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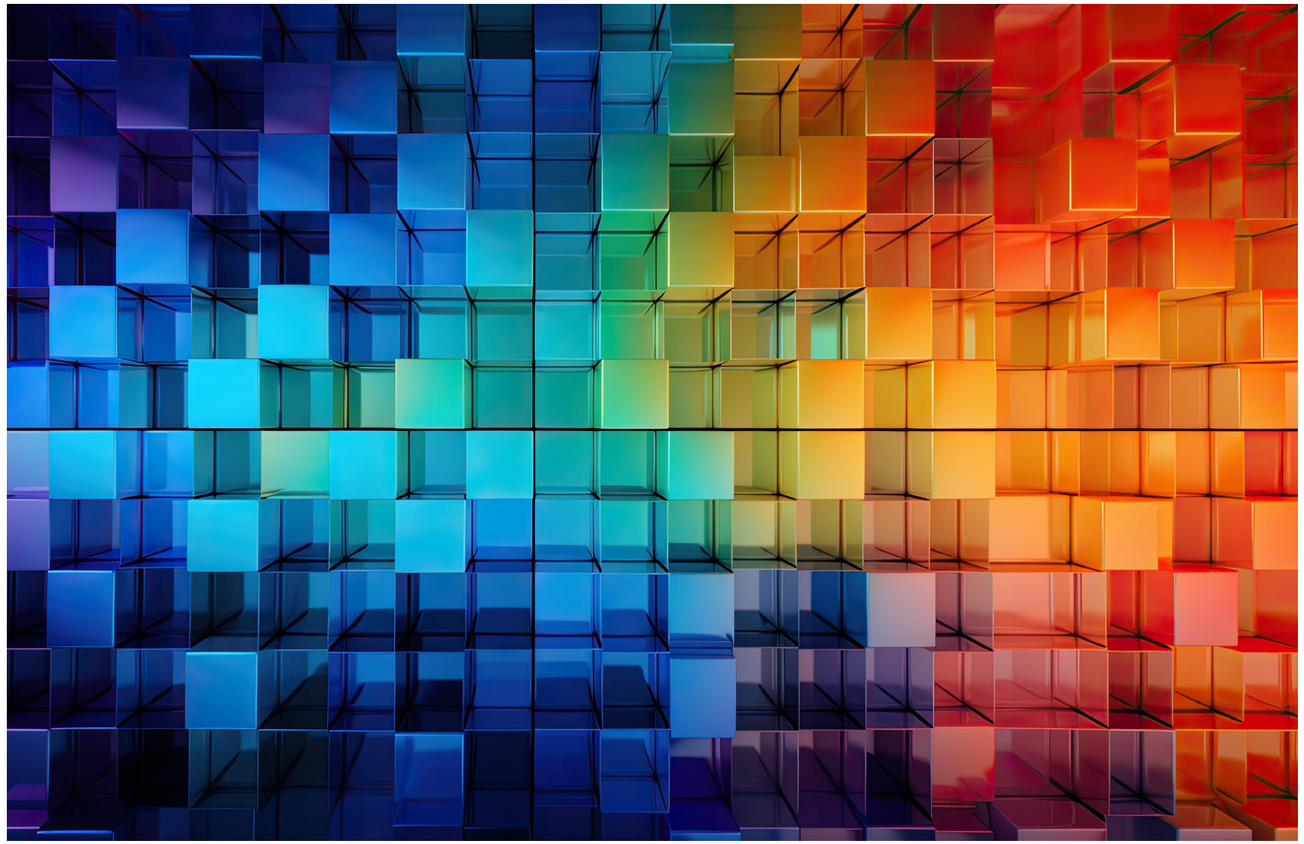

In vivo Imaging and Quantification of Retinal and Choroidal Vasculature in Cynomolgus Monkeys using Optical Coherence Tomography Angiography

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BACKGROUND & PURPOSE

Optical coherence tomography angiography (OCTA) is a novel non-invasive technique for visualizing the retinal and choroidal microvascular system. Non-human primates (NHPs) are widely used in preclinical ocular research due to their anatomical and genetic similarities shared with human eyes. The purpose of this study was to characterize the OCTA feature of NHPs, and establish standardized methods for evaluating retinal vascular complexes in NHP for preclinical ocular research.

The posterior ciliary arteries supply the multi-layered choroidal circulation in NHPs. The vessels of the choriocapillaris are fenestrated and allow passage of oxygen and nutrients to supply the retinal pigmented epithelium (RPE) and the photoreceptor layer constituting the outer one third of the retina. The central retinal artery (CRA) supplies the inner two thirds of the retina, which divided into four branches to supply different quadrants of the retina. The vessels distribute in the retinal nerve fiber layer, and generate four distinct diffuse capillary networks on histology (Fig.1).

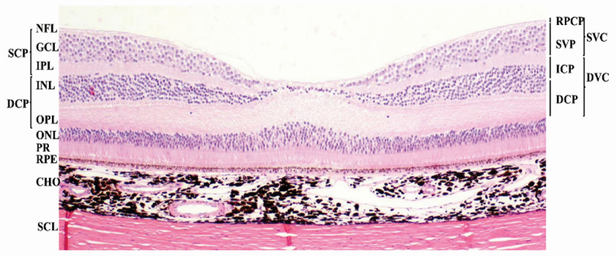

Fig.1 A retinal section near the macula, hematoxylin-eosin staining, 100×, showing retinal vascular plexuses (right labels) and anatomic layers from spectral domain optical coherence tomography (left labels). (NFL nerve fiber layer, GCL ganglion cell layer, IPL inner plexiform layer, INL inner nuclear layer, OPL outer plexiform layer plus Henle's fibre layer, ONL outer nuclear layer, PR photoreceptor layers, RPE retinal pigment epithelium, OCTA optical coherence tomography angiography, RPCP radial peripapillary capillary plexus, SVP superficial vascular plexus, ICP intermediate capillary plexus, DCP deep capillary plexus).

METHODS

The OCTA images (20°×20°,512 A-scans/B-scan and 512 B-scans/volume) were obtained from the macula (fovea-centered) and peripapillary (optic nerve head-centered) region using the OCTA module of Heidelberg Spectralis HRA+OCT. After segmentation into different layers, images were processed using Fiji/ImageJ software, and quantitative parameters of the retinal vasculature were evaluated. Nine eyes from six healthy adult cynomolgus monkeys and one eye from a laser-induced CNV (choroidal neovascularization) cynomolgus monkey were included in this study.

RESULTS

In cynomolgus monkeys, retinal and choroidal microvasculature can be visualized using the OCTA system. The superficial vascular complex (SVC, ILM to IPL [-]) and deep vascular complex (DVC, IPL [-] to OPL) can be clearly distinguished in the retinal layer. The superficial capillary plexus (SCP) appears as a fine capillary network with an intense signal. Deep capillary plexus (DCP) presents a dense capillary network developing all around the perifoveal area and participates in contouring the foveal avascular zone (FAZ). The corresponding B scan image displays hyperreflective dots stratified in two layers. In the choroidal layer, choriocapillaris exhibit numerous tiny hyper- or hypo-intense dots in a homogeneous pattern, while large choroidal vessels exhibit distinct hypo-intense linear structures in OCTA images. A standard method to quantitatively analyze OCTA images of the macular and peripapillary vessels was provided in this study (Fig.2).

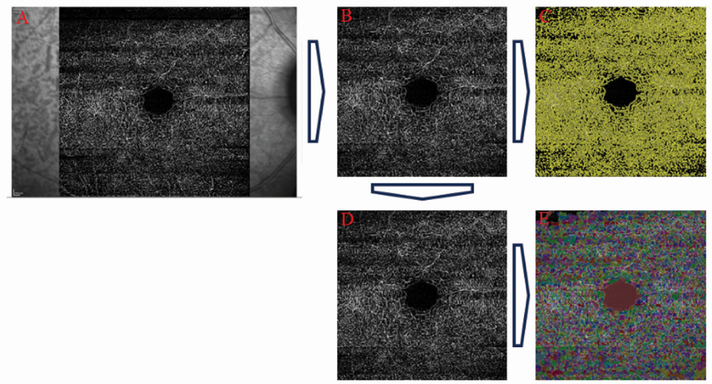

Fig.2 OCTA scan of the macular deep vascular complex (A). Post-process images to quantify vascular density (B and C) and shape parameters of foveal avascular zone (D and E). The original images exported from the Spectralis HRA+OCT (A) was cropped to the size of 800×800 pixels, with the color channel of RGB (B). Adjust the brightness value range in the module of color threshold to select areas with blood flow signals (C). Convert the color channel from RGB to 8-bit (D). Segment foveal avascular zone by the plugin of Morphological Segmentation (E).

At the level of SVC, mean vascular density (VD) of the macular (mSVC) and peripapillary (pSVC) vessels was 47.698 ± 2.636% and 48.176 ± 2.916%, respectively. At the level of DVC, mean VD was 34.14 ± 3.54% in the macular area. At the level of DVC, the mean area, circularity, aspect ratio, roundness, and solidity of the FAZ were (1.447 ± 0.381)^104 μm2, 0.67 ± 0.1, 1.16 ± 0.1, 0.868 ± 0.08, 0.895 ± 0.038, respectively (Fig.3).

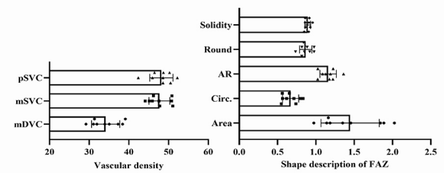

Fig.3 Normal values of vascular density (left) and shape parameters of FAZ (right) using a standard method to quantitatively analyze OCTA images of the macular and peripapillary vessels. Data are presented as mean ± SD. The solid points represent individual values.

Moreover, OCTA images of one eye from a laser-induced CNV cynomolgus monkey was processed using this method (Fig.4).

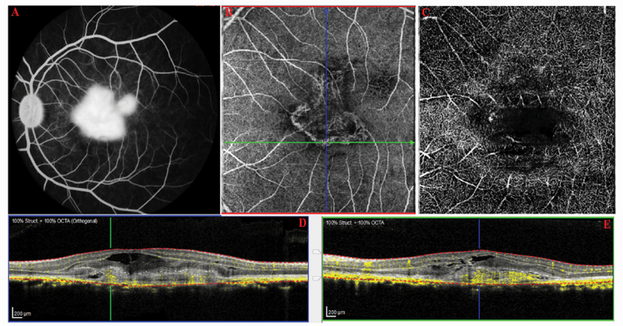

Fig.4 Fundus fluorescein angiography and OCTA images of one eye from a laser-induced CNV cynomolgus monkey. (A) Fluorescence leakage in the late phase indicated the progression of neovascularization. (B) Abnormal blood flow signals in all complexes of retina (confirmed to be presented in the avascular complex, from ONL to RPE). (C) Severely disrupted capillary network of DVC, with slightly decreased vascular density in DVC and SVC (29.963% and 43.039%, respectively) but severely disrupted capillary network in FAZ (the area, circularity, aspect ratio, roundness, and solidity were 4.702^104 μm2, 0.446, 1.375, 0.727, 0.837, respectively), which may be attributed to macular edema caused by neovascularization. (D and E) The b scan image from the correspond position of (B), and the yellow dots represents the blood flow signal.

CONCLUSION

OCTA enables non-invasive visualization of retinal and choroidal micro-vasculature in NHPs with high resolution, providing quantifiable *in vivo* measurements for longitudinal analysis, suggesting that OCTA is useful for investigating novel therapies in NHP animal models in preclinical ocular research.