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The ocular pulse amplitude at different intraocular pressure: a prospective study

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Abstract: Purpose: To investigate changes in ocular pulse amplitude (OPA) during a short-term increase in intraocular pressure (IOP) and to assess possible influences of biometrical properties of the eye, including central corneal thickness (CCT) and axial length. Methods: In a prospective, single centre study, OPA and IOP as measured by dynamic contour tonometry (DCT) were taken before baseline- and post-OPA (delta) intravitreal injection of 0.05 ml anti-vascular endothelial growth factor agents. Analysis was performed employing linear regression with baseline- and post (delta)-OPA differences as the dependent and post-IOP as well as delta IOP as the independent variable. A multilinear regression analysis with delta OPA as the dependent variable and baseline IOP, post-IOP, CCT and axial length as independent variables was conducted. Results: Forty eyes of 40 patients were included. IOP and OPA increased significantly after injection (IOP mean increase \pm SD: 17.83 ± 9.83 mmHg, $p < 0.001$; OPA mean increase \pm SD: 1.39 ± 1.16 mmHg, $p < 0.001$). For every mmHg increase in IOP, the OPA showed a linear increase of 0.05 mmHg (slope 0.05, 95% CI: 0.02–0.09, $p = 0.003$, $r^2 = 0.20$). Multiple regression analysis with delta OPA as the dependent variable revealed a partial correlation coefficient of 0.47 ($p = 0.003$) for post-IOP as the only significant contribution. Conclusion: A clear positive relationship between OPA measurements and IOP levels was shown in a clinical routine setting using DCT focusing on baseline and postinterventional comparisons of OPA values after intravitreal injections in patients with exudative age related macular degeneration. When considering the OPA for diagnostic purposes, we recommend indication of corresponding IOP values.

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The ocular pulse amplitude at different intraocular pressure: a prospective study

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ABSTRACT.

Purpose: To investigate changes in ocular pulse amplitude (OPA) during a short-term increase in intraocular pressure (IOP) and to assess possible influences of biometrical properties of the eye, including central corneal thickness (CCT) and axial length.

Methods: In a prospective, single centre study, OPA and IOP as measured by dynamic contour tonometry (DCT) were taken before baseline- and post-OPA (delta) intravitreal injection of 0.05 ml anti-vascular endothelial growth factor agents. Analysis was performed employing linear regression with baseline- and post (delta)-OPA differences as the dependent and post-IOP as well as delta IOP as the independent variable. A multilinear regression analysis with delta OPA as the dependent variable and baseline IOP, post-IOP, CCT and axial length as independent variables was conducted.

Results: Forty eyes of 40 patients were included. IOP and OPA increased significantly after injection (IOP mean increase \pm SD: 17.83 ± 9.83 mmHg, $p < 0.001$; OPA mean increase \pm SD: 1.39 ± 1.16 mmHg, $p < 0.001$). For every mmHg increase in IOP, the OPA showed a linear increase of 0.05 mmHg (slope 0.05, 95% CI: 0.02–0.09, $p = 0.003$, $r^2 = 0.20$). Multiple regression analysis with delta OPA as the dependent variable revealed a partial correlation coefficient of 0.47 ($p = 0.003$) for post-IOP as the only significant contribution.

Conclusion: A clear positive relationship between OPA measurements and IOP levels was shown in a clinical routine setting using DCT focusing on baseline and postinterventional comparisons of OPA values after intravitreal injections in patients with exudative age related macular degeneration. When considering the OPA for diagnostic purposes, we recommend indication of corresponding IOP values.

Key words: dynamic contour tonometry – intraocular pressure – intravitreal injection – ocular pulse amplitude

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Introduction

Since the introduction of dynamic contour tonometry (DCT), the ocular pulse amplitude (OPA) has become of increasing interest for clinical application (Kaufmann et al. 2004; Kniestedt et al. 2004; Kanngiesser et al. 2005). Intraocular pressure (IOP) has been shown to fluctuate with the heart beat. During the systolic phase, IOP increases by 2–3 mmHg compared to the diastolic phase (Kaufmann et al. 2006). This difference is the OPA and is mainly generated by pulsatile filling of the choroid with blood via the short ciliary arteries (Thiel 1928; Bynke & Schele 1967; Perkins 1981; Schmidt et al. 2001). During the filling phase, the outer layers of the globe inhibit the choroid from expanding outwards. The choroid thickens because of the influx of blood, which inevitably leads to an increase in IOP.

The OPA has been investigated and evaluated in different clinical settings: to detect carotid artery stenosis, to differentiate between arteritic and nonarteritic anterior ischaemic optic neuropathy, to observe the course of Grave's disease and in particular to acquire a new prognostic parameter in different types of glaucoma (Perkins 1985; Bienfang 1989; Tsai et al. 2005; Kniestedt et al. 2006; Romppainen et al. 2007). However, to be able to use the OPA for diagnostic purposes,

confounding influences on the OPA need to be determined. As of yet, OPA has been shown to be dependent on heart rate and axial length (James et al. 1991; Trew et al. 1991).

Recent studies have reported a positive linear correlation between IOP and OPA readings, i.e. eyes with higher IOP measurements showed higher OPA values (Kaufmann et al. 2006; Kniestedt et al. 2006). This result seems surprising at first, because choroidal blood flow has been shown to decrease when IOP is elevated, which should lead to a decrease in OPA (Dollery et al. 1968; Langham et al. 1989; Polska et al. 2007). In contrast, Davenger et al. had found an enlarged ophthalmic pulse at higher IOP already in 1964. Lawrence et al. (1966) showed in an animal experiment with rabbits and dogs and Dastiridou et al. (2009) in a human experiment that OPA increases after an increase in IOP. Their experiments were performed by infusing micro-volumes of saline to increase IOP from 15 to 40 mmHg and IOP was measured by manometry. Furthermore Dastiridou et al. showed a median OPA increase of 0.075 mmHg/mmHg (range 0.006/0.140).

To our knowledge, no study has been conducted showing changes in OPA before and after a short-term increase in IOP in human eyes as of yet. The purpose of this study was to investigate these changes and to assess possible influences by biometrical properties of the eye, including central corneal thickness (CCT) and axial length.

Methods

This was a prospective, single centre study conducted at the Department of Ophthalmology, University Hospital of Zurich. As an easily accessible and non-hazardous *in vivo* human eye model for short-term IOP changes, we chose eyes of patients with exudative age related macular degeneration (AMD) who underwent intravitreal anti-vascular endothelial growth factor (VEGF) treatment. It is known that IOP is increased shortly after the intervention (Kim et al. 2008; Knecht et al. 2009).

Patients with exudative AMD were enrolled. Informed written consent was obtained from each subject, adhering to the tenets of the Declaration of Helsinki. The study protocol was approved by the local ethics committee. Patients

with a history of glaucoma, a history of ocular surgery (except previous intravitreal injections and uncomplicated cataract surgery), use of IOP-lowering agents, inability to comply with repeated contact IOP measurements or an IOP > 25 mmHg prior to injection were excluded from the study.

All injections were performed by the same ophthalmic surgeon (SM) employing two different injection techniques (tunnelled or straight scleral intravitreal injection) (Knecht et al. 2009). This protocol leads to different amounts of vitreous reflux and therefore to different postoperative IOP levels after identical amounts (in this study: 0.05 ml) of anti-VEGF injection (Benz et al. 2006; Knecht et al. 2009). The patients were randomly allocated to one injection technique.

The main outcome measures were postoperative (post)-OPA and postoperative-IOP values. Secondly, we investigated the potential relationship between the IOP before and after intravitreal injection and the difference between baseline and post-OPA (delta OPA). Additionally, the influence of CCT and axial length on OPA changes after short-term IOP elevation was assessed.

IOP, OPA, central corneal thickness and axial length measurement procedure

Intraocular pressure and OPA measurements were performed with a slit lamp-mounted dynamic contour tonometer (PASCAL; Swiss Microtechnology AG, Port, Switzerland) by the same experienced investigator (PBK). Post-IOP measurements were taken immediately after moving the patient from the operating table to the slit lamp. Only readings with the quality index ('Q') 1 or 2 (range: 1–5, 5 being the lowest measurement quality) were considered for analysis. Because the displayed result on the pressure device cannot be modified by the investigator, the IOP readings were not masked.

Central corneal thickness and axial length were determined with the Tomey AL-2000 biometer/pachymeter (Tomey Corp., Nagoya, Japan). The average of 10 measurements was included in statistical analysis.

Statistical analysis

Normal distribution of the data was analysed using the Kolmogorov–Smir-

nov test. Baseline OPA and post-OPA as well as baseline IOP and post-IOP were compared employing a paired *t*-test. Delta OPA was calculated for every patient and two linear regressions were performed with post-IOP and delta IOP as the independent and delta OPA as the dependent variable. A multiple regression analysis was used to analyse relations between delta OPA and independent variables (baseline IOP, post-IOP, CCT, axial length). Differences in delta OPA and delta IOP between patients treated with the tunnelled versus the straight intravitreal injection technique were assessed employing an unpaired *t*-test.

A *p*-value below 0.05 was considered to be statistically significant. No outliers were excluded. Randomization was performed using <http://www.randomization.com>. Statistical analysis was performed using the statistics software GRAPHPAD PRISM Version 4.02 (GraphPad software Inc., San Diego, CA, USA).

Results

Six patients were excluded because of IOP readings > 25 mmHg prior to injection. One patient was excluded due to failure of output routine of the DCT device to calculate an accurate IOP because of a low OPA (< 1.0 mmHg) prior to the injection. Forty eyes of 40 patients remained eligible for the study. Baseline characteristics and demographics of the study patients are presented in Table 1. No intraoperative or short-term postoperative complications occurred.

Ocular pulse amplitude changes

There was a significant increase in IOP (mean \pm SD in mmHg) right after the injection (Fig. 1A, post-IOP 36.58 ± 9.7 , range: 14.20–58.10, $p < 0.001$, mean of paired differences: 17.83 ± 9.83 , 95% confidence interval (CI) 14.68–20.97). A significant increase in OPA right after the injection was also observed (Fig. 1B, post-OPA 4.13 ± 1.65 range: 1.40–7.70, $p < 0.001$, mean of paired differences: 1.39 ± 1.16 , 95% CI 1.02–1.76). Twenty-one patients were injected with the tunnelled intravitreal injection technique and 19 with straight intravitreal injection. There was no significant difference between the two injection

techniques regarding delta OPA (mean of differences tunnelled versus straight intravitreal injection: 0.58 ± 0.36 mmHg, $p = 0.118$) or delta IOP (mean

of differences tunnelled versus straight intravitreal injection: 3.19 ± 3.11 mmHg, $p = 0.311$). A summary of all measurements splitted for different intravitreal injection techniques is presented in Table 2.

Table 1. Baseline demographic information.

Age (years \pm SD)	
Mean	79 \pm 8
Range	63–91
Sex (%)	
Male	13 (32.5)
Female	27 (67.5)
Study eye (%)	
Right	22 (55)
Left	18 (45)
Drug (0.05 ml) (%)	
Ranibizumab	36 (90)
Bevacizumab	4 (10)
Lens status in study eye (%)	
Phakia	23 (57.5)
Pseudophakia	17 (42.5)
Measurements (mmHg \pm SD)	
Intraocular pressure	18.75 \pm 3.20
Ocular pulse amplitude	2.74 \pm 1.03
Biometrical properties	
Central corneal thickness (μ m \pm SD)	549.93 \pm 32.03
Axial length (mm \pm SD)	23.18 \pm 0.93

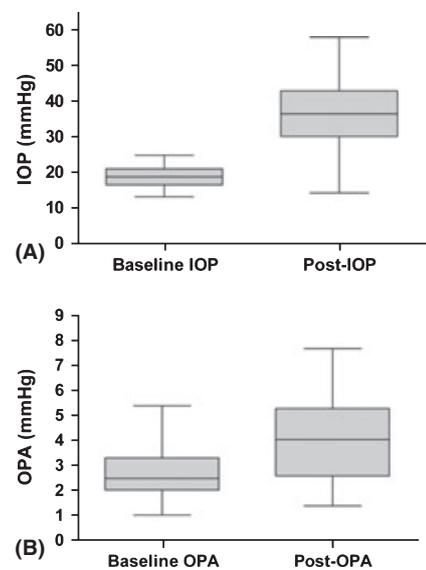


Fig. 1. Box plots show the distribution of intraocular pressure (IOP) (A) and ocular pulse amplitude (OPA) (B) measurements before (baseline), and < 1 min after (post)-intravitreal injection of 0.05 ml anti-VEGF agent.

Regression analyses

Post-IOP showed a statistically significant linear regression with the corresponding delta OPA values (slope 0.05, 95% CI: 0.02–0.09, $p = 0.003$, $r^2 = 0.20$, Fig. 2A). For every mmHg

increase in IOP, the OPA showed an increase of 0.05 mmHg. A similar analysis with delta IOP as the independent variable was also statistically significant (slope 0.06, 95% CI: 0.03–0.09, $p = 0.001$, $r^2 = 0.26$, Fig. 2B).

Multiple regression analysis with delta OPA as the dependent variable and baseline IOP, post-IOP, CCT and axial length as independent variables revealed a partial correlation coefficient of -0.26 ($p = 0.084$) for baseline IOP, 0.47 ($p = 0.003$) for post-IOP, 0.09 ($p = 0.518$) for CCT and 0.024 ($p = 0.873$) for axial length. The correlation coefficient r was 0.525 , $p < 0.021$. Multicollinearity was not observed.

Discussion

This study reveals three main findings. First, there is a significant increase in OPA upon short-term IOP increase. Secondly, we found no influence on OPA increase by CCT or axial length. Additionally, the extent of the OPA increase became less at very high IOPs.

Several studies established that increased IOP results in reduction of the choroidal blood flow (Dollery et al. 1968; Polska et al. 2007). Because Schilder (1994) suggests that the OPA may be regarded as a clinical window to ocular blood flow, in particular its pulsatile component (Silver et al. 1989), a decrease in choroidal blood flow should lead to a decrease in OPA, as shown by Langham et al. (1989). Our data clearly show the opposite and are consistent with results from Dastiridou et al. (2009) and Stalmans et al. (2008), who also reported an increase in OPA when IOP is elevated. It seems that high OPA measurements at elevated IOP levels are not necessarily a direct sign of increased choroidal blood flow and may be misleading when applied for this particular diagnostic purpose. It is known that the elastic properties of the eye change at higher IOP levels (Silver & Geyer

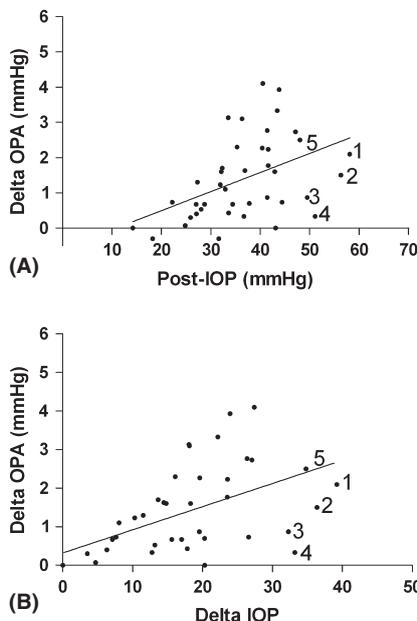


Fig. 2. (A) Concordance of intraocular pressure (IOP) measurements after intravitreal injection (Post-IOP) and difference of ocular pulse amplitude measurements before and after intravitreal injection (Delta OPA). Black solid line: the linear function of the data Post-IOP versus Delta OPA. Linear regression using Delta OPA as the dependent variable and Post-IOP as the independent variable gives a slope of 0.05. In patients numbered 1 through 4, the OPA increase is markedly reduced compared to patients with post-IOP levels < 49 mmHg. (B) A similar analysis using delta OPA as well as the dependent but delta IOP as the independent variable (slope 0.06). Patient no. 5 shows a high delta IOP similar to no. 1–4 but a markedly higher delta OPA which might be explained by a lower post-IOP (47 mmHg).

Table 2. A summary of the mean OPA and IOP measurements (mmHg \pm SD) splitted for different injection techniques.

	Baseline OPA	Post OPA	Delta OPA	Baseline IOP	Post IOP	Delta IOP
Tunnelled injected patients ($n = 21$)	2.84 \pm 1.00	4.51 \pm 1.57	1.67 \pm 1.26	18.19 \pm 3.19	37.54 \pm 8.45	19.35 \pm 9.26
Straight injected patients ($n = 19$)	2.62 \pm 1.08	3.71 \pm 1.67	1.09 \pm 0.99	19.37 \pm 3.18	35.53 \pm 11.05	16.15 \pm 10.42

OPA, ocular pulse amplitude; IOP, intraocular pressure.

2000). Scleral wall tension increases and exerts more resistance to the expanding choroid during the systolic phase. The pulsatile increase in choroidal thickness is pronounced and leads to an increase in OPA rather than an additional expansion of the already prestretched outer shells of the globe (Wegner 1930).

The continuous linear increase in the difference between baseline and post-OPA and post-IOP seems to discontinue at very high values above 49 mmHg. Regarding the post-IOP levels of patients numbered 1 through 4 (two with each injection technique) in Fig. 2, the OPA increase is tendentially lower compared to most patients with post-IOP levels below 49 mmHg. Patient no. 5 shows a high delta IOP similar to no. 1–4 but a markedly higher delta OPA. Because the post-IOP is 47 mmHg, this patient's measurements do not contrast the postulated hypothesis. However, this may be attributed to random scatter of data. An infinite continuity of an OPA increase is obsolete, because the ocular perfusion is defined by the pressure gradient between the blood pressure within the ophthalmic artery and the IOP (Langham et al. 1989; Polska et al. 2007). IOP levels greater than the blood pressure within the ophthalmic artery lead to an interruption of blood flow into the eye and therefore annihilation of the OPA. Bynke reported in early 1968 that in an experimental setting with rabbit eyes, the increase in IOP is paralleled by an increase in OPA (Bynke 1968). At higher IOP levels, the OPA diminished again. This might also be true for live human eyes. However, because our protocol did not include arterial blood pressure measurements, and because there was only a small number of patients with very high IOP values, further studies are needed to confirm this hypothesis.

It is well known that biomechanical properties of the eye might influence the OPA. A long axial length leads to smaller OPA measurements because of several reasons:

(1) The longer the eye, the higher the intraocular volume and the smaller the relative intraocular volume change caused by the same amount of choroidal blood inflow.

(2) Changes in ocular rigidity with increasing axial length.

(3) The longer the axial length, the less the amount of pulsatile flow (To'mey et al. 1981; James et al. 1991).

Thus, we assumed that a longer axial length would lead to a smaller increase in OPA after increasing the IOP. However, our multilinear regression analysis did not reveal such a dependency. There may be two underlying reasons: First, we also did not find any correlation between baseline OPA and axial length (Pearson's $r = 0.07$, $p = 0.66$), in contrast to other studies (James et al. 1991; Kaufmann et al. 2006; Berisha et al. 2010). Kaufmann et al. reported a negative correlation of OPA and axial length. Their study population showed a median axial length of 24.3 mm with an interquartile range (IQR) from 22.8 to 26.4 mm. Also, the study of Berisha et al. reported a mean axial length of 25.15 mm with a standard error of mean of 2.07 mm and a wide range from 19.98 to 29.50 mm. Our study population showed a median of 23.17 mm with a considerably smaller IQR from 22.58 to 23.61 mm. This might be the reason why we did not find such correlation. One strength of the study was to be able to exclude axial length as an influence on possible correlation of IOP with OPA.

Secondly, because only 0.05 ml of anti-VEGF agent was injected, longer eyes might have shown less increase in IOP and therefore the OPA increase was not that pronounced. However, this would have been indicated by our multilinear regression analysis, where we did not find multicollinearity. CCT may also influence IOP and therefore OPA measurements, which is extensively discussed in the literature. DCT has been shown to be largely independent of CCT, which is also confirmed by our own data (Kniestedt et al. 2004; Kaufmann et al. 2006).

A deficit in our study design might be the fact that our model is based on eyes with pathologic changes, i.e. exudative AMD. Pallikaris et al. (2006) reported that eyes with exudative AMD show increased ocular rigidity measurements. This leads to a steeper pressure–volume relation and, according to the study reported by Friedman et al. (1989), to an impaired filling of

the vortex veins as well as an increase in resistance of the choroidal vessels. Accordingly, Mori et al. (2001) reported a low OPA in patients with exudative AMD compared with patients with non-exudative AMD and normal subjects. Overall decreased choroidal blood with increasing severity of the AMD [e.g. (Grunwald et al. 2005)] would impair a demonstration of a positive relationship between IOP and OPA and therefore rather strengthens our findings. In addition, no significant impairment of the choroidal autoregulation has been shown for patients with AMD (Metelitsina et al. 2010). Only within a – in comparison with the whole choroidal circulation – relatively small choroidal neovascularization (CNV), a secondary focal increase in blood flow as indicator for focal loss of autoregulation has been reported in patients with AMD (Pournaras et al. 2006). It is highly unlikely that this might influence the OPA.

The arterial blood pressure, as demonstrated by Polak et al. (2003), has a small but significant influence on choroidal blood flow. And because a decrease in choroidal blood flow should lead to a decrease in OPA, as shown by Langham et al. (1989), it is hence reasonable to assume that the OPA must be dependent on arterial blood pressure. However, there are studies that clearly show the opposite (Grieshaber et al. 2009; Schmidt et al. 1998), where no changes in OPA despite different or varying (in terms of physical exercise) arterial blood pressure were found. We therefore chose not to measure the arterial blood pressure because of lack of methodological evidence. The lack of arterial blood pressure measurements however did not give us the possibility to declare whether the delta IOP was influenced by systemic hypertension. Kiel (1995) and in particular Bayerle-Eder et al. (2005) demonstrated a dependence of the ocular rigidity on mean arterial blood pressure. It is reasonable to assume that elevated mean arterial blood pressure, which yields an increased ocular rigidity, might lead to an increased elevation in OPA because of the stronger resistance of the ocular shells as described in the introduction.

To describe the influence of IOP on the function of the eye, considerable

effort has been made to establish a model. Silver & Geyer (2000) developed a more general relationship between pressure and volume on the basis of a globe. Kotliar et al. (2007) published a biomechanical model also using a globe shape. Berisha et al. (2010) elaborated on a geometrical model with different radii between the sclera and the choroid/retina to describe the dependence on ocular pulse pressure. These articles portray a highly sophisticated understanding of the physiological changes of the globe shape during different phases of the cardiac cycle.

These models may be amended by further considerations. We can assume two interface areas, one where the eye encounters a surrounding allowing only a very low compressibility, thus the posterior segment, and in contrast, the highly compressive air interface of the anterior segment. The lens plane could be considered as the dividing anatomical site, because the eyelid exerts only little rigidity on this part of the sclera. Adhering to these assumptions, most of the action on a change in internal pressure of the eye, being it static or dynamic, will manifest at the cornea. The combined lens and iris diaphragm might act dynamically as a moving plunger. To understand the physical properties, we would then consider the cornea as a flexible membrane in a first approximation. Assuming viscoelastic properties, one expects a linear dependence on e.g. increasing IOP. The dynamic behaviour OPA, our site of interest, should also behave linear. The topic of this work was not designed to prove a pursuing model, but it might be worthwhile to design further studies to do so.

In conclusion, we showed a clear positive correlation between OPA and IOP measurements in a clinical routine setting using DCT focusing on baseline and postinterventional comparisons of OPA values in patients with exudative AMD, and that this linear correlation might be interrupted at very high IOP levels, assuming an impaired filling of the blood vessels within the eye. We found no correlation of the increase in OPA with biometrical properties of the eye. In further studies employing the OPA for diagnostic purposes, we urgently rec-

ommend indication of the corresponding IOP values.

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