The regular practice of physical exercise is associated with a better health status and well-being. The positive effects of physical exercise are even greater in clinical populations, with the implementation of therapeutic exercise being linked to a better prognosis and quality of life in a wide range of medical conditions. However, it is important to prescribe exercise programs taking into account the underlying condition to maximize benefits and minimize risks. Therefore, sport scientists and health care professionals should cooperate to find the most effective and efficient exercise strategies for each particular condition.

Physical exercise has been proposed as an effective adjuvant strategy for the prevention and management of glaucoma through the reduction of baseline intraocular pressure (IOP) values. Normobaric hypoxia and the alteration of the exchange of gases during dynamic and isometric resistance training cause an increase in IOP. In recent years, the implementation of novel techniques (eg, blood flow restriction or airflow restriction masks) that are thought to improve the physiological adaptations to exercise has gained popularity. In this regard, to elucidate whether the techniques that are being frequently used in training could be suitable for people with glaucoma or those at risk, it is important to determine the effects of these novel techniques on IOP values.

Notably, the use of the elevation training mask (ETM) appears to improve some specific markers of endurance performance, but it should be noted that the ETM acts as a respiratory muscle training device rather than as a simulator of altitude. There is scientific evidence that both normobaric hypoxia and the alteration of the exchange of gases during dynamic and isometric resistance training cause an increase in IOP. On the basis of these findings, it is plausible to speculate that using an ETM during exercise may affect the IOP behavior. However, no study has explored the impact of wearing an ETM during exercise on IOP, which may be of relevance for the prevention and management of glaucoma. In view of the previously described limitations, this study aimed to assess the short-term effect of using an ETM on IOP changes during low-intensity endurance exercise [30 min of cycling at 10% of maximal power production (Pmax)]. Specifically, we hypothesize that altering the exchange of gases with the ETM could partially or completely counteract the IOP-lowering effect of low-intensity continuous cycling.
within factors using the G* Power 3.1 software. On the basis of an assumed effect size of 0.25, α of 0.05, power of 0.80, and level of correlation between repeated measures of 0.5, the required sample size to achieve this desired level of accuracy is 16 participants. Consequently, 16 physically active university students (8 women and 8 men) took part in this study (age = 23.9 ± 2.9 years, body mass = 70.5 ± 12.8 kg, body height = 1.70 ± 0.10 m; data presented as mean ± SD). As an inclusion criterion, participants had to be free of any systemic or ocular pathology that could affect the results of this study. Participants were asked to avoid alcohol or caffeine consumption within 12 hours preceding each visit to the laboratory, and strenuous exercise 48 hours before each experimental session.

Physical Task
The $P_{\text{max}}$ during the leg cycle ergometer exercise was determined in the first session following the procedure described by García-Ramos et al. First, we determined for each participant the most comfortable position of the saddle and handlebar. An electronically braked cycle ergometer was used in all experimental sessions (Excalibur Sport; Lode, Groningen, The Netherlands). The warm-up consisted of pedalling for 5 minutes at 75 W with a cadence of 80 to 90 rpm, while 3 maximal accelerations of 3 to 4 seconds were performed in the minutes second, third, and fourth. Once the warm-up was completed, participants were given 5 minutes of rest before performing the sprints used for the force-velocity relationship modelling. Participants performed 1 sprint against 4 to 5 different resistances separated by 5 minutes of passive rest. The minimal resistive force applied to the flywheel was 0.4 N/kg for all participants and the highest resistive force was individualized as the load associated with a cadence of ~110 rpm. Power (W) was determined with the LOAD manager software (Lode, Groningen, The Netherlands) from the 4 seconds interval with the maximum pedalling cadence of each sprint. Linear velocity (m/s) was calculated from the cadence (rpm) and the crank length (0.17 m), while force was calculated as power divided by velocity. Thereafter, force and velocity data collected at each loading condition were used to determine the force-velocity relationship through a linear regression model: $F(V) = F_0 - aV$, where $F_0$ represents the theoretical maximal force, $a$ is the slope that corresponds to $F_0/V_0$, $V_0$ is the theoretical maximal velocity, and $P_{\text{max}}$ was computed as $P_{\text{max}} = (F_0V_0)/4$. The 2 main experimental sessions consisted of pedalling for 30 minutes at 10% of the $P_{\text{max}}$ determined in session 1 with a constant pedalling cadence of 90 rpm. The only difference between the 2 sessions was the use or not of the ETM. Before this task, the participants completed a 5 minutes warm-up consisting of pedalling at 5% of $P_{\text{max}}$ with a cadence of 90 rpm.

Dependent Variables

IOP
The Icare TA01i (Icare Finland, Helsinki, Finland) rebound tonometer was used to acquire IOP data from the right eye. This instrument has been clinically validated, and has demonstrated to be highly comparable to Goldman applanation tonometry. On the basis of the manufacturer recommendations, participants were instructed to fixate on a distance target, and a board-certified optometrist took 6 rapidly consecutive measurement against the central cornea.

Heart Rate
Upon arrival to the laboratory in the 2 main experimental sessions (sessions 2 and 3), participants were fitted with a Polar RS800 CX (Polar Electro Oy, Kempele, Finland) in order to monitor their heart rate throughout the session. We recorded heart rate data during the 30 minutes cycling and the recording was divided into 5 blocks of 6 minutes. Heart rate was also monitored for 10 minutes after exercise, and the recording was divided into 2 blocks of 5 minutes.

Study Design and Procedure
A crossover study was designed to assess the impact of wearing an ETM on the IOP response to a low-intensity cycling task (see Fig. 1 for a schematic illustration of the procedure). The experimental condition (control vs. ETM) and the point of measure [baseline, after warm-up, during exercise (6 to 12 to 18 to 24 to 30 min), and after exercise (5 to 10 min)] were considered as within-participants factors. The main dependent variable of this study was IOP, while the impact of wearing the ETM on the cardiovascular function was assessed through the heart rate. Participants attended to the laboratory on 3 occasions separated by 48 to 96 hours, which were performed at the same time of the day for each participant (± 1 h). The first session was used to determine the $P_{\text{max}}$ in cycling (see the Physical task section), as well as to check the inclusion criteria (see the Ethical approval and participants section). The 2 remaining sessions comprised the main part of this study, with both experimental sessions being identical except from use of the ETM. In the control session, participants did not wear the mask at any point of the session. For the ETM condition, participants wore an ETM (The Elevation Training Mask 2.0; Training Mask LLC, Cadillac, MI) during the 30 minutes of cycling but not during the warm-up or after exercise completion. The ETM was set to simulate an altitude of 9,000 feet (2,743 m). Upon arrival to the laboratory, we obtained the baseline IOP measurement. Then, participants were asked to perform a 5 minutes warm-up, and another IOP measure was taken at this moment. After it, all participants performed the cycling task (30 min of cycling at 10% of $P_{\text{max}}$), with IOP reading being obtained in regular intervals of 6 minutes while cycling. Lastly, 2 IOP measurements were taken after 5 and 10 minutes of recovery. For the IOP measurements taken during the exercise, participants were asked to continue pedalling and maintain their heads as stable as possible while fixating on a distant target. Participants were not allowed to drink or eat during the experiment.

![FIGURE 1. Schematic illustration of the procedure followed in this study. ETM indicates elevation training mask; HR, heart rate; IOP, intraocular pressure.](image-url)
**Statistical Analysis**

The normal distribution of the data and the homogeneity of variances were confirmed with the Shapiro-Wilk and the Levene tests, respectively \((P > 0.05)\). In order to assess the short-term effects of using an ETM on the IOP response during low-intensity endurance exercise, we performed a repeated measures ANOVA \((2 \times 9)\), considering the experimental condition (control vs. ETM) and the point of measure [baseline, after warm-up, during exercise (6-12-18-24-30 min), and after exercise (5 to 10 min)] as within-participants factors. Pairwise comparisons between the different points of measures were conducted, and they were corrected with the Benjamini-Hochberg procedure. The magnitude of the changes was reported by the Cohen \(d\) effect size \((d)\) and \(\eta^2\) for \(T\) and \(F\) tests, respectively. Complementarily, the cardiovascular response to exercise was assessed by a repeated measures ANOVA \((2 \times 7)\) applied on heart rate values, with the experimental condition (control vs. ETM) and the point of measure [during exercise (6 to 12 to 18 to 24 to 30 min), and after exercise (5 to 10 min)] as within-participants factors. The Mauchly test was used to check the assumption of sphericity in ANOVAs \((P > 0.05\) in all cases). An \(\alpha\) of 0.05 was adopted to determine statistical significance. All statistical analyses were carried out with the JASP statistics package (version 0.13.1).

**RESULTS**

Descriptive values for IOP and heart rate at the different points of measure in both experimental conditions are displayed in Table 1.

The ANOVA applied on IOP values revealed statistically significant differences for the experimental condition \((F_{1.15} = 28.56, P < 0.001\), \(\eta^2 = 0.66)\) and the interaction experimental condition×point of measure \((F_{8.120} = 14.02, P < 0.001\), \(\eta^2 = 0.48)\), whereas the main effect of the point of measure did not reach statistical significance \((F_{8.120} = 1.68, P = 0.111\), \(\eta^2 = 0.10)\). Complementarily, we performed 2 separate unifactorial ANOVAs for each experimental condition (ETM and control) using the point of measure as the only within-participants factor. These analyses showed statistically significant effects of the point of measure for both the ETM \((F_{8.120} = 5.91, P < 0.001\), \(\eta^2 = 0.28)\) and the control condition \((F_{8.120} = 10.35, P < 0.001\), \(\eta^2 = 0.41)\) because of a progressive increase in heart rate values during exercise. However, no effects were obtained for the experimental condition \((F_{1.15} = 1.76, P = 0.204\), \(\eta^2 = 0.11)\) or the interaction experimental condition×point of measure \((F_{8.120} = 0.62, P = 0.717\), \(\eta^2 = 0.04)\).

**DISCUSSION**

This study aimed to examine whether the use of an ETM, which limit the interchange of gases, modulate the IOP behaviour during a low-intensity cycling task. As expected, for the control condition, lower IOP values were obtained during exercise compared with pre-exercise and postexercise measurements. However, the use of the ETM not only prevented the decrease in IOP during exercise, but also caused a significant increase in IOP during the acute reduction in IOP during exercise. Therefore, the use of the ETM should be avoided when low-intensity endurance exercise is prescribed to induce an acute reduction in IOP, which is important for glaucoma patients or those at risk.

The findings of our study with respect to the control condition are in agreement with numerous studies that have

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**TABLE 1. Descriptive Values (Mean ± SD) for the Intraocular Pressure and Heart Rate Parameters at the Different Points of Measures in the Elevation Training Mask and Control Conditions**

|                  | Before Cycling | During Cycling | After Cycling |
|------------------|---------------|----------------|--------------|
|                  | Baseline | Warm-up | 6 min | 12 min | 18 min | 24 min | 30 min | 5 min | 10 min |
| IOP (mm Hg)      |         |          |       |       |       |       |       |       |       |
| ETM              | 15.9 ± 2.6 | 15.1 ± 2.5 | 17.4 ± 3.3 | 17.7 ± 3.2 | 17.4 ± 3.2 | 16.7 ± 3.6 | 17.3 ± 3.7 | 16.1 ± 3.2 | 15.4 ± 3.1 |
| Control          | 15.6 ± 3.0 | 14.4 ± 3.0 | 13.3 ± 3.0 | 12.9 ± 3.2 | 13.3 ± 2.8 | 14.0 ± 3.1 | 14.4 ± 2.8 | 15.0 ± 3.0 | 15.1 ± 3.3 |
| Heart rate (bpm) |         |          |       |       |       |       |       |       |       |
| ETM              |          |          | 124.7 ± 13.1 | 146.3 ± 16.0 | 149.9 ± 17.8 | 153.2 ± 18.5 | 152.9 ± 17.6 | 124.1 ± 14.2 | 105.2 ± 12.1 |
| Control          |          |          | 115.9 ± 12.4 | 138.4 ± 15.4 | 141.6 ± 16.7 | 145.2 ± 17.1 | 147.5 ± 17.1 | 119.1 ± 19.3 | 102.3 ± 13.1 |

ETM indicates elevation training mask; IOP, intraocular pressure.
demonstrated an IOP-lowering response to low-intensity endurance exercise. Specifically, a recent work from our research group, where we used the same physical effort to determine the impact of caffeine intake on the IOP response to cycling, showed comparable IOP changes in the control condition to those observed in the current study. In fact, the greater IOP reduction is observed after 12 minutes of exercise, which also agrees with our previous findings. Regarding IOP recovery, our data show that 5 minutes of recovery are sufficient for returning IOP to baseline levels, whereas 10 minutes of recovery were required to reach baseline IOP levels in the study of Vera et al. For its part, research from the group of Najmanova and colleagues revealed that at least 20 minutes were required to recover baseline IOP levels. Summing up, the IOP behavior observed in the current study for the control condition is in line with previous investigations, confirming an IOP reduction (~2 to 3 mm Hg) during the execution of low-intensity endurance exercise which quickly return to baseline levels after exercise cessation. However, the time required to reach baseline IOP levels after exercise vary across studies, with the times of recovery ranging from 5 to 20 minutes. Future studies should elucidate the characteristics of exercise protocols that induce longer IOP-lowering responses.

In relation to the main objective of this study, which was to determine the impact of wearing an ETM during low-intensity continuous cycling on the IOP behaviour, we found that using an ETM not only counteracted the IOP-lowering response to cycling but also increased the IOP values during exercise. The main effect of wearing the ETM is that the exchange of gases is involuntarily altered. Recent evidence showed that a reduced interchange of gases led to a heightened IOP rise during dynamic and isometric resistance training. Similarly, the exposure to normobaric hypoxia and the execution of the Valsalva maneuver provokes a significant increase in IOP. Nowadays, the widespread use of face masks because of the SARS-CoV2 pandemic has gained research attention. In particular, wearing face masks is mandatory or highly recommended, depending on the regulatory laws, during the practice of physical exercise in order to minimize the spread of droplets and aerosol particles. However, its use during physical effort has demonstrated to have a physiological effect on the cardiopulmonary function. Further research is required to ascertain whether altering the exchange of gases with the use of different types of face masks (eg, surgical and FFP2/N95) may provoke IOP alterations, which may be of special relevance for exercise prescription in glaucoma patients or those at risk.

As explained in the introduction section, there are claims the use of the ETM can be compared with training in hypoxic conditions. Nevertheless, experts agree that the ETM does not induce hypoxia and its effects are in fact mediated by the restriction of airflow acting as a respiratory muscle training device. Here, we found that the use of the ETM has a detrimental effect when reducing IOP levels is desirable and, thus, sport scientists and eye care specialists should be aware of this fact for the appropriate management of glaucoma patients or those at risk. The average difference observed between both experimental conditions while performing the 30-minute low-intensity continuous cycling was 3.7 ± 2.2 mm Hg, with greater IOP values always observed wearing the ETM in comparison to the control condition. In glaucoma patients, a 10% risk of glaucoma progression has been associated with IOP fluctuations of 1 mm Hg, suggesting that the differences observed in this study may be considered of clinical significance. However, it should be noted that our experimental sample was formed by healthy individuals and, thus, the external validity of the current findings to glaucoma patients requires further investigation. Notably, glaucoma patients or those at risk have demonstrated a greater IOP rise when compared with healthy individuals to different activities or conditions (ie, water drinking test, sleeping position or caffeine intake). On the basis of this, greater IOP differences could be expected in glaucoma patients while using the ETM, but it requires confirmation in future investigations.

The current findings show that the use of the ETM counteracts the IOP-lowering effect of a 30-minute low-intensity cycling task. However, there are some aspects that may limit the validity of our results, and they must be acknowledged. First, we chose a specific physical task (30 min of cycling at 10% of Pmax), which has demonstrated to reduce IOP levels. However, the IOP response to exercise is dependent on exercise type and intensity, and accumulated effort. Therefore, the results of this study should not be generalized to other physical efforts. Second, fitness level is a significant modulator of the IOP changes caused by exercise, and our experimental sample was composed by physically active young adults. Further studies should assess the role of fitness level on the IOP response to exercise while restricting the exchange of gases. Lastly, glaucoma patients have an altered mechanism of ocular hemodynamics and commonly they also present other physical dysfunctions associated with age (eg, diabetes or hypertension) that may affect their physical capacity and physiological responsiveness to exercise. These factors should be taken into account when interpreting the outcomes of this study.

CONCLUSIONS

This study shows that using an ETM while performing low-intensity cycling exercise causes an IOP rise, counteracting the IOP-lowering effect observed in the control condition. There was a rapid IOP recovery after exercise (IOP decrement and increment following the ETM and control conditions, respectively), with 5 minutes of passive recovery being sufficient to reach baseline levels. Future studies in glaucoma patients are required to determine the validity and reproducibility of these novel findings.

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REFERENCES

1. Warburton DER, Bredin SSD. Reflections on physical activity and health: what should we recommend? Can J Cardiol. 2016;32:495–504.
2. Kinner C, Colby LA, Borstad J. Therapeutic Exercise: Foundations and Techniques. 7th ed. Philadelphia, PA: Fa Davis; 2017.
3. Pedersen BK, Saltin B. Evidence for prescribing exercise as therapy in chronic disease. Scand J Med Sci Sports. 2006;16(suppl 1):3–63.
4. Zhu MM, Lai JSM, Choy BNK, et al. Physical exercise and glaucoma: a review on the roles of physical exercise on intraocular pressure control, ocular blood flow regulation, neuroprotection and glaucoma-related mental health. Acta Ophthalmol. 2018;96:676–691.
5. Ong SR, Crowston JG, Loprinzi PD, et al. Physical activity, visual impairment, and eye disease. Eye. 2018;32:1296–1303.
6. Lee MJ, Wang J, Friedman DS, et al. Greater physical activity is associated with slower visual field loss in glaucoma. Ophthalmology. 2019;126:958–964.
7. Tham YC, Li X, Wong TY, et al. Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. Ophthalmology. 2014;121:2081–2090.

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8. Wylegala A. The effects of physical exercises on ocular physiology: a review. *J Glaucoma*. 2016;25:e843–e849.

9. Najmanova E, Pluhaček F, Botek M. Intraocular pressure response to moderate exercise during 30-min recovery. *Optom Vis Sci*. 2016;93:281–285.

10. Vera J, Redondo B, Bardón A, et al. Effects of caffeine consumption on intraocular pressure during low-intensity endurance exercise: a placebo-controlled, double-blind, balanced crossover study. *Clin Exp Ophthalmol*. 2020;48:602–609.

11. Natsis K, Asouhidou I, Nousios G, et al. Aerobic exercise and intraocular pressure in normotensive and glaucoma patients. *BMC Ophthalmol*. 2009;9:6.

12. Vera J, Jiménez R, Redondo B, et al. Investigating the immediate and cumulative effects of isometric squat exercise for different weight loads on intraocular pressure: a pilot study. *Sports Health*. 2019;11:247–253.

13. Vera J, Jiménez R, Redondo B, et al. Effect of the level of effort during resistance training on intraocular pressure. *Eur J Sport Sci*. 2019;19:394–401.

14. Rüfer F, Schiller J, Klettner A, et al. Comparison of the influence of aerobic and resistance exercise of the upper and lower limbs on intraocular pressure. *Acta Ophthalmol*. 2014;92:249–252.

15. Vera J, Jiménez R, Redondo B, et al. Fitness level modulates intraocular pressure responses to strength exercises. *Curr Eye Res*. 2018;43:740–746.

16. Vera J, García-Ramos A, Jiménez R, et al. The acute effect of strength exercises at different intensities on intraocular pressure. *Graefe’s Arch Clin Exp Ophthalmol*. 2017;255:2211–2217.

17. Vera J, Perez-Castilla A, Redondo B, et al. Influence of the breathing pattern during resistance training on intraocular pressure. *Eur J Sport Sci*. 2020;20:157–165.

18. Vera J, Redondo B, Perez-Castilla A, et al. The intraocular pressure response to lower-body and upper-body isometric exercises is affected by the breathing pattern. *Eur J Sport Sci*. 2020. [Epub ahead of print].

19. Loenneke JP, Wilson JM, Marin PJ, et al. Low intensity blood flow restriction training: a meta-analysis. *Eur J Appl Physiol*. 2012;112:1849–1859.

20. Barbieri JF, Gáspari AF, Tecedoro CL, et al. The effect of an airflow restriction mask (ARM) on metabolic, ventilatory, and electromyographic responses to continuous cycling exercise. *PLoS One*. 2020;15:e0237010.

21. Romero-Arenas S, López-Pérez E, Colomer-Poveda D, et al. Oxygenation responses while wearing the elevation training mask during an incremental cycling test. *J Strength Cond Res*. 2019. [Epub ahead of print].

22. Granados J, Gillum T, Castillo W, et al. “Functional” respiratory muscle training during endurance exercise causes modest hypoxemia but overall is well tolerated. *J Strength Cond Res*. 2016;30:755–762.

23. Porcari JP, Probst L, Forrester K, et al. Effect of wearing the elevation training mask on aerobic capacity, lung function, and hematological variables. *J Sport Sci Med*. 2016;15:379–386.

24. Sellers J, Monaghan T, Schnaiter J, et al. Efficacy of a ventilatory training mask to improve anaerobic and aerobic capacity in reserve officers’ training corps cadets. *J Strength Cond Res*. 2016;30:1155–1160.

25. Najmanová E, Pluhaček F, Botek M, et al. Intraocular pressure response to short-term extreme normobaric hypoxia exposure. *Front Endocrinol (Lausanne)*. 2019;10:1–7.

26. Franza F, Edgar E, Albert-George L, et al. *G* Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav Res Methods*. 2007;39:175–191.

27. García-Ramos A, Torrejón A, Morales-Artacho AJ, et al. Optimal resistive forces for maximizing the reliability of leg muscles’ capacities tested on a cycle ergometer. *J Appl Biomech*. 2018;34:47–52.

28. Jarc S. Force-velocity relationship of muscles performing multi-joint maximum performance tasks. *Int J Sports Med*. 2015;36:699–704.

29. Pakrou N, Gray T, Mills R, et al. Clinical comparison of the Icare tonometer and Goldmann application tonometry. *J Glaucoma*. 2008;17:43–47.

30. Najmanová E, Pluhaček F, Botek M. Intraocular pressure response to maximal exercise test during recovery. *Optim Vis Sci*. 2018;95:136–142.

31. Zhang Z, Wang X, Jonas J, et al. Valsalva manoeuvre, intraocular pressure, cerebrospinal fluid pressure, optic disc topography: Beijing intracranial and intraocular pressure study. *Acta Ophthalmol*. 2014;92:e475–e480.

32. Ayyak U, Erdurmus M, Yilmaz B, et al. Intraocular pressure and ocular pulse amplitude variations during the Valsalva maneuver. *Graefe’s Arch Clin Exp Ophthalmol*. 2010;248:1183–1186.

33. Meselson M. Droplets and aerosols in the transmission of SARS-CoV-2. *N Engl J Med*. 2020;382:2063.

34. Fikenzer S, Uhe T, Lavall D, et al. Effects of surgical and FFP2/N95 face masks on cardiopulmonary exercise capacity. *Clin Res Cardiol*. 2020;109:1522–1530. e143.

35. Leske M, Heijl A, Hussein M, et al. Factors for glaucoma progression and the effect of treatment: the early manifest glaucoma trial. *Arch Ophthalmol*. 2003;121:48–56.

36. Susanna R, Clement C, Goldberg I, et al. Applications of the water drinking test in glaucoma management. *Clin Exp Ophthalmol*. 2017;45:625–631.

37. Prata TS, De Moraes CGV, Kanadani FN, et al. Posture-induced intraocular pressure changes: considerations regarding body position in glaucoma patients. *Sarv Ophthalmol*. 2010;55:445–453.

38. Li M, Wang M, Guo W, et al. The effect of caffeine on intraocular pressure: a systematic review and meta-analysis. *Graefe’s Arch Clin Exp Ophthalmol*. 2011;249:435–442.

39. Vera J, Jiménez R, Redondo B, et al. Intraocular pressure responses to maximal cycling sprints against different resistance: the influence of fitness level. *J Glaucoma*. 2017;26:881–887.

40. Vera J, Jiménez R, Redondo B, et al. Effect of a maximal treadmill test on intraocular pressure and ocular perfusion pressure: the mediating role of fitness level. *Eur J Ophthalmol*. 2020;30:506–512.

41. Galambos P, Valađis J, Vlček SE, et al. Compromised autoregulatory control of ocular hemodynamics in glaucoma patients after postural change. *Ophthalmolology*. 2006;113:1832–1836.