Ultra-widefield retinal imaging: an update on recent advances

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Abstract: The development of ultra-widefield retinal imaging has accelerated our understanding of common retinal diseases. As we continue to validate the diagnostic and prognostic significance of pathology in the retinal periphery, the ability to visualize and evaluate these features in an efficient and patient-friendly manner will become more important. Current interest in ultra-widefield imaging includes the development of potential biomarkers of disease progression and indicators of preclinical disease development. This article reviews the current ultra-widefield imaging systems and recent advances in their applications to clinical practice with a focus on diabetic retinopathy, retinal vein occlusion, uveitis, and pediatric retina.

Keywords: diabetic retinopathy, telemedicine, ultra-widefield imaging, widefield imaging

Received: 29 September 2019; revised manuscript accepted: 10 December 2019.

Introduction

Photographic imaging of the fundus has evolved significantly over the past century. The first fundus camera was developed by the Carl Zeiss Company in 1926, providing a 20° and later 30° view of the posterior pole.1 Early widefield imaging, capturing more than the standard 30° view, was performed using a traditional camera; the use of a fixation lamp and mirror then allowed for the creation of a 19-photo, 96° montage.2 Currently, advances in fundus imaging and technology have allowed physicians to capture up to 200° of the retina in a single capture.

As our ability to capture the peripheral retina has improved, clinicians have developed a greater appreciation for how the peripheral retina is an important element in the effective diagnosis, management, and prognosis of a variety of retinal disorders. The ability to capture images of the peripheral retina with relative ease has provided insights into the importance of disease-related peripheral pathology that was previously unknown. The purpose of this article is to review current advances in ultra-widefield (UWF) retinal imaging and their applications to clinical practice.

Widefield and UWF imaging defined

The terms widefield and UWF imaging are frequently used without a clear agreement on the definitions of the terms. Previously, UWF and widefield imaging were variably defined based on degrees of freedom of the retinal capture using device-specific terminology. DRCR.net has previously defined UWF images to have at least 100° view of the fundus. Recently, a consensus group of retinal imaging experts formalized a definition of the terms based on anatomic landmarks (Table 1).3 Based on their consensus, widefield images were defined as a single-capture image, centered on the fovea, which captures retinal anatomic features beyond the posterior pole, but posterior to the vortex vein ampulla, in all four quadrants. UWF was defined as a single-capture image, centered on the fovea, which captures retinal anatomic features anterior to the vortex vein ampullae in all four quadrants.

Widefield images can be montaged to create an UWF field of view, but that technique requires significantly more time for capture and montaging. The consensus group also defined the term “panretinal” as a goal that would allow for imaging of the entire retina. No technology can do this in a single-capture image as of 2019.
Current UWF imaging systems

Optos
The Optos cSLO (confocal scanning laser ophthalmoscopy) (Optos PLC, Dunfermline, United Kingdom) is capable of imaging up to 200° of the fundus in a single capture or approximately 82% of the retina. First commercially available in 2000, Optomap technology is available in three product platforms: California, Daytona, and Monaco. The multimodal Optos system now includes the capability to perform pseudocolor imaging, fundus autofluorescence (FAF), fluorescein angiography (FA), indocyanine green angiography (ICGA), and most recently, optical coherence tomography (OCT). The integrated OCT in the Optos Monaco provides cross-sectional 40° views of retinal structures. In addition, the Optos automontage feature increases the portion of the retina that can be captured without dilation to 220° (or 97%) of the retina by combining four gaze-steered images (up, down, left, and right). Limitations of this device include peripheral distortion, pseudocolor imaging, and lash artifact.

Newly developed software has reduced peripheral distortions through image processing calculations, and improves contrast in the posterior pole and portions of the periphery. The Optos cSLO system does not require the use of a contact lens or mydriasis and is useful in imaging vitreoretinal pathology even through limited views of the posterior segment, such as through a permanent keratoprosthesis or in a gas-filled eye following vitrectomy. It also has a very quick acquisition time which is helpful in eyes with nystagmus.

Staurenghi lens system
A wide-angle contact lens system by Staurenghi and colleagues images up to 150° of the retina using two biconvex aspheric lenses and a two-element convex–concave lens in conjunction with a cSLO-based platform (Ocular Staurenghi 230 SLO Retina Lens; Ocular Instruments Inc, Bellevue, Wash). Its use with angiography has been shown to be a valuable tool in the evaluation and management of retinal pathologies difficult to assess clinically or with conventional angiography. The main limitation is the need for a skilled photographer who is able to place and maintain a contact lens on the ocular surface to acquire images.

Table 1. Definitions of widefield and ultra widefield imaging.

| Region                  | Anatomic location                                                                 | Field of view   |
|-------------------------|-----------------------------------------------------------------------------------|-----------------|
| Posterior pole          | Retina within the major temporal vascular arcades and slightly just beyond         | 50°             |
| Mid periphery (widefield)| Retina extending from the vascular arcades to the posterior edge of vortex vein ampulla | 60°–100°       |
| Far periphery (ultra-widefield) | Anterior edge of vortex vein ampulla and beyond to pars plana | 110°–220°     |
| Panretinal              | Imaging of the entire retina                                                      | 360°           |

RetCam
The RetCam (Clarity Medical Systems, Inc, Pleasanton, CA; Table 2) is primarily used to...
image neonatal and pediatric patients in a range of conditions, including screening for retinopathy of prematurity (ROP)\textsuperscript{14,15} and evaluation of retinal hemorrhages in cases of suspected abusive head trauma.\textsuperscript{16} It is a contact-based system capable of imaging up to 130° of retina, but is limited in which illumination occurs through the cornea and any media opacities will result in poor image quality.

Limitations of current imaging systems

The biggest limitation of current imaging systems is the inability to image the entire retina ora-to-ora with a single acquisition. Ideally, UWF will allow for the quantification of peripheral pathologies with subsequent analysis of changes to these pathologies over time. However, there are inherent challenges with representing a three-dimensional image on a two-dimensional flat surface. A common example to illustrate this effect is the representation of the world on a flat map, called a Mercator projection. Although this type of projection is useful for ship navigation, a Mercator projection grossly distorts the size of landmasses closer to the poles (i.e. “Greenland effect” on world maps). Similarly, in retinal imaging, this distortion leads to areas of nonlinearity such that a line drawn near the posterior pole will be very different in true size from one drawn in the periphery, even if they appear to be the same length on a flat monitor.

The distortion is particularly apparent in the far temporal and nasal periphery such that lesions found in the periphery may look bigger than they truly are with indirect ophthalmoscopy.\textsuperscript{8} To address measurement issues, the Optomap produced a tool that transforms Optomap images into a stereographically projected image using assumptions based on a model eye with a diameter of 24 mm and thus reducing the impact of peripheral distortion.\textsuperscript{17} This measurement algorithm calculates the position of each pixel and then translates that into square millimeters, providing a consistent geometry that accurately represents anatomic features in the retina. This algorithm allows users to measure distance and area anywhere on the retina or to identify an area of clinical interest with confidence that can be compared to other areas of the retina.

Clinical utility of widefield imaging

Diabetic retinopathy

The importance of utilizing UWF imaging to visualize the periphery in diabetic retinopathy (DR) has been consistently demonstrated in prior studies and is the most well-studied and published pathology in the era of UWF imaging (Figure 1). When seven standard field (SSF) imaging became the gold standard for DR management, it represented a compromise between the excessive time needed to capture up to 30 fields required to document 100% of the retina and getting a “wide enough” view in a more reasonable timeframe. The use of UWF imaging in DR management has grown since research validated that it is at least as sensitive and specific as the Early Treatment Diabetic Retinopathy Study (ETDRS) SSF montages, as nonmydriatic UWF imaging have been reported to have a high sensitivity (84–94%) and specificity (90–100%) for the screening of DR.\textsuperscript{18–21}
Peripheral pathology in diabetic retinopathy. Recent research has begun to highlight the role of peripheral pathology in early disease detection and determination of risk of DR progression. Although the traditional ETDRS SSF includes the central posterior 90° of the retina, which equates to about 30% of the entire retina surface, DR studies have shown that pathology often exists outside the ETDRS SSF, and in some cases, peripheral pathology is associated with greater disease severity and higher risk of disease progression. Ischemia, which is an important factor in DR progression, may appear in the periphery first and has been associated with the presence of peripheral lesions on color images. Compared to the SSF images, UWF-FA in particular has higher utility in demonstrating peripheral pathology, imaging 3.9 times more nonperfusion, 1.9 times more neovascularization, and prompting 3.8 times more panretinal photocoagulation in one study. This study also showed that UWF-FA detected findings that would have otherwise been missed on SSF imaging in 10% of eyes. Correlations between peripheral nonperfusion/vascular leakage and neovascularization, peripheral ischemia and an enlarged foveal avascular zone, and peripheral nonperfusion and diabetic macular edema show that the ability to detect abnormalities in the periphery may have clinically significant implications.

The ongoing prospective DRCR Protocol AA will further assess whether evaluation of the retinal periphery using UWF imaging, compared to SSF, improves the ability to assess DR and predict worsening disease. In particular, DRCR Protocol AA has the primary objective of (1) assessing whether any predominance versus no predominance of DR lesions in any field of the retinal periphery on UWF images is associated with rates of DR worsening over time; (2) redefine DR severity grading level based on the status of the periphery and assess whether differences in severity level assessment between grading with or without inclusion of peripheral findings is associated with rates of DR worsening over time; (3) evaluate how often mydriatic 200° UWF digital photographs are comparable to ETDRS SSF for the grading and assessment of DR; and (4) determine whether extent and location (peripheral vs. posterior) of nonperfusion on UWF fluorescein angiograms is associated with baseline DR and diabetic macular edema (DME) severity as well as rates of DR and DME worsening over time.

UWF imaging for telemedicine in DR. UWF imaging has also been shown to be an effective tool in the detection and screening of DR in non-ophthalmic practice settings. Telemedicine applications for UWF imaging have been established and are likely to expand, particularly with the increasing prevalence of diabetes worldwide. Within the endocrinology department of a multi-specialty private hospital, UWF fundus photography resulted in the detection of DR in 9.3% of 1,024 screened patients. In a medical retina virtual clinic, UWF imaging was performed on 274 patients who were being evaluated for diabetic eye disease, facilitating the assessment of retinal pathology and subsequent triage to either follow-up or discharge. Recently, a novel hybrid telemedicine system using both fixed (located within high-volume clinics) and mobile (mounted within a traveling van) UWF cameras allowed for the
screening of 2788 diabetic patients and detection of DR in 27% of patients. The newly Food and Drug Administration (FDA)-approved IDx-DR, an autonomous, artificial intelligence (AI)-based diagnostic system, is used with fundus imaging (TRC-NW400, Topcon Medical Systems, Oakland, NJ) to detect the presence of DR. Although this system uses widefield imaging (four pairs of digital images with visualization of 45°–60° by each pair), there may be a potential role for use with UWF imaging in the future.

In addition to detection of pathology, UWF-FA images have been used for enhancing classifications and defining characteristics of DR. In treatment-naive patients with DR, one study of 122 eyes reported that peripheral retinal ischemia may correlate to the presence of diabetic macular edema. A study assessing the extent and distribution of nonperfusion in eyes with DME did not find an association between severity of DME and extent of retinal nonperfusion, but did note more extensive nonperfusion in the midperiphery compared to the far periphery and posterior pole and also a higher ischemic index (ISI) with increasing distance from the fovea. Furthermore, the RECOVERY study reported that eyes with proliferative diabetic retinopathy (PDR) treated with monthly aflibercept injections experienced a stable retinal nonperfusion area after 1 year, whereas patients treated with quarterly aflibercept injections had a 29% increase in retinal nonperfusion area. A recent study by Nicholson and colleagues using UWF-FA established a threshold of 118.3 disk areas of retinal capillary nonperfusion in the development of PDR, highlighting the need for further studies using UWF-FA to evaluate and stratify high-risk patients.

The use of UWF-FA in the management of DR has increased in recent years. Multiple studies have suggested that it is a complementary tool to guide retinal photocoagulation, targeting specific areas of nonperfusion and thereby potentially minimizing complications associated with full panretinal photocoagulation. Other studies have found that UWF-FA is useful in monitoring and quantifying the response to treatment, particularly by measuring peripheral ischemia after intervention. Querques and colleagues found that a dexamethasone intravitreal implant (Ozurdex) reduced peripheral ISI by 2.4 fold at 10 weeks. In a small case series of 16 eyes that received anti–vascular endothelial growth factor (VEGF) therapy for DME and high-risk PDR, 75% demonstrated apparent reperfusion of retinal areas that had previously demonstrated nonperfusion on UWF-FA. In contrast, in a recent case series of 18 eyes with DR treated with monthly anti-VEGF therapy, there was an improvement in the DR severity scale on UWF imaging without any changes in retinal reperfusion on UWF-FA.

Retinal vein occlusion

Retinal vein occlusion (RVO) is one of the most common retinal vascular diseases by prevalence and may lead to peripheral retinal ischemia, neovascularization, and macular edema (Figure 2). UWF-FA effectively evaluates leakage, nonperfusion, and ischemia in both the macula and in the retinal periphery. Several studies have found that retinal nonperfusion and its correlate (ISI) are significantly associated with macular edema and neovascularization in central retinal vein occlusion (CRVO), branch retinal vein occlusion (BRVO), and hemispheric retinal vein occlusion (HRVO), and that these markers are inversely associated with visual acuity. The ISI may also predict response to treatment. Baseline retinal ischemia demonstrated by UWF-FA is strongly associated with disorganization of retinal inner layers, which in turn is predictive of worse visual acuity at follow-up.

These prior studies have demonstrated that the ISI has both predictive and prognostic value; however, accurately assessing the nonperfusion area and the total area of visible retina to compute the ISI can be challenging. Although the ISI is an imperfect measure of nonperfused retina, recent advances in UWF software that reduce the amount of peripheral distortion inherent in widefield images have led to more precise calculations of percentages of peripheral nonperfusion, and may potentially better characterize disease severity. Other methods of measuring topographic areas of nonperfusion, such as concentric rings centered on the fovea, have also been investigated.

UWF-FA is a particularly important tool in RVO in that it can also be used to guide targeted laser photocoagulation (TRP) similar to DR treatment. In treatment-naive patients with BRVO and macular edema, UWF-guided TRP may reduce the number of anti-VEGF injections while improving visual acuity and decreasing central subfoveal thickness. However, the RELATE
and WAVE study found that in patients with ischemic RVO and cystoid macular edema (CME) incompletely responsive to prior anti-VEGF therapy, TRP did not significantly affect treatment burden or visual outcomes at 12 months of follow-up. Nonetheless, it may result in reduced ischemic indices in the perimacular and near-peripheral areas of the retina and a subsequent reduction in CME, indicating a need for further studies to elucidate the role and parameters of TRP in treating RVO.

Uveitis
UWF imaging in various types of intraocular inflammation has provided important information about the role of the retinal periphery in assessing disease activity. Some reports have shown the potential for UWF-FA to prognosticate the severity of retinal disease and response to treatment in intermediate and posterior uveitis (Figure 3). Traditional clinical markers of disease activity including CME, retinal vascular leakage and nonperfusion are often more readily evident on FA than on clinical examination.

There is growing evidence that in uveitic patients, peripheral vascular leakage (PVL), which describes angiographic leakage occurring outside the ETDRS SSF, may influence the grading of disease activity and the decision to augment therapy. Recently, Campbell and colleagues reported that PVL was more likely to be present among uveitis patients who felt to have clinically active disease compared to those with well-controlled disease and may be associated with other signs of activity such as CME. Another study reported that the presence of PVL in uveitic patients at the baseline visit was associated with the decision to augment clinical treatment of uveitis even after adjusting for CME and clinical grading of uveitis activity. In a study of 243 patients comparing UWF-FA to simulated 50° FA images, Pecen and colleagues reported UWF-FA added additional information regarding the presence of PVL in 25%, peripheral nonperfusion in 14%, peripheral lesions in 7%, and peripheral neovascularization in 4% of patients. Although it is unclear whether PVL in isolation warrants treatment, the incorporation of UWF imaging parameters into a grading scheme could help us better understand treatment indications for PVL in patients with uveitis.

Prospective studies of UWF imaging, particularly UWF angiography, are needed to further determine the clinical significance of peripheral findings in a myriad of uveitic conditions.

Pediatric retina
Many pediatric vitreoretinal disorders can manifest with significant peripheral retinal pathology including ROP, familial exudative vitreoretinopathy (FEVR), and Coats disease. However, wide-field imaging in the pediatric population has several unique challenges related to patient cooperation and potential need for examination under anesthesia.

Although the primary imaging platforms utilized in the pediatric population include the RetCam system and Optos, several new imaging systems are on the horizon (Figure 4). The PanoCam LT (Visunex Medical Systems) widefield handheld system is now approved in the United States and offers a wireless, contact-based system for newborn widefield imaging (130°). The 3nethra Classic (Forus Health) is a compact, table-top, non-mydriatic digital imaging system offering a...
40°–45° field of view. The 3nethra neo is a lightweight, non-wireless but compact, contact-based system for high-definition imaging with a 120° field of view. The Heidelberg Spectralis UWF imaging module (Heidelberg Engineering) uses a camera attachment to capture non-contact-based, high-contrast images of up to 102° of the retina. This system has been used for imaging of babies under anesthesia at 33 weeks gestational age through 12 months.

The recent widespread availability of widefield imaging systems with FA capabilities such as the RetCam has brought to light the utility of FA for ROP diagnosis. Recent studies have suggested that compared to color fundus photographs alone,
FA resulted in increased sensitivity for diagnosis of stage 2 or worse ROP, stage 3 or worse ROP, pre-plus or worse disease, and type 2 or worse ROP56 but did not improve diagnosis of the macular center and only marginally improved sensitivity for zone diagnosis.57 These findings have important implications for the use of FA in ROP surveillance as well as in remote, imaging-based, telemedicine screening.

Recent advancements in peripheral retinal imaging in patients with FEVR have led to a proposed revision of the original five-stage FEVR classification scheme as one study recently reported a wide range of previously undescribed clinical features in 174 eyes with FEVR.58 Furthermore, in another study, UWF-FA was used to assess asymptomatic relatives of individuals who have FEVR, and nearly 58% of patients exhibited subtle stage 1 and 2 FEVR features, resulting in updated recommendations for clinical and widefield imaging screening of family members of patients with FEVR.59

UWF imaging has also improved our understanding of the possible relationship between FEVR and ROP. Based largely on UWF-FA features and clinical course, a new clinical entity, aggressive posterior vitreoretinopathy, has been described in premature infants who exhibit retinal findings more characteristic of FEVR than ROP.60,61

Other conditions
The utility of UWF imaging has continued to expand into other retinal pathologies. With UWF-FAF and UWF ICGA, new insights into the extent of choroidal vessel hyperpermeability have been appreciated in the pachychoroid clinical spectrum of diseases.62 The use of UWF-FAF has also been studied in retinal and choroidal dystrophies, including gyrate atrophy,63 Stargardt disease,64 and retinitis pigmentosa.65,66 In addition to DR and RVOs, UWF-FA has also been useful in diagnosing and managing other retinal vascular pathologies including sickle cell retinopathy and radiation retinopathy (Figure 5). For surgical patients, UWF imaging has been studied as an adjuvant for documentation of rhegmatogenous retinal detachments and their postoperative course.67,68 Although the clinical management of age-related macular degeneration (AMD) is focused on macular imaging including OCT and FA, UWF imaging has allowed for monitoring of concurrent peripheral findings in both non-neovascular and neovascular AMD.69–71 These studies have suggested that peripheral changes were found to be highly prevalent in eyes with AMD, supporting the claim that the disease is panretinal and not macula only; however, the clinical significance of peripheral lesions in AMD remains incompletely understood.

As imaging technology improves, our understanding of “normal” peripheral retinal findings also continues to evolve. In a recent study of 58 eyes without reported peripheral disease, UWF-FA showed a high prevalence of peripheral vascular anatomic variations, including vessels crossing the horizontal raphe, right angle vessels, absence of capillary detail, and microaneurysms.72 Other studies have noted that normal peripheral retinas may show a granular background fluorescence with a mottled fluorescent band.73 These

Figure 5. Sickle cell retinopathy: [a] Optos color fundus SLO of right eye with patient with sickle cell disease appears normal without hemorrhage or peripheral sclerotic vessels. [b] UWF–FA reveals superonasal nonperfusion with early retinal neovascularization that would not otherwise be detected on standard 50°–75° non-widefield FA.
findings suggest that there may be a wide range of what constitutes normal anatomic variations in patients undergoing UWF imaging.

**Future directions**
The indications and utility of UWF imaging continue to evolve as the imaging technology improves. Current multimodal imaging platforms include FAF, FA, and ICGA and additional imaging technologies such as swept-source OCT; non-invasive widefield OCT angiography will continue to push the capabilities of widefield and UWF imaging. The incorporation of these new modalities to evaluate various retinal pathologies may translate into improved disease diagnosis and management.

In addition, traditional color fundus drawings for various vitreoretinal conditions are not identically reproducible in the era of electronic medical records (EMRs). The digital interface of EMRs have traditionally been designed to prioritize billing criteria and have produced inefficient paradigms for fundus drawings. With the increased use of EMRs, digital UWF imaging may become a useful adjunct or replacement for documentation of the fundus drawing in ophthalmology clinics.

**Conclusion**
UWF imaging has evolved significantly over the past decade and has improved our understanding of the pathophysiology of various vitreoretinal disorders. Current studies with UWF imaging have suggested important clinical applications for numerous retinal diseases including DR, RVO, pediatric vitreoretinal disorders, and uveitis. Further research into the utility of UWF imaging in areas of increasing interest such as telemedicine will serve to refine and optimize the use of this technology.

**Funding**
The authors received no financial support for the research, authorship, and/or publication of this article.

**Conflict of interest statement**
The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: M.A.K. has served as speaker and consultant (Genentech), consultant (Novartis), consultant (Allergan). The remaining authors have no conflicts to declare.

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