

# Ocular Rigidity, Ocular Pulse Amplitude, and Pulsatile Ocular Blood Flow: The Effect of Intraocular Pressure

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**PURPOSE.** The purpose of this study was to characterize the pressure–volume relation in the living human eye, measure the ocular pulse amplitude (OPA), and calculate the corresponding pulsatile ocular blood flow (POBF) in a range of clinically relevant IOP levels.

**METHODS.** Fifty patients with cataract (50 eyes) were enrolled in the study. After cannulation of the anterior chamber, a computer-controlled device for the intraoperative measurement and control of IOP was used to artificially increase the IOP in a stepping procedure from 15 to 40 mm Hg. The IOP was continuously recorded for 2 seconds after each infusion step. The pressure–volume relation was approximated with an exponential fit, and the ocular rigidity coefficient was computed. OPA, pulse volume (PV), and POBF were measured from the continuous IOP recordings.

**RESULTS.** The average rigidity coefficient was  $0.0224 \mu\text{L}^{-1}$  (SD 0.0049). OPA increased by 91% and PV and POBF decreased by 29% and 30%, respectively, when increasing the IOP from 15 to 40 mm Hg. The OPA is positively correlated with the coefficient of ocular rigidity ( $r = 0.65$ ,  $P < 0.01$ ).

**CONCLUSIONS.** The present results suggest a nonlinear pressure–volume relation in the living human eye characterized by an increase in rigidity at higher IOP levels. The increased OPA and decreased pulse volume relate to the decreased POBF and the increased mechanical resistance of the ocular wall at high IOP levels. (*Invest Ophthalmol Vis Sci.* 2009;50:5718–5722) DOI: 10.1167/iovs.09-3760

Intraocular pressure (IOP) is the primary mechanical load that affects ocular structures and the primary risk factor for the development of glaucoma. The fluctuation of IOP with the heart rate, being equal to the difference between systolic and diastolic IOP is the ocular pulse amplitude (OPA). OPA is a parameter that can easily and noninvasively be measured with pneumotonometers or dynamic contour tonometry. The pulsatile blood volume that flows through the eye is directly related to the OPA through the derivative of the eye's pressure–volume relationship. Moreover, real-time recordings of intraocular pressure (IOP) variations with the cardiac pulse are used in ocular blood flow systems that employ pneumotonom-

eters to estimate the pulsatile component of ocular blood flow (POBF) through processing algorithms.<sup>1–2</sup>

POBF is a global index of blood flow in the eye and has been suggested to represent a significant percentage of the total (pulsatile and steady) ocular blood flow. It reflects primarily (by 85%) the choroidal circulation,<sup>3</sup> whereas the retinal contribution is small. The noninvasive measurement of the pressure waves with pneumotonometry has yielded important determinants of POBF. In various studies, it has been shown to vary with age,<sup>4,5</sup> posture,<sup>6</sup> axial length,<sup>7</sup> and the presence of diabetic retinopathy,<sup>8</sup> glaucoma,<sup>9,10</sup> retinitis pigmentosa, and age-related macular degeneration.<sup>11,12</sup>

The effect of IOP on ocular blood flow has been investigated by various methods,<sup>13–17</sup> and IOP has been suggested to affect both OPA and POBF. An increase in OPA with increased IOP has been reported in studies comparing OPA between individuals.<sup>18,19</sup> A decrease in POBF during an induced increase in IOP has been suggested,<sup>20</sup> whereas no relationship between IOP and POBF was found in a study comparing POBF between individuals.<sup>21</sup> However, a limitation to the noninvasive POBF estimate is the lack of a method that can accurately assess ocular rigidity.

There is therefore evidence that OPA and POBF can be affected by IOP. The purpose of this study was to establish the pressure–volume relationship in the living human eye and also to investigate and quantify the change in OPA and POBF during a short-term artificial increase in IOP, in the same range of clinically relevant IOP levels in all eyes.

## METHODS

Fifty patients (50 eyes) who were undergoing cataract surgery were enrolled in this study. Subjects who had a systemic medical history, had other ocular disease, or had undergone previous ophthalmic surgery were excluded. A thorough ophthalmic examination, including slit lamp biomicroscopy and funduscopy, was performed before the patients were included. IOP was measured in patients in the sitting position with Goldmann applanation tonometry before surgery.

The study adhered to standards outlined in the Declaration of Helsinki and was approved by the Institutional Review Board. The purpose of the study and the measurement procedure were fully explained to all patients, and they were eligible to participate after they signed an informed consent.

The measurement was performed in one eye per patient. Tropicamide and phenylephrine drops were applied to the eye scheduled for operation according to the standard procedure. Systemic blood pressure and pulse rate were monitored. The measurement was performed under sterile conditions before cataract surgery, under topical anesthesia with proparacaine and lidocaine drops, and with the patient in a supine position. A computer controlled device for the intraoperative measurement and control of IOP was used. In brief, the device consists of three units: a pressure sensor (sampling rate 200 Hz, effective pressure sensitivity 0.05 mm Hg), a dosimetric syringe drive unit (volume sensitivity 0.08  $\mu\text{L}$  per step), and a circuit of sterile inextensible tubes (Vygon, Ecouen, France), filled with balanced salt solution. During the preparation of the system, an effort was made to avoid the possibility of leakage or trapped air bubbles in the system. Custom

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software was developed (LabView; National Instruments Inc., Austin, TX) to control the measurement procedure.

In the beginning of the procedure, the system is calibrated to the height of the eye. To cannulate the anterior chamber, the surgeon performs a long tunnel cornea cut, using a 19-gauge knife, in a way that only part of the tip of the knife cuts through Descemet's membrane, and a 21-gauge needle is inserted in the anterior chamber allowing for free communication between the eye and the measurement system. This technique along with the continuous inspection of the cannulation site under the operating microscope throughout the measurement was followed to avoid and visualize probable leaks, so that the measurement would be discarded.

After insertion of the needle, initial IOP is recorded, and the IOP is set to 15 mm Hg with appropriate balanced salt solution-aqueous exchange. The IOP is artificially increased from 15 to 40 mm Hg, by perfusing the anterior chamber with balanced salt solution in steps of 4  $\mu\text{L}$ . The same range of pressures was used in every eye. After each step, IOP is continuously recorded with a sampling frequency of 200 Hz for 2 seconds, to measure the pulsatile change in IOP during this interval. In practice, there is a need for an equilibration period after each infusion step, which was 0.5 seconds for the system used, based on experiments conducted in rabbit eyes. When the IOP is raised to 40 mm Hg, the infusion stops and the system is left to record the decaying IOP for a period of 1 minute. The duration of the measurement was 2 to 3 minutes.

### Data Analysis

An algorithm based on the SD of the pressure readings was developed to assess the maximum IOP fluctuation in synchrony with the heart rate, during each 2-second recording, to evaluate OPA. The pressure-volume curve was estimated by plotting the average IOP after each infusion step against the infused volume. An estimation of the outflow facility, based on the eye's recorded decay curve, was used to correct the initial pressure-volume curve for volume loss through the outflow pathways of the eye during the stepping procedure. The corrected pressure-volume relationship was fitted with an exponential curve, and the corresponding rigidity coefficient  $K$  was estimated for every eye, according to the equation  $P = P_0 \cdot \exp(K \cdot \Delta V)$ . The individual eye's pressure-volume relationship can be used to transform the pressure recordings to volume readings. Pulse volume was calculated as the product of the OPA to the local derivative of the pressure-volume curve. To calculate POBF, the real-time pressure signal was filtered, and POBF was estimated as the lowest value of volume flow  $dV/dt$  as proposed by Silver and Farrel<sup>1</sup>, during each 2-second tracing.

### Statistical Analysis

Statistical analysis was performed (SPSS ver. 16; SPSS, Inc., Chicago, IL) for Windows. Measured parameters are presented as the mean (SD). Intra-individual measurements of OPA and POBF values were analyzed in an analysis of variance, with IOP at five different levels as a within-subjects factor. Post hoc comparisons were performed using the Bonferroni adjustment for multiple comparisons. The level of significance was set at 0.05. Pearson correlation coefficients were computed to assess the relation between parameters. Multiple linear regression analysis was used to control for parameters that may also have affected the outcome variable.

### RESULTS

Fifty eyes were included in the study. The patients' baseline characteristics are presented in Table 1. The measurement proved to be safe and effective, as there were no intra- or postoperative complications related to the procedure. Systemic blood pressure and pulse rate remained stable in all patients during the measurement. Mean blood pressure (MBP) was calculated from systolic (SBP) and diastolic blood pressure (DBP) as  $\text{MBP} = \text{DBP} + 0.33(\text{SBP} - \text{DBP})$ .

TABLE 1. Patients' Characteristics

Variable	Mean $\pm$ SD (range)
Sex	20 men/30 women
Age, y	62 $\pm$ 12 (39-86)
Mean systemic blood pressure, mm Hg	94.9 $\pm$ 10.2 (70.3-111.7)
Pulse rate, beats/min	64 $\pm$ 9 (46-94)
Preoperative GAT IOP, mm Hg	12.9 $\pm$ 2.9 (6/18)

An exponential fit to the pressure-volume experimental data was justified by  $R^2$  (higher than 0.97). The coefficient of ocular rigidity ranged from 0.0127 to 0.0343  $\mu\text{L}^{-1}$  (mean, 0.0224, SD 0.0049  $\mu\text{L}^{-1}$ ; Fig. 1).

The average OPA was 2.00 (0.54) mm Hg for measurements conducted at 15 mm Hg, increasing by 91 (40)% to 3.83 (1.19) mm Hg at 40 mm Hg (Fig. 2A). A linear positive correlation between OPA and IOP was found in every eye (Pearson  $r > 0.93$ ,  $P < 0.01$ ). The median OPA increase was 0.075 (range, 0.006/0.140) mm Hg/mm Hg increase in IOP. Pulse volume was 6.00 (1.33)  $\mu\text{L}$  at 15 mm Hg decreasing by 29 (14)% to 4.26 (1.24)  $\mu\text{L}$  at 40 mm Hg. POBF was estimated to be 880 (162)  $\mu\text{L}/\text{min}$  at baseline, decreasing by 30 (13) % to 616 (144)  $\mu\text{L}/\text{min}$  (Fig. 2B). OPA, PV, and POBF at different IOP levels are shown in Table 2.

IOP was found to influence both OPA and POBF (repeated-measures ANOVA,  $P < 0.01$ ). Post hoc analysis revealed statistically significant differences in OPA and POBF between any IOP level ( $P < 0.01$ ), whereas pair-wise comparisons of POBF between the levels of 30 to 35 and 35 to 40 mm Hg of IOP resulted in a borderline  $P = 0.049$ .

A positive correlation between the rigidity coefficient and OPA (at an IOP of 15 mm Hg;  $r = 0.65$ ,  $P < 0.01$ ; Fig. 3), as well as the increase in OPA ( $r = 0.40$ ,  $P < 0.01$ ) was documented. The relation of OPA with the rigidity coefficient remained significant ( $P < 0.01$ ), after controlling for age ( $P = 0.91$ ), pulse rate ( $P = 0.71$ ), and mean blood pressure ( $P = 0.29$ ), by multiple regression analysis. The effect of the rigidity coefficient on the OPA increase was also significant ( $P < 0.01$ ) after controlling for age ( $P = 0.25$ ), pulse rate ( $P = 0.08$ ) and MBP ( $P = 0.40$ ).

The effect of systemic hemodynamics on OPA and rigidity was also evaluated. OPA did not correlate with systemic pulse pressure amplitude estimated from the difference between SAP and DAP ( $P = 0.22$ ). No correlation was found between the

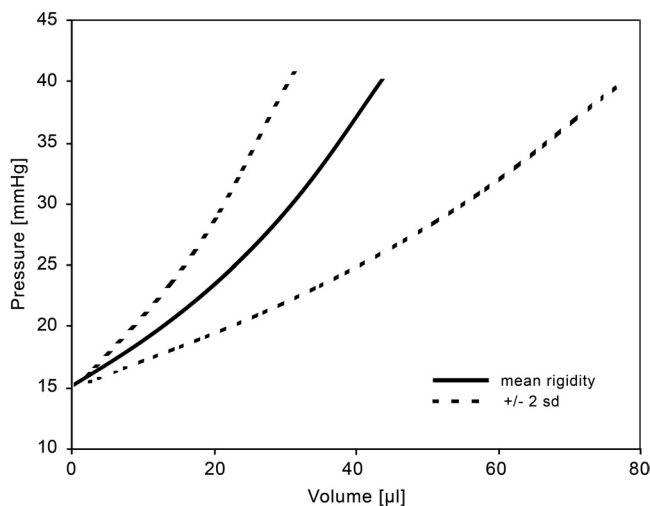
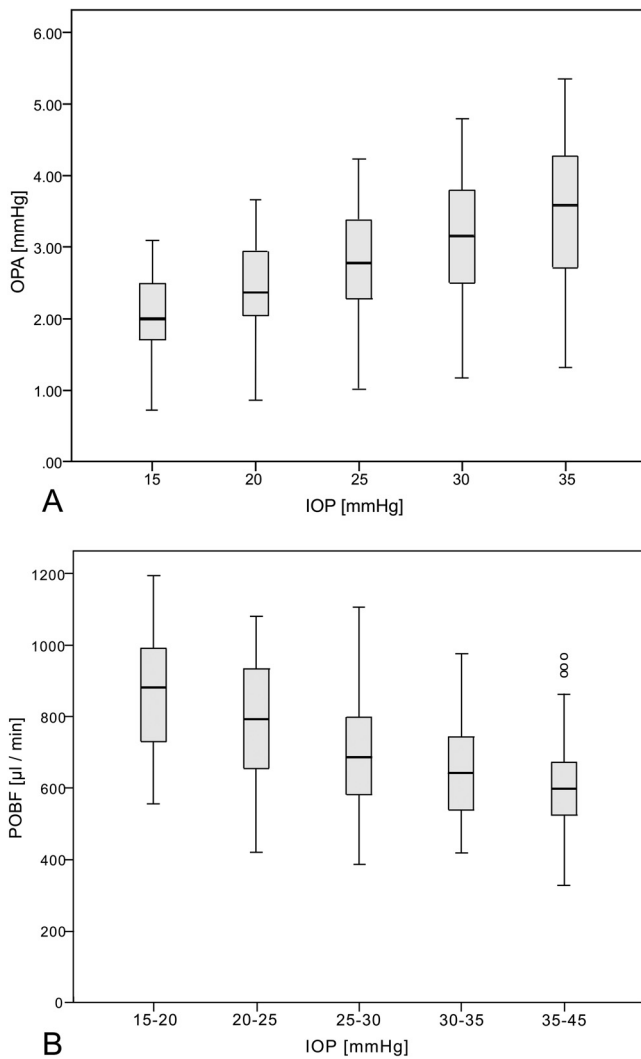


FIGURE 1. The average (and 95% confidence intervals) measured pressure-volume relation.

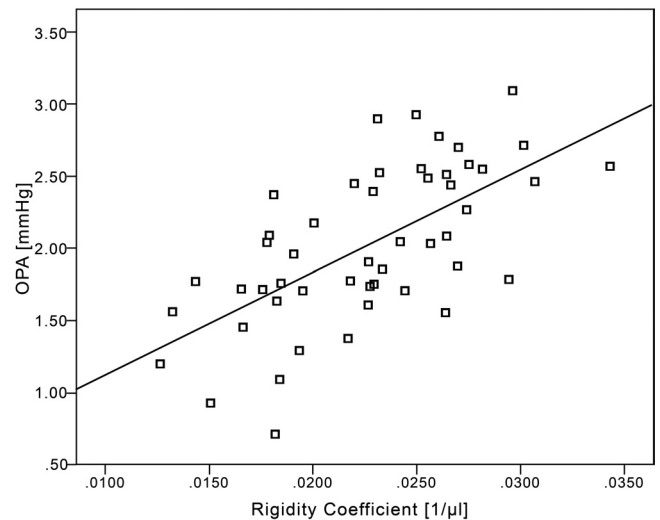


**FIGURE 2.** (A, B) OPA and POBF in five different IOP levels (repeated-measures ANOVA  $P < 0.01$ ). Pair-wise comparisons revealed a statistically significant difference ( $P < 0.05$ ) in OPA and POBF between any of the five IOP levels (outliers are marked by open circles).

rigidity coefficient and mean arterial blood pressure ( $P = 0.41$ ).

## DISCUSSION

In this study, an invasive manometric approach was used to establish the pressure-volume relationship in the living human



**FIGURE 3.** Relationship between the rigidity coefficient and OPA at an IOP of 15 mm Hg ( $r = 0.65$ ,  $P < 0.01$ ).

eye over a range of IOP from 15 to 40 mm Hg. This pressure range was selected because of its high clinical significance and was the same in all eyes tested, so as to avoid the possible effect of the initial IOP on the measurement. This is the first study to our knowledge that quantifies the pressure-volume relation in the living human eye under topical anesthesia with drops. A pilot study initially conducted to test the effect of retrobulbar anesthesia indicated altered results for the measured parameters compared with anesthesia with drops (data not shown). The difference was attributed to the volume of the anesthetic and the edema in the retrobulbar space and also its known hemodynamic effect<sup>22</sup> on the ocular circulation.

Friedenwald<sup>23</sup> in his original study proposed a coefficient of ocular rigidity as a measure of the resistance that the eye exerts against distending forces, based on a logarithmic pressure-volume relationship derived from data from enucleated eyes. Most measurements since then were performed in enucleated human eyes or *in vivo* by means of Schiøtz tonometry (paired readings, two IOP levels or applanation and indentation tonometry) and recently with the use of laser interferometry and ocular pulse amplitude measurements.<sup>24</sup> Pallikaris et al.<sup>25</sup> proposed a linear pressure-volume relation based on measurements conducted with an invasive manometric device on a large series of eyes measured under retrobulbar anesthesia. The present study demonstrates a nonlinear pressure-volume relation in the living human eye characterized by an increase in the slope of the curve in higher IOP levels, suggesting that the eye becomes more rigid as the IOP increases. The relation of the derivative of the pressure-volume relation (i.e., ocular rigidity

**TABLE 2.** Measured Parameters

	IOP (mm Hg)				
	15	20	25	30	35
Ocular pulse amplitude, mm Hg	2.02 $\pm$ 0.54 (0.71-3.09)	2.38 $\pm$ 0.63 (0.86-3.66)	2.75 $\pm$ 0.75 (1.01-4.22)	3.11 $\pm$ 0.88 (1.16-4.79)	3.47 $\pm$ 1.03 (1.31-5.36)
Pulse volume, $\mu\text{L}$	6.03 $\pm$ 1.32 (2.61-8.74)	5.33 $\pm$ 1.17 (2.37-7.87)	4.91 $\pm$ 1.15 (2.23-7.67)	4.63 $\pm$ 1.17 (2.13-7.53)	4.43 $\pm$ 1.20 (2.06-7.43)
Pulsatile ocular blood flow, $\mu\text{L}/\text{min}$	880 $\pm$ 163 (556-1195)	791 $\pm$ 173 (420-1080)	700 $\pm$ 160 (386-1106)	649 $\pm$ 142 (418-975)	616 $\pm$ 144 (328-970)

Data are presented as the mean  $\pm$  SD (range). OPA is estimated from the linear fit to the OPA versus IOP in each eye. PV is the volume corresponding to the OPA. POBF is presented as the mean of values corresponding to the IOP ranges of 15-20, 20-25, 25-30, 30-35, and 35-40 mm Hg, accordingly.

( $dP/dV$ ), with IOP also suggests that the latter is a major determinant when comparing estimates of ocular rigidity.

Moreover, the pressure-volume relation in the human eye is generally in accordance with the results presented by Silver et al.,<sup>26</sup> who reanalyzed the data in the literature obtained with manometric techniques by different investigators from 21 living eyes scheduled for enucleation. The values for the coefficient of ocular rigidity are also similar to the results by Pallikaris et al.,<sup>25</sup> but lower, and they contradict the results of Friedenwald<sup>23</sup> based on paired Shiotz readings. The corresponding Friedenwald coefficient of ocular rigidity estimated from our data would be  $0.0098 \mu\text{L}^{-1}$ , suggesting a smaller pressure increment due to a given volume change than the value of  $0.0215 \mu\text{L}^{-1}$  described by Friedenwald. The relation presented herein may be more accurate to incorporate in the estimation of outflow facility coefficient by means of tonography, and the noninvasive measurement of POBF with pneumotometry. They may also have implications in the prediction of the short term effect of a rise in ocular volume (e.g., by means of an intravitreal injection).

Kiel<sup>27</sup> in his experiments on anesthetized rabbits suggested that the initial part of the pressure-volume curve is influenced by systemic blood pressure. Similar findings were not observed in our measurements, a difference that may be attributed to the measurement methodology. It is possible that the eye responds differently to changes in perfusion pressure induced by changes in systemic blood pressure compared with manipulations of the IOP.<sup>28</sup>

OPA has been proposed as an indirect index of ocular hemodynamics and is regarded as the pulsatile fluctuation in IOP produced by the inflow of each bolus of blood. This pulsatile change in IOP is directly related to the rigidity of the ocular coats that dampen the pulsations, suggesting that a higher OPA may be found in eyes with increased rigidity, due either to a higher rigidity coefficient or a higher IOP.

Lawrence and Schlegel,<sup>29</sup> with their cannulation experiments on anesthetized rabbit eyes noticed a marked increase in OPA with IOP in the same range of pressures presented herein, in accordance with our results. On the contrary, Langham and To'Mey<sup>30</sup> reported a marked decrease in OPA in the range of IOPs of 20 to 40 mm Hg in each of the eyes measured. They induced large increments of IOP employing a suction cup in humans and recorded the OPA with the use of a pneumotonometer. It is possible that the deformation of the globe produced by the suction cup may have altered the OPA readings or that the induced IOP change was significantly higher than that reported.<sup>31</sup> In the present study, an increase in OPA with increasing IOP in every eye tested was obtained.

OPA has also been shown to be affected by IOP in studies comparing OPAs between individuals.<sup>18,19</sup> In the study by Kaufmann et al.,<sup>18</sup> the mean OPA increase measured with dynamic contour tonometry in normal eyes was 0.12 mm Hg/mm Hg increase in IOP, a value that is higher than the 0.075-mm Hg/mm Hg increase in IOP reported herein. Furthermore, a decrease in OPA has been reported in patients with glaucoma after trabeculectomy and the amount of the decline has been suggested as a prognostic index of the long-term outcome.<sup>32</sup> The present study also demonstrates a positive correlation between OPA and IOP during a stepped increase in IOP in each individual eye. The increased OPA when IOP was artificially raised suggests that IOP is critical to interpreting this parameter, even for intraindividual comparisons and that IOP and rigidity should be taken into account when OPA is used as an indirect estimate of POBF.

During the measurement, the artificial increase in the tissue pressure of the eye leads to a decrease in ocular perfusion pressure. As a result, an increase in OPA and decrease in POBF were observed. The increased OPA and decreased PV relate to

the decreased POBF and the increased mechanical resistance of the ocular walls at high IOP levels. The rigidity coefficient as a measure of both morphologic and biomechanical properties of the eye plays a key role to the fluctuation in pressure that results from the inflow of blood in every pulse. Although the pressure head, as the driving force of the pulsatile component of ocular blood flow, remained stable throughout the measurement procedure, the decrease in POBF suggests a change in vascular resistance with increasing IOP and possibly an altered pattern of pulsatile to steady blood flow in the eye in different IOP levels.

Moreover, in this study, the relationship between pulsatile ocular blood flow and IOP in normal eyes without ophthalmic history was documented, implying that IOP is a factor that can affect ocular blood flow in the absence of ocular disease and influence both mechanical and vascular properties of the eye. The results of this report cannot be necessarily extrapolated to glaucomatous eyes, as further studies are needed to characterize the relationship of OPA and POBF with IOP in patients with glaucoma. Our findings are in keeping with results from Quaranta et al.,<sup>20</sup> who reported a decrease in POBF in both normal subjects and patients with normal-tension glaucoma when IOP was increased in each eye in increments of 5 and 10 mm Hg. Moreover, decreased POBF has been reported in open-angle glaucoma and ocular hypertension,<sup>33,34</sup> whereas in treated glaucomatous eyes no difference could be detected,<sup>21</sup> compared with the control group. Aydin et al.<sup>21</sup> also reported a negative correlation between IOP and POBF in patients with glaucoma, whereas in the control group no relation was found.

Some limitations in the outcome of our study have to be considered, such as the subjects' supine position,<sup>6</sup> which has been associated with a change in steady state IOP, episcleral venous pressure, OPA, and POBF compared with the sitting position, and also the possible pharmacologic effect of mydriatics. The vasoconstrictive effect of phenylephrine may have affected our results, although it has been suggested not to have an impact on fundus pulsation amplitude measurements.<sup>35</sup> It should also be noted that measurements were conducted in otherwise healthy eyes scheduled for cataract surgery. The procedure's duration was kept short to minimize the effect of the presence of the cannula in the anterior chamber.

It is also of importance that the algorithms used for the estimation of POBF are based on the assumption that the outflow of blood is constant throughout the pulse.<sup>1,36</sup> Measurements conducted in animals<sup>37</sup> suggest that the relation between IOP and venous pressure is almost linear in primates in the range of IOPs studied herein.

Finally, the invasive technique used is shown to provide accurate estimates of OPA and POBF based on precise values of heart rate, rigidity, and the IOP variation as a function of time. Moreover, the IOP is manipulated in a way that can be thought to approximate the physiologic conditions, being more accurate compared with the application of a suction cup and without the confounding influence of medically induced IOP lowering.

In conclusion, IOP is a parameter that affects the pressure-volume relation, ocular pulse amplitude, and pulsatile ocular blood flow in the human eye. Quantifying the hemodynamic impact of IOP may aid in understanding glaucoma and ocular hypertension, as well as the beneficial effect of IOP lowering.

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