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EDITORIAL

Retinal non-perfusion: recognizing and defining what is important

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Tissue ischemia due to pathologic retinal non-perfusion (RNP) is a fundamental component of diabetic retinopathy (DR), retinal venous occlusive disease, and possibly even age-related macular degeneration if underlying choroidal ischemia is included. Specifically within the context of DR, RNP may be a very early marker of disease progression [1] and increased RNP area has been correlated with increased DR severity [2, 3].

From prospective clinical trials, we have known since the Early Treatment Diabetic Retinopathy Study (ETDRS) that the presence of fluorescein-angiographically-identified RNP is an important prognostic indicator [4]. More recent prospective trials have also identified RNP as a predictor of higher risk of disease progression, both with [5] and without concurrent anti-vascular endothelial growth factor (anti-VEGF) therapy [6, 7]. The retinal ischemic index, measured by the ratio of RNP area over total fundus area, has also been used as a marker for RNP burden, with a strong association between ischemic index and DR severity [8, 9].

Given its importance in assessing retinal vascular disease progression, tremendous effort has been invested towards identifying possible therapeutics that could impact RNP. These efforts include slowing RNP progression, which anti-VEGF therapy may be able to achieve with consistent, frequent dosing in some populations [10–12], or ideally lead to reperfusion, a phenomenon not commonly observed with anti-VEGF therapy [13]. Additionally, multiple molecular entities pursuing new mechanisms of action, including manipulating the Sema-3A-Nrp1 pathway, are actively being explored in prospective clinical trials [14, 15].

Despite these advancements, RNP is not a registration trial endpoint that can be utilized for regulatory approval. Work towards defining the correlation between perfusion status and visual function – in combination with adequately powered clinical trials with robust methodology assessing RNP as the primary outcome—are needed in order to validate RNP as a potential surrogate outcome that could be acceptable for regulatory approval. One relevant ongoing study is the Safety and Efficacy of Faricimab in Patients with NPDR (MAGIC [*NCT05681884*]), which aims to measure RNP area change in eyes with NPDR [16].

RNP location also appears to be relevant. For example, the far and mid-peripheral retinal zones may be more sensitive to the impact of diabetes mellitus [17, 18]. Confusingly however, RNP localization has been inconsistently defined in the literature, ranging from broad categorizations (peripheral, mid-peripheral, central, and generalized) [19], to more specific categories (posterior (<10 mm from the disc), mid-peripheral (10 mm to 15 mm), and peripheral (>15 mm)) [20]. Within this sphere, Romano et al. describe current nomenclature challenges associated with topographical localization of images captured with optical coherence tomography angiography (OCTA) images [21].

To build on their proposals, there are other dimension to consider—for example, depth and location. Retinal vasculature is complex, with up to four layers of vasculature, including the radial peripapillary capillary network, the superficial vascular plexus, and the deep capillary complex. These various networks are region specific [22] and may be differentially impacted by retinal vascular diseases. For example, lower capillary density has been reported in the deep vascular plexus compared to the superficial vascular plexus among diabetic patients, both with [23] and without clinically detectible DR [24, 25].

In order to facilitate robust prospective analyses of RNP, and its longitudinal change with current and future therapeutics, it is critical to have a standardized approach to nomenclature and quantification. Ideally, such nomenclature would reflect relevant physiology, including known topographic differences in the retinal vascular tree, and not simply be determined by distances.

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COMPETING INTERESTS

The authors declare no competing interests.