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Comparison of Polypoidal Choroidal Vasculopathy Lesion Sizes Measured on Multicolor Imaging and Indocyanine Green Angiography

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Purpose: To evaluate the areas of lesion components of polypoidal choroidal vasculopathy (PCV) measured using multicolor imaging compared to indocyanine green angiography (ICGA).

Methods: In a prospective study of 50 consecutive treatment-naïve PCV patients, multicolor imaging and ICGA were performed. The images were independently graded by reading center-certified retinal specialists to confirm the diagnosis of PCV and identify lesion components. The areas of the respective lesion components were compared.

Results: The mean age of the participants was 67.8 years. PCV was diagnosed in 96% of eyes using multicolor imaging. The mean numbers of polypoidal lesions identified using ICGA and multicolor were 4.0 and 2.1, respectively ($P < 0.001$), with mean total polypoidal lesion areas of 0.32 mm^2 versus 0.30 mm^2 ($P = 0.727$). The area of the branching vascular network (BVN) on ICGA was 7.8 mm^2 compared to 5.7 mm^2 on multicolor imaging ($P = 0.289$). Patients with four or more polypoidal lesions on ICGA had larger differences in total lesion area between ICGA and multicolor imaging (4.07 vs. –0.70 mm^2, $p = 0.039$). Those with total lesion area $\geq$ 2.0 mm^2 on ICGA had larger differences in mean polypoidal lesion number compared to those with smaller areas (2.2 vs. 0.5; $P = 0.026$).

Conclusions: Multicolor imaging is a useful, noninvasive adjunct for detecting PCV lesion components, revealing lesion areas similar to but generally smaller than those seen on ICGA. This is important to consider when making treatment decisions with different imaging modalities

Translational Relevance: New features seen on multicolor imaging can aid in the diagnosis and treatment of PCV.

Introduction

Polypoidal choroidal vasculopathy (PCV) is characterized by the presence of vascular dilatations (which are known as polypoidal lesions or polyps), as well as abnormal vessels, referred to as branching vascular networks (BVNs), that supply these polypoidal lesions. PCV is considered by some to be a variant of neovascular age-related macular degeneration (AMD), and it is important because of its higher prevalence in some populations,[1–3] particularly among Asians. In addition, the visual prognosis differs from typical neovascular AMD.[4,5] Another important consideration is that the treatment of PCV is more variable, and the options include a combination of verteporfin photodynamic therapy (PDT) and anti-vascular endothelial growth factor (anti-VEGF) agents, or monotherapy with anti-VEGFs.[6–11] In contrast, typical AMD has been shown to be effectively treated using anti-VEGF agents alone.

The gold standard for PCV diagnosis is indocyanine green angiography (ICGA)[9,10,12–14]; however, this

investigation is not available in many regions for a variety of reasons, including cost, the invasive nature of angiography, and the possibility of allergy to the ICG dye. In the absence of ICGA, ophthalmologists have used other imaging modalities such as optical coherence tomography (OCT),[15,16] OCT angiography (OCTA),[17,18] and fluorescein angiography (FA)[19] to detect the presence of lesions that are suggestive of PCV. Features such as a double-layer sign and notched pigment epithelial detachment (PED) seen on OCT,[16,20] as well as occult choroidal neovascularization with a peripheral notch at the margin of a serous PED or a nodular hyperfluorescent lesion on FA, have been reported to be associated with PCV.[19] On OCTA, polypoidal lesions have been described as regions of hypoflow, often appearing as round structures, whereas a BVN was seen as a hyperflow lesion between the retinal pigment epithelium and Bruch's membrane.[21]

Recent advances in multicolor imaging have provided clinicians with a new imaging modality to help diagnose PCV.[22,23] Reflectance imaging from three separate wavelengths are obtained simultaneously and combined to form a composite pseudo-color image. The individual wavelength images enable visualization of different layers of the retina and retinal pigment epithelium. The infrared laser (815 nm) penetrates deeper into the retina, as longer wavelengths are minimally absorbed by blood and melanin. This makes infrared imaging ideal for visualization of the retinal pigment epithelium and choroid. The green wavelength (518 nm) visualizes structures located within the retina, including blood vessels, intraretinal hemorrhage, and exudates. In contrast, the blue wavelength (486 nm) is better for visualization of superficial structures, such as the vitreoretinal interface and retinal nerve fiber layer.[22,24] Based on this capability to image features in the different layers, it was postulated that it may be possible to image the polypoidal lesions and BVNs that arise from the choroidal vasculature.

Since multicolor imaging is faster, non-invasive, and less costly, it is likely to be performed more frequently during clinical assessment. In the absence of ICGA, some ophthalmologists may rely on adjunct imaging modalities such as multicolor imaging to assess patients and make treatment decisions.

Recent papers have described the features of PCV seen on multicolor imaging.[22,23] It was reported that multicolor imaging was superior to color fundus photography (CFP) for the detection of PCV lesions, as multicolor imaging offered higher sensitivity (86.4% vs. 59.1%) and specificity (73.9% vs. 52.2%).[23]

Although multicolor imaging has been shown to be useful qualitatively in detecting PCV, it remains unclear whether the sizes of the lesion components detected are comparable to those measured on ICGA. This would be of relevance in assessing the potential role of multicolor imaging in the assessment and planning of treatment zones for PCV, especially if PDT or focal laser photocoagulation is used. If there are clinically relevant differences in the size of lesion components measured using different imaging modalities, it is important for ophthalmologists to be aware of the extent of the differences and account for these in their clinical management decisions.

Hence, the objective of this study was to compare the size of the lesion components of PCV seen on multicolor imaging with those on ICGA. This will help to assess the potential role of multicolor imaging as an adjunct imaging modality and to determine the accuracy of multicolor imaging compared to ICGA in detecting the presence of the different features of PCV.

Methods

This was a prospective study of 50 treatment-naïve patients with PCV seen at the National Healthcare Group Eye Institute, Tan Tock Seng Hospital, Singapore. This study was approved by the institutional review board of the National Healthcare Group and conformed to the tenets of the Declaration of Helsinki. Written, informed consent was obtained from all patients prior to enrollment.

Multimodal imaging using standardized imaging protocols was performed on both eyes, as has been described in detail previously.[22,23] In brief, FA, ICGA, and multicolor imaging were performed using the Heidelberg Spectralis (Heidelberg Engineering, Heidelberg, Germany).

Grading of Images

All imaging modalities were graded independently by two masked graders from the Fundus Image Reading Center, National Healthcare Group Eye Institute, Singapore. PCV was diagnosed after clinical examination and review of the CFP, FA and ICGA, using standardized diagnostic criteria used in recent multicenter clinical trials.[8,11,13]

PCV was diagnosed by the presence of early focal, subretinal hyperfluorescence on ICGA, together with at least one of the following criteria: (1) nodular appearance of the area of hyperfluorescence on stereoscopic examination, (2) hypofluorescent halo around the nodule, (3) branching vascular network, (4) pulsation of the polypoidal lesion, (5) orange–red subretinal nodules corresponding to the hyperfluorescence on

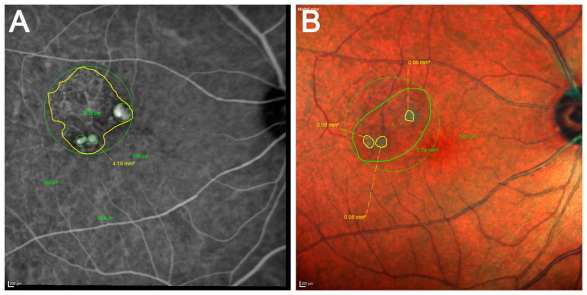

Figure 1. Comparison of imaging modalities for polypoidal choroidal vasculopathy. (**A**) ICGA illustrating the polypoidal lesions (*green outlines*), and total lesion area (*yellow outline*). (**B**) Multicolor imaging showing the polypoidal lesions (*yellow outlines*) and total lesion area (*green outline*).

ICGA, or (6) submacular hemorrhage of four disc areas or greater.[12,14,25]

After the diagnosis of PCV, polypoidal lesions and BVNs were separately identified on ICGA and multicolor images. The ICGA images and multicolor images were graded at separate times, independent of each other. For multicolor imaging, composite multicolor images and the infrared images were reviewed, as these have been shown to provide better detection of PCV lesions compared to the blue or green channels.[22,23] The characteristics of polypoidal lesions and BVNs have been described in earlier reports.[22,23] Using multicolor imaging, polypoidal lesions appeared as distinct green oval or round lesions on the composite multicolor image and as dark gray lesions on the infrared image. BVNs appeared as mottled dark green areas with outlines that were less distinct (Fig. 1).[22] The size and number of polypoidal lesions and BVN areas were measured for both the multicolor imaging and ICGA using proprietary measurement tools of software. These features were then compared and analyzed.

Statistical Analysis

Statistical analysis was performed using SPSS Statistics 23 (IBM, Armonk, NY). Paired *t*-tests were used to compare the areas of the polypoidal lesions and BVNs as seen on multicolor imaging and on ICGA.

Results

The mean age of the 50 patients was 67.8 years (range, 46–87; SD ±8.73), with 30 males (60.0%) and 20 females (40%). The majority were Chinese (45 patients, 90%); 8% were Malay and 2% were Indian. All patients had unilateral PCV with 56% affecting the left eye.

The diagnosis of PCV was confirmed in 50 eyes (100%) using ICGA. In contrast, PCV was diagnosed using multicolor imaging in 48 eyes. The sensitivity and specificity of multicolor imaging compared to ICGA were 73.9% and 86.4%, respectively.

Detection of Polypoidal Lesions

Polypoidal lesions were detected in all 50 eyes using ICGA, with a mean of 4.0 polypoidal lesions (range 1–22; SD ±3.5). In contrast, polypoidal lesions were detected using multicolor imaging in only 48 eyes (96%), whereas in two eyes no polypoidal lesions were detected. Using multicolor imaging, the mean number of polypoidal lesions was 2.1 (range, 0–7; SD ±1.3), with a mean difference of 1.9 compared to ICGA being statistically significant ($P < 0.001$). The number of polypoidal lesions detected using ICGA and multicolor imaging correlated well (Pearson correlation coefficient = 0.552; $P < 0.001$). The median difference in the number of polypoidal lesions when comparing ICGA and multicolor imaging was 1. In 68% of patients, the difference in number of polypoidal lesions between ICGA and multicolor was ≤2, and in 16 patients (32%) there were no differences in polypoidal lesion number.

The mean total polypoidal lesion areas correlated well using both ICGA and multicolor imaging (Pearson correlation coefficient = 0.68; $P < 0.01$) (Fig. 2). The polypoidal lesion area using ICGA was slightly larger (0.32 mm^2; range, 0–1.96; SD ±0.32) compared to 0.30 mm^2 (range, 0–1.05; SD ±0.26) using multicolor imaging ($P = 0.727$). The Bland–Altman plots are shown in Figure 2D.

Detection of BVNs

BVNs were detected in 94% of eyes using ICGA compared to 60% using multicolor imaging. The mean area of BVNs revealed by ICGA (7.8 mm^2; range, 0–62.2; SD ±12.6) was larger than that for multicolor imaging (5.7 mm^2; range, 0–23.4; SD ±4.6; $P = 0.289$). The BVN lesion areas correlated well using both ICGA and multicolor imaging (Pearson correlation coefficient = 0.635; $P < 0.001$) (Fig. 2B).

Comparison of Total Lesion Areas Between ICGA and Multicolor Imaging

The total lesion area seen on ICGA was 5.93 mm^2 (range, 0.07–64.11; SD ±10.11), which was

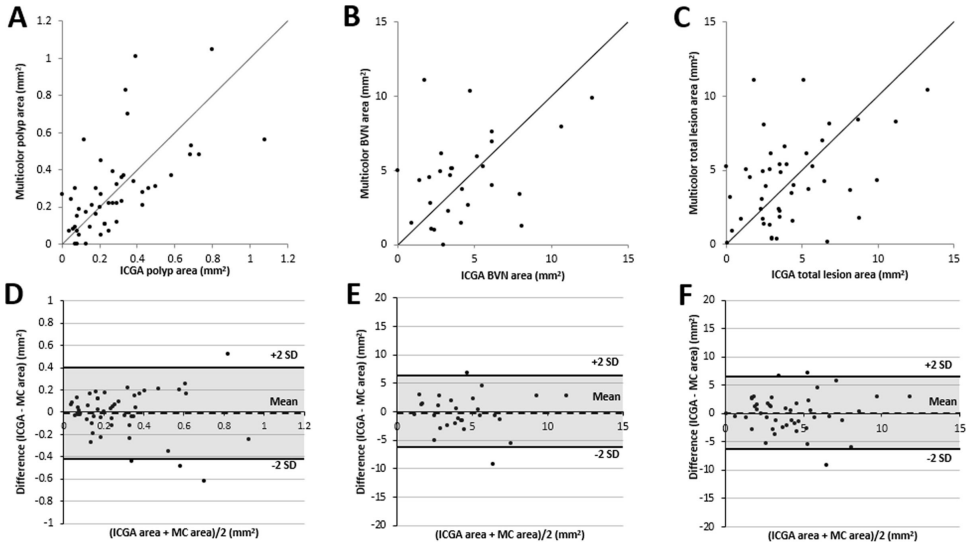

Figure 2. Scatterplots showing the correlation for mean total polypoidal lesion area (**A**), BVN area (**B**), and total lesion area (**C**) between ICGA and MC. Bland–Altman plots of the total polypoidal lesion area (**D**), BVN area (**E**), and total lesion area (**F**) for ICGA and MC. MC, multicolor imaging.

significantly larger than on multicolor imaging (mean, 4.53 mm^2; range, 0.07–23.57; SD ±4.21), although there was good correlation in the areas measured using both modalities (Pearson correlation coefficient = 0.629; $P < 0.01$) (Fig. 2C).

Effect of Lesion Numbers or Size on Comparability Between ICGA and Multicolor Imaging

Among patients with four or more polypoidal lesions on ICGA, there was a larger difference in the number of polypoidal lesions seen on ICGA compared with multicolor imaging than was found for patients with fewer than four polypoidal lesions (mean difference, 4.18 vs. 0.04 polyps; $P < 0.001$). Patients with four or more polypoidal lesions also showed more variability in the difference in the total lesion area between ICGA and multicolor imaging compared to those with fewer than four polypoidal lesions (4.07 vs. –0.70; $P = 0.039$).

Comparing Larger Lesions Versus Smaller Lesions on ICGA

Patients with total lesion areas ≥ 2.0 mm^2 on ICGA showed greater difference and variation in lesion areas between ICGA and multicolor imaging compared with smaller lesion areas < 2 mm2 (2.34 ± 8.75 vs. –2.38 ± 3.15; $P = 0.08$). Patients with larger total lesion areas also showed larger differences and variations in polypoidal lesion number (2.2 ± 3.34 vs. 0.5 ± 1.58; $P = 0.026$).

Discussion

In this study, we have evaluated the accuracy of multicolor imaging, which is a relatively new imaging modality compared to ICGA, and we found that polypoidal lesion size, BVN area, and total lesion area were comparable between multicolor imaging and ICGA.

There were, however, differences in lesion characteristics, which should be noted. Our study showed that the areas of polypoidal lesions, BVNs and total lesion area were larger using ICGA compared to multicolor imaging. This has an important impact on the treatment of PCV if multicolor imaging is used for clinical assessment or to make management decisions. When considering the use of PDT for treatment of PCV, it is essential to map out the treatment zone, which typically includes the entire lesion plus a margin of 500 µm on either side of the greatest linear dimension. If a smaller lesion area is used to plan the PDT treatment zone, it is possible that the treatment zone may exclude parts of the PCV lesion. The EVEREST II study showed that PDT resulted in complete polypoidal lesion regression in approximately 70% of PCV cases after the first PDT treatment.[8,11] If a polypoidal lesion is excluded from the treatment zone, this could be a source of further disease

activity. This consideration, however, is less of a concern if anti-VEGF monotherapy is used to manage PCV.

We have also shown that a larger lesion size on ICGA is associated with a larger difference in lesion size assessment and the number of polypoidal lesions detected. In eyes with four or more polypoidal lesions, there was a significantly larger difference in the number of polypoidal lesions detected on multicolor imaging as compared to ICGA. Similarly, larger PCV lesions also demonstrated more variability in lesion size and polypoidal lesion area between ICGA and multicolor imaging. We postulate that this could be due to fact that in larger lesions there is more variability in the size measured and more potential for differences between the two imaging modalities.

The strengths of this study include a standardized imaging protocol for all patients, as well as standardized diagnostic criteria for PCV. The diagnostic criteria for PCV were the same as those used in multicenter clinical trials for PCV.[6,8,13] In all patients, PCV was confirmed using ICGA, which remains the gold standard for diagnosis. In addition, grading of all images was performed by qualified graders in a central reading center with experience in PCV clinical trials. This is important, as studies have shown that many related retinal conditions may appear similar to PCV,[25] and it is necessary to differentiate these from actual PCV. The ICGA and multicolor images were graded independently of each other to avoid bias

This study is not without limitations. We did not evaluate the role of other investigations such as OCT, OCT angiography, and FA. However, the intention of this study was to compare the accuracy of multicolor imaging to ICGA only to assess how multicolor imaging may be helpful in detecting PCV. Incorporating other imaging modalities would have made assessment of the usefulness of multicolor imaging uncertain. Furthermore, these other investigations are also limited in their diagnosis of PCV. For example, only 74% to 78.6% of polyps were detected on OCTA.[18,26,27] In addition, the features seen on FA are not specific in the diagnosis of PCV, as previous studies have reported that FA did not increase the accuracy of PCV diagnosis when combined with CFP and OCT. In addition, because all patients in this cohort had PCV, the detection rate may be higher compared to a cohort including other retinal diseases.

In summary, we have investigated the role of a new imaging modality and shown that multicolor imaging is comparable to ICGA in detecting PCV lesions. Multicolor imaging is a useful adjunctive investigation for detecting and monitoring patients with PCV. However, there are differences in the lesion sizes determined by each modality, and it is important for ophthalmologists to take these into account, especially when making treatment decisions.

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