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ORIGINAL PAPER

Retinal perfusion 6 months after trabeculectomy as measured by optical coherence tomography angiography

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Abstract

Purpose To investigate potential changes of vessel density (VD) at the optic nerve head (ONH) and the macula 6 months after trabeculectomy (TE).

Methods In a prospective monocentric study, 19 eyes with open-angle glaucoma were treated with TE + MMC (mitomycin C). At four different time points multiple morphological papillary parameters were measured by OCT, and the ONH VD in the radial peripapillary capillary layer and the superficial and deep plexuses of the macula was determined by OCTA (optical coherence tomography angiography, RTVue-XR, Optovue). The mean defect was determined by visual field examination (mode 30-2, Humphrey Field Analyzer). The duration of follow-up was 6 months.

Results Nineteen eyes, one each from 19 patients (11 females; 8 males) with a mean age of 66.0 (58.07, 70.94) years and a mean intraocular pressure (IOP) of 21.0 mmHg (17.07, 23.87), were included in the study. All showed a significant reduction in IOP at each follow-up after TE ($p < 0.0001$). There was no significant change in the peripapillary retinal nerve fiber layer thickness ($p = 0.88$), the ganglion cell complex ($p = 0.97$), the cup–disk ratio ($p = 0.63$), the rim area ($p = 0.78$), or the mean visual field defect ($p = 0.82$). With regard to VD, no significant difference could be determined in either the ONH or the macular area.

Conclusions After significant surgical reduction of IOP by TE, there are no significant detectable morphological changes in the ONH or the ganglion cell complex as measured by OCT, nor does the papillary or macular OCTA-determined VD change significantly.

Trial registration 2016-409-f-S Avanti-OCT-A. Registered December 1, 2016.

Keywords OCT angiography · Glaucoma · Intraocular pressure · Trabeculectomy · Blood flow · Vessel density

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Introduction

It is estimated that approximately 80 million people worldwide will suffer from glaucoma in the year 2020 [1]. The question of whether structural and functional changes occur during and after the surgical reduction of intraocular pressure (IOP) has often been raised. To answer this question, it is important to first consider the morphological consequences of glaucoma. This disease is characterized by damage to the retinal ganglion cell axons, thinning of the peripapillary retinal nerve fiber layer (RNFL) thickness and intrapapillary nerve fiber loss ("cupping"). Furthermore, there is accompanying posterior displacement of the lamina cribrosa. This anatomical change is thought to affect the circulation, resulting in ischemic insults [2]. The aim of therapy is to reduce the IOP at the earliest possible stage of the disease and thus avoid the occurrence of morphological and functional changes in the form of visual field defects. If drug therapy fails, or in the event of drug intolerance, surgery can be used to achieve the target IOP. There are many surgical techniques to reduce IOP. Trabeculectomy is still considered the gold standard. This filtering technique provides good results in IOP reduction and is also a cost-effective procedure. In the study reported here we set out to evaluate the morphological and functional consequences of this surgical pressure relief. Our primary goal was to assess by means of optical coherence tomography angiography (OCTA) the change in the circulatory status (vessel density, VD) in the area of the optic nerve and the macula after surgical pressure relief using. The duration of follow-up was 6 months.

Methods

Study design

This was a prospective monocentric study conducted at the Department of Ophthalmology, St. Franziskus Hospital Muenster (Germany). The study followed the tenets of the Declaration of Helsinki and was approved by the Ethics Committee of the Medical Association of Westfalen-Lippe, Germany. All patients gave their informed consent before study entry.

Inclusion criteria:

- Glaucomatous optic neuropathy, defined as the presence of at least two of the following characteristics:
  - Vertical cup-to-disk ratio (VCDR) ≥ 0.5 (based on HD-OCT measurements) with corresponding reduced RNFL thickness and ganglion cell complex (GCC) defects on OCT analysis consistent with glaucoma
  - VCDR asymmetry ≥ 0.2
  - IOP ≤ 21 mmHg on the day of examination, with or without antiglaucomatous eye drop.

Exclusion criteria:

- Significant media opacity preventing high-quality imaging
- Age < 18 years
- Refractive error $> \pm 6$ D sphere and ± 2 D cylinder
- Previous intraocular surgery except for uncomplicated cataract extraction with IOL implantation in the bag
- Any ocular disease other than glaucoma or cataract
- Arterial hypertension, hypotension, diabetes or any other vascular diseases such as status post-heart failure, apoplexy or thrombosis
- Systemic drugs with an effect on vascular diameter either dilation or construction.

Subjects

The patients' characteristics are shown in Table 1. The study population was recruited from among patients with open-angle glaucoma (OAG) scheduled for trabeculectomy at the Department of Ophthalmology, St. Franziskus Hospital Muenster. OAG was defined as the presence of at least two of the following characteristics:

- Vertical cup-to-disk ratio (VCDR) ≥ 0.5 (based on HD-OCT measurements) with corresponding reduced RNFL thickness and ganglion cell complex (GCC) defects on OCT analysis consistent with glaucoma

Table 1 Demographic and ocular characteristics of the study population preoperatively

Age, years	66.0 (58.07, 70.94)
Female/male, *n*	11/8
Glaucoma entity	POAG, high-tension 12
	SOAG, XFG 7
First diagnosis of glaucoma, months	84.16 ± 80.76
Refractive error	0.07 ± 1.78 D
IOP, mmHg	21.0 (17.07, 23.87)
MAP, mmHg	98.87 ± 10.18
Visual acuity, logMAR	0.14 ± 0.09
Visual field mean deviation, dB	− 10.70 ± 8.26
Topical medications, *n*	3.21 ± 0.92
Type of topical medication, number of active ingredients	
Prostaglandins	1.0 (1.0, 1.0)
Beta blockers	0.74 ± 0.45
CAI	1.0 (1.0, 1.0)
Alpha-adrenergics	0.68 ± 0.48
Pretreatment surgery, *n*	Cataract surgery 2
	Argon laser trabeculoplasty, 4

Values expressed as mean ± standard deviation or as median and interquartile range

POAG primary open-angle glaucoma, *SOAG* secondary open-angle glaucoma, *XFG* exfoliation glaucoma, *IOP* intraocular pressure, *MAP* mean arterial pressure, *CAI* carbonic anhydrase inhibitor

- VCDR asymmetry ≥ 0.2
- IOP ≤ 21 mmHg on the day of examination, with or without antiglaucomatous eye drop.

The indication for surgery was progressive glaucoma (OCT, visual field and/or optic disk) with insufficient IOP reduction under a topical medication or topical incompatibility of the topical antiglaucomatous therapy. All patients used exclusively topical IOP-lowering medication, with no systemic glaucoma treatment. The inclusion criteria were diagnosis of OAG with spherical refraction of $< \pm 6$ *D* sphere and ± 2 *D* cylinder, no significant media opacity to hinder high-quality imaging, and age over 18 years. The exclusion criteria were the presence of any ocular disease other than glaucoma and cataract or systemic diseases such as arterial hypertension or hypotension, diabetes, or any other vascular diseases such as status post-heart failure, apoplexy, or thrombosis. Persons taking systemic drugs with an effect on vascular diameter (dilation or constriction) were also excluded. Postoperative IOP < 6 mmHg and hypotensive maculopathy were reasons to exclude patients from follow-up.

Examination

The measurements detailed below were carried out at four different times: before operation and 3 weeks, 3 months, and 6 months thereafter. An additional assessment within the first 3 days after surgery was excluded from consideration due to insufficient image quality. At all examination times the relevant medical history and the current glaucoma medication were documented. Prior to OCTA measurement all patients underwent detailed ophthalmic examination including best-corrected visual acuity (BCVA), slit-lamp biomicroscopy with indirect ophthalmoscopy, Goldmann applanation tonometry, and visual field examination (mode 30-2, Humphrey Field Analyzer; Zeiss, Jena, Germany). Visual field examination was not performed 3 weeks postoperatively. The thickness of the peripapillary (RNFL and ganglion cell complex (GCC), the focal loss volume (FLV), the cup–disk ratio and the rim area were measured with spectral-domain optical coherence tomography (SD-OCT, RTVue-XR; Optovue, Inc., Fremont, California, USA; software version 2016.2.035). At each visit the blood pressure was measured (Riva-Rocci method) and the mean arterial pressure (MAP) was calculated. MAP is the average blood pressure during a single cardiac cycle, and it is considered a better indicator of

perfusion to vital organs than systolic blood pressure (SBP). MAP was calculated as follows:

$$\mathrm{MAP} = \mathrm{SBP} + \frac{2 \times \mathrm{DBP}}{3} \text{ or MAP} = \frac{\mathrm{SBP} + 2 \times \mathrm{DBP}}{3}$$

Optical coherence tomography angiography

AngioVue™ (RTVue-XR; Optovue, Fremont, CA, USA, software version 2016.2.035) was used to capture the OCTA images. All participants underwent SD-OCT and OCTA imaging on the same day. Poor-quality images—defined by a signal strength index (SSI) ≤ 40—were excluded from analysis. Two OCTA volume scans (one horizontal and one vertical) were acquired to decrease motion artifacts and fixation changes. A 6 × 6 mm grid centered on the fovea was chosen to scan the macular region, while a 4.5 × 4.5 mm grid centered on the optic disk was used to scan the nerve head. The macula scans were automatically segmented into two layers with the following boundaries: a superficial retinal layer (SL = ILM 3 µm to IPL 15 µm) and a deep retinal layer (DL = IPL 15 µm to IPL 71 µm). The ONH scan had a "radial peripapillary capillary" (RPC) segment. This is a slab from the ILM to the RNFL posterior boundary. At the same time as OCTA, blood pressure measurement according to Riva-Rocci was carried out. All scans were performed on non-drug-dilated pupils except for a few 3 weeks postoperatively, as some patients were still using atropine drops. At all other postoperative measurement times the pupil was not dilated.

VD was measured using the automated density measure tool in the AngioVue™ software. Since Software Update 7, the device manufacturer has modified the numerical representation of the VD: The optic disk is now divided into eight sectors based on the Garway-Heath map. At the macular region there is a subdivision into two circles: The inner circle (fovea) is 1 mm and the outer circle (parafoveal) is 6 mm in diameter. Both are divided into four quadrants (Fig. 1).

Statistical analysis

MedCalc® version 12.4 (Ostend, Belgium) and R version 3.2.5 (Dormagen, Germany) were used for all statistical analyses. Normal distribution of the data was checked by means of the Kolmogorov–Smirnov test, and data were expressed as mean ± standard deviation (range) for Gaussian distributed values (*t* test) and medians (interquartile range) for non-Gaussian distribution (Wilcoxon rank-sum test). Analysis of variance (ANOVA) was used to analyze the differences among group means. Correlations were

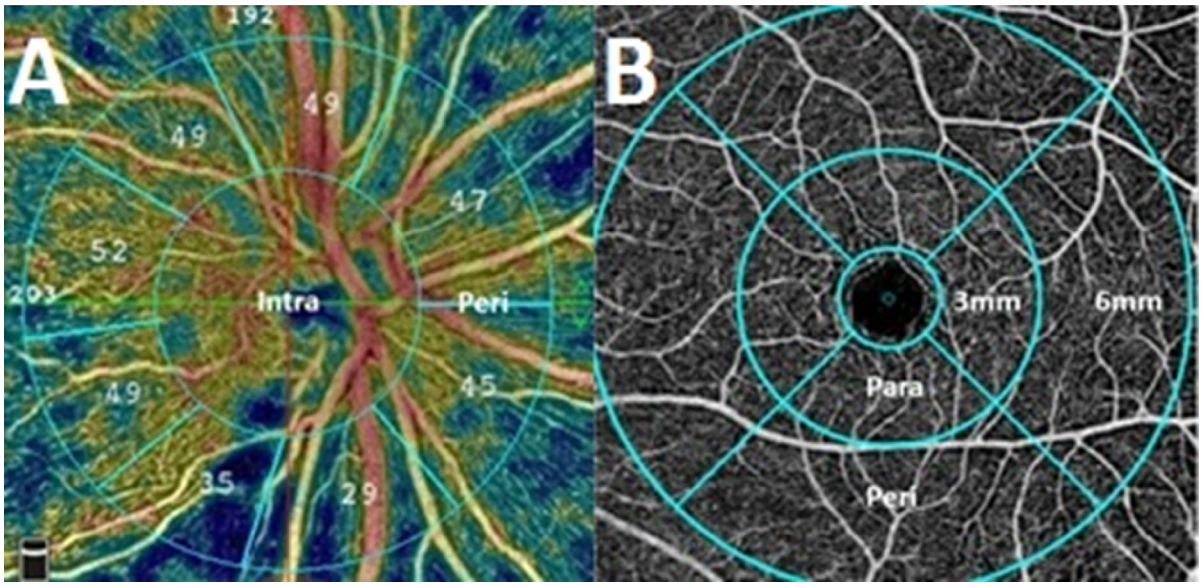

Fig. 1 Subdivision of the ONH (**a**) and macula **b** by the AngioVue™ software to calculate the VD

analyzed by Pearson's rank correlation. Differences with $p < 0.05$ were defined as statistically significant.

Results

All 19 eyes of 19 persons (11 females; 8 males) could be included in the evaluation (Table 1). All had open-angle glaucoma (OAG): 12 of them POAG (all high-tension glaucoma, no normal-tension glaucoma) and seven exfoliation glaucoma (XFG). Age, refractive error, time since initial diagnosis of glaucoma, IOP, visual field (VF) mean defect, number of topical medications, and logMAR visual acuity were, respectively, 66.0 (58.07, 70.94) years, 0.07 ± 1.78 D, 84.16 ± 80.76 months, 21.0 (17.07, 23.87) mmHg, − 10.70 ± 8.26 dB, 3.21 ± 0.92, and 0.14 ± 0.09. Two eyes were pseudophakic, and four eyes had previously been treated with argon laser trabeculoplasty.

The IOP was significantly higher before surgery than at all measurement times thereafter. By the 6-month follow-up the IOP had decreased from 21.0 (17.07, 23.87) mmHg to 10.26 ± 2.81 mmHg ($p < 0.0001$, Wilcoxon rank-sum test) and the local medication was significantly reduced ($p < 0.0001$, paired t-test); there was no significant change in VF mean defect ($p = 0.82$, paired t test) (Fig. 2).

With regard to the OCT morphology of the ONH and GCC, there was no significant measurable change in morphology at any postoperative time point. Also with regard to the MAP, no significant differences were found (Table 2). In addition, there was no correlation between calculated MAP and peripapillary (Fig. 3) or macular VD (data not shown).

With regard to the evaluation of the postoperative development of VD there is no significant papillary or macular change in image quality (signal strength index, SSI) over time (Figs. 4, 5 and 6).

Figure 4 shows the whole papillary VD (pVD whole) at the RPC layer as well as in the intrapapillary (pVD inside) and peripapillary (ppVd) subdivisions. Overall, there was no significant difference in VD at any postoperative time point.

As for macular VD, neither in the superficial (Fig. 5) nor in the deep (Fig. 6) segmentation layer was any significant change in the VD evident at any postoperative time.

Furthermore, we investigated whether there was a significant change in VD after 6 months depending on preoperative IOP values, which we subdivided into two groups: IOP < 20 mmHg ($n = 7$) and IOP ≥ 20 mmHg ($n = 12$). The course of VD was considered for all parameters (ONH-RPC and macula SL + DL). Again, there was no significant difference. Figure 7 shows total papillary VD.

Although the severity of the disease was subdivided according to VF mean defect, there was no significant difference in any VD parameter. In order not to let the groups get too small, in the mean defect values were divided only into 0 to -9 dB ($n = 9$) and < − 9 dB ($n = 10$). Thus, only the results for whole papillary

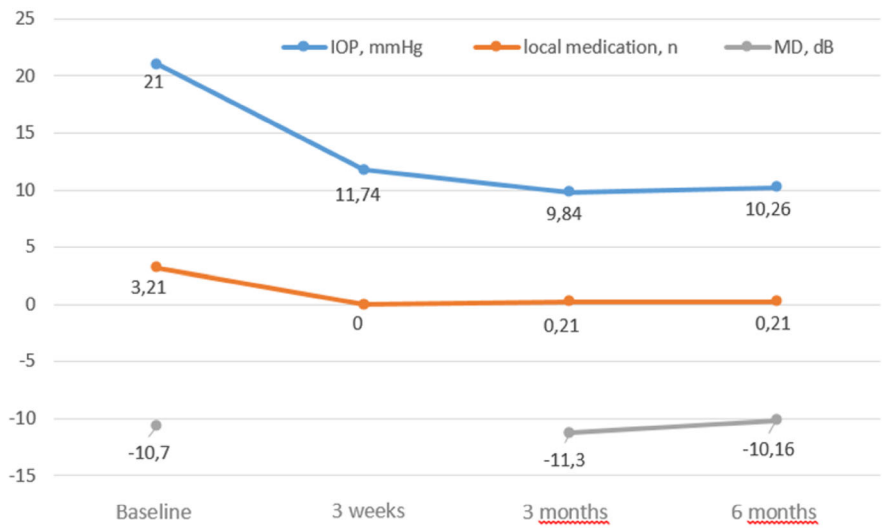

Fig. 2 Time course of intraocular pressure (IOP), local medication and mean defect (MD) visual field

Table 2 Change in morphological features and MAP over 6 months

	Baseline	3 weeks	3 months	6 months	*p* value
Cup–disk ratio	0.67 ± 0.16	0.67 ± 0.17	0.61 ± 0.16	0.62 ± 0.19	0.63
GCC (µm)	79.28 ± 14.18	79.47 ± 14.56	78.26 ± 14.16	77.47 ± 13.55	0.97
FLV (%)	6.59 ± 4.42	6.42 ± 4.0	11.25 ± 19.26	8.03 ± 4.87	0.5
RNFL (µm)	74.0 ± 13.02	77.33 ± 14.56	75.73 ± 14.19	73.94 ± 13.72	0.88
Rim area (mm^2)	0.73 ± 0.37	0.74 ± 0.39	0.32 ± 0.33	0.82 ± 0.38	0.78
MAP (mmHg)	98.87 ± 10.18	97.49 ± 10.01	98.71 ± 8.05	98.03 ± 10.25	0.98

Values expressed as mean ± standard deviation; *p* value: one-way ANOVA

GCC ganglion cell complex average, *FLV* focal loss volume, *RNFL* retinal nerve fiber layer average (all measured by OCT scan), *MAP* mean arterial pressure

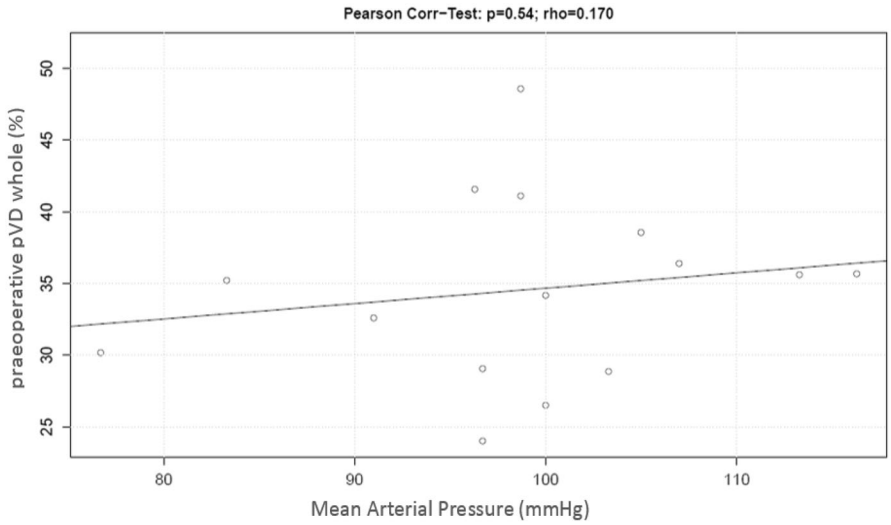

Fig. 3 Correlation of preoperative MAP to whole papillary VD (pVD whole); Pearson's rank correlation

VD difference preoperatively and 6 months postoperatively are presented (Fig. 8).

Discussion

Glaucoma causes many morphological changes in the eye (e.g., damage to the retinal ganglion cell axons, thinning of the peripapillary RNFL and intrapapillary nerve fiber loss), with the consequence of ONH excavation [3]. Patients with OAG exhibit a variety of ocular and non-ocular vascular abnormalities [4, 5]. Thus, vascular dysregulation unstable perfusion of the optic nerve and the retina are considered to be risk factors for the development of OAG and its progression. For glaucoma, the ONH, the peripapillary perfusion in the RNFL, and the superficial and deep perifoveal macular vasculature are the areas of interest. There is evidence that retinal perfusion is auto-regulated in humans [6]. Impaired autoregulation may be a critical factor in several vascular diseases including glaucoma [7].

In the past many imaging techniques have been used to show that glaucomatous eyes have an altered circulatory pathology [8–10]. Due to the specific limitations of each technique, none has completely satisfied the requirements. OCTA, first described for glaucoma detection by Jia et al. [11], is a novel examination technique for imaging blood flow in vessels (vessel density, VD). The exact technique has been described previously [12]. The advantage of OCTA lies in on the fact that the examination is noninvasive, can be conducted very quickly, and above all quantifies blood flow reproducibly [13]. In

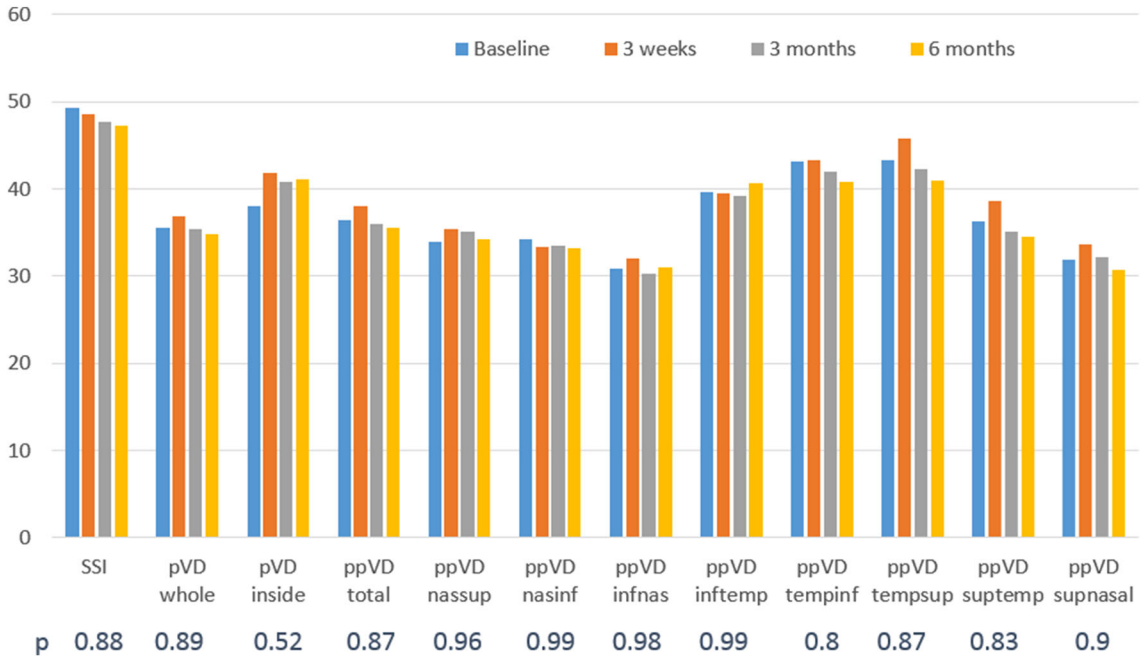

Fig. 4 OCTA (AngioVue^{TM}) results for ONH vessel density in the RPC layer. All values expressed as means; *p* value one-way ANOVA; SSI, signal strength index; pVD whole, whole papillary vessel density (%); pVD inside, inside disk vessel density (%); ppVD total, whole peripapillary vessel density (%)

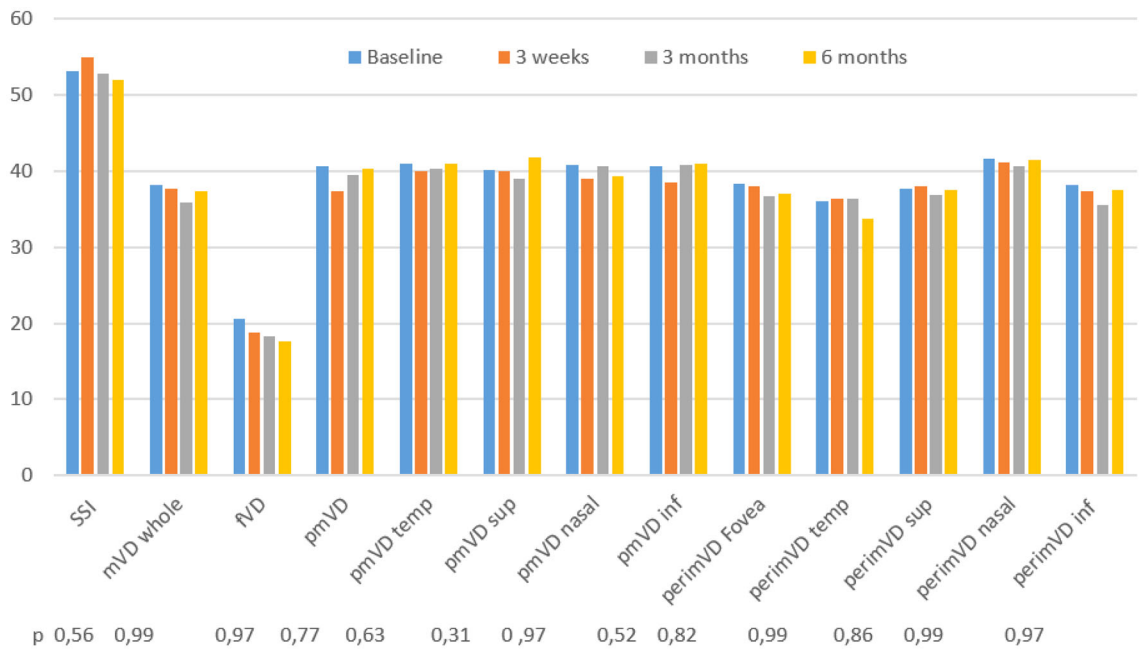

Fig. 5 OCTA (AngioVue^{TM}) parameters for macular VD segmentation of the superficial layer (SL). All values expressed as means; *p* value one-way ANOVA; SSI, signal strength index; mVD whole, whole macular vessel density (%); fVD, foveal vessel density (%); pmVD, perimacular vessel density (%)

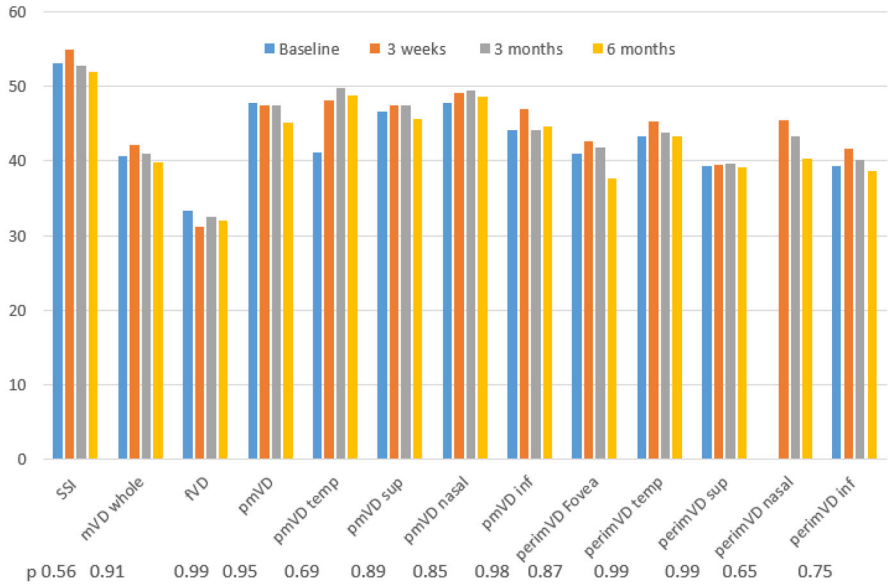

Fig. 6 OCTA (AngioVue^{TM}) parameters for macular VD segmentation of the deep layer (DL). All values expressed as means; *p* value one-way ANOVA; SSI, signal strength index; mVD whole, whole macular vessel density (%); fVD, foveal vessel density (%); pmVD, perimacular vessel density (%)

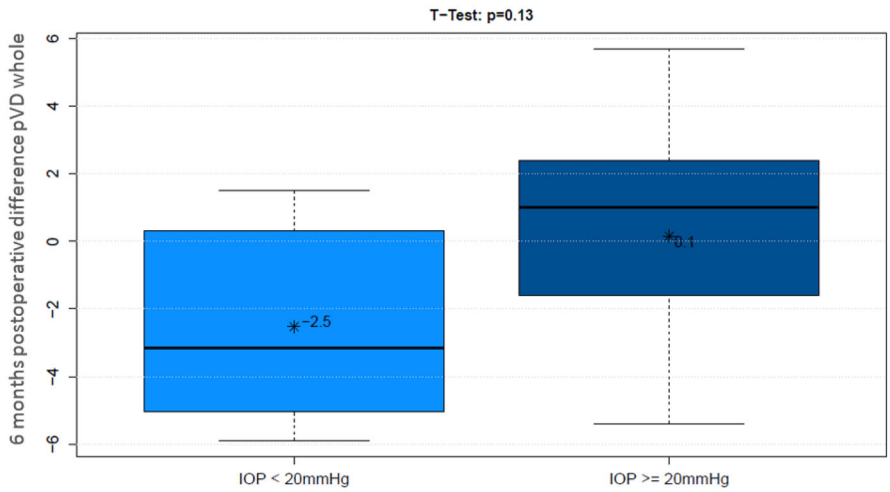

Fig. 7 OCTA (AngioVue^{TM}) parameters for papillary ONH whole vessel density in the RPC layer differentiated by preoperative IOP level < 20 mmHg and ≥ 20 mmHg. All values expressed as means; *p* value t-test; pVD whole, whole papillary vessel density

glaucoma, VD has been shown to be reduced in the area of the ONH and the macula [11, 14–16].

It is now of interest to consider what happens after reduction of VD by pressure relief, whether by medical or surgical means. Previous research on this topic has used different observation techniques showing different results. Most hemodynamic measurements were made after trabeculectomy (TE). Most of the time it could be shown that blood velocity was increased after IOP reduction [17–19]. Cantor et al., on the other hand, stated that the ocular hemodynamic parameters were not significantly different at 3.6 and 12 months after TE [20].

With the emergence of new modalities for imaging the retinal blood circulation, the topic of IOP change has now moved back into the focus of research.

To date, only a few studies have been conducted on IOP change and VD as measured by OCTA.

An animal experiment by Patel et al. [21] investigated the effect of an acute short-term increase in eye pressure and subsequent pressure reduction on the papillary VD (Spectralis OCTA 2 system). In six rhesus monkeys the IOP was slowly and gradually increased to 60 mmHg and then decreased in 10 mmHg steps to the baseline of 10 mmHg. For a wide range of IOP values, the VD was constant. The

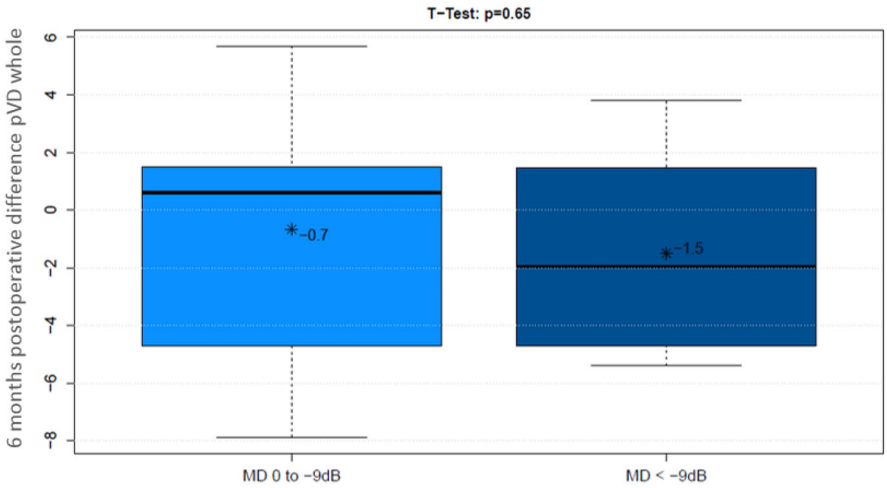

Fig. 8 OCTA (AngioVue™) parameters for papillary ONH whole vessel density in the RPC layer differentiated according to preoperative VF mean defect 0 to − 9 dB (n = 9) and < − 9 dB (n = 10). All values expressed as means; p value t test; pVD whole, whole papillary vessel density

VD decreased statistically significantly when IOP exceeded 50 mmHg ($p \leq 0.001$) and recovered to baseline when IOP returned to the baseline of 10 mmHg. These observations indicate that there is an autoregulatory capacity when IOP increases, so that the vascular supply situation does not change discernibly. Beyond this range, however, the autoregulatory capacity fails.

The first OCTA observations of VD in the human eye were made by Holló et al. [22]. They evaluated the peripapillary angioflow density (PAFD) in six eyes (four young male patients) after topical IOP lowering of at least 50% by means of medication and IOP $\leq$ 18 mmHg in newly diagnosed glaucoma. The duration of follow-up was 2–4 weeks. The untreated IOP level ranged between 35 and 42 mmHg. Five of the six eyes showed a clinically significant PAFD increase in the RPC layer. The differences between these results and ours are striking. The IOP level before pressure relief was higher in Holló et al.'s patients. This may explain the discrepancy in results and is a possible explanation for the autoregulation range. Furthermore, four of Holló et al.'s group had ocular hypertension rather than glaucoma, two had pigment dispersion, and two had pigmentary glaucoma. Only three eyes presented a cup–disk ratio above 0.7 with corresponding reduction in peripapillary RNFL thickness. The mean value of the mean deviation was 1.95 ± 3.31 dB. Moreover, the glaucoma disease in our patient population was significantly more advanced. We detected a mean defect of − 10.70 ± 8.26 dB. Thus, it could possibly be concluded that eyes with less glaucomatous damage have significantly better VD. However, no significant improvement of the VD could be determined even in our subgroup with less advanced MD (Fig. 8). Another potential explanation for the difference in results is the method of pressure reduction. Holló et al. used eye drops for this purpose. All patients were given an atopical beta blocker as well as a prostaglandin analogue, and additionally a local carbonic anhydrase inhibitor was used in four eyes and brimonidine in two eyes. Hypothetically, therefore, the altered VD could be a pharmacological effect. Many studies have reported changed microcirculation in ONH resulting from topical antiglaucomatous medications. With regard to OCTA, to date only one study has investigated the effect of glaucoma drops on peripapillary VD. It was shown that the topical ROCK inhibitor ripasudil enhanced peripapillary VD in POAG and OH, whereas the alpha-2 agonist brimonidine did not [23]. Other techniques have demonstrated differing effects on retinal perfusion, e.g., a fixed combination of timolol with a prostaglandin analogue did not exert a significant action on ocular blood flow parameters [24], whereas the combination of dorzolamide and timolol affected retinal vascular autoregulation [25]. Regarding the work of Holló et al. a pharmacokinetic influence on the blood circulation cannot be ruled out with certainty. Another possible explanation for the improvement in VD achieved by Holló et al. may be that the reduced VD is a consequence of the glaucoma disease and that our study collective already had chronic damage from the advanced disease. This severe damage may not

regenerate whatever the pressure. Holló et al., on the other hand, studied eyes with less advanced glaucoma.

Three studies looked at the change in VD (as determined by OCTA Optovue) following significant pressure reduction by filtering surgery. Zéboulon et al. [26] found no significant change in VD 1 month after deep non-penetrating sclerectomy for the whole peripapillary area ($p = 0.788$) in 21 glaucomatous eyes (baseline IOP 23.7 mmHg). The patients were divided into two groups with superior and inferior VF defects. In the macular region there was a significant change only in the inferotemporal area of patients with predominantly superior visual field defects ($p = 0.024$).

Shin et al. [27] reported an improvement in microvascularity at 3 months after TE. Furthermore, they investigated the influence of lamina cribrosa position (LC surface depth, LCD) on circumpapillary microvascular changes. The area of vascular dropout was measured by a computer program. A total of 31 POAG patients with baseline IOP of 26.3 mmHg had no significant improvement in circumpapillary VD. However, 61.3% of the eyes had an improvement in peripapillary microvascularity. The circumpapillary VD exhibited a significant increase at 1 and 3 months postoperatively in eyes with microvascular improvement ($p = 0.0008$). The most relevant factor for microvascular improvement was the maximum reduction in LCD. For this reason, it is concluded that LCD reduction is associated with an improvement of microvascular structures.

The results of Zéboulon et al. and Shin et al. with regard to VD correspond to our observations after 6 months; however, we could not confirm the only significant difference in the inferior temporal area of the VD macula in either the superficial or the deep plexus. Again, it is suspected that the difference in results compared with the study by Holló et al. may be due to the different heights of the baseline IOP. The patients in the study by Zéboulon et al. and Shin et al. had baseline IOP values similar to those in our study (21.0 mmHg). It can be assumed that the level of the baseline IOP has an influence on the amount of VD change, since Holló [22] showed significant changes at a much higher baseline value.

The third publication describing the position after successful filtering surgery is that by Kim et al. [28]. In 54 eyes with a mean preoperative IOP of 23.1 mmHg, they studied the microvascular changes in the deep structures of the optic nerve head and the peripapillary tissue after TE and compared the results with the extent of change in the lamina cribrosa after IOP reduction (LC curvature reversal). Interestingly, at 3 months after operation the authors found no changes in the VD in the prelaminar optic section, the peripapillary retina, or the peripapillary choroid, but a significant increase in VD in the region of the LC. The VD increase was more strongly associated with the reduction in LC curvature than with the lowering of IOP. Again, these same findings in the area of the radial peripapillary capillaries are an indication of effective blood flow regulation in the sections of the optic or macula we have studied. Kim et al.'s observation that in the lower optic areas the VD improves despite moderate mean preoperative IOP has to be further investigated.

Alnawaiseh et al. [29] reported alteration of macular and papillary VD after iStent inject insertion in combination with phacoemulsification in patients with POAG ($n = 24$) compared with eyes having cataract surgery only ($n = 24$). Despite a relatively low baseline IOP of 18.2 mmHg in the iStent group, the study demonstrated a significant increase in VD in the superficial ($p = 0.002$) and deep plexus ($p = 0.034$) of the macular region after significant postoperative IOP reduction. In the area of the ONH at the RPC layer, there was a significant improvement in VD with respect to the intrapapillary value (pVD inside $p = 0.012$) and the total papillary value (pVD whole $p = 0.011$). However, the peripapillary total VD (ppVD) was not significantly changed ($p = 0.421$). We have already critically questioned the measurement and usability of the intrapapillary VD, and thus of the total papillary value [15, 16]. Nevertheless, in the work of Alnawaiseh et al. a significant improvement in VD remains in the superficial plexus over the entire macular area after combined cataract surgery and iStent implantation, despite low baseline IOP. Unfortunately, these authors did not mention at what time the postoperative measurement was taken. Another possible explanation for the postoperative increase in VD is that the iStent group received intracameral acetylcholine to narrow the pupil for iStent implantation after phacoemulsification. Acetylcholine results in vasodilatation, so the increase in VD may have been due to pharmacology.

Our study features limitations. The small number of cases is explained by the difficulties imposed on

recruitment by the exclusion criteria: Most people are older at the time of glaucoma surgery. We only included patients who had no arterial hypertension, hypotension, diabetes, or any other vascular diseases such as status post-heart failure, apoplexy, or thrombosis. Individuals on systemic drugs with an effect on vascular diameter (dilation or constriction) were also excluded. These exclusion criteria hampered the recruitment of study participants, since in our society there is a significant increase in vascular disease prevalence with increasing age.

The repeatability of OCTA was not measured in this study, but previous studies have demonstrated high intra-visit consistency and inter-visit reproducibility [30, 31].

Owing to the small number of cases, it is difficult to investigate a potential confounding effect of the preoperatively applied topical antiglaucoma therapy. For ethical and medical reasons we did not discontinue the topical medication before the start of the study. We therefore cannot absolutely exclude the possibility that the different medications affected our results.

To ascertain whether VD changes after TE, we investigated the VD of the ONH and macula by OCTA with a follow-up period of 6 months. To the best of our knowledge, there are currently only a few published studies on this topic and none with a follow-up period of 6 months.

We could not detect any significant effect on VD of significant IOP reduction at any postoperative time with consistent morphologic criteria such as cup–disk ratio, rim area, and RNFL/GCC. It is conceivable that a change in the height of the LC has an influence on VD. However, as not every eye undergoes reversal of the LC by IOP-lowering treatment [32] this relationship should be investigated in future work. We can also speculate that a change is only present at higher baseline IOP values, since in the lower pressure range autoregulation can compensate the changes in VD.

Further pursuit of this topic appears to be warranted, as OCTA is a promising technique that has the potential to further enhance our understanding of ocular perfusion and may also yield valuable insights into the prognosis of patients undergoing surgery to change their IOP.

Authors' contributions CL designed the study, collected data, and wrote the manuscript. KR performed all statistical analysis. JMK, CH, and SG assisted in manuscript writing. All authors read and approved the final manuscript.

Availability of data and materials The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Compliance with ethical standards

Conflict of interest CL: lecture, Optovue
All other authors declare that they have no conflict of interest.

Ethical approval and consent to participate All procedures performed in studies involving human participants were in accordance with the ethical standards of the institution and/or national research comittee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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