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Three-dimensional Assessment of Vascular and Perivascular Characteristics in Subjects with Retinopathy of Prematurity

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Abstract

Purpose—To study vascular features detected with Spectral-Domain Optical Coherence Tomography (SDOCT) in subjects undergoing retinopathy of prematurity (ROP) screening.

Design—Cross-sectional study.

Participants and Controls—Fifty-seven premature neonates, 10 with plus disease in at least one eye and 47 without plus disease.

Methods—Bedside non-contact SDOCT imaging was performed after obtaining parental consent on 97 consecutive infants between January 2009 and September 2012. Fifty-seven subjects (31–49 weeks postmenstrual age) who had a SDOCT scan in at least one eye containing the edge of the optic nerve and at least one major retinal vascular arcade were included. One eye per subject was randomly selected for analysis. Two masked graders evaluated scans for 1) retinal vessel elevation, 2) scalloped retinal layers, 3) hyporeflective vessels and 4) retinal spaces. To coalesce the weight of these features, a Vascular Abnormality Score by OCT (VASO) was created. For quantitative assessment of vessel elevation, retinal surface maps were created.

Main Outcome Measures—Prevalence of SDOCT vascular abnormalities, the VASO, inter-grader agreement, presence of elevation on surface maps.

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Results—From among 67 SDOCT characteristics that were recorded, the most common characteristics found were vessel elevation (44%), hyporeflective vessels (40%), scalloped layers (22%) and retinal spaces (11%). Features significantly associated with plus disease were vessel elevation ($p=0.01$), hyporeflective vessels ($p=0.04$) and scalloped retinal layers ($p=0.006$). Intra-grader agreement was between 74-90% for all features. VASO was significantly higher in subjects with plus disease ($p=0.0013$). On three-dimensional SDOCT volumes, eyes with plus disease had greater retinal surface elevation which more often matched *en face* retinal vascular patterns.

Conclusions—We present a novel three-dimensional analysis of vascular and perivascular abnormalities identified in SDOCT images of eyes with ROP. SDOCT characteristics which are more common in eyes with plus disease provide the first *in vivo* demonstration of the effects of vascular dilation and tortuosity on perivascular tissue. The VASO and surface maps also delineate the severity of vascular pathology in plus disease. Further studies evaluating these findings in eyes with pre-plus versus with normal posterior pole vessels may determine the usefulness of SDOCT in early detection of vascular abnormalities in ROP.

Introduction

In 1982, Quinn et al introduced for the first time, the terminology *retinopathy of prematurity plus* (ROP plus) to describe a form of ROP characterized by rapid progression of vessel dilation and tortuosity.¹ However, even before the term “plus” was introduced, other physicians such as Owen and Owen in 1949 and Harris and McCormick in 1977² had described slight dilation of retinal arteries and veins as the first detectable abnormality in ROP.³ Through the years, the importance of vascular dilation and tortuosity has remained, to the point that plus disease is now considered the primary indicator for laser treatment in ROP^{4,5} although ROP in zone 1 with stage 3 and no plus warrants laser therapy according to the Early Treatment for Retinopathy of Prematurity study guidelines.⁴

Unfortunately, the diagnosis of plus disease is subjective, and several studies have found disagreement among expert examiners even when grading still photographs.⁶

Research efforts have been geared towards finding more objective methods to assess vessel abnormalities in plus disease.⁷ Software applications such as ROPtool, RISA, CAIAR and ROPnet have been developed to accomplish this objective assessment from still photographs.^{8,9} These software applications have shown tortuosity to be helpful in distinguishing between ROP stages and have found tortuosity to be positively correlated with ROP stage.¹⁰ Investigators using ROPtool have also found large changes in tortuosity over time in individual eyes but only subtle changes in dilation.⁵

Much of the description of ROP in screening involves the *en face* appearance of vascular structures both in the posterior pole and in the periphery. If current technologies evaluate vessels in ROP on flat, two-dimensional *en face* images, we wondered if SDOCT could provide more information on vascular disease in ROP from a different perspective.

Spectral Domain Optical Coherence Tomography (SDOCT) is a diagnostic imaging tool widely used in retinal adult diseases for diagnosis and treatment monitoring. It provides cross-sectional images of the retina and has impacted the management of adult retinal

diseases. In pediatric retinal diseases, SDOCT is in a developing stage, so far providing contributions in several areas such as evaluation of normal and abnormal foveal development^{11,12,13,14}, and detection of subclinical pathology such as epiretinal membranes and pre-retinal tissue.^{15,16} SDOCT has also brought to light a new intriguing finding known as macular edema of prematurity.^{17,18} In addition to the previously mentioned capabilities, SDOCT is a non-contact imaging technique that is advantageous compared to a contact camera for evaluating infant vascular dilation. SDOCT removes the influence caused by pressure on the infant eye induced by the contact camera or scleral depressor. The description of an age-customized methodology to obtain SDOCT scans in non-sedated neonates has improved image acquisition in terms of feasibility, image quality and infant comfort.¹⁹

The purpose of this study was to investigate whether a cross sectional SDOCT view of the vascular architecture of the neonatal posterior pole could provide useful information about vascular changes in ROP. Furthermore, we wished to investigate vascular features on SDOCT unique to plus disease and to evaluate utility of describing these features using qualitative and quantitative approaches.

Methods

Between January 2009 and September 2012, 96 prematurely born neonates undergoing conventional ROP screening were imaged by SD-OCT, after Institutional Review Board approved consent was obtained from parents or legal guardians. Subjects underwent SDOCT imaging immediately after scheduled ophthalmoscopic examination for ROP screening. SDOCT imaging was performed using a portable handheld SDOCT system (Bioptigen INC, NC, USA) in the non-sedated neonate following an age specific imaging protocol described by Maldonado et.al.¹⁹ Volumetric and linear scans were captured in each imaging session. The analysis done by authors Cynthia Toth and Ramiro Maldonado of SDOCT scans of one subject (not included in the analysis but shown on figure 1) highlighted SDOCT features that may be explained by physical effects of dilation and tortuosity and raised the rationale for this study.

Subjects Selection Criteria

From the 96 subjects, 17 subjects were initially excluded: 2 were discharged before imaging occurred, 3 were examined due to systemic conditions with ocular pathology and 12 did not have ROP screening up to 42 weeks post menstrual age (PMA) to determine final ROP outcome. From the remaining 79 subjects, 28 had ROP requiring laser treatment and 51 had ROP with maximum stages 0-3 that did not require laser treatment at any point. The maximum stage ever clinically identified in the control group was: stage 0 in 18 eyes (35%), stage 1 in 3 eyes (6%), stage 2 in 25 eyes (53%) and stage 3 in 4 eyes (6%) whereas in the plus disease group the maximum stage was: stage 2 in 1 eye (10%) and stage 3 in 9 eyes (90%). Stage 0 denotes no ROP stage but presence of peripheral avascular retina. In the ROP group that required laser, 11 subjects had stage 3 ROP and pre-plus disease but no plus disease and thus were excluded from the primary analysis. From the remaining 17 subjects with plus disease, 11 had a SDOCT scan that had the optic nerve edge and one major

vascular retinal arcade. The observation of SDOCT scans of one of these subjects motivated the hypothesis of this study and thus, this subject's scan was only used for observation of characteristics to be graded, hence was excluded from analysis. The remaining 10 subjects formed the Plus Group. From the 51 subjects with ROP not severe enough to require laser, four did not have SDOCT scans that met scan inclusion criteria (SDOCT volumetric scan containing at least the edge of the optic nerve and one major vascular arcade). The remaining 47 subjects formed the Control Group.

SDOCT Scan Analysis

SDOCT scans were converted to Digital Imaging and Communication in Medicine (DICOM) format. Review of SDOCT scans from an eye with plus disease by authors (RM, CT) identified unique SDOCT features that were transcribed into a grading form. Two non-physician SDOCT graders were formally trained on the definitions of these findings (see below) and tested on a separate dataset before they independently graded the study eyes while masked to clinical status, vascular status, ROP stage or zone and any treatment. SDOCT features evaluated were: 1) *retinal vessel elevation* (presence, absence, severity) (Figure 2, A and B); 2) *scalloped retinal layers* (location: near or away from optic nerve; profundity: if inner plexiform layer or outer plexiform layer looked scalloped) (Figure 2, E and F); 3) *hyporeflective vessels* (presence, absence and location: near or away from optic nerve) (Figure 3); and 4) retinal spaces (presence or absence) (Figure 1).

Of note, all SDOCT features were graded only outside the optic nerve. This precaution was taken because over the optic nerve and at the optic nerve margin, vessels are usually wider and elevated and thus we hypothesized that vessel elevations, scalloped retinal layers or hyporeflective vessels near the optic nerve (less than ½ disc diameters) could represent a normal feature rather than an abnormal condition.

Vessel elevation was distinguished by graders as any spiked, pointy vessels which were easily distinguished from the “normal” smooth retinal surface found in subjects that did not have severe ROP. More details on how these features were graded can be found in figures 1-3. Of note, all these features were called present if they were not detected near the optic nerve (farther than 1/2disc diameter away from the optic nerve disc margin. All these features were hypothesized to be a manifestation of vascular disease. More on the rationale and background can be found in the discussion section. After grading was completed, intergrader agreement was conducted. When graders disagreed on any characteristic, a third grader performed arbitration.

Proposal of a Scoring System

In order to reduce the influence of a particular SDOCT characteristic and to provide a more global assessment of vascular changes, a Vascular Abnormality Score on OCT (VASO) was proposed (Table 1). This proposed score was designed to assign appropriate weights to the unique SDOCT features proportional to their frequency of occurrence. Rarer, uncommon features more heavily influence the VASO than does a more frequent feature.

Statistical Analysis

The relation of each SDOCT characteristic and VASO to plus disease was analyzed using JMP software v 10.0.

Mapping retinal vessel elevation

Quantitative analysis of retinal layer thickness and construction of retinal surface maps was achieved by 1) semi-automatic segmentation of inner limiting membrane (ILM) using DOCTRAP Pediatric v16.1; 2) placing a smooth curve aligned to the retinal surface and 3) plotting the difference between the previous two layers in a map with a color scale from -100 to 120 microns using a custom designed MatLab code (EY) (Figure 4 available at <http://aaojournal.org>). For analysis of the retinal surface maps we proposed two specific features, 1) retinal vessel elevation resembling the vascular pattern of the SDOCT en-face retinal image and 2) elevations bigger than 80 microns. The first would filter focal non-contiguous elevations that may appear on the surface map due to a computer segmentation error. The second feature was set up arbitrarily at 80 microns because that is the height at which the surface map color appears red making this noticeable to the observer's naked eye.

In addition, three-dimensional mapping of hyporeflective retinal spaces (Figure 1) was achieved by aligning and labeling each b-scan in the SDOCT volume and labeling each vessel and retinal spaces using AVIZO version 7.0 (VSG, MA, USA).

Evaluation of Predictive Value of Vascular Analysis with SDOCT

To evaluate the value of the proposed grading system, VASO, and retinal surface maps as early markers of disease, we performed several secondary analyses. The first analysis was on 28 subjects from the primary study group who were imaged before 37 weeks PMA. We selected images before 37 weeks PMA because the median onset of ROP stage 3 and plus disease is 36 weeks PMA.²⁰ In addition, in the plus disease group, we performed an analysis of four available preceding imaging sessions (when the subjects had a normal vasculature (no clinical pre-plus or plus) according to ophthalmoscopic examination).

Results

Baseline Characteristics of Study Participants

The mean gestational age for the study participants was 26 $\pm$ 2.1 weeks and the mean birth weight was 872 grams ($\pm$ 267). (Table 2 available at <http://aaojournal.org>) Mean age at imaging (for the scans included in the study) was 37 weeks ($\pm$ 4.4). The percentage of females and males or Caucasians and African-Americans was equal. Gender, race and birth weight were similar in both cases and controls ($p > 0.05$). The plus group had an expected lower gestational age when compared to the controls (Table 2 available at <http://aaojournal.org>).

Intergrader Agreement

Graders on this study were masked to any subject's information. Agreement between the two graders was: for retinal vessel elevation (90%), hyporeflective vessels (79%), scalloped layers (77%) and retinal spaces (74%) (Table 3 available at <http://aaojournal.org>).

Vascular Related SDOCT Characteristics

The SDOCT characteristic most commonly found in the 57 subjects was elevated vessels (n=25, 44%), followed by hyporeflective vessels (n=23, 40%), scalloped retinal layers (n=13, 22%) and retinal spaces (n=6, 11%) (Figure 5 available at <http://aaojournal.org>). The majority of elevated vessels were subjectively graded as mild (92%). The scalloping of retinal layers extended to the outer plexiform layer (OPL) in 8 of 13 eyes with scalloping (62%). The location of hyporeflective vessels was near the optic nerve (within ½ disc diameter) in more than 50% of the cases (Figure 5 available at <http://aaojournal.org>).

In our study, all the SDOCT characteristics, except retinal spaces, were significantly more prevalent in the plus disease group than in the control group (Table 4 available at <http://aaojournal.org>). In the plus disease group, vessel elevation was present in 8/10 subjects (80%), scalloped retinal layers in 7/10 (70%), hyporeflective vessels in 7/10 (70%) and retinal spaces in 3/10 (30%). These SDOCT characteristics were present to a much lesser degree in the control group (Figure 5 available at <http://aaojournal.org>). Some SDOCT characteristics were not infrequent in the control group. For example, elevated vessels were present in 17/47 (36%) and hyporeflective vessels in 16/47 (34%) controls. When performing a sub-analysis of the control group, the elevated vessels were graded as “mild” in 16/17 (94%) and the hyporeflective vessels were identified within ½ disc diameter to optic nerve in 8/16 (50%) (Table 4 available at <http://aaojournal.org>).

Vascular Abnormality Score on OCT (VASO)

After primary analysis of SDOCT characteristics was conducted, we proposed a scoring system of these features to provide an overall assessment of an abnormal vascular condition. To accomplish this, we more heavily weighted the most uncommon features; retinal spaces and hyporeflective vessels accounted for two points each if present. Accordingly, the most common features found in the study, elevated vessels and scalloped retinal layers, scored one point each if they were present. These two features could have a higher weight if they were severe (severe vessel elevation of scalloped retinal layers affecting OPL counted for two points each). Although the mean VASO was higher in the plus disease group 4.10 (+/-1.9) than in the control group 1.38 (+/- 1.7) (Table 4 available at <http://aaojournal.org>), the scoring for the two groups still overlapped. On secondary analysis of imaging session before 37 weeks PMA, the VASO showed an even more pronounced higher value in the plus disease group compared to the controls (mean 4.25 vs. 0.6, p=0.0003) (Table 4, Figure 6 available at <http://aaojournal.org>).

Quantitative Evaluation of Retinal Vessel Elevation

In a more comprehensive assessment of retinal vessel elevation, this elevation was also mapped out as a thickness map. Analysis of vessel elevation on retinal surface maps demonstrated a clear difference in retinal vessel elevation between the plus disease group and the controls (Table 5 available at <http://aaojournal.org>, Figure 7). All the subjects with plus disease (10 of 10) had areas of elevation on the surface maps and these elevations followed a distinct vascular pattern (9 of 10). In addition, six subjects in the Plus group

(60%) had areas of elevation higher than 80 microns (Table 5 available at <http://aaojournal.org>, Figure 7).

In the controls group, our custom designed software detected retinal vessel elevation in (23 of 47 subjects, 49%). Of these, 12 (26%) showed only small, focal, isolated areas of elevation (Figure 7 F-G) and 11 (23%) an elevation that resembled the vascular pattern. In addition, the areas of elevation of more than 80 microns occurred in only one subject (1 of 47, 2%).

These particular characteristics of the retinal surface maps (any elevation, elevation resembling a vascular pattern and elevation > 80 microns) were noted to be significantly different in the plus disease group compared to controls ($p=0.002$, 0.025 , 0.001 respectively). All the subjects with plus disease showed elevation at the optic nerve versus 21 (45%) in the control group ($p=0.001$) (Table 5 available at <http://aaojournal.org>).

Secondary Analysis of Imaging Sessions from 31 to 36 weeks PMA

When considering only the subjects with imaging sessions under 37 weeks post menstrual age, there remained an association between retinal vessel elevation, scalloped retinal layers and hyporeflexive vessels to the plus disease group (p -values <0.0005 , 0.0005 and 0.01 respectively) while there was a trend toward an association between retinal spaces and plus disease ($p=0.06$) (Table 6 available at <http://aaojournal.org>). In addition, there was a bigger VASO difference between groups (mean 4.25 vs 0.6 in the plus and controls respectively, $p<0.0003$) as compared to the difference obtained when considering all subjects (4.10 vs 1.38 respectively).

Analysis of retinal surface maps at this time period of prematurity confirmed that “any elevation” on the retinal surface maps and an elevation following the vascular pattern are statistically more frequent in the plus disease group ($p=0.002$ and 0.02 respectively, Table 6 available at <http://aaojournal.org>). The presence of red areas (higher than 80 microns) was significantly different among groups ($p=0.001$). An elevation around the optic nerve was present in all the plus disease group subjects (100%) versus 21 (45%) in the control group ($p=0.001$).

Preceding Scans

From the 10 subjects with plus disease, four had SDOCT imaging sessions 1-3 weeks before plus disease was diagnosed (Figure 8 available at <http://aaojournal.org>). At that preceding visit, the ophthalmoscopic examination was negative for plus disease and the retinal images created from the SDOCT scans showed no vascular tortuosity. On the other hand, the VASO was increased in 2 of 4 subjects (Figure 8 A and D available at <http://aaojournal.org>) and one subject presented with retinal vessel elevation on the retina surface map (Figure 8 A).

Discussion

This is the first SDOCT study specifically investigating the retinal vasculature characteristics in prematurely born subjects undergoing ROP screening (PubMed search for terms Retinopathy of prematurity, plus disease, optical coherence tomography from 1981 up

to date). In this study we present unique information of vascular changes occurring in neonates with ROP that cannot be appreciated with any other imaging modality. This information can help us to understand the characteristics of vascular dilation and tortuosity and their effects on the surrounding retinal tissue from a different perspective by giving information on depth of tortuosity, vessel elevation, disorganization and disruption of surrounding retinal tissue and indirect assessment of blood flow velocity. Furthermore, we identify and define vascular and perivascular SDOCT characteristics that are associated with plus disease and translate these findings into a predictive score that can potentially detect early vascular abnormalities in subjects undergoing ROP screening.

The SDOCT features described in this study enhance our understanding of the effects of vessel dilation and tortuosity on the retina. We demonstrate that the progressive dilation and tortuosity properties of plus disease causes the vessels to shift not only laterally as seen on fundus photographs, but also in the antero-posterior direction, which distorts the architecture of retinal layers on SDOCT producing a scalloped appearance to inner retinal layers on perivascular SDOCT cross sectional images. For instance, in 4 subjects, the vessels looked dilated on SDOCT (noticeable increased horizontal and vertical diameter of vascular lumen) but no vessel elevation was noted at the retinal surface. In those cases, scalloped layers were present as a marker of vessel dilation despite the absence of vessel elevation pointing out the need to integrate these features to provide a better assessment of vascular disease. The scalloped pattern is the result of both vessel dilation and confluent vessels. For instance, a single dilated vessel alone may not create scalloping of layers, but scalloping was produced when dilated and antero-posteriorly distorted vessels were adjacent in the same scan. With the increased tortuosity of plus disease, this scalloped pattern was revealed. The opposite was also true. Normal vessels, even if adjacent, lacked both the dilation and the antero-posterior tortuosity and did not produce layer scalloping. It is important to note that SDOCT is a non-contact imaging technology and thus it does not produce changes in vessel width or tortuosity that may be caused with scleral depression or when using contact retinal imaging photos.²¹

We present SDOCT as a functional imaging tool for evaluation of retinal flow velocity. We hypothesize that the hyporeflective vessels found are representative of high-speed flow velocity. This hypothesis is based on studies of blood flow velocity using SDOCT. For instance, Hendargo et al²² demonstrated in phantom capillaries that, at normal velocity, the capillaries appeared hyperreflective and as the flow progressively increased, the SDOCT signal is washed out. This theory linking presence of hyporeflective vessels to plus disease opens a new door for the use of SDOCT as a functional imaging tool in research studies of ROP especially because ultrasound Doppler imaging of flow at the central retinal artery have been inconclusive.^{23,24} The use of SDOCT systems with faster speed scanning or the use of swept-source OCT seems to be the next step in research imaging to validate the assessment of speed velocity findings in ROP.

Retinal spaces (Figure 1) were not significantly associated with plus disease ($p=0.06$) and were the least common SDOCT feature in the study group, being present in 7 (12%) subjects. We hypothesize that these retinal spaces are the result of disruptive mechanical forces created by abnormal vessel growth, dilation, and tortuosity. In Figure 1 we present a

three dimensional reconstruction of the SDOCT scan, where we labeled the areas with retinal spaces in green. As shown, the spaces were located at the most prominent angulations of tortuous vessels where retinal tissue was perhaps displaced or disrupted. We claim that these are spaces because they are completely hyporeflective (black) areas surrounding the vessels. These spaces do not cast the normal shadow caused by blood vessels and don't have the round-oval shape of vessels seen on OCT scans. It seems that these spaces are proper of severe plus disease and thus the low frequency of the finding.

To integrate the qualitative SDOCT features related to vascular changes into a single clinical tool, we proposed a scoring system that gives slightly more weight to the most uncommon SDOCT characteristics. This Vascular Abnormality Score on OCT (VASO) (Table 1) was significantly higher in the plus disease group with a mean score of 4.45 (+/-2.1) versus a mean of 1.3 (+/-1.7) in the control group. As we can see in Figure 6 (available at <http://aaojournal.org>), there is some score overlap between groups which makes it difficult to set a cut-off point. Interestingly, the VASO mean difference between groups is even more pronounced when we consider imaging sessions before 37 weeks PMA (Figure 6, available at <http://aaojournal.org>). In addition, there is no score overlap among groups, thus we propose a cut-off value of 2 for future studies. We acknowledge that a predictive score based on these data is very likely to perform well when applied to the same data, so application of this score to future data sets will be critical to assess its usefulness.

Another important contribution of this study is the proposal of a method to overcome subjectivity on retinal vessel elevation. This technique maps out elevations over a normal smooth retinal surface at the precise site of the vessel. The results obtained are retinal surface maps that are easy to view. Any area colored in yellow represents an elevation that we consider significant (>25 microns). In some cases we can observe how the elevations form a yellow vascular pattern that resembles the vessel vascular pattern observed in the OCT-retinal images (Figure 7). Analysis of retinal surface map characteristics showed that areas of elevation following the vascular pattern and elevations of more than 80 microns (represented as red areas) were significantly associated to plus disease ($p=0.0173$ and $p=0.004$, respectively). On Figure 7, we can observe that some maps have tiny areas of elevation but do not form a vascular pattern. The same observation applies for elevation higher than 80 microns. Retinal surface maps from SDOCT scans in premature neonates could play a role in the evaluation of disease progression and in monitoring response to therapy. For example, Kwon et al reported a 20% decrease on vascular width after laser treatment⁸ and thus, retinal surface map analysis before and after treatment of laser or anti-VEGF may prove to be useful to the clinician.

We believe that the findings from this study can be translated in to clinical practice. The grading system demonstrated reproducibility with an intergrader agreement of 77-90% retinal vessel elevation 90%, hyporeflective vessels 79%, scalloped layers 77% and retinal spaces 76%. The SDOCT features were significantly associated with plus disease. In addition, when we analyzed these features in sessions before 37 weeks PMA the difference and significance was greater. The VASO system appears to have a clear cut-off value between normal and abnormal and the retinal surface maps abnormalities were also significantly associated with plus disease. Furthermore, the retinal surface maps

abnormalities are easy to observe if this was used as a bedside imaging technique. In addition, in Figure 8 (available at <http://aaojournal.org>), we analyzed preceding visits of the plus disease group. We were able to observe that despite normal ROP screening, two of those subjects had an abnormal VASO and one subject had abnormal retinal surface maps. From this comparison we can argue that the VASO and the retinal surface maps were able to detect early abnormalities. This is important because early detection of vascular abnormalities such as pre-plus has been shown to have a prognostic significance early in the disease.²⁵

This study has limitations inherent to the design. Our data was gathered from SDOCT imaging sessions that were conceived for the purpose of imaging the macula as a primary goal and the optic nerve as a secondary goal. This limitation decreased the number of imaging sessions focused on the major retinal vascular arcades. Because of this, the scans compared in this study are of different retinal regions, making it difficult to make precise comparisons between scans especially when comparing the retinal surface maps. Designing a focused imaging study on the retinal vasculature with doppler and scanning techniques to better visualize the vessels is the next step to take. In addition, it is important to note that the concepts proposed in this study can be applied to other pediatric and adult retinal diseases especially those with vascular abnormalities such as diabetic retinopathy or vein occlusions for example.

In conclusion, this study demonstrates that SDOCT can detect anatomical and functional abnormalities proper of plus disease. The features detected by SDOCT can provide information beyond the details obtained by other imaging modalities or ophthalmoscopy. Furthermore, the SDOCT features described can be reliably graded in the research setting in a reproducible manner. This study proposes a vascular abnormality scoring system and a method to map the retinal vessel elevation which could play a role in early detection of disease progression or in monitoring response to therapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Three-dimensional reconstruction of Spectral Domain Optical Coherence Tomography (SDOCT) scans of a 42 week post-menstrual age (PMA) neonate (A). Vessels were labeled on each SDOCT cross-sectional frame (B-scan) and then the three-dimensional reconstruction with volume rendering was achieved using AVIZO software. Green areas correspond to retinal spaces. These areas were located at acute vessel angulations. SDOCT scans on B and C show the corresponding retinal spaces (green arrows) which are hyporeflective spaces located between vessels. These spaces do not create a shadowing effect as opposed to the normal shadowing effect produced by blood vessels.

Figure 2.

Spectral Domain Optical Coherence Tomography (SDOCT) scans from a 31 weeks post-menstrual age (PMA) neonate (A) with Retinopathy of Prematurity (ROP) zone II, stage 2, and normal vasculature per clinical exam and a 48 weeks PMA neonate, ROP zone II, stage 3 and Plus disease (B). Left panel shows no vessel elevation on (A) and severe vessel elevation on (B). Middle panel images (C,D) are retinal images created from axial compression of SDOCT scans. Panels E and F contain same scans as A and B respectively but highlights the smooth retinal layer contour (E) and the scalloped pattern on (F). Red asterisks are placed over vessels and the corresponding location on the retinal image is shown on (C and D). White arrows point to shadow produced by the corresponding vessels. On E and F, the light green line (upper) represents inner plexiform layer and dark green line (lower) represents the outer plexiform layer.

Figure 3.

Spectral Domain Optical Coherence Tomography (SDOCT) scans from a 35 weeks post-menstrual age (PMA) neonate (A) and a 43 weeks PMA neonate (B) showing retinal vessels as hyperreflective round-oval structures located at the level of ganglion cell layer. SDOCT on (C) is from a 39 weeks-old PMA neonate with a mid-reflective vessel. SDOCT scan on (D) is from a 48 weeks-old PMA neonate where multiple hyporefective vessels can be observed (under red asterisks. These vessels are also identified on SDOCT scans due to the hyporefective “shadowing” columns they produce.

Figure 7.

Comparison of color thickness maps in controls and subjects with plus disease. The black area corresponds to the optic nerve. In the plus disease group, all the color thickness maps, except (C) presented retinal elevation that followed the vascular pattern (shown in the corresponding retinal images). The color map on (C) presented elevation only near the optic nerve. Most of the control group maps (A-E) showed no elevation and few of them (F,G,H) had only small islands of elevation near the optic nerve.

Table 1
Vascular Abnormality Score on Optical Coherence Tomography

Optical Coherence Tomography characteristics	Points
Vessel Elevation	-
Mild	<u>1</u>
Severe	<u>2</u>
Scalloped retinal layers	-
Involving IPL	<u>1</u>
Involving OPL	<u>2</u>
Hyporeflective vessels	<u>2</u>
Retinal Spaces	<u>2</u>

IPL= inner plexiform layer, OPL= outer plexiform layer