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Original article

Peripapillary non-flow area measurement for progressive localized glaucomatous perfusion damage: a case series

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Abstract

Purpose: To investigate the applicability of peripapillary non-flow area (PNFA) measurement in the radial peripapillary capillaries (RPC) layer for the measurement of progressive localized glaucomatous perfusion damage.
Methods: A research software version of the Angiovue /RTVue-XR OCT (Optovue, Fremont, CA, USA) was used to measure localized PNFA progression by clicking on a predefined peripapillary non-perfusion area on prospectively acquired images. Capillary vessel density (VD) in the corresponding peripapillary sector was also measured. High-quality peripapillary Angiovue OCT VD images of an open-angle glaucoma population prospectively imaged for 2 to 2.5 years (5 or 6 visits at 6-month intervals) were investigated. Eyes with both localized PNFA at baseline and statistically significant peripapillary VD progression in the hemifield of the PNFA were selected for the analysis.
Results: Four eyes of four patients were eligible. In three eyes, the Octopus visual field cluster mean defect in the cluster spatially corresponding to the area of the PNFA progressed significantly ($P < 0.01$) at a rate of 1.5 to 3.4 dB/year. In two eyes, neither PNFA nor sector VD showed significant correlation with the follow-up time. In one eye, significant negative correlation for sector VD ($r = -0.841$, $P = 0.036$) and almost significant positive correlation for PNFA ($r = 0.803$, $P = 0.055$) was found, while in another eye significant positive correlation for PFNA ($r = 0.875$, $P = 0.022$) but no correlation for sector VD was found.
Conclusion: Our results suggest that PNFA measurement in the RPC layer is a

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potentially useful tool for the measurement of progression of localized glaucomatous capillary perfusion damage in open-angle glaucoma eyes with localized peripapillary non-perfusion.

Keywords: Angiovue optical coherence tomography angiography, glaucoma progression, peripapillary capillary vessel density, peripapillary non-flow area measurement, retinal nerve fiber layer thickness

Introduction

Primary open-angle glaucoma is one of the most common, irreversible, and potentially blinding painless progressive optic neuropathies, in which the retinal ganglion cells and their axons are progressively lost.[1] Treatment of open-angle glaucoma is mainly intraocular pressure reduction, which slows down progression in most of the cases, but cannot fully stop disease progression. The manifest glaucomatous structural damage is characterized by optic nerve head cupping (loss of the neuroretinal rim of the optic nerve head), reduced peripapillary retinal nerve fiber layer thickness (RNFLT), and reduced inner macular retina thickness, while the functional deterioration is best characterized and quantitatively measured with threshold perimetry of the central 30° portion of the visual field.[2] Since vision-related quality of life of a glaucoma patient is determined both by the severity of damage at the time of diagnosis and the speed of progression (rate of progression expressed as worsening of a parameter per year), long-term glaucoma management requires regularly repeated functional and structural testing of the eye under treatment.

Vascular dysregulation and unstable perfusion of the optic nerve head and the peripapillary retina have been considered as important risk factors for the development and progression of primary open-angle glaucoma.[3,4] Therefore, in the last decades, several ocular perfusion measurement methods have been established and investigated for glaucoma.[5] However, due to their limitations, their use remains minimal in clinical glaucoma care. Optical coherence tomography (OCT) angiography is a non-invasive technology that has been recently developed to measure capillary perfusion in various layers of the retina, in the macula, the optic nerve head, and the peripapillary area, respectively.[6-10] The most important difference between the information provided by earlier blood flow measurement methods and OCT angiography is that the latter provides segmented measurement data for various retinal layers and areas separately, while the former methods provide results for the whole eye, whole optic nerve head, retina, or large retinal areas, respectively. The segmented and localized information offered by OCT angiography on the peripapillary perfusion and its stability or progressive reduction can be coupled with the spatially corresponding structural and functional test results.

Early and significant reduction of peripapillary vessel density (VD) in the RNFL

(radial peripapillary capillaries layer, RPC layer) has been established in open-angle glaucoma.[6-10] Measurement of glaucomatous progression of the peripapillary capillary perfusion damage, however, remains a challenge in clinical practice.[11-18] The software in some OCT angiography instruments automatically presents and calculates 360°, superior and inferior hemifield VD progression for change analysis.[12,13,19] However, in a similar fashion to progressive glaucomatous RNFLT reduction, capillary perfusion damage may progress in small isolated areas with little effect on 360° and hemifield average values provided by the software. In order to better focus on local VD changes, the Angiovue/RTVue-XR OCT (Optovue Inc., Fremont, CA, USA) offers peripapillary sectors and sector VD values for the RPC layer.[19] The peripapillary sectors follow the distribution of the sectors established by Garway-Heath and colleagues for spatial correspondence with the visual field test points and glaucomatous visual field deterioration pattern (the Garway-Heath map).[20] However, in localized progressive capillary perfusion damage, the sector VD values may still not be entirely satisfactory, since the damage area may not respect the sector borders, and the between-visit fluctuation of the preserved perfusion within the sector may blunt the effect of localized progression.

Non-flow area measurement is an established method in macular OCT angiography scans to quantify non-perfusion in macular disease.[19,21] In the retinal layer of interest, the investigator selects a dark (non-perfused) area by clicking on the appropriate point on the screen, and the software automatically delineates those pixels that form a non-perfused area continuous with the site of the click-point. The area of the total delineated surface is automatically given in mm^2.

In the current case series, we investigated whether peripapillary non-flow area (PNFA) measurement in the RPC layer can be used to measure the progression of localized peripapillary capillary perfusion damage in open-angle glaucoma. We used a research version of the Optovue 2017.1 software that allows measuring PNFA in the RPC layer. PNFA was measured in high-quality peripapillary OCT angiography images that had been obtained earlier from open-angle glaucoma eyes in a prospective study.[12]

2. Methods

The research protocol was approved by the Institutional Review Board for Human Research of Semmelweis University, Budapest. Written informed consent was obtained from all participants before enrolment. All applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed. All participants were white Europeans participating in a long-term imaging study in the Glaucoma Center of Semmelweis University in Budapest. OCT angiography and RNFLT imaging were conducted prospectively between March 2015 and September 2017. The detailed methodical description is provided in our original publication.[12]

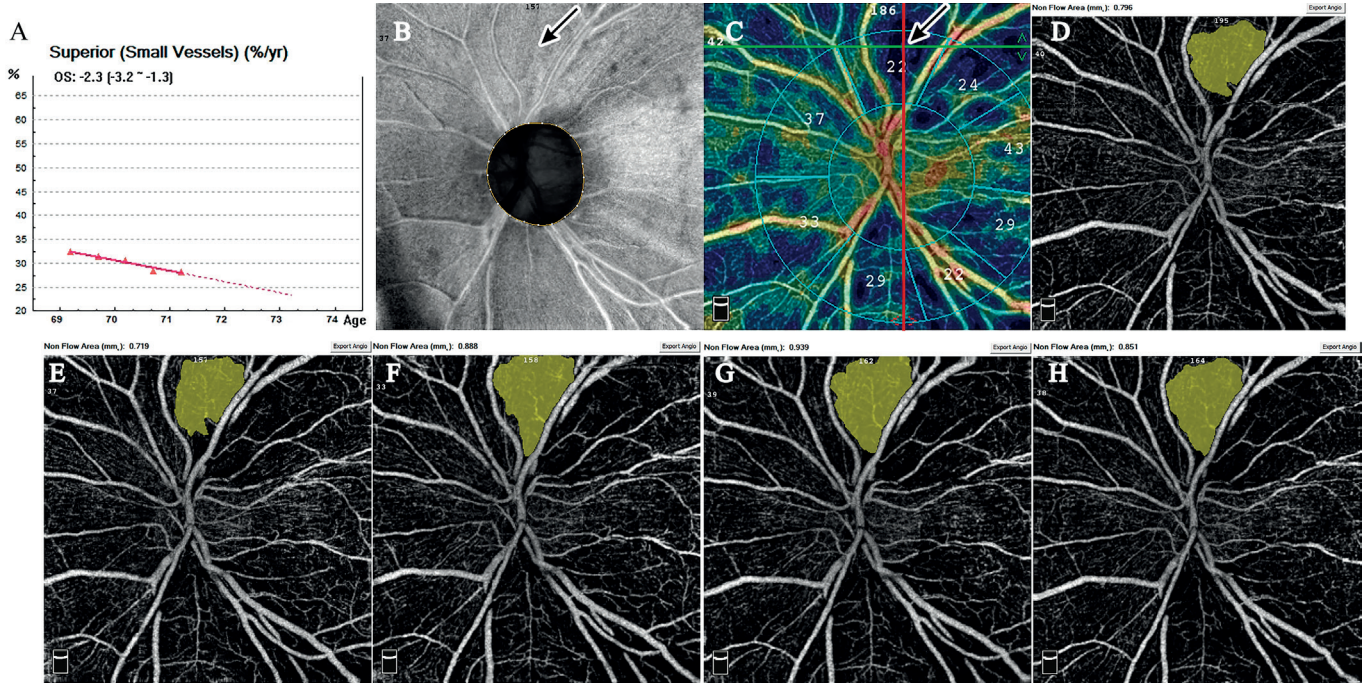

Fig. 1. Determination and measurement of PNFA progression for Case 1, left eye. (*A*) Statistically significant capillary vessel density progression indicated by the OCT instrument's software in the superior hemifield. (*B*) *En face* image of the RNFL. The arrow shows the location of the PNFA adjacent to a severe superotemporal retinal nerve fiber bundle damage. (*C*) The color-coded perfusion map shows both the location of the PNFA (superior sector, arrow) and the use of the intersection tool (cross of the green and red lines) for the determination of the position of clicking-point. (*D*) Baseline perfusion image with the software-determined PNFA. (*E-H*) The software determined PNFA on the follow-up images during the 2-year follow-up.

In brief, five or six prospective study visits at 6-month intervals were made (2 to 2.5-year follow-up). A reliable Octopus normal G2 perimetry test was conducted on all study eyes in all visits.[12,22,23] To be included in the analysis, the participants had to have clear optical media, no eye disease other than glaucoma, and no eye surgery during the study period. For peripapillary VD measurements, we used the Angiovue/RTVue-XR OCT and the Optovue 2015.100.0.33 software version (Optovue Inc., Fremont, CA, USA) via undilated pupil. Only images with optimal image quality, no motion artifacts, vitreous floaters, or other artifacts were used for research purposes. The 4.5 mm x 4.5 mm scan size was used. All image acquisitions were made by the same investigator (GH). In the current investigation, the previously acquired VD images were reanalyzed using a research software version of software 2017.1 with the Phase 7 update.[13] This software version provides selective information on capillary vessel density (expressed in percentage of the measured area) in the RPC layer for the superior and inferior hemifields, and for each of eight peripapillary sectors, respectively. The research software version also offers PNFA measurement in the RPC layer, irrespective to the VD sector borders. The software automatically offers linear regression analysis for superior and inferior peripapillary VD, separately, based on the Garway-Heath map.[20] No exact P-value is given; significant progression is defined as $P < 0.05$.

For the current analysis, eligible eyes had to have open-angle glaucoma and both localized PNFA in the baseline image and a statistically significant peripapillary VD progression for the hemifield containing the PNFA. One eye per patient was investigated; therefore, when one eye of a patient qualified for the analysis, the other eye was not considered eligible. One PNFA location per eye was investigated. The exact location of the clicking-point for PNFA measurement was determined in the baseline image using anatomical landmarks and the cross-line tool of the VD image (Fig. 1C). This image was saved and used for the exact repetition of the clicking-point on all corresponding VD images. PNFA was determined three times in each VD image. The measured value was accepted and used for analysis when all three PNFAs reflected the same area and provided exactly the same area value. Baseline Octopus visual field cluster mean defect (MD) and the software-provided cluster MD progression (in dB/year)[22,23] for the corresponding OCT angiography follow-up period were recorded for the cluster that spatially corresponded to the PNFA location. In Octopus perimetry, a visual field cluster comprises all test points that project to the same peripapillary retinal nerve fiber bundle, based on the Garway-Heath map.[20,22,23] In Octopus perimetry, abnormal sensitivity values are indicated with positive numbers.

2.1. Statistics

Pearson correlation with the follow-up time was used to determine progression. A significant VD progression was defined with a negative slope, and a significant PNFA progression with a positive slope at $P < 0.05$ level. The ROPstat 2.0 program package was used.

Results

Of the 24 prospectively imaged open-angle glaucoma cases, 4 eyes of 4 patients qualified for analysis (Table 1). Case 1 was an advanced primary open-angle glaucoma eye of a 73-year-old male patient with 51 µm baseline mean RNFLT and 18.5 dB baseline Octopus visual field MD. No significant RNFLT progression was measured during the follow-up, probably due to the low values, which had decreased below the measurement threshold (floor effect). PNFA was defined in the superior sector adjacent to an advanced superotemporal RNFL bundle defect (Fig. 1B and C). Neither PNFA nor sector VD progressed in a statistically significant manner (Table 1). In the spatially corresponding visual field cluster, the cluster MD progressed significantly at 2.9 dB/year rate ($P < 0.01$).

Case 2 was a primary open-angle glaucoma eye of a 65-year-old male patient with early visual field deterioration (baseline visual field MD 4.1 dB), high myopia (spherical equivalent: 8.0 diopter), and 71 µm baseline average RNFLT. PNFA was found in the inferotemporal sector. No sector VD progression and no PNFA progression were found (Table 1). No significant average RNFLT progression was measured, and the spatially corresponding visual field cluster progression was not statistically significant.

Case 3 was an early primary open-angle glaucoma eye of a 71-year-old female patient with multiple vascular white matter lesions in the brain. The baseline RNFLT was 81 µm and the baseline visual field MD 0.3 dB. The RNFLT progression rate was 3.77 µm/year ($P = 0.004$) and the visual field cluster MD progression rate 1.5 dB/year ($P < 0.01$) in the cluster spatially corresponding to the inferonasal peripapillary sector, where sector VD progressed significantly ($r = -0.841$, $P = 0.036$) and PNFA progressed in an almost significant manner ($r = 0.803$, $P = 0.055$, Table 1).

Case 4 was an advanced juvenile open-angle glaucoma eye of a 48-year-old female patient with 59 µm baseline RNFLT and 18.7 dB baseline visual field MD. No RNFLT progression was found during the follow-up, probably due to floor effect. In the superotemporal sector, significant PNFA progression ($r = 0.875$, $P = 0.022$) was found without sector VD progression (Table 1). The visual field cluster MD progression in the spatially corresponding cluster was 3.4 dB/year.

4. Discussion

In the current case series, prospectively acquired peripapillary OCT angiography images of four open-angle glaucoma eyes with PNFA and significant hemifield VD progression were investigated using a research software version that offers both PNFA measurement and peripapillary sector VD measurement in the same images. Our goal was to investigate whether PNFA measurement in the RPC layer can add clinically useful information regarding localized progression of glaucomatous

Table 1. Demographics and progression data of the patients

Patient	Baseline average RNFLT (µm)	Baseline Octopus VF MD (dB)	Baseline sector≠ RNFLT (µm)	Baseline Octopus VF cluster± MD (dB)	Average RNFLT progression (µm/year, P-value*)	Octopus VF cluster ± progression (dB/year, P-value*)
Case 1 73-yr old male, left eye, superior sector	51	18.5	50	14.1	0.26 P = 0.410	2.9 P < 0.01
Case 2 65-yr old male, left eye, inferotemporal sector	71	4.1	53	10.8	0.04 P = 0.820	1.1 P > 0.05
Case 3 71-yr old female, left eye, inferonasal sector	83	0.3	91	0.0	-3.77 P = 0.004	1.5 P < 0.01
Case 4 48-yr old female, left eye, superotemporal sector	59	18.7	60	17.7	-0.44 P = 0.31	3.4 P < 0.01

*: Pearson correlation; ≠: sector in which the peripapillary non-flow area is located; ±: visual field cluster that spatially corresponds to the sector in which the peripapillary non-flow area is located; RNFLT: retinal nerve fiber layer thickness; VF: visual field; MD: mean defect; VD: vessel density

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	r-value*
Sector VD (%)	22	22	22	21	17		-0.802 P = 0.102
Non-flow area (mm^2)	0.796	0.719	0.888	0.939	0.851		0.615 P = 0.270
Sector VD (%)	29	33	26	28	29		-0.310 P = 0.612
Non-flow area (mm^2)	0.215	0.248	0.468	0.434	0.427		0.816 P = 0.092
Sector VD (%)	36	37	35	32	33	23	-0.841 P = 0.036
Non-flow area (mm^2)	0.101	0.282	0.548	0.595	0.404	0.647	0.803 P = 0.055
Sector VD (%)	24	29	25	26	27	22	-0.330 P =0.523
Non-flow area (mm^2)	0.384	0.519	0.524	0.512	0.669	0.620	0.875 P = 0.022

*: Pearson correlation; VD: vessel density

perfusion damage to the information provided by the corresponding sector VD in eyes with PNFA. The background to our investigation is that localized progression of capillary perfusion damage in such eyes can theoretically be caused both by a more-or-less diffuse reduction in a peripapillary VD sector and by an isolated increase of a non-perfusion area. In the latter case, sector VD may not detect progression since PNFA may not respect the sector borders, and the between-visit variability of the preserved perfusion in the sector may mask the effect of PNFA change.

In two of the four cases, neither sector VD nor PNFA correlated with the follow-up duration. This suggests that, in these cases, no OCT angiography progression was present in the investigated areas. In another case, high correlations (progression) were found for the spatially corresponding sector VD and PNFA, although for the latter parameter the relationship was not quite statistically significant. In the last case, a high and significant correlation was found for PNFA, but no correlation was found for the corresponding sector VD. These results show that PNFA and sector VD provide similar but not identical information, and their clinical usefulness can be different in different cases. In this small case series, we did not find any clear relationship between sector VD and PNFA progression, and visual field cluster MD progression in the spatially corresponding visual field cluster.

It is important to note that in the current work our goal was to evaluate one technical aspect of peripapillary OCT angiography for the evaluation of open-angle glaucoma progression. Thus, we present the between-parameter differences for the detection of progression within an eye, and do not interpret the between-patient differences or the differences between the systemic health conditions of the patients. Since only four eyes qualified for the current analysis, such interpretation would not be scientifically or medically established. There was a considerable difference in the age of the patients, ranging from 48 and 73 years at baseline. However, in progressive late-stage glaucoma, age plays no role in the development of glaucomatous progression in a 2.5-year follow-up period.[12,13] One may speculate that Patient 3, with both primary open-angle glaucoma and white matter lesions in the brain, progressed rapidly due to a combination of both diseases. This, however, has no influence on the technical aspects of perfusion measurement investigated by us in the current case series. In real-life glaucoma care, elderly glaucoma patients frequently suffer from systemic vascular and cerebrovascular diseases. Therefore, Case 3 represents one type of open-angle glaucoma patient commonly seen in clinical practice.

Our case series has limitations. Even though we had 24 open-angle glaucoma patients prospectively followed for 2.5 years in the original study, in the current case series the analyzed sample size was small due to the small number of eyes with both PNFA and significant hemifield VD progression, as well as high-image quality. We could not extend the length of the analyzed period beyond 2.5 years (6 visits) since we replaced the imaging software with a different, higher resolution version. Currently, PNFA measurement has not been validated by the OCT manufacturer.

Thus, further research is necessary before this parameter can be considered for clinical application. Extension of a PNFA toward the image periphery can be limited by the image frame. This can decrease the probability of measuring true progression.

In conclusion, our results suggest that PNFA measurement in the RPC layer may provide additional information to sector VD measurement. Therefore, it may become a potentially useful new tool for the measurement of progression of localized glaucomatous peripapillary capillary non-perfusion. Evaluation of PNFA for glaucoma progression requires prospective high-quality imaging and long follow-up. Therefore, ongoing prospective clinical investigations conducted on large open-angle glaucoma populations may provide the possibility of a more detailed and sufficiently powered future investigation on the usefulness of PNFA in glaucoma progression analysis.

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