Original Article

Pulsatile Ocular Blood Flow Registered with Optical Coherence Tomography Angiography in Patients with High Intraocular Pressure

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Abstract

Purpose: To present a series of cases demonstrating pulsatile ocular blood flow registered with optical coherence tomography angiography (OCTA) and to describe the clinical characteristics of this phenomenon.

Methods: Seven primary open-angle glaucoma patients (eight eyes) were included, with a median age of 67.0 years (range, 39–73 years), who demonstrated alternating hypointense bands of OCTA flow signal on the macular scan at increased intraocular pressure (IOP). All patients received comprehensive ophthalmic examination, OCTA examination with RTVue-XR, and infrared video scanning laser ophthalmoscopy. Changes in retinal microcirculation were assessed on the raw OCTA scans as well as the resultant vessel density maps before and after IOP reduction.

Results: Median IOP in study eyes was 39.0 mmHg (range, 36–58 mmHg). Hypointense bands of OCTA flow signal were associated with arterial pulsation on video scanning laser ophthalmoscopy in all eyes and agreed with the heart rate and resulted in a spotted grid pattern of hypoperfusion on vessel density maps in seven eyes. Median vessel density in superficial capillary plexus and deep capillary plexus was 32.4% and 47.2%, respectively, at high IOP, and increased statistically significantly to 36.5% ($P = 0.016$) and 50.9% ($P = 0.016$), respectively, after IOP reduction.

Conclusions: Alternating hypointense flow signal bands on OCTA scans are possibly caused by the pulsatile character of retinal blood flow during the cardiac cycle in eyes with high IOP and may reflect the imbalance between IOP and perfusion pressure. This phenomenon is responsible for the reversible decrease of vessel density at high IOP.

Keywords: Glaucoma, Intraocular pressure, Optical coherence tomography angiography, Vessel density

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Introduction

Optical coherence tomography angiography (OCTA) is becoming an important clinical tool in ophthalmology. OCTA has several advantages, including high resolution, noninvasive nature, and provides an opportunity to analyze retinal microcirculation by looking at different vascular plexuses in a depth-resolved manner. However, OCTA is associated with several limitations, including a number of imaging artifacts requiring additional precautions in the interpretation of the OCTA data.[1,2] A specific group of limitations is due to the sensitivity of OCTA algorithms to the velocity of the blood flow.[3] Particularly, blood flow which is too slow or too fast, or a turbulent blood flow is poorly registered by OCTA. In a clinical situation, this results in insufficient visualization of retinal aneurysms or some terminal vessels in ischemic regions of the retina.[4]

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Intraocular pressure (IOP) is a known determinant for intraocular perfusion since the retinal vasculature is in direct contact with the IOP. In raised IOP, the blood flow of the optic nerve head and the choroid is reduced.[5] However, the impact of raised IOP on retinal blood flow is not fully understood. Several studies showed a decrease in retinal blood flow when IOP is increased,[6,7] and acute changes of retinal vessel density at high IOP were shown with OCTA.[8] Recently, the changes in OCTA flow signal were shown in animals by an experimentally induced increase of IOP.[9] These changes in the flow signal appear as alternating regular hypointense bands on the OCTA image arranged perpendicularly to the scanning direction.

In clinical practice, we meet similar hypointense OCTA flow signal bands on the macular scan in patients with elevated IOP. However, the clinical relevance of this phenomenon has not been described until now. The aim of this study was to present a series of cases demonstrating hypointense OCTA flow signal bands and to describe the clinical characteristics of this phenomenon.

Methods

The study followed the ethical standards stated in the Declaration of Helsinki and was approved by the Local Ethics Committee of Military Medical Academy St. Petersburg. All individuals signed written informed consent before participating in the study. In this study, we included patients who demonstrated alternating regular hypointense bands of OCTA flow signal on the macular scan. Exclusion criteria were any vascular posterior segment disease, significant opacifications of optical media affecting OCTA imaging, the inability of a patient to maintain gaze fixation, the high number of motion artifacts, quality of OCTA image Q5 or lower, or the absence of follow-up data.

All participants underwent comprehensive ophthalmic examination, including OCTA examination with RTVue-XR Avanti (Optovue, Fremont, CA) software version 2017.1.0.150. All OCTA examination procedures were performed after medically induced mydriasis. Each patient received 3-mm (304 repeated B-scans each of 304 A-scans) and 6-mm (400 repeated B-scans each of 400 A-scans) OCTA scan patterns. IOP measurement with Goldmann applanation tonometry was performed prior OCTA examination and pupil dilation. Electronic medical records of the patients were reviewed. The data collected included medical history, IOP-lowering medication, and previous ocular surgery.

The hallmark of OCTA imaging with RTVue-XR is the use of motion correction technology which includes obtaining two consecutive orthogonal scans: first, with the scanning along the y-axis and second, with the scanning direction along the x-axis. The merging of the orthogonal scans in the resultant OCTA volume scan allows the reduction of motion artifacts from eyeball movements. After two orthogonal scans are obtained, the software presents them for visual inspection before merging. At this stage, an experienced retina specialist was assessing the raw OCTA scans and, if OCTA flow signal bands were detected, the images were captured for further analysis [Figure 1]. All captured images were reviewed in a masked fashion by another retina specialist who had to define the presence or absence of OCTA flow signal bands.

If the patient demonstrated OCTA flow signal bands, the heart rate and blood pressure were assessed with M3 Eco blood pressure monitor (OMRON, Kyoto, Japan), and the patient was also examined with infrared video scanning laser ophthalmoscopy (F-10, NIDEK, Gamagori, Japan) to detect possible retinal vessel pulsation. All patients with flow signal bands were included consecutively. Patients with elevated IOP (but lower than 35 mmHg) and patients with open angle with glaucoma with controlled IOP were observed between cases with flow signal bands, but no flow bands were detected in those cases.

For the patients who were recognized as having OCTA flow signal bands, the vessel density maps were exported, and mean vessel density in superficial capillary plexus (SCP) and deep capillary plexus (DCP) was assessed. Corresponding structural *en face* projections were evaluated for the presence of motion artifacts. In addition, in a subset of patients demonstrating OCTA flow signal bands at high IOP levels who achieved normalization of IOP under IOP-lowering medication, the changes in the appearance of the flow bands and vessel density were assessed. In all cases, maximum medical therapy (carbonic anhydrase inhibitor, alpha-adrenergic receptor agonist, beta blocker, and prostaglandin analog) without or with oral acetazolamide (250 mg daily) was prescribed, and IOP was measured 1–3 days after prescription.

Statistical analysis was performed with MedCalc 18.4.1 (MedCalc Software, Ostend, Belgium). Normality was checked using the Kolmogorov–Smirnov test (which indicated that the data were not normally distributed). Descriptive data were presented as a median and interquartile range (IQR). The Wilcoxon signed-rank test was used to assess the changes in vessel density before and after the lowering of IOP. For statistical comparisons, differences with a $P < 0.05$ were considered significant.

Results

In total, eight eyes of seven patients showing OCTA flow signal bands on 3-mm OCTA scans were included in this study. All eyes were diagnosed as having open-angle glaucoma stage 2 to 3. IOP, measured before OCTA examination, ranged from 36 to 58 mmHg (median: 39.0 mmHg) [Table 1]. The appearance of mires remained static during applanation tonometry. Two patients had previous antiglaucoma surgery in the study eye. No highly myopic or hyperopic patients were presented among this series. All patients were in good general health with systolic blood pressure ranging from 128 to 142 mmHg and diastolic blood pressure ranging from 83 to 95 mmHg. Heart rate varied from 60 to 74 BPM (median: 66.0).

In four patients, scan quality allowed counting of the frequency of OCTA bands (a mean of 3 bands over a scan obtained in 3

Table 1: Demographic and clinical characteristics of participants

Patient	Age, year	Laterality	Gender	IOP, mmHg	Heart rate, bpm	Systolic BP, mmHg	Diastolic BP, mmHg	Baseline topical medication
1	73	Left	Male	44	60	120	83	No
		Right		38				
2	67	Right	Male	40	74	127	79	Maximum therapy
3	71	Right	Male	42	66	134	94	PA
4	70	Left	Male	36	54	138	90	Maximum therapy
5	39	Right	Male	45	61	142	95	No
6	67	Right	Male	58	67	128	85	PA+CAI
7	66	Left	Male	45	69	132	79	PA+CAI
Median (IQR)	67.0 (66.3-70.8)			43.0 (39.0-45.0)	66.0 (60.3-68.5)	132.0 (127.3-137.0)	85.0 (80.0-93.0)	

Maximum therapy included CAI, alpha-adrenergic receptor agonist, beta blocker, and PA. BP: Blood pressure, CAI: Carbonic anhydrase inhibitor, IOP: Intraocular pressure, IQR: Interquartile range, PA: Prostaglandin analog

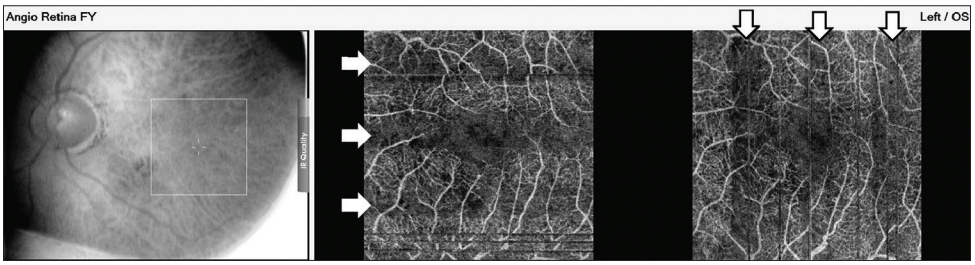

Figure 1: Screenshot showing raw orthogonal optical coherence tomography angiography scans with hypointense flow signal bands. Arrows indicate hypointense flow signal bands

s) which agreed with the heart rate. In all cases, OCTA flow signal bands appeared as a decrease of perfusion in retinal microcirculation mostly affecting retinal capillaries but sparing the largest retinal vessels in both 3-mm [Figures 2a and b] and 6-mm [Figures 2c and d] scan patterns. The deepest decrease of the flow signal within the bands was among eyes with the highest IOP. Video scanning laser ophthalmoscopy revealed arterial pulsation of the main arterial vessels close to the optic disc in all cases.

No eyes demonstrated any motion artifacts on structural *en face* projection images. Median vessel density in eyes with OCTA flow signal bands in SCP and DCP was 32.4% (IQR, 30.5%–36.4%) and 47.2% (IQR, 42.2%–50.3%), respectively. In all cases, the spotted grid pattern of decreased vessel density was noted on the DCP (six eyes) or on both DCP and SCP vessel density maps (three eyes) [Figures 3a-c] but not on the structural *en face* image [Figure 3d]. In all cases, maximum medical therapy without or with oral acetazolamide (cases 1, 5, 6, and 7) was prescribed and OCTA examination was repeated by the same operator. After the reduction of IOP, the OCTA flow signal bands [Figures 4a and b] and spotted grid pattern of hypoperfusion on the vessel density map disappeared [Figures 4c and d]. After the decrease of IOP, median vessel density increased statistically significantly in both SCP and DCP to 36.5% (IQR, 34.8%–39.1%) ($P = 0.016$, excluding clustered data) and 50.9% (IQR, 47.9–52.9%) ($P = 0.016$, excluding clustered data), respectively [Table 2]. The median scan quality index before and after IOP reduction was 6.0 and 6.5, respectively.

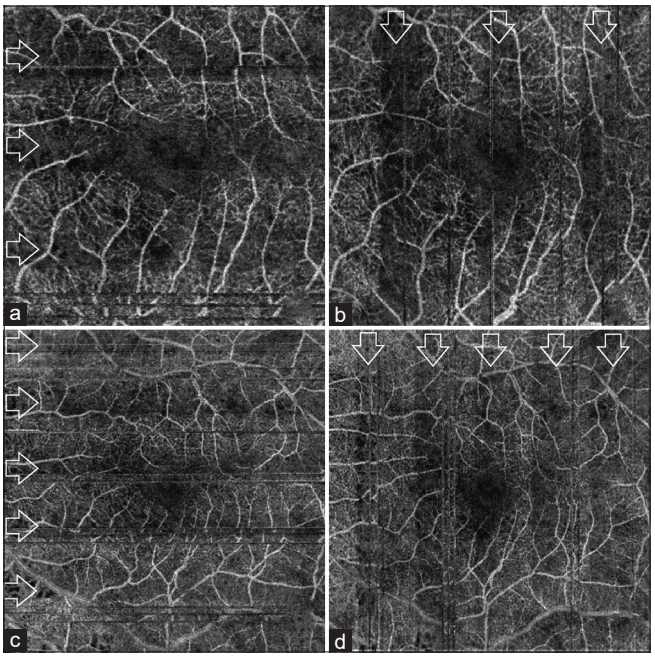

Figure 2: Representative example of registration of hypointense flow signal bands in 3-mm (a and b) and 6-mm (c and d) optical coherence tomography angiography scans. Arrows indicate hypointense flow signal bands

In three of eight cases with the most prominent hypointense OCTA flow signal bands, large choroidal vessels were distinguishable due to complete loss of the flow signal of the overlying choriocapillaris and retinal capillaries [Figure 5].

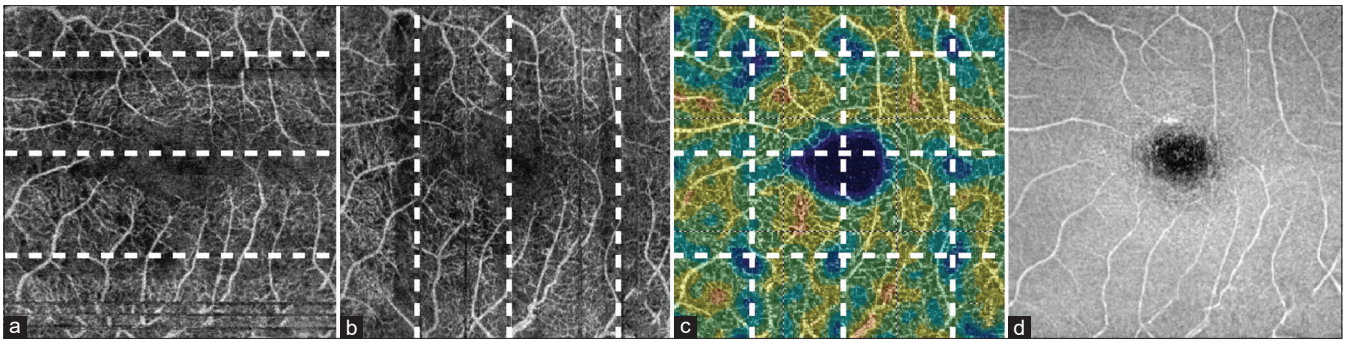

Figure 3: Proposed mechanism for the appearance of spotted grid pattern of hypoperfusion on vessel density map. (a) Raw optical coherence tomography angiography (OCTA) scan obtained in the y-axis. (b) Raw OCTA scan obtained in the x-axis. (c) Resultant vessel density map demonstrating spotted grid pattern of hypoperfusions. Dashed lines represent positions of hypointense flow signal bands. (d) Corresponding *en face* structural projection showing absence of any artifacts.

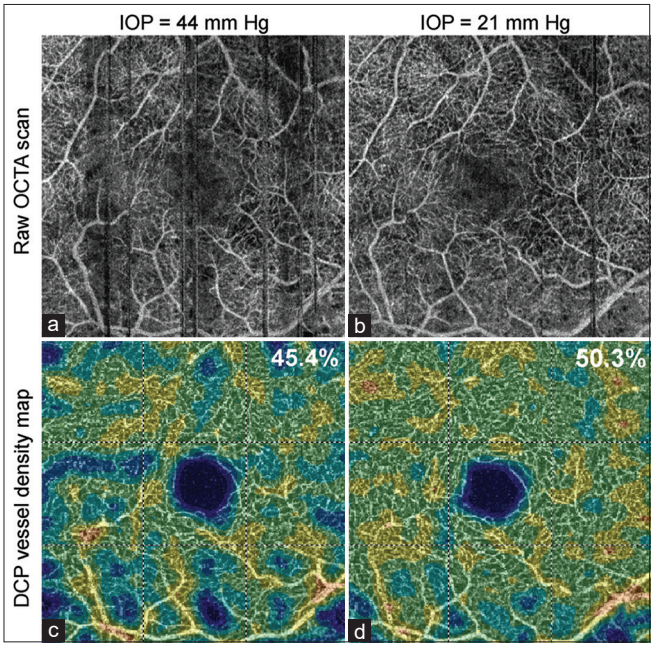

Figure 4: Changes in retinal microcirculation registered by optical coherence tomography angiography (OCTA) after decrease of intraocular pressure (IOP). Raw OCTA scans showing hypointense flow signal bands at high IOP (a) and their disappearance after decrease of IOP (b). Vessel density map of deep capillary plexus showing spotted grid pattern of hypointense flow signal at high IOP (c) and normalization of retinal perfusion and increase of vessel density after decrease of IOP (d).

Discussion

In this article, in a series of cases, we showed that in eyes with high IOP and glaucoma, the OCTA flow signal on the macular scans may have an unstable character and may appear as an alternation of hypointense flow signal bands arranged perpendicularly to the scanning direction. When a scan is not affected by motion correction technology, the bands are organized in a regular pattern with a frequency equal to the heart rate. The appearance of OCTA flow signal bands is associated with arterial pulsation registered on the video scanning laser ophthalmoscopy and likely results from the pulsatile character of the blood flow. The lowest IOP threshold for registration of these bands in this study was 35 mmHg. However, the mean IOP among patients who demonstrated this phenomenon was 42.0 mmHg. In addition, we did not observe any cases with flow bands during the consecutive inclusion of all cases. These hypointense bands affect only OCTA projections and leave structural *en face* projections unaffected which suggests that they are purely angiographic in nature. Taking all the above into consideration, together with the fact that the flow signal decorrelation is sensitive to the blood flow velocity, we can infer that hypointense flow signal bands result from the slowing down of the blood flow in the diastole.

The appearance of the OCTA flow signal bands was associated with a decreased retinal vessel density in both SCP and DCP. Taking into consideration the motion correction technology used by the OCT device in this study, we can note that the decrease of vessel density is most apparent at the intersections of the hypointense bands of two orthogonal scans. This forms a spotted grid pattern of hypoperfusion on the vessel density maps, which indicates the pulsatile character of the retinal blood flow. Reversible decrease of the vessel density in eyes with high IOP has already been reported in the peripapillary area using OCTA.[8] However, the mechanism which contributes to this decrease has not been proposed. This study, therefore, provides an explanation for the mechanism of the reduction of retinal vessel density at high IOP. The main issue which may have practical significance is the potential variability in vessel density depending on how many hypointense bands occupy the scan area and where the intersections of the bands occur. To evaluate vessel density at high IOP, the averaging of several measurements/scans may provide a more reliable estimation. This phenomenon also shows that gating of the OCTA scanning according to the heart rate may be necessary for future studies to ensure accurate measurements. The data on the effects of high IOP rise on OCTA imaging is limited. To the best of our knowledge, the only article of Cheung *et al*. described flow signal bands in association with IOP experimentally spiked by intravitreal injection in monkeys. However, the flow bands and severe hypoperfusion of DCP were observed in very high IOP of above 90 mmHg, and these data are not likely relevant to

Table 2: Vessel density parameters baseline and at decreased intraocular pressure

Patient	Laterality	Baseline			Decreased IOP			Prescribed medication
		IOP	SCP vessel density	DCP vessel density	IOP	SCP vessel density	DCP vessel density	
1	Left	44	34.9	45.4	29	40.1	50.3	Maximum therapy
	Right	38	31.7	49	21	31.9	51.5	
2	Right	40	33.1	43.2	16	35.7	44.4	Maximum therapy and oral CAI
3	Right	42	31.1	39.9	15	35	47.2	Maximum therapy
4	Left	36	37.8	49.9	16	39.6	52.1	Maximum therapy and oral CAI
5	Right	45	38.3	54.6	12	38.5	54.8	Maximum therapy
6	Right	58	29.4	50.6	27	37.2	53.7	Maximum therapy and oral CAI
7	Left	45	29.8	41.2	18	34.5	48.6	Maximum therapy and oral CAI
Median (IQR)		43.0 (39.0-45.0)	32.4 (30.5-36.4)	47.2 (42.2-50.3)	17.0 (15.5-24.0)	36.5 (34.8-39.1)	50.1 (47.9-52.9)	
P					0.016*	0.016*	0.016*	

*Compared to baseline after exclusion of the right eye of patient 1. Maximum therapy included CAI, alpha-adrenergic receptor agonist, beta blocker, and PA. CAI: Carbonic anhydrase inhibitor, DCP: Deep capillary plexus, IOP: Intraocular pressure, IQR: Interquartile range, SCP: Superficial capillary plexus, PA: Prostaglandin analog

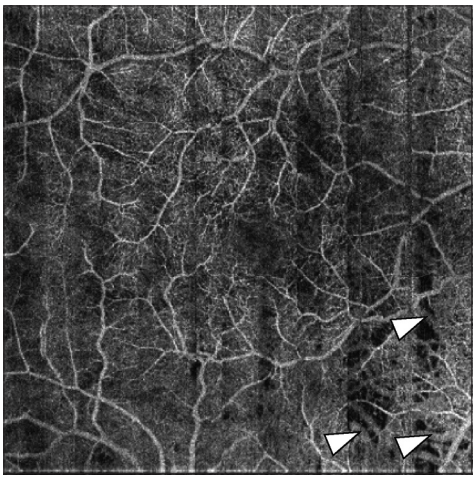

Figure 5: Raw optical coherence tomography angiography scan showing pulsatile blood flow in choriocapillaris and choroid in patient with high intraocular pressure (IOP). The image represents a full-thickness slab. Arrowheads indicate large choroidal vessels which become visible due to hypoperfusion of the retinal microcirculation and choriocapillaris. The IOP in this case was 38 mmHg.

clinical settings. Nevertheless, based on this data, the author theorized that this phenomenon may lead to ischemic damage in DCP. [9] Other studies focusing on relationships between high IOP and posterior segment perfusion addressed rather long-term changes[10] or when considering acute changes (such as those after intravitreal injections) do not analyze underlying mechanisms in changes of the perfusion.[11]

Arterial pulsation is a known phenomenon, which occurs when IOP and blood pressure are equalized, for example, in ophthalmodynamometry.[12] In such cases, arterial pulsation appears when IOP is raised to the level of diastolic pressure. If the IOP continues to grow, arterial pulsation halts at the level of systolic pressure. Arterial pulsation, therefore, is not a stable condition but may vary in intensity within the range of IOP values. In our study, the blood pressure of the patients was within a normal range or only slightly elevated. Therefore, arterial pulsation occurred before IOP reached the level of diastolic blood pressure. This could be explained by the use of scanning laser ophthalmoscopy for registration of arterial pulsation, which may be more sensitive than the observation of the arterial pulse with indirect ophthalmoscopy. Indeed, in some cases, pulsatile movements of the arterial vessels were hardly visible even with scanning laser ophthalmoscopy. The clinical implication of these OCTA bands reflects the concept of perfusion pressure, which is the difference between systemic arterial pressure and IOP. [13] Since, from the current article, we know that critical IOP can cause pulsatile ocular blood flow, we believe that these bands in normal IOP may indicate an imbalance between ocular perfusion pressure and IOP even if IOP is not very high, for example, in normal tension glaucoma. Indeed, systemic hypotension is a significant risk factor for glaucomatous optic neuropathy,[14] but further studies are required to elucidate flow signal bands in patients with systemic hypotension. However, updating of OCTA algorithms may be required to detect mild changes in blood flow velocity in relatively low IOP.

The slowing down of the blood flow at high IOP allows the role of ischemic damage in glaucoma pathogenesis to be discussed. However, it is not clear how close the registration of the OCTA flow signal bands lies to the threshold where ischemic retinal damage begins. It is known that flow signal decorrelation appears when the blood flow is more than 0.3 mm/s.[15] However, several other factors, such as blood oxygen saturation, may contribute to the process of ischemic damage.

At least in some cases, the pulsatile blood flow on the OCTA scans occupied not only the retinal microcirculation but was also visible in the choriocapillaris. Involvement of the choriocapillaris and, possibly, deeper choroid appears as a total loss of flow signal from these structures leading to visualization of underlying large choroidal vessels. Since the choroid supplies the optic disc, the slowing down of the blood

flow in the choroid may be one of the links between high IOP and optic neuropathy in glaucoma through ischemic damage.

The registration of OCTA flow signal bands is dependent on the process of OCTA scan acquisition. In addition, motion correction technology may also reduce the visibility of OCTA flow signal bands. To avoid the influence of the motion correction technology, we analyzed nonaveraged raw OCTA scans for detecting of pulsatile blood flow.

We believe that this phenomenon may have clinical significance for several reasons. First, it is a new source of artifactual changes in vessel density metric, and when rectangular patterns or bands identified vessel density, readings should not be considered true ones. Second, this phenomenon may indicate high IOP where its measuring is not reliable or not available. Third, assessment of the bands may help in the estimation of perfusion pressure and identify normal-tension glaucoma progression. However, we suppose the severity of glaucoma may affect the appearance of the flow signal bands since retinal perfusion as well as OCTA vessel density decreases in advanced glaucoma and make flow signal bands less pronounced. However, our study included open-angle glaucoma stages 2 to 3 and alternating flow signal remains detectable in those cases.

This study has several limitations, mainly the small number of cases included. Therefore, we do not know if the OCTA flow signal bands are an essential phenomenon for eyes with high IOP. Since blood flow velocity also depends on systemic factors such as blood pressure, it is possible not to see this phenomenon in some patients with increased IOP and simultaneously elevated blood pressure. Furthermore, in this study, we have used only one OCT device and do not know if this phenomenon is detectable with other scanning speeds, decorrelation algorithms, and motion correction techniques. In this study, we included only open-angle glaucoma patients. The phenomenon of the OCTA flow signal bands in patients with ocular hypertension or with other causes for high IOP should, therefore, be explored in future studies. The absence of a control group could be another limitation of this study. However, during the process of inclusion of patients, we saw that flow bands were absent in patients with controlled IOP, and those patients were not included. In addition, dynamic contour tonometry may correlate with the findings of this study since it shows ocular pulse amplitude which in turn may be indicative of the status of ocular blood flow. However, this type of tonometry was not available in our study. Finally, although analysis of cofounders such as axial length and pachymetry with respect to frequency or intensity of flow signal bands would be useful, we did not perform this analysis due to the limited number of cases included in the study.

In conclusion, in this study, we have described the pulsatile blood flow in the retina and choroid registered with OCTA on the macular scan in eyes with high IOP. This pulsatile blood flow generally appears in eyes with IOP which exceeds 35 mmHg as regular hypointense flow signal bands on raw *en face* OCTA projection and does not affect structural *en face* projections. The appearance of these hypointense flow signal bands is associated with arterial pulsation and results in a spotted grid pattern of hypoperfusion on the vessel density maps when two raw orthogonal OCTA scans are merged. The hypointense flow signal bands likely result from the slowing down of the blood flow in the diastole and are responsible for the decrease of the retinal vessel density in an acute increase of IOP. Further studies with larger sample sizes are warranted to evaluate the clinical significance of this phenomenon.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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