IOP, IOP Transient Impulse, Ocular Perfusion Pressure, and Mean Arterial Pressure Relationships in Nonhuman Primates Instrumented With Telemetry

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Purpose. To characterize relationships between intraocular pressure (IOP), mean arterial pressure (MAP), ocular perfusion pressure (OPP), IOP transient impulse, and IOP baseline impulse using continuous telemetry in nonhuman primates.

Methods. We used our validated implantable telemetry system to wirelessly record bilateral IOP and arterial BP at 500 Hz in 7 eyes of 4 male rhesus macaques, aged 4 to 5 years. IOP, MAP, OPP, IOP transient impulse, and IOP baseline impulse were averaged into 1-hour periods over 20 days for each NHP. IOP transient impulse was defined as the portion of total IOP due to transient IOP fluctuations <0.5 seconds duration alone and IOP baseline impulse as the remaining area under the IOP versus time curve. OPP was defined as arterial BP-IOP (calculated continuously), and MAP was the hourly average of the continuous BP curve. Relationships between the variables were analyzed for each 24-hour period using either multivariate linear regression or Spearman Correlation Coefficients as appropriate.

Results. Over twenty 24-hour periods, IOP transient impulse and OPP showed significant positive relationship in all eyes, which was driven largely by the data during waking hours. There was no significant relationship between IOP and MAP, IOP transient impulse and MAP, or IOP baseline impulse and IOP transient impulse.

Conclusions. There are significant positive relationships between the frequency and/or size of transient IOP fluctuations (IOP transient impulse) and OPP. A possible explanation of this finding is that higher OPP, as well as a greater number of blinks and saccades (the primary sources of IOP transients), are associated with increased activity.

Keywords: IOP, ocular perfusion pressure, mean arterial pressure, nonhuman primate, telemetry

Glaucoma, one of the leading causes of irreversible blindness, is generally thought to be caused by damage to the retinal ganglion cell axons at the optic nerve head (ONH).[1] Intraocular pressure (IOP) is a known risk factor for both the development and progression of glaucoma.[2,3] Lowering IOP is the only clinically proven method to prevent glaucoma and slow disease progression, although some patients develop glaucoma at statistically normal IOP levels,[4,5] and others continue to progress even after IOP is lowered.[6] Diurnal IOP fluctuations, measured hourly, have been reported as higher in glaucoma patients in some studies[7] and may be predictive of disease progression.

There have been conflicting reports as to whether mean arterial pressure (MAP) and ocular perfusion pressure (OPP) contribute to glaucoma or whether they have an influence on IOP.[5,8–13] Most studies have suggested that IOP and OPP are not strongly correlated despite IOP being a factor in the calculation of OPP (OPP = BP − IOP).[5,10–12] When interpreting these findings, it is important to consider that most previous studies have either used applanation tonometry, which cannot measure IOP continuously, or contact lens sensors, which can only measure circumferential corneal stretch presumably due to IOP fluctuations and not IOP itself. These IOP measurement methods either fail to capture transient IOP fluctuations (tonometry) or lack a method of calibration (contact lens sensor). Only contact lens sensors have been able to capture the frequency (but not magnitude) of transient IOP fluctuations over periods longer than a few seconds, and even then, only for discrete 24-hour periods of use.[14,15] Blood pressure (BP) is also generally measured with sphygmomanometry, which captures BP at a single time point using an indirect measurement that is also subject to errors.[16] As a result, studies of IOP dynamics as they relate to OPP dynamics have been impractical to date.

IOP is known to fluctuate at multiple timescales,[7,17–21] ranging from days to milliseconds, and current clinical approaches generally rely on single time point IOP measurements taken periodically during clinic office hours, which does not capture short-term IOP fluctuations. Hence, little is known about IOP fluctuations and how they relate to ocular physiology and disease. In addition, little is known about how

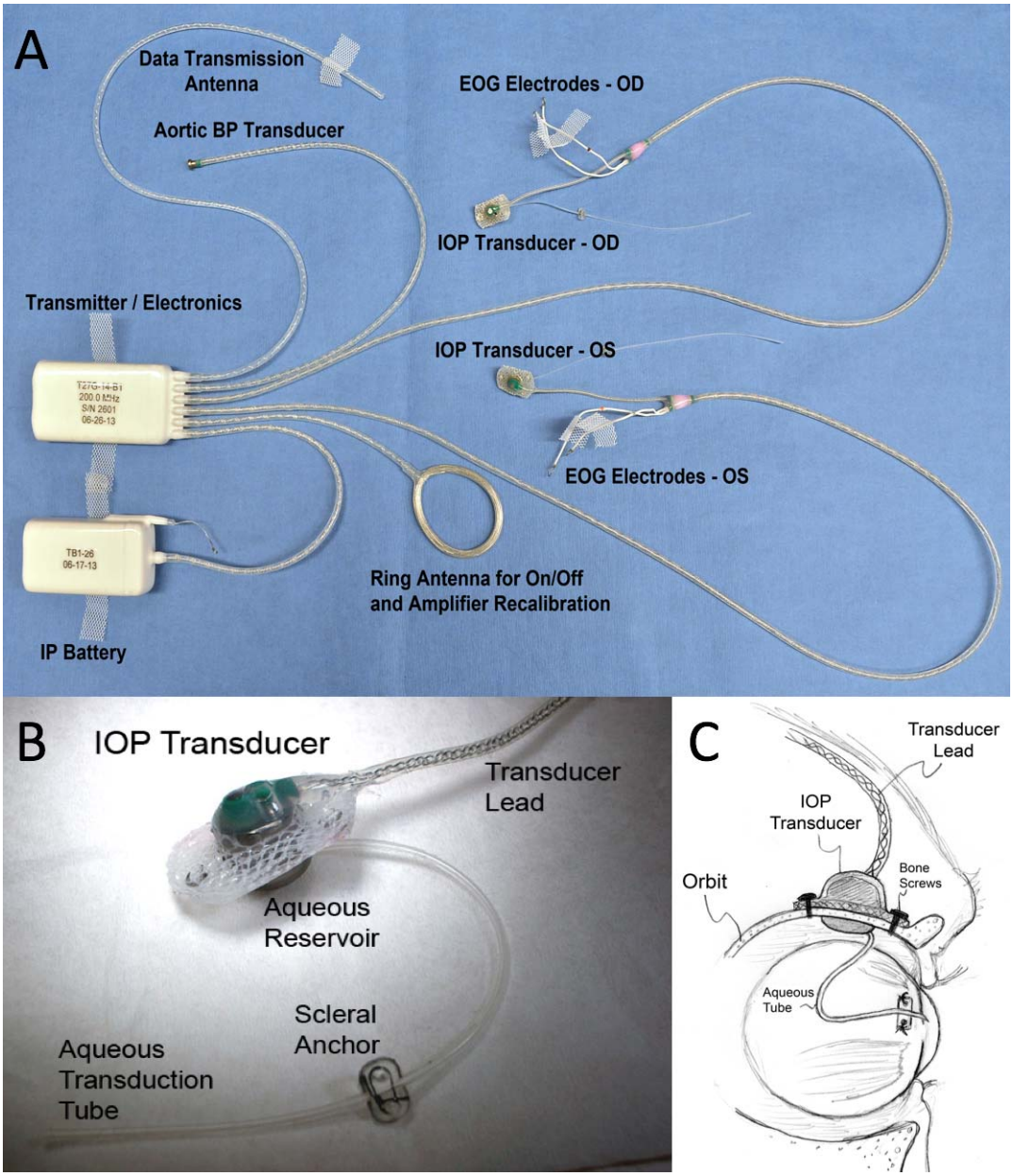

Figure 1. (**A**) The IOP/BP telemetry implant. (**B**) Close-up photo of the IOP transducer and aqueous transduction tube. (**C**) Surgical placement of the IOP transducer in the orbital wall and the aqueous transduction tube in the NHP eye.

dynamic IOP relates to other relevant physiologic variables, such as OPP and MAP that are known to influence ocular health. Although progress has been made on devices to monitor IOP continuously, there is no reliable method to do so at the time of this writing. Despite its inability to measure true IOP[22] (output is in millivolts), the contact lens sensor used (Sensimed Triggerfish; Sensimed AG, Lausanne, Switzerland) is able to measure the frequency of IOP transients such as blinks, and studies with Pascal dynamic contour tonometry (DCT; Ziemer Ophthalmic Systems AG, Switzerland) can assess ocular pulse amplitude (OPA).[20,21]

The purpose of the present study is to better understand the relationships between IOP and transient IOP fluctuations as they relate to MAP and OPP. We used a validated implantable telemetry system that wirelessly records 500 measurements of bilateral IOP and arterial BP per second continuously for up to 2.5 years[17] in rhesus macaques (NHPs). We recorded calibrated bilateral IOP and arterial BP, calculated and calibrated OPP, and examined the correlations between these variables in multiple 24-hour periods in multiple NHPs.

Methods

Animals

Animal studies were performed in accordance with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research, with procedures authorized and overseen by the Institutional Animal Care and Use Committee of the University of Alabama at Birmingham. The collection of data used in this study was a part of a larger study assessing the contribution of transient IOP fluctuations to the onset and progression of glaucoma. All animals were fed at approximately 6 AM and 2

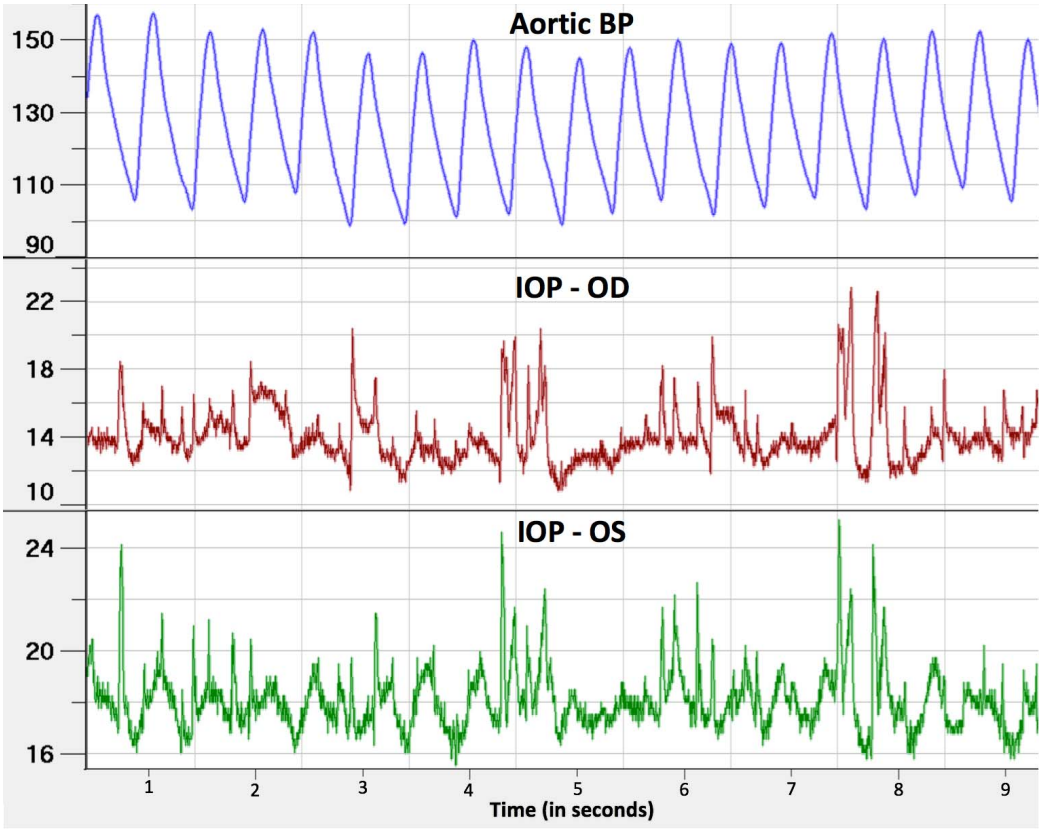

Figure 2. Sample of 9 seconds of pressure data from the telemetry system (in mm Hg). Note the similarity in transient IOP fluctuations between fellow eyes.

PM with a continuous feed available for water, neither of which were measured for this study. All animals were kept on a wake-sleep cycle from 6 AM to 6 PM. Seven normal eyes from four young adult male rhesus macaques 4 to 5 years of age were used in this study.

Bilateral IOP Telemetry System

We have developed and validated an implantable telemetry system that wirelessly records 500 measurements of IOP per second continuously for up to 2.5 years[1] (Fig. 1). Using an enhanced version of this system, bilateral IOP and MAP were continuously recorded using transducers in the orbital wall connected to the anterior chamber of both eyes with a silicone tube, and in the lumen of the aorta (Fig. 2). MAP was calculated directly as the mean of the continuous telemetric aortic blood pressure data, and not approximated using systolic and diastolic values. In order to obtain the most accurate data, both IOP and OPP were calibrated approximately every 2 weeks to account for transducer measurement drift, which is typically less than 1 mm Hg per week.

IOP Calibration

For IOP and OPP calibration, each NHP was placed under anesthesia every 2 weeks with both eyes cannulated with a 27 G needle placed through the cornea into the anterior chamber at the limbus. The needle was connected to a manometer bottle of sterile isotonic saline solution via a sterile infusion set, and the connecting tube fitted with an in-line digital pressure gauge (Model XP-2i; Crystal Engineering, San Luis Obispo, CA, USA) placed level with the needle insertion site in the eye. The manometer bottle was lowered until the in-line pressure gauge read 5 mm Hg, allowed to stabilize, and then the telemetric IOP readings from the implanted transducers were recorded for comparison. Similarly, manometer-controlled IOP was raised in increments of 5 mm Hg up to 45 mm Hg and the telemetric IOP readings were compared to that from the calibrated in-line pressure gauge at each step. Repeated aortic cannulation and direct site measurement would be required to calibrate the aortic BP transducer. Hence, the absolute values of MAP are not accurate, but relative changes in MAP within the 24-hour periods that are the basis of this study are accurately captured. We developed a novel approach to calibrate OPP from calibrated IOP telemetry measurements and uncalibrated aortic BP telemetry measures, using direct real-time observation of the IOP levels necessary to cause both momentary and full collapse of the central retinal artery (CRA) as it exits the ONH.

OPP Calibration

Ocular perfusion pressure is defined as the arterial blood pressure within the eye (BP – IOP) and we calculate it directly from the continuous IOP and aortic BP telemetry data as follows. To calibrate OPP using the calibrated IOP telemetry data and the uncalibrated aortic BP telemetry data, we measured central retinal artery (CRA) diastolic and systolic BP using ophthalmodynamometry (Fig. 3; Supplementary Video) as a function of continuous telemetric measurement of both IOP and aortic systolic and diastolic BP. By raising the IOP via manometry and observing the IOP levels at which momentary and full CRA collapse first occur (Fig. 3), we calculated the CRA diastolic (Fig. 3B) and systolic BPs (Fig. 3C).

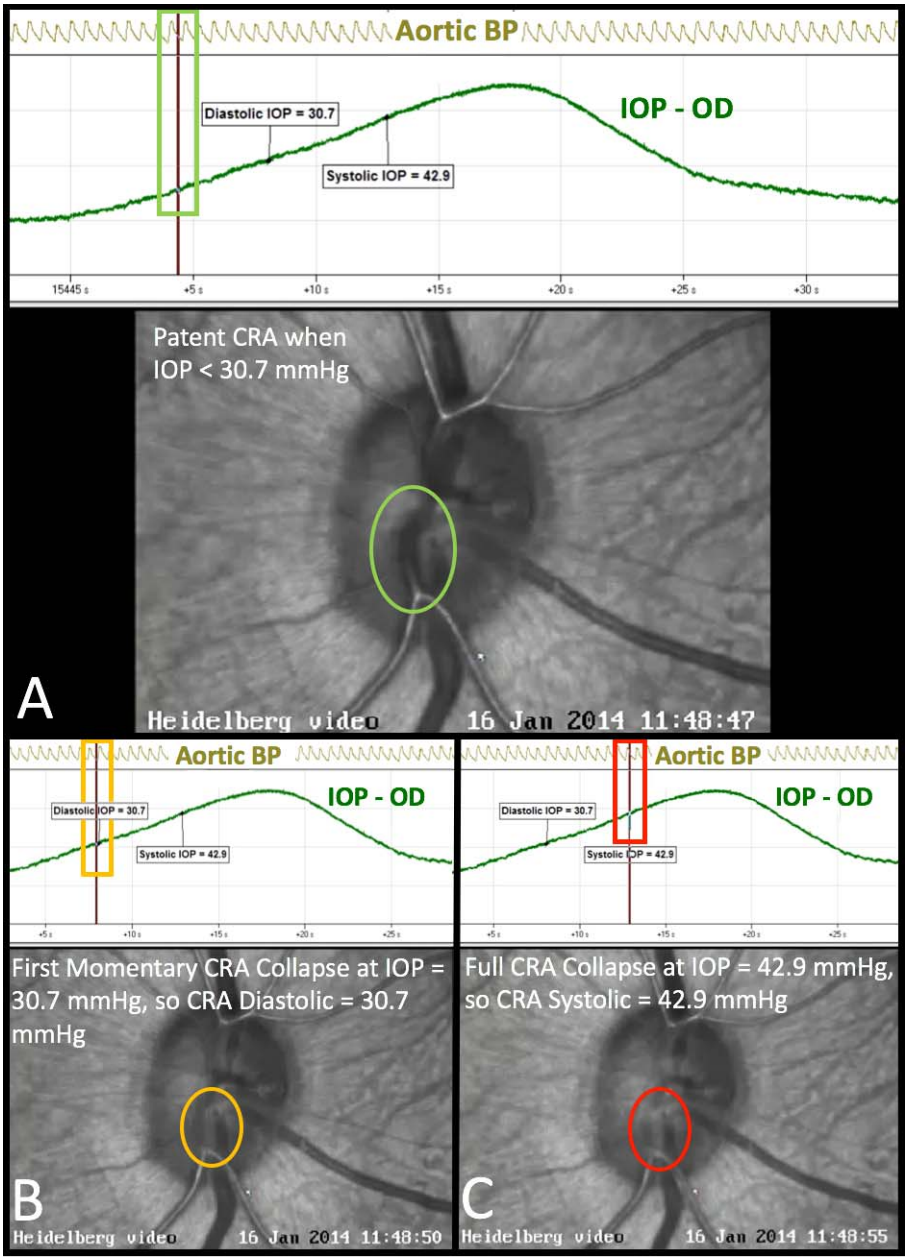

Figure 3. (**A**) IOP is manually elevated while IOP and aortic BP are monitored via telemetry and the ONH is visualized in real time using the infrared image from the Heidelberg Engineering Spectralis OCT device (Spectralis; Heidelberg Engineering, Heidelberg, Germany). The ONH video image is slaved into the NOTOCORD-hem data acquisition system along with the telemetry data stream; CRA patency is monitored. (**B**) The CRA first collapses momentarily at 30.7 mm Hg when IOP equals CRA BP, so CRA diastolic BP is 30.7 mm Hg. (**C**) The CRA fully collapses at 42.9 mm Hg when IOP equals CRA BP, so CRA systolic BP is 42.9 mm Hg. Please see Supplementary Video.

We then calculated continuous OPP directly from the telemetric aortic BP and IOP data streams between OPP calibration exams in Equation 1 below as:

$$OPP = \frac{(CRA\ systolic\ BP - CRA\ diastolic\ BP)}{(aortic\ systolic\ BP - aortic\ diastolic\ BP)} \times (aBP - aortic\ systolic\ BP) + CRA\ systolic\ BP - IOP, \quad (1)$$

where *aBP* and *IOP* denote the continuous aortic BP and IOP telemetric data, respectively. The aortic systolic and diastolic BP values in Equation 1 are captured along with the CRA diastolic BP at the time of OPP calibration (orange box, Fig. 3B). This estimate of OPP was calculated directly from the IOP and aortic BP (aBP) telemetry signals 500 times per second using aortic and CRA systolic and diastolic BP values as shown.

Quantification of IOP Impulse

To quantify the total IOP stress that the eye must withstand over time, we define Total IOP Impulse as the area under the continuous IOP versus time curve (Fig. 4). The IOP transient impulse was quantified as the portion of the area under the IOP versus time curve due to transient IOP fluctuations (the orange area above the momentary baseline IOP as shown in Fig. 4), which was used to quantify the IOP stress the ocular coat must absorb over time due to transient IOP fluctuations.

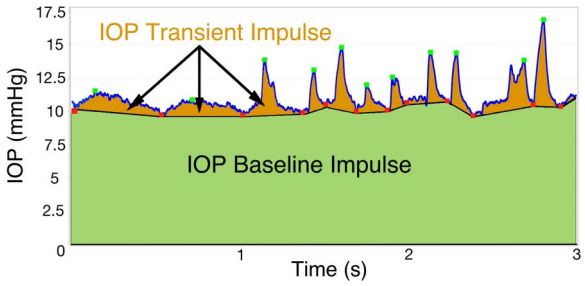

FIGURE 4. Three seconds of continuous IOP data that exhibit both slow and fast transient IOP fluctuations. Total IOP impulse is the area under the IOP versus time curve and is the sum of IOP transient impulse and IOP baseline impulse, as shown.

The IOP baseline impulse is a measure of the amount of IOP energy the eye must withstand due to static levels of IOP (the green area under the IOP troughs as shown in Fig. 4).

Data Filtering

After obtaining all data, IOP, MAP, OPP, and IOP transient impulse were averaged in 1-hour periods for 24 hours over 20 randomly chosen days of continuous telemetric data for each eye; each day of data was obtained 2 to 4 days after calibration to ensure the most accurate result. Wireless telemetry invariably involves momentary periods of signal loss or excessive noise, which was quantified continuously and eliminated from the data analyzed via fully automated post hoc filtering. Any day in which 25% or more data were rejected was excluded from the analysis. Twenty days of data for each eye satisfied these criteria and were used in the analysis.

Statistical Analysis

We used multivariate linear regression to assess relationships between IOP, IOP transient impulse, and OPP over all twenty 24-hour periods, waking hours, or sleeping hours, with significance defined as $P \leq 0.05$. We also analyzed the effect of waking hours (7:00 AM to 6:00 PM) and sleeping hours (7:00 PM to 6:00 AM) by establishing the wake-sleep cycle as a dummy variable in 24-hour analyses (wake = 1, sleep = 0) and by running separate analyses for the data from waking and sleeping hour periods to confirm that the relationships reported are not driven by the inherent differences in parameters between the wake and sleep periods. MAP could not be analyzed using multivariate linear regression because of the inability to calibrate the aBP transducer, necessitating separate analyses within each 24-hour period when aBP transducer drift is insignificant. Also, the MAP data were not normally distributed. Hence, Spearman Correlation Coefficients were used to examine the relationships between MAP and IOP, OPP, and IOP transient impulse within each 24-hour period within each eye, with significance defined as $P \leq 0.05$.

RESULTS

Animal demographics are shown in Table 1. Mean values and standard deviation for IOP (mm Hg), OPP (mm Hg), IOP transient impulse (mm Hg·hour), and IOP baseline impulse (mm Hg·hour) are shown in Table 2.

Graphical representations showing all 20 days of hourly data with linear regression trend lines for each eye are shown for IOP transient impulse versus both OPP (Fig. 5) and IOP baseline impulse (Fig. 6). A similar figure showing the relationship between IOP and OPP is shown in Figure 7. Table 3 shows the multivariate linear regression coefficients and their significance values for the effects of IOP baseline impulse, OPP, and Wake/Sleep on IOP transient impulse.

On average, IOP transient impulse significantly increases ~0.01 mm Hg·hour (~1%) for every 1 mm Hg increase in OPP and is ~0.56 mm Hg·hour (71%) higher during waking hours compared to sleeping hours (Table 3). Separate univariate analyses of the relationships between IOP transient impulse and OPP for waking and sleeping hours (Table 4) showed that OPP significantly affected IOP transient impulse during waking hours (a 1 mm Hg of OPP increased IOP transient impulse by ~0.012 mm Hg·hour, or about 1% of the overall mean), with P values generally less than 0.01 and significant positive regression coefficients. Similar sleeping hours analyses of these relationships did not yield consistent results, with smaller regression coefficients and varying levels of significance (Table 4).

Note that although the multivariate linear regression coefficients were generally positive and significant in six of seven eyes in the multivariate analysis shown in Table 3, the relationship between IOP transient impulse and IOP baseline impulse is muddied by inconsistent differences (both positive and negative multivariate linear regression coefficients and P values mostly ≤ 0.05) in the wake/sleep periods (univariate analyses in Table 5 and Fig. 6), and eye-specific differences in the level of influence that IOP baseline impulse has on IOP transient impulse during the wake/sleep periods.

IOP and OPP were found to have a significant negative relationship as shown in Figure 7 and quantified by significant negative linear regression coefficients in five of seven eyes (Table 6). Additionally, the wake/sleep cycle was found to have a significant impact on the relationship (Table 6). As expected, OPP decreased ~1 mm Hg for every 1 mm Hg increase in IOP (OPP = MAP − IOP), and OPP was ~5 mm Hg higher during waking hours compared to sleeping hours (Table 6).

Graphical representations of the relationships between MAP and both OPP (Fig. 8) were divided into individual graphs

TABLE 1. Animal Demographics

NHP	Eye	Age, y	Sex	Time Period of Monitoring		Number of Days of Data	Axial Length, mm
				Start	End		
9160	OD	4.5	Male	9/21/2013	3/27/2015	412	18.1
9160	OS	4.5	Male	9/21/2013	3/27/2015	412	18.44
9140	OD	4.5	Male	9/28/2013	6/26/2014	182	19.42
9140	OS	4.5	Male	9/28/2013	6/26/2014	200	19.67
0804025	OD	5	Male	10/3/2013	4/11/2015	451	20.33
0804025	OS	5	Male	10/3/2013	4/11/2015	451	20.32
9028	OS	4.5	Male	2/25/2014	3/2/2015	301	18.06

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Table 2. Mean Parameter Values With Standard Deviations

	IOP, mm Hg			OPP, mm Hg			IOP Transient Impulse, mm Hg·hour			IOP Baseline Impulse, mm Hg·hour		
NHP, Eye	24-Hour	Sleep	Wake	24-Hour	Sleep	Wake	24-Hour	Sleep	Wake	24-Hour	Sleep	Wake
9160, OD	13.2 ± 2.0	13.1 ± 1.9	13.3 ± 2.0	52.7 ± 6.2	50.6 ± 6.0	54.9 ± 5.5	1.17 ± 0.34	0.87 ± 0.12	1.47 ± 0.17	12.0 ± 1.9	12.2 ± 1.9	11.8 ± 2.0
9160, OS	11.4 ± 1.3	11.8 ± 1.2	11.0 ± 1.2	54.5 ± 5.8	51.8 ± 5.4	57.2 ± 4.9	1.17 ± 0.35	0.86 ± 0.14	1.47 ± 0.18	10.3 ± 1.4	11.0 ± 1.2	9.6 ± 1.2
9140, OD	14.1 ± 3.3	14.7 ± 3.2	13.5 ± 3.3	56.0 ± 6.9	53.1 ± 5.6	59.0 ± 6.8	1.15 ± 0.35	0.86 ± 0.12	1.45 ± 0.22	12.9 ± 3.4	13.8 ± 3.2	12.0 ± 3.4
9140, OS	14.8 ± 3.2	15.3 ± 3.2	14.2 ± 3.0	55.4 ± 6.4	52.5 ± 5.2	58.4 ± 6.3	1.19 ± 0.33	0.90 ± 0.12	1.47 ± 0.22	13.6 ± 3.2	14.4 ± 3.2	12.8 ± 3.0
0804025, OD	12.1 ± 1.6	11.7 ± 1.5	12.5 ± 1.6	47.6 ± 7.7	45.5 ± 6.1	49.6 ± 8.5	1.03 ± 0.41	0.67 ± 0.10	1.39 ± 0.27	11.1 ± 1.5	11.0 ± 1.5	11.1 ± 1.5
0804025, OS	12.1 ± 1.9	11.7 ± 1.8	12.4 ± 2.1	47.6 ± 7.4	45.5 ± 6.0	49.7 ± 8.1	1.04 ± 0.44	0.65 ± 0.10	1.42 ± 0.28	11.0 ± 1.8	11.1 ± 1.7	11.0 ± 1.9
9028, OS	10.8 ± 1.1	11.4 ± 0.8	10.2 ± 1.0	48.2 ± 6.4	45.4 ± 5.2	51.0 ± 6.2	0.92 ± 0.32	0.73 ± 0.18	1.10 ± 0.32	9.9 ± 1.2	10.6 ± 0.8	9.1 ± 1.0

Table 3. Regression Coefficients for IOP Transient Impulse

	IOP Transient Impulse		
NHP, Eye	OPP	IOP Baseline Impulse	Wake/Sleep
9160, OD	0.0066**	0.0166**	0.582**
9160, OS	0.0069**	0.0364**	0.626**
9140, OD	0.0093**	0.0051	0.544**
9140, OS	0.0106**	0.0122**	0.524**
0804025, OD	0.0110**	0.0369**	0.666**
0804025, OS	0.0089**	0.0384**	0.735**
9028, OS	0.0141**	−0.0418**	0.229**

Calculated as intercept + *coefficient* × OPP + *coefficient* × IOP baseline impulse + *coefficient* × wake/sleep over 24 hours, where wake/sleep = 1 during waking hours and wake/sleep = 0 during sleeping hours.

* $P \leq 0.05$.

** $P \leq 0.01$.

by eye, with each trend line representing a 24-hour period. Corresponding Spearman correlation coefficients are shown in Table 7. MAP and OPP were strongly, positively, and significantly correlated as shown in Figure 8, with high Spearman Correlation Coefficients and *P* values less than 0.01 (Table 7).

MAP and IOP showed no consistent relationship, quantified by varying significance and both positive and negative Spearman correlation coefficients (data not shown). MAP and IOP transient impulse were correlated over 24 hours as shown by high Spearman correlation coefficients and low, significant *P* values (not shown). However, there was no relationship when analyzing waking and sleeping hours separately, suggesting that this relationship is driven primarily by the sleep-wake cycle, and/or we had too little statistical power to detect the relationship (data not shown).

Discussion

The most prominent, significant relationships were the positive relationship between IOP transient impulse and OPP, the negative relationship between OPP and IOP, and the positive relationship between MAP and OPP. No consistent relationship was found between IOP transient impulse and IOP baseline impulse, IOP and MAP, and IOP transient impulse and MAP.

IOP transient impulse quantifies the amount of second-to-second fluctuation in IOP, and therefore represents high-frequency variability in IOP. While we would expect hourly average IOP (IOP baseline impulse) to be correlated with

Table 4. Regression Coefficients for IOP Transient Impulse

	IOP Transient Impulse vs. OPP	
NHP, Eye	Waking Hours	Sleeping Hours
9160, OD	0.0061**	0.00305*
9160, OS	0.0092**	0.00503**
9140, OD	0.0145**	−0.00207
9140, OS	0.0152**	−0.00281
0804025, OD	0.0142**	−0.00068
0804025, OS	0.0141**	−0.00303**
9028, OS	0.0117**	0.02082**

Calculated as intercept + *coefficient* × OPP for both waking and sleeping hours.

* $P \leq 0.05$.

** $P \leq 0.01$.

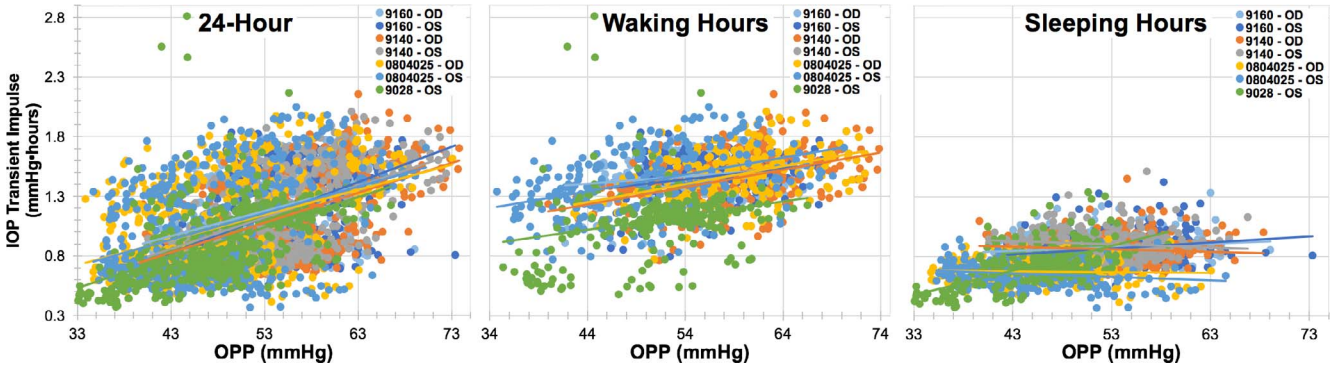

FIGURE 5. IOP transient impulse and OPP relationships for all twenty 24-hour periods, waking hours, and sleeping hours by eye and NHP. Each data point represents an hourly average, and each color represents an eye, with linear regression trend lines shown for each eye. Note that the positive 24-hour relationship is clearly driven by that same trend during waking hours, with little relationship apparent during sleeping hours.

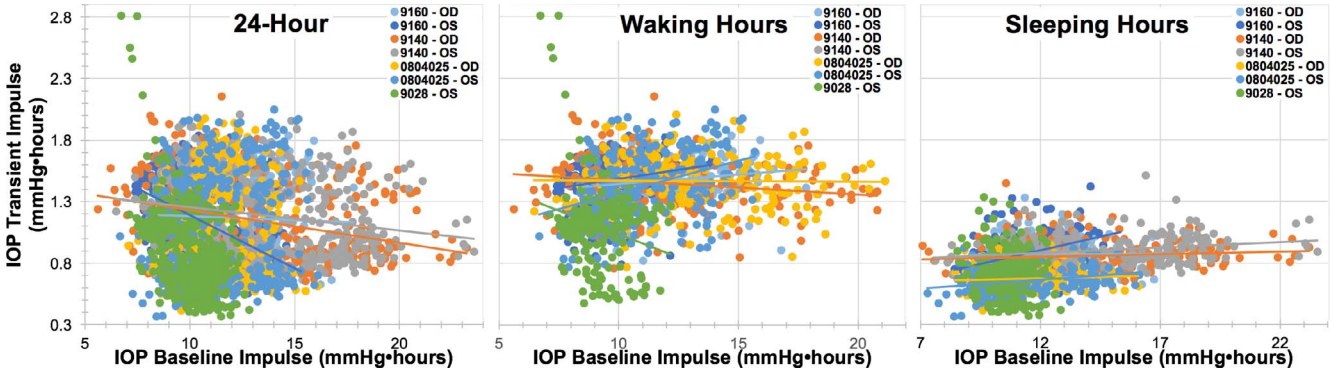

FIGURE 6. IOP transient impulse and IOP baseline impulse relationships for all 20 days of 24-hour periods, waking hours, and sleeping hours by eye and NHP. Each data point represents an hourly average, and each color represents an eye. Note that the negative relationship seen in the 24-hour period plot is not reflected in the separate waking and sleeping hours plots.

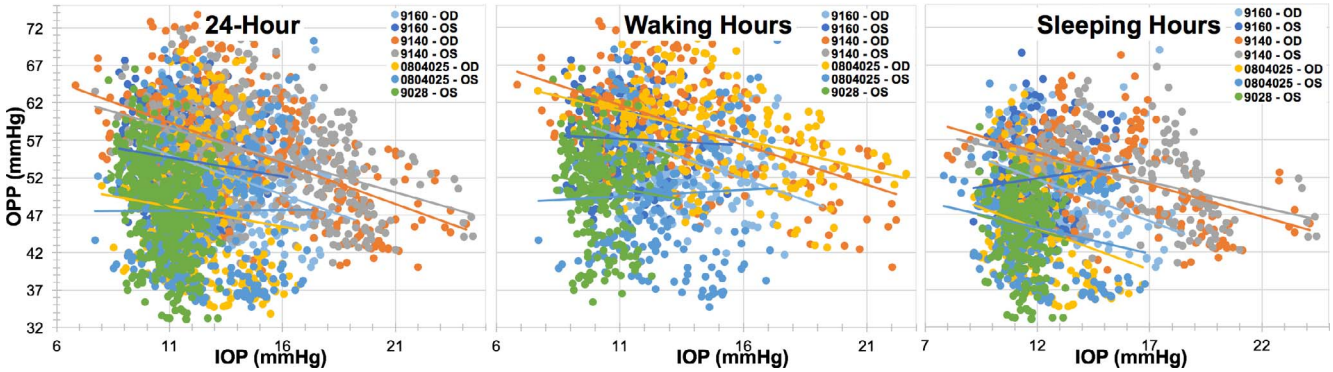

FIGURE 7. IOP and OPP relationships for twenty days of 24-hour periods, waking hours, and sleeping hours by eye and NHP. Each data point represents an hourly average, and each color represents an eye.

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Table 5. Regression Coefficients for IOP Transient Impulse

	IOP Transient Impulse vs. IOP Baseline Impulse	
NHP, Eye	**Waking Hours**	**Sleeping Hours**
9160, OD	0.01515**	0.0012
9160, OS	0.02926**	0.0440**
9140, OD	−0.01135**	0.0041
9140, OS	−0.00075	0.0086**
0804025, OD	0.04134**	0.0045
0804025, OS	0.05211**	0.0145**
9028, OS	−0.07586**	−0.0292*

Calculated as intercept + *coefficient* × IOP baseline impulse for both waking and sleeping hours.

* $P \leq 0.05$.

** $P \leq 0.01$.

hourly average OPP because OPP = MAP − IOP, the interesting finding is that IOP transient impulse (a measure of second-to-second IOP variability) shows a significant positive relationship with OPP. A possible explanation for the significant positive relationships between IOP transient impulse and OPP is that during greater periods of activity during waking hours, more blood flows into the eye (larger ocular pulse amplitude or OPA) and more blinks and saccades occur. Thus, it is reasonable that OPA drives some portion of IOP transient impulse, especially at night when the more dominant components of transient IOP fluctuations such as blink and saccade are largely absent. Surprisingly, the effect of OPP on IOP transient impulse is significant, large, and very consistent across eyes during the waking hours, with IOP transient impulse increasing ~1% with every 1 mm Hg increase in OPP, and yet this relationship is weak and inconsistent during sleep. IOP transient impulse is also over 70% higher during waking hours than during sleeping hours. One possible explanation for this finding is that OPP is much lower at night with less variability, which may explain why the relationship was significant for waking hours, but not for sleeping hours. In addition, past studies have suggested that ocular blood flow is related to the level of visual stimuli,[5,8,23,24] and pulsatile ocular blood flow is an important factor in the ocular pulse amplitude (OPA). Hence, we might expect that IOP transient impulse and OPP will be larger during periods of intense activity, when visual system is stimulated, blood flow (and OPA) are high, and blinks and saccades are frequent.

A surprising result was that IOP transient impulse was not significantly and consistently higher when IOP baseline impulse was high in all analyses, which we would expect given the results of previous studies that have shown that transient IOP fluctuations are larger in eyes with stiffer corneoscleral shells.[25–28] Ocular biomechanics studies indicate

Table 6. Regression Coefficients for OPP

	OPP	
NHP, Eye	**IOP**	**Wake/Sleep**
9160, OD	−1.126**	4.591**
9160, OS	0.137	5.481**
9140, OD	−0.963**	4.813**
9140, OS	−0.721**	5.081**
0804025, OD	−0.940**	4.892**
0804025, OS	−0.185	4.380**
9028, OS	−0.662*	4.882**

Calculated as intercept + *coefficient* × IOP + *coefficient* × wake/sleep over 24 hours, where wake/sleep = 1 during waking hours and wake/sleep = 0 during sleeping hours.

* $P \leq 0.05$, ** $P \leq 0.01$.

Table 7. Spearman Rank Correlation Coefficients for OPP vs. MAP

	MAP vs. OPP																			
NHP/Day	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
9160, OD	0.97**	0.92**	0.93**	0.97**	0.98**	0.98**	0.98**	0.98**	0.98**	0.90**	0.96**	0.90**	0.98**	0.97**	0.96**	0.99**	0.99**	0.95**	0.97**	0.97**
9160, OS	0.98**	0.95**	0.97**	0.98**	0.98**	0.98**	0.97**	0.98**	0.98**	0.97**	0.71**	0.89**	0.91**	0.91**	0.96**	0.97**	0.99**	0.95**	0.97**	0.96**
9140, OD	0.89**	0.99**	0.91**	0.98**	0.85**	0.59**	0.78**	0.88**	0.95**	0.92**	0.93**	0.96**	0.97**	0.89**	0.97**	0.96**	0.98**	0.99**	0.96**	0.93**
9140, OS	0.94**	0.97**	0.87**	0.98**	0.86**	0.54**	0.78**	0.84**	0.93**	0.87**	0.92**	0.96**	0.96**	0.92**	0.96**	0.96**	0.98**	0.99**	0.95**	0.93**
0804025, OD	0.73**	0.66**	0.98**	0.98**	0.97**	0.89**	0.96**	0.95**	0.90**	0.96**	0.90**	0.95**	0.94**	0.87**	0.96**	0.98**	0.83**	0.79**	0.96**	0.97**
0804025, OS	0.72**	0.65**	0.99**	0.97**	0.96**	0.88**	0.95**	0.95**	0.92**	0.96**	0.93**	0.94**	0.96**	0.75**	0.85**	0.97**	0.85**	0.87**	0.95**	0.96**
9028, OS	0.97**	0.98**	0.97**	0.96**	0.95**	0.99**	0.98**	0.98**	0.98**	0.96**	0.96**	0.96**	0.97**	0.94**	0.96**	0.97**	0.98**	0.96**	0.93**	0.93**

* $P \leq 0.05$.

** $P \leq 0.01$.

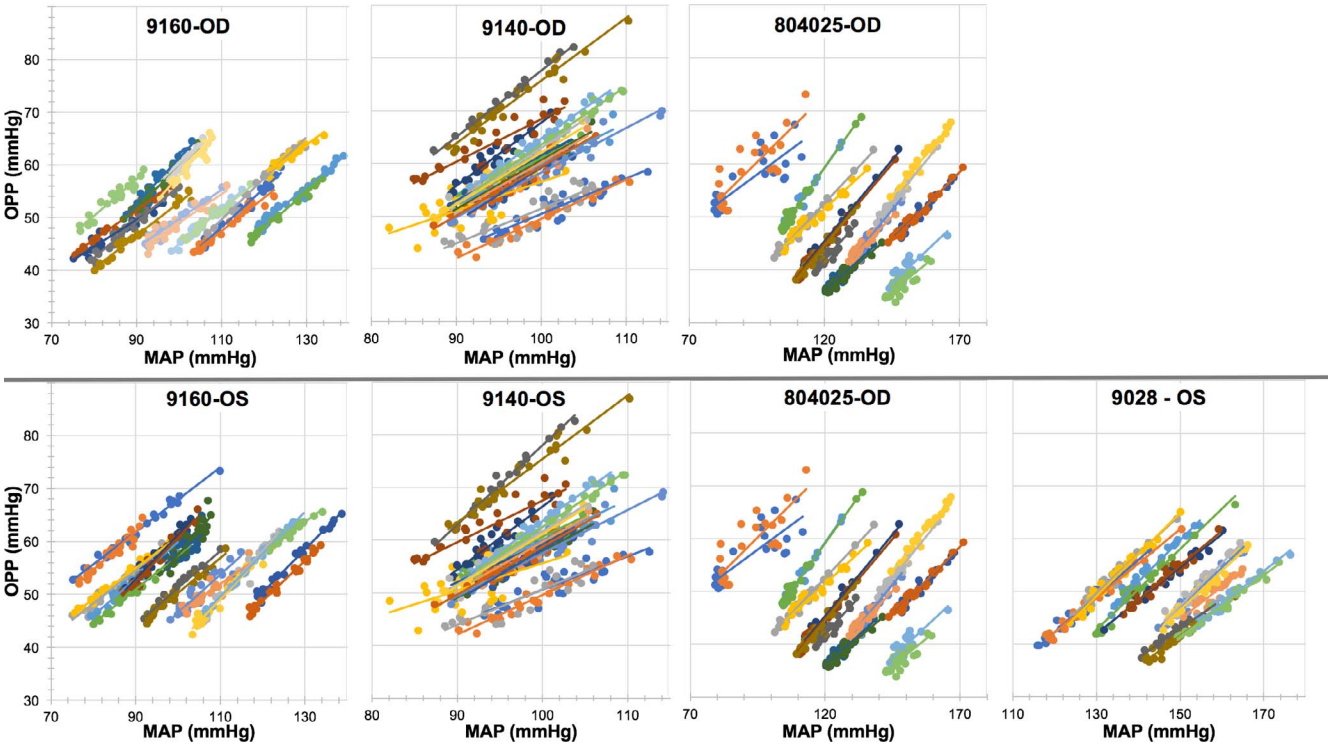

FIGURE 8. OPP and MAP relationships within ten 24-hour periods by eye and NHP. Each data point represents an hourly average, and each color represents one of the 20 days of data analyzed.

that the corneoscleral shell is stiffer at higher IOPs,[25] and so the transient IOP fluctuations, and hence IOP transient impulse should also be larger at higher baseline IOPs (quantified by IOP baseline impulse). The range of baseline IOP variation observed in this study is small and hence may not reach the thresholds necessary to elicit significant corneoscleral shell stiffening, so this result deserves more investigation in future studies, especially in eyes subjected to a wider IOP variation as seen in ocular hypertension and glaucoma.

We would expect that MAP and IOP would be highly correlated/related to OPP, since OPP = BP − IOP, with MAP defined in this study as the hourly average of continuous aortic BP. The significant positive correlations between MAP and OPP we observed support this, and also serve as a check on the underlying data in this report. IOP and OPP also demonstrate a significant negative relationship as expected, as IOP is a major contributor to OPP by definition. This is an important confirmatory finding, as it supports the notion that BP management could be an important treatment modality for patients in whom low BP/OPP is suspected as contributing to glaucoma progression as suggested in prospective trials.[10,12]

The main limitation of this study is that our results in NHPs may not translate directly to humans, as the NHP body size is significantly smaller than the average human, there may be differences in scleral rigidity from human eyes and NHPs sleep sitting up rather than in the supine position. Also, the relatively small sample size of seven eyes within four NHPs may be insufficient to represent the population. The results reported herein are more robust than previous studies due to the continuous nature of the pressure measurements, the fact that they were acquired in undisturbed, behaving NHPs, and across many days, weeks, and months apart. That said, the NHPs' environment was not completely controlled, stress-free, and natural, so periodic anesthetic events for calibrations, and interactions with the animal handling staff and other NHPs could affect our results. Also, it is possible that including data with a signal loss and noise filtering rejection threshold of less than the 25% level we used as an exclusion threshold could have affected our results. However, it is very unlikely that there are widespread or persistent periods with extensive data rejection included in our analyses since the results presented were very consistent across days, animals, and eyes, which indicates robust findings. Finally, we cannot be certain that the exact IOP at which vessel collapse occurs is captured to 0.1 mm Hg accuracy, although the method we used does support this level of precision. During the OPP calibration procedure, the live infrared ONH video is captured and synchronized to the continuous IOP data at 33 ms precision by the data acquisition software (the length of one image frame in the video). Our observers are trained to identify the first video image frame in which momentary/full CRA collapse occurs and report the exact IOP (to 0.1 mm Hg precision) measured by the transducer at that instant. There is no reason to believe that even an accuracy of less than 1 mm Hg in the OPP calibration procedure would be consequential to the analysis or bias the results in any way given that OPP is relatively large (45–65 mm Hg) and the procedure was repeated in exactly the same way for each calibration session in each animal.

In trying to understand the variables that affect IOP, results show that MAP is not related to IOP itself, but both MAP and IOP contribute significantly to OPP as expected. Results also show that IOP transient impulse (a time-weighted measure of the magnitude and frequency of transient IOP fluctuations) is related to OPP, which indicates that OPP is higher during periods of elevated ocular activity as quantified by elevated transient IOP fluctuations. The lack of a clear relationship between IOP baseline impulse and IOP transient impulse indicates that that a relatively large variation in baseline IOP is needed before the known stretch-induced stiffening of the ocular coats begins to significantly affect the magnitude of transient IOP fluctuation-related mechanical stress the eye must withstand.

Conclusions

Using continuous telemetry in nonhuman primates, significant relationships were found between IOP transient impulse and OPP (positive), IOP and OPP (negative), and OPP and MAP (positive), but were not found between IOP transient impulse and IOP baseline impulse, IOP and MAP, or IOP transient impulse and MAP. The wake-sleep cycle was found to have a large impact on these relationships.

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Supplementary Material

Supplementary Video. Ocular perfusion pressure calibration video.