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# Fractal-Based Oscillation of Macular Arteriogenesis and Dropout During Progressive Diabetic Retinopathy

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## Purpose

To examine fractal-based remodeling of macular arterial vessels with progression of diabetic retinopathy (DR).

## Methods

A binary (black/white) branching pattern of arterial vessels was extracted from the macular region within retinal images obtained by 50° fluorescein angiography (FA) of eyes diagnosed with mild, moderate, or severe nonproliferative DR (NPDR) or proliferative DR (PDR). A box of 1024 by 1024 pixels centered at the fovea centralis was overlayed upon the macular region of each 2392 by 2048 binary image. One representative image of each DR stage was selected for this preliminary study. Focusing on a region around the macula, rather than studying the entire funduscopic image, considerably reduces the analysis required for diagnosis. Using VESsel GENeration Analysis (VESGEN) software, the 1024 by 1024 arterial binary pattern was mapped automatically to measure the density of total vessel length ($L_v$), as well as the fractal dimension ($D_f$) by a box-counting algorithm. VESGEN maps and quantifies vascular pattern as a function of vessel branching generation.[1-7]

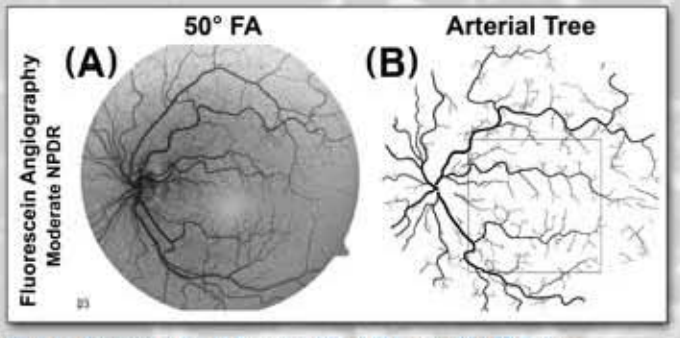


**Figure 1.—Extraction of Arterial Trees from Clinical FA Images of the DR Retina.**
**(A and B)** Arterial trees were extracted as branching vascular patterns from ophthalmic grayscale images obtained by FA using semiautomatic computer processing.[1-7] **(B)** A box of 1024 by 1024 pixels centered on the fovea centralis is overlayed upon the arterial pattern (2392 by 2048 pixels). This example is the moderate NPDR image represented by its vascular skeleton in Fig. 2(B).

## Results

For macular arterial vessels, angiogenesis oscillated strongly with vascular dropout during progression of DR. $D_f$ and $L_v$ increased significantly from mild NPDR (1.28 and 0.0096 per pixel, respectively) to moderate NPDR (1.34 and 0.0130 per pixel), decreased from moderate NPDR to severe NPDR (1.28 and 0.0095 per pixel), and again increased from severe NPDR to PDR (1.30 and 0.0108 per pixel). Previously, we showed by a similar fractal analysis[8] that for the combined density of macular arteries and veins, $D_f$ decreased with progression from normal to mild NPDR.

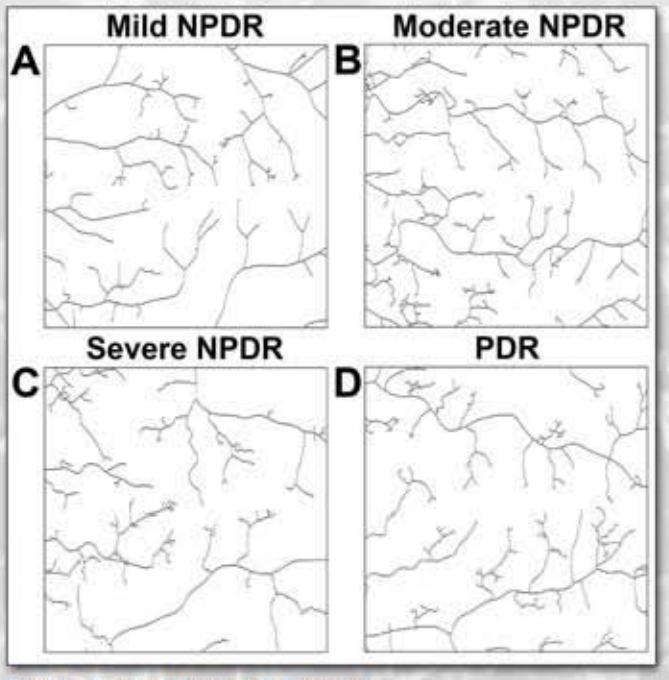


**Figure 2.—Skeletonized Images of DR Progression.**
**(A to D)** DR progression from mild NPDR to PDR is illustrated by the skeletonized pattern of the arterial tree, as mapped by VESGEN software within the square box centered on the fovea centralis, as described in Figure 1. VESGEN then quantified the fractal dimension (D) and vessel length density ($L_v$) for these representative images. The increase in arterial density from severe NPDR to PDR is not as great as the increase from mild to moderate NPDR, both in visible appearance and as measured by VESGEN (see Results section). This result was also obtained by the VESGEN generational branching analysis reported in Ref. 1 below.

## Conclusions

By both fractal ($D_f$) and branching ($L_v$) analysis, macular arterial density oscillated with progression from mild NPDR to PDR. Results are consistent with our study reported recently for the entire arterial and venous branching trees within 50° FAs by VESGEN generational branching analysis.[1] Current and previous results are important for advances in early-stage regenerative DR therapies, for which reversal of DR progression to a normal vessel density may be possible. For example, potential use of regenerative angiogenesis stimulators to reverse vascular dropout during mild and severe NPDR is not indicated for treatment of moderate NPDR.

Author Disclosure Information: P.A. Parsons-Wingerter, None; K. Radhakrishnan, None; and P.K. Kaiser, None.

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