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Advancing optical coherence tomography angiography to the clinic

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Abstract:

Optical coherence tomography (OCT) angiography (OCTA) is a new clinical technology that advances the capabilities of OCT imaging by adding the ability to readily visualize vascular anatomy down to the capillary scale. With this level of detail, OCTA can be used to identify many important vascular pathologies such as capillary dropout, microaneurysms, or neovascularization. Because it offers high-resolution, high-contrast imaging of these and similar features, OCTA is useful not just for visualization but also for quantification. Quantification is a powerful feature that enables the potential for diagnostics, staging, evaluation of treatment response, and patient monitoring in a more rigorous way than simple observation. In this review, we will examine several OCTA measurements with either demonstrated clinical utility or clinical potential through the lens of three prevalent blinding diseases: diabetic retinopathy, age-related macular degeneration, and glaucoma. We will discuss the merits of these various measurements and care that should be taken in their interpretation and analyze their role in patient management.

Keywords:

Biomarkers, optical coherence tomography angiography, retinal disease

Introduction

Optical coherence tomography (OCT) is high-resolution, depth-resolved imaging modality that has found important applications in ophthalmic clinical practice.^[1,2] In the retina, the subject of this review, it has proven exceptionally useful for the identification of exudation and edema, where it has clear advantages relative to allied imaging modalities, primarily for its ability to provide cross-sectional images.^[3,4] It is also useful for imaging a host of other retinal structural pathologies.^[5,6]

These capabilities already make OCT a powerful clinical ophthalmic imaging modality. However, its utility can be extended through alternative processing to achieve highly detailed vascular imaging with OCT angiography (OCTA).^[7] OCTA complements OCT with a degree of

functional imaging by detecting blood flow using motion contrast.^[8,9] This works because the motion of erythrocytes is typically much faster than the motion of other retinal cells and tissues. The flow signal, then, can highlight vessels down to the capillary scale. Furthermore, OCTA can be captured simultaneously with (structural) OCT during any imaging session, and both these signals will be automatically coregistered, enabling correlation between vascular and other pathologic features. Combined, structural OCT and OCTA give a much more complete image of the retina.^[10]

OCTA imaging allows us to detect many pathologies by inspection.^[11,12] Examples include neovascularization and vessel dropout.^[3,13,14] These capabilities already represent a use case for the technology in the clinic. However, OCTA imaging can be made much more powerful through quantification. Another example: one of the most commonly quantified OCTA metrics is vessel density, which can be hard to assess by inspection. Nonetheless, vessel

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density and several other quantifications can be used to stage disease severity and improve our understanding of etiology.^[15,16] In this review, we will explain some important OCTA quantifications through applications within three prevalent blinding diseases, starting with diabetic retinopathy (DR).

Diabetic Retinopathy

DR is a leading cause of blindness and is particularly important in terms of life quality since the demographics it affects are young relative to other prevalent retinal diseases.^[17,18] It is a common complication due to diabetes mellitus, ultimately related to damage to capillaries and other vessels.^[19] This makes it a good target for OCTA imaging.^[20]

Vessel density is probably the most common quantification performed in OCTA analysis of DR and probably in OCTA analysis in general. There are many different approaches to quantifying vessel density. It should be noted that these do not always agree, but they are usually repeatable.^[21] They are useful in diagnosing DR.^[22-24] Capillary dropout occurs throughout the course of DR progression, so it is also useful for staging. Vessel density measurements are available in many commercial devices.

Vessel density is an example of a perfusion metric, which are proxies for how well blood supply is functioning in the retina. It is not the only one. Other metrics that relate to vessel location/morphology include tortuosity,^[25] fractal dimension,^[26] and intraretinal microvascular abnormalities^[27] which are also indicative of disease status but not typically measured using commercial devices.

A metric that is often measured on commercial devices is the foveal avascular zone (FAZ) area. FAZ area can be measured similarly to vessel density and the other perfusion metrics we mentioned by binarizing OCTA images. It is possible to determine that the FAZ grows in eyes with DR.^[28,29] However, on the other hand, FAZ area suffers due to the fact that there is a large natural population variation in healthy eyes. This means that FAZ area is not the most precise measure of DR pathology (or perfusion loss in general). How do you know if a particular individual is being affected by DR versus just having a normal but large FAZ area? One nice way to make this determination is to use a baseline FAZ identified from retinal thickness, in this way taking advantage of the volumetric nature of OCTA imaging [Figure 1].^[30]

Another way to measure perfusion loss in DR is with nonperfusion area (NPA).^[31-34] A useful feature for NPA

measurements is that they easily indicate the location of perfusion loss in addition to its extent. This is different than vessel density which must make use of heatmaps or similar displays to convey the same information. Even with heatmaps however regions of vessel density loss are less easily interpreted as regions of NPA. On the other hand, NPA measures regions with a sparsity of vessels, or, equivalently, with a large space between them. This can be readily visualized. And this aspect of NPA measurements has clinical utility since, for example, we might be more concerned with vessel density loss near the macula and in different plexuses since DR seems to affect some more than others [Figure 2].^[13,35] This would be a way to help distinguish DR from other diseases causing perfusion loss.

Technical aside

There are many ways to measure metrics like NPA and most of the other quantifications we will discuss in this review. Broadly speaking, we could group these into two approaches: “rules-based” and artificial intelligence based. Rule-based algorithms are the more traditional and are hand-designed for a specific context. They lack the context sensitivity for AI, and so, in the case of NPA measurements in DR, they are less repeatable and more sensitive to signal quality in the superficial vascular complex.^[35] While AI algorithms can often achieve superior results in ophthalmology,^[36,37] they require large datasets to train on. Furthermore, generating ground truths for training is very time-consuming. Rules-based approaches can help for this requirement. Both approaches are therefore useful. The respective merits of each approach are summarized in Table 1.

Perfusion loss is not the only DR-related pathology related to retinal vasculature. Microaneurysms are an important early-stage indicator of DR visible with OCTA.^[38] They can be identified because they noticeably change vessel morphology. OCTA is a useful way to characterize microaneurysms since it can anatomically locate them,^[39] but it is not clear that it achieves the same detection sensitivity as dye angiography,^[40] particularly if we consider the field of view. However, we can consider more than just detection sensitivity. In addition to its

Table 1: Merits of rules-based and artificial intelligence-based algorithms

	AI	Rules
Data requirement	Needs large datasets	Can be developed without large datasets
Context sensitive	Yes	No
Robust	More	Less
Algorithm specificity	Generic algorithms can achieve most tasks	Requires developing novel algorithms for most tasks

AI: Artificial intelligence

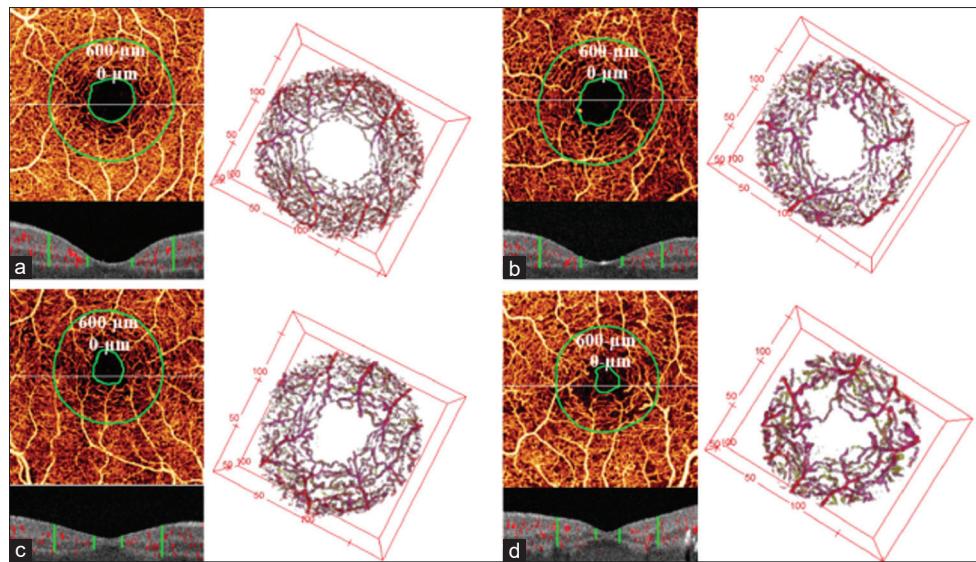


Figure 1: Foveal avascular zone (FAZ) area calculated using a theoretical baseline. In this approach, the width of the FAZ is used to determine a theoretical para-FAZ. The vessel density within this theoretical baseline FAZ can then be calculated to assess perfusion loss. Note that this works either two-dimensionally in *en face* images or volumetrically. (a) Healthy control participants and (b) Diabetes without retinopathy, (c) Mild-to-moderate nonproliferative DR (NPDR), D: proliferative DR (PDR). Upper panel of (a-d): *En face* maximum projection of inner retinal angiogram. The inner green line represents the theoretical baseline FAZ boundary; the outer green line represents 600 μm distances from the theoretical baseline boundary in the transverse direction. The white horizontal line indicates the position of a representative B-scan in the panel below. Lower panel of (a-d) Cross-sectional B-scan overlaid with angiographic signal (red). The green vertical lines indicate the analytic para-FAZ volume boundary locations in the inner retina. Right panel of (a-d) corresponding volumetric para-FAZ OCTA. 3D display using the ImageJ software (<http://imagej.nih.gov/ij/>; provided in the public domain by the National Institutes of Health, Bethesda, MD, USA). With permission from Wang *et al.*^[30]

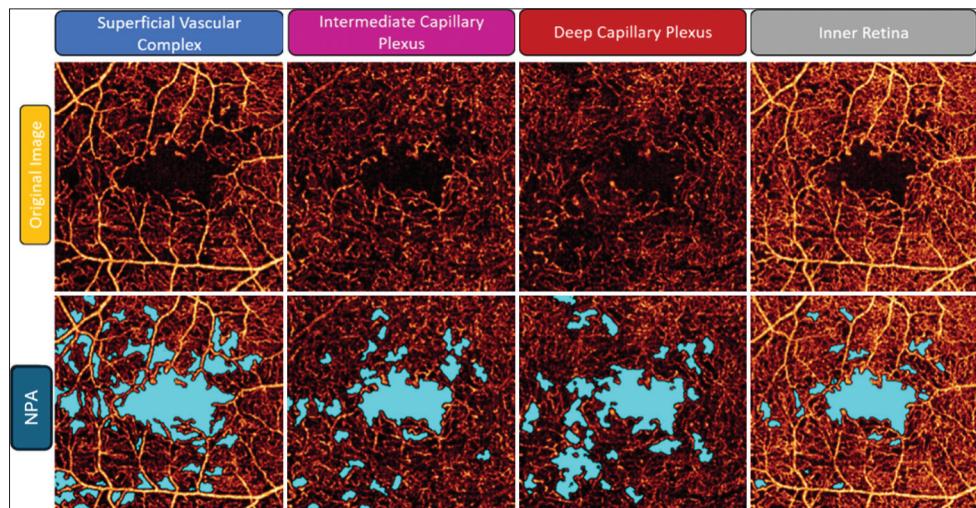


Figure 2: Non-perfusion area (NPA) detection. Top row: OCTA angiograms. Bottom row: NPA (teal) detected using a deep learning based approach. Columns show three different plexus/complexes, with their combined project on the right column (inner retina). Note the variation in detected NPA between the different plexuses: these patterns of perfusion loss can help distinguish between eyes affected by different diseases and consequently can help improve diagnostics. With permission from Hormel *et al.*^[35]

ability to anatomically (i.e. in 3D) locate microaneurysms, because OCTA achieves high resolution it is well-suited to assessing microaneurysm morphological characteristics and, in conjunction with structural OCT, perfusion status [Figure 3].^[10]

Another quantifiable feature in DR is retinal neovascularization (RNV). RNV of course indicates the proliferative form of the disease and, since it is a treatment indicator, this represents a potentially powerful use of OCTA technology. RNV is relatively

easily identifiable using OCTA using depth resolution since we can check for the location of vessels superior to the inner limiting membrane (ILM).^[41] OCTA has been demonstrated to be capable of identifying RNV missed during clinical examination.^[42] Actually, *en face* OCTA should be supplemented with OCT for this purpose.^[43] Another recently indicated application of the technology is assessment of RNV sprouts visible on cross-sectional, but not *en face*, OCTA [Figure 4].^[44] OCTA then offers complementary RNV detection analysis: *en face* visualizations can provide more rapid but sensitive

detection, while cross-sectional visualizations can provide even more detailed identifications.

Technical aside

A major recent development in OCTA is widefield and ultra-widefield imaging.^[45] There are several technical hurdles that had to be overcome to expand the field of view in OCTA, but probably the most important technological advance has been the adoption of high-speed swept source illumination.^[46,47] Improved fields of view in turn improve OCTA quantification, for example, in the context of RNV detection,^[42] NPA analysis,^[48,49] microaneurysms, and intraretinal microvascular abnormalities (IRMA) [Figure 5].^[50] Wider fields of view also improve OCTA-based diagnostics.^[51] Commercially available ultra-widefield imaging devices include the Zeiss PlexElite and Intalight DREAM.

Age-related Macular Degeneration

Age-related macular degeneration (AMD) is another leading cause of blindness.^[52] It primarily affects elderly demographics, but since the global population is aging this makes it a clinical priority. It has two advanced states: wet (which includes exudation due to macular neovascularization) and dry (which includes geographic atrophy [GA]).^[53] Macular neovascularization (MNV) is treatable.^[54,55] GA also is, but only to an extent: GA lesion growth can only be slowed, not reversed.^[56,57] Furthermore, eyes with wet AMD can still go on to develop GA. This makes AMD research and development of new, advanced therapies among the major unmet needs in ophthalmology. Since exudation is ultimately due to MNV, it is an obvious target for OCTA.^[58] It turns out vascular measurements in the choriocapillaris (CC)

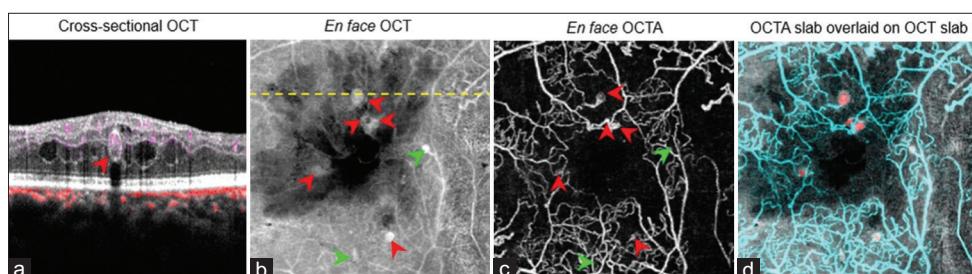


Figure 3: Characterization of microaneurysms in an eye with macular edema. (a) A microaneurysm presents as an oval structure with a strongly reflective wall (red arrow) and flow in cross-sectional structural optical coherence tomography (OCT)/OCT angiography (OCTA). (b) The lesions appear as bright round spots in *en face* OCT. The dashed yellow line indicates the location of the cross-sectional image. (c) The *en face* OCTA shows flow signal in some microaneurysms (red arrows), whereas some microaneurysms do not contain flow signal (green arrows). (d) There is very discernible flow (red) in some microaneurysms shown by overlaid *en face* OCT (gray) and OCTA (c). Adapted from Gao *et al.*^[10]

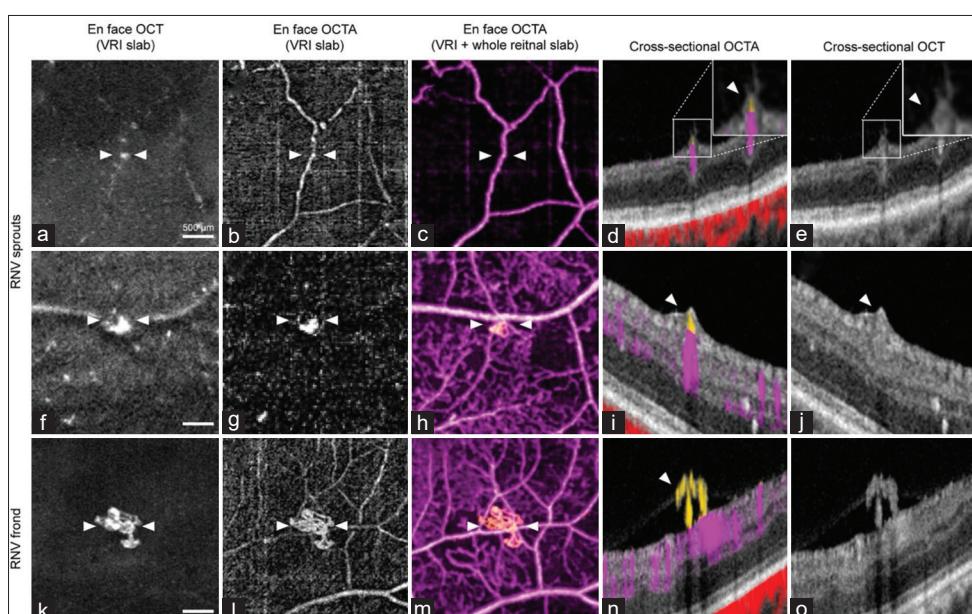


Figure 4: Classification of early signs of retinal neovascularization (RNV) using cross-sectional optical coherence tomography (OCT) and OCT angiography (OCTA). (a-o) The first and second rows show RNV sprouts. *En face* OCT (a and f) shows RNV sprouts as foci of epiretinal hyperreflective material with flow signal above the internal limiting membrane (ILM) (orange vs. magenta for flow below the ILM) on cross-sectional OCTA (d and i). The cross-sectional OCT illustrates the pyramid-shaped proliferation emerging on the retinal vessels (e and j). However, the abnormal flow signal either cannot be detected (b and c) or is not distinct as a vascular structure (g and h) on *en face* OCTA. (k-o). The bottom row shows an RNV frond, which is recognizable as a vascular network on *en face* OCT (k) and OCTA (l and m) with a clear flow signal above the ILM on the cross-sectional OCTA (n and o). With permission from Tsuboi *et al.*^[44]

are also useful for AMD progression. We will discuss both.

First, the more obvious application: MNV. OCTA is a powerful technology for assessing MNV.^[59,60] OCTA in combination with standard OCT is useful in particular for determining MNV lesion type because it can determine whether neovascular vessels lie above or below the retinal pigment epithelium (RPE). OCT-based lesion types correspond to occult (type I, below the RPE) and classic (type II, above the RPE). OCTA can also visualize type III MNV, sometimes called angiomatous

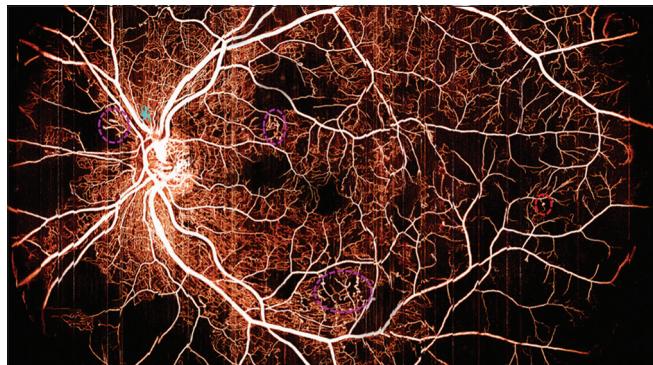


Figure 5: Single-shot 75° field of view optical coherence tomography angiography image of an eye with proliferative diabetic retinopathy. Shown is the superficial vascular plexus; the device that captured this is a prototype. Neovascularization (teal), intraretinal microvascular abnormalities (magenta circle), and microaneurysms (red circle) are all visible. With permission from Liang et al.^[51]

proliferation.^[11,61] Moreover, of course, RNV can also be visualized as discussed above, so that each neovascular lesion type can be assessed using OCTA [Figure 6].^[62] OCTA can also reveal lesion complexity, which is an additional prognostic indicator.^[63] Moreover, quantitative OCTA imaging is a good way to predict MNV treatment response^[64] and prognosticate exudation.^[65] Because it can detect neovascular vessels before exudation, OCTA should be considered a powerful approach for the early detection of wet AMD.^[66,67]

An important thing to consider for MNV quantification is projection artifacts. These artifacts, due to multiple scattering and time-varying shadows cast by vessels anterior to the tissue in which they occur, mimic superficial vasculature. This is a pernicious effect for quantification since projection artifacts look like real vessels, and therefore are hard to distinguish. They can be removed volumetrically.^[68,69] Cleaning them is important for correctly assessing MNV: projection artifacts could lead to false detections, and they will mess up the quantification of MNV metrics [Figure 7].^[69]

Projection artifacts affect do not just affect MNV quantification but rather any OCTA metrics in deeper tissue. This includes vessel density, tortuosity, fractal dimension, and NPA. There is another perfusion metric we have not discussed yet: flow deficits in the CC. Flow deficits are typically quantified in this layer in place of vessel density or NPA since it is dense

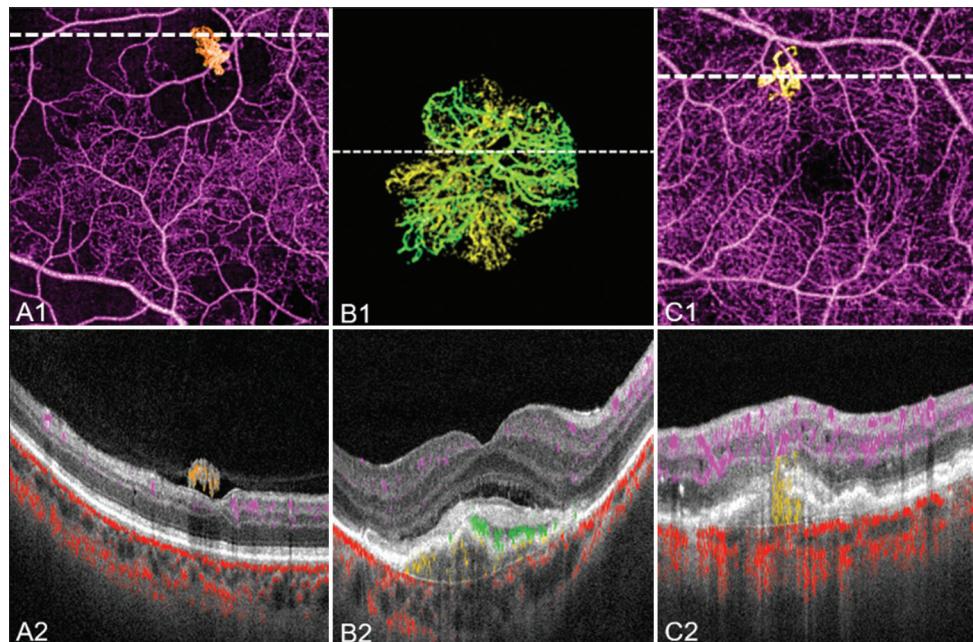


Figure 6: Differentiating neovascular lesion type with optical coherence tomography angiography (OCTA) and OCT. By overlaying the flow signal on the structural signal, a combination of structural OCT and OCTA is uniquely capable of ascertaining neovascular lesion type. Row 1: en face images; row 2: cross-sectional images taken at the location of the dotted white lines in row 1, with flow signal overlaid on the structural image. (a) Retinal neovascularization can be identified due to the location of the neovascular vessels above the internal limiting membrane. (b) A mixed type I/type II macular neovascular (MNV) lesion, with the type I component shown in yellow and the type II in green. The separate components can be identified by their location, respectively, below and above the retinal pigment epithelium. (c) Type III MNV, with the cross-sectional image showing vessels extended between the choroid and retina. With permission from Hormel et al.^[62]

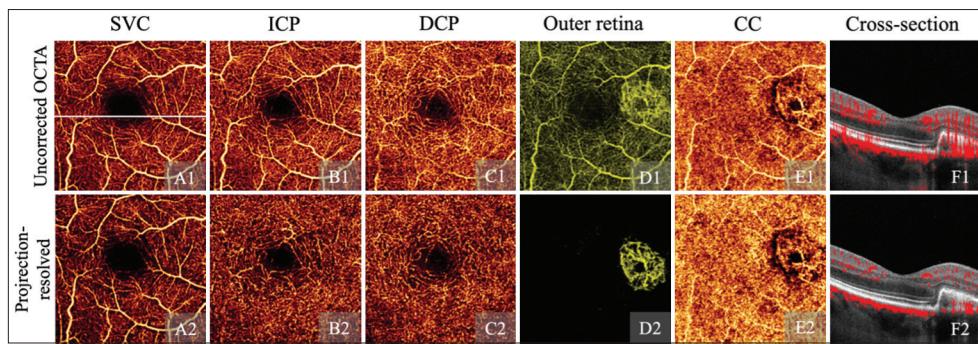


Figure 7: Projection-resolved optical coherence tomography angiography (OCTA). Row 1: Uncorrected OCTA *en face* images of the superficial vascular complex (a), intermediate (b) and deep (c) capillary plexuses, outer retina (d), choriocapillaris (CC) (e), and cross-sections at the location of the white line in (A1) (f). Row 2: Corresponding projection-resolved outputs. In the uncorrected output, *en face* images clearly show superficial vasculature reproduced in the ICP, outer retina, and CC. This is also apparent to a lesser extent in the DCP. Note, in particular, that the outer retina should be avascular except for pathologic neovascularization- any vessels visible in D1 outside of the macular neovascularization lesion are artifacts. In the cross-section (F1), the projection artifacts appear as tails extending beneath *in situ* vessels. These artifacts are absent in the projection resolved result; also note in particular that this enables simple identification (and consequently quantification) of the MNV lesion (D2). With permission from Wang et al.^[69]

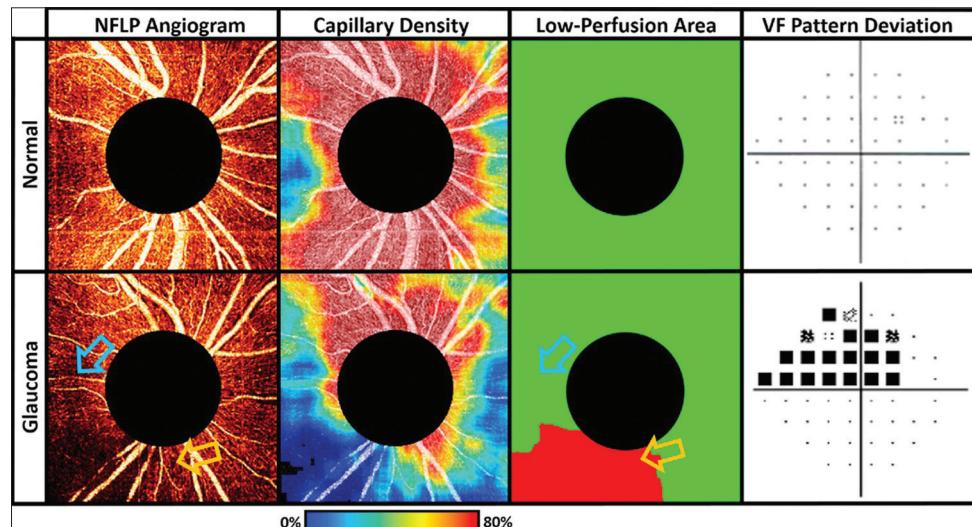


Figure 8: Low-perfusion area (LPA) in the peripapillary NFLP distinguishes glaucomatous eyes from normal. The glaucomatous eye (bottom row) has capillary loss identified in the LPA map. The LPA map identifies areas with significantly lower capillary density than that of the same location in a normal eye, providing a more accurate perfusion loss localization than either the raw angiogram or the capillary density map. In the bottom row, the blue arrow marks a region of low capillary density that is normal, while the orange arrow indicates a region that retains high capillary density but that is nonetheless relatively low in comparison to healthy populations. The orange arrow, but not the blue arrow, therefore indicates a low-perfusion area, even though the capillary density is higher at the location of the orange arrow. The LPA locations correlate well with the locations of visual field loss in the glaucomatous eye. With permission from Hormel et al.^[70]

and because OCTA transverse resolution limits our ability to accurately/anatomically measure these other metrics. The difference between anatomic vessel density and OCTA measurements of vessel density matter more in this context. On the other hand, flow deficit measurements can still identify areas of low perfusion. Similar to NPA measurements, they are easily translatable to indications of the location of perfusion loss, which can be useful for understanding and identifying pathologies like related pathologies like GA. Actually, it turns out CC flow deficits are a good leading indicator for both progression GA^[71,72] and MNV^[73,74] development. They are also indicative of AMD progression in general.^[75-79]

Glaucoma

A last leading cause of blindness is glaucoma.^[80] OCT also has an important application in this disease because it can assess nerve fiber layer thinning, a prognostic and important pathologic feature.^[81-84] Unfortunately, there is a well-known “floor effect” for nerve fiber layer thinning. Specifically, at a certain point, the nerve fiber layer stops thinning while pathology continues to develop.^[85,86] This means that this particular metric has limited utility for assessing vision loss due to glaucoma.

One way out of this dilemma is to instead measure vessel density in the nerve fiber layer [Figure 8].^[87,88] This does at

Table 2: Other diseases with optical coherence tomography angiography applications and example studies

Disease	Example study
Inherited retinal dystrophies	Gao <i>et al.</i> ^[100]
Occlusions	Seknazi <i>et al.</i> ^[101]
Retinopathy of prematurity	Yang <i>et al.</i> ^[102]
Sickle cell retinopathy	Jung <i>et al.</i> ^[103]
Uveitis	Zahid <i>et al.</i> ^[104]

just as good of a job of assessing glaucomatous damage as nerve fiber layer thinning.^[89] However, vessel density can also identify damage earlier than tissue loss^[89] and after the tissue loss has reached its floor value.^[90] It is consequently useful for assessing disease progress^[91,92] and has prognostic value.^[93]

Discussion

Many of the metrics discussed in this work are not limited to applications specific to the sections in which we discussed them. For example, CC deficits grow in eyes with DR,^[94,95] as they do in glaucomatous eyes.^[96] The FAZ grows in glaucoma.^[97] Vessel density is decreased in AMD^[98] and NPA increases.^[99] This list could continue. There are also many disease deserving of OCTA quantification which make use of these same metrics, for example, inherited retinal dystrophies may include progressive patterns of perfusion loss. Here, our intent was to introduce some of the most important of these quantifications by way of example in some of the most prevalent blinding diseases.

This review used three prevalent diseases to highlight OCTA capabilities. These were meant as examples, but OCTA also has applications in several other diseases [Table 2].

This review presented several different quantification methods for evaluating perfusion status: vessel density, FAZ area, and NPA. While these metrics all approach the same physiological characteristic, they have important differences that should be emphasized. Vessel density and FAZ area have one major advantage over NPA: they are often integrated into commercial devices. This means that there are large datasets available with these measurements and that they are currently clinically available. However, at the same time, relative to NPA, they are less reliable: vessel density because it is more prone to signal strength variation, and FAZ area due to the difficulty distinguishing between pathology and a naturally large population variation. NPA is both less prone to signal strength variation, and there is not much of a population variation in intercapillary spacing (the measurement used to define NPA). NPA can also visualize regions of perfusion loss in an intuitive way. These are advantages that should be considered when

considering clinical trial endpoints or for clinical practice when more OCTA quantifications become commercially available, which the authors believe is likely to happen.

So within categories of OCTA metrics that measure similar physiological attributes like perfusion, not all are equal. A similar note should be made about quantification in general. As noted for vessel density calculations, there are many means of arriving at a vessel density value. This is in general true for quantifications. Often calculations include tacit information like kernel sizes used for image filtering or morphological operations; these design parameters are often not accessible. It furthermore may be difficult to distinguish between performance between them. On the other hand, we can make two broad claims when comparing different quantification approaches. (1) Quantifications that effectively deal with noise and artifacts are to be preferred. Signal attenuation, motion artifacts, and projection artifacts all often appear in OCTA images. Quantifications that do not account for these will produce erroneous values. Consequently, when we want to distinguish between NPA in the DCP in eyes with DR versus healthy eyes (for example), if we do not account for projection artifacts, we will instead be measuring an amalgam vessel locations in the DCP and any superficial vasculature, which only partially reflects the *in situ* NPA. This will obviously make distinguishing between these categories more difficult. (2) Artificial intelligence methods are generally more resilient to noise and artifacts than traditional methods. This is mostly due to context sensitivity. This advantage can be read off of performance results between traditional methods and AI results, but in the few studies that have performed direct comparisons, this can also be measured (see the first technical aside above).

Conclusion

Quantification of vascular pathology using OCTA has demonstrated clinical utility. Research measurements using the same modality demonstrate that there are more OCTA metrics that, if and when commercialized, could have a similarly beneficial clinical impact. These capabilities become more powerful when care is taken to ensure that quantifications effectively account for artifacts and scan quality variation. More effective quantification, and new OCTA-based measurements, could continue to increase the relevance of OCTA in clinical practice.

Data availability statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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Conflicts of interest

Tristan T. Hormel: Ifocus Imaging (I).

Optovue/Visionix (P, R), Genentech/Roche (P, R, F), Ifocus Imaging (I, P), Optos (P), Boeringer Ingelheim (C), Kugler (R).

The potential conflicts of interest have been reviewed and managed by Oregon Health and Science University.

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