Results of Perimetry at Age of 10 Years in Severe ROP Eyes Receiving Laser or Anti-VEGF Treatment as Primary Monotherapy

- Alay S. Banker, MD
- Harita Shah
- Binita Thakore, MS

OBJECTIVE Primary monotherapy with anti-VEGF injections preserves peripheral fields as compared to laser

PURPOSE To examine binocular visual fields at the age of 10 years in children with severe ROP who were treated with either laser or intravitreal anti-VEGF injection as primary therapy.

METHODS Eyes with severe ROP (APROP or threshold stage ROP in posterior zone 2) were treated with either laser (n=6 eyes) or intravitreal anti-VEGF injection only (n=12 eyes) as primary mono- therapy. All subjects underwent standard automated perimetry at 10 years age after refraction using program 30-2/60-2 and the Swedish Interactive Thresholding Algorithm (SITA).

RESULTS Mean birth weight and gestational age in the laser group was 1063.33gm and 27.66 weeks and in the anti-VEGF group was 985gm and 28 weeks, respectively. All eyes in both groups showed regression of ROP disease after treatment. At 10 years age,automated perimetry showed that the visual field area was significantly restricted in the laser-treated group as compared to the only-Anti-VEGF treated group.

CONCLUSION Primary anti-VEGF therapy preserves significant peripheral vision in eyes with severe ROP as compared to those treated with laser. Use of anti-VEGF as a primary therapy in severe ROP followed by laser in the peripheral zone could help us achieve preserve peripheral visual fields in cases of severe ROP. This is the first report of the effect of treatment on visual fields in eyes with severe ROP.

HUMAN RESEARCH Yes: Approved by institutional review board
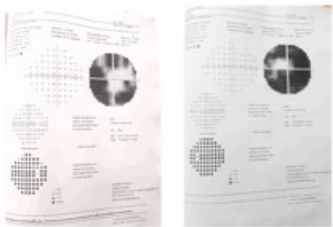
Fields after laser for APROP
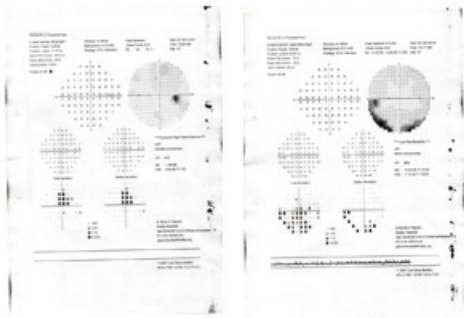
Fields after primary Anti-VEGF for APROP

Long-term Risk of Retinal Detachment in Pediatric Patients With Familial Exudative Vitreoretinopathy Previously Treated With Peripheral Laser

- Irina De la Huerta, MD PhD
- Carolyn G Ahlers, BS
- Kimberly A. Drenser, MD
- Michael T. Trese, MD
- Antonio Capone, MD

OBJECTIVE To assess the long-term risk of progression to retinal detachment of pediatric patients treated with peripheral laser photocoagulation for familial exudative vitreoretinopathy (FEVR)

PURPOSE Laser treatment of the avascular retina in FEVR is recommended if any vascular irregularity or neovascularization is present. However the long-term risk of retinal detachment in eyes with FEVR that received peripheral laser treatment has not been well characterized. We aimed to determine the rate of progression to retinal detachment in children with FEVR previously treated with peripheral laser.

METHODS We conducted a retrospective consecutive case series of 101 eyes of 75 pediatric patients with stage 1 or 2 FEVR at presentation who received peripheral laser photocoagulation between 1998 and 2014 at a single tertiary referral pediatric vitreoretinal practice. Pediatric patients with a clinical diagnosis of FEVR confirmed by fluorescein angiography, with no history of prematurity, and with at least 2 years of follow-up were included. The main outcome measure was the rate of progression to retinal detachment. Secondary outcome measures were the rate of progression in FEVR stage, the time to retinal detachment, and the number of laser treatments administered.

RESULTS The mean age at diagnosis in our case series was 4.2 years (range: 0.9 months – 18 years). There were 33 stage 1 eyes (32.7%) and 68 stage 2 eyes (67.3%). Peripheral laser treatment was administered an average of 3.1 months after diagnosis. Most eyes (52%) received more than 1 laser treatment, and the mean number of laser treatments per eye was 2.1 (range: 1 – 8). The mean length of follow-up was 6.8 years (range: 2.1 – 14.5 years). An

increase in stage from diagnosis, signifying worsening disease, was noted in 48.5% of the stage 1 eyes, and in 13.2% of the stage 2 eyes. The rate of retinal detachment was 12.9% (13 eyes of 12 patients) with a mean time from the last laser treatment to retinal detachment of 4.2 years (range: 1.3 – 14.1 years). No significant differences in the age at diagnosis, stage at diagnosis, number of lasers, or time between diagnosis and first laser were found between the patients that developed retinal detachments and those that did not.

CONCLUSION FEVR has a progressive long-term course associated with a risk of retinal detachment even in patients that received early intervention with laser treatment. Life-long screening for all patients with FEVR, including those previously treated with peripheral laser, is indicated.

HUMAN RESEARCH Yes: Approved by institutional review board

Laser Photocoagulation for Type 2 Retinopathy of Prematurity (ROP) or Less: When and Why?

- Edward H Wood, MD
- Kimberly A. Drenser, MD
- Prethy Rao, MD, MPH
- Marco Ji, MD
- Rocco V Sbrocca, BS
- Itsara Lertjirachai, MD
- Tran H Nguyen, D.O.
- Neil Shah

OBJECTIVE The objective of this study was to determine the utility of fluorescein angiography in guiding the decision for ablative laser therapy in type 2 retinopathy of prematurity (ROP) or less.

PURPOSE It is increasingly understood that residual peripheral avascular retina in patients with retinopathy of prematurity (ROP) may increase the risk of late disease recurrence, retinal tear(s), and retinal detachment. The objective of this study was to determine the utility of fluorescein angiography (FA) in guiding the decision for ablative laser therapy in type 2 ROP or less.

METHODS This was an observational retrospective case series performed at Associated Retinal Consultants, PC and William Beaumont Hospital in Royal Oak, MI. All infants born between 01/01/2006 and 12/31/2016 with Stage 2 or Stage 3 ROP that did not meet Type 1 ROP criteria who received ablative laser therapy at 41 weeks of postmenstrual age (PMA) or later were reviewed with approved IRB protocol. Pretreatment fundus photos (FP) as well as FA images were obtained using RetCam (Natus Medical Incorporated, Pleasanton, CA) using a wide-field 130-degree lens. FP and FA images were randomized and sent to 9 expert graders (retina specialists) to assess the severity and inter-grader variability in scoring the same eye at the same time point with different imaging modalities.

RESULTS A total of 10 babies (19 eyes, one babies received unilateral treatment) were enrolled in this study. 53 FAs and 27 fundus photos of these 19 eyes were selected to be interpreted by the 9 graders. The number of eyes deemed to be abnormal and warranted for treatment was higher with FA; whereas with fundus photography more people considered eyes as normal (Table 1). By comparing the overall gradings on the same eye, the 9 retina specialists rated FAs as more severe than fundus photos in 105 cases (61.4%), FAs as severe as fundus photos in 52 cases (30.4%) and fundus photos more severe than FAs in only 14 cases (8.2%) (Table 2). In 98 cases (32.0%) the grader labeled the fundus photo as 'normal and observe' whereas when shown the FA from the same eye, the same grader labeled the FA as 'abnormal and laser.'

CONCLUSION In children with Stage 2 or 3 ROP after 41 weeks PMA that did not meet type 1 ROP criteria , the number of eyes deemed to be abnormal and warranted for

treatment with 'late laser' was higher with FA compared to FP. Herein, we present data supporting the use of FA in evaluating patients with persistent avascular retina for possible 'late laser,' typically performed between 50-60 weeks PMA.

HUMAN RESEARCH Yes: Approved by institutional review board

Table 1

	Fundus Photography	Fluorescein Angiography
Normal Observe	35.95%	6.72%
Abnormal Observe	53.23%	54.75%
Abnormal Laser	10.82%	38.53%

The number of eyes deemed to be abnormal and warranted for treatment was higher with Fluorescein Angiography (FA) compared to Fundus Photography (FP)

Table 2

More severe on		
FA	105	61.4%
Photo	14	8.2%
Same	52	30.4%
Total	171	

Comparisons between graders regarding overall degree of severity within the same eye.

Long-term Complications of Laser Treated Infants With Retinopathy of Prematurity

- Audina M. Berrocal, MD
- Dhariana Acon , MD

OBJECTIVE What are the long-term complications of advanced treated ROP?

PURPOSE Purpose: To characterize the clinical features in young people referred with angle closure, and to determine the incidence of and risk factors for acquired anterior segment abnormality following advanced retinopathy of prematurity (ROP) treatment.

METHODS Methods: We performed two retrospective case-control series. First series – consecutive young angle closure patients without prior surgeries, with and without a history of ROP treatment; second series – consecutive patients who underwent ROP treatment, without and without acquired anterior segment abnormalities.

RESULTS Results: In the first series, 25 eyes of 14 consecutive angle closure patients were included. 19 eyes (11 patients, 78.6%) had a history of treated ROP, while 6 eyes (3 patients) belonged to full-term patients. The treated ROP eyes had significantly shallower anterior chambers (1.77 +/- 0.17 mm vs 2.72 +/- 0.18 mm, P < 0.0001) and thicker lenses (5.20 +/- 0.54 mm vs 3.98 +/- 0.20 mm, P = 0.0002) compared to the full-term controls. In the second series, 79 eyes of 40 patients were included, with median gestational age of 24.6 weeks. Acquired iridocorneal adhesion was noted in eight eyes (10.1%) at a mean age of 4.7 years and was associated with prior zone 1 and plus disease (P = 0.0013), a history of initial intravitreal bevacizumab treatment (IVB, P = 0.0477) and a history of requiring additional IVB after initial treatment (P = 0.0337).

CONCLUSION Conclusions: Many young angle closure patients may have a history of advanced ROP treated with laser, and may present with the triad of increased lens

thickness, microcornea and angle closure.

HUMAN RESEARCH Yes: Approved by institutional review board

Persistent Tunica Vasculosa Lentis as an Independent Risk Factor for Treatment in Retinopathy of Prematurity

- Nimesh A Patel, MD
- Kenneth C Fan, MD, MBA
- Hasenin Al-khersan, MD
- Nicolas A Yannuzzi, MD
- Dhariana Acon , MD
- Catherin I Negron, MBA
- Audina M. Berrocal, MD

OBJECTIVE Does the presence of persistent tunica vasculosa lentis found during retinopathy of prematurity (ROP) screening have an association with the severity of disease?

PURPOSE Tunica vasculosa lentis (TVL) is the vascular network that supplies the lens during fetal development and regresses by term. In pre-term neonates, TVL may persist and be found on clinical exam. The purpose of this study was to assess whether persistent TVL on neonatal screening exams may predict a higher rate of treatment in retinopathy of prematurity (ROP).

METHODS This was a retrospective 1:1 case-matched series form a single tertiary care center. All patients seen from 2000 to 2019 for ROP screening were included. Those noted to have TVL on exam were matched 1:1 based on birth weight and gestational age at birth with ROP patients without TVL. Data collected at each exam included age, weight, examination findings, and treatment status. Outcomes included rate of treatment with laser or intravitreal bevacizumab, plus disease, zone 1, and stage 2 or 3 ROP. Paired t-test was used to compare baseline demographics and characteristics between the two groups. McNemar's test was used to determine characteristics correlating with ROP severity and treatment.

RESULTS Overall, 196 patients were included in the study, of which 98 were patients with TVL (group 1) and 98 were case matched controls (group 2). In group 1, TVL was found in 80.6% of patients at the first visit at an average post-conception age of 32.3 weeks. Between group 1 and group 2, there was no statistical difference in average birth weight (722.6g and 721.6g, p=0.84) or gestational age at birth (25.8 vs 25.8 weeks, p=0.56). There was no statistical difference in incidence of ROP (80.6% to 73.47%, p=0.07). The average post-conception age at treatment was 36.8 weeks and 37.6 weeks, respectively. There was an increased rate of treatment in group 1 vs group 2 (31.6% vs 11.2%, p=0.0003, odds ratio of 1.88). Group 1 also had an increased rate of zone 1 disease (15.3 % vs 1.02% p= 0.002, odds ratio of 7.5). Lastly, group 1 had a higher absolute rate of plus disease, however, this was not statistically significant (27.55% vs 17.35%, P=0.09).

CONCLUSION The present study suggests that persistent tunica vasculosa lentis is a significant independent risk factor for retinopathy of prematurity requiring treatment.
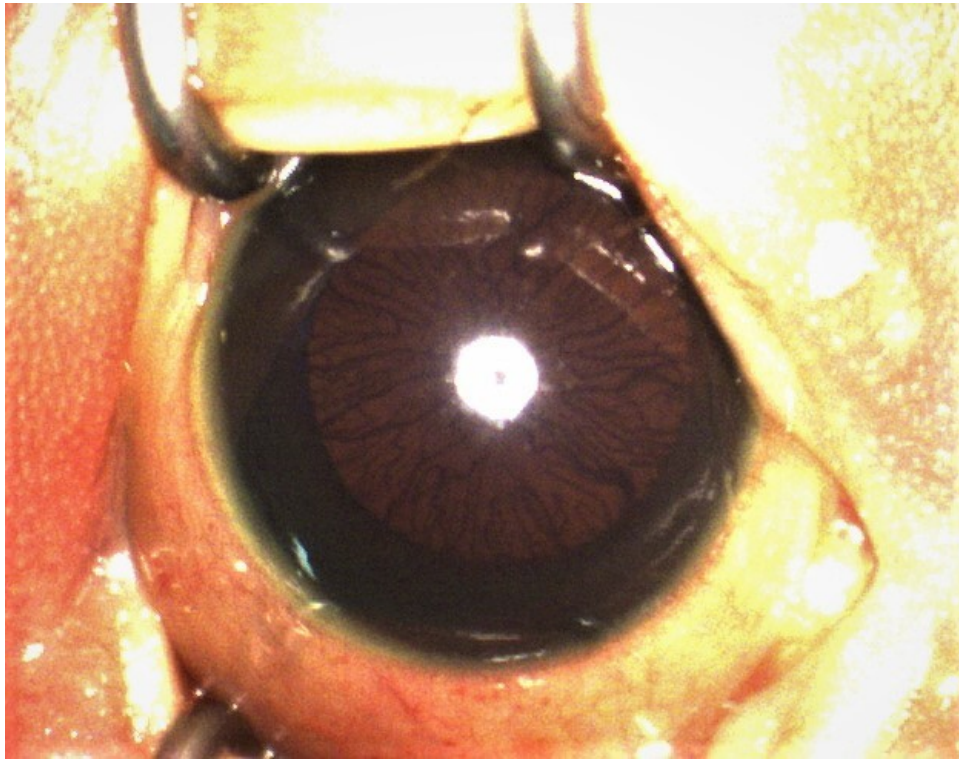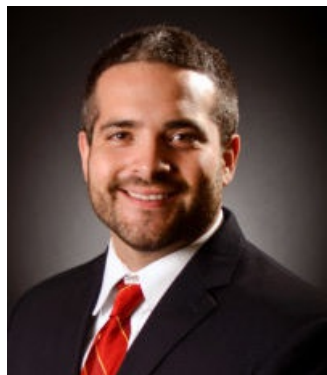
External photo with persistent tunica vasculosa lentis
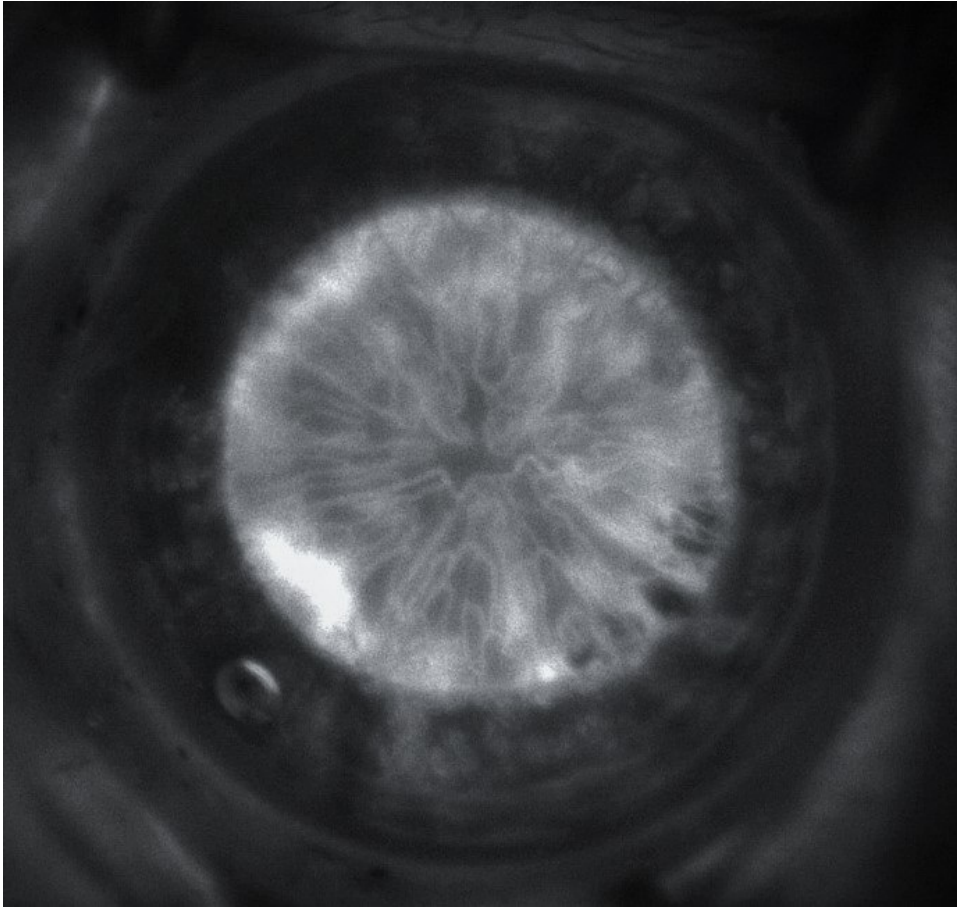
Fluorescein angiography with filling of tunica vasculosa lentis vessels and leakage

Efficacy of Aflibercept Treatment and Its Long-term Effect on Physiological Angiogenesis in a Mouse Model of Oxygen-Induced Retinopathy of Prematurity

- Andres Gonzalez, M.D.
- Swati Agarwal-Sinha, MD
- Sarina M Amin, MD
- Jade G Guevara, MD, MS
- Lorick Andersen, MD
- Wesley Smith
- Charlotte A Bolch, MS

OBJECTIVE To study the effective dosage of intravitreal aflibercept (IVA) on the vascular development in a mouse model of oxygen-induced retinopathy of prematurity (OIR).

PURPOSE Literature on the efficacy and long –term effects of aflibercept in the treatment of retinopathy of prematurity (ROP) is scarce despite promising outcomes in animal models. The study determines the effective dosage and its effects on physiologic angiogenesis.

METHODS 105 mouse eyes were assigned to room air control (n=21) or hyperoxic conditions with 75% O2 (n=84). The hyperoxic eyes were assigned to 1 of 3 groups: 0 ng (n=14), 100 ng (n=35), or 1000 ng (n=35) of intravitreal aflibercept administered on day 14. Eyes were enucleated 3 days (P17) or 12 days post-injection (P25). Retinas were stained with anti-collagen IV antibody to highlight vasculature. Areas of perfusion and non-perfusion were quantified using imageJ software. Ratios between mean nonperfused area of the hyperoxic groups and mean perfused area of the control groups were determined. Two-sample test for equality of ratios was done to determine statistical significance.

RESULTS On day P17, normal retinas displayed decreased nonperfusion when compared to hyperoxic controls, 100 ng, and 1000 ng group ($p<0.05$). There was no significant difference in the area of non-perfused retina between the hyperoxic control and both the 100 ng and 1000 ng aflibercept treated groups. On P25, the 100 ng ($p<0.05$) and 1000 ng (p=0.008) treatment group displayed less nonperfusion compared to hyperoxic controls. At

the 1000 ng dose, there was increased nonperfusion when compared to the 100ng dose (p=0.02). There was reduced nonperfusion by P25 compared to P17 for the 100ng group (ρ<0.05). There was no difference for the 1000 ng group.

CONCLUSION The study highlights that the non-perfused retina decreases effectively with intravitreal aflibercept treatment in the OIR model when followed post-injection until day P25 with dosage of 100ng. At higher dosage of 1000ng, there is an inhibition of the physiologic angiogenesis with a higher non-perfused retina.

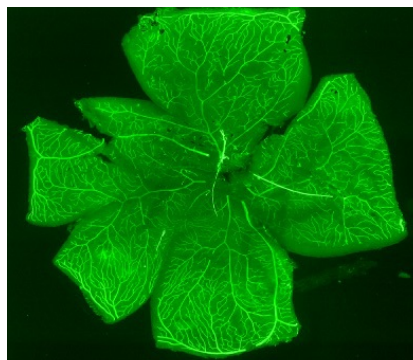**HUMAN RESEARCH** No: Study does not involve human research

Figure 1: Normal Control Group
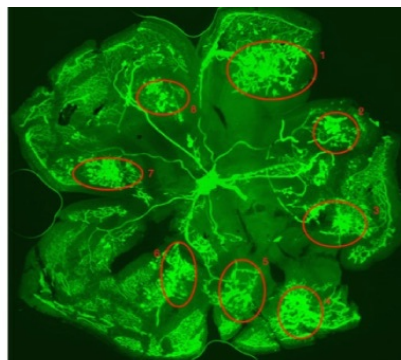Mice were housed under room air, and did not receive treatment with aflibercept

Figure 2: Hyperoxic Control Group
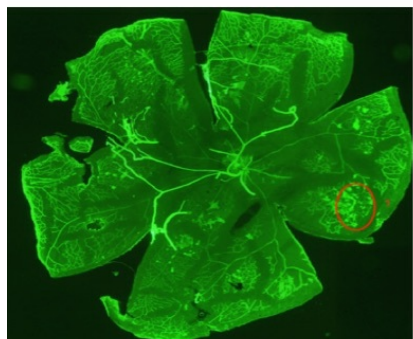Mice were housed in 75% oxygen but did not receive treatment with aflibercept

Figure 3: P17 1000 ng Group
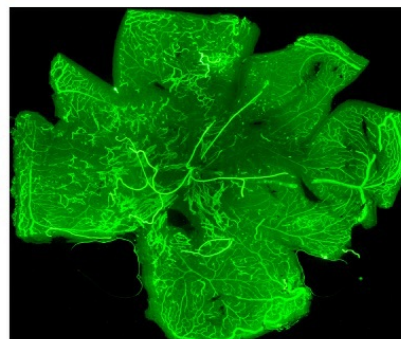Mice housed in 75% oxygen, received 1000 ng aflibercept, analyzed 3 days post injection

Figure 4: P25 1000 ng Group
Mice housed in 75% oxygen, received 1000 ng aflibercept, analyzed 12 days post injection

Retinopathy of Prematurity Screening Using a Novel Method of Advanced Image Processing and Deep Machine Learning

- Omar S. Punjabi, MD
- Ishaan Maitra
- Akash N
- Anand Vinekar, MD, FRCS
- Grace Prakalapakorn

OBJECTIVE To develop an automated computer algorithm using machine learning to diagnose eyes with early and advanced stages of Retinopathy of Prematurity (ROP) for the purpose of tele-medicine screening.

PURPOSE Retinopathy of prematurity (ROP) is a potentially blinding disease that affects millions of preterm infants annually, many of whom are in developing countries with limited resources. Prior efforts using deep machine learning to analyze image datasets have been limited. The purpose of this study was to develop and test a set of novel deep machine learning algorithms for tele-medicine screening.

METHODS Wide-field retinal images were prospectively obtained with RetCam (Natus, USA) and Neo (Forus Health, India) as part of the KID-ROP program in Bangalore, India. A masked pediatric retina specialist graded the images (reference standard). Multiple analyses were performed on the images using Python and ResUNet (deep learning framework) to train and test for retinal vessels and ROP stage. Region-Convolutional Neural Network (R-CNN) was used to detect stage of ROP. Component level retinal analysis was applied to detect the optic disc and macula. Homography was applied to stitch together multiple images and identify zones. Tortuosity and dilation metrics were used to detect plus disease.

RESULTS We included 1400 consecutive retinal images of 111 prematurely-born infants.

Of all images, 966 (69%) had some stage of ROP. As part of this study, we developed novel computer-aided approaches and verified them for traceability and clinical accuracy using a confusion matrix analysis. We used variations of ResUNet-CNN and Mask R-CNN to train and test for vessels and to detect the stage of ROP, and to generate quantitative metrics. Accuracy, sensitivity, specificity, and F1-scores for vessel detection were 98.5%, 92.9%, 98.6%, and 74%, respectively. The main metrics for ROP stage detection included global accuracy (98.3%), sensitivity (99.3%), precision (98.9%), and F1-score (99.1%). Image processing was used for detection of zone, plus and pre-plus disease, all yielding >95% accuracy. Multiple-image stitching (Homography) results for zone detection had 95.5% accuracy.

CONCLUSION Automated image processing and deep machine learning approaches have the potential to accurately detect zone, different stages of ROP and the presence of plus disease. These results demonstrated high sensitivity and specificity levels in detection of ROP; which has the potential to improve tele-medicine screening for this major cause of global blindness.

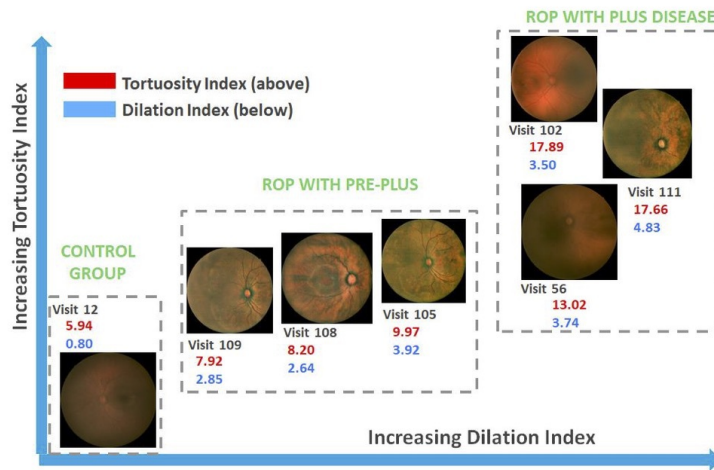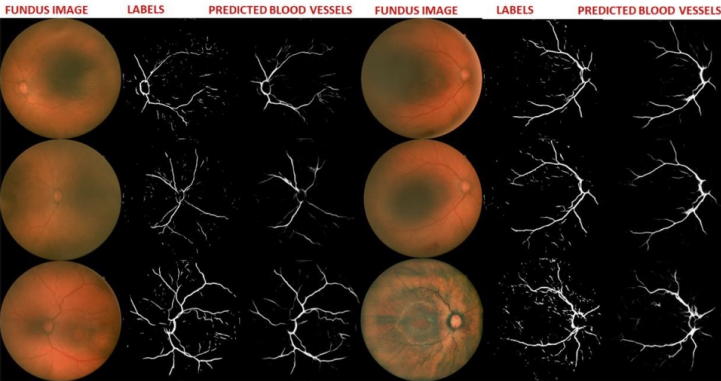**HUMAN RESEARCH** Yes: Exempt from approval

Figure 1. Pictorial Representation of Tortuosity and Dilation Index for Control Group, Pre-Plus ROP, and Plus ROP Disease

Figure 1: Pictorial Representation of Tortuosity and Dilation Index for Control Group, Pre-Plus ROP, and Plus ROP Disease

Model	AC	AUC	SE/Recall	SP	F1-Score
ResUNet	98.5%	96%	92.9%	98.6%	73.8%
R2-Unet	89.6%	85%	73%	65%	54%

Figure 1. ROP Blood Vessel Segmentation Results from Train/Test using ResUNet CNN

Figure 2: ROP Blood Vessel Segmentation Results from Train/Test using ResUNet CNN

Angiographic Review of Choroidal Involution in Eyes With Retinopathy of Prematurity Post Bevacizumab Treatment

- Swati Agarwal-Sinha, MD
- Yasmin Islam, MD
- Lorick Andersen, MD

OBJECTIVE To study the choroidal loss seen angiographically in infants treated with intravitreal bevacizumab (IVB) for retinopathy of prematurity (ROP).

PURPOSE Central choroidal thinning is reported in children with history of ROP using optical coherence tomography. ROP is a disease of the inner retina; however, there is evidence that choroidal vasculature is also affected leading to degeneration of outer retina and visual function. The purpose of the study is to review the extent of choroidal loss seen angiographically in infants treated with IVB.

METHODS Retrospectively reviewed the fluorescein angiography (FA) images of 62 eyes of 31 IVB monotherapy treated infants performed at an average 65 weeks PMA (9 months chronological age). The eyes with good quality early-mid and late phase imaging were included in the study. The the presence and extent of choroidal hypofluoresence involving the central and or peripheral retina were noted.

RESULTS The mean age and birth weight was 24.4 weeks PMA and 683 grams respectively. The infants received IVB monotherapy at an average of 33.5 weeks PMA. 24 of 62 angiography images were of good quality. The reviewed images showed the presence of choroidal hypofluorescence involving central loss and or peripheral lobular loss in early choroidal phase and mid and late phases on FA. 12 eyes demonstrated persistent choroidal loss on sequential FA's done as late past three years of age.

CONCLUSION The study demonstrates the sustained choroidal vascular loss

angiographically both central and peripheral in infants with ROP beyond three years of age. It highlights the role of choroidal involution in progressive outer retinal function with prematurity. The subsequent loss of retinal pigment epithelium and photoreceptors from choroidal loss can affect the visual outcomes in infants with ROP.

HUMAN RESEARCH Yes: Approved by institutional review board
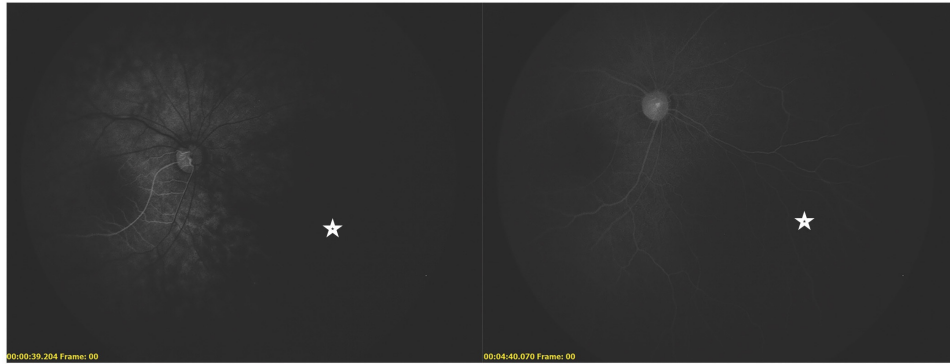
Fluorescein angiographic images of early and late phase of the right eye of an infant treated with bevacizumab for stage 3 ROP, showing large lobular peripheral loss of choroidal hypofluorescence (astrix) involving the nasal quadrant. The overlying retinal vasculature is seen in the late phase in the nasal quadrant.