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Clinical Application of Multicolor Imaging Technology

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Key Words
Imaging · Scanning laser ophthalmoscopy · Retina · Multicolor

Abstract
Purpose: To assess the clinical application of multicolor imaging by confocal scanning laser ophthalmoscopy (cSLO). ***Methods:*** Retinal imaging was performed in 76 patients including cSLO multicolor imaging (SPECTRALIS SD-OCT, Heidelberg Engineering, Heidelberg, Germany) and color fundus photography (CFP). ***Results:*** The use of confocal optics, reduced light scatter and automated eye tracking enable high-resolution cSLO reflectance images. Compared to CFP, the appearance of pigment alterations and hemorrhages were some of the differences observed. Various artifacts including those derived from optical media alterations need to be considered when interpreting images. Specific pathological findings including epiretinal membranes, fibrovascular proliferations, and reticular pseudodrusen may be better visualized on multicolor images. ***Conclusions:*** When using multicolor imaging, ophthalmologists need to be mindful about differences in the appearance of pathological changes and artifacts. Multicolor imaging may offer information over and above conventional CFP; it can be performed through undilated pupils and is less affected by media opacities.

Introduction

Advances in retinal imaging have provided insights into many ocular pathologies, influenced the management of retinal diseases and have allowed accurate, reproducible documentation of retinal abnormalities [1, 2]. Digital imaging for the use in color fundus photos, fundus angiography, three-dimensional ultrasound and optical coherence tomography has revolutionized modern ophthalmic practices [2]. Digital imaging has the advantage over previous film-based photography because it can produce instant, reproducible, high-quality images that can be transmitted to clinicians, to be used for the immediate diagnosis and management of eye conditions [2]. Direct comparisons that can be made against images taken at previous visits, three-dimensional analysis and comparisons against normal populations are some of the applications of digital retinal imaging [3].

Color fundus photography (CFP) imaging was first described in the late 1800s, but it was only in the 1950s that CFP imaging became available for widespread clinical use due to the advances in electronic flash photography and commercial availability of fundus cameras [1]. Numerous enhancements such as digital imaging, nonmydriatic functions, stereoscopic image acquisition and wide-field technology have expanded this type of imaging over the years [3–7]. Digital CFP allows the accurate and

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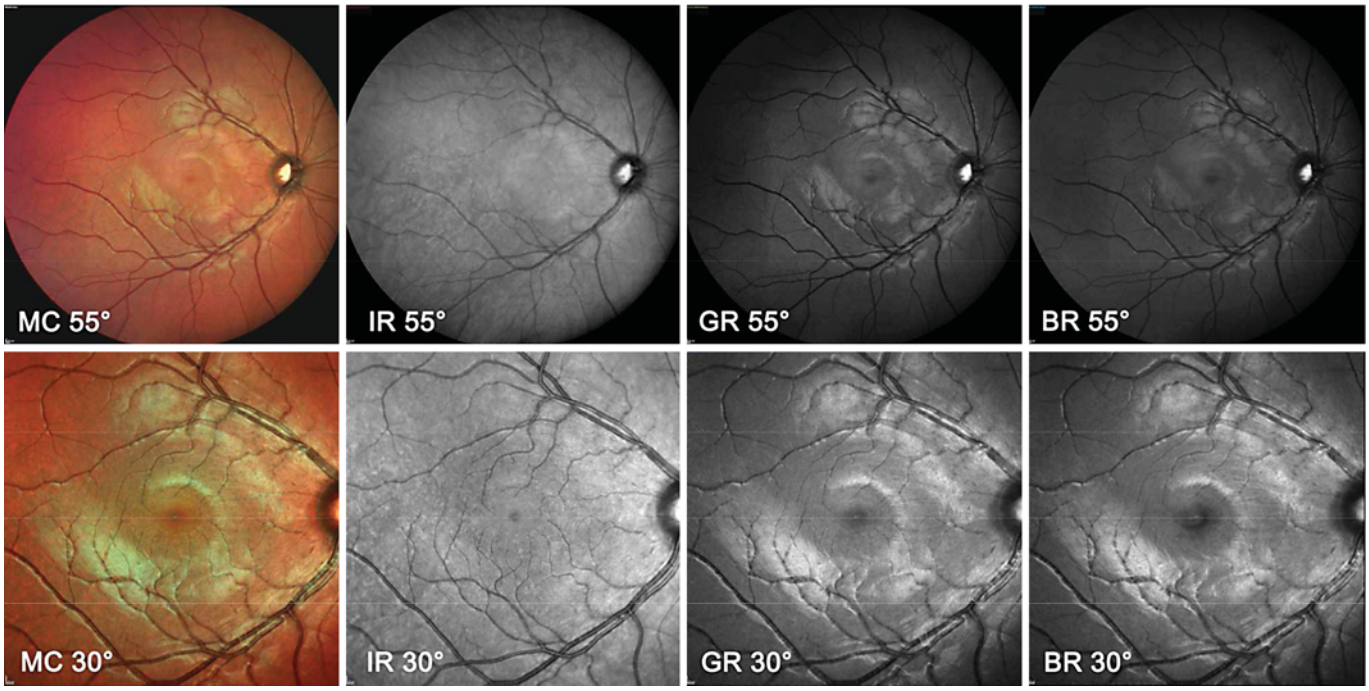

Fig. 1. 55° and 30° multicolor image (MC) of a healthy eye. MC images are composed of three separate images taken with IR, GR and BR wavelengths of light.

reproducible documentation of retinal structures and pathology. The appearance on CFP closely resembles findings on clinical examination. However, the limitations of CFP include: (1) media opacities, which influence the quality of images, (2) limited resolution and contrast, and (3) interpatient variability of the fundus pigmentation and illumination which make automated or semiautomated analysis difficult [8].

The scanning laser ophthalmoscope (SLO), first introduced in 1980, was described as the 'flying spot TV ophthalmoscope' [9]. A single point of laser light at a specified wavelength was scanned across the retina in a series of parallel lines and enabled an alternative method of capturing fundus images [1, 10]. Compared to standard fundus cameras, images produced by the SLO have a higher resolution due to reduced light scatter. In addition, confocal SLO (cSLO) systems allow image acquisition at different planes and higher contrast due to suppression of scatter light. Furthermore, images can be acquired through a nonmydriatic pupil.

The so-called 'multicolor' mode developed for the SPECTRALIS Optical Coherence Tomography SD-OCT (SPECTRALIS SD-OCT, Heidelberg Engineering, Heidelberg, Germany) uses the cSLO to capture three simultaneous reflectance images using three monochromatic laser sources: (1) blue reflectance (BR; 488 nm), (2) green reflectance (GR; 515 nm) and (3) infrared reflectance (IR; 820 nm). These different wavelengths of light penetrate the retinal surfaces at different depths to demonstrate details at the various layers of the retina (fig. 1). The BR particularly enables details of the inner retina and the vitreoretinal interface such as epiretinal membranes, retinal nerve fiber layer thinning and macular pigment changes. GR images specifically allow deeper details such as retinal blood vessels and intraretinal lipid exudation to be seen. IR predominantly visualizes structures at the level of the outer retina and choroid including drusen and retinal pigmentary epithelium alterations [11, 12].

Herein, we describe the clinical use of multicolor imaging in a variety of retinal and macular diseases. In particular, multicolor imaging was compared with conventional CFP addressing differences in appearance. Other multimodal forms of imaging available were correlated to features seen on these multicolor images where applicable. Multicolor images were captured at both 30° and 55°.

Methods

Patients at the Department of Ophthalmology, University of Bonn, Germany, were selected between November 2014 and June 2015.

CFP was performed using a standard fundus camera (Visucam 500, Carl Zeiss Meditec AG, Jena, Germany) after pupil dilation with 1.0% tropicamide eyedrops. The field of view was set at 30–40°, centered on the macula, and additional images were taken in cases where the lesion was not well seen at the posterior pole. High-speed combined and simultaneous cSLO + SD-OCT imaging was performed with a SPECTRALIS OCT including MultiColor and the 70-kHz OCT prototype module device using the multicolor mode on an area of the central 30° and 55° (Heidelberg Engineering). Image acquisition included near-IR [λ = 820 nm, automatic real time (ART) at least 15 frames], GR (λ = 518 nm, ART at least 15 frames) and BR (λ = 488 nm, ART at least 15 frames) (fig. 1a, top image). In some cases, fundus autofluorescence (FAF; exc λ = 488 nm, em λ = 500–800 nm, at least 15 frames) images and combined cSLO + SD-OCT scans through the fovea with a volume scan (λ = 870 nm, 20° × 15°, ART at least four frames, 19 B-scans, distance 240 μm) were taken.

If applicable, fluorescein and indocyanine green angiography was performed with a field of view of 30° and 55° using SPECTRALIS (Heidelberg Engineering).

The study followed the tenets of the Declaration of Helsinki. Informed consent was obtained from those patients examined with the prototype module device after explanation of the nature and possible consequences of the study.

Clinical Applications of Multicolor Imaging

Images were taken in 150 eyes of 76 patients who presented with a variety of retinal pathology. Figure 1 shows a healthy eye imaged by 55° and 30° multicolor that is composed of three reflectance images (BR, GR and IR). A hyperreflective spot may be seen in multicolor images. This artifact has previously been reported in 25% of cases of all multicolor images and has been associated with posterior chamber intraocular lens [11]. The SPECTRALIS Widefield Imaging module now uses a software algorithm to remove the bright central artifact normally seen on reflectance images acquired with the acquisition modes IR, BR and multicolor. The software algorithm automatically identifies the central artifact. During eye motion, structural information previously hidden by the artifact becomes visible. The ART mean function is used to superimpose a series of images while filling in structural information at the initial location of the artifact.

The main difference observed between the multicolor image and the CFP was the improved definition of the optic disc, retinal vessels as well as larger choroidal vessels. The contrast of the optic disc cup was more distinct compared to the CFP, which may have potential for future applications in glaucoma.

Age-Related Macular Degeneration

Improved imaging techniques in the context of age-related macular degeneration (AMD) have allowed earlier detection of the disease and treatment as well as monitoring during anti-VEGF therapy. In particular, the detection of retinal hemorrhages is an important sign of neovascular AMD (fig. 2b, c) in high-risk patients with early or intermediate AMD (fig. 2a). Reticular pseudodrusen (fig. 2b), a feature that is associated with all stages of AMD that may represent a high-risk phenotypic feature for progression, can also be imaged more distinctly on multicolor imaging (fig. 2b, far right) [13–15]. On multicolor imaging, reticular pseudodrusen appear as a central hyperreflective lesion with a hyporeflective border. A recent study reported superior rates of reticular pseudodrusen detection on multicolor imaging when compared to CFP [12]. The boundaries of geographic atrophy (GA) are more clearly demarcated on the multicolor images than in the CFP (fig. 2d). A recent study has shown that there was a higher intra- and intergrader agreement for the measurement of the area with GA using both multicolor and FAF imaging compared to CFP [8]. However, to determine foveal sparing, SD-OCT was superior compared to the other imaging modalities [8].

Polypoidal choroidal vasculopathy (PCV) in a 71-year-old woman was imaged with multimodal imaging (fig. 3). The 55° image showed signs of the 'ghost' maculopathy artifact, but this was less when the 30° image was taken.

'Ghost maculopathy' was a term used in a previous study to describe an artifact that appears as a hyperreflective spot on near-IR and multicolor imaging, near or adjacent to the macula, which did not correspond to any apparent lesion on color and red-free fundus photography [11].

Details of the lesion such as hard exudation and surrounding subretinal fluid were seen in greater detail on the multicolor image when compared to the CFP (fig. 3). The PCV lesion on CFP appeared as an orange-red nodule (black arrow). In contrast, the PCV lesion was darker red with a greenish tinge on multicolor imaging. This is likely due to the PCV lesion being located deep under the retinal pigment epithelium in contrast to more superficial subretinal bleeding as imaged in figure 2b, which appeared red. Hence, the multicolor imaging

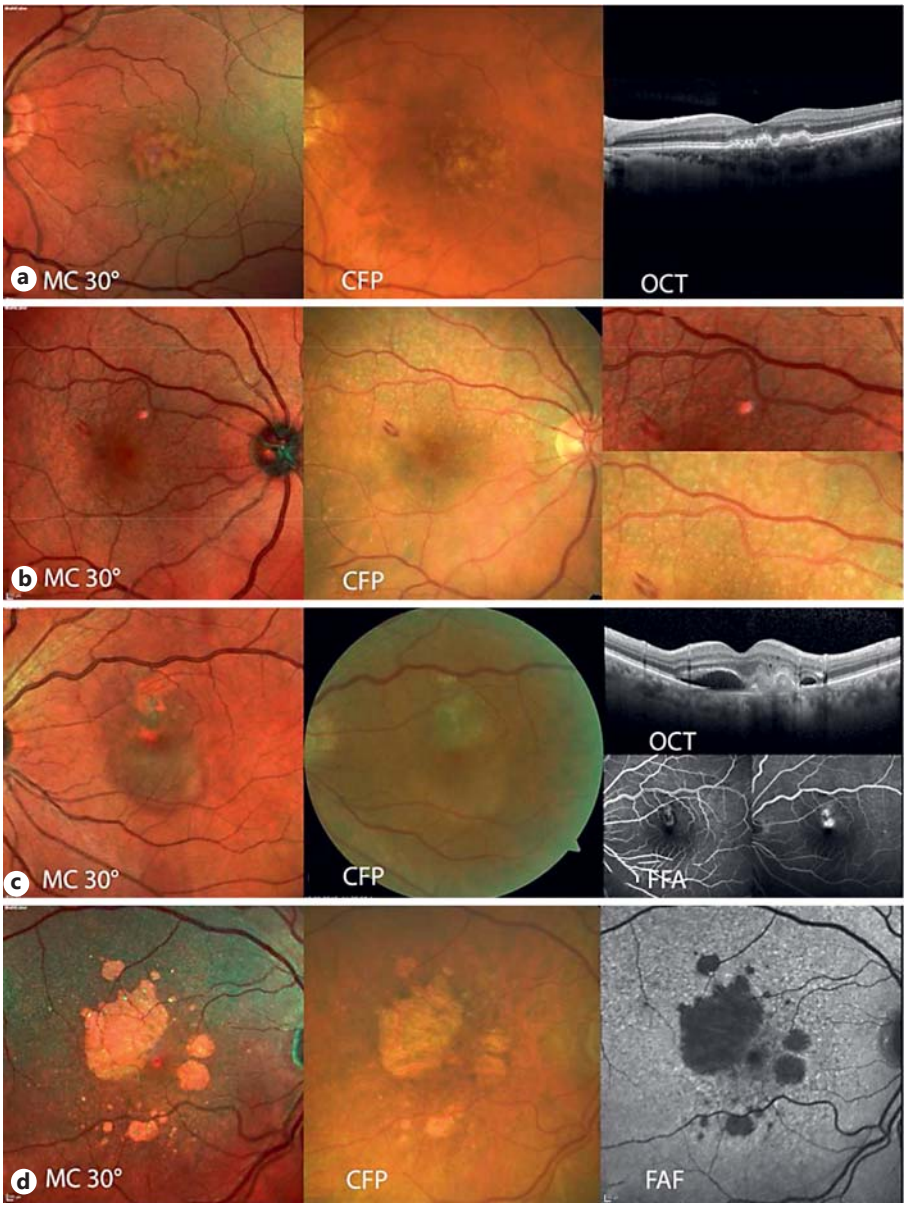

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Fig. 2. AMD. **a** Intermediate AMD with drusen. **b** Reticular pseudodrusen with an area of hemorrhage (magnified view for comparison, far right). **c** CNV and surrounding pigment epithelial detachment compared with multimodal imaging including fundus fluorescein angiography (FFA) showing early hyperfluorescence with late leakage. **d** Multifocal GA with foveal sparing. MC = Multicolor; FFA = fundus fluorescein angiography.

may have the added advantage of being able to distinguish hemorrhages in different layers of the retina when compared to CFP, although this finding will need to be verified in larger studies. Using other modalities of imaging available on the combined cSLO and SD-OCT system, a faint border seen on the multicolor image was correlated with the boundary of fluid seen on SD-OCT (fig. 3). The more distinct border seen on the multicolor image shows a correlation with the loss of the photoreceptor layer seen on SD-OCT (fig. 3, yellow arrows). None of these features could be clearly distinguished in CFP. Also, in contrast to the area of leakage seen on fundus fluorescein angiography and indocyanine green angiography, the abnormal area imaged on both multicolor imaging and FAF was larger. This finding has been reported in previous studies suggesting that the structural retinal damage seen on FAF and IR imaging may extend beyond the boundaries of the leakage in the PCV lesion [16, 17]. Further studies should be conducted to confirm if this finding is also consistent in multicolor imaging.

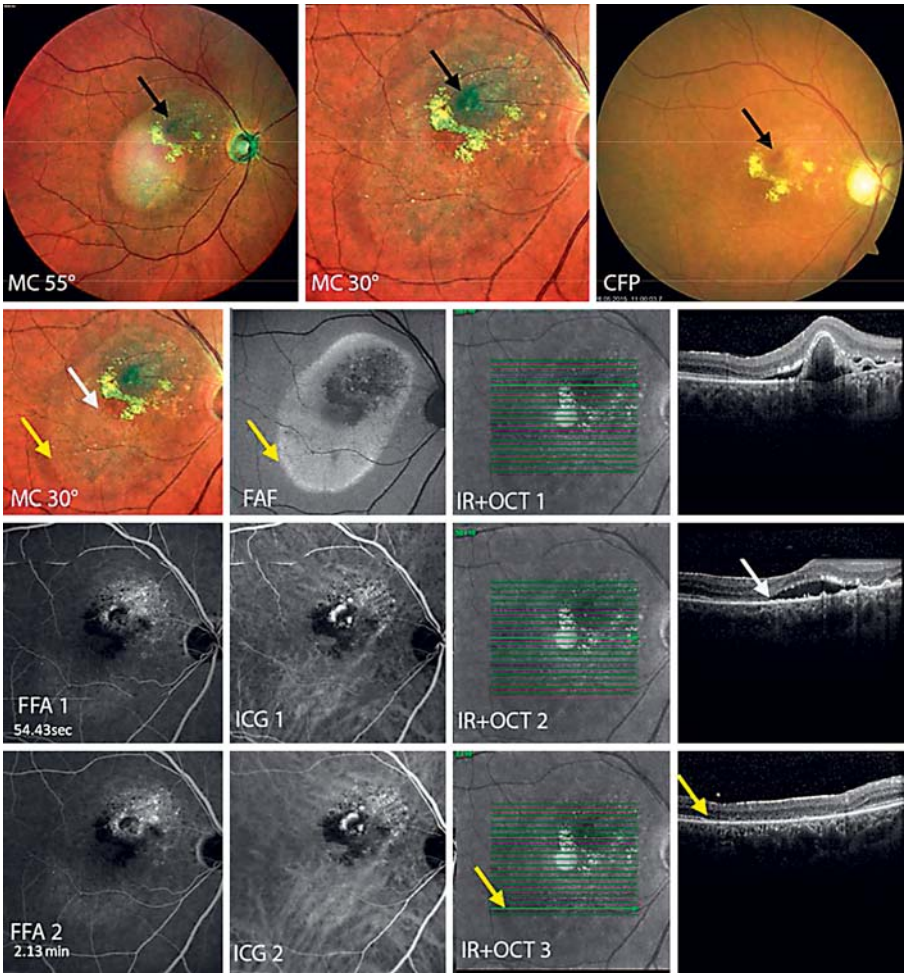

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Fig. 3. PCV. The white arrow indicates the boundary of subretinal fluid; the yellow arrow indicates the loss of the photoreceptor layers in different imaging modalities (colors refer to the online version only). Details of the lesion such as hard exudation and surrounding subretinal fluid were seen in greater detail on the multicolor image when compared to the CFP. The PCV lesion on CFP appeared as an orange-red nodule (black arrow). MC = Multicolor; FFA = fundus fluorescein angiography; ICG = indocyanine green angiography.

Diabetic Eye Disease

Screening and early detection of diabetic eye disease to prevent vision loss is beneficial to both the individual patient and their community [18]. The standard for the detection and classification of diabetic retinopathy is the 7 standard field stereoscopic color fundus photos proposed by the Early Treatment of Diabetic Retinopathy Study (ETDRS) group [19]. This technique was unsuitable for widespread screening as it was labor intensive and not cost-effective. Other studies have tested and modified screening protocols using nonmydriatic imaging, single-field imaging and automated detection systems with variable results [3, 4, 20–22]. A recent study using wide-field imaging and OCT showed improvements in the detection rates of higher grades of diabetic retinopathy compared to clinical examination [23]. From the ophthalmologist perspective, an advantage of the multicolor imaging on the combined cSLO + SD-OCT platform is that a single device can perform all imaging modalities required. Patients can benefit from a one-stop service, and this may mean time saved and improved cost-effectiveness for the practice. In addition, cSLO imaging can also be performed in an undilated pupil [24]. Further studies will need to assess the quality of the 55° multicolor images taken in the mydriatic versus nonmydriatic states. Multicolor imaging in combination with SD-OCT has the potential to improve detection rates of diabetic eye screening programs, and further studies should be performed to evaluate this further.

Figure 4a shows an example of a patient with a residual fibrotic tractional epiretinal membrane, and new vessels were seen at the disc. These features were imaged more clearly on the multicolor image than the CFP. Diabetic macular edema (DME) as a complication of diabetic retinopathy is difficult to detect on CFP during screening in the absence of hard exudation [25, 26]. Stereo-

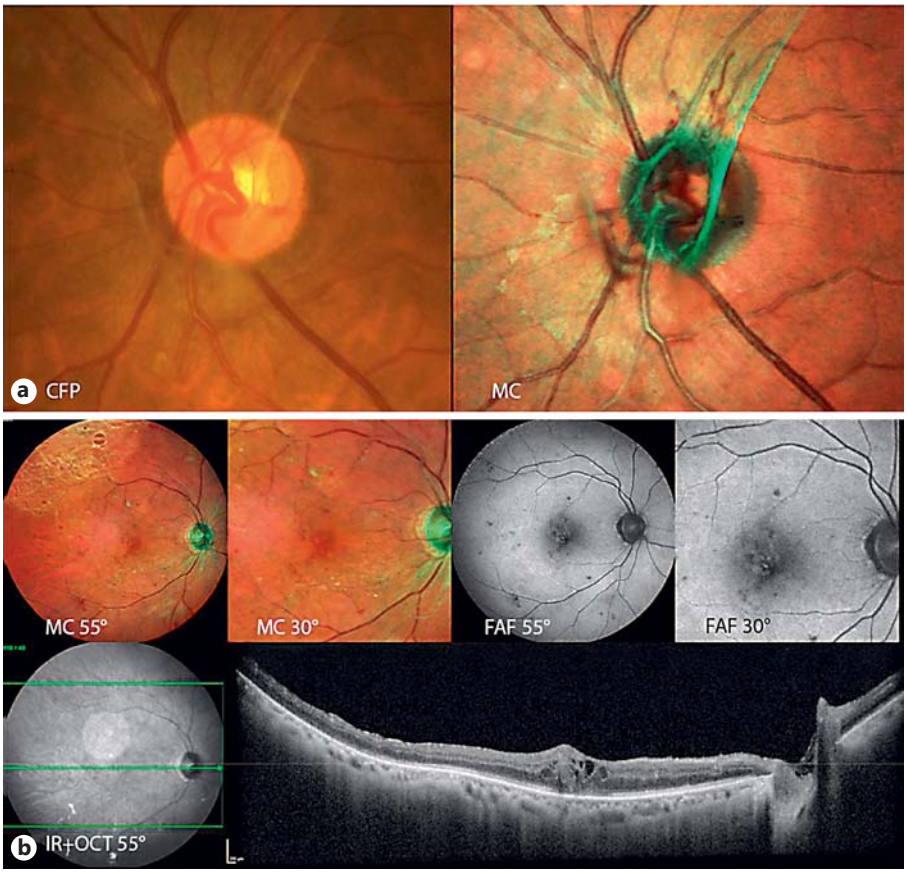

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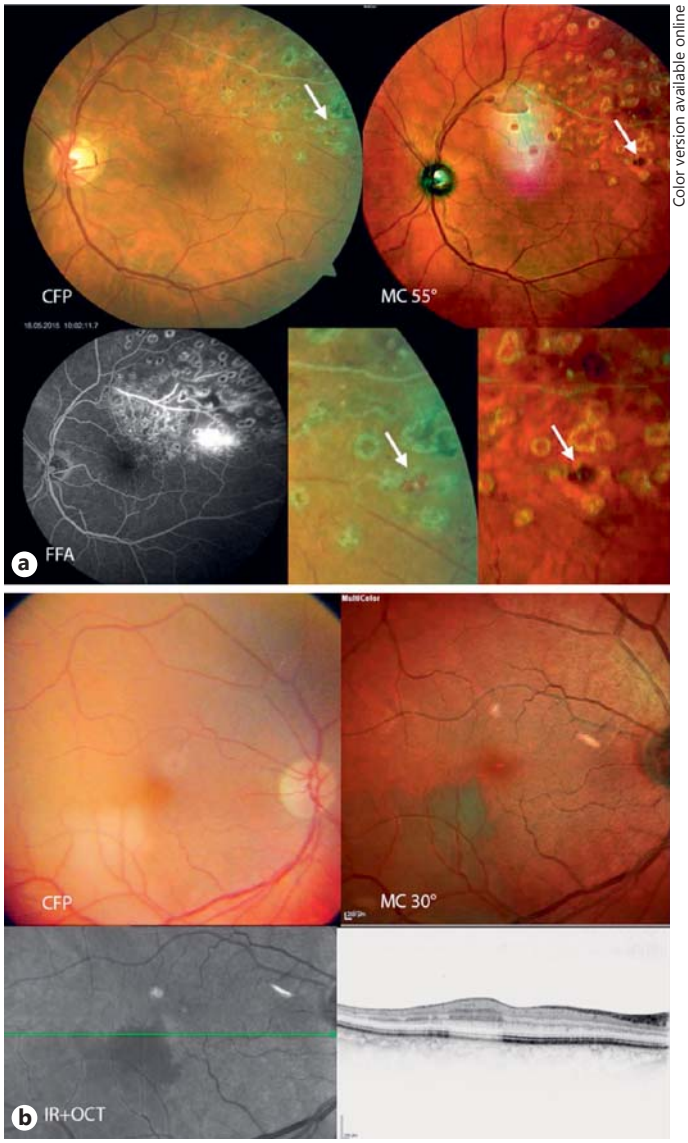
Fig. 4. Proliferative diabetic retinopathy with fibrovascular proliferation at the optic disc (**a**) and diabetic macula edema with severe nonproliferative diabetic retinopathy (**b**) shown on multimodal imaging. MC = Multicolor.

scopic photographs improve the detection of retinal thickening; however, they cannot be performed in an undilated pupil. Multicolor imaging with superior resolution may be an alternative to improve the detection rates of DME. Multicolor imaging of DME in our patient showed the presence of intraretinal cysts (fig. 4b). FAF and OCT imaging confirms the presence of the intraretinal cystic changes seen on the multicolor image. The 55° multicolor image enables documentation of the status of the diabetic retinopathy, and the 30° image allows closer details to be seen such as a sclerosed vessel along the inferior arcade. However, potential challenges for detecting DME on multicolor images could include 'ghost' maculopathy artifacts and poor optical media.

Retinal Vascular Occlusions

Retinal vascular occlusions can cause visual impairment when complicated by macular edema and neovascularization [27, 28]. Close monitoring of this disease and the detection of complications early allows treatment to prevent vision loss. Fundus imaging allows the accurate documentation of disease progression and the response to treatment. Figure 5a shows an ischemic branch retinal vein occlusion after treatment with sectoral retinal laser photocoagulation. The appearance of the neovascularization is compared in three imaging modalities (white arrows). In this case, the quality of the CFP was superior to the multicolor image demonstrating features such as collateral and sclerosed vessels. The artifact on the multicolor image obscured the collateral vessels. However, the area of neovascularization was seen clearly in both modalities.

The appearance of a branch retinal artery occlusion is seen on CFP and multicolor imaging in figure 5b. The boundary of the intraretinal thickening is seen on both the CFP and the multicolor image. The appearance on the multicolor image had a greenish tinge versus the pale area seen on the CFP. When compared to clinical ophthalmoscopic examination, the CFP shows the most similarities to clinical examination. However, the clinician may need to appreciate that the exact color may differ from what is observed clinically on multicolor imaging.



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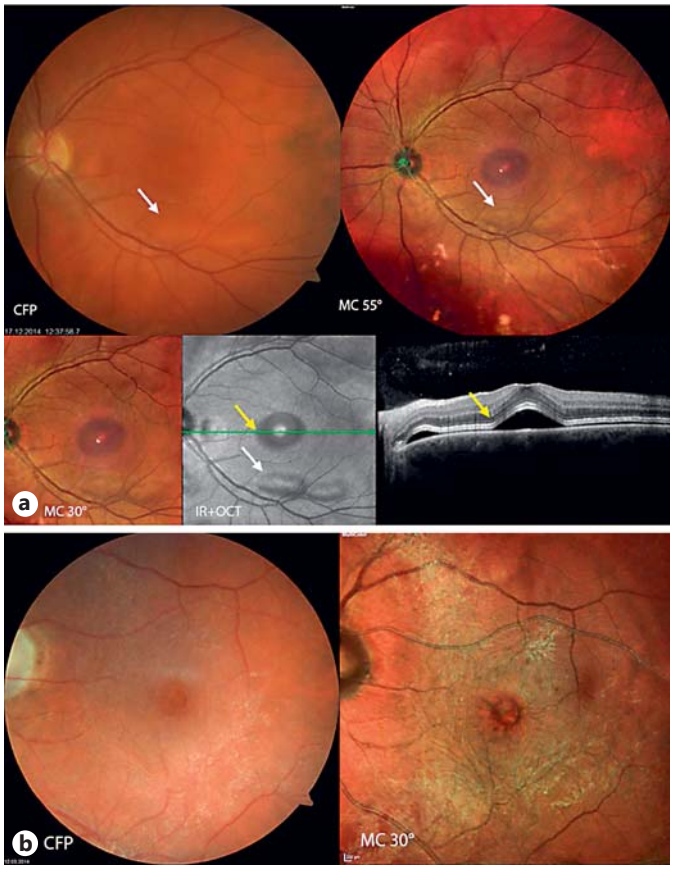

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Fig. 6. a Idiopathic multifocal CSCR. The appearance of extrafoveal collections of subretinal fluid on multimodal imaging (white arrows) and the boundary of the subretinal fluid around the central CSCR seen on MC, IR and OCT (yellow arrows; colors refer to the online version only). **b** Epiretinal membrane compared on CFP and MC imaging. MC = Multicolor.

Fig. 5. a Ischemic branch retinal vein occlusion with secondary retinal neovascularization (arrow) with an area of hyperfluorescence on fundus fluorescein angiography (FFA) showing leakage from neovascularization. A magnified view of the area of neovascularization seen on both CFP (second row, middle) and MC (second row right). **b** A branch retinal artery occlusion seen on multimodal imaging. MC = Multicolor.

Other Acquired Macular Diseases

Acute central serous chorioretinopathy (CSCR) is characterized by the serous detachments of the neurosensory retinal associated with the area of focal pigment epithelial detachments [29, 30]. Figure 6a compares the appearance of multifocal CSCR seen on CFP, 55° and 30° multicolor imaging. The boundaries (yellow arrows) of the CSCR and the multifocal areas of neurosensory detachments (white arrows) are seen more distinctly on multicolor imaging than CFP. Previous studies have reported reduction of macula function as a result of chronic CSCR due to degenerative and atrophic changes [31–33]. Multicolor imaging, in addition to IR and FAF imaging may be useful to detect subtle changes in the retinal structure which may not be clinically apparent after the resolution of the subretinal fluid from CSCR.

The appearance of epiretinal membranes on CFP and multicolor imaging are compared (fig. 6b). Details such as the foveal center and the orientation of the folds can better characterize this pathology.

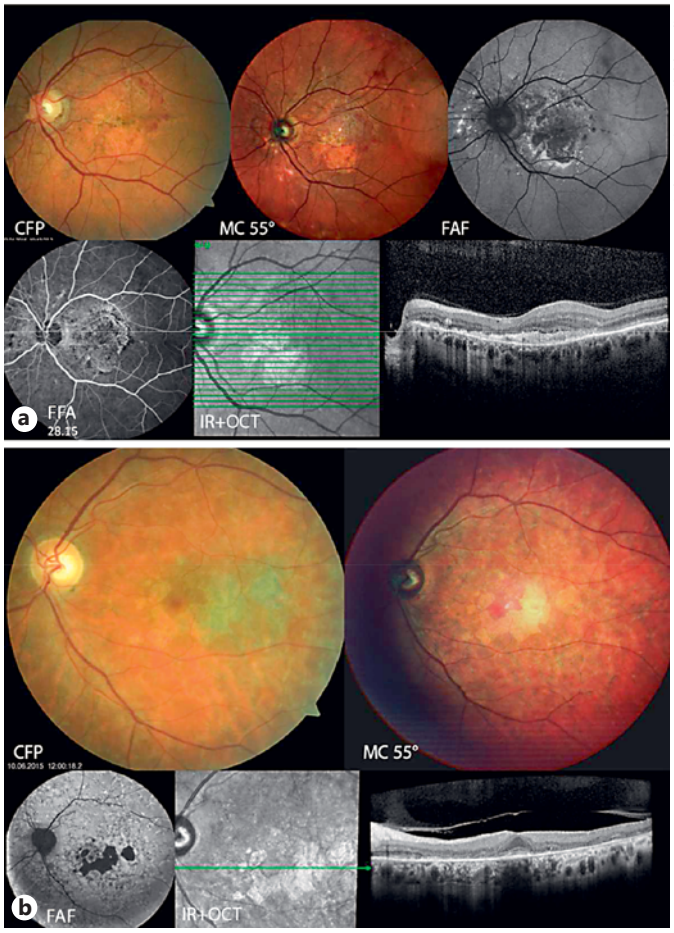

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Fig. 7. a PXE complicated by choroidal neovascularization, subretinal hemorrhage and atrophy seen on multimodal imaging. **b** Stargardt macular dystrophy with atrophy of the outer retinal layers that spares the fovea. MC = Multicolor; FFA = fundus fluorescein angiography.

Inherited Retinal Dystrophies

Inherited retinal diseases are a heterogeneous group of conditions that are responsible for visual impairment in young patients. Limited treatment options for these diseases exist, and imaging is useful for diagnosis, prognosis and monitoring the progression of the disease. Pseudoexanthoma elasticum (PXE) is a systemic connective tissue disease that is characterized by breaks in the Bruch's membrane called angioid streaks. Secondary choroidal neovascularization (CNV) development is a common complication seen in 72–86% of these patients and is associated with severe visual impairment [34–36]. Early detection of CNV allows treatment with anti-VEGF injections that can stabilize vision and prevent further deterioration [37]. Hemorrhage associated with CNV is one of the early signs that can be detected on fundus imaging. Figure 7a compares the CFP, multicolor and FAF image of a patient with PXE complicated by a CNV. Around the CNV lesion, subretinal bleeding is seen in both CFP and multicolor imaging. The inferior area of atrophic change is more clearly demarcated on the multicolor image and shows better correlation with the FAF than the CFP image. The angioid streak was best seen on FAF and was less distinct on both CFP and multicolor imaging.

Stargardt disease is a type of macular dystrophy characterized by bilateral white yellowish deep retinal lesions (flecks) seen in the posterior pole which can extend to the mid-periphery with progression to a loss of the foveal reflex, granulation in the retinal pigmentary epithelium and macular atrophy [38–40]. In both CFP and multicolor imaging, the white flecks of the fundus can be seen (fig. 7b). The demarcation of the central area of atrophy is more clearly seen on multicolor imaging and correlates better with FAF imaging than the CFP. This helps to distinguish the area of foveal sparing as confirmed on OCT imaging to help explain why despite central atrophy causing a central scotoma, visual acuity is still preserved.

Other Pathologies

Fundus imaging in retinal and choroidal tumors is important for accurate documentation and to detect changes in the appearance and size of the lesion over time. Comparing CFP to multicolor imaging, pigmented lesions such as choroidal nevus (fig. 8a) and choroidal melanomas (fig. 8b, c) show a varying degree of color when imaged by multicolor imaging. The depth of the lesion, the degree of pigmentation and surrounding changes like blood, fluid or atrophy all influence the appearance of lesion on multicolor imaging. In the case of choroidal rupture (fig. 8d) due to ocular trauma, areas of atrophy and rupture can be clearly imaged with both modalities; however, the areas of pigmentation also show a variation in color.

Discussion

In ophthalmic practice, high-quality fundus imaging is important for the diagnosis, documentation and management of retinal diseases. Multicolor imaging available for use on the combined cSLO + SD-OCT platform has the advantage of enabling fundus images to be taken with a single device without the need for an additional color fundus camera. This combined platform can also be used

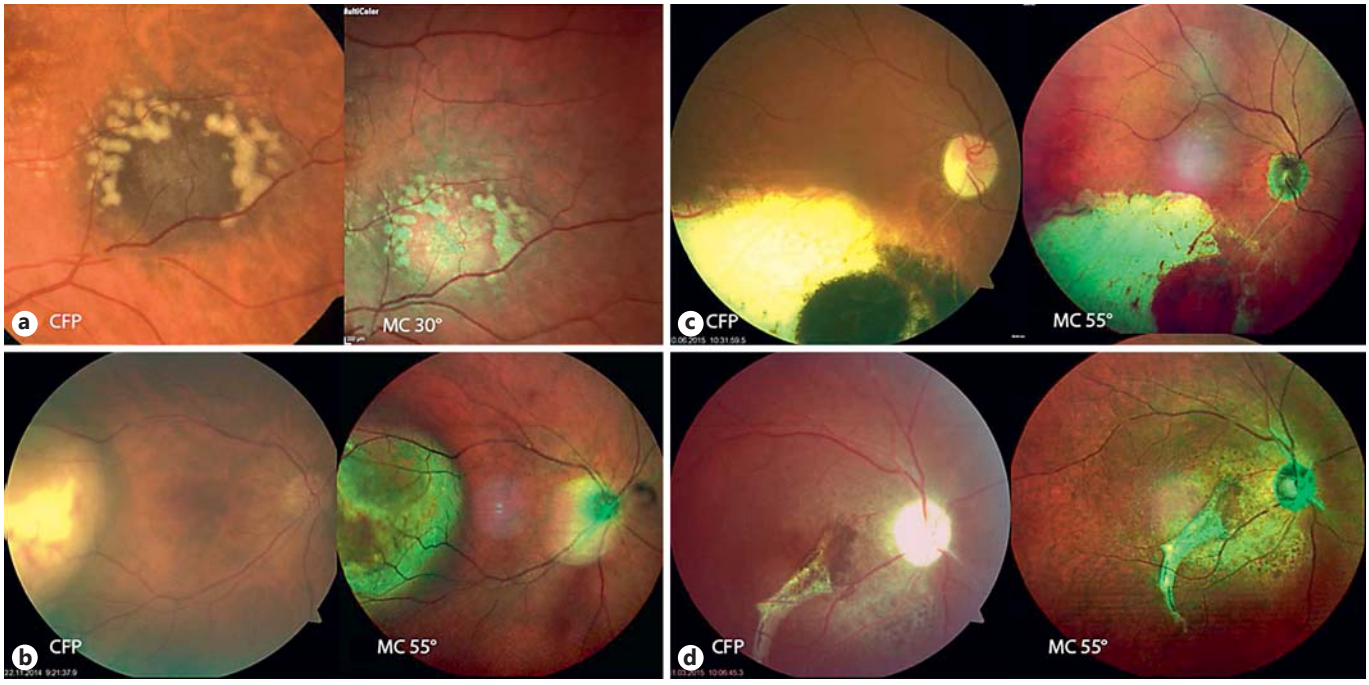

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Fig. 8. Choroidal nevus (**a**), choroidal melanoma (**b**), choroidal melanoma after brachytherapy (**c**) and choroidal rupture after a traumatic injury to the eye (**d**). MC = Multicolor.

to take multimodal images such as FAF, infra-red imaging, spectral-domain optical coherence tomography, fluorescein and indocyanine green angiography. In addition, with the use of different lens attachments, there is the option of taking 55° images to capture more peripheral changes. The multimodal single device may have an advantage to save time in high-volume clinics and may also be an advantage in smaller ophthalmic practices where cost and space restraints only allow for limited imaging equipment.

Compared to CFP, which requires a bright flash of light to capture images, single-wavelength small laser spots are used in multicolor imaging, which may cause less photophobia. Nonmydriatic multicolor imaging in combination with OCT may be considered for use in future screening programs following validation studies to improve the accuracy of screening for diseases such as diabetic retinopathy and AMD. Also the three reflectance images that make up the multicolor image can be viewed separately to enable the detail at each level to be imaged if required. Retinal atrophy imaged with multicolor images shows good correlation with FAF images, and this may be an advantage over CFP for certain diseases such as GA and macular dystrophies.

Current systems of multicolor imaging, however, have some disadvantages when compared to conventional CFP. Multicolor imaging may require a slightly longer period of fixation to take the three separate images compared to CFP. Artifacts must be considered. Also, conventional CFP is very comparable to clinical examination findings, while on multicolor images there are variations of the color produced compared to the clinical examination especially in cases of pigmentary lesions. Ophthalmologists need to be mindful of these differences when interpreting the multicolor images.

In summary, multicolor imaging has many clinical applications, and in some cases may be used to replace conventional CFP. As the use of multicolor imaging becomes more widespread, further studies will need to validate the retinal details seen on multicolor imaging with conventional CFP and other imaging modalities.

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