1 Introduction

1.1 Retinopathy of Prematurity

Retinopathy of prematurity (ROP) is a disorder that affects the development of blood vessels in the retina of premature infants, and is the leading cause of preventable childhood blindness [1]. Because advanced ROP can progress rapidly in the first 8 to 12 weeks of life, prompt identification of high-risk features of the disease is critical to the clinical management of the affected infants. Premature infants with a birth weight of less than 1250 – 1750 g or a gestational age of less than 28 – 32 weeks are required to be screened for possible development of ROP based on screening protocols established around the world [2–4]. Out of the 6998 infants screened during a two-year period for the Early Treatment for ROP study in the United States, 68% developed ROP [5]. The severity of ROP has previously been assessed solely based on its staging, which is determined based on the abnormal vascular response at the junction of the vascularized and the avascular parts of the retina, and consists of five stages [1]. However, in the past decade, it has been established that early treatment of ROP would benefit from, and should mainly be based on, the diagnosis of plus disease [6–9].

1.2 Plus Disease

Plus disease is diagnosed by the presence of a certain level of increase in venular dilation and arteriole tortuosity in at least two quadrants of the eye [1]. Determination of the presence of sufficient dilation and tortuosity of the posterior vessels for the diagnosis of plus disease is performed by visual qualitative comparison to gold-standard retinal fundus photographs [1, 10]. The presence of venular dilation and arteriole tortuosity that is not sufficient for the diagnosis of plus disease is indicative of preplus disease [1]. The Early Treatment for ROP Cooperative Group [6] proposed to determine the need for early treatment of ROP by defining two types of ROP. Type 1 ROP consists of any stage of ROP in Zone I (a circle centered on the optic nerve head (ONH) with a radius of two times the distance from the center of the ONH to the fovea) accompanied by plus disease, Stage 3 ROP in Zone I without the presence of plus disease, and Stages 2 and 3 ROP in Zone II (a circle centered on the ONH which extends up to the nasal or serrata) accompanied with plus disease. Type 2 ROP consists of Stages 1 and 2 ROP in Zone I and Stage 3 ROP in Zone II, both without the presence of plus disease [6]. The presence of plus disease is now considered to be the main indicator for the need for early treatment, and even though the staging and zone of ROP are still indicated, they are of secondary importance [7–9].

The current method for diagnosis of plus disease is subjective. As shown by Chiang et al. [8], among 22 recognized ROP experts who performed diagnosis of plus disease on 34 images of preterm infants based on a 3-level classification (plus, preplus, and neither), the experts agreed on the diagnosis of only 12% of the images (4 out of 34). Using a 2-level classification (plus and no plus), the experts agreed on the diagnosis of just 21% of the images.
ages (7 out of 34). Disagreement could also exist among experts in the diagnosis of plus disease as compared to pre-plus disease, as shown by Wallace et al. [11]. Such studies show the need for methods to quantify the changes in blood vessels in the presence of plus disease.

There have been various semiautomated computer programs developed to assist in the diagnosis of plus disease by quantification of the changes in the thickness and tortuosity of the blood vessels [9, 10, 12]. Even though a direct relationship appears to exist between increasing venule thickness and increasing severity of ROP, the detection of small changes in venule thickness requires high-resolution imaging as these changes are at, or below, the spatial resolution of typical retinal imaging systems [10]. Arteriole tortuosity has shown higher correlation with the presence of plus disease in some studies, but this factor has also not been consistent across all trials [7, 13]. Moreover, the detection of arterioles presents an image processing challenge: arterioles have lower contrast as compared to venules and their thickness can be below the resolution limit of even high-resolution retinal fundus images of premature infants [14]. These factors and limitations indicate a need for quantification of other diagnostic factors, such as changes in the angle of insertion and the straightening of the major temporal arcade (MTA) [1, 10, 15–17].

Change in the openness of the MTA has been used as an indicator of compromised structural integrity of the macular region, as well as a sequela of ROP [1, 15]. The angle of insertion of the MTA has been loosely defined as the angle between the superior and inferior temporal arcades (STA and ITA) as they diverge from the ONH and extend towards the periphery of the retina [15, 16]. Despite the clinical importance of abnormal changes in the architecture of the MTA, the angle of insertion or the openness of the MTA has been quantified in only three studies dealing with ROP [16–18]. It has been observed that the openness of the MTA decreases with cicatricial ROP in the scarring phase; the major temporal vessels straighten and are dragged to the peripheral part of the retina. We hypothesize that the openness of the MTA decreases with progression of plus disease and relaxes or increases after favorable treatment.

As shown in our previous studies [18, 19], parabolic modeling of the MTA can be useful in analyzing changes to the openness of the MTA for the diagnosis of proliferative diabetic retinopathy [19] and ROP [18]. It would be of interest to determine whether such changes also occur in the presence of plus disease. The aim of the present paper is to test the hypothesis that plus disease affects the architecture of the MTA and reduces the angle of insertion or the openness of the MTA, via parabolic modeling of the MTA and by measuring the temporal arcade angle (TAA) for comparative analysis.

2 Materials and Methods

2.1 Database of Fundus Images of the Retina

The proposed methods were tested with retinal fundus images from the Telemedicine for ROP In Calgary (TROPIC) database [20]. The images were captured using the RetCam 130 camera [wide-field (130°)] and have a size of 640 × 480 pixels. The spatial resolution is estimated to be 30 μm/pixel [21]. In total, 110 images of Stages 0, 1, 2, and 3 ROP were selected from the database for the present study; the TROPIC database does not contain any cases of Stages 4 and 5 ROP. Nineteen of the selected images were associated with plus disease (Stages 2 and 3 of ROP) and 91 showed no signs of plus disease. At most, two images of the same patient were included for the same stage of ROP, with one image from each eye. Images of the same eye were included only if the ROP stages were different at the time of imaging, as diagnosed by an expert pediatric ophthalmologist and retinal specialist (A.L.E.).

2.2 Procedure for Measurement of the Arcade Angle

The present work employs the principal concepts of the method of Wong et al. [17] for the measurement of the TAA via a graphical user interface (GUI) [19] for comparative analysis. The procedure for the measurement of the TAA starts by prompting the user to mark the center of the ONH, after which a circle with a radius that is specified by the user is drawn on the image [17]. The procedure then prompts the user to mark the point of intersection of the circle with the superior venule; the same is repeated for the inferior venule. The TAA is measured as the angle between the three manually marked points, where the center of the ONH is the vertex of the angle [19]. In the present work, circles of radii r = 60 and 120 pixels (1.8 and 3.6 mm) were used to measure the TAA. These two radii were selected based on the method of Wong et al. [17] and were found to be suitable to measure the TAA close to the ONH (posterior pole) or to the macula, respectively.

2.3 Detection and Modeling of the MTA

In the present work, Gabor filters, which are sinusoidally modulated Gaussian functions, are used for the detection of the MTA. A type of the generalized Hough transform (GHT) for the detection of parabolic forms is used with the result of Gabor filtering for single- and dual-parabolic modeling of the MTA, STA, and ITA [22]. The proposed methods are implemented via a GUI, which facilitates user input for selection of the parameters of the Gabor filters and the binarization steps used for detection and modeling of the MTA, as well as measurement of the TAA [19].

Thresholding the green component of the given retinal fundus color image at 0.075 of its maximum value provides a mask image, which indicates the effective area of the image. The green component is extended beyond the
effective area to avoid the detection of its edges by the Gabor filters [22]. In the present work, 30 Gabor filters evenly spaced over the range $[-90^\circ, 90^\circ]$ are used to detect the MTA. A set of values of $\tau = \{10, 12, 14\}$ pixels are used for the thickness parameter of the Gabor filters [22]. The value for the elongation parameter of the Gabor filters is fixed at $l = 2$ [22].

The Gabor magnitude response image is thresholded using a sliding threshold via the GUI. The user can specify the maximum number of connected pixels to be removed to eliminate small vessel segments that may remain after the thresholding step by using the morphological operation of area open. For each image, a suitable threshold is selected via the GUI to obtain a binary image of only the MTA.

The modeling method requires a binary image to perform the GHT procedure. The user is required to indicate if the current image is an image of the left eye or the right eye. The user is then prompted to mark the approximate location of the ONH in a separate window. The range of the openness parameter, $a$, used in the parabolic modeling procedure [22], was set to $10 \leq a \leq 400$ for the selected images of the TROPIC database. Given an average width of the ONH (ONHW) of about $1.05 \text{ mm}$ in preterm infants [21] and the spatial resolution of the RetCam images, the vessel skeleton map used to derive the GHT is horizontally restricted from $0.25 \times \text{ONHW}$ nasal to $2 \times \text{ONHW}$ temporal to the ONH center (resulting in the size of each Hough space slice $= 80 \times 480$ pixels) [22].

The $p$-value, indicating the statistical significance of the differences between the values of the parameter $a$ as well as the TAA for cases with no plus disease as compared to the values of the same for the cases with plus disease were obtained via the $t$-test. To assess the diagnostic performance of the parameters derived, receiver operating characteristic (ROC) analysis was performed using ROCKIT [23].

### 3 Results

Figures 1 and 2 show the results of single- and dual-parabolic modeling, as well as the measurement of the TAA using circles of radii $r = 60$ and 120 pixels for two images from the TROPIC database; one image contains no signs of plus disease (Fig. 1) and the other shows signs of plus disease (Fig. 2). In both cases, it can be observed that the single- and dual-parabolic models are providing accurate fits to the arcade closer to the posterior pole (closer to the ONH). The TAA obtained using the circle of radius $r = 120$ pixels is providing a measure closer to the macular region, whereas the TAA obtained using the circle of radius $r = 60$ pixels is providing a measure closer to the posterior pole.

Table 1 shows the results of statistical analysis of the parabolic model parameters and TAA measurements. The results obtained using 91 cases with no plus disease as compared to 19 cases with plus disease indicate highly statistically significant differences ($p$-value $< 0.01$) for TAA using circles of radii $r = 120$ and 60 pixels. The area under the ROC curve, $A_z$, for TAA with $r = 60$ pixels and $|a_{STA}|$ are $\geq 0.70$, indicating satisfactory performance in classification or diagnosis.

Considering the fact that the numbers of available cases for the two categories are not similar, 19 cases with no plus disease were selected randomly and the analysis
Table 1. Values of $A_z$, their standard error (SE), and $p$-values obtained in the discrimination of 91 normal cases against 19 cases with plus disease using the $|a|$ parameters of the single- and dual-parabolic models as well as the TAA using radii of $r = 120$ and 60 pixels. (*$p < 0.05$ and **$p < 0.01$).

<table>
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<th>p-value</th>
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<td>$</td>
<td>a_{MTA}</td>
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<tr>
<td>$</td>
<td>a_{STA}</td>
<td>$ 0.70 (0.064) 0.0941</td>
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<tr>
<td>$</td>
<td>a_{ITA}</td>
<td>$ 0.66 (0.073) 0.4134</td>
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<tr>
<td>TAA, $r = 120$ 0.69 (0.064) 0.0052**</td>
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<tr>
<td>TAA, $r = 60$ 0.73 (0.066) 0.0001**</td>
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was performed again with equal numbers of cases from the two categories; Table 2 presents the results. The $A_z$ values are improved for all parameters, with TAA with $r = 120$ and 60 pixels and $|a_{STA}|$ having $A_z \geq 0.80$. The differences between $|a_{STA}|$ of the normal cases as compared to the cases of plus disease are statistically significant.

Table 2. Values of $A_z$, and $p$-values obtained in the discrimination of 19 normal cases against 19 cases with plus disease. (*$p < 0.05$ and **$p < 0.01$).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>$A_z$ (SE)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
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<td>$</td>
<td>a_{MTA}</td>
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<tr>
<td>$</td>
<td>a_{STA}</td>
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<tr>
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<td>a_{ITA}</td>
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<tr>
<td>TAA, $r = 120$ 0.84 (0.062) 0.0002**</td>
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<tr>
<td>TAA, $r = 60$ 0.80 (0.071) 0.0006**</td>
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4 Discussion and Conclusion

This is the first study to quantify the effects of plus disease on the openness of the MTA, STA, and ITA, using semi-automated methods to perform single- and dual-parabolic modeling as well as measurement of the TAA for comparative analysis. The diagnostic performance ($A_z$) of the parameters of the parabolic models is similar to that provided by TAA based on the method of Wong et al. [17] via the GUI (see Tables 1 and 2). However, the TAA measures provide lower $p$-values as compared to the parameters of the parabolic models. All of the studied measures show a similar trend and the proposed hypothesis is validated: there is a decrease in the openness of the MTA in the presence of plus disease. Although the $A_z$ values obtained for TAA and the parameters of the parabolic models are not high, the results are encouraging.

Eells and MacKeen [24] illustrated that the changes that occur in the MTA are dynamic as they alter the posterior architecture of the MTA over time. The TAA measure proposed by Wong et al. [17] may not accurately reflect such changes that occur over the entire posterior architecture of the MTA, as it only defines the openness of the MTA based on three points. Furthermore, the TAA is sensitive to the exact position of the center of the ONH. The parabolic modeling procedure is dependent only on an approximate location of the ONH [22].

The parabolic modeling procedure presented in this paper does not suffer the same limitations as the thickness and tortuosity measurement procedures, reviewed in Section 1.2, because it only requires a skeleton of the MTA and is influenced by the spatial resolution of the images, which in the case of the TROPIC database, and RetCam images in general, is relatively low.

If the retinal raphe angle (the line going through the center of the ONH and the fovea) is large with respect to the horizontal axis of the image, it could lead to a much larger openness parameter for one of the dual-parabolic models than the other. The retinal raphe angle may be corrected either manually or by using methods to detect the fovea. However, as shown by Chiang et al. [25], retinal fundus images of preterm infants typically lack a clear depiction of the fovea. The two parameters of the dual-parabolic models may be combined using a neural network or a nonlinear classifier to incorporate the independent information from both the STA and ITA models into the classification methods.

Upon close inspection, it becomes clear that the STA and the ITA are asymmetric. More accurate modeling of each arcade may be possible by applying higher-order models.

The parameters of the methods used for the detection and modeling of the MTA will need to be determined automatically or adaptively. The center of the ONH could be automatically detected using the Gabor angle information and phase portrait analysis [26]. The threshold used for the binarization of the Gabor magnitude response image could be determined adaptively for each image using an automatic thresholding method such as histogram concavity [27]. The optimum parameter values for the Gabor filters would need to be determined empirically; implementation of these methods is currently in progress.

In this study, we have demonstrated, for the first time, that the openness of the MTA decreases in the presence of plus disease. Combinations of measures of tortuosity and thickness of the blood vessels with the openness of the MTA may yield better results in the diagnosis of plus disease or ROP as well as discrimination between the various stages of ROP; this work is currently in progress.

References


[23] ROCKIT. Metz ROC Software. radiology.uchicago.edu/page/metz-roc-software.


