Widefield Imaging in AMD: Unanswered Questions and Untapped Potential

Although AMD is classically thought of as a macular disorder, pathologic changes in the peripheral retina may be diagnostic and prognostic for disease progression.

BY SZILÁRD KISS, MD

Early detection of age-related macular degeneration (AMD) offers an opportunity to intervene early in the course of disease and thus effect a more positive outcome. As imaging technology has improved over the past 2 decades, the ability to detect subclinical disease has gotten better. Now, with the ability to expand the field of view beyond the central 20° to 55° of the macula captured by most imaging devices, interest has shifted to the peripheral retina and the clues it may hold either for early disease detection or for markers of progression.

Although this is a hot topic of research at the current time, there is still a lot of work left to do before clinicians can reliably image the peripheral retina and make treatment decisions based on those findings. This article reviews some of the issues inherent to imaging the peripheral retina, as well as some of the promise this undiscovered area may hold for the classification, follow-up, and management of patients with AMD.

WIDEFIELD IMAGING MODALITIES

The treatment of AMD today is founded on a wealth of research into the natural history of AMD, with much of it deriving from recent enhancements in imaging technology. There are currently 3 devices with the ability to easily capture images of the peripheral retina, although each has unique properties that may yield vastly different results.

The Optos 200 Tx incorporates ultra-widefield scanning laser technology to permit a 200° view, or over 80% of the entire retina, in a single steered image. To scan the optical surface, the Optos device uses 2 lasers that are reflected off an ellipsoid mirror and processed by proprietary software to produce the Optomap. In this system, the focal point is inside the eye, meaning that images are not affected by media opacities—an important consideration in eyes with cataracts or hazy vitreous.

A second device, from Heidelberg Engineering, is actually an add-on ultra-widefield angiography module to the Spectralis or Heidelberg Retina Angiograph platforms. This system is lens-based and can capture images of the retina far wider than the 30° or 55° of standard lenses. Anyone familiar with photography, however, will recognize an inherent shortcoming of lens-based systems, namely the inverse relationship between depth of focus and field of view, resulting in warping of images.

A third device was introduced late last year by Optovue; its Avanti Widefield Enface OCT, with a 40° field of view. I have not had experience with this device.

COMPARATIVE STUDY

Our research center was involved in a study comparing the Heidelberg and Optos devices.1 The differences seen in that analysis are important and may have clinical implications. In the study, 10 eyes of 5 patients underwent ultra-widefield fluorescein angiography with the Optos and Heidelberg devices in succession. The goal of our study was to compare the 2 resulting images for quality and overall depiction of the retina. It is possible to “steer” the focus on these devices to gather an image from a desired position on the retina; however, for the purposes of the study, we obtained a single, non-steered shot so as to mimic what a clinician might do during a typical examination.

After gathering both images, the overall surface area and the quality of the images in all 4 quadrants were compared by 3 masked, independent reviewers. Overall, the Optos device delivered images with a wider retinal area, and the difference was significant (average 151 362 pixels [range 116 998–205 833] with Optos vs an average of 101 786 [range 73 424–116 319] with Heidelberg; P = .0002). Although there were some differences in how these devices imaged the superior and inferior regions, the differences between Optos and Heidelberg were not...
statistically significant. Compared to the Optos, Spectralis delivered images of the superior and inferior vasculature at more distal points compared with the Optos device. There were statistically significant differences in the average area captured in the nasal and temporal regions, both considerably favoring the Optos device. The retinal vasculature in the nasal and temporal regions was also imaged to more distal points with Optos.

This was a small, single-center study with a limited data set. Despite the limitations of this study, however, differences between the 2 widefield imaging modalities were apparent (Figure 1). It is yet to be determined how these differences might affect decision-making in the clinical setting (Figure 2).

DISTORTION AND NONLINEARITY

An inherent problem with widefield imaging is that images appear distorted. This is a physical problem of the lenses and mirrors used in all imaging devices, wherein a spherical 3-dimensional surface is flattened to yield a 2-dimensional image. A flattened optical coherence tomography map distorts the sizes and shapes of objects, with greater distortion occurring farther from the center. This is the same effect seen in nautical maps, which use a standard known as the Mercator projection to depict the earth’s globe on a conformal map. Named for the late 16th century Flemish cartographer Geradaus Mercator, these maps preserve the nature of horizontal lines and their angularity to the meridians of longitude—a necessity for understanding one’s relationship to true north for navigational purposes. However, correction of the spherical Earth to a flattened image results in size and shape distortions that grow larger at the Earth’s poles. This explains why Greenland appears the same size as Africa on Mercator projection maps of the earth, when in reality Africa is about 14 times larger than Greenland.

This same effect occurs with widefield imaging. The images from both the Heidelberg as well as the Optos have the same peripheral nonlinearity (the so-called peripheral distortion). There appears to be more nonlinearity with the Optos only because the area of the retina imaged is significantly greater than that imaged by the Heidelberg, as well as the ellipsoid mirror used with the Optos device. For ultra-widefield imaging to be truly clinically relevant, more work will be needed to correct for these distortions. For instance, a nevus in the periphery as seen with a widefield view will appear much larger than it actually is, and the same can be said for areas of ischemia and nonperfusion. Once the distortion is corrected for, however, measurements can be performed that are at least within an acceptable tolerance for accuracy. Optos is currently beta testing software that will easily be able to correct for this peripheral nonlinearity and make accurate measurements of peripheral pathologies.

WIDEFIELD IMAGING IN AMD

Several studies have now been published and present-
ed highlighting important peripheral features in eyes with dry or wet AMD that were identified with ultra-widefield imaging. Collectively, these data suggest that there may be distinct phenotypic presentations of AMD that may correlate with different genetic and epigenetic factors. Although more research is needed, the potential to identify AMD subtypes is intriguing for potentially individualizing therapy, understanding response to therapy, and predicting disease progression.

In a retrospective review of 83 consecutive patients (157 eyes) diagnosed with AMD or macular drusen, there was a significantly higher rate of peripheral autofluorescent abnormalities among eyes with AMD (63.6%) versus control eyes (35.7%). Controls were defined as AREDS category 1: eyes with few or no small drusen and no pigment abnormalities. Furthermore, both granular fluorescent changes and patchy hypofluorescence were more common in eyes with advanced AMD compared with eyes with early AMD or controls. Granular fluorescent changes were more commonly identified in eyes with choroidal neovascularization or GA, while patchy hypofluorescence was more common among patients with GA.

An interesting finding in this study was that 17.8% of eyes displayed pinpoint hyperfluorescence with an even distribution among eyes with all categories of AMD. This suggests that peripheral drusen may be an incidental finding in some individuals in much the same manner that hard macular drusen are sometimes innocuous. On the other hand, these peripheral drusen may precede the development of a more advanced disease process in the macula.

Another implication of common pathologic findings in AMD and control eyes is that they lend credence to pathology noted only in eyes with AMD as being specific to the disease process. For instance, 45.5% of eyes in the study had granular autofluorescent changes that were associated with the presence of AMD, choroidal neovascularization, and GA. It is possible that these depositions were secondary to the aging process, but their decreased presence in control eyes undermines this theory. Additionally, these lesions were noted in the peripapillary region in some patients, in the periphery only in others, and in both regions in some patients. These different patterns of lesion distribution may represent distinct subtypes or differences between localized and diffuse peripheral disease.

Patterns of peripheral autofluorescence have been noted in other studies. Tan and colleagues noted abnormal findings more frequently in eyes with neovascular or nonneovascular AMD compared with eyes without AMD. In that study, AMD type, older age, and female sex were identified as significant risk factors for peripheral fundus autofluorescence (FAF) abnormalities. The authors also noted a high correlation between specific FAF abnormalities on imaging and clinical findings, namely granular FAF with peripheral drusen, and mottled FAF with retinal pigment epithelium depigmentation.

The ongoing Optos Peripheral Retina AMD (OPERA) study is designed to look for possible morphologic changes in the peripheral retina that may be diagnostic of AMD or prognostic of progression. Investigators have already identified the presence of peripheral reticular pigmentation in eyes with AMD more frequently than in control eyes in a population of Croatian subjects. In a separate report, the OPERA study group reported a higher frequency of paving stone degeneration in addition to higher rates of reticular pigmentary changes among AMD eyes compared with controls.

CONCLUSION

As with all aspects of research, correlation does not necessarily equal causation. Although several reports have now identified morphologic features in the peripheral retina more frequently in eyes with AMD compared with eyes without, the weight of the evidence is not yet enough to change clinical decision-making. Perhaps in the future, genotype-phenotype correlation studies will elucidate differing genetic and epigenetic factors underlying the formation of peripheral findings. In the meantime, more work is needed to correct for the inherent optical shortcomings of devices designed to image the peripheral retina.

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