A common denominator for all types of glaucoma is the progressive optic neuropathy with corresponding visual field defects. Although it is the leading cause of irreversible blindness worldwide, the pathophysiology of glaucoma is still not fully understood. The most important risk factor for the development and progression of glaucoma is an elevated IOP. To date, this is also the only treatable risk factor and all current glaucoma treatment is focused on the lowering of IOP. However, despite considerable IOP decrease and all current glaucoma treatment is focused on the lowering of IOP, many patients still progress at an unacceptable rate, indicating that there are other important aspects of the pathophysiology of glaucoma than an elevated IOP.

Apart from the predominant theory of mechanical insult to the retinal ganglion cells owing to raised IOP, disturbed ocular blood flow has been proposed as a potential contributing factor of glaucoma pathophysiology. Thus, there is an interest in blood flow in glaucomatous eyes, and it has been suggested that autoregulation is not fully capable of compensating aberrant IOP levels. This finding calls for investigating the relationship between these two suggested main components in glaucoma pathophysiology.

The arterial blood supply of the ocular system and optic nerve is primarily provided by main branches of the ophthalmic artery (OA), that is, the central retinal and the ciliary arteries. Phase-contrast magnetic resonance imaging (PCMRI) is a noninvasive technique to quantify the blood flow rate during a cardiac cycle. Traditionally, PCMRI has only been used to measure larger arteries (>2 mm diameter) intracranially. However, by prioritizing high resolution in the sequence setup, it is possible to accurately measure volumetric blood flow rate in small arteries such as the OA, which has a diameter of approximately 1.5 mm.

As pointed out recently by Harris et al, imaging of the retrobulbar blood supply has been restricted to color Doppler imaging (CDI) which main limitation is that CDI...
Blood Flow in Ophthalmic Artery Unaffected by IOP Decrease

is unable to quantify blood flow. By assessment of blood vessel diameter, the PCMRI technique meets this unmet need. The interplay between IOP and blood flow to the eye is not entirely known. To address this knowledge gap, we used high-resolution PCMRI to test our hypothesis that a significant IOP reduction would result in increased blood flow in the OA. Because glaucomatous damage in itself, irrespective of IOP level, may cause disturbed blood flow, we chose to include subjects with elevated IOP but no glaucomatous damage in the study.

METHODS

This prospective, single-center study analyzed subjects diagnosed with untreated ocular hypertension who were monitored at the Department of Ophthalmology at Umeå University Hospital in Umeå, Sweden. The study followed the tenets of the Declaration of Helsinki and was approved by the Regional Ethical Review Board at Umeå University. All participants signed a written informed consent after oral and written information of the study. The study was registered at clinicaltrials.gov (ID: NCT02656979).

Subjects with untreated ocular hypertension and normal visual fields were asked to participate. Forty-seven subjects were included; of these, 17 subjects were excluded from final analysis owing to latanoprost being instilled in both eyes \( n = 1 \), patient unable to perform MRI \( n = 1 \), withdrawal of informed consent before the second MRI scan \( n = 4 \), nonmeasurable OA blood flow likely owing to anatomic variations where OA originates from the middle meningeal artery \( n = 2 \), missing data \( n = 3 \), or poor quality MRI data \( n = 6 \) in either the treatment or control eye at any visit. Thus, 30 subjects with complete data were analyzed.

The study included two visits for each subject. After the first visit, the participants received a bottle of latanoprost. At each visit, subjects were assessed with an ophthalmology examination as outlined elsewhere in this article, an MRI scan, and in conjunction with the MRI a blood pressure measurement in a sitting position. The ocular perfusion pressure (OPP) in supine position for each eye was calculated as 115/130 of the mean arterial pressure, minus the IOP; the mean arterial blood pressure was calculated as the diastolic blood pressure plus one-third of the difference between systolic and diastolic blood pressure.\(^ {11,12} \)

Ophthalmology Examinations

Apart from a standard ocular examination, the participants underwent the following ophthalmologic investigations at both visits: measurement of axial length (AL) with IOLMaster (Carl Zeiss Meditec AG, Jena, Germany), central corneal thickness and corneal curvature with a Scheimpflug camera (Pentacam, Oculus GmbH, Wetzlar, Germany), corneal hysteresis (CH) with an Ocular Response Analyser (Reichert Ophthalmic Instruments, Inc., Buffalo, NY), and IOP with Goldmann Applanation Tonometry (Haag-Streit, Bern, Switzerland).

MRI Protocol

On the same days as the ophthalmologic examinations, an MRI scan of the brain was performed with a 3T scanner (GE Discovery MR 750, General Electric Healthcare, Waukesha, WI) with a 32-channel head coil. The same measurements were performed at both visits and followed a detailed protocol previously described (Ambarki 2013).\(^ {10} \) For localization of the OA, a three-dimensional time-of-flight MR angiography sequence was used. Flow was then measured with a two-dimensional PCMRI sequence, with the imaging plane perpendicular to the OA, approximately 10 mm distally of the bifurcation from the internal carotid artery. The location was chosen where the artery was relatively straight and not immediately adjacent to the air-filled sinuses. The PCMRI sequence parameters were: velocity encoding 35 cm/s, TR/TE 9/5 ms, flip angle 15\(^ {\circ} \), acquisition matrix \( 512 \times 512 \), field of view \( 180 \times 180 \text{ mm}^2 \), six views per segment, and two signal averages. The resultant image resolution was 0.35 \( \times \) 0.35 mm\(^2 \). A peripheral pulse detector was used for retrospective cardiac gating and 32 timeframes were reconstructed, corresponding with a full cardiac cycle.

PCMRI Analysis

To quantify the flow, the PCMRI data was analyzed using the software Segment (version 1.8, http://medviso.com/segment/).\(^ {13} \) A region of interest was manually drawn around the vessel in the magnitude image, with adjustments made based on the signal in the phase image. The region of interest was drawn so that the whole vessel was included during the entire cardiac cycle, with the size and position of the region of interest kept constant across all cardiac timeframes. Eddy current correction (“background correction”) of the flow velocities was performed using the automated tool of the Segment software.

For each measurement, mean OA blood flow rate was calculated as the average flow rate over the cardiac cycle. The pulsatility index (PI) was calculated as the difference between the maximum and minimum flow rates over the cardiac cycle, divided by the mean flow rate.

Statistical Analysis

Treated and control eyes were compared using paired samples \( t \) tests. Changes in flow and IOP after treatment were also assessed with paired sample \( t \) tests. Correlations between blood flow, PI, and ocular measurement were analyzed using Spearman’s rho (rank correlation), because three of the relevant parameters were not normally distributed (according to a Kolmogorov–Smirnov and/or Shapiro–Wilk test). Analyses where the \( P \) value was less than 0.05 were considered as statistically significant. In the power analysis, the flow of OA is expected to be 10 mL/min,\(^ {10} \) and we assumed that a change of 20%, that is, 2 mL/min, would be clinically relevant. Furthermore, assuming a within-subject variability of 3 mL/min in standard deviation and 80% power, the sample size was estimated as 36 subjects.

RESULTS

Patient demographics and ophthalmologic measurements are presented in Table 1. Blood flow rate and PI before and after treatment are presented in Table 2. Latanoprost
decreased the IOP by 7.2 ± 3.1 mm Hg ($P < 0.01$) in the treated eye, with no significant effect in the untreated control eye (mean change, −0.3 ± 1.8 mm Hg; $P = 0.44$). There was no significant effect on the mean blood flow rate of the treated eye ($P = 0.92$). Measured changes in the blood flow rate after treatment did not differ between the treated and control eye and there was no difference between the eyes at the first visit (Table 2).

The blood pressure after treatment (systolic, 161.6 ± 20.7 mm Hg; diastolic, 92.6 ± 10.8 mm Hg) was not significantly different from before treatment ($P = 0.45$ and $P = 0.65$, respectively). The OPP in the treated eye was 78.2 ± 11.2 mm Hg before treatment and increased significantly after treatment (85.6 ± 11.0; $P < 0.01$). The OPP in the control eye was not significantly changed between the two visits (before, 82.8 ± 11.7 mm Hg; after, 83.2 ± 11.7 mm Hg; $P = 0.84$). The OPP was significantly lower in the treated eye than the control eye before treatment ($P < 0.01$), and significantly higher after treatment ($P < 0.01$).

In a post hoc test analyzing only those subjects where the IOP of the treated eye was decreased by at least 5 mm Hg, no difference was seen between the treated and control eyes ($n = 23$; change in blood flow rate, 0.4 ± 3.2 mL/min (treated eyes) vs 0.1 ± 3.8 mL/min (control eyes); $P = 0.70$).

Regarding biomechanical parameters, the AL of the treated eyes showed a small but significant reduction after treatment (23.59 ± 0.98 mm vs. 23.53 ± 0.98 mm; $P < 0.01$) and the CH increased significantly (9.3 ± 2.7 mm Hg vs. 10.5 ± 1.7 mm Hg; $P < 0.01$; $n = 29$) (no corresponding effect in the control eye; $P = 0.32$). There were no significant changes in central corneal thickness or corneal curvature of the treated eye ($P ≥ 0.1$).

There was a significant correlation between PI and IOP (Spearman's rho, −0.39; $P < 0.05$) before treatment, but this correlation was not significant after treatment ($P > 0.8$). There was no rank correlation between blood flow rate and IOP in the treated eye ($P = 0.13$). Neither blood flow rate nor PI in the treated eye correlated significantly to OPP, AL, CH, central corneal thickness, or corneal curvature before treatment, although there was a trend between PI and AL (rho, −0.36; $P = 0.053$ for PI vs. AL; otherwise, $P ≥ 0.13$).

Although the eddy current correction affected the magnitude of the blood flow values, the results when analyzing changes in blood flow with treatment were similar for uncorrected values (i.e., no change with treatment).

**DISCUSSION**

This study is the first to use PCMRI to investigate changes in volumetric blood flow rate after lowering of IOP. Assuming a physiologically relevant change of 2 mL/min in the power calculations, this study showed that the blood flow rate of the OA was not altered by a decrease in IOP in subjects with ocular hypertension. As expected, the OPP was significantly increased in the treated eye and, because the blood pressure remained unchanged between the visits, this increase in OPP can be explained by the localized reduction in IOP.

Measurements of blood flow velocity in the OA have previously been performed with a CDI technique where IOP has been lowered. Similarly to us, Marjanovic et al. used latanoprost to reduce IOP and found no change in retrobulbar velocity parameters. This finding is further supported by Harris et al. and Hommer et al., where a decrease in the IOP induced by prostaglandins did not alter retrobulbar flow velocities. However, contradictory results also exist where latanoprost as only therapy, or together with timolol, have been shown to increase velocity in OA.

There are several potential explanations for our findings. First, ocular blood flow autoregulation could contribute. Ocular autoregulation is the capability to uphold an appropriate level of blood flow to the eye during varying metabolic demand and in the presence of changes in OPP. Under
healthy conditions, this balance is maintained, but a defective autoregulation has been proposed to play an important role in the pathophysiology of ocular diseases such as glaucoma.\textsuperscript{20} Despite an elevated IOP, the pretreatment blood flow in this group was in the same range as data for healthy controls measured with the same PCMRI technique.\textsuperscript{20} Given that ocular hypertensive subjects can be considered to be healthy, it is possible that the blood flow was unaffected prior to IOP lowering and, thus, an increase in blood flow would not occur when the IOP was decreased. This finding is supported by the lack of difference between the blood flow rate in the control and treated eyes before treatment, despite a significant difference in IOP. In other words, the autoregulation was likely functioning adequately and maintained a normal blood flow level in the studied subjects before treatment. It has been suggested that the upper limit for autoregulation of retinal blood flow is approximately 2 mL/min which could be due to an insufficient IOP-lowering effect of latanoprost treatment in this study? To answer this question, we performed a subanalysis of subjects with an IOP reduction of at least 5 mm Hg and this analysis did not change the results.

Second, is it possible that the lack of altered blood flow could be due to an insufficient IOP-lowering effect of latanoprost treatment in this study? To answer this question, we performed a subanalysis of subjects with an IOP reduction of at least 5 mm Hg and this analysis did not change the results.

Third, the retrobulbar arterial anatomy may elucidate the results. Although the OA is the main supplier of blood to the ocular system, a considerable amount of the blood is conveyed to extraocular tissues.\textsuperscript{25} In fact, calculations based on previously published data on number of vessels and vessel area\textsuperscript{25} as well as flow,\textsuperscript{24} indicate that only approximately 15% to 20% of the blood flow in the OA is delivered onward to the central retinal artery and the ciliary arteries supplying the eye. Furthermore, the OA, originating from the internal carotid artery, anastomoses with vessels from the external carotid artery circulation. Albeit small, the OA could be too large and proximal a vessel to study a possible effect on blood flow owing to reduced IOP. Being end arteries and solely providing blood to the ocular system, the ciliary and retinal arteries would thus be preferable for studying a possible effect of IOP reduction on ocular blood flow. However, the resolution of the current 3T PCMRI is not sufficient for such a purpose owing to the small diameter of these vessels; however, with the higher resolution available using 7T PCMRI,\textsuperscript{25} it might be feasible to explore this idea.

Of the biomechanical properties measured, only AL and CH changed significantly after treatment. A decrease in the AL after the IOP decrease was seen, without a corresponding change in the control eye. This finding is in accordance with published literature, where a decrease in the AL has been reported after IOP reduction.\textsuperscript{26,27} Our results also showed an increase in CH in the treated eye, which also is in line with previous results.\textsuperscript{28–30} Although contrary results also exist.\textsuperscript{31} Interestingly, a significant negative correlation was found between PI and IOP in the treated eye before treatment, but not after the IOP had been decreased. This result could indicate that the capacity for cardiac-related arterial expansion in the eye is decreased when the IOP is high.

Strengths of this study were its prospective design, that all participants were previously untreated with IOP-lowering medications, and the fact that they then received latanoprost according to a standardized protocol. A potential limitation is that the untreated IOP level was not higher; in retrospect, an IOP greater than 30 mm Hg would have been preferable considering possible compensation of autoregulatory mechanisms. Our results suggest that if there exists a within-patient change in blood flow rate after an IOP reduction, it is less than the 2 mL/min assumed in the power calculation. However, given that only 15% to 20% (i.e., approximately 2 mL/min) of the OA blood flow rate are conveyed to vessels that supply the eye, a physiologically relevant difference could possible be as small as 0.5 mL/min which means that a sample size of $n = 30$ could give a type II error.

In summary, this study showed that blood flow in the OA measured with PCMRI was not affected by IOP reduction in previously untreated ocular hypertensive subjects. This outcome is most likely due to effective ocular autoregulation. We suggest that, to further explore the role of autoregulation and IOP in OA blood flow, a future study with a similar design should focus on patients with glaucoma, where the autoregulation can be expected to be dysfunctional, and ocular hypertension subjects with an IOP of more than 30 mm Hg, where autoregulation can be expected to be exhausted.

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