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Article

# Modulation of Human Intraocular Pressure Using a Pneumatic System

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**Methods:** A force sensor as key component of a customized measurement setup was used to check the applied pressure through the balloon. The IOP of 10 healthy subjects (4 female, 6 male, aged  $28.8 \pm 6.64$  years) was modulated and increased linearly to at least 40 mmHg. At this point, the pressure inside the balloon was kept constant for 2 minutes, with IOP measurements taken every 40 seconds using a rebound tonometer.

**Results:** The technical setup led to an IOP decrease of 0.71 mmHg within 2 minutes at an operating point of 40 mmHg. For all subjects, the IOP could be increased up to 42.8  $\pm$  3.6 mmHg, whereby a mean pressure decrease of 2.4 mmHg/min was determined, which seems to be caused mainly by physiological processes.

**Conclusions:** With the new pneumatically based setup, a targeted modulation in terms of level and constancy of the IOP can be realized.

**Translational Relevance:** Additional and, compared with the technique according to Löw, a more precise and more constant methodology for the modulation of the IOP, can significantly simplify the determination of retinal vessel pressures for clinical application. It is suitable for practical questions concerning an enhanced retinal venous pressure.

# Introduction

In the past 15 years, it has been shown that a widely postulated axiom—the retinal venous pressure (RVP) is equal to the intraocular pressure (IOP) is not correct and does not represent the current knowledge about physiology, especially pathophysiology.<sup>1–7</sup> For example, in patients with glaucoma it has been shown that one-third to one-half of all patients have, compared with the IOP, a clinically relevant increased the RVP.<sup>3–9</sup> Similar results could be found in patients with diabetic retinopathy<sup>7,10,11</sup> or vessel occlusions,<sup>7,10,12,13</sup> for instance. Additionally, Balaratnasingam et al.<sup>4</sup> demonstrated that, if the RVP is higher than the IOP, the risk of optic nerve damage enhances by a factor of 1.3 with every millimeter of mercury of difference. However, up to now, the RVP was not considered in clinical use, because there was no adequate technology available

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to examine the pressure relationships inside the eye.

The clinical method to measure blood pressures in vivo in the retina is called ophthalmodynamometry and was invented in 1917 by Bailliart, P.: Ann. Ocul. 154, 648–666 (1917). With this method, the extravascular pressure—in this case the IOP—is slowly and continuously increased or decreased until the retinal vessels show characteristic visible pulsations. At that point, the extravascular pressure equals the intravascular pressure. Hence, the blood pressure is determined by measuring the modulated IOP.<sup>14</sup>

In the case of arterial pressure measurement, the extravascular pressure is increased to suprasystolic values, where no arteriolar pulsations are present, followed by a slow decrease of this increased extravascular pressure. At the moment the pulsations occur during this decrease, the extravascular pressure is similar to the arterial systolic pressure. As soon as these pulsations disappear subsequently, during an ongoing decrease, the extravascular pressure is equal to the arterial diastolic pressure.<sup>15</sup>

For measurement of the RVP, the IOP is slowly increased until the first visible spontaneous venous pulsations occur at the optic nerve head. Then, the increased IOP equals the RVP and can be determined by measuring the increased IOP.<sup>3-5,8</sup>

The only currently available device to perform this examination is the contact lens dynamometer by Löw. The key element of this device is a Goldmann contact lens to ensure retinal vessel observation and the modulation of the IOP at the same time. Thereby, the increase of the force brought to the eyeball can be measured by force sensors placed between a retaining ring and the contact lens. The ring is connected to an evaluation unit, which indicates the pressure difference induced by the contact lens. To increase the force, the examiner has to press the contact lens manually against the cornea. Simultaneously, the examiner has to observe the retinal vessels in the optic disc. The moment the pulsations appear or disappear as described elsewhere in this article, the increased IOP equals one of the retinal blood pressures, and the pressure difference shown by the evaluation unit is noted. By adding this pressure difference to the initial IOP, the respective retinal blood pressure can be determined. Originally, the contact lens dynamometer was developed to measure the arterial blood pressure in the retina. Only in recent years has it also been used to measure the RVP, which is the focus of this article.<sup>16,17</sup>

However, there are various limitations to the application of the contact lens dynamometer. For example, in the case of a tilted contact lens or blepharospasm, overestimated values are measured. It is also necessary to change the IOP slowly and continuously to obtain reliable retinal blood pressure values. For this process, the patient must keep her or his head stable and calm in the forehead control, which requires a high level of patient compliance.<sup>18,19</sup> Furthermore, the slew rate of the increase of the IOP is not equal between both eyes of the patient. This factor could again lead to a onesided overestimated RVP caused by a faster increase in the pressure, and with that a delayed detection of the examination criterion.<sup>19</sup> Also, for the examiner, it is technically almost impossible to measure very slightly increased RVPs, because the RVP is sometimes just a few millimeters of mercury higher than the IOP. For this reason, the contact lens-based method requires a highly trained and experienced examiner. Although, there are still limitations in accuracy owing to the technical limitations described herein.<sup>18</sup>

All these limitations led to a common nonacceptance of the methodology, and it is therefore rarely used. To overcome these limitations, a new pneumatically based setup and method have been developed. First, we present a technical validation of the system, which aims to verify the pressure stability of the pneumatics. After this discussion, we present the proof of principle by means of an application study on subjects, which includes two tests. The aim of test 1 (the modulation test) was to verify if it is possible to modulate and raise the IOP to at least 40 mmHg. Several publications show, particularly for different diseases, RVP values between 30 and 40 mmHg.<sup>4,6,8,9,11</sup> With this finding, patients with an increased RVP can be examined. The aim of test 2 (the constancy test) was to quantify how long a modulated IOP can be held at a constant level with the new method. For this purpose, the IOP was increased and kept constant for 2 minutes. During these 2 minutes, the IOP was measured every 40 seconds.

# **Methods**

### Subjects

A study was conducted in which both tests (for modulation and constancy) were carried out on 10 healthy subjects (6 male, 4 female, 1 eye each, mean age of  $28.8 \pm 6.64$  years, range of 21-43 years old). Before the study, all subjects passed an ophthalmic examination procedure, including the determination of visual acuity, objective refraction, tonometry, slit lamp microscopy, and ophthalmoscopy to ensure that there was no preexisting illness, no medical treatment, and no vision impairment. Exclusion criteria were myopia of less than -8 diopters, corneal scars, anamnestic



**Figure 1.** Pressure modulator (IOPstim, Imedos Systems GmbH) consisting of the basic unit, the spectacle-like frame and the pressure applicator. The display shows the start screen with top left the right eye (OD) chosen for stimulation (a). Person wearing the spectacle-like frame with the pressure applicator placed at the temporal corner of the open right eye, directly on the conjunctiva. The balloon is connected to the basic unit via tube for pressure modulation (b).

surgeries, diabetic retinopathy, glaucoma, optic nerve disease, ocular hypertension (IOP > 25 mmHg), and ongoing ocular local therapy like eye drops or intravitreal operative administration of drugs. No anesthetics were used. The study was approved by the local ethics committee of the Friedrich Schiller University of Jena, Germany. All procedures complied with the Declaration of Helsinki, and the subjects gave their written, informed consent before the start of the study.

# **Technical Setup**

Based on the technical and methodological process of ophthalmodynamometry, a pressure modulator (IOPstim, Imedos Systems GmbH, Jena, Germany) was used to increase the IOP (Fig. 1a).<sup>14,16,17</sup> This increase is achieved by deformation (impression) of the eyeball.

The deformation of the eyeball is realized by a small balloon made out of medically approved silicone (SILPURAN 6000/20 A/B, Wacker Chemie AG, Munich, Germany) with a diameter of 8 mm (Fig. 1a). The whole modulator system is CE certified and eye safety is covered according to ISO 14971. Before the start of the IOP modulation, the balloon is placed in the temporal corner of the open eye, directly on the conjunctiva, and is fixed to the head by a spectacle-like frame (Fig. 1b). The balloon is connected firmly to a mechanical mount (Fig. 2a, Fig. 2b), forming the pressure applicator. This pressure applicator is connected to the basic unit (Fig. 1a) via a tube system. The basic unit regulates the pressure inside the balloon. This pressure can be controlled via a foot switch or buttons at the front. If the pressure is increased, the balloon starts to dilate. With the subject wearing the spectacle-like frame together with the mounted pressure applicator, the IOP can then be modulated.



Figure 2. Pressure applicator under normal conditions (a) and with a negative pressure of -15 mmHg inside (b).

The pressure inside the balloon can be set in the range of -15 to 400 mmHg. The slew rate is about 20 mmHg/s in the event of a pressure increase. This corresponds with an increase of the IOP between 1 and 2 mmHg/s. Decreasing the pressure inside the balloon occurs at a rate of 5 mmHg/s. Modulation of the pressure can be performed continuously or stepwise.

# **Technical Validation**

Because the pressure modulator is based on a pneumatic setup, which, in principle, can suffer from leaks, stick-slip effects during pressure generation or compression losses, the system was initially technically validated. The aim was to check the applied pressure to the conjunctiva for stability. To minimize measurement errors caused by variable mechanical conditions of the measurement setup, internal and external temperature variations, and electrical influences, we preferred a force measurement setup instead of pressure



Figure 3. Setup for technical validation, which consists of pressure modulator (IOPstim, Imedos Systems GmbH) and pressure applicator, including balloon, force sensor (KD34s, ME-Meßsysteme GmbH) (placed in front of the balloon), and measuring amplifier (GSV-2MSD-DI, ME-Meßsysteme GmbH), used for sampling and analog-to-digital conversion of the measured values.

measurement. Thus, we placed a force sensor (KD34s, ME-Meßsysteme GmbH, Hennigsdorf, Germany) in front of the balloon. Concerning future applications, stability was analyzed for 2 minutes. The force data were sampled at 10 Hz and converted from analog to digital using a measuring amplifier (GSV-2MSD-DI, ME-Meßsysteme GmbH). The force values were recorded for five different target pressures from 50 mmHg to 250 mmHg in steps of 50 mmHg, and this sequence was repeated 10 times. A new balloon was used for each sequence. Within a sequence, the balloon again was brought into contact with the force sensor after each selected pressure value. The complete setup is shown in Figure 3.

### Study Design and Procedure

#### **Modulation Test**

At the beginning. the baseline IOP was measured using a rebound tonometer (Icare PRO, Icare Finland Oy, Helsinki, Finland). Using the tonometer, a small pen is placed 3 to 7 mm in front of the cornea and accelerated perpendicularly toward the eye. The moment the pen touches the cornea, the movement is retarded, and the pen is thrown back. This backward movement is detected by the device and the user can read the measured IOP value. This process is repeated six times and leads finally to the IOP value.<sup>20–22</sup>

After that, the spectacle-like frame was attached to the head of the subject, where the pressure applicator was aligned perpendicularly to the conjunctiva and slowly brought directly in front of the eye. By starting the examination program, the moment when the balloon touches the conjunctiva is detected, and the intra-balloon pressure is set to -15 mmHg. As a result, the outer part of the balloon is drawn into the mechanical mount (Fig. 2). In this condition, the balloon can be placed much closer to the conjunctiva, which prevents the pressure applicator from tilting. After the placement, a second measurement of the IOP was made. Subsequently, the pressure inside the balloon was raised in steps of 50 mmHg, up to a maximum pressure of 250 mmHg. At every step, the pressure inside the balloon was kept constant for 20 seconds, and the modulated IOP was determined using the rebound tonometer. After the last measurement at 250 mmHg, the balloon was vented completely, and the pressure decreased to 0 mmHg. All measured IOP values were taken to estimate a linear behavior between the pressure inside the balloon and the modulated IOP for each subject, by regression. The whole examination procedure of the modulation test is shown in Figure 4.

#### **Constancy Test**

In test 2, the decrease in the IOP during a constant modulation by an unvarying pressure inside the balloon should be examined. For this reason, the IOP was modulated in each subject's eye by setting the pressure to that value, determined by the individual linear behavior within the modulation test, which is needed to increase the IOP up to 40 mmHg. The pressure inside the balloon was then kept constant at



Figure 5. Constancy test. Flow chart to examine the decrease in the IOP during a constant modulation.

this enhanced level for 2 minutes. During this phase, the modulated IOP was measured at equal intervals of 40 seconds (4 times), using the rebound tonometer. After this, the balloon was completely vented, and the IOP was measured four more times in 40-second intervals. This resulted in a total of 4 minutes of measuring time.

A period of 2 minutes of constant pressure was chosen, because of the intended application of the RVP measurement. Beside the modulation of the IOP, this includes the detection of the beginning pulsations, setting up the tonometer, and the measurement of the IOP. Depending on the examiner and the used method to measure the IOP, this process normally takes about 30 seconds. To also cover longer IOP measurement procedures, 40 seconds was chosen as the sampling interval. The whole examination procedure of the constancy test is shown in Figure 5.

# **Data Analysis**

#### **Modulation Test**

Because of low sampling, with five data points on an individual regression line, the relationship between the increased IOP and the pressure inside the balloon was calculated for each subject. With the help of this regression line, the pressure inside the balloon, which is needed to increase the IOP to 40 mmHg, was determined. The value obtained was then used for the modulation in the constancy test. Further, the maximum measured IOP of each subject was extracted. All these values should be greater than 40 mmHg.

#### **Constancy Test**

To show the trend of temporal stability over 2 minutes, the average slope (n = 10) was calculated by linear regression. With the IOP values measured every 40 seconds, four data points were considered for each subject. With the average negative slope in mmHg per second (mmHg/s), the period of an IOP decrease of 2 to 3 mmHg was determined.

# **Results**

### **Technical Validation**

Performing force measurements in 10 sequences, with 1 balloon per sequence, at 5 pressure setups, from 50 mmHg to 250 mmHg in steps of 50 mmHg, Figure 6 shows the force progression characteristics attained. Two different phases can be distinguished clearly: the steep slope before 0 seconds (the prestimulus phase) and the slow decrease after 0 second (the stability phase). In the prestimulus phase, the force increased by an average of  $0.228 \pm 0.011$  N/s. From 0 to 120 seconds, the average drop of the five curves was determined to be  $-1.7 \pm 0.9\%$ . The greatest decrease over time was found for the 250 mmHg curve, at -2.6%. Considering an IOP value at 0 second of 40 mmHg, the IOP after 120 seconds of constant pressure modulation decreased by 0.71 mmHg.



**Figure 6.** Force progression for five different pressure setups from 50 to 250 mmHg in steps of 50 mmHg. The respective operating points are reached at 0 s. Solid lines represent mean values. Dashed lines give the  $\pm$  standard errors of mean. All five curves decrease approximately linearly, with  $-1.7 \pm 0.9 \%$  (n = 5) related to their maximum. The prestimulus skew rates of the pressure curves show similar behavior between them and rises with 0.228  $\pm$  0.011 N/s (n = 5).

#### **Modulation Test**

The results of the modulation test, in which the IOP should be increased to a minimum of 40 mmHg, are listed in Figure 7a, right column. The mean IOP was  $15.5 \pm 2.68$  mmHg for the baseline IOP and  $42.8 \pm 3.59$  mmHg for the maximum IOP modulated by the pressure modulator. Subjects 6 and 7 had slightly lower maximum IOP values (38 mmHg and 39.4 mmHg, respectively), whereas subject 4 exceeded the target limit clearly (51 mmHg). The distribution of the individual baseline and maximum IOP values are shown in the violin plot in Figure 7b. Although the baseline IOP data show a standard distribution, those of the maximum IOPs are slightly more widely distributed because of the three outliers.

### **Constancy Test**

Figure 8 shows the individual pressure profiles of all subjects with a constant modulation of the IOP over a period of 2 minutes. Additionally, the average regression line is plotted. The mean decrease of the pressure profiles was 2.4 mmHg/min. The distribution of the slopes (n = 10) is shown by the violin plot Figure 8. The data show a standard distribution, which is slightly widened by individual outliers.

# Discussion

The aim of this study was to test a pneumatically based system for pressure modulation at the eye and to prove its function for the first time. Therefore, a study with two tests was undertaken: the modulation test showed that we can modulate and increase the IOP to at least 40 mmHg and the constancy test quantified how long a modulated IOP can be held constant at a chosen level.

The results of the modulation test showed that, in 8 out of the 10 measured subjects, a modulated IOP of a minimum 40 mmHg could be generated. Only two subjects (6 and 7) had maximum IOP values that were slightly lower than 40 mmHg. Nevertheless, the IOP was enhanced by 20.4 mmHg for subject 6 and 26.4 mmHg for subject 7, which is a significant increase from the baseline IOP. Apart from that, measurements with an increased RVP that are more than 20 mmHg above the IOP would be pathological anyway. For this reason, the two values do not represent a limitation of the IOPstim.

The value of 40 mmHg as a minimum for a modulated IOP was chosen because it can be linked clearly with various diseases like glaucoma, diabetic retinopathy, and vessel occlusions. All these diseases were put in context with enhanced RVP values between



Figure 7. Data and results of the modulation test (a). Violin plot showing the distribution of the baseline IOP and maximum IOP values (b) (— mean, o median,—whisker, 1.–3. Quartile).



Figure 8. Individual pressure profiles and average regression line of all subjects (n = 10) during a constant modulation of the IOP over a period of 2 minutes; circles indicate measurements (a). A violin plot showing the distribution of the decrease of the IOP during the modulation of the IOP (b) (— mean, o median, — whisker, 1.-3. Quartile).

30 and 40 mmHg by several studies.<sup>4,6,8,9,11</sup> To ensure that all these disease patterns could be treated, the upper end of the range was selected as the lower limit.

One reason for both low values measured could be the stepwise sampling and the defined maximum pressure inside the balloons, of 250 mmHg. Both parameters were chosen to guarantee a shorter and gentler examination. With this safeguard in place, the stress for the involved subjects was minimized. However, this approach led to a fundamental deviation from the normal examination procedure. In this case, the pressure would be enhanced continuously until the veins in the area of the optic disk begin to pulsate visibly. At this point, the modulation of the IOP would be stopped and kept constant by the pressure modulator. Subsequently, the modulated IOP can be measured by a tonometer. Because there is no direct correlation between the pressure inside the balloon and the modulated IOP, the threshold of 40 mmHg for every subject is reached at different stages of modulation. This means that the threshold value can never be approached directly during a stepwise modulation of the IOP. However, by using the measured IOP values for individual regression lines, it becomes clear that just a slight further increase in pressure inside the balloon would lead to a modulated IOP of more than 40 mmHg in every subject.

Furthermore, the pressure inside the balloon was only increased to 250 mmHg. Technically, pressure values of up to 400 mmHg can be generated by that type of pressure modulator. This means that the slight further increase needed to reach the 40 mmHg in every subject is not a problem, either.

Another case that clearly deviates from 40 mmHg can be seen in subject 4, with a maximum measured IOP of 51 mmHg. However, because the selected threshold is a minimum requirement, this value does not represent a limitation of the method itself. It rather shows the potential of this method to also enable examinations of the arterial blood pressures. Studies regarding this property should be done in the future.

The constancy test showed a mean decrease in the IOP change of 2.4 mmHg/min during a constant modulation by the pressure modulator. This means that the IOP will decrease by 1 mmHg over 25 seconds. To be able to guarantee an accuracy of the examination of 2 to 3 mmHg, the measurement of the increased IOP by the examiner must be taken within 50 to 75 seconds. Considering the current clinically used methods of tonometry, this represents a sufficient time interval.

The accuracy chosen is based on the current standard method of tonometry—namely, applanation tonometry. With this method, the interindividual variance between remeasurements is 2 to 3 mmHg.<sup>23</sup> Because it is not possible to attain grater accuracy of the whole examination of the RVP measurement as that of the tonometer used for the actual measurement, the modulation of the IOP does not have to be more exact than 2 to 3 mmHg during one examination period.

Because a large number of different tonometers can be used to measure the modulated IOP, we have basically oriented toward the applanation tonometer as the standard method. For small and medium IOP values, the rebound tonometer correlates well with the applanation tonometer. Only for higher values are there some documented differences.<sup>23,24</sup>

To discuss the decrease of the IOP during a constant modulation, we have to consider both technical and physiological aspects.

Technical issues could be seen in leakage caused by a defect or an improperly attached balloon. Also, the elastic components of the pressure modulator could be deformed. In addition, the measuring accuracy of the tonometer must be considered here. The influence of the technical issues was examined in the technical validation of the pressure modulator. It could be shown that the force used to modulate the IOP drops by 2.6% within 2 minutes of constant modulation was the maximum pressure of 250 mmHg. In relation to the modulated IOP, this would mean a pressure decrease of approximately 0.71 mmHg.

One of the most frequently mentioned physiological reasons for a drop of the IOP is the "tonographic effect," which is described as a decrease in the IOP caused by an artificial increase in the IOP. This phenomenon has been observed in occulopression, repeated tonometry, or ophthalmodynamometry.<sup>5,24–25</sup> For healthy eyes, the decrease in the IOP caused by the tonographic effect was shown to be 4 to 6 mmHg over a 2-minute period of constant modulation. In patients with glaucoma, a decrease of 2 to 4 mmHg was reported.<sup>24</sup> However, because this study includes only subjects with healthy eyes, a lesser decrease in the IOP can be expected in patients with glaucoma. Further physiological reasons could be observed in movements of the eyeball, blinking, or tear film thickness. There is a large number of influencing factors that are able to trigger a decrease in the IOP during a constant modulation. As shown by the technical validation, the influence of the technical ones (0.71 mmHg) is significantly less than that of the tonographic effect (4–6 mmHg). In addition, there are a number of other physiological factors that have not yet been investigated. Their contribution to the decrease in the IOP remains unclear.

In summary, with the new pneumatically based setup, a targeted modulation of the IOP can be achieved that is suitable for practical questions concerning an enhanced RVP. With regard to the consistency of the new method, the examination of the RVP could be carried out with a high degree of accuracy.

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