Semiautomated digital image analysis of posterior pole vessels in retinopathy of prematurity

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Plus disease is a major indicator for treatment in retinopathy of prematurity (ROP), and computer-assisted image analysis of vessel caliber and tortuosity in the posterior pole may indicate disease progression and severity. We sought to determine whether semiautomated digital analysis of posterior pole vessels using narrow field images with varying severity of ROP correlated with vessel width and tortuosity.

Retinopathy of prematurity (ROP) is an abnormal neovascular proliferation of the retinal vessels that occurs between the avascular and vascular peripheral retina in premature infants. The present standard for diagnosing ROP is the examination by an ophthalmologist using an indirect ophthalmoscope. However, poor interexpert agreement (as determined by paired ophthalmologic examinations)[1] and of subjectivity in interpreting digital images suggest the need for an objective measure such as digital image analysis.[2-5]

Currently, two digital cameras are in use for ROP examinations: the RetCam 3 or RetCam Shuttle (Clarity Medical Systems, Pleasanton, CA)—a contact camera providing a wide-field, 130° view of the fundus—and the Nidek NM200D (Nidek, Inc., Aichi, Japan), a noncontact camera providing a narrow-field, 30° view of the fundus. Most studies have examined vessel caliber from wide-field digital images with less pixel density per vessel than narrow-field images.[2-5] In this small pilot study, we sought to determine whether digital image analysis, adapted for use with narrow-field images, could identify posterior pole vessel abnormalities in eyes with ROP, specifically measuring vessel width and tortuosity.

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Methods

This study was approved by the Institutional Review Board of Children's Hospital of Philadelphia and conformed to the requirements of the United States Health Insurance Portability and Accountability Act. From a longitudinal study at the Children's Hospital of Philadelphia using the NM200D camera on eyes of babies at risk for ROP, 11 high-quality images from 11 different babies representing a range of posterior pole vascular abnormalities with ROP were selected. Images from three eyes with no or minimal ROP (no ROP or less than or equal to stage 1 ROP), five eyes with moderate ROP (stage 2 to 3 ROP without plus disease), and three eyes with severe ROP (stage 3 ROP with plus disease) were analyzed. Eyes were classified based on the diagnosis recorded by the attending physicians in the patients' charts on the date of image acquisition on indirect ophthalmoscopy. No significant differences were found among the groups for birth weights ($p = 0.75$), post menstrual ages ($p = 0.43$), gestational ages ($p = 0.42$), and weights on date of image acquisition ($p = 0.69$) using analysis of variance. No image rotation or contrast adjustment was performed, and images were analyzed as downloaded from the camera.

Computer-Aided Image Analysis of the Retina (CAIAR; Department of Physics, Imperial College London and Department of Optometry and Visual Science, City University, London, UK) is a digital analysis program that can determine vessel width and tortuosity. Parameters were set to optimize digital image analysis for NIDEK images by its developers.[6] All vessels in each image were analyzed in accordance with the methodology outlined by Wilson and colleagues[6] (see e-Supplement 1, available at jaapos.org). Width and tortuosity measures were calculated by CAIAR from the final image (Figure 1A).

Vasculo-matic ala Nicola version 1.1 (IVAN, Department of Ophthamology and Visual Science, University of Wisconsin–Madison, Madison, WI) is a digital image analysis software that can detect width and has been validated previously[7,8] (e-Supplement 1). Vessels were measured between one-half to one disk diameter from the margin of the optic disk. Width was calculated by IVAN from the final image (Figure 1B).

All vessels within an image were analyzed by CAIAR and IVAN and classified as arteriole or venule by an expert ophthalmologist. Correlation between vessel width using digital image analysis and disease severity from ophthalmoscopic examination was performed. All analyses were adjusted for correlation among measurements from different vessels of the same image using generalized estimating equations. Spearman rank correlation coefficients were calculated to determine correlation between vessel caliber and tortuosity and severity of ROP. The area under receiver operating characteristic curves for distinguishing plus

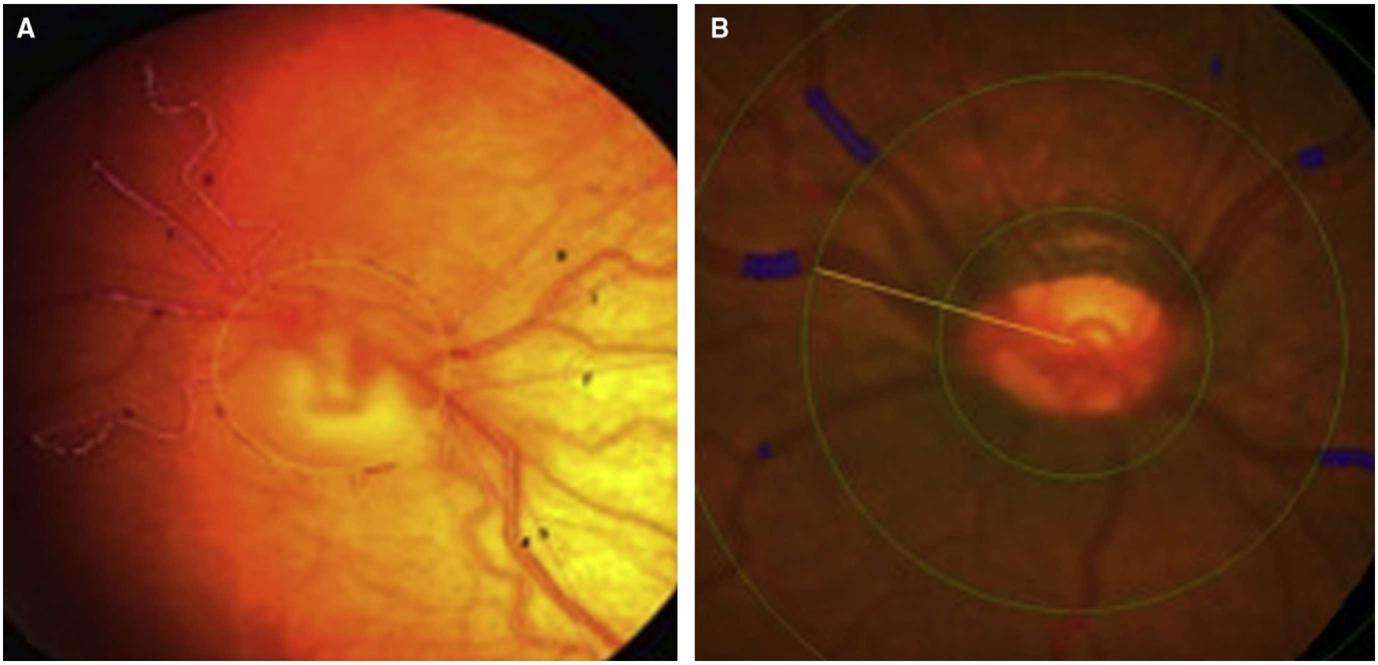

FIG 1. Final image of a stage 3 plus disease eye from CAIAR (A) and IVAN (B) after user input and semiautomated analysis.

Table 1. Comparison of vessel diameter and tortuosity with varying severity of ROP using narrow field digital images

Digital image analysis	Vessel type	Mean (SE) Minimal ROP ≤stage 1, no plus	Stage 2-3, pre-plus	Stage 3 plus	p for linear trend[a]	Spearman correlation coefficient (r)
CAIAR	Venule width	4.91 (0.10)	5.65 (0.22)	7.63 (0.58)	0.035	0.64
	Arteriole width	3.73 (0.17)	3.80 (0.14)	5.15 (0.54)	0.072	0.42
	Combined width	4.32 (0.08)	4.72 (0.10)	6.39 (0.51)	0.035	0.45
	Venule tortuosity	12.7 (0.47)	18.1 (0.99)	18.4 (1.12)	0.027	0.16
	Arteriole tortuosity	10.7 (1.27)	23.1 (4.12)	78.4 (9.52)	0.024	0.70
	Combined tortuosity	11.7 (0.75)	19.9 (2.29)	48.4 (6.28)	0.025	0.45
IVAN	Venule width	77.3 (2.25)	85.2 (1.28)	118 (6.77)	0.040	0.60
	Arteriole width	74.2 (5.07)	60.3 (2.78)	81.1 (10.3)	0.570	0.12
	Combined width	77.5 (2.91)	72.9 (1.54)	99.8 (8.76)	0.100	0.38

[a]Correlation among vessel measurements from different vessels of the same image adjusted by using generalized estimating equations.

disease was calculated. Pearson correlation coefficients were calculated to determine correlation between CAIAR and IVAN for vessel width. Correlations were considered weak if $r < 0.5$, moderate if $r = 0.51\text{-}0.75$, and strong if $r > 0.75$.

Results

Mean vessel width as measured by CAIAR and IVAN increased with disease severity (Table 1). Venule width and width of all vessels combined were moderately correlated with ROP using CAIAR. Venule width by IVAN was moderately correlated with ROP status.

Mean tortuosity measured by CAIAR was found to increase significantly with disease severity (Table 1), especially for arteriolar tortuosity, which had the highest correlation with ROP status.

Spearman rank correlation coefficients were moderate for venule width ($r = 0.64$) and arteriolar tortuosity ($r = 0.70$) using CAIAR and venule width ($r = 0.60$) using IVAN. Pearson correlation coefficients between IVAN and CAIAR for width were moderate for venules ($r = 0.52$, $p = 0.001$) and for arterioles and venules combined ($r = 0.61$, $p < 0.0001$). Arteriole tortuosity measured by CAIAR and venule width measured by CAIAR and IVAN were the best at distinguishing plus disease using receiver operating characteristic analysis (Table 2).[9]

Discussion

Semiautomated digital analysis of posterior pole vessels of eyes at risk for ROP can identify vessel width and tortuosity in narrow-field images. This is promising because there is

Table 2. ROC analysis for discriminating eyes with plus and without plus disease in ROP

Image analysis program	Vessel type	Area under ROC curve (95% CI)[a]
CAIAR	**Venule width**	**0.909 (0.702-1.00)**
	Arteriole width	0.814 (0.620-1.00)
	Combined width	0.804 (0.619-0.954)
	Venule tortuosity	0.538 (0.473-0.628)
	Arteriole tortuosity	**0.920 (0.855-0.968)**
	Combined tortuosity	0.730 (0.658-0.796)
IVAN	**Venule width**	**0.909 (0.577-1.00)**
	Arteriole width	0.617 (0.430-1.00)
	Combined width	0.734 (0.530-0.972)

[a]Confidence intervals for area under ROC curve were calculated based on the 2.5th percentile and 97.5th percentile from 2000 replications of bootstrap, to adjust for correlations among multiple measures from vessels of same image.[9]

significant interexpert disagreement on the diagnosis of plus disease.[3,5]

There are several advantages to using narrow-field images from the NM200D camera relative to wide-field images.[10] As a non-contact camera, no pressure was applied to the fundus that could potentially alter the vessel caliber and tortuosity. Transmission between infants is minimized without direct contact of the camera lens to the eye. Higher pixel density using the NM200D camera provides greater information regarding the vessels measured relative to other cameras. The camera is compact and portable, making it ideal for screening in a large nursery with a large volume of infants requiring screening. Our results indicate that in spite of the inability to visualize peripheral disease, there is likely good agreement between ophthalmoscopic examination and image-based interpretation using narrow-field images, similar to results obtained using wide-field images.[11]

The semiautomated software programs utilized are promising. CAIAR measures both width and tortuosity, crucial indicators of plus disease. Furthermore, peripapillary vessels, which may cause vessel variability, can be excluded in CAIAR. In contrast, IVAN measures vessel width and differentiates arterioles from venules. However, IVAN can measure only a specific segment of the vessel. Width measurements correlated moderately well between CAIAR and IVAN. We suspect that this may be due to the fact that CAIAR measures vessels more proximal to the edge of the disk (the area generally considered important in clinical diagnosis), while IVAN measures more peripheral retinal vessels.

In conclusion, analysis of posterior pole vessels using narrow-field images detects varying severity of ROP by measuring tortuosity and width in this pilot study. Further analysis of additional ROP images will determine if semiautomated digital software analysis can reliably detect such vessel changes.

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