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Auto-Processed Retinal Vessel Shadow View Images From Bedside Optical Coherence Tomography to Evaluate Plus Disease in Retinopathy of Prematurity

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Purpose: To describe the creation of en face retinal vessel shadow view (RVSV) optical coherence tomography (OCT) images and assess the feasibility of using these for evaluating vascular disease in preterm infants at risk for retinopathy of prematurity (ROP).

Methods: In this exploratory study, we selected images from eyes with a range of ROP vascular disease, prospectively acquired from preterm infants using an investigational, noncontact, handheld, bedside swept-source OCT. We autosegmented OCT volumes using custom infant-specific software, extracted RVSV-OCT images from volumetric data bracketed around the retinal pigment epithelium, and automontaged the resulting RVSV-OCT images. Three masked ophthalmologists graded the RVSV-OCT montages as plus, pre-plus, or neither and ranked them by relative vascular disease severity.

Results: We selected images from 17 imaging sessions (7 plus, 4 pre-plus, 6 neither on clinical examination). On review, 15/17 (88%) RVSV-OCT montages were gradable for plus, pre-plus, or neither and all 17 montages were rankable for relative severity. Intergrader agreement for plus, pre-plus, or neither grading was good (κ, 0.67; 95% confidence interval, 0.42–0.86) and for relative severity ranking was excellent (intraclass correlation coefficient, 0.98; 95% confidence interval, 0.96–0.99).

Conclusions: Our novel automatic processing method can create RVSV-OCT montages optimized for retinal vessel visualization for ROP screening. Although our data support the feasibility of using RVSV-OCT montages for ranking relative vascular disease severity, there is room for improved OCT image capture and processing methods in preterm infants screened for ROP.

Translational Relevance: Creation and grading of RVSV-OCT images could eventually be integrated into an alternative method for ROP screening.

Introduction

Retinopathy of prematurity (ROP) is a potentially blinding disease characterized by delayed and disordered retinal vascularization in preterm infants.[1] Screening at-risk infants is imperative for ROP management, as early detection and treatment of severe disease can decrease the risk of blindness.[2] An important feature of most treatment-requiring ROP is the presence of plus disease, first described by the International Classification of ROP (ICROP)[3,4] and further defined in major ROP trials as posterior pole vascular dilation and tortuosity, in at least 2 quadrants, which meets the minimum of that in the standard photograph for plus disease.[2,5–7] Detection of plus disease with high sensitivity is therefore essential for any ROP screening system. The current gold standard

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for ROP screening is bedside indirect ophthalmoscopy, but this method is time-intensive and limited by access to trained ophthalmologists.[8,9]

Store-and-forward telemedicine systems have the potential to address these limitations by increasing the efficiency of and access to ROP screening. Under this paradigm, images are captured by nonphysicians at bedside, transmitted to a secure server, interpreted remotely by clinicians, crowd-sourced analysis, or deep learning methods, and the findings are used to determine if an infant requires a bedside examination by an ophthalmologist. Telemedicine screening with fundus photography has been shown to reliably detect severe ROP, including plus disease,[10–14] and several live programs have been implemented in the United States and internationally.[15–17] However, vessel visualization on fundus photographs may be limited in darkly pigmented eyes, and confounded by choroidal vascular patterns in lightly pigmented eyes.[18] Additionally, most telemedicine systems rely on images acquired from contact fundus cameras, which have been shown to induce physiologic stress in preterm infants.[19–21] Ideally, stress-inducing procedures should be minimized in preterm infants, as they have been associated with poorer neurodevelopmental outcomes.[22–24]

An alternative imaging modality, optical coherence tomography (OCT), uses near-infrared light to capture cross-sectional scans of the retina with micron-scale resolution. OCT has been applied to ROP in the research setting: it has provided insight into the in vivo development of the vascular and nonvascular tissue of the premature retina,[25–29] and illustrates subclinical features of ROP not visible on ophthalmoscopic examination.[30–36] One study used OCT to generate three-dimensional vascular maps and calculated a Vascular Abnormality Score by OCT (VASO), which correlated well with the presence of plus disease.[37] Two-dimensional en face projections of OCT volumes illustrate retinal vascular patterns and resemble fundus photographs that ophthalmologists and analytic software are accustomed to grading for plus disease. Currently, these en face images are limited by the 32 kHz A-scan capture speed of the commercially available handheld spectral domain OCT system (Envisu C2300; Leica Microsystems, Wetzlar, Germany). This restricts the number of A-scans per volume that can be practically captured in an awake, nonfixating infant, and therefore limits the resolution of the en face image.

The purpose of this study was to describe a novel method we developed to create an en face "retinal vessel shadow view" (RVSV)-OCT image, optimized for visualization of the retinal vasculature, from investigational, high-speed, noncontact, swept source (SS)-OCT captured at the bedside in awake infants. We evaluated the feasibility of using montaged RVSV-OCT images for grading posterior pole ROP vascular disease severity by ophthalmologists and queried whether there are differences in RVSV-OCT vessel visualization based on fundus pigmentation.

Methods

We performed this exploratory study as part of the analysis of retinal vasculature in ROP for BabySTEPS (an institutional review board–approved prospective, observational study registered with clinicaltrials.gov [registration: NCT02887157]). The study was approved by the Duke University Health System institutional review board, is compliant with the Health Insurance Portability and Accountability Act of 1996, and is adherent to all tenets of the Declaration of Helsinki. Between September 2016 and November 2019, 118 preterm infants were enrolled in BabySTEPS, 102 of which underwent research bedside, noncontact, handheld SS-OCT imaging of both eyes performed on the same day as clinical ROP screening examinations. Prior to enrollment, we obtained informed consent from a parent or legal guardian after explanation of the nature and possible consequences of the study.

We performed bedside SS-OCT imaging with an investigational system featuring a 200 kHz, 1060 nm SS laser (Axsun Technologies Inc., Billerica, MA) and a 700 g handheld, noncontact probe.[38] We captured anisotropic 10 x 10 mm OCT volumes with 950 A-scans per B-scan and 256 B-scans per volume. Two B-scans were acquired at each lateral location on the slow axis to allow for averaging in post-processing. The primary imaging goal was to capture the fovea, optic nerve, and papillomacular bundle for each eye; a secondary goal was to capture a portion of the temporal peripheral retina. During standard-of-care clinical ROP examinations, fellowship-trained pediatric ophthalmologists (SFF and SGP) recorded fundus pigmentation (blond, medium, or dark) and ROP posterior pole vascular severity (plus, pre-plus, or neither) on a standard template.[3,4] We reviewed participants' medical records for these clinical examination findings, as well as demographic and general health information.

As part of our primary BabySTEPS study goal to "determine severity of ROP by analysis of OCT" (clinicaltrials.gov registration: NCT02887157), we explored numerous methods to extract vascular information from segmented OCT volumes. After developing a novel method to maximize visualization of the

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posterior pole vasculature, we carried out a pilot test to evaluate the feasibility of grading the resulting images for plus, pre-plus, or neither. We selected a stratified random sample of 17 imaging sessions from 15 eyes of 13 infants from the BabySTEPS cohort. For two eyes with plus or pre-plus on clinical examination, we included images from two imaging sessions for each eye, with the goal of yielding an enriched sample with an approximately equal number of imaging sessions with plus, pre-plus, or neither on clinical examination. For this study, we excluded images captured from eyes after ROP treatment.

We automatically segmented all OCT volumes using proprietary infant-specific software, the Duke OCT Retinal Analysis Program Marking Code (DOCTRAP) v63.9, and Pediatric v1.2 (MATLAB R2017b, MathWorks, Natick, MA). The DOCTRAP software contains retinal layer segmentation algorithms that were developed based on graph theory and dynamic programming, in which images are represented as a graph of nodes that are connected by weighted edges.[39] The algorithms vary the values of the weights based on the layer boundary of interest. The shortest weighted path from one side of the image to the other results in a segmented layer boundary.[33]

We tried several approaches to extract en face vascular information from segmented OCT volumes to improve on the OCT-generated conventional retina view images, which originate from the mean pixel intensity of data from the entire cross-sectional scan. Our methods included extracting en face images from the inner or outer retinal layers, or from volumetric data centered around individual retinal layers (Fig. 1). From this preliminary exploration, we developed a favorite visualization, RVSV-OCT. We extracted the RVSV-OCT images from the mean pixel intensity of volumetric data restricted to a narrow axial window bracketed around the retinal pigment epithelium (RPE), for the purpose of enhancing the view of retinal vessel shadows and removing choroidal patterns (Fig. 2). Thus the RVSV-OCT images were centered on vessel shadowing at the level of the RPE. We compared RVSV-OCT to the OCT-generated conventional retina view images. We loaded all images into previously validated, commercially available automontage software (i2k Retina; DualAlign, Inc., Clifton Park, NY).[40,41] The software created a single conventional retina view montage and a single RVSV-OCT montage for each eye; in most eyes, the two montages had identical fields of view. However, in five eyes the software automontaged more RVSV-OCT images than conventional retina view images; we manually removed these extra images from the RVSV-OCT montage to ensure the same number of images were included in the two montages, creating equal fields of view for the reviewers.

Three fellowship-trained pediatric ophthalmologists who actively perform ROP screening (SFF, SFG, and SGP) reviewed and graded the OCT montages independently. We sent graders three separate electronic slideshows. The first slideshow presented one slide per imaging session with the conventional retina view and RVSV-OCT montages side-by-side, and asked graders to indicate their preferred montage (conventional retina view or RVSV-OCT) for grading of posterior pole vasculature. The second slideshow presented a reference slide with standardized photographs of plus and pre-plus disease, taken from the ICROP Revisited,[3,5] on the first slide, followed by RVSV-OCT montages, one per slide, and asked graders to grade the RVSV-OCT montages for plus, pre-plus, or neither based on the provided reference slide.[3] The third slideshow presented all 17 RVSV-OCT montages on a single slide, and asked graders to rank each RVSV-OCT montage for ROP vascular disease severity relative to the other RVSV-OCT montages (with a ranking of 1 indicating least severe, and 17 indicating most severe). Reviewers graded the montages as "ungradable" if they did not completely capture the optic disc and have 2 or more quadrants, each with 1 or more vessels visible for a length of 1 or more optic disk diameter, or approximately 1.5 mm. Graders were masked to clinical examination diagnoses and other graders' gradings. Although two of the three graders (SFF and SGP) performed the clinical examination on the eyes included in this study, neither had to recuse themselves from grading the images as neither recognized any of the eyes imaged.

Statistical analysis was performed using R v3.6.1 (R Foundation for Statistical Computing, Vienna, Austria). We calculated the sensitivity and specificity of using RVSV-OCT grading for detecting plus disease present on clinical examination (reference standard) by binarizing the grades as "plus" or "not plus". We assessed intergrader agreement of plus, pre-plus, or neither grades using the weighted κ statistic,[42] and assessed intergrader agreement on relative vascular disease severity rankings using the intraclass correlation coefficient (ICC).[43] We interpreted both the weighted κ and ICC using a standardized scale: 0 to 0.4, poor; 0.4 to 0.59, fair; 0.6 to 0.74, good; and 0.75 to 1.0, excellent.[44] We used the median relative vascular disease severity ranking for the three graders as a summary (consensus) reference score for relative vascular disease severity.

In a post hoc secondary analysis of color photographs versus RVSV-OCT montages, we collected

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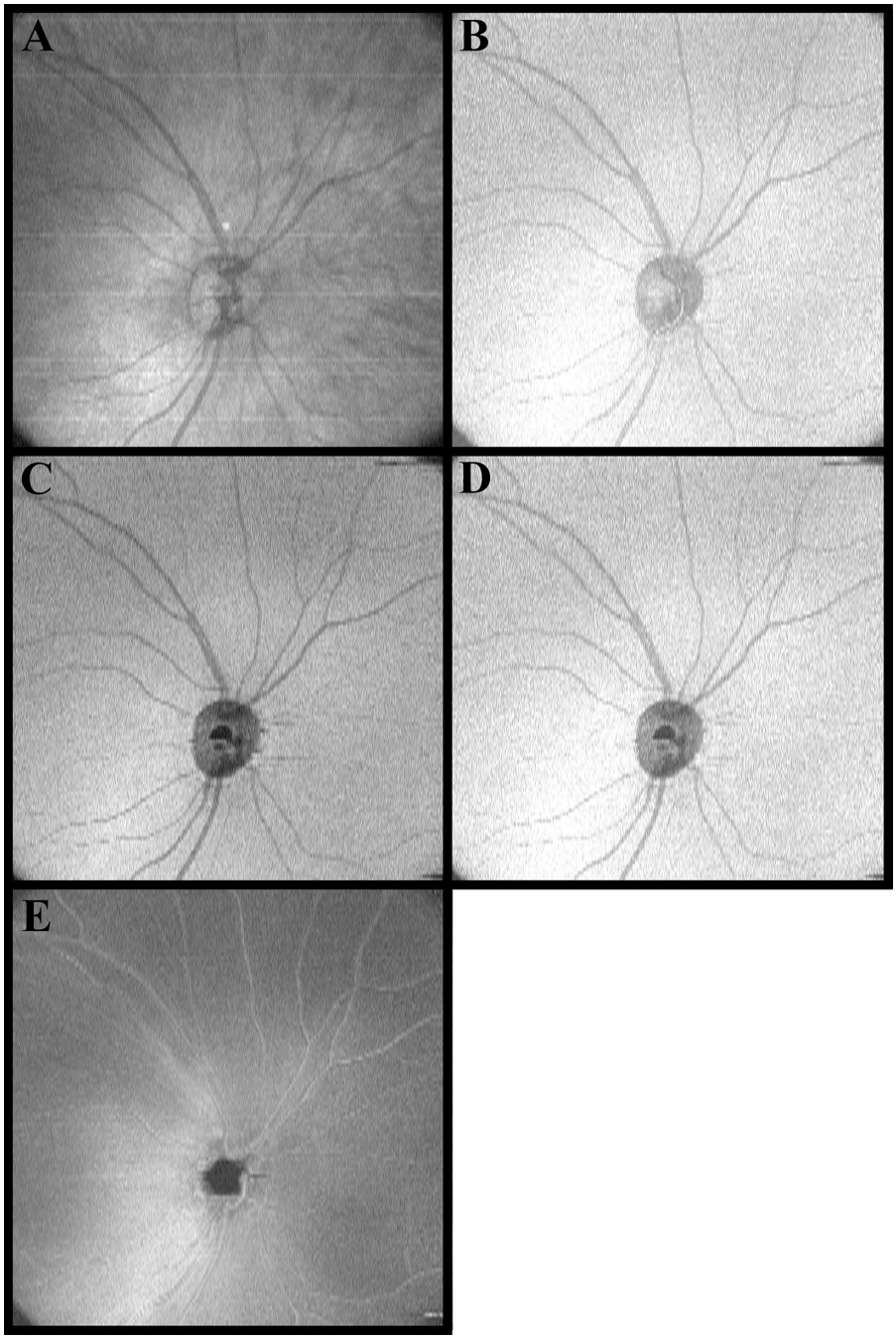

Figure 1. En face OCT images taken from a preterm infant extracted using different parameters. (A) Mean pixel intensity from the entire cross-sectional scan (resulting in the "conventional retina view OCT image"); (B) maximum pixel intensity from the entire volume; (C) mean pixel intensity from around the RPE (resulting in the RVSV-OCT); (D) maximum pixel intensity from around the RPE; (E) mean pixel intensity from the internal limiting membrane to the outer boundary of the inner nuclear layer (representing the inner retina). The RVSV-OCT (C) best illustrates retinal vessel patterns, as the conventional retina view image (A) has distracting choroidal vasculature, the two maximum intensity images (B and D) demonstrate retinal vessel washout, and the inner retinal layer image (E) features low vessel contrast.

fundus photographs (RetCam; Natus Medical, Inc., Pleasanton, CA) acquired the same day as the BabySTEPS OCT imaging session from the clinical record. We included 6 imaging sessions from 5 eyes of 3 infants that included both fundus photography and OCT imaging. Two eyes from the main study described earlier were among these five eyes with color photographs; however, the color photographs and OCT images were acquired from different imaging sessions than were included in the main study described

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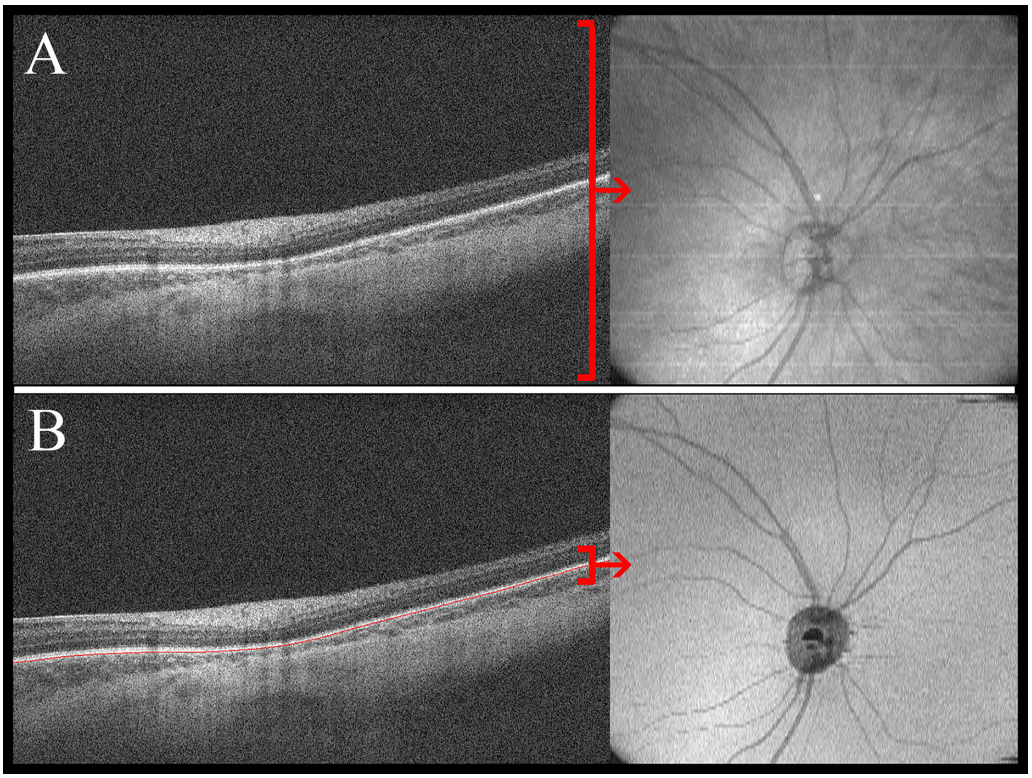

Figure 2. En face images extracted from cross-sectional OCT scans. (A) Conventional retina view image extracted from the entire OCT volume; and (B) RVSV-OCT image extracted from volumetric data bracketed around the autosegmented level of the RPE (*red line*). Graders reported that compared with conventional retina view image, RVSV-OCT images eliminated potentially distracting choroidal vasculature and improved visibility and distinctness of retinal vessels, as shown here.

earlier. For one eye, we included images from two imaging sessions in this analysis, with the goal of maximizing sample size. We autosegmented the SS-OCT volumes and extracted and automontaged the RVSV-OCT images, as described earlier. Unlike the main study, we did not remove RVSV-OCT images from the automontage and manually added peripheral images to maximize montage field of view. We selected a set of three RetCam photographs for each visit to maximize total field of view, and manually adjusted a duplicate set for brightness and contrast to maximize vessel visibility. In a grading session separate from the main study as described earlier, the graders first evaluated the RVSV-OCT montages for fundus pigmentation (blond, medium, or dark). They then answered the question: "Does fundus pigmentation impact image gradeability for plus, pre-plus, or neither?" Next, they repeated their evaluation of pigmentation and its impact on gradeability on the sets of uncorrected and corrected fundus photographs. Finally, they indicated their preference for either fundus photographs or RVSV-OCT montages for grading for the presence of plus, pre-plus, or neither.

Results

From the BabySTEPS cohort, 17 imaging sessions from 15 eyes of 13 infants were included in the conventional retina view versus RVSV-OCT analysis. At the time of clinical examination, 7 had plus disease, 4 had pre-plus, and 6 had neither; with regard to fundus pigmentation, 11 were classified as blond, 5 as medium, and 1 as dark. Mean gestational age was 26.1 (SD = 2.8) weeks; mean birth weight was 742.1 (SD = 242.4) grams; mean postmenstrual age at imaging was 38.3 (SD = 4.7) weeks.

The three pediatric ophthalmologist graders preferred the RVSV-OCT montage over the conventional retina view montage for grading posterior pole vascular severity in 36/51 (71%) gradings (17 images times 3 graders, equals 51 total gradings), and the majority of graders preferred the RVSV-OCT montage in 11/17 (65%) cases. Graders frequently mentioned improved retinal vessel visualization on RVSV-OCT montage compared with the conventional retina view, citing "more distinct retinal vessels" (n = 15/51), "crisper retinal vessel margins" (n = 8/51),

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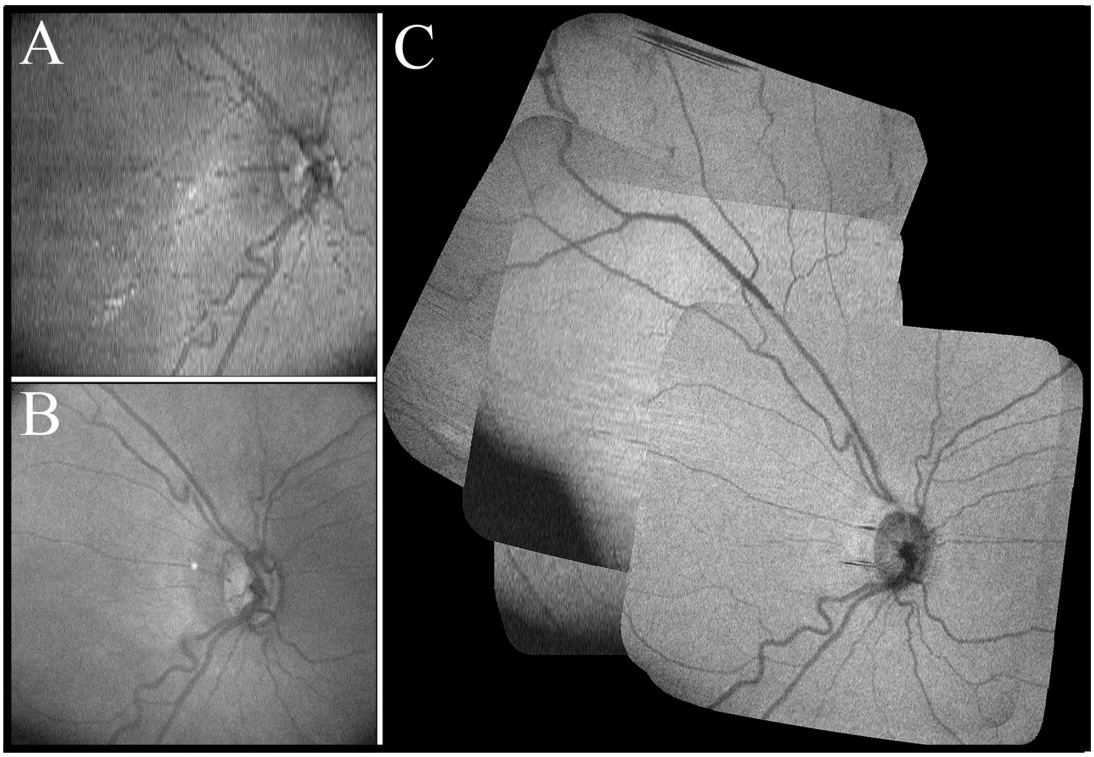

Figure 3. Comparison of en face OCT images taken at the bedside of the same preterm eye. (A) Commercial spectral domain OCT (Envisu C2300, Leica Microsystems); (B) conventional retina view image from investigational, high-speed SS-OCT; and (C) RVSV-OCT montage. The RVSV-OCT montage features improved pixel density, retinal vessel pattern visualization, and field of view compared with the commercial image.

"better retinal vessel contrast" (n = 5/51), "more retinal vessels visible" (n = 3/51), and "absence of distracting choroidal vasculature" (n = 2/51) (Figs. 2–4). When graders preferred the conventional retina view montage over the RVSV-OCT montage, they cited decreased vessel dilation (n = 7/51) or presence of artifact (n = 5/51) in the RVSV-OCT.

Graders found 15/17 (88%) RVSV-OCT montages gradable for plus disease, pre-plus, or neither and all 17 montages rankable for relative ROP vascular disease severity. Of the two ungradable montages, one (ranked 11/17 on the consensus reference score for vascular disease severity) was deemed ungradable by one grader, and one (ranked 8/17) was deemed ungradable by two graders. In these two montages, central artifact from autosegmentation errors distorted retinal vascular patterns (Fig. 5). These three ungradable calls (from two montages) were classified as "not plus" for sensitivity and specificity analyses, and all gradings of these two montages were excluded from intergrader agreement analysis of plus, pre-plus, or neither grades.

When each individual graded plus, pre-plus, neither, or ungradable using RVSV-OCT, they agreed with the reference standard (diagnosis on clinical examination) in 36/51 (71%) gradings (Fig. 6). The three graders together agreed with the reference standard on 9/17 (53%) images; this included all 6 images of eyes with neither plus nor pre-plus on clinical examination (Fig. 6). When the 51 grades were instead binarized as "plus" or "not plus" (which included pre-plus, neither plus nor pre-plus, and ungradable), the sensitivity and specificity for detecting plus disease were 11/21 (52.4%) and 28/30 (93.3%), respectively. Of the 10 instances of missed plus disease, 9 were graded as pre-plus and 1 was deemed ungradable; no eyes with plus disease on clinical examination were graded as neither plus nor pre-plus (Fig. 6). In 6/9 (67%) instances in which RVSV-OCT montages of eyes with plus disease on clinical examination were graded as pre-plus, graders specifically cited insufficient venous dilation for plus disease in their rationale (Fig. 7).

Among the 15 RVSV-OCT montages that all three graders found to be gradable for plus, pre-plus, or neither, graders agreed with each other in 35/45 (78%) grading pairs. Overall, intergrader agreement for plus, pre-plus, or neither was good (weighted κ 0.67; 95% confidence interval, 0.42–0.86). In contrast, relative ROP vascular disease severity rankings exhibited

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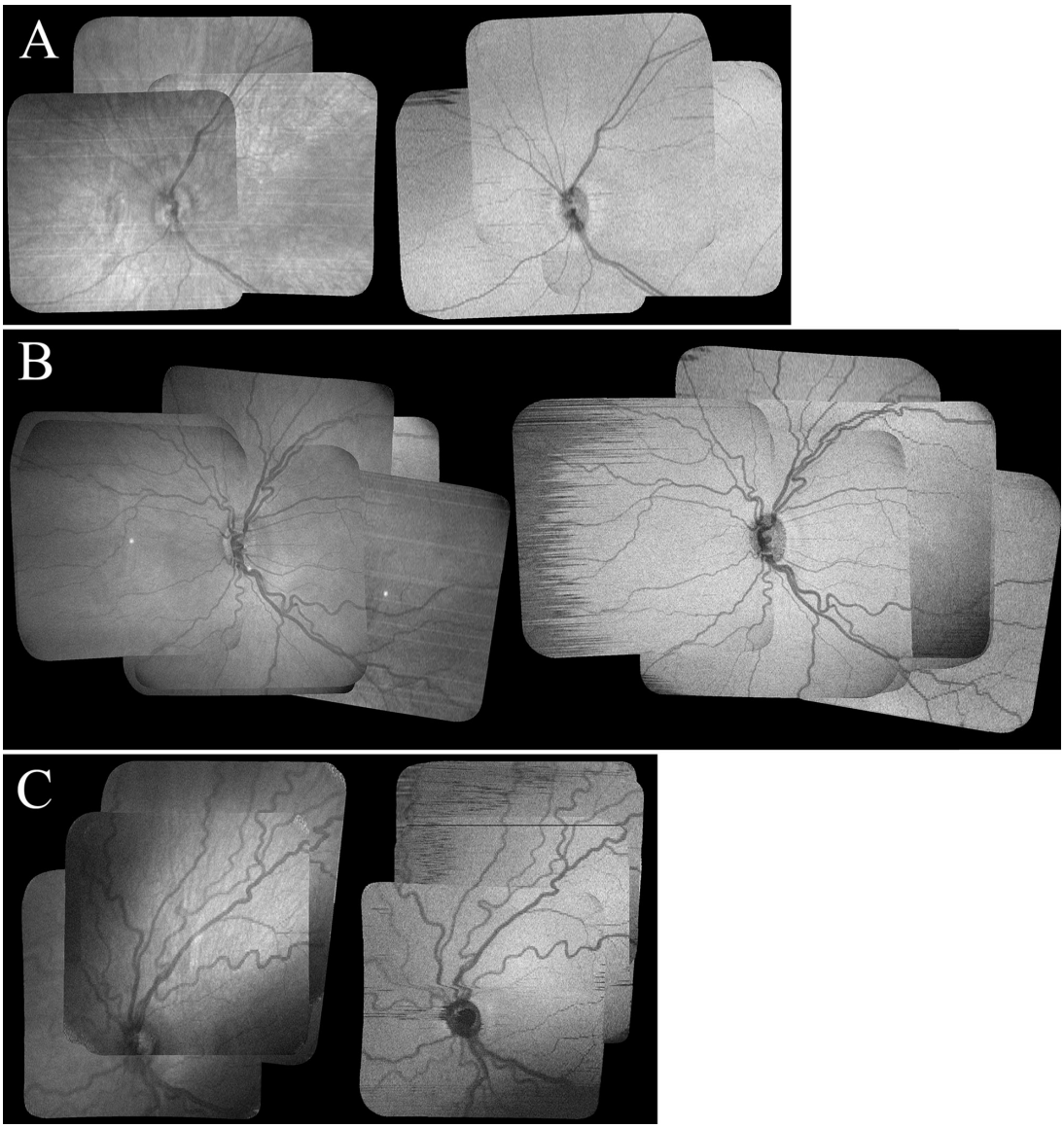

Figure 4. Montaged conventional retina view OCT images (left) and RVSV-OCT images (right) from investigational, bedside OCT of preterm eyes with (A) neither plus nor pre-plus; (B) pre-plus; and (C) plus disease. *Horizontal black lines* in RVSV-OCT images represent artifact due to autosegmentation errors.

excellent intergrader agreement (ICC 0.98; 95% confidence interval, 0.96–0.99). The relative severity rankings also correlated well with plus, pre-plus, or neither grades on clinical examination (Fig. 8).

In the post hoc review, grader comments regarding RVSV-OCT montage quality and vessel contrast did not appear to be impacted by fundus pigmentation, which inspired the post hoc pigmentation analysis. For this post hoc analysis of color photographs versus RVSV-OCT, we included 6 imaging sessions from 5 eyes of 3 infants. At time of clinical examination, 2 had plus disease, 2 had pre-plus disease, and 2 had neither; and 3 had blond pigmentation, and 3 had dark pigmentation. Graders correctly identified fundus pigmentation in 2/18 (11%) gradings using RVSV-OCT montages compared with 14/18 (78%) gradings using sets of fundus photographs (Fig. 9). Graders reported that fundus pigmentation impacted their ability to grade plus, pre-plus, or neither in 2/18 (11%) RVSV-OCT montages compared with 12/18 (67%) sets of fundus photographs. Graders preferred the RVSV-OCT montages for grading in 8/18 (44%) gradings and the majority of graders preferred RVSV-OCT montages for grading plus, pre-plus, or neither in 2/6 (33%) cases, citing clearer vessel visibility (n = 5/18) or reduced glare (n = 4/18). Graders preferred the fundus

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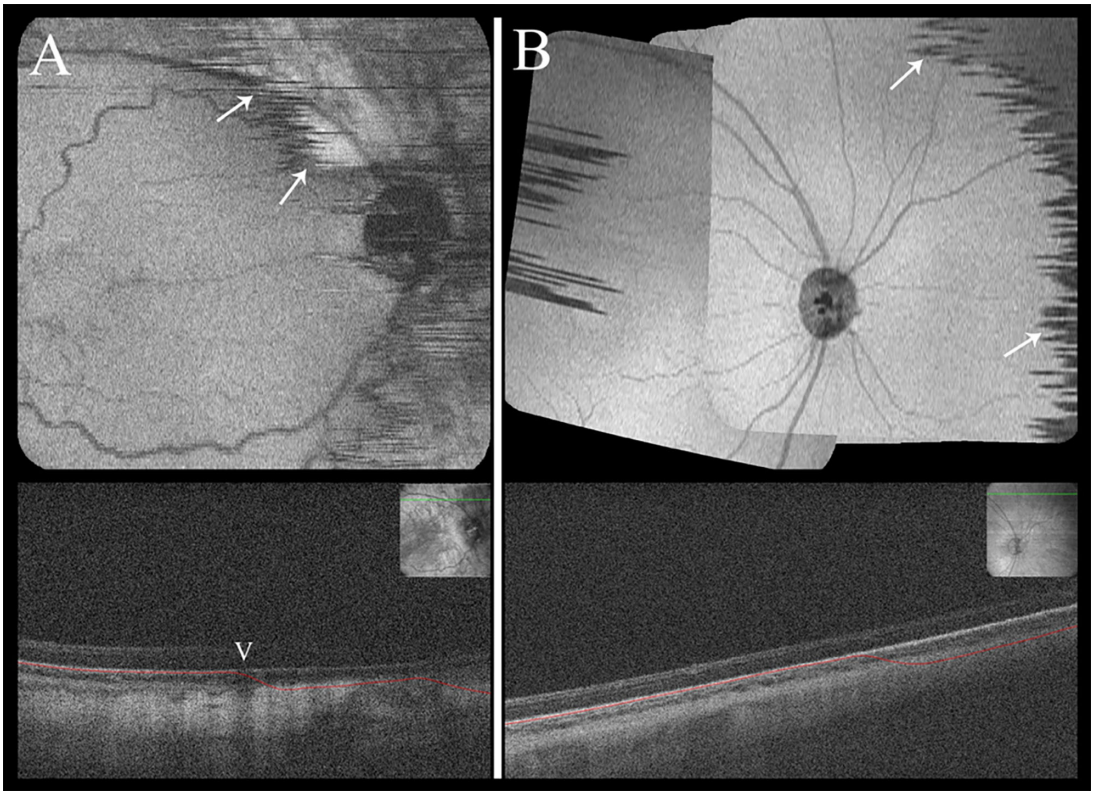

Figure 5. RVSV-OCT images demonstrating artifact (*white arrows*) due to errors in segmentation of the RPE (*red line*) in the corresponding cross-sectional scans. (A) Central artifact traced along dilated and tortuous posterior pole vessels in this eye with plus disease on clinical examination. Artifact obscured retinal vessel visualization and resulted in one grader deeming the image ungradable for plus, pre-plus, or neither. The dilated and tortuous vessels (V) may represent a transition point between regions of accurate and inaccurate autosegmentation. (B) In contrast, peripheral artifact occurred in a majority of RVSV-OCT scans but did not impact image grader's assessment of posterior pole retinal vessel visualization or image gradability.

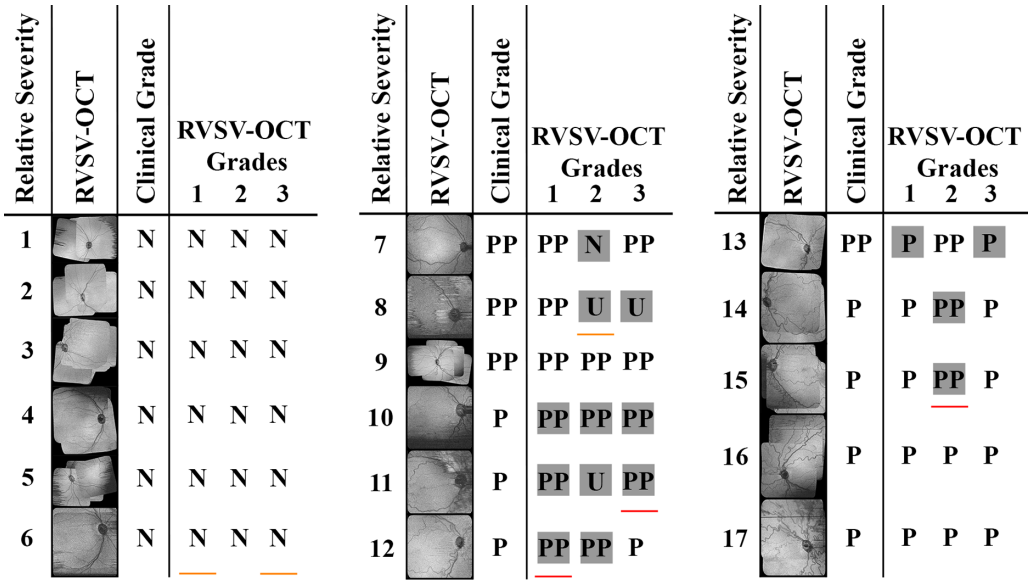

Figure 6. RVSV-OCT images ordered by the median (consensus) relative vascular disease severity ranking from least (1) to most (17) severe, with corresponding clinical examination grades and plus (P), pre-plus (PP), or neither (N) RVSV-OCT grades for each grader. U, ungradable. Shading indicates disagreement with clinical examination grade. Each grader had a unique cutoff point for the diagnosis of pre-plus (*orange line*) and plus (*red line*) disease.

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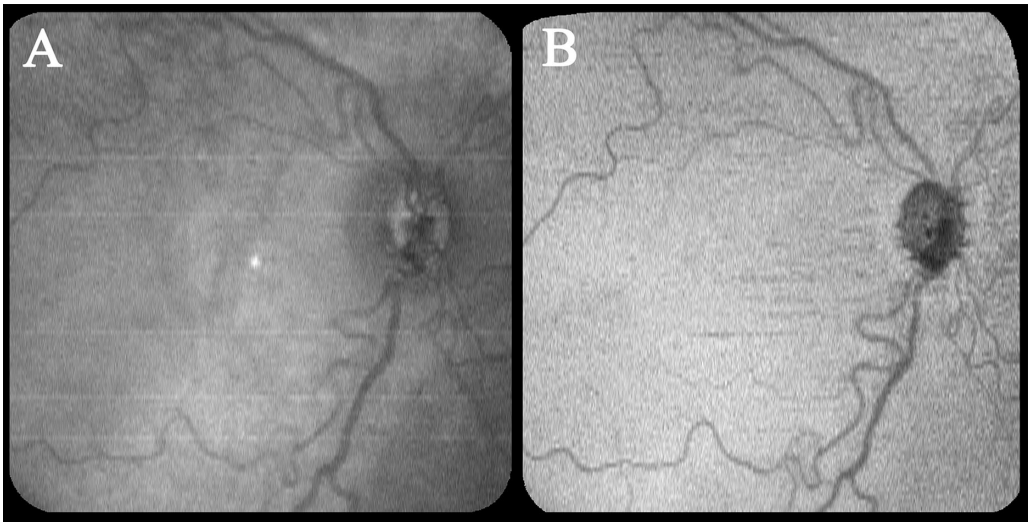

Figure 7. Inconsistent representation of vessel dilation on en face OCT images of a preterm eye with plus disease on clinical ROP examination. Graders noted more vessel dilation in the (A) conventional retina view OCT image compared with the (B) RVSV-OCT image. This resulted in two graders incorrectly grading this eye as having pre-plus disease, rather than plus disease. In their grading rationale, these two graders noted that the eye had insufficient dilation for plus disease on RVSV-OCT.

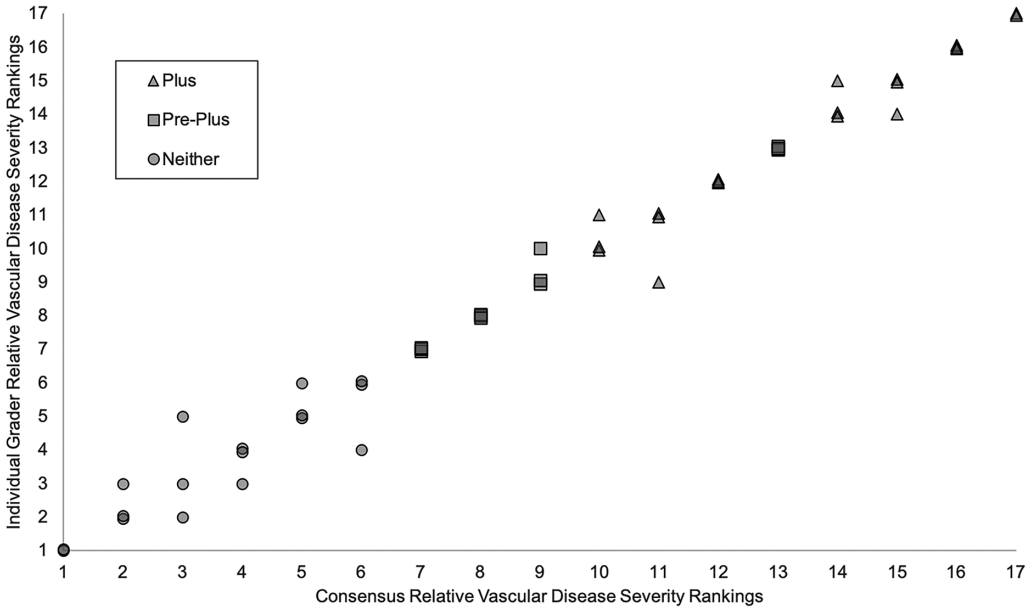

Figure 8. Consensus (median) relative vascular disease severity rankings for 17 RVSV-OCT montages, from least (1) to most severe (17), versus individual grader rankings. Relative vascular disease severity rankings exhibited excellent intergrader agreement (ICC 0.98) and correlated well with plus, pre-plus, or neither diagnosis on clinical examination.

photographs for grading in 10/18 (56%) gradings and the majority of graders preferred fundus photographs for grading in 4/6 (67%) cases, citing greater field of view (n = 6/18) or lack of apparent artifact (n = 3/18). Despite varying preferences for RVSV-OCT versus fundus photograph for grading plus, pre-plus, or neither, all graders expressed comfort using either imaging modality for grading.

Discussion

This report describes a novel method for extracting two-dimensional en face RVSV-OCT images from structural OCT scans in preterm infants, a comparison of montaged RVSV-OCT to both conventional retina view OCT and wide-field fundus photographs, and

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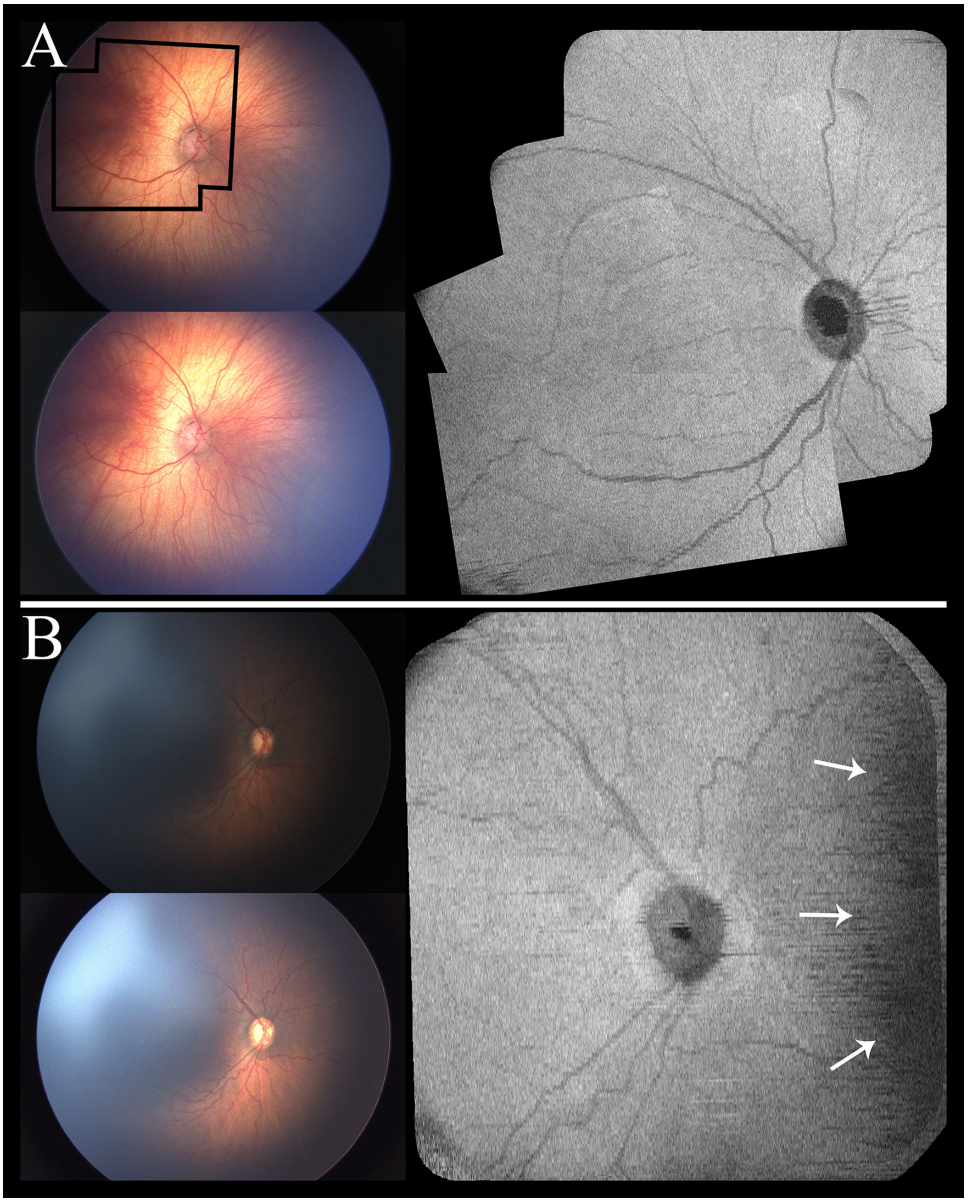

Figure 9. Comparison of fundus photographs and montaged RVSV-OCT images in preterm eyes with (A) blond and (B) dark fundus pigmentation. Fundus pigmentation appeared to impact retinal vessel visualization in the unadjusted (top left) and brightness- and contrast-adjusted (bottom left) fundus photographs, but not in the RVSV-OCT (right). In the darkly pigmented eye, autosegmentation errors resulted in artifact in the nasal periphery of the RVSV-OCT (*white arrows*, B). Montaged RVSV-OCT field of view was smaller than that of a single fundus photograph (*black outline*, A).

the application of montaged RVSV-OCT for grading and ranking ROP posterior pole vascular disease by ophthalmologists. Our study found that montaged RVSV-OCT was preferred to conventional retina view OCT for grading of posterior pole vascular disease in a majority of cases and gradings, that fundus pigmentation did not appear to impact vessel visualization on RVSV-OCT, and that ROP screeners were able to reliably and consistently rank relative posterior pole vascular disease severity for ROP using RVSV-OCT montages.

The optimized RVSV-OCT images have several advantages over conventional retina view OCT images. The extraction of RVSV-OCT images exclusively from volumetric data around the autosegmented RPE results in the elimination of distracting choroidal vasculature. Our findings suggest that the elimination of choroidal patterns improves visualization of

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retinal vessels, and is advantageous for grading by clinicians. By extracting volumetric data around the RPE, we also eliminated choroidal pigment, which develops at approximately 34 weeks post-menstrual age[45] and has been shown to impact OCT scan depth and quality,[46] which may explain graders' inability to identify fundus pigmentation on RVSV-OCT images. However, the preponderance of blond fundi in this pilot study (9/17) may limit the generalizability of this finding. This selective extraction procedure is enabled by custom infant-specific autosegmentation software that accurately delineates retinal layers in preterm eyes, despite a range of post-menstrual ages and stages of retinal development. The autosegmentation process also produces retinal thickness data across the volume. This provides a measure of axial tortuosity and has been one factor used in the VASO.[37] We did not test it here, as it is an additional OCT measure that does not have an equivalent in current plus disease grading. In future studies, we will examine the value of combining thickness map data with RVSV-OCT images. Additionally, automontage combines individual RVSV-OCT images, which have a relatively small field of view because of the noncontact nature of the investigational system, into a single montage that covers a larger area of the posterior pole. Overall, these montaged RVSV-OCT images appear to be a significant improvement over individual en face OCT images currently available at the bedside.

The investigational SS-OCT system used to capture these RVSV-OCT images also overcomes several limitations of current bedside imaging systems. The high capture speed of the 200 kHz investigational OCT system maximizes data acquisition during scan periods that are necessarily limited in awake, nonfixating infants. This enables the creation of RVSV-OCT images with greater pixel density, and therefore higher quality, than commercial en face OCT images. Second, the use of a noncontact probe enables the capture of retinal vessel patterns, potentially useful for ROP screening, without retinal vessel changes[47] or the stress response that can be created by a contact fundus camera.

Our findings support the feasibility of using RVSV-OCT montages for ranking relative posterior pole vascular disease severity in preterm infants at risk for ROP. All 17 RVSV-OCT montages were rankable for relative vascular disease severity, and the rankings featured excellent intergrader agreement and correlated well with plus, pre-plus, or neither diagnoses on clinical examination. RVSV-OCT images may therefore have sufficient retinal vessel visualization for the reliable demonstration of relative ROP vascular disease severity in preterm eyes.

However, having graders evaluate RVSV-OCT montages to assess for plus or pre-plus disease, or even the single clinician determining plus or pre-plus at the bedside, had limitations. For example, in the RVSV-OCT versus conventional retina view analysis, central artifact from automated image processing errors obscured retinal vessel patterns and resulted in two RVSV-OCT montages being deemed ungradable by at least one grader. Additionally, in the RVSV-OCT versus fundus photograph analysis, the presence of artifact contributed to graders' preference for the fundus photograph over the RVSV-OCT in a majority of cases, despite graders' observations that vessel visualization on the fundus photograph was impacted by fundus pigmentation. In these RVSV-OCT montages, all from eyes with plus or pre-plus disease on clinical examination, this central artifact itself may be an indication of the presence of dilated and tortuous retinal vessels, comparable to the VASO score.[37] We have recently developed a new version of the segmentation algorithm, which may improve autosegmentation accuracy and decrease RVSV-OCT artifact in the future. Graders also frequently disagreed on plus, pre-plus, or neither grades, despite high agreement on relative vascular disease severity ranks. Intergrader variation in the diagnosis of plus disease has been well documented in the literature,[48–50] and may be attributable to grader-specific biases to undercall or overcall pre-plus and plus disease.[51,52] This can also apply to a single clinician who determined the plus disease at the bedside (our gold standard). The relatively low intergrader agreement for plus, pre-plus, or neither grades may therefore be due not to limitations of the RVSV-OCT montages themselves, but to unique disease thresholds for each grader, despite the existence of standardized grading criteria. We attempted to minimize this limitation by providing standardized photographs of pre-plus and plus disease and instructing graders to grade the RVSV-OCT based on standardized criteria, but our findings suggest that some degree of bias remained. In a future study, the application of either an objective, semi- or fully automatic plus disease classification system (i.e., machine learning), or a rigorous three-grader consensus, to these RVSV-OCT images and to the reference color fundus image, may address this bias. Finally, reviewer comment that there was decreased vessel dilation on RVSV-OCT suggests that the process of restricting volumetric OCT data to a narrow axial window bracketed around the RPE may impair the representation of venous dilation on RVSV-OCT. Previous work suggests that retinal vessels are significantly wider than their corresponding shadows, as measured on spectral domain OCT.[53] Therefore a

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potential explanation for this decreased representation of vessel dilation is that the RVSV-OCT illustrates the relatively narrow retinal vessel shadows on the hyperreflective RPE, rather than the vessels themselves. This may in part explain the low sensitivity RVSV-OCT gradings had for detecting plus disease; in the majority of instances of missed plus disease, graders cited insufficient dilation for plus disease in their grading rationale.

Although promising, these RVSV-OCT creation methods need to be further optimized. The imaging protocol used in BabySTEPS resulted in anisotropic, 950 × 126 pixel scans, which although higher quality than commercial images, are not optimized for en face viewing. Isotropic scan protocols may improve retinal vessel visibility and graders' ability to detect posterior pole vascular disease on RVSV-OCT images. Similarly, RVSV-OCT capture was not optimized for automontaging, which requires overlap between adjacent en face images. This may have limited the number of images automontaged and the field of view of the resulting RVSV-OCT montage, which was smaller than that of a single wide-field fundus photograph. More consistent overlap between adjacent scans and capture of the peripheral retina may improve the utility of RVSV-OCT montages, as increased field of view contributed to graders' preference for fundus photographs over RVSV-OCT and has been shown to improve the reliability of plus disease diagnoses.[54] Aditionally, a rigorous comparative analysis is needed to optimize RVSV-OCT extraction protocol and standardize representation of venous dilation in RVSV-OCT images. We also recognize the need for a larger study to more rigorously assess sensitivity and specificity against a less subjective reference standard than was possible with this limited dataset and single bedside clinical assessment. A larger goal-directed prospective study, with color fundus photographs and an imaging and processing protocol prioritizing the production of high-quality RVSV-OCT images taken from preterm infants with a more representative distribution of fundus pigmentation, would aim to address these limitations.

Conclusions

This report of an exploratory pilot study describes the automatic creation of montaged RVSV-OCT images, optimized for retinal vessel visualization in preterm infants. Our findings suggest that RVSV-OCT montages have sufficient quality and retinal vessel visualization to enable grading of relative ROP posterior pole vascular disease severity by ophthalmologists. Although there is clearly future work to be done, especially for assessment of vessel dilation, these RVSV-OCT images could eventually represent an alternative to current ROP screening methods.

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References

1. National Eye Institute. Retinopathy of prematurity. Available at: https://www.nei.nih.gov/learn-about-eye-health/eye-conditions-and-diseases/retinopathy-prematurity. Updated July 10, 2019. Accessed March 30, 2020.
2. Early Treatment For Retinopathy Of Prematurity Cooperative Group. Revised indications for the treatment of retinopathy of prematurity: results of the early treatment for retinopathy of prematurity randomized trial. *Arch Ophthalmol*. 2003;121:1684–1694.
3. International Committee for the Classification of Retinopathy of Prematurity. The international classification of retinopathy of prematurity revisited. *Arch Ophthalmol*. 2005;123:991–999.
4. An international classification of retinopathy of prematurity. The Committee for the Classification of Retinopathy of Prematurity. *Arch Ophthalmol*. 1984;102:1130–1134.
5. Capone A, Jr., Ells AL, Fielder AR, et al. Standard image of plus disease in retinopathy of prematurity. *Arch Ophthalmol*. 2006;124:1669–1670.
6. Multicenter trial of cryotherapy for retinopathy of prematurity: preliminary results. Cryotherapy for Retinopathy of Prematurity Cooperative Group. *Pediatrics*. 1988;81:697–706.
7. Supplemental Therapeutic Oxygen for Prethreshold Retinopathy Of Prematurity (STOP-ROP), a

Downloaded from abstracts.iovs.org on 04/20/2024

randomized, controlled trial. I: primary outcomes. *Pediatrics*. 2000;105:295–310.
8. Richter GM, Williams SL, Starren J, Flynn JT, Chiang MF. Telemedicine for retinopathy of prematurity diagnosis: evaluation and challenges. *Surv Ophthalmol*. 2009;54:671–685.
9. Fierson WM; American Academy of Pediatrics Section on Ophthalmology; American Academy of Ophthalmology; American Association for Pediatric Ophthalmology and Strabismus; American Association of Certified Orthoptists. Screening examination of premature infants for retinopathy of prematurity. *Pediatrics*. 2018;142:e20183061.
10. Ells AL, Holmes JM, Astle WF, et al. Telemedicine approach to screening for severe retinopathy of prematurity: a pilot study. *Ophthalmology*. 2003;110:2113–2117.
11. Chiang MF, Keenan JD, Starren J, et al. Accuracy and reliability of remote retinopathy of prematurity diagnosis. *Arch Ophthalmol*. 2006;124:322–327.
12. Chiang MF, Wang L, Busuioc M, et al. Telemedical retinopathy of prematurity diagnosis: accuracy, reliability, and image quality. *Arch Ophthalmol*. 2007;125:1531–1538.
13. Biten H, Redd TK, Moleta C, et al. Diagnostic accuracy of ophthalmoscopy vs telemedicine in examinations for retinopathy of prematurity. *JAMA Ophthalmol*. 2018;136:498–504.
14. Photographic Screening for Retinopathy of Prematurity (Photo-ROP) Cooperative Group. The photographic screening for retinopathy of prematurity study (photo-ROP). Primary outcomes. *Retina*. 2008;28(3 Suppl):S47–S54.
15. Weaver DT, Murdock TJ. Telemedicine detection of type 1 ROP in a distant neonatal intensive care unit. *J AAPOS*. 2012;16:229–233.
16. Wang SK, Callaway NF, Wallenstein MB, Henderson MT, Leng T, Moshfeghi DM. SUNDROP: six years of screening for retinopathy of prematurity with telemedicine. *Can J Ophthalmol*. 2015;50:101–106.
17. Vinekar A, Jayadev C, Mangalesh S, Shetty B, Vidyasagar D. Role of tele-medicine in retinopathy of prematurity screening in rural outreach centers in India–a report of 20,214 imaging sessions in the KIDROP program. *Semin Fetal Neonatal Med*. 2015;20:335–345.
18. Hartnett ME. *Pediatric retina*. Philadelphia, PA: Lippincott Williams & Wilkins; 2005.
19. Mehta M, Adams GG, Bunce C, Xing W, Hill M. Pilot study of the systemic effects of three different screening methods used for retinopathy of prematurity. *Early Hum Dev*. 2005;81:355–360.
20. Wade KC, Pistilli M, Baumritter A, et al. Safety of retinopathy of prematurity examination and imaging in premature infants. *J Pediatr*. 2015;167:994–1000.e2.
21. Szigiato AA, Speckert M, Zielonka J, et al. Effect of eye masks on neonatal stress following dilated retinal examination: the MASK-ROP randomized clinical trial. *JAMA Ophthalmol*. 2019;137:1265–1272.
22. Smith GC, Gutovich J, Smyser C, et al. Neonatal intensive care unit stress is associated with brain development in preterm infants. *Ann Neurol*. 2011;70:541–549.
23. Brummelte S, Grunau RE, Chau V, et al. Procedural pain and brain development in premature newborns. *Ann Neurol*. 2012;71:385–396.
24. Ranger M, Grunau RE. Early repetitive pain in preterm infants in relation to the developing brain. *Pain Manag*. 2014;4:57–67.
25. Maldonado RS, O'Connell RV, Sarin N, et al. Dynamics of human foveal development after premature birth. *Ophthalmology*. 2011;118:2315–2325.
26. Vajzovic L, Hendrickson AE, O'Connell RV, et al. Maturation of the human fovea: correlation of spectral-domain optical coherence tomography findings with histology. *Am J Ophthalmol*. 2012;154:779–789.e2.
27. Yanni SE, Wang J, Chan M, et al. Foveal avascular zone and foveal pit formation after preterm birth. *Br J Ophthalmol*. 2012;96:961–966.
28. Vajzovic L, Rothman AL, Tran-Viet D, Cabrera MT, Freedman SF, Toth CA. Delay in retinal photoreceptor development in very preterm compared to term infants. *Invest Ophthalmol Vis Sci*. 2015;56:908–913.
29. Lee H, Purohit R, Patel A, et al. In vivo foveal development using optical coherence tomography. *Invest Ophthalmol Vis Sci*. 2015;56:4537–4545.
30. Chavala SH, Farsiu S, Maldonado R, Wallace DK, Freedman SF, Toth CA. Insights into advanced retinopathy of prematurity using handheld spectral domain optical coherence tomography imaging. *Ophthalmology*. 2009;116:2448–2456.
31. Lee AC, Maldonado RS, Sarin N, et al. Macular features from spectral-domain optical coherence tomography as an adjunct to indirect ophthalmoscopy in retinopathy of prematurity. *Retina*. 2011;31:1470–1482.
32. Vinekar A, Avadhani K, Sivakumar M, et al. Understanding clinically undetected macular changes in early retinopathy of prematurity on

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spectral domain optical coherence tomography. *Invest Ophthalmol Vis Sci*. 2011;52:5183–5188.
33. Maldonado RS, O'Connell R, Ascher SB, et al. Spectral-domain optical coherence tomographic assessment of severity of cystoid macular edema in retinopathy of prematurity. *Arch Ophthalmol*. 2012;130:569–578.
34. Dubis AM, Subramaniam CD, Godara P, Carroll J, Costakos DM. Subclinical macular findings in infants screened for retinopathy of prematurity with spectral-domain optical coherence tomography. *Ophthalmology*. 2013;120:1665–1671.
35. Anwar S, Nath M, Patel A, et al. Potential utility of foveal morphology in preterm infants measured using hand-held optical coherence tomography in retinopathy of prematurity screening. *Retina*. 2019 Jul 24. doi:10.1097/IAE.0000000000002622. Online ahead of print.
36. Chen X, Mangalesh S, Dandridge A, et al. Spectral-domain OCT findings of retinal vascular-avascular junction in infants with retinopathy of prematurity. *Ophthalmol Retina*. 2018;2:963–971.
37. Maldonado RS, Yuan E, Tran-Viet D, et al. Three-dimensional assessment of vascular and perivascular characteristics in subjects with retinopathy of prematurity. *Ophthalmology*. 2014;121:1289–1296.
38. Viehland C, Chen X, Tran-Viet D, et al. Ergonomic handheld OCT angiography probe optimized for pediatric and supine imaging. *Biomed Opt Express*. 2019;10:2623–2638.
39. Chiu SJ, Li XT, Nicholas P, Toth CA, Izatt JA, Farsiu S. Automatic segmentation of seven retinal layers in SDOCT images congruent with expert manual segmentation. *Opt Express*. 2010;18:19413–19428.
40. Patel SN, Klufas MA, Douglas CE, et al. Influence of computer-generated mosaic photographs on retinopathy of prematurity diagnosis and management. *JAMA Ophthalmol*. 2016;134:1283–1289.
41. Chen J, Ausayakhun S, Ausayakhun S, et al. Comparison of autophotomontage software programs in eyes with CMV retinitis. *Invest Ophthalmol Vis Sci*. 2011;52:9339–9344.
42. Viera AJ, Garrett JM. Understanding interobserver agreement: the kappa statistic. *Fam Med*. 2005;37:360–363.
43. Shrout PE, Fleiss JL. Intraclass correlations: uses in assessing rater reliability. *Psychol Bull*. 1979;86:420–428.
44. Cicchetti DV. Guidelines, criteria, and rules of thumb for evaluating normed and standardized assessment instruments in psychology. *Psychol Assess*. 1994;6:284–290.
45. Mund ML, Rodrigues MM, Fine BS. Light and electron microscopic observations on the pigmented layers of the developing human eye. *Am J Ophthalmol*. 1972;73:167–182.
46. Moreno TA, O'Connell RV, Chiu SJ, et al. Choroid development and feasibility of choroidal imaging in the preterm and term infants utilizing SD-OCT. *Invest Ophthalmol Vis Sci*. 2013;54:4140–4147.
47. Koreen S, Lopez R, Jokl DH, Flynn JT, Chiang MF. Variation in appearance of severe zone 1 retinopathy of prematurity during wide-angle contact photography. *Arch Ophthalmol*. 2008;126:736–737.
48. Gelman R, Jiang L, Du YE, Martinez-Perez ME, Flynn JT, Chiang MF. Plus disease in retinopathy of prematurity: pilot study of computer-based and expert diagnosis. *J AAPOS*. 2007;11:532–540.
49. Wallace DK, Quinn GE, Freedman SF, Chiang MF. Agreement among pediatric ophthalmologists in diagnosing plus and pre-plus disease in retinopathy of prematurity. *J AAPOS*. 2008;12:352–356.
50. Chiang MF, Jiang L, Gelman R, Du YE, Flynn JT. Interexpert agreement of plus disease diagnosis in retinopathy of prematurity. *Arch Ophthalmol*. 2007;125:875–880.
51. Campbell JP, Kalpathy-Cramer J, Erdogmus D, et al. Plus disease in retinopathy of prematurity: a continuous spectrum of vascular abnormality as a basis of diagnostic variability. *Ophthalmology*. 2016;123:2338–2344.
52. Kalpathy-Cramer J, Campbell JP, Erdogmus D, et al. Plus disease in retinopathy of prematurity: improving diagnosis by ranking disease severity and using quantitative image analysis. *Ophthalmology*. 2016;123:2345–2351.
53. Ouyang Y, Shao Q, Scharf D, Joussen AM, Heussen FM. Retinal vessel diameter measurements by spectral domain optical coherence tomography. *Graefes Arch Clin Exp Ophthalmol*. 2015;253:499–509.
54. Rao R, Jonsson NJ, Ventura C, et al. Plus disease in retinopathy of prematurity: diagnostic impact of field of view. *Retina*. 2012;32:1148–1155.

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