directed researchers to investigate other factors besides IOP alone in the pathogenesis of glaucoma. Multiple studies have shown the importance of vascular dysregulation in glaucoma patients, since they are more prone to having lower ocular perfusion pressures, more often peripheral vasospasms and migraine, low retrobulbar flow velocities, and decreased OPA [37–39]. There are several noninvasive ways to investigate ocular blood flow-related variables. DCT with determination of OPA, color Doppler imaging of the retrobulbar circulation, Doppler optical coherence tomography, enhanced depth imaging optical coherence tomography for choroidal thickness measurements, and retinal oximetry are methods that provide information about bulbar perfusion and oxygenation [40–45]. However, the therapeutic impact of these measurements remains unclear.

Researchers have reported significantly lower OPA values in glaucoma patients versus age-matched healthy individuals [44, 45]. In addition, OPA has also been correlated with more severe glaucomatous damage in POAG patients after controlling for IOP [46]. These lower OPA readings could indicate a decrease in choroidal flow, already suggested to exist in glaucoma [47, 48].

Using Doppler analysis to evaluate ocular blood flow and its variables, our research group speculated that OPA reflects the vascular resistance of the retrobulbar vessels in healthy subjects but not in glaucoma patients [44]. Moreover, there appears to be a reduction in retrobulbar flow velocities in glaucoma patients. These results were confirmed using Doppler waveform analysis, which suggested that the relationship between OPA and both systemic and ocular vascular parameters was weaker in POAG and normal tension glaucoma (NTG) compared to healthy controls [45]. This may suggest that in glaucoma patients other nonvascular variables may be important determinants of OPA, probably related to the biomechanical properties of the ocular compartment walls. The influence of these properties on OPA measurements could thus be more relevant in glaucoma patients than in healthy individuals. This is in agreement with previous reports that have failed to prove any correlation between OPA and vascular systemic and ocular parameters in glaucoma patients [50].

Several studies have reported the influence of the globe’s structure on OPA [2, 51]. Kaufmann et al. [2] found OPA not to be influenced by the structure of the anterior segment (CCT, corneal curvature, and anterior chamber depth). These findings were confirmed by Ishii et al. [51], but there was a significant correlation with IOP, AL, and peripheral corneal thickness 4 mm away from the corneal center. The latter observation is believed to be due to the effects of the probe configuration on measurements with DCT – the central part of the cornea is closely approached, so the movements of the central cornea are limited and peripheral corneal thickness could be important in pulse propagation or contribute to the outer shell stiffness.

**OPA and OR**

To quantify the compliance of the globe, researchers introduced OR. It refers to the relationship between the extensibility in function of an IOP change and has been used as a clinical concept that characterizes the biomechanical properties of the ocular wall [52, 53]. However, the pressure-volume relation does not conform to a simple law, and several mathematical formulations have been proposed to quantify it. The one proposed by Friedenwald [54] uses the OR coefficient (E) based on a logarithmic pressure-volume relationship:

\[ E = (\log IOP_1 - \log IOP_2)/(V_1 - V_2), \]

where the slope of the log-transformed pressure-volume relationship of the eye is the coefficient of OR (E) [54]. A higher E value signifies that the eye is stiffer, with a consequentially larger increase in pressure (IOP) as the volume (V) increases; a lower E signifies a less stiff eye, with a smaller increase in IOP for the same volume increase. Other than the method of the OR coefficient of Friedenwald [54], other authors have proposed equations that include anterior chamber manometry, AL changes, measurement of pulse amplitude and fundus vessel pulsations, ultrasound elastography, and evaluation of corneal hysteresis [52]. However, there are some drawbacks for most of these methodologies, such as poor accuracy or reproducibility, technical complexity, and, above all, invasive measurement techniques [52, 55, 56]. Recently, Wang et al. [49] used a noninvasive technique to estimate OR in vivo. Substituting OPA and pulsatile ocular blood flow (POBF) with ΔIOP and ΔV, respectively, into the equation of Friedenwald [54], an estimation of E (E_r) was calculated. The E_r calculated via this method using DCT and laser Doppler flowmetry was lowest in glaucoma patients and highest in OHT subjects. This supports the idea that a more compliant ocular shell may predispose the optic nerve head to IOP-related damage. Some authors have suggested the OR to be the link between the mechanical and vascular hypotheses for glaucoma pathogenesis [57]. Especially deformation of the lamina cribrosa and subse-
quent kinking of the pores might influence the axonal flow and cause metabolic stress [58]. Its clinical use has been limited due to difficulties in performing accurate measurements, but the advent of new modalities such as ultrasound elastography for ocular tissues may enable the use of an OR index in glaucoma management. DCT with OPA determination could help in defining a measure for OR.

**OPA and AL**

Another important factor influencing OPA is the AL [51, 56]. This is illustrated by the observation that a defined blood volume change in the choroid results in a smaller relative change in pressure in myopic eyes than in shorter emmetropic eyes [5, 56]. In addition, the reduced scleral rigidity in myopic eyes results in less resistance to enlargement of the pulsatile volume [59]. Moreover, a longer AL implicates a longer distance to travel by the pulse wave, possibly resulting in dampening of the wave as it passes through various tissues. Furthermore, myopia itself serves as a risk factor for glaucoma [60].

**OPA and Ocular Blood Flow**

Although many advocate OPA as an estimate for POBF, the interpretation of OPA as a direct measure of POBF is not straightforward. OPA reflects a change in pressure induced by the varying ocular blood volume during the cardiac cycle. Furthermore, since ocular perfusion is inversely related to IOP and (following the equation of Friedenwald [54]) OPA is directly related to IOP, it follows that OPA may not be regarded as a direct measure for POBF [44, 61]. This has been illustrated by numerous reports indicating no relationship between blood pressure, heart rate, and OPA, although the left-ventricular ejection time has shown a correlation with OPA [5, 50]. Interestingly, when investigating the difference between POAG and NTG, Abegão Pinto et al. [45] reported OPA to be correlated with retrobulbar flow in the former group, whereas OPA was correlated with systemic hemodynamic measures in the latter diagnostic group. This is in agreement with previous reports that in NTG patients vascular dysregulation is prominent [62]. When looking at patients with CAS, responsible for decreasing blood flow and oxygen delivery to the eye, researchers have reported OPA to be linked to the severity of the occlusion [63]. Especially when comparing OPA between eyes in unilateral CAS, the predictive value is significantly increased. Therefore, OPA could serve as a screening tool for unilateral CAS. Since CAS serves as a risk factor for developing asymmetrical glaucomatous damage, OPA could aid in narrowing down the differential diagnosis. This also illustrates that various vascular related disorders could influence OPA and could be linked to the development of glaucoma.

**OPA and Filtering Surgery**

Trabeculectomy is performed to decrease IOP and stabilize glaucomatous optic neuropathy. A decrease in OPA has been reported after trabeculectomy. However, those investigators did not correct for changes in IOP [64]. Others have found no change in OPA when correcting the outcome for IOP changes [65]. Besides the drop in IOP following trabeculectomy, changes in OR might influence OPA measurements. By creating a partial-thickness scleral flap, ocular biomechanical properties might change significantly. Detorakis et al. [66] reported a greater difference between GAT and DCT IOP measurements following trabeculectomy versus IOP-matched untreated eyes. Other surgical interventions possibly influence OPA by inducing changes in OR. Researchers have reported no change in OPA following Descemet’s stripping endothelial keratoplasty [30–32]. Probably because the graft is not anchored to the sclera, the influence on OR is limited. LASIK did not seem to influence the OPA either [33]. After scleral buckling for retinal detachment repair, the OPA did decrease significantly [9].

Besides the properties of the ocular wall, the content of the eye might also play a role since the pressure pulse needs to travel from the posterior pole to the cornea. Various investigators have found no difference in OPA following cataract surgery [67–69]. Lens status apparently does not affect OR or pulse propagation to an extent sufficient to alter OPA readings.

**Conclusions**

The DCT, which is a relatively new contact type tonometer, can simultaneously measure OPA and IOP. OPA is believed to be derived from changes in ocular blood volume secondary to POBF during the cardiac cycle. Based on published reports, it has been suggested that OPA may add value in the diagnosis and follow-up of glaucoma. Low OPA values are found in glaucoma patients, especially in those suffering from NTG, and are correlated with more severe visual field defects. Furthermore, there is evidence that OPA also depends strongly on OR, which has also been reported to be altered in glaucoma patients. Future studies are needed both to improve our understanding of how OPA is influenced by several ocular and systemic variables and to define its clinical relevance in daily glaucoma management.
## Appendix

### Schematic Overview of Published Research on OPA

<table>
<thead>
<tr>
<th>Topic</th>
<th>Author(s) [Ref.]</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR</td>
<td>Dastiridou et al. [55] Ethier [57] Wang et al. [49]</td>
<td>OR may be important in the pathophysiology of glaucoma; OPA can be related to OR following the modification of Wang et al. [49] of the Friedenwald [54] formula</td>
</tr>
<tr>
<td>IOP and POBF</td>
<td>Choi et al. [50] Dastiridou et al. [53] Kaufmann et al. [2] Stalmans et al. [39]</td>
<td>OPA and IOP are positively correlated; it remains unclear what exactly OPA represents and if it can be related to POBF; since OPA is dependent on IOP and IOP changes in ocular perfusion pressure</td>
</tr>
<tr>
<td>AL and myopia</td>
<td>Dastiridou et al. [56] Grieshaber et al. [5] Kaufmann et al. [2] Tabuchi et al. [68]</td>
<td>OPA and AL are negatively correlated; it remains unclear what the exact relationship between myopia and OPA is</td>
</tr>
<tr>
<td>CCT</td>
<td>Cook et al. [19] Erickson et al. [21] Herndon et al. [28] Ishii et al. [51] Kaufmann et al. [2] Stalmans et al. [39]</td>
<td>OPA and CCT do not seem correlated; CCT itself is a significant risk factor for glaucoma</td>
</tr>
<tr>
<td>BP and HR</td>
<td>Abegão-Pinto et al. [45] Choi et al. [50] Grieshaber et al. [5] Pourjavan et al. [4] Stalmans et al. [39]</td>
<td>There is a controversial relationship between OPA and BP/HR; subjects OPA seems to be correlated to left ventricular ejection time; OPA is more related to ocular vascular parameters in healthy than in glaucoma</td>
</tr>
<tr>
<td>CAS</td>
<td>Knecht et al. [6]</td>
<td>OPA could serve as a tool in unilateral carotid artery stenosis screening</td>
</tr>
<tr>
<td>Trabeculectomy</td>
<td>Breusegem et al. [65] Detorakis et al. [66] Kaufmann et al. [2] Von Schulthess et al. [64]</td>
<td>Trabeculectomy might alter the biomechanical properties of the globe and thus affect OPA; correction of OPA for a decrease in IOP is mandatory</td>
</tr>
<tr>
<td>Cataract surgery</td>
<td>Plange et al. [67] Tabuchi et al. [68] Turk et al. [69]</td>
<td>It remains unclear whether OPA is dependent on lens status</td>
</tr>
</tbody>
</table>

BP = Blood pressure; HR = heart rate; DSEK = Descemet’s stripping endothelial keratoplasty.
Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no conflicts of interest to disclose.

References


