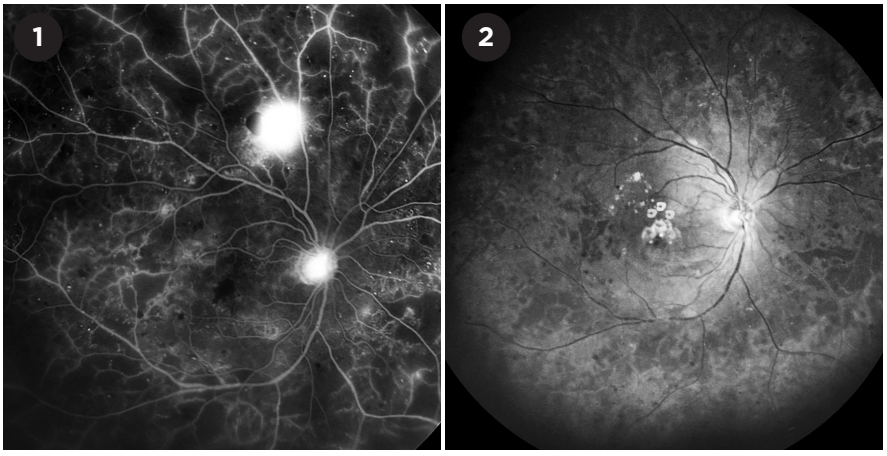
Nonperfusion in DR: Imaging Update

New imaging technologies are shedding light on nonperfusion and its role in worsening diabetic retinopathy (DR).

"Multiple studies have shown that nonperfusion is a key predictor of the progression of DR and is correlated to the stage of retinopathy," said Jennifer I. Lim, MD, at the University of Illinois in Chicago.

For instance, greater nonperfusion in otherwise comparable patients with nonproliferative DR means a greater likelihood of advancing to proliferative DR, Dr. Lim pointed out.

Understanding nonperfusion, then, has the potential to improve best practices in staging retinopathy risk and progression to improve patient care.



NUANCES. *Nonperfusion, as shown on (1) blue-filter SLO (note hyporeflective area) and (2) UWF-FA (note dye leakage from new vessels).*

Early Warning System

Nonperfusion can herald DR even before clinical symptoms appear.[1]

"Once nonperfusion develops, the ischemic retina produces angiogenic factors that cause abnormal neovascularization, and the prognosis gets worse," said Kyoko Ohno-Matsui, MD, PhD, at Tokyo Medical and Dental University in Japan. "Detecting nonperfusion before new vessels develop is critically important."

Role in staging DR risk. "There's strong enthusiasm in the field to update the diabetic retinopathy severity scale [DRSS], and how we stage retinopathy, and nonperfusion may be part of that," said Jennifer K. Sun, MD, MPH, at Harvard in Boston. "The [DRSS] scale has been extremely helpful over the years but doesn't incorporate our newer knowledge about the disease."

For instance, as Dr. Sun pointed out, the DRSS is graded only within the 7 standard fields that incorporate about 90 degrees of the posterior retina, so it doesn't include large swaths of the retinal periphery. In contrast, ultra-widefield (UWF) imaging is capable of capturing this retinal territory in a single 200-degree image.[2]

UWF studies have found that 40% to 50% of eyes had DR lesions greater in extent and severity in the peripheral retina than in the posterior fields, said Dr. Sun. Thus, these results may help clinicians better stage and triage patients with regard to their risk of retinopathy worsening, she said.

Nonperfusion Pathophysiology

What imaging reveals. While the healthy retina is crisscrossed with vessels, nonperfusion appears on imaging as areas of capillary dropout. For some experts, nonperfusion and ischemia now carry slight distinctions.

"You can have ischemia without complete nonperfusion," said Dr. Lim. "Ischemia is decreased vascular perfusion, and this hypoxia can range from mild to severe, while nonperfusion is typically present or absent."

Structure and function. Nonperfusion involves both the structure of capillary walls and blood flow within them. "I think the structural changes happen first, when pericytes, which cover the outer surface of endothelial cells in the capillaries, are lost," said Dr. Ohno-Matsui. Leaky blood vessels

BY REBECCA TAYLOR, CONTRIBUTING WRITER, INTERVIEWING **JENNIFER I. LIM, MD, KYOKO OHNO-MATSUI, MD, PHD,** AND **JENNIFER K. SUN, MD, MPH.**

and angiogenesis follow pericyte loss, added Dr. Lim.

"The underlying mechanism behind the hallmark lesions of DR—hemorrhages, microaneurysms, intraretinal microvascular abnormalities—is probably the onset and worsening of nonperfusion due to compromise to the diabetic microvasculature," said Dr. Sun. She added, "Typically, we see more lesions in areas associated with nonperfusion. The ETDRS evaluated whether 30-degree–field fluorescein angiography (FA) could help predict eyes at risk for DR worsening, but although FA findings were associated with retinopathy worsening, they didn't add enough benefit to findings on color fundus photographs to warrant an invasive test."

Is it nonperfusion or cloaked vessels? Diagnosing nonperfusion is tricky without a precise view of blood vessels.

"Diagnosis of nonperfusion depends upon knowing that the apparent lack of blood flow isn't due to [that] flow being cloaked by preretinal blood, intraretinal pigment, overlying retinal lipid, or other opacity that blocks visibility, such as overlying vitreous hemorrhage," said Dr. Lim. "Anything that blocks the transmission of light or visibility of fluorescein dye with angiography can give a false appearance of absence of blood flow."

Imaging Options

FA. After decades of use, FA's profile is well understood. "FA is widely available, the images are clear, and we're all trained to interpret the images," said Dr. Ohno-Matsui. "The disadvantages are its invasiveness and occasional serious complications, and many diabetics cannot have FA due to renal dysfunction."

"We understand how to incorporate FA metrics better than we do OCT angiography, which is not to say that in the future they won't be complementary," said Dr. Sun. "Fluorescein has the additional ability to look at leakage from vessels, and some studies suggest that global estimates of leakage may be associated with retinopathy outcomes."

OCT angiography (OCTA). "OCTA is quick, easy, and noninvasive," said Dr. Lim. One caveat: "Because OCTA relies on measuring differences between images over time to detect differences within vessels (inferred to be blood flow), eyes with very slow blood flow or OCTA systems without high-enough scan speeds may not detect retinal blood flow, and this can appear as falsely positive areas of nonperfusion."

"OCTA is a very appealing technology, and the images of the microvasculature are fabulous," Dr. Sun noted. "But we haven't successfully defined ways to use OCTA metrics that definitively improve our ability to triage patients' risk of disease worsening."

Swept-source OCTA takes even faster, higher-resolution, 3-D images of retinal blood flow, revealing up to 10 layers of retinal histology.[2]

UWF imaging. UWF imaging, defined as greater than 100 degrees field of view, solves the problem of imaging the peripheral retina.[2] One device covers 200 degrees; others cover 163 and 133 degrees.[2] "The ability of the UWF systems to image peripheral nonperfusion is key to assessing total nonperfusion for DR eyes, since macular nonperfusion alone doesn't describe its totality," said Dr. Lim.

"With ultra-widefield imaging, we've seen more nonperfusion in the periphery than many of us expected, even in eyes with mild disease," said Dr. Sun. "There will be eyes where DR is driven by nonperfusion in the posterior retina, and others where it's driven more by nonperfusion in the periphery, so perhaps we should pay more attention to the periphery than what's been standardized in our protocols until now."

Will UWF technology added to other imaging systems become the new standard? "Earlier studies suggested that predominantly peripheral lesions on color photographs and peripheral nonperfusion on UWF fluorescein angiograms (UWF-FA) were associated with greater risk of DR severity worsening," said Dr. Sun.

She added, "The DRCR Network's Protocol AA study didn't validate an association between predominantly peripheral lesions and retinopathy worsening [on color photographs], but we did see that predominantly peripheral lesions and nonperfusion on UWF-FA were both strongly associated with retinopathy worsening over time."[3]

The question remains whether the addition of invasive FA confers enough benefit to become the clinical standard, Dr. Sun said.

Blue-filter scanning laser ophthalmoscopy (SLO). SLO has been replacing color fundus photography and has

A Note on Nonperfusion Metrics

As researchers identify various biomarkers for nonperfusion, study results can differ based on which metrics were used, Dr. Lim cautioned. Common biomarkers are as follows:

Vessel perfusion density. "We analyze vessel perfusion density using Image J [NIH's imaging processing software] to compare the normal amount of area occupied by blood vessels with the reduced area [deficit of vessels] in the ischemic eye," said Dr. Lim. "Let's say 75% of this area should have blood vessels, but imaging shows vessel perfusion density is decreased to 50%." (Note: some studies use the shorter term vessel density.)

Geographic perfusion deficit. This proxy measure of nonperfusion is based on how much oxygen theoretically diffuses outward from the center of vessels.[1] Several studies have shown a correlation between nonperfusion in the deep capillary foveal avascular zone and vision-threatening DR progression.[1]

Vessel diameter. Vessel diameter can be determined using calculus and then compared in normal and DR vessels, said Dr. Lim. "Vessel diameter decrease may not equate to nonperfusion, but with greater ischemia there is usually vascular narrowing and less blood flow, and that might be a biomarker predicting nonperfusion."

1 Ong JX et al. *Ophthalmol Retina.* Published online July 5, 2022.

been improved with a red-, green-, and blue-filter system.[2] The result? "When we extract the blue-filter image only, we see the nonperfusion area as a hyporeflective image without using invasive dye or expensive OCTA equipment," said Dr. Ohno-Matsui. "Taking one color fundus photo, we can now detect nonperfusion noninvasively."

Predicting DR Progression

Once quantified via imaging, nonperfusion is a useful biomarker for the likelihood of progressing to more severe DR, said Dr. Lim. "If there's significant nonperfusion present, I'm going to watch that eye more closely than an eye with less severe nonperfusion," she said.

In the future, more nuanced categorizing of nonperfusion into mild, moderate, and severe—within each stage of nonproliferative DR—would improve clinical care, said Dr. Lim. Depending on the degree of nonperfusion, she said, she could then subcategorize patients with a predictive number linked to their prognosis, to help inform the frequency of follow-up and perhaps guide the initiation of anti-VEGF treatment to slow progression.

In one study of 61 eyes with nonproliferative DR, OCTA findings of nonperfusion predicted "clinically significant" DR progression after one year.[4] The vessel density and geographic perfusion deficit (GPD) metrics of nonperfusion were assessed in the superficial, middle, and deep capillary plexus. At the one-year mark, lower vessel density and higher GPD predicted worsening of retinopathy. Further, GPD had a sensitivity of 89% and specificity of 98% for DR worsening when seen in the deep capillary plexus.[4]

Anti-VEGF Paradox

A curiously confounding factor in diagnosing nonperfusion is the prevalence of anti-VEGF treatment. Does it change the disease process, thereby moving clinical goal posts?

While it's clear that many eyes improve in their DRSS score with anti-VEGF treatment, accumulating evidence indicates that the underlying nonperfusion is probably not substantially improved, said Dr. Sun. "The question is whether we should be treating eyes with nonproliferative disease earlier with injections or not."

The DRCR.net Protocol W study may help address this issue, Dr. Sun added. "It's an open question: how do you develop treatments that address underlying nonperfusion, restore perfusion to the retina, and protect the cells even longer term?"

"If we give anti-VEGF, we can make severe nonproliferative DR look like mild nonproliferative DR," said Dr. Lim. "The real question is: have we driven down nonperfusion to what mild nonproliferative DR would typically have in its natural history? We know that retinal swelling can appear on imaging as nonperfusion, and after anti-VEGF, you can see vessels you couldn't see before, so it looks like you've improved the nonperfusion."

"It's a hotly debated topic right now," said Dr. Lim. "No drug to date can actually decrease the level of nonperfusion, but does anti-VEGF stop nonperfusion from progressing? We don't know yet."

1 Wykoff CC et al. *Ophthalmol Retina.* 2022;6(7):557-566.

2 Horie S, Ohno-Matsui K. *Diagnostics.* 2022;12(7):1684.

3 Silva PS et al. *JAMA Ophthalmol.* 2022;140(10):936-945.

4 Ong JX et al. *Ophthalmol Retina.* Published online July 5, 2022.

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